INDIAN JOURNAL OF PRACTICAL PEDIATRICS

CONTENTS

TOPIC OF INTEREST - "RHEUMATOLOGY"

INSTRUCTIONS TO AUTHORS

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Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1") in double space typescript on each side. Use American English using Times New Roman font 12 size. Submit four complete sets of the manuscript.

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250 – 600 words, 8 – 10 recent references

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150 – 200 words write up

With 1 or 2 images of clinically recognizable condition

(of which one could be in the form of clinical photograph / specimen photograph / investigation)

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RHEUMATOLOGY

FEBRILE CHILD - WHEN TO SUSPECT AND HOW TO WORK UP FOR CONNECTIVE TISSUE DISORDERS

Mahesh Janarthanan

Abstract: *Connective tissue disorders are rare compared to common infectious diseases in children. Making a diagnosis of connective tissue disorder may sometimes be easy when they have classical manifestations such as Kawasaki disease or Henoch Schonlein purpura. However at times fever may be the only manifestation or children may present with rare or atypical manifestations of a disease. A meticulous clinical examination and analysis of basic blood tests may provide a clue to the diagnosis or the need for further specific investigations in these situations.*

Keywords: *Febrile child, Connective Tissue disorder, Work up*

Children present with febrile illness commonly to general pediatricians. It's often easy to identify a focus of infection e.g. upper respiratory infection. A proportion of these patients may need inpatient admission and further investigations to diagnose infectious diseases. Of these patients a much smaller proportion may have non-infective cause of fever such as malignancy, connective tissue disorders, etc. In children with fever of unknown origin, approximately 10% of patients are ultimately diagnosed with connective tissue disorder.[1] Sometimes a suspicion of connective tissue disorder is raised when children present with malar rash, arthritis, rashes over body, etc. Difficulty in making a diagnosis arises when children present with prolonged fever without any other signs and symptoms. The features leading to suspicion of connective tissue disorders are listed in Box.1.

While investigating a child with prolonged fever for connective tissue disorders the possibilities are narrowed down to five major diagnoses: Systemic onset juvenile idiopathic arthritis (SoJIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM),vasculitides and

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Box.1.Features to suspect connective tissue disorders

- Prolonged fever(PUO)
- Rashes(maybe urticarial)
- Dermal necrosis / gangrene of digits
- Peripheral neuropathy
- Unexplained arthritis, myositis, serositis
- Unexplained pulmonary, cardiovascular, neurological or renal disease
- Unexplained abdominal /testicular pain
- Unexplained hypertension
- Multisystem disease

periodic fevers. Although there is a wide range of clinical possibilities, only the relatively common diagnostic conditions have been discussed along with case scenarios.

Scenario 1

Four-year-old boy presented with history of daily fever in the preceding 2 months, along with evanescent rash which appeared with fever and disappeared soon after. He also had swelling of his right knee for the past 2 weeks. His fever chart is shown Fig.1 and rashes are shown in Fig.2.

The clinical diagnosis in this case is possible SoJIA. The presence of quotidian fever (daily fever), high fever spikes but almost always touching baseline, an evanescent rash with arthritis should raise this clinical suspicion.
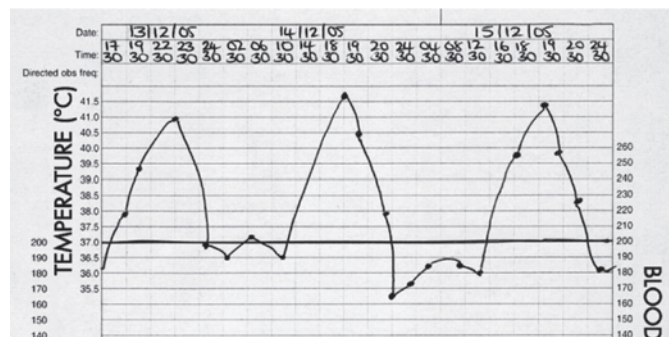

Fig.1. Quotidian fever[2]

Fig.2.Evanescent rash

Typically these children look well in between the fever spikes. The other features may include hepatosplenomegaly and lymphadenopathy. The ILAR (International League of Associations for Rheumatology) classification of JIA requires the presence of arthritis in 1 or more joints with fever more than 2 weeks that is documented to be quotidian for at least 3 days accompanied by at least 1 or more of evanescent rash, hepatosplenomegaly, generalized lymphadenopathy or serositis.[3]

Investigations may reveal a low Hb, leucocytosis, neutrophilia, thrombocytosis, raised ferritin, high inflammatory markers and transaminitis (elevation of transaminases in the liver). Extensive investigations including bone marrow may be needed to rule out infection and malignancy. In a sick looking child with very high ferritin and falling ESR, macrophage activation syndrome should be considered.

Scenario 2

Fifteen-year-old adolescent girl presented with history of fever of 2 months duration with rashes on her face and ears, oral ulcers and increased hair loss. The rashes are shown in Fig.3 and Fig.4.

The clinical diagnosis in this situation is SLE with the presence of malar rash, oral ulcers and alopecia. Blood investigations are likely to show low Hb, low white cell count (WCC), lymphopenia, thrombocytopenia, high ESR, positive direct Coomb's test (DCT), low complement C3, C4 and positive antinuclear antibody (ANA). About 50%-60% of patients may have positive double stranded DNA (dsDNA). Abnormal renal function tests, urine analysis showing proteinuria, RBCs and casts with or without hypertension indicate renal involvement. Coagulation abnormalities maybe present due to lupus, anticoagulant and antiphospholipid antibodies (anticardiolipin antibodies and anti beta-2 glycoprotein antibodies) may be positive. In a child with SLE, presence of high CRP should raise the

Fig.3. Malar rash–SLE

Fig.4. Vasculitic lesions over ear lobe

suspicion of infection or serositis and low ESR with high ferritin the possibility of macrophage activation syndrome.

Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE 2012 (Table I) was introduced for classification purposes from a research point of view. The SLICC criteria requires 4 or more of these criteria to be present with at least one clinical and one immunological criteria or biopsy proven nephritis with the presence of ANA or dsDNA.[4] Other autoimmune conditions such as mixed connective tissue disorder (MCTD), Sjogren's syndrome, systemic sclerosis are rarer in children but can present with unexplained fever.

Scenario 3

An 18-month-old girl presented with history of fever, puffiness of face and swelling of limbs for 1 month. On examination, she had a papular rash on her trunk. She was unable to roll over or sit up. Mother reported that the child had a weak voice and nasal regurgitation of feeds. Patient's creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels were elevated. Magnetic resonance imaging (MRI) of thighs shows altered signal intensity involving all thigh muscles suggestive of JDM (Fig.5). The diagnosis is juvenile dermatomyositis (JDM). Complete blood count (CBC) may be normal, differential

Table I. SLICC classification criteria for SLE 2012

Clinical criteria	Immunological criteria
Acute cutaneous lupus	ANA
Chronic cutaneous lupus	Anti DNA
Oral or nasal ulcers	Anti-Sm
Non-scarring alopecia	Antiphospholipid
Arthritis	Low complements
Serositis	DCT
Renal involvement	
Neurologic	
Hemolytic anemia	
Leukopenia	
Thrombocytopenia	

count may show lymphopenia and inflammatory markers (ESR and CRP) may be elevated. Serum CPK, LDH, aldolase and alanine aminotransferase (ALT) may be elevated. ANA positivity can be variable.

The traditional Bohan and Peter 1975 diagnostic criteria requires the presence of 1 of characteristic rashes (heliotrope rash, Gottron's papules) with 3 of following, symmetric proximal muscle weakness, raised muscle enzymes, abnormal muscle biopsy or EMG.[5] These criteria were later expanded based on an international survey to include features such as microvascular abnormalities by nailfold capillaroscopy, calcinosis, skin ulcerations, dysphagia and dysphonia.[6] In most centres MRI of thighs is increasingly used to make diagnosis while EMG and muscle biopsy are being done less frequently. Children can sometimes present only with fever, edema and proximal muscle weakness as illustrated in this case.
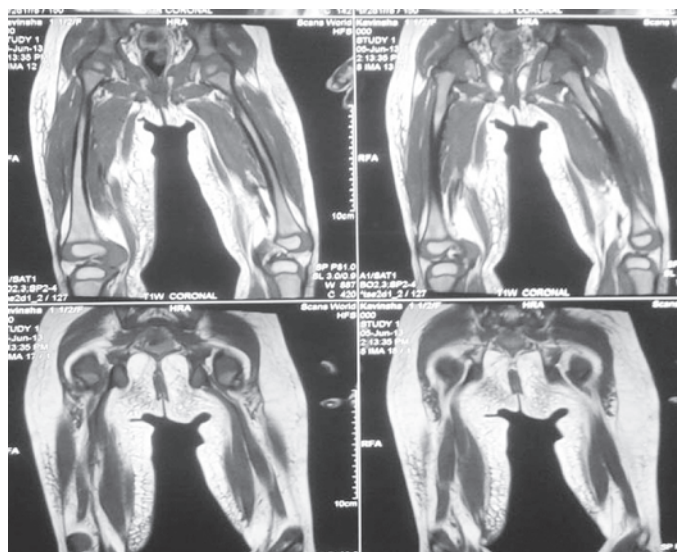
Scenario 4

A 6-year-old girl presents with 7 day history of fever and left side neck swelling, she was suspected to have suppurative lymphadenitis and underwent incision and drainage at presentation. In the 2nd week of illness she developed oral mucosa changes, conjunctival congestion and limb edema (Fig.6). Her blood tests revealed high WCC, neutrophilia, thrombocytosis and raised inflammatory markers. She continued to have fever spikes in spite of antibiotics. A diagnosis of Kawasaki disease was made and she responded well to IVIG and aspirin. This case is unusual in that the patient presented first to the surgeons for suspected suppurative lymphadenitis but had no evidence of suppuration on exploration and cultures were sterile. The diagnostic criteria for Kawasaki disease are given in Box 2. In the presence of coronary abnormalities KD can be diagnosed with less than 4 criteria. It is then called incomplete Kawasaki disease. If presenting with unusual features it is atypical Kawasaki disease.[7]

Fig.6. Oral lesions and left sided adenopathy (dressing on left side of neck for incision & drainage)

Scenario 5

A nine-year-old boy presented with 45 days history of fever and generalized tonic clonic convulsion in the preceding 24 hours prior to admission. On examination he had systemic hypertension and there were no rashes. Investigations revealed WCC-30900 cells/cu.mm, Polymorphs-88%, Hb- 10 g/dL, platelets of 7.63 lakhs/cu.mm, ESR-50 mm/hr. He had bilateral grade 1 hypertensive retinopathy. Autoimmune work up was

Fig.5. MRI -Altered signal intensity involving all thigh muscles

Box 2. Diagnostic criteria for Kawasaki disease[7,8,9]

Fever of 5 days duration or more

PLUS

4 of 5 of following:

Conjunctivitis - Bilateral, bulbar, non-suppurative

Lymphadenopathy - Cervical, often >1.5 cm

Rash - Polymorphous, no vesicles or crusts

Changes of lips or oral mucosa - Red cracked lips; 'strawberry' tongue; or diffuse erythema of oropharynx

Changes of extremities - Initial stage: erythema and oedema of palms and soles. Convalescent stage: Peeling of skin from finger tips

negative. A CT angiogram done showed bilateral renal artery stenosis, alternate constriction and dilatation of branches of celiac trunk - 'beads on string appearance' suggestive of polyarteritis nodosa (PAN) (Fig.7).

The clinical features of polyarteritis nodosa may be non-specific including fever, rashes, abdominal pain, testicular pain, arthralgia, livedo reticularis, etc. Children may sometimes present with subcutaneous nodules, gangrene of digits, or seizures. The European League Against Rheumatism/Paediatric Rheumatology European Society (EULAR/PRES) childhood PAN classification criteria requires either histopathological or angiographic abnormalities and one of the following skin involvement, myalgia/muscle tenderness, hypertension, peripheral neuropathy or renal involvement.[8,9] Children presenting with skin nodules when biopsied may show evidence of medium vessel vasculitis.

Scenario 6

A seventeen-year-old girl presented with 4 months history of low grade fever, loss of appetite and weight. On examination she had weak pulses and 4 limb blood pressure discrepancy. Laboratory investigations revealed anemia (Hb 8g/dL) and elevated ESR (71 mm/hour). Echocardiogram showed left subclavian stenosis, dilated
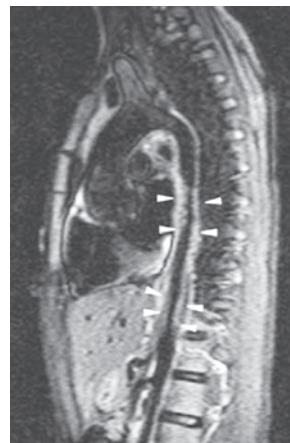
Fig.8a. Aortogram - Thickened and edematous abdominal aorta (white arrow heads)

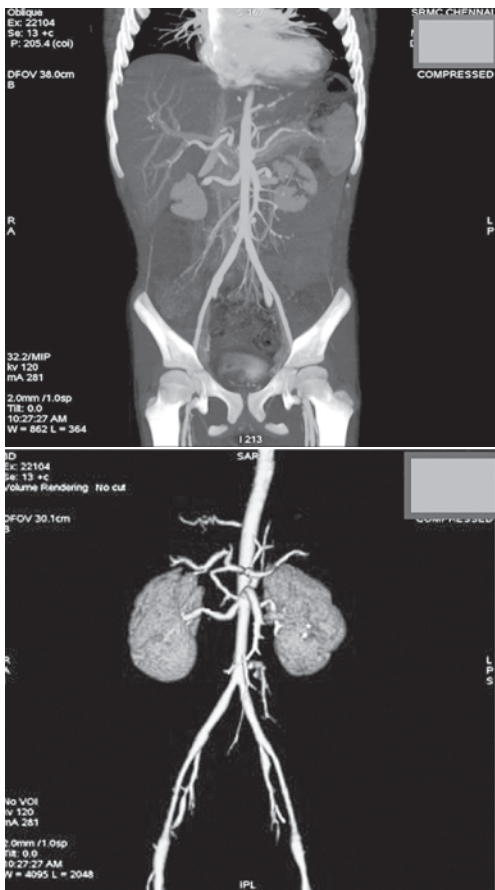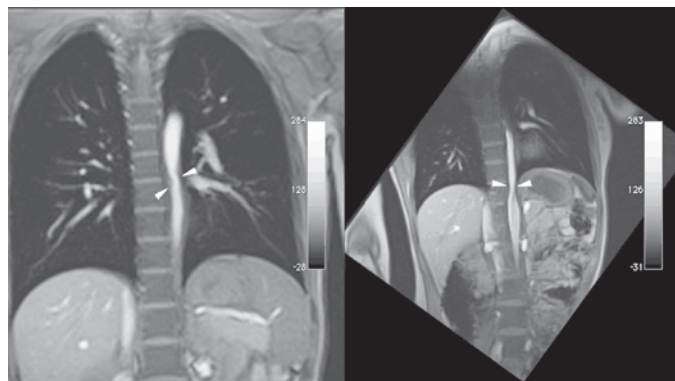**Fig.8b. Aortogram – Two areas of significant narrowing (white arrow heads) in descending thoracic aorta**

Fig.7. CT angiogramof abdomen - bilateral renal artery stenosis,alternate constriction and dilatation of branches of celiac trunk- "beads on string appearance"

ascending aorta and normal abdominal aorta. An aortogram done showed two areas of significant narrowing in descending thoracic aorta and thickened and edematous abdominal aorta suggestive of Takayasu arteritis (Fig.8a and b).

Children can either present during the acute phase with fever and non-specific systemic symptoms or during chronic phase with absent pulses, BP discrepancy, cardiac failure, bruits, hypertension, eye or renal manifestations. Blood tests are likely to show low hemoglobin, high total and neutrophil counts, thrombocytosis and elevated inflammatory markers.

The classification criteria for childhood Takayasu arteritis requires the presence of angiographic abnormalities of the aorta or its major branches and pulmonary arteries plus one of following five: a) difference in pulse volume or claudication, b) four limb blood pressure discrepancy, c) bruits, d) hypertension and e) elevated acute phase reactants.[8,9]

An algorithmic approach to diagnose connective tissue disorders in a child with fever is given in Fig.9 and 10.

Other vasculitides

In a child presenting with fever, paranasal sinus involvement, lung infiltrates and renal involvement a suspicion of Wegener's granulomatosis, now known as granulomatosis with polyangitis, should be raised. In addition, if there is history of asthma with peripheral eosinophilia or peripheral neuropathy Churg Strauss syndrome, now known as eosinophilic granulomatosis with polyangitis should be considered in the differential diagnosis. Apart from routine blood tests and autoimmune work up, testing for antineutrophil cytoplasmic antibody (ANCA) may be useful in this situation. Wegener's granulomatosis (granulomatosis with polyangitis) is associated with cytoplasmic c-ANCA with specificity against PR3 (Proteinase 3). Microscopic polyangitis and Churg Strauss Syndrome (eosinophilicgranulomatosis with polyangitis) is associated with perinuclear p-ANCA with specificity against myeloperoxidase (MPO).[9] Biopsy and histopathology of involved organs like kidneys, skin rashes or nasal septum may also help in diagnosis

Microscopic polyangiitis, sarcoidosis, Cogan's syndrome, primary angiitis of CNS (PACNS) are other rare
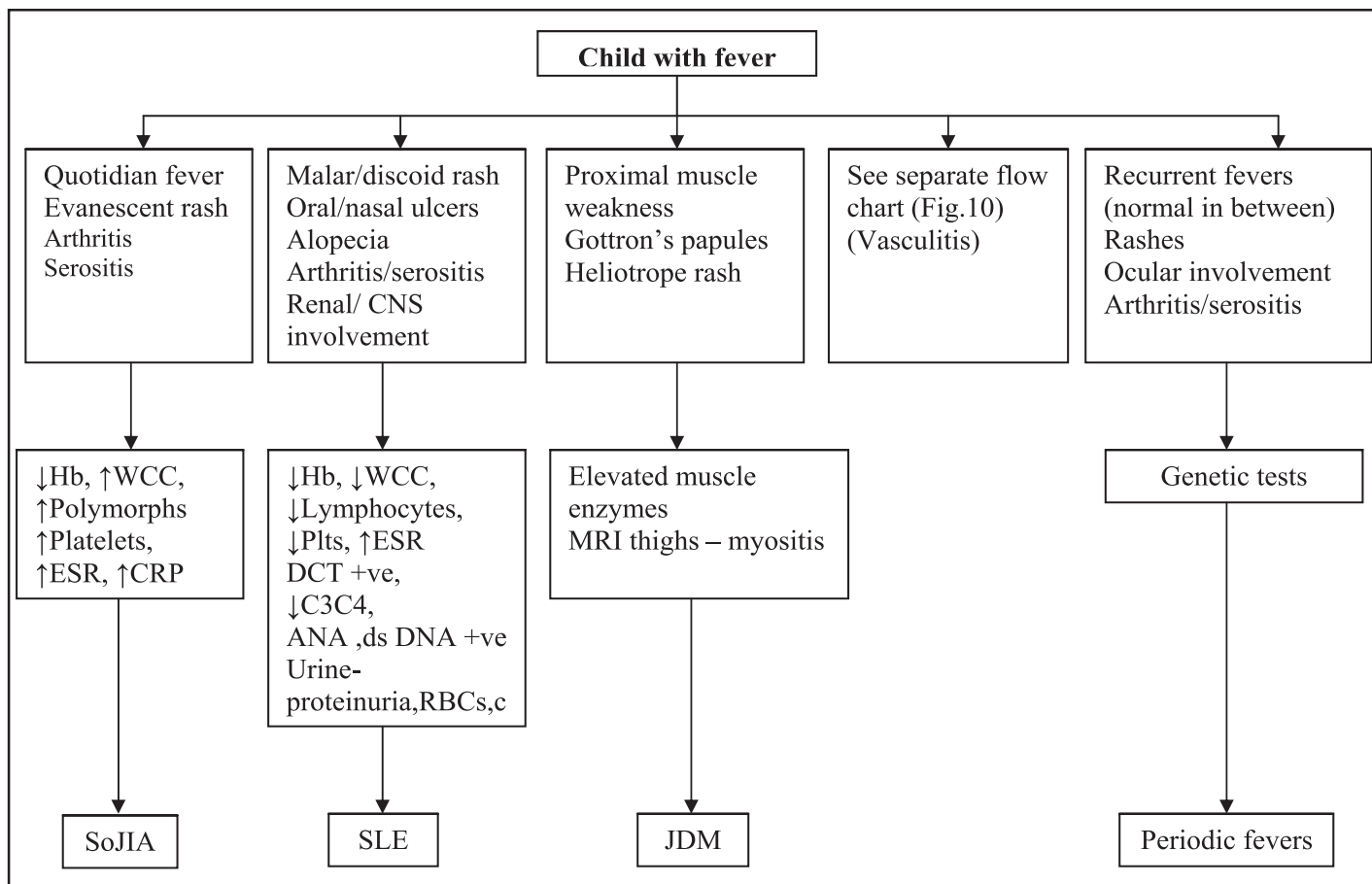
Fig.9. Summary - work up for connective tissue disorders

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                        ┌─────────────────────────────┐
                        │ Child with fever-suspected  │
                        │          vasculitis         │
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Conjunctivitis Lymphadenopathy Rash Oral mucosa/lip changes Extremities changes	Skin nodules Livedo reticularis Dermal necrosis/gangrene Hypertension Renal involvement Abdominal pain	Hypertension Asymmetric or absent pulses Arterial bruits Claudication 4 limb BP discrepancy Chest/abdominal pain Congestive cardiac failure	Paranasal sinus involvement Lung infiltrates Renal involvment Orbital psuedotumour	Asthma Neuropathy Lung infiltrates Paranasal sinus involvement
Clinical diagnosis	Histopathology Angiographic abnormalities	Angiogram abnormalities	ANCA positive Histopathology	Blood eosinophilia ANCA positive Histopathology
Kawasaki disease	Polyarteritis nodosa	Takayasu arteritis	Wegener's granulomatosis	Churg-Strauss syndrome

Fig.10. Summary - work up for vasculitis

causes of vasculitides in children. Henoch Schonlein purpura has not been discussed, as in this type of vasculitis, patients more often present after a prodromal illness rather than with fever.

Periodic fevers

These are very rare diseases in children characterized by recurrent episodes of fever and systemic symptoms, with periods of normal health in between these episodes. The systemic symptoms may include serositis, arthritis, rashes and ocular involvement. The febrile episodes are always associated with raised white cell counts and inflammatory markers which drop to normal in between episodes. The seven major syndromes under this group include familial Mediterranean fever (FMF), TNF receptor - associated periodic syndrome (TRAPS), cryoporin associated periodic syndrome (CAPS), hyper IgD syndrome (HIDS), pyogenic arthritis, pyoderma gangrenosum and acne (PAPA syndrome), deficiency of IL-1 receptor antagonist (DIRA), early onset sarcoidosis (Blau syndrome). The list of syndromes under periodic fevers is expanding and newer diseases are being included. Diagnosis is confirmed by detecting genetic mutations.[10] These fevers are common in western countries particularly Europe. There are case reports of periodic fevers in India.[11] Among disorders of unknown aetiology presenting as periodic fevers, PFAPA (periodic fevers, aphthous ulcers, pharyngitis, cervical adenopathy) is a relatively common clinical condition that one may come across. This again is a clinical diagnosis but other conditions such as immunodeficiency and cyclical neutropenia may need to be ruled out.

Conclusion

When investigating a child with fever, it is important to rule out common infections and malignancy. A thorough clinical examination including palpation of peripheral pulses, 4 limb BP measurement, auscultation for bruits and checking urine dipstick may provide a clue to diagnosis rather than expensive investigations. When possible, a clinical diagnosis should be arrived at before requesting relevant investigations. Using investigations as screening tools should be avoided. In children, connective tissue disorders may evolve over a period of time or present with acute symptoms. Aggressive or atypical presentations are common in children and therefore early detection is vital to prevent morbidity and mortality.

Points to Remember

- *When children present with prolonged fever, connective tissue disorders should be considered as differential diagnosis.*

- *Most diagnosis in rheumatology is clinical and blood tests should be used as corroborative evidence and not as screening tool.*

- *A complete clinical examination is vital*

- *Connective tissue disorders may evolve over time.*

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CLIPPINGS

Inhaled Laninamivir Octanoate as Prophylaxis for Influenza in Children

A single 20mg dose of inhaled laninamivir octanoate is an effective treatment of influenza. However, the efficacy of laninamivir octanoate for the prevention of influenza in children <10 years of age has not yet been established.

A doubleblind, multicenter, randomized, placebo controlled study was conducted to determine whether the efficacy of a single 20mg dose of inhaled laninamivir octanoate to prevent the development of influenza was superior to that of placebo as prophylaxis for influenza in pediatric (<10 years) household members of index cases. Eligible subjects without influenza, in contact with an influenza infected index case living in the same household, were blindly randomly assigned in a 1:1 ratio to receive 20 mg of laninamivir octanoate or placebo. The primary end point was the proportion of subjects who developed clinical influenza during a 10day period. A total of 343 subjects were randomly assigned, with 341 subjects included in the full analysis set for the primary analysis. The proportions of subjects who developed clinical influenza were 11% (18/171) in the laninamivir octanoate group and 19% (33/170) in the placebo group ($P = .02$). The relative risk reduction was 45.8% (95% confidence interval, 7.5% to 68.2%). The incidence of adverse events was similar in both groups.

A single 20mg dose of inhaled laninamivir octanoate was found to be effective and well tolerated as prophylaxis for influenza.

Takashi Nakano, Naruhiko Ishiwada, Tokuhito Sumitani, Mitsutoshi Uemori, Koji Isobe, for the Laninamivir Prophylaxis Study Group. Inhaled Laninamivir Octanoate as Prophylaxis for Influenza in Children. Pediatrics. 2016 Dec;138(6). pii: e20160109. Epub 2016 Nov 2.

RHEUMATOLOGY

JUVENILE IDIOPATHIC ARTHRITIS

*Chitra Sundaramurthy

Abstract: *Juvenile idiopathic arthritis comprises a heterogeneous group of inflammatory arthritides of unknown etiology with onset before 16 years of age and persisting for longer than 6 weeks. Several genetic associations have been identified but the etiopathogenesis is still unclear. The different subtypes have distinct clinical presentations and varied prognosis. Although none of the treatments available are curative, recent advances, particularly the introduction of biologics, have greatly improved outcomes. Continued research to understand the pathogenesis and identify specific molecules or pathways that need to be targeted will further improve the outlook for these patients in the future.*

Keywords: *Juvenile idiopathic arthritis, Classification, Management, Biologics*

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The term JIA was introduced in 1994 and has largely replaced juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis (JRA). JIA comprises of a heterogeneous group of inflammatory arthritis. The International League Against Rheumatism (ILAR) defines JIA as arthritis of unknown etiology which starts before the sixteenth birthday and persists for at least 6 weeks where all other causes have been excluded. The cause of the disease is still poorly understood. Recent advances in management, although not curative has greatly improved the prognosis for children with JIA.

Epidemiology

Juvenile idiopathic arthritis has been described in all races and geographic areas and its incidence and prevalence vary widely worldwide. The incidence of chronic arthritis of childhood ranges from 0.008 to 0.226 per 1000 children and the prevalence from 0.07 to 4.01 per 1000 children worldwide.[1] Estimated prevalence of JIA in India is 48/100,000 (95% CI 10-280).[2]

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Etiopathogenesis

Juvenile idiopathic arthritis is a complex autoimmune disorder with both genetic and environmental influences. JIA is a complex genetic trait and is associated with several genetic polymorphisms.[3] Genes linked with JIA include HLA system [HLA B27 is strongly associated with enthesitis related arthritis (ERA), DRB1 with Rheumatoid Factor (RF) negative polyarthritis and DR4 with RF positive polyarthritis], cytokine related genes and immune associated genes. No clear infectious trigger for JIA has been identified. It is hypothesised that exposure of the genetically pre-disposed host to unknown environmental influences triggers the disease.[4]

The immune system fails to differentiate between self and non-self and attacks the synovium. The synovium becomes thickened, highly vascular, infiltrated with inflammatory cells and secretes an exudate. This inflammatory response recruits immune cells into the joint by attaching to the upregulated adhesion molecules on the inflamed endothelium. Synoviocytes and recruited immune cells secrete chemokines (which further amplifies the inflammatory response) and angiogenic factors (highly vascular synovial proliferation). T cells are increased in synovium and synovial fluid and secrete several cytokines (TNFα, IFN γ, etc) leading to cartilage and bony damage. Circulating B cells secrete cytokines as well as produce autoantibodies (Rheumatoid factor(RF), anti-cyclic citrullinated protein (anti-CCP), anti-nuclear antibody (ANA) which are associated with specific subtypes of JIA but are not pathogenic. In SoJIA, increased levels of IL1β and IL6 cause the systemic features.

Classification

The revised ILAR classification which was developed in 1993 and modified in 2001[5,6] is currently the most frequently used system worldwide. The classification was based on clinical and laboratory features and was intended for use in research studies rather than as clinical diagnostic criteria. However it is frequently used in the clinical setting as a diagnostic tool. Seven subsets of JIA (which are mutually exclusive) have been defined by the revised ILAR classification[5,6] (Table I).

Table I. ILAR Classification of JIA (modified from the Second Revision, Edmonton, 2001)[6]

Category	Definition
Systemic onset JIA	1. Arthritis in one or more joints and 2. Present or preceding fever for at least 2 weeks that is documented as daily(quotidian) for at least 3 days and 3. One or more of i. Evanescent erythematous rash ii. Generalised lymph node enlargement iii. Hepatomegaly and/or splenomegaly iv. Serositis
Oligoarticular JIA	Arthritis affecting 1 to 4 joints in the first 6 months of the disease Subcategories: Persistent oligoarthritis: Arthritis affecting ≤ 4 joints throughout the disease course Extended oligoarthritis: Arthritis affecting > 4 joints after the first 6 months of the disease
Polyarticular JIA (Rheumatoid factor negative) (RF-)	Arthritis affecting ≥5 joints within the first 6 months of the disease, RF negative
Polyarticular JIA (Rheumatoid factor positive) (RF+)	Arthritis affecting ≥5 joints within the first 6 months of the disease, RF positive (at least 2 tests positive at least 3 months apart during the first 6 months of the disease)
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least 2 of i. Dactylitis ii. Nail pitting or onycholysis iii. Family history of psoriasis in a first degree relative
Enthesitis related arthritis	Arthritis and enthesitis or, arthritis or enthesitis with at least 2 of i. Present or history of sacroiliac joint tenderness and/or lumbosacral pain ii. HLA B27 antigen positive iii. Onset of arthritis in a male over 6 years old iv. Acute (symptomatic anterior uveitis) v. First degree relative with AS, ERA, sacroilitis with IBD, Reiter's syndrome or acute anterior uveitis
Undifferentiated arthritis	Arthritis that fulfils criteria in none or ≥2 of the above categories

Clinical manifestations

Typically a joint affected by arthritis is swollen, painful with some restriction of movement. Very young children may not report pain and may present with delayed walking. The older child may refuse to get out of bed, refuse to stand, limp or walk first thing in the morning but may run around later in the day. Careful clinical examination can detect subtle loss of range of movement by comparing with the normal side. Children who present late may show evidence of complications including leg length discrepancy, deformities, contractures, bony ankylosis, growth failure,

delayed puberty. JIA is a heterogeneous group of conditions and clinical presentation varies according to the subtype.The different subtypes varies widely in their distribution, age at onset and gender ratio (Table II).

Systemic onset JIA

Systemic onset JIA (SoJIA) frequently presents as a systemically unwell child with fever, characteristic rash and one or more of the manifestations such as serositis, hepatosplenomegaly and lymphadenopathy. Arthritis may not be present at the time of initial presentation and may

Table II. Age and sex distribution of ILAR subtypes (modified from Ravelli and Martini 2007)[7]

ILAR Subtype	Distribution (%)	Age at onset	Sex ratio
Systemic onset arthritis (SoJIA)	4-17	4-7yrs, throughout childhood	M=F
Oligoarthritis (OJIA)	27-56	2-4 yrs	F>>>M
RF- polyarthritis	11-28	Biphasic, 2-4 years and 6-12 yrs	F>>M
RF + polyarthritis	2-7	Late childhood and adolescence	F>>M
Enthesitis related arthritis(ERA)	3-11	Late childhood and adolescence	M>>F
Psoriatic arthritis (PSA)	2-11	Biphasic, 2-4 yrs and 9-11 yrs	F>M

take several weeks/months to appear making diagnosis very difficult. Fever spikes occur daily, usually in the evenings. In between the spikes of fever, the temperature falls below the baseline and the child appears relatively well. The characteristic evanescent, macular, salmon pink rash occurs during the fever spikes and disappears when the fever subsides. Change in the pattern of fever and rash (to continuous fever and persistent rash) and disproportionately low counts should alert one to consider macrophage activation syndrome (MAS).

MAS is a serious life-threatening complication that can develop in the presence of uncontrolled inflammation and can be the presenting feature of SoJIA. According to the new classification criteria for MAS complicating SoJIA[8], a febrile patient with known or suspected SoJIA is classified as having MAS if the following criteria are met: Ferritin >684ng/mL and any 2 of : platelet count $\leq 181 \times 10^9/L$, aspartate aminotransferase >48 U/L, Triglyceride level >156mg/dL, fibrinogen $\leq$ 360mg/dL. SoJIA may be monocyclic, recurrent or persistent (50%) with predominantly systemic or polyarticular phases.

Oligoarticular JIA

Oligoarticular JIA presents in the well toddler commonly as knee, ankle or wrist arthritis but it can involve any joint. There is an increased risk of uveitis in children who are ANA positive but uveitis can occur in ANA negative children as well. Upto 50% of children with oligoarticular JIA may achieve remission. Possible predictors of extension to extended oligoarticular JIA include initial high ESR, early upper limb joint involvement.

Polyarticular JIA, RF negative

Presentation may vary widely from an acute onset with systemic signs to an insidious onset and delayed presentation. Arthritis involves fewer joints with lower tendency to involve small joints of hands or feet and may not always be symmetrical. It has an associated increased risk of chronic asymptomatic uveitis especially if ANA positive.

Polyarticular JIA, RF positive

Arthritis affects large or small joints, is often symmetrical and can be aggressive and highly deforming. Uveitis is rare. Children can develop tenosynovitis, rheumatoid nodules, systemic features such as fever, vasculitic rash, serositis, carditis, interstitial lung disease and pulmonary hypertension. These features are however less common than seen in adults.

Psoriatic arthritis

Arthritis involves any number of large or small joints and can follow an oligo- or polyarticular course. Dactylitis which is diffuse swelling of a finger or toe may be present. Uveitis is not uncommon.

Enthesitis related arthritis (ERA)

Inflammation of insertion of tendons into bone (enthesitis) is a characteristic feature of ERA. Arthritis usually affects large joints of the lower limb (hip being quite common). Sacroiliitis occurs in a minority of patients and may not be evident until late adolescence or early adulthood. Depending on ethnicity, 30%-50% of patients are HLA B27 positive. The disease may evolve insidiously to involve the spine, the risk being higher in HLA B27 positive patients. These patients are also at an increased risk for acute anterior uveitis and inflammatory bowel disease.

JIA associated uveitis

Chronic anterior uveitis associated with most subtypes of JIA (rare in RF+polyarticular disease, uncommon in

SoJIA) can be completely asymptomatic in young children. Uveitis may precede the development of arthritis. Although ANA positive children are at a greater risk, 50% of children with uveitis are ANA negative. Hence the need to screen all children with JIA at the time of diagnosis. Screening should be continued at least until 12 years of age. Acute anterior uveitis associated with ERA presents with a painful red eye.

Investigations

Laboratory investigations are useful to support a diagnosis of JIA and to exclude other differential diagnosis. They are useful for providing evidence of inflammation and monitor toxicity of medications. There is no single diagnostic test for JIA.

Blood parameters in general reflect the extent of inflammation. Children with moderately severe disease may have anemia of chronic disease. Leucocytosis is common in active disease. Very high white cell counts (>30,000cells/mm^3) and platelet counts are seen in SoJIA. The ESR is useful but not a reliable measure of disease activity, CRP may be more reliable. Normal inflammatory markers do not rule out JIA (eg: Oligoarticular JIA, RF-polyarticular JIA).

ANA and rheumatoid factor are not screening or diagnostic tests for JIA. ANA or RF negativity does not rule out JIA. ANA is positive in 15% of normal children. RF can be positive in other connective tissue diseases like SLE, systemic sclerosis and can be elevated as an acute phase reactant in bacterial endocarditis. ANA is positive in 50%-60% of oligoarticular JIA and may be positive in RF- polyarticular JIA, especially with the younger onset. They are useful for risk assessment to watch for complications. Anti-cyclic citrullinated peptide (CCP) antibody may be positive in RF+ polyarticular JIA.

Radiological imaging is a very useful tool in diagnosing arthritis and in the assessment of disease progression. Plain radiographs are useful for an initial assessment but are less sensitive than MRI in identifying early changes. Ultrasound is very helpful to assess joint effusion in joints where there may be no obvious swelling (hips, shoulders). MRI with intravenous gadolinium can identify abnormalities in non-calcified tissue (before they can be detected on plain radiographs) and demonstrate active synovitis. It is especially useful for the assessment of the lumbosacral spine and sacroiliac joints. Synovial fluid analysis is useful to exclude other differential diagnosis, especially infective etiology.

Differential diagnosis

JIA is a diagnosis of exclusion. Detailed history and comprehensive examination with particular attention to the pattern of pain and joint involvement are important. Joint swellings, early morning stiffness or gelling phenomenon (ie, stiffness after long periods of sitting or inactivity) are features of inflammatory pain. If the pattern is not classical, extensive investigations may be required as JIA has a broad differential diagnosis as described below.

1. Reactive arthritis

2. Hypermobility with mechanical pain, growing pains

3. Arthritis occurring at a very young age should raise suspicion of primary immunodeficiencies.

4. In monoarticular presentations, high index of suspicion for TB, septic arthritis and malignancy should be maintained.

5. In the child presenting with a limp and isolated hip pathology, alternative diagnosis like Perthes disease and slipped capital femoral epiphysis should be considered.

6. In polyarticular presentations, infections (streptococcal, leptospirosis, mycoplasma, Lyme disease etc), connective tissue disease (eg: SLE, juvenile dermatomyositis, sarcoidosis, autoinflammatory diseases, etc) should be considered in the differential diagnosis. In a child with JIA, thrombocytopenia or the appearance of anti-ds DNA antibodies may indicate evolution of the disease into SLE.

7. Migratory polyarthritis should raise suspicion of rheumatic fever.

8. In a child presenting with suspected SoJIA, differential diagnosis includes infection, malignancy and Kawasaki disease.

9. Arthritis can also occur in association with other conditions like inflammatory bowel disease, cystic fibrosis, Down syndrome, Turner syndrome and DiGeorge syndrome.

10. Other important arthritis mimics include mucopolysaccharidoses.

Common diagnostic pitfalls

a) Infectious arthritis should be suspected in acute monoarticular arthritis (can be polyarthritis in streptococcal infections and in the immunocompromised) with or without fever, particularly in patients at risk. Systemic symptoms

may be minimal or absent. Normal ESR or CRP do not exclude infection. WBC count is usually > 20,000/mL with > 95% polymorphs but may also be lower in early or partially treated infections. Plain X-rays of the involved joint are not diagnostic of acute infection. Synovial fluid analysis and culture is the key to confirm or exclude the diagnosis. Gram stain reveals organisms in only 50% to 75% of joints.

b) TB arthritis often has an indolent and non-specific presentation, is monoarticular in > 90% cases, involving large weight-bearing joints. However in children and the immunocompromised, small joints of hands and fingers may be involved.

c) Arthritis is seen in more than 25% of leukemic children at presentation (Box 1). The white cell count may be normal or low and not all leukemia patients would have blasts in their peripheral blood at initial presentation. Diagnosis of malignancy may be delayed and response to chemotherapy may be impaired in patients inadvertently treated with corticosteroids.

Box.1. Leukemia as arthritis mimic

- Unusual pattern of joint involvement

- Non-articular bone pain, back pain

- Pain disproportionate to findings, intense continuous pain, night time pain

- Exquisite metaphyseal tenderness

- Low white blood cell count ($< 4 \times 10^9/L$), low platelet count ($<150 \times 10^9/L$) with or without raised inflammatory markers

- Progressive anemia, raised LDH

- Metaphyseal radiolucent bands, periosteal reaction, sclerotic and osteolytic lesions

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d) Growing pains - JIA is frequently misdiagnosed as growing pains causing significant diagnostic delay and risking joint damage. Growing pains usually presents in a well child with deep aching pain, usually symmetrically over lower limbs (not limited to joints), usually in late evenings/after activity, is relieved with massage/simple anesthesia and resolved by the next morning. There are no swellings, early morning stiffness, limp or limitation of activity. Deviation from this pattern should raise suspicion of alternative diagnosis.

Morbidity

JIA is a disease with significant morbidity - pain, joint damage, disability, growth, blindness with knock on effects on education and psychosocial wellbeing and has a significant mortality risk. Children with JIA have poor health related quality of life (HRQOL) compared to their peers with pain and disability affecting both physical and psychosocial wellbeing.[9]

JIA was previously thought to be a self-limiting illness in most children. Several studies have now shown that the disease persists into adulthood and is associated with significant morbidity.[10] Patients with JIA scored higher in education at all levels but unemployment was 137% higher than in the general population.[11]

Radiographic joint damage occurs early in the disease course especially in polyarticular JIA and less commonly in persistent oligoarticular disease. In a study by Mason, et al, 61% of patients with polyarticular JIA had radiographic abnormalities at diagnosis with 28% having erosions or joint space narrowing.[12] A study of 94 patients with JIA showed that radiographic progression was greater in the first year and predictive of yearly radiographic progression.[13]

Studies have shown that early and aggressive treatment is associated with a better outcome.[14,15] Long-term studies have shown sustained benefits from early disease suppression.[16] There is evidence to show that patients who reach a state of clinical inactivity at least once in the first 5 years of disease have lower long term joint damage as assessed by restricted joint count and juvenile arthritis damage index (JADI) after a median follow up of 7.1 years.[15] Guided by this, the goal of treatment presently is to achieve early disease remission,[17,18] prevent joint damage and maintain function by early aggressive treatment.

Management of JIA

Aims of treatment

Although available treatments for JIA do not provide a cure, current treatment approach is to provide holistic care to improve outcomes in all areas. The primary aims are to rapidly control disease activity and induce remission, thus prevent secondary joint damage. Secondary aims are to decrease pain, improve physical function and thus prevent disability, reduce the risk of complications including growth failure, osteoporosis, amyloidosis, improve psycho-social functioning and minimise treatment related toxicity. This would result in better opportunities for continuing in education, employment and independence and decrease the impact on the family. In order to achieve these goals, it is vital that children with JIA are managed by specialized pediatric rheumatologists from the very early stages along with input from a multi-disciplinary team.

Therapeutic agents

Treatment approach, response and overall outcomes vary amongst the different subtypes. There is lack of good evidence for many aspects of JIA management and hence practices around the world vary widely.

Oligoarticular JIA is treated with intra-articular steroid injections with triamcinolone hexa-acetonide.

Pharmacological treatment approaches to JIA have changed dramatically over the last two decades.[19] NSAIDs and steroids remain important components of treatment along with methotrexate even in the biologic era. Polyarticular JIA, enthesitis related JIA, psoriatic JIA and systemic onset JIA are treated with systemic steroids (pulses of IV methylprednisolone and/or oral prednisolone) along with methotrexate (or sulfasalazine in ERA), monitoring for toxicity. In children who respond well, steroids are weaned off first. Methotrexate is continued longer, monitoring disease activity.

In children who have medication side effects and inadequate or no response by 3 months, addition of a biologic agent should be considered. Choice of the biologic agent (etanercept, adalimumab, infliximab, rituximab, anakinra, tocilizumab, abatacept) is guided by the overall clinical presentation. Although only few of these drugs are licensed for use in JIA, many of them are being used off-license in resistant cases of JIA. Although short term safety data of biologics have been promising, concerns remain regarding the long term safety particularly in children with regards to risk for infection, malignancy, neurological complications and autoimmune disorders.[20] This is particularly important in light of current evidence for early and aggressive treatment but lack of evidence regarding their withdrawal.[21,22] In children with refractory disease, bone marrow transplantation should be considered. Children with joint destruction may require joint replacement surgery.

Multidisciplinary care

It is important to maintain the muscle strength despite the on-going active inflammation. Physiotherapy plays a vital role in maintaining function aiming for near normal function. Monitoring for JIA associated eye disease and modifying treatment appropriately by an experienced ophthalmologist is crucial.

Prognosis

Adverse prognostic factors in children with JIA include delayed diagnosis, delayed referral to pediatric rheumatologists, late disease control and on-going disease activity.

Disease associated indicators of poor outcome (long term damage) are given in Box 2.

Box.2. Indicators of poor outcome[23,24]

- Polyarticular onset
- Involvement of hips/wrists/small joints of hands and feet,
- RF+
- Early onset
- Female sex
- Longer disease duration

Conclusion

Early access to specialised care will help greatly to improve outcomes in JIA and prevent permanent joint damage in these young children who have a long future ahead. On going research may in the future help to identify non-responders to specific therapy and personalized medicine may become the norm.

Points to Remember

- *Juvenile idiopathic arthritis is a diagnosis of exclusion.*

- *Anti-nuclear antibody and rheumatoid factor are not screening or diagnostic tests for Juvenile idiopathic arthritis.*

- *Uveitis screening at diagnosis is mandatory for all children with Juvenile idiopathic arthritis.*

- *Radiographic joint damage occurs early in the disease course. Early referral to specialized care to initiate aggressive treatment will improve outcomes and prevent permanent joint damage.*

- *Macrophage activation syndrome is a serious lifethreatening complication of Systemic onset Juvenile idiopathic arthritis and needs prompt aggressive treatment.*

- *In children with unacceptable side effects or inadequate response to first line drugs biologics may be considered.*

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<div style="text-align:center">**RHEUMATOLOGY**</div>

SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract: *Pediatric systemic lupus erythematosus (pSLE) is a rare autoimmune disorder which tends to have multisystemic involvement characterized by chronic course interspersed with remissions and exacerbations. It is caused by immune dysregulation in both innate and adaptive immunity and has a female preponderance. Renal involvement more often than not tends to determine the prognosis. With newer drugs and more aggressive treatment regimens the prognosis of this otherwise dreadful condition has undergone a paradigm shift with more and more pSLE patients having a near normal life expectancy.*

Keywords: *Pediatric systemic lupus erythematosus, Lupus nephritis, Immune complex*

Childhood onset or pediatric systemic lupus erythematosus (pSLE) is a severe, chronic, life-threatening multisystem autoimmune disease. Although rare, it is found that nearly 20% of adult onset SLE have origin in childhood.[1] It is a heterogeneous disease and manifestations can range from mild to severe and life-threatening. It is an aggressive disease and if left untreated, the 5-year mortality rate reaches 95%.[2]

Although the facial rash of lupus was identified as early as the thirteenth century (rash and superficial ulcerations on cheeks resembled wolf bites, hence the term lupus), the other acute and chronic skin manifestations were described in the 1800s and the systemic nature of the illness was identified at the end of the 19th century. Treatment strategies were designed in 20th century and are undergoing continuous reviews to improve the outcomes still further.

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Epidemiology

Studies have described incidence of pSLE from 0.36 to 2.5 per 100,000 children per year.[3] The incidence and prevalence of pSLE vary according to racial background, with higher incidence seen in Asian and the African American population, as compared to Caucasian population. Average age of onset is 12 years, but cases have been reported in children younger than 5 years, who seem to have monogenic forms of SLE and in whom the severe disease is more common.[4] Like most autoimmune diseases, pSLE is more common in females. Female male ratio being 5:1, while in adults it is 9:1 and this may be due to the lack of hormonal (female sex hormones) differences in children. It is important to recognize the fact that pSLE can be seen in boys too.

Etiopathogenesis

Exact etiology of SLE is not fully understood. It is a classical prototype of autoimmune disease associated with loss of tolerance to self-antigens and alterations in both innate (complement, neutrophils, monocyte-macrophages) and adaptive immunity (B-cells and T-cells).[5,6] The contributing factors leading to the onset of disease include genetic, hormonal and environmental factors.

Genetic susceptibility: Family history of autoimmunity is a risk factor for developing SLE. Siblings are at 10% chance of having the disease and the risk increases to 24% in homozygous twins.

Complement plays a role in apoptosis and hereditary complement deficiencies (homozygous C1q, C1r, C1s, C4, C2) lead to impaired clearance of apoptotic cells and immune complex formation leading to very early onset pSLE.[4,5,7]

Immune dysfunction: SLE is a classic example of immune dysfunction with production of autoantibodies against self-antigens being the hallmark of the disease. These antibodies include antinuclear antibody (ANA) in the majority of cases which is the umbrella term for other antibodies (extractable nuclear antigens) which include anti-dsDNA, anti-Ro, anti-La, anti-RNP, etc.

Hormones: Estrogen plays an important role, as seen in the increased prevalence of SLE in women.

Environmental factors: Ultraviolet radiation (UV), infections and drugs can cause flare ups. UV radiation can trigger a SLE flare, hence it is important to advise sun protection measures in children. Viral infections (EBV, CMV and Parvo virus) have been thought to trigger SLE in genetically susceptible individuals. A number of drugs (antiarrhythmics, antihypertensives, thyroxine, antibiotics, anticonvulsants) have been associated with drug-induced lupus.

Clinical features

There are two SLE classification criteria currently in use: American College of Rheumatology (ACR) criteria, modified in 1997 (Table I) and Systemic Lupus International Collaborating Clinics (SLICC), published in 2012.[8,9] It is important to remember that these are not diagnostic criteria but are guides to clinical judgement. ACR criteria is more specific (76.6% sensitivity and 93.4% specificity) while SLICC criteria was more sensitive (98.7% sensitivity and 85.3% specificity).[2]

Constitutional features

The pSLE patients present with fever which can sometimes be prolonged, continuous or intermittent and is usually brought to the notice of pediatrician as fever of unknown origin (FUO). Fatigue, weight loss and hair loss are commonly seen in these patients. Many of the patients of pSLE tend to have hepatosplenomegaly and lymphadenopathy.

Table I. ACR criteria for classification of SLE[8]

Mucocutaneous criteria	• Malar Rash: Butterfly rash over cheeks and nasal bridge normally spares the nasolabial folds. • Discoid Lupus: Erythematous lesions of adherent keratotic scaling and follicular plugging which may lead to scarring. • Photosensitivity: Rash due to sensitivity to sunlight and some indoor light sources. • Oral or nasal ulcers: Recurrent, usually painless sores in mouth or nose.
Systemic criteria	• Non-erosive arthritis: Inflammation of two or more joints with tenderness, swelling or effusion. • Serositis: Pleuritis which may present with pleuritic pain, a rub or pleural effusion, or pericarditis which may show on ECG or present with a rub or pericardial effusion. • Nephritis: Persistent proteinuria >0.5g/day or 3+ or microscopy showing cellular casts, red cells or haemoglobin. • Neurological: Seizures or psychosis without any other underlying cause (drug-induced or metabolic disturbances).
Laboratory criteria	• Hematology: Hemolytic anaemia with reticulocytosis, or leucopenia <4000 per cmm on more than 2 occasions, or lymphopenia <1500 per cmm on more than 2 occasions or thrombocytopenia <100,000 per cmm in absence of other causes • Immunological: Anti-DNA antibody, anti-Sm antibody or anti-phospholipid antibodies including - (1) anti-cardiolipin antibody IgG, IgM (2) positive Lupus anticoagulant (3) false positive for syphilis for >6months. • Anti-nuclear antibody (ANA): Abnormal ANA titre by immune fluorescence at any point not associated with drugs known to cause drug included lupus.

Note a) A person is defined as having SLE if any 4 of 11 criteria are present, serially or simultaneously, during any period of observation.

b) It is to be kept in mind that organ involvement in pSLE normally does not happen at the same time, but can happen sequentially.

Mucocutaneous involvement

The mucocutaneous involvement in patients with SLE includes:

Malar (butterfly) rash (Fig.1): This is a classical rash seen over the cheeks and nose. The nature of rash can range from mild erythema to an erythematous, scaly rash. It tends to spare the nasolabial folds. Post-inflammatory scarring is very unusual.

Fig.1. Erythematous, scaly malar rash

Photosensitive rash: This tends to be more common over the exposed areas, namely the face, neck, upper limbs. These rashes can range from annular to diffuse rash.

Discoid lupus: This more commonly seen in the regions of the face, scalp and limbs. The classical description of this rash is that of hyper pigmented rashes with adherent scales. Alopecia can be seen when it involves the scalp.

Raynaud's phenomenon and purpuric rashes can be seen in a few patients.

Mucosal involvement: Palatal ulcers which are usually painless (Fig. 2).

Fig.2. Palatal ulcers

Table II. International society of nephrology (ISN) / Renal pathology society (RPS) 2003 classification of lupus nephritis

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (<50% of glomeruli)
	III (A): active lesions
	III (A/C): active and chronic lesions
	III (C): chronic lesions
Class IV	Diffuse LN (>50% of glomeruli)
	IV (A): active lesions
	IV (A/C): active and chronic lesions
	IV (C): chronic lesions
Class V	Membranous LN
Class VI	Advanced sclerosing LN

Musculoskeletal involvement

Arthritis in lupus tends to be symmetrical and non-erosive and involves the small and large joints. The arthritis tends to be more distal in localization than proximal. Myositis can rarely be seen.

Lupus nephritis (LN)

As many as 48%-100% of pSLE patients will develop lupus nephritis during their lifetime. Of those patients, 80%-90% develop lupus nephritis in the first year after diagnosis of pSLE.[10] Lupus nephritis is a disease driven by immune complexes and complement activation which leads to progressive renal damage leading on to end stage renal disease (ESRD) unless diagnosed and treated early. The International society of nephrology (ISN) / Renal pathology society (RPS) classification of LN is given in Table II.

Clinical features of lupus nephritis

The clinical features of lupus nephritis can vary from benign presentation like asymptomatic hematuria to an acute glomerulonephritis to a frank nephrotic syndrome like presentation. The microscopic examination of urine usually points to renal involvement, but there can be rare cases where in the urine examination might be normal. Hence, it is of prime importance to have every child with

SLE screened for evolving lupus nephritis at every visit by doing urine microscopy especially in the first 2 years.

The urine would normally show hematuria and/or non-nephrotic proteinuria (spot urine protein to creatinine ratio (UP:UC >0.2 - 2 or 24 hours urinary protein excretion of >4mg/m²/hr) in class II nephritis. The classical nephritis like manifestations with hematuria, hypertension and azotemia is seen in Class III and IV LN. Class V (Membranous GN) typically presents with nephrotic-like presentation with nephrotic range proteinuria (Up/Uc >2) or 24 hrs urinary protein excretion of >40mg/m²/hr), hypoalbuminemia, hyperlipidemia and edema. It must be mentioned that at the time of diagnosis it might be useful to confirm the proteinuria by 24 hrs urine protein estimation in older continent children.[11] The follow up of proteinuria

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Box 1. LN – Renal biopsy indications

- Acute nephritic syndrome
- Nephrotic syndrome
- Isolated elevated serum creatinine
- Persistent hematuria
- Persistent proteinuria (Up/Uc >0.2)

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can be done by urine protein creatinine ratio. Indications for renal biopsy in LN are given in Box 1.

Clinical manifestations involving other systems are shown in Table III.

Investigations

Complete blood count: A normocytic normochromic anemia is seen commonly. Coomb's positive hemolytic anemia can be seen in some patients. In active lupus leucopenia and lymphopenia are seen which resolve once the activity of the disease abates. Thrombocytopenia is seen in active lupus in a few patients.

Acute phase reactants: ESR tends to be very high but CRP tends to be normal in this condition. CRP is increased due to a few conditions such as infection and serositis in pSLE.

Urine routine and microscopy: It is a useful test to look for renal involvement in SLE and should be done at initial visit and every follow up visit. Varying degrees of proteinuria and hematuria may be seen.

Serum creatinine: Elevation of serum creatinine is very useful to identify progressive lupus nephritis.

Table III. Systems involvement in pSLE

System	Manifestations
Neuropsychiatric	Worsening headaches, chorea and other movement disorders, stroke, seizures, depression / mania, behavioural changes and memory loss
Cardiovascular	Pericarditis, Myocarditis, Endocarditis (Libman-Sack's), premature coronary artery disease (dyslipidemia)
Respiratory	Pleurisy Pulmonary alveolar hemorrhage: Fever, cough and breathlessness and rarely hemoptysis (acute emergency with high mortality unless treated early).
Hematological	Anemia (Anemia of chronic disease, Coomb's positive autoimmune hemolytic anemia, iron deficiency anemia, anemia due to chronic kidney disease, pure red cell aplasia (rare) Leukopenia (seen in active lupus and decreases when lupus activity abates) Thrombocytopenia (ITP can be the initial manifestation of lupus in up to 15 % of cases and can precede the diagnosis of SLE by 10 years) Secondary Antiphospholipid antibody syndrome (APS) Rare - Evan's syndrome (association of autoimmune hemolytic anemia and thrombocytopenia), thrombotic microangiopathies
Endocrine	Hypothyroidism

Antinuclear antibody (ANA) by immunofluorescence (IF): It is an essential test for diagnosis of SLE as it tends to be positive in 99% of patients with SLE. IF is the preferred method for ANA assay. ANA has a very high sensitivity and relatively lower specificity in the diagnosis of SLE. 33% of healthy children can have ANA positivity without having SLE.[12] ELISA test which is more commonly available and more rapid and easily done has more false positive test results as compared to IF.

Antibodies against double stranded DNA (dsDNA antibodies): This test has lower sensitivity and higher specificity. Crithidia luciliae immunofluorescence test (CLIFT) is used for diagnosis and ELISA test for monitoring. (C.luciliae is a eukaryotic single-cell protozoan. The kinetoplast found in C.luciliae is rich in double stranded DNA and anti-dsDNA antibodies attach to this organelle which is brilliantly highlighted by IF).

Antibodies against extractable nuclear antigens (ENA profile): This is an expensive antibody profile against a host of antinuclear antibodies. It may not be needed in every patient of SLE.

Complement assay: C3 and C4 estimation is a useful test for monitoring as a declining complement level would indicate a flare or impending flare of the disease.

Other tests: (a) Antiphospholipid antibody tests and lupus anticoagulant test, (b) liver function tests, (c) chest X ray and Mantoux test - screening for tuberculosis infection, (d) 2D Echo if clinically indicated, (e) Pulmonary function test if clinically indicated.

Treatment

SLE is a chronic multisystem disease characterised by remissions and exacerbations. It is important that a pediatric rheumatologist or a pediatrician with a special interest in pediatric rheumatology be involved in the care of the patient with this condition. The most important part of management of this condition is education and counselling and having a team approach for continued care of these patients. Adolescents especially need to be spoken to about continuation of treatment and need for continued follow up. The sensitization for the need of sunscreen lotions half an hour before sun exposure even on cloudy days needs to be impressed on both the patients as well as their parents.

Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are very useful for musculoskeletal manifestations of pSLE patients. But many of these patients would require steroids and other immunosuppressant drugs. Low dose aspirin is useful in patients with secondary anti-phospholipid antibody syndrome. NSAID associated toxicity is common when these are used for long time and can manifest with gastric ulcers, drug hypersensitivity reactions and interstitial nephritis. These drugs are best avoided in such patients.

Glucocorticoids

It is the foundation on which treatment protocols for management of SLE have been built. The treatment of a patient with pSLE with significant organ involvement e.g diffuse proliferative lupus nephritis, typically begins with use of pulse methylprednisolone (30mg/kg) with a maximum of 1 gm which is given once a day for 3 to 5 days followed by oral steroids (usually prednisolone at 0.5mg-2mg/kg/d) in 2 to 3 divided doses. This dosage of steroids is continued for about a month's time following which the drug is tapered every 1 to 2 weeks (10 mg decrements from 60-30mg/day, 5 mg decrements from 30 to 20mg/day and 2.5 mg decrements from 20 mg/day). Symptoms and signs of flare are to be looked for in all patients while on tapering regimen. It is also a practice to add on calcium and vitamin D to prevent steroid-induced osteoporosis at the time of initiation of treatment. Bone densitometry is checked every 1½ to 2 years of steroid intake to look for steroid induced osteoporosis. Proton pump inhibitors and H2 blockers are used only in the setting of drug induced gastritis and are not routinely used by authors. Gastritis can be prevented by using the drugs after food intake. The steroids are continued at very low dose (<0.25mg/kg) for a considerable period of time to consolidate and maintain remission and prevent flares.[13]

Hydoxychloroquine (HCQ)

The beneficial effects attributed to HCQ in pSLE are: (a) useful for skin and musculoskeletal disease, (b) ameliorates steroid induced dyslipidemia, (c) maintains disease remission, (d) reduces the risk of premature atherosclerosis. Dose is 4-7 mg/kg. In view of retinal toxicity every patient with lupus should have annual screening after 5 years of continuous HCQ therapy.

Cyclophosphamide (CYC)

It is a potent immunosuppressant medication used in certain complications of SLE (Box 2). Intravenous CYC is given monthly as per NIH protocol or fortnightly as per EUROLUPUS protocol.[14]

Azathioprine

This is a useful drug for maintenance of remission in

<table>
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Box 2. Cyclophosphamide in pSLE

- Lupus nephritis- Class III and IV
- CNS lupus
- Diffuse alveolar hemorrhage in pSLE
- Severe involvement of any other organ

</td></tr>
</table>

lupus nephritis and other organ system involvement. It is cheap with once a day dosing and has a good steroid sparing effect. Leukopenia is sometimes problematic in patients with SLE.

Mycophenolate mofetil

It has been found to be very useful in management of lupus nephritis for both consolidation and maintenance of lupus nephritis.[15] It also useful in other severe forms of SLE.

Other drugs used in SLE include cyclosporine, tacrolimus, methotrexate, IVIG rituximab (anti CD20 monoclonal antibody) and belimumab (inhibitor of B-cell activating factor/BlyS).[16,17]

Prognosis

The prognosis of pSLE has definitely improved from what it was earlier. The life expectancy has also increased from 40%-50% of that expected in 1960s to 90%-95% of the current life expectancy. The common causes of mortality are infection, renal failure and cardiopulmonary disease. Morbidity is usually due to end stage renal disease, steroid-induced osteoporosis, infections, obesity, cataract, growth retardation, hypertension and increased risk of developing diabetes.

Conclusion

Pediatric systemic lupus erythematosus is a rare autoimmune disorder with a tendency to cause damage to multiple organs unless it is diagnosed early and treated appropriately. It is a classical chronic disease which requires periodic evaluation and appropriate modification of treatment to prevent and treat disease flares, drug toxicity and organ damage. The prognosis has significantly improved and is expected to still get better as we understand the disease better and improve our treatment strategies.

Points to Remember

- *Pediatric systemic lupus erythematosus is a multisystem, chronic disease with remissions and exacerbations.*

- *It tends to affect more preadolescent and adolescent girls than boys.*

- *Lupus nephritis is more often seen in the first 2 years of disease onset.*

- *Early diagnosis and treatment can prevent organ damage and improve the disease outcomes significantly.*

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CLIPPINGS

Antibiotics in the first year of life and subsequent neurocognitive outcomes.

There may be a link between disruption to the gut microbiota in early life and later neurocognitive outcomes. We hypothesised that antibiotic use in early life is associated with a detrimental effect on later neurocognitive outcomes.

Eight hundred and seventy-one European mothers and their children enrolled in the Auckland Birth weight Collaborative Study at birth. Information on antibiotic use during the first year of life and between 12 months and three-and-a-half years of age was gathered via maternal interview. Intelligence test scores and measures of behavioural difficulties were obtained when children were three-and-a-half years, seven years and 11 years of age.

Antibiotic use in the first year of life was reported in 70% of the 526 children with antibiotic data assessed at age three-and-a-half years. Those who had received antibiotics had more behavioural difficulties and more symptoms of depression at follow-up. Results were consistent across all standardised psychologist administered tests, as well as parent rated, teacher rated and self-report measures.

This study demonstrates an association between antibiotic use in the first year of life and subsequent neurocognitive outcomes in childhood. If confirmed by further research, these findings could have implications for the use of antibiotics for minor illnesses in infancy.

Slykerman RF, Thompson J, Waldie KE, Murphy R, Wall C, Mitchell EA. Antibiotics in the first year of life and subsequent neurocognitive outcomes. Acta Paediatr 2017 Jan;106(1):87-94. doi: 10.1111/apa.13613.

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<div style="text-align:center">**RHEUMATOLOGY**</div>

KAWASAKI DISEASE - UPDATE

* Surjit Singh
** Ankur Kumar Jindal

Abstract: *Kawasaki disease is the commonest form of vasculitis in children with predilection to involve coronary arteries. The etiology of this disease is not well known but it is believed to be triggered in a genetically susceptible host by an infectious agent. This update describes the recent advances in Kawasaki disease with an emphasis on its etiopathogenesis, newer laboratory and radiological investigations and therapeutic options. IVIg and aspirin remain the mainstay of treatment in acute stage. Infliximab is an effective and safe treatment option in IVIg resistant cases.*

Keywords: *Coronary artery aneurysm, Intravenous immunoglobulin, Kawasaki disease, Update*

Kawasaki disease (KD) is a medium vessel systemic vasculitis with a predilection for the coronary arteries. Increased awareness among pediatricians has led to more frequent diagnosis of KD and it is now recognized to be the commonest childhood vasculitis and the most common cause of acquired heart disease in children from several countries including Japan, Korea, Taiwan, United States and European Union.[1] This disease was first recognized in 1961 by Dr.Tomisaku Kawasaki based on a constellation of clinical signs and symptoms and was reported in 1967 as 'muco-cutaneous lymph node syndrome'.[2,3] Since then it has been reported from all parts of the world, including India. However, in many developing countries, KD is not being recognized as frequently as it should be. This warrants more awareness among pediatricians about the clinical manifestations and diagnosis.

Epidemiology

KD is predominantly a disease of young children with

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a majority of the patients below 5 years of age. It affects boys more commonly than girls and there is a distinct geographical variation. Japan has reported the highest incidence of KD with an estimate of 265 cases/100,000 children below five years of age.[4] Korea has the second highest incidence in the world with an estimate of 135 cases/100,000 below five years[5] followed by Taiwan (83 cases/100,000 children below 5).[6] A hospital-based analysis in India has estimated the incidence to be at least 4.54 cases/100,000 children below 15[7] and 9.1 cases/ 100,000 children below 5 in Chandigarh.[8] KD follows a seasonal pattern in some countries. At Chandigarh a seasonal pattern is seen with more cases in the month of October and May and a nadir in February.[7] On the other hand, in Japan and Korea the highest numbers are observed in January and July. In USA the peak season for KD is spring and winter, while in Europe the peak is observed during winter.[9]

Etiopathogenesis

More than 4 decades have passed since the first case of this disease was identified and extensive research has been carried out to elucidate the exact etiology and pathogenesis, but the disease still remains an enigma. However, the epidemiology gives us important clues to the etiology of KD. It is more prevalent in certain populations and cases do occur in clusters with a seasonal variation. This prompts one to speculate that KD has a genetic predisposition and is probably triggered by some unidentified agent in a genetically susceptible host. Few susceptibility genes (such a ITPKC, CASP3, CD40L, FCGR2A, BLK, HLA DQB2 and CASP3) have been identified using transmission dysequilibrium and genome-wide association studies.[10–13] Though a trigger for KD has not been clearly identified, it is believed to be an infectious agent that enters through upper respiratory tract and elicits an immunological response in the host.[14,15] Superantigen theory has also been proposed to be one of the important pathogenic mechanisms.[10] It has recently been postulated that the triggering agent is carried by tropospheric winds from a common source of origin. A densely cultivated area in the region of northeast China has been demonstrated to be one such source and the reason for seasonal clustering and epidemics of KD in Japan.[16]

Activation of both innate and adaptive immune system has been implicated in the disease pathogenesis. Neutrophils are supposed to be the first cells to invade the coronary walls. In addition, the endothelial damage by infiltration of T cells (CD8+ predominate over CD4+ T cells) and macrophages as well as the inflammatory cytokines such as interleukin (IL) 2, 6, 17, interferon (IFN-γ) and tumour necrosis factor (TNF-α) are important in the disease pathogenesis.[10,17–19] Increase in T helper 17 (Th17) cells and a decrease in T regulatory (Treg) cells have been implicated in causing inflammation in KD.[20] Pathology in the acute stage is predominated by infiltration of neutrophils in the vessel wall (beginning in the endothelium) leading to necrotizing vasculitis and is the only self-limiting process in the pathology of KD. This is followed by a subacute to chronic vasculitis (with predominant infiltration of CD8+ T lymphocytes, beginning in the adventitium) and luminal myofibroblast proliferation [result of smooth muscle proliferation towards the lumen mediated by transforming growth factor beta (TGF-β) and may lead to luminal occlusion].[21-23] A universal pathological finding during chronic stage is the presence of calcification in the vessel wall in patients who have had coronary artery abnormality during acute stage.[24] However, it is important to understand that these pathology studies have largely been conducted on autopsy specimens in patients who have died of severe KD.

There are practically no data to suggest this pathology in a patient who has been treated during the acute stage.

Clinical manifestations and diagnosis

Diagnosis of KD is essentially based on a group of clinical signs and symptoms and supported by a few laboratory investigations. In 2004, the American Heart Association (AHA) had proposed a set of diagnostic criteria for complete KD (Box 1).[25] Fever is the most common presenting clinical manifestation, seen in nearly 100% patients. While fever is essential for the diagnosis of KD as per AHA criteria but according to the Japanese criteria, fever need not be present in all patients.[26] As per the Japanese criteria, fever lasting more than 5 days (or less than 5 days if it has responded to IVIg) is one out of the 6 criteria for diagnosis of KD as compared to AHA criteria where fever > 5 days is an essential criteria. The duration of fever is variable and is usually less than 2 weeks but may persist for even longer. Clinical manifestations of KD evolve over days and many signs and symptoms might have disappeared by the time the patient presents to a health care facility. Hence a meticulous history from parents or documented clinical findings by a physician who has seen the child previously will be useful in reaching a diagnosis. The illness can be divided into three phases viz. acute, subacute and chronic but there is no distinct demarcation and features tend to overlap.

Box 1. Diagnostic criteria for complete Kawasaki disease, American Heart Association (AHA) 2004[25]

A case of complete KD must fulfil all these features

1. Fever persisting for at least 5 days

            with

2. At least four of the five principal features:

     i) Changes in extremities

         Acute: Erythema of palms, soles; edema of hands, feet

         Subacute: Periungual peeling of fingers, toes in weeks 2 and 3

     ii) Polymorphous exanthema (diffuse maculo-papular, urticarial, erythroderma, erythema-multiforme like, not vesicular or bullous)

     iii) Bilateral bulbar conjunctival injection without exudates

     iv) Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa

     v) Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral

3. Exclusion of other diseases with similar findings (e.g., scarlet fever, viral infections like measles, adenovirus, Stevens-Johnson syndrome, toxic shock syndrome)

Acute phase, (which lasts up to 10-14 days) is characterized by abrupt onset of fever usually without any localizing features. Fever with marked irritability may be the only clinical presentation especially in young infants.[27] KD must be considered as a differential diagnosis in all children in whom fever has persisted for more than 5-7 days with or without other supportive clinical manifestations.[28] Children with KD have a peculiar irritability that persists even during afebrile period and responds dramatically to therapy. Although a small proportion of children can have cough, the presence of coryza is unusual in KD. Non-exudative conjunctivitis with typical limbal sparing, edema of hands and feet, arthritis (usually large joints oligo arthritis) or arthralgia, red and vertically cracked lips, red strawberry tongue, congested pharynx and erythematous rash are other common clinical presentations.[29] Erythema and induration at BCG injection site is an important clinical sign during acute stage and is virtually diagnostic of KD.[30] It may be seen in more than 50% children, predominantly younger ones. However, it is less commonly seen in India especially in older children.[31] The degree of inflammation at BCG site has also been correlated with severity of disease manifestations.[32] Orange brown chromonychia at finger nails has recently been described during the acute stage of KD by investigators from Kolkata.[33,34]

Subacute stage lasts for another 2-3 weeks during which fever usually subsides. Periungual and perianal peeling are characteristic clinical signs during this stage (even in children who receive adequate treatment).[35]

Chronic phase lasts for weeks to months. There are usually no symptoms during this phase and the inflammation tends to subside. A typical Beau's line (horizontal ridging over nails; better felt than seen) develops during this phase.[36] Beau's line is thought to be representative of an arrest in the nail growth that has occurred as a result of intense inflammation during acute stage of KD.

The terms 'incomplete' and 'atypical' KD are often used interchangeably but are distinct. 'Incomplete' KD refers to a patient who fulfils less than 4 criteria in presence of fever and has laboratory features suggestive of KD. On the other hand, 'atypical' KD refers to some unusual clinical manifestation of KD such as nephritis.[37]

There are several manifestations which are not included in the diagnostic criteria but may provide important clue towards diagnosis. These include sterile pyuria (as a result of urethritis), hydrops of gall bladder, aseptic meningitis and BCG reactivation.

Investigations

There is no specific laboratory investigation that can conclusively confirm the diagnosis of KD. Presence of elevated C- reactive protein (CRP), high erythrocyte sedimentation rate (ESR), neutrophilic leukocytosis and thrombocytosis suggest systemic inflammation. Thrombocytopenia during acute stage is uncommon and can be due to immune or non-immune destruction of platelets. Low platelet count has also been found to correlate with development of coronary aneurysms and is a poor prognostic marker.[38-41] N terminal pro-B-type natriuretic peptide (NT-proBNP) is a cardiac biomarker and has been found to be significantly elevated during acute stage of KD when compared to febrile controls. The values are higher in patients who develop coronary artery abnormalities as compared to those with normal coronaries. Thus it has both diagnostic and prognostic implications.[42-45] Recently a diagnostic algorithm based on NT- proBNP was proposed and its diagnostic accuracy has been found to be better than the AHA 2004 algorithm for incomplete KD.[45] Serum levels of NT- proBNP have also been found to correlate with IVIg responsiveness with higher levels in those whose disease is IVIg resistant.[43] A high neutrophil to lymphocyte ratio during acute stage has been found to predict IVIg resistance and development of coronary artery lesions.[46-48]

Two dimensional (2D) echocardiography is a useful tool to assess the status of coronary arteries and other cardiac structures during acute stage as well as on follow up. Coronary artery z-score less than 2 is reassuring but by no means excludes the diagnosis of KD. Coronary artery aneurysms (CAA) are classified as small (z-score between 2.5 to 5), medium (z-score between 5 to 10) and large or giant (either a z-score more than10 or an absolute value of coronary artery diameter greater than 8 mm).[49] Other useful echocardiography findings during acute stage include pericardial effusion (usually small), brightness of coronary walls, absence of normal tapering of coronary vessels and myocardial dysfunction in the form of low ejection fraction. An echocardiography should be done at diagnosis. If initial echocardiography is normal, it is recommended to repeat it frequently till the time of discharge as coronary changes may appear even later. Repeat echocardiography should be carried out 1-2 weeks later and then at 4-6 weeks. A normal echocardiography examination during the first week of illness does not rule out the development of coronary artery aneurysms later. Echocardiography should be repeated more frequently in children who have coronary artery z-scores more than 2. Detailed analysis of coronary arteries in patients with CAA is recommended. 128 slice

dual source CT angiography is usually performed in these patients but requires a high degree of technical expertise to carry out the procedure. Recently the role of cardiac MRI has also been investigated.[50, 51] However, due to lack of expertise in the interpretation of cardiac MRI scans, CT angiography remains the imaging modality of choice after echocardiography.

Treatment

The goal of management is to abruptly suppress the systemic inflammation and prevent thrombosis. Intravenous immunoglobulin (IVIg) has been the standard first line treatment. It should be given in a dose of 2 gm/kg infused slowly over 12-24 hours. IVIg acts by neutralization of pathogenic auto antibodies and super antigens. It also suppresses production of inflammatory cytokines including TNF-α_2, and enhances the regulatory T cells.[52] IVIg must be administered as soon as the diagnosis is made and preferably within 10 days of onset of fever. IVIg must also be given even after 10 days, if fever is persisting or in the absence of fever if inflammatory parameters are elevated or if coronary artery abnormalities are present.[19,53,54] However, in a child presenting late when fever has subsided, inflammatory parameters have normalized and there is no coronary artery abnormality, the decision to give IVIg has to be individualized.[55] In such cases there is no recommendation to administer IVIg, but can be considered in very young children (especially in infancy) and in the presence of certain high risk factors such as male sex and thrombocytopenia, hyponatremia or hypoalbuminemia during acute stage. Administration of IVIg during acute stage reduces the risk of CAA to 3%-5% as compared to a risk of around 20%-25% in untreated patients.[10,25]

There is a controversy regarding the usefulness of high dose aspirin during the acute stage and recent literature suggests that there is no difference between high dose (80-100 mg/kg/day) and low dose (30-50 mg/kg/day) aspirin during acute stage. Aspirin is given in a dose of 30-50 mg/kg/day in 3-4 divided doses (anti-inflammatory dose) till fever subsides and then shifted to antithrombotic dose of 3-5 mg/kg/day.[56] This should be continued for a period of 6 weeks if no coronary abnormality is detected. Prolonged therapy with low dose aspirin is required in patients with persistent coronary artery abnormalities. In addition to aspirin, patients with giant CAA also need anticoagulation with either low molecular weight heparin (LMWH) or warfarin.[57] LMWH has been found to be superior to warfarin in effecting vessel wall remodelling.[58] There are no definite recommendations for discontinuation

of anticoagulation in patients with giant CAA. One may consider doing this once coronary artery diameters have normalized. As the child grows older, the reliability of echocardiography to discern the coronary artery dimensions reduces significantly because of thick chest wall.[59] In that case if a decision to discontinue anticoagulation has been taken, it must not entirely be based on echocardiography assessment only and must always be supplemented with dual source CT angiography. Other inherent limitations of echocardiography include inability to accurately measure distal coronary artery dimensions and poor visualization of left circumflex artery. Other drugs that have been found to be useful in long term management of patients with giant CAA include statins and beta blockers but there is no definite recommendation for their use.

Response rate with a single dose of IVIg is as high as 80%-90%, but still a proportion of patients (10-20%) will experience either the persistence of fever or reappearance of fever even 36 hours after giving IVIg (resistant or refractory KD).[60] IVIg-resistant KD patients are at relatively higher risk of developing coronary artery abnormalities and need more aggressive anti-inflammatory therapy. There is no definite recommendation for treatment of IVIg resistant KD; however, a number of therapeutic regimens have been tried. A repeat dose of IVIg is recommended by AHA and is effective in around 80% of resistant cases.[25]

As compared to the attractiveness of steroids in other rheumatic and autoimmune diseases, its use in KD has not gained much popularity. Addition of methylprednisolone to the combination of IVIg and aspirin, failed to show additional benefits in a randomized controlled trial in 2007.[61] However, a trial of addition of prednisolone to the standard therapy in severe KD patients (RAISE study) significantly reduced the coronary artery abnormalities.[62] Despite these encouraging results, steroids have not been included in the standard management protocol for primary treatment of KD.

Studies have found that addition of methylprednisolone to the treatment regimen, after failure of first dose IVIg was as effective as addition of second dose of IVIg.[63] Addition of methylprednisolone to patients who were considered refractory to IVIg therapy (using Egami score) found significant benefit.[64] There is controversy regarding its use in IVIg refractory cases. Some authors believe that it should be given after failure of first dose of IVIg, while others prefer giving it after failure of 2 doses of IVIg.[65] The dose for methylprednisolone pulse is 30 mg/kg/pulse (intravenous) for 3 days.

Infliximab (TNF-α inhibitor) is an effective treatment option in IVIg resistant cases and also if coronary artery aneurysms develop despite giving IVIg. Evidence suggests that infliximab is an effective treatment option in children who are resistant to either the 1st or 2nd dose of IVIg.[66-70] It is usually administered in a single intravenous dose of 5 mg/kg. Majority of these children are not routinely screened for underlying infection (such as pulmonary tuberculosis) before giving this drug. There are no long term data available regarding the safety of this drug after single use in children. In our experience, infliximab is an effective and safe therapeutic option when used in these circumstances.

Other treatment options for resistant KD include cyclosporine,[71] cyclophosphamide,[72] methotrexate,[73] and plasma exchange.[74,75]

Outcome and long term follow up

Patients with KD need long term follow-up. The goal of long term management is to prevent the development of coronary artery thrombosis. Occurrence of KD can be associated with several cardiovascular sequelae and some of these can occur even in children who do not have coronary artery abnormalities. It has been proved that coronary arteries may look structurally normal on follow-up but their functional abnormities usually persist.[76-79] Increased stiffness and abnormal reactivity of coronary arteries may lead to impaired blood flow and decrease in myocardial reserve.[50,80] In addition, long term follow-up studies in KD patients have also demonstrated persistent lipid abnormalities that pose an additional cardiovascular risk factor.[81-83] Patients with KD are at risk of acute coronary event which has been found to be highest during the first year after disease onset;[84] however, cases of MI have also been reported many years after the onset of disease.[85,86]

Points to Remember

- *Kawasaki disease is the commonest form of vasculitis and the most common cause of acquired heart disease in children.*

- *The etiopathogenesis is believed to be triggered by an infectious agent in genetically predisposed individuals.*

- *Diagnosis is essentially clinical and can be challenging in infants and young children as they often present with incomplete form of the disease.*

- *Two-dimensional echocardiography is a useful diagnostic modality during acute stage as well as on follow-up.*

- *Intravenous immunoglobulin (IVIg) is the standard first line therapy and should be administered as early as possible.*

- *If left untreated, the risk of developing coronary artery aneurysms is up to 25%. With prompt diagnosis and appropriate treatment, this risk can be brought down to 3%-5%.*

- *Patients with KD must be kept on long-term follow up as they are at a higher risk of cardiovascular events later in life.*

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NEWS AND NOTES

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<div style="text-align:center">**RHEUMATOLOGY**</div>

VASCULITIS SYNDROMES

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Abstract: *Childhood vasculitis is a challenging and complex group of conditions that are multisystem in nature and often require integrated care from multiple subspecialties including rheumatology, dermatology, cardiology, nephrology, neurology and gastroenterology. Primary systemic vasculitides of the young are relatively rare diseases, but are associated with significant morbidity and mortality, particularly if there is a delay in diagnosis. The site of vessel involvement, size of the affected vessels, extent of vascular injury and underlying pathology determine the disease phenotype and severity. This review explores the classification and general features of pediatric vasculitis as well as the clinical presentation, diagnostic evaluation and therapeutic options for the common vasculitides.*

Keywords: *Vasculitis, Primary, Children.*

Vasculitis is characterized by the presence of inflammation in the walls of blood vessels, with resultant tissue ischemia and necrosis. Estimated overall an-nual incidence of new cases of vasculitis is 53.3 per 100,000 children under 17 years of age.[1] Two common vasculitides were Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD). Reported geographical variations in vasculitides may reflect an environmental influence. A number of factors have been reported to be associated with the development of vasculitis, including infections, drugs, allergy, vac-cination and desensitization procedures. In this review, we provide an overview of pediatric vasculitides with emphasis on key differences in vasculitis presentation and management in children.

Classification

International consensus conference held in Vienna in June 2005 under the auspices of the Pediatric rheumatology European Society (PReS) resulted in a new proposal for childhood vasculitis classification summarized in Table I.[2]

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These were validated and given the final form at the 2008 Ankara consensus conference with support from the European league against rheumatism (EULAR) and the Pediatric rheumatology international trials organization (PRINTO).[3] Revisions in the commonly used terms for the various vasculitides have been proposed by the 2012 International Chapel Hill Consensus Conference (CHCC) on nomenclature of vasculit-ides.[4] Among the notable changes suggested by the 2012 CHCC were use of the term eosinophilic granulomatosis with polyangiitis (EGPA), in place of Churg Strauss syndrome and formal adoption of the term anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) for the three disorders microscopic polyangiitis, granulomatosis with poly-angiitis and EGPA.It is important to emphasize that these classification criteria are intended to define homogenous patient groups for research and are not the same as diagnostic criteria. The classification criteria for each pediatric vasculitis as per EULAR /PRES criteria are given in Table II.

Predominantly small vessel disease

Henoch Schönlein purpura / IgA vasculitis

HSP is the most common vasculitis in children. It occurs most frequently between the ages of 3 and 10 years.[6] Skin or renal biopsies demonstrate the deposition of IgA (mainly IgA1) in the wall of der-mal capillaries and post-capillary venules and me-sangium. HSP is associated with numerous triggers, pri-marily infections. Several recent studies have reiter-ated that upper respiratory tract infections precede HSP in 30% to 50% of cases.

The main clinical features of HSP include pur-pura, arthritis, abdominal pain, gastrointestinal bleeding and nephritis. Palpable purpura is the presenting sign in 100% of the patients. Renal disease, most often characterized by hematuria and proteinuria, is seen in 20% to 50% of affected chil-dren with 2% to 5% progressing to end-stage renal failure. Sano, et al. found that 97% of cases of HSP nephritis appeared within the first 3 months of disease.[7] Risk factors included children old-er than 4 years, purpura lasting more than 1 month, those with gastrointestinal bleeding, factor XIII ac-tivity less than 80% of normal and/or those treat-ed with factor XIII concentrate. The risk of

Table I. Classification of pediatric vasculitis

I.   Predominantly large vessel vasculitis
     Takayasu's arteritis

II. Predominantly medium-sized vessel vasculitis
     Childhood polyarteritis nodosa
     Cutaneous polyarteritis
     Kawasaki disease

III. Predominantly small vessel vasculitis
     A. Granulomatous
        Granulomatous polyangiitis
        Churg-Strauss syndrome (eosinophilic polyangiitis)
     B. Non-granulomatous
        Microscopic polyangiitis
        Henoch-Schönlein purpura (IgA vasculitis)
        Isolated cutaneous leukocytoclastic vasculitis
        Hypocomplementemic urticarial vasculitis

IV. Other vasculitides
     Behçet's syndrome
     Vasculitis secondary to infection (including hepatitis B-associated polyarteritis nodosa), malignancies
     and drugs (including hypersensitivity vasculitis)
     Vasculitis associated with connective tissue diseases
     Isolated vasculitis of the central nervous system
     Cogan's syndrome
     Unclassified

chron-ic renal failure is related to the initial clinical pre-sentation.[7]

The diagnosis of HSP is established by the pat-tern of clinical manifestations. No specific laboratory test is available. Skin biopsy reveals leukocyto-clastic vasculitis with IgA deposition in blood ves-sel walls but is not required in typical presentation of HSP. Renal biopsy is rarely necessary for diagno-sis but may have prognostic utility.

The extrarenal manifestations of HSP can be managed by symptomatic treatment. Joint complaints respond well to non-steroid anti-inflammatory drugs (NSAIDs). Cutaneous manifestations are often self-limited, but may have a relapsing pattern. Abdominal pain is common and usually self-limited. Glucocorticoids can reduce tissue edema, arthritis and abdominal pain and decrease the rate of intussusception. However, glucocorticoid therapy does not prevent the recurrence of abdominal symp-toms, skin involvement or renal disease and does not appear to shorten the duration or lessen the likelihood of relapse.[8] Glucocorticoids combined with a cytotoxic agent might be beneficial in patients with active glomerulonephritis and progressive renal insufficiency.

In the case of mild renal involvement with isolated hematuria or mild proteinuria, no treatment is required. Steroid treatment is indicated in patients with nephrotic range proteinuria or impaired renal function. Combination therapy (steroid and other immunosuppressive drugs) may be considered in patient with advanced histopathological classes. In case of established HSP with severe nephritis, drugs such as cyclosporine A, azathio-prine and cyclophosphamide have been reported to be effective.[9]

Anti-neutrophil cytoplasmic antibody - associated vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) comprise granulomatosis polyangitis (GPA) [previously Wegener's granulomatosis (WG), but hereafter only referred to as GPA], microscopic polyangiitis (MPA), eosinophilic granulomatous polyangiitis [(EGPA); previously Churg-Strauss syndrome] and single organ disease including renal-limited vasculitis. Although rare, AAV do occur in childhood and are associated with significant morbidity and mortality, especially if the diagnosis is delayed. The classification criteria for GPA in children are summarized in Table II. There are no classification criteria in children for MPA or

Table II. Classification criteria for childhood vasculitis[5]

Vasculitis	Classification criteria
Henoch Schönlein purpura/ IgA vasculitis (IgAV/HSP)	Purpura or petechia (mandatory) with lower limbpredominance plus one among the four: • Abdominal pain • Histopathology (IgA deposit in a biopsy) • Arthritis or arthralgia • Renal involvement
Childhood polyarteritis nodosa (c-PAN)	Histopathology or angiographic abnormalities (mandatory)plus one of five: • Skin involvement • Myalgia/muscle tenderness • Hypertension • Peripheral neuropathy • Renal involvement
Granulomatous polyangitis (GPA)	At least three of six: • Histopathology (granulomatous inflammation) • Upper airway involvement • Laryngo-tracheo-bronchial stenosis • Pulmonary involvement • Anti-neutrophil cytoplasmic antibody positivity • Renal involvement
Childhood Takayasu arteritis (c-TA)	Angiographic abnormalities of the aorta or its majorbranches and pulmonary arteries showing aneurysm/dilatation (mandatory) plus one of five: • Pulse deficit or claudication • Four limbs blood pressure discrepancy • Bruit • Hypertension • Elevated acute phase reactants

EGPA. Consequently, these diseases are recognized using CHCC 2012 definitions.[4]

Two types of ANCA have been identified in patients with vasculitis, ANCA directed against the neutrophil serine protease proteinase 3 (PR3), which causes a cytoplasmic immunofluorescence pattern (cANCA) on ethanol fixed neutrophils and ANCA directed against the neutrophil enzyme myeloperoxidase (MPO), which results in a perinuclear immuno-fluorescence pattern (pANCA). Approximately 82% to 94% of patients with either GPA or MPA are ANCA positive. GPA is primarily associated with PR3-ANCA, while MPA is primarily associated with MPO (myeloperoxidase) -ANCA. In patients with GPA, the sensitivity of PR3-cANCA has been reported to be 28% to 92%, whereas specificity has been reproducibly high, ranging from 80% to 100%.[10] ANCA levels will vary during the course of GPA. It was observed that patients with active disease had higher levels of ANCA compared with those who were in remission. However, increases in ANCA levels were not associated with relapse and only 43% relapsed within 1 year of an increase in ANCA levels.[11]

Granulomatous polyangitis (GPA)

GPA is uncommon in children. It is a necrotizing granulomatous inflammation of small to medium sized vessels involving the kidneys and upper and lower respiratory tracts. Children with GPA frequently present with sinusitis, otitis media, persistent rhinorrhea, purulent/bloody nasal discharge, oral and/or nasal ulcers. Nasal and sinus mucosal inflammation can produce sinus pressure and pain, epistaxis, persistent otitis media with effusion or decreased hearing and cartilage ischemia with nasal septal perforation, resulting in a saddle nose deformity. Pulmonary radiographic abnormalities can include nodules or infiltrates, cavities and ground glass infiltrates. Renal involve-ment occurs as microscopic hematuria, proteinuria and rapidly progressive renal failure. The characteristic renal histology is focal, segmental

necrotizing, crescentic glomerulonephritis with few to no immune complexes on immunoflu-orescence and electron microscopy. The diagnosis of GPA is usually based on biopsy results, viz. non-renal tissues demonstrating the presence of granulomatous inflammation and necrosis, with necrotizing or granulomatous vasculitis.

Initial immunosuppressive therapy in GPA typically consists of cyclophosphamide and glucocorti-coids. The use of aggressive initial immunosuppression is justified because the mortality rate in untreat-ed generalized GPA is as high as 90% at two years. Mortality has markedly diminished with the introduction of initial therapy with cyclophosphamide and glucocorticoids.Cyclophosphamide dosing regimens of daily oral and monthly intravenous pulses, have been used for initial immunosuppressive therapy of GPA. Two randomized trials have suggested that rituximab may be an effective alternative to cyclophosphamide for the initial treatment of patients who have newly diagnosed disease or have relapsed following treatment with cyclophosphamide or other immunosuppressive therapy.[12] Weekly oral methotrexate has been used as initial therapy in patients with GPA who have non-organ threatening and non-life threatening disease and as maintenance therapy in patients treated initially with cyclophosphamide.[13]

Microscopic polyangitis (MPA)

MPA is characterized by necrotizing vasculitis with few or no immune deposits affecting small vessels. Clinical features of MPA include disease involving the kidneys, lungs, joints, skin, gastrointestinal tract and peripheral nerves. The cardinal features of MPA include glomerulonephritis, pulmonary hemorrhage, fever and mononeuritis multiplex. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs, but not become granulomatous lesions of the respiratory tract. The renal histology is similar to that observed in GPA in being a focal segmental necrotizing glomerulonephritis with few to no immune complexes.

The initial treatment phase is an induction phase with cyclophosphamide (6 intravenous doses of 500 - 1,000 mg/m^2 every 3 to 4 weeks, or oral doses at 2 mg/kg daily for 2-3 months) and high-dose corti-costeroids, followed by weekly methotrexate or daily azathioprine (AZA), after the 3-6 month induction period.[14]

Predominantly medium vessel disease

Kawasaki disease

Kawasaki Disease (KD) is a self-limiting vasculitic syndrome that predominantly affects medium and small sized arteries. KD has a worldwide distribution with a male preponderance, an ethnic bias towards Oriental children, some seasonality and occasional epidemics. The current reported incidence in the UK is 8.1/100 000 children while in Japanese children is much higher- 360/100 000 in children under 5 years old.[15] Etiology of KD remains unknown. Pronounced seasonality and clustering of cases have led to the hunt for infectious agents as a cause.[16] So far, however, no single agent has been consistently identified. Many candidate genes have previously been suggested as either susceptibility genes for developing KD or increasing risk of cerebral amyloid angiopathy (CAA).

Children with fewer than five of the six principal features can be diagnosed with KD when coronary aneurysm or dilatation is recognized by echocardiography or coronary angiography. The cardiovascular features are the most important manifestations of the condition with widespread vasculitis affecting predominantly the medium size muscular arteries, especially the coronary arteries. Coronary artery involvement occurs in 15%-25% of untreated cases. Other clinical features include arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis, dysuria, otitis, reactivation of the BCG scar. Infants may have fewer classic signs of KD. Coronary artery lesions are responsible for most of the disease-related morbidity and mortality. Aneurysms appear 1 to 4 weeks after the onset of fever and develop in 15% to 25% of untreated chil-dren. All children with known or suspected KD should have an echocardiogram at the time of presentation and again after 2 to 3 weeks of illness. There are definitive characteristic laboratory features of KD. An elevated leukocyte count or a normal leukocyte count with a left shift is typical in the acute phase of illness. Elevations in the levels of acute phase reactants are present in the first week of illness. The platelet count is generally normal in the first week of illness. Thrombocytosis during the second to third week of illness is classically associated with KD.

Standard treatment of Kawasaki disease in the acute phase is with intravenous gamma globulin (IVIG) (2g/kg single dose in a 10-12 hour infusion) and aspirin (50-80 mg/kg/day divided into four doses). Usually there is a dramatic response to therapy with alleviation of fever and other systemic manifestations. This regimen has also been shown to significantly reduce the development of coronary artery dilatation.[16] The dose of aspirin is usually decreased from anti-inflammatory to antithrombotic doses (3-5mg/kg/day as a single dose) after the patient has been afebrile for 48 hours. Aspirin is continued for 6-8 weeks after illness onset and discontinued in those who have

normal Echo finding throughout the course of illness. Patients with CAA will continue and repair anticoagulation depending on coronary dilatation. The efficacy of treating patients using IVIG after 10 days of illness is unknown. IVIG should be administered to children presenting after day 10 of illness (i.e., patient with delayed diagnosis) if they have either persistent fever without explanation or aneurysms and ongoing systemic inflammation (elevated ESR or CRP). After additional IVIG therapy, intravenous methylprednisolone is considered for KD patients with persistently poor responses to the second IVIG treatment. Infliximab can also be used as alternative treatment options in IVIG resistant KD.[17]

Polyarteritis nodosa (PAN)

PAN is characterized by necrotizing inflammatory changes in medium and/or small sized arteries. The disease is rare in childhood. The classification criteria for childhood PAN are histologic evidence of necrotizing vasculitis in me-dium or small sized arteries or angiographic abnormalities (aneurysm or occlusion) as a mandatory criterion, plus two of the following; i) muscle tenderness or myalgia, ii) skin involvement (livedo reticu-laris, tender subcutaneous nodules, other vasculitic lesions), iii) systemic hypertension, iv) mononeuropathy or polyneuropathy, v) abnormal urine analysis and/or impaired renal function, vi) testicular pain or tenderness, vii) signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary, or central nervous system) (Table II).

The etiopathogenesis of PAN is unknown, but infections such as viral hepatitis (commonly associated with hepatitis B or C infections and now classified under vasculitis due to infections), streptococcal infections and parvovirus infections have been implicated.

Disease manifestations range from the benign cutaneous form to the severe disseminated multi-systemic form. The most common clin-ical manifestations of PAN include constitution-al symptoms (fever, weight loss, malaise), arthralgia, myalgia, mononeuritis multiplex, gastrointestinal disease (ischemia, infarction, hemorrhage or perforation), cardiac disease (ischemic heart disease), hypertension, livedo reticularis and testicular pain.[18]

Laboratory evaluation usually reflects the ongoing systemic inflammation including anemia, leukocytosis, thrombocytosis and elevated ESR and CRP. Anti-neutrophil cytoplasmic antibodies are expect-ed to be negative. A positive ANCA with pauci immune glomerulonephritis suggests microscopic polyangitis (MPA) and not PAN.

PAN is diagnosed by means of biopsy or arteriography based on the organ system involved. Biopsy specimens reveal necrotizing inflammation involving the medium sized or small arteries with abundant neutrophils, fibrinoid changes and disruption of the internal elastic lamina. Angiographic changes suggesting PAN include microaneurysms, occlusion or a beaded pattern.

The mainstay of therapy for PAN includes steroids and various immunosuppressive medications, depending on disease severity. For induction of remission, cyclophosphamide (usually as IV month-ly doses for 6 months) and high doses of cortico-steroids are used until remission is achieved. Azathioprine can be considered as maintenance therapy after cyclophosphamide or as a corticoste-roid sparing agent. Adjunctive plasma exchange cer-tainly still plays an important role in some children for gaining rapid disease control where life or criti-cal organs are threatened.

Cutaneous polyarteritis nodosa

Cutaneous PAN is usually limited to skin with possible manifestations in the musculoskeletal system. Cutaneous polyarteritis characterized by the presence of painful subcutaneous nodules, non-pur-puric lesions with or without livedo reticularis, with no systemic involvement (except for myalgia, ar-thralgia, and non-erosive arthritis). It commonly oc-curs after a sore throat or streptococcal pharyngitis. ANCA tests are negative and there is often an as-sociation with serologic and microbiologic evidence of streptococcal infection. Skin biopsy shows necrotizing, non-granulomatous vasculitis.

Treatment for cutaneous PAN is typically much less aggressive. Agents commonly utilized include low dose prednisolone, anti-platelet agents, colchicine, hydroxychloroquine, or azathioprine.[19]

Predominantly large vessel disease

Takayasu arteritis

Takayasu arteritis (TAK) is a disease that affects the aorta, its main branches and the pulmonary arteries in which granulomatous vasculitis results in ste-nosis, occlusion or aneurysms of affected vessels. Women are affected in 80% to 90% of cas-es, with an age of onset that is usually between 10 and 40 years.[20] The etiology of the disease is unknown. It is presumed to be autoimmune in nature, although genetic and infectious factors including exposure to tuberculosis have been proposed. Pathologically TA lesions consist of granulomatous changes progressing from the vascular adventitia to the media. Systemic

symptoms are common in the early phase of Takayasu arteritis, including fatigue, weight loss and low-grade fever. Vascular symptoms are related to the location and nature of the lesion or lesions and the collateral blood flow. Involvement of the carotid and vertebral arteries causes decreased cerebral blood flow, leading to vertigo, syncope, headaches and convulsions. Visual impairment is a late manifestation and is due to cerebral ischemia. Abdominal pain, diarrhea and gastrointestinal hemorrhage may result from mesenteric artery ischemia. Chest pain, dyspnea, hemoptysis and pulmonary hypertension may result from pulmonary artery involvement.

Laboratory changes reflect the inflammatory process but are mostly non-specific. A normochromic normocytic anemia is present in most patients. Acute-phase reactants are usually elevated.

Magnetic resonance angiography (MRA) can be useful in detection of early signs of large vessel disease and has the added advantage of potentially revealing evidence of ongoing large arterial wall inflammation. Positron emission tomography (PET) scanning with radioactive-labeled 18-fluoro-deoxyglucose (FDG) has been shown to be useful in monitoring disease activity and response to treat-ment in preliminary studie.[21]

The mainstay of therapy for Takayasu arteritis is glucocorticoids. Cytotoxic therapy (methotrexate, cyclophosphamide) and anti-TNF agents are primarily used in patients who have persistent disease activity despite glucocorticoid treatment or in whom glucocorticoids cannot be tapered. Surgical intervention may be required to alleviate end organ ischemia and hypertension resulting from vascular stenosis.

Conclusion

There have been significant advances recently in the field of pediatric vasculitis research including the development of classification criteria and tools to assess disease outcome. Pediatric vasculitis research is rapidly coming of age, but there is much to be done; multicenter collaboration remains essential in order to continue to advance our understanding of vasculitis etiopathogenesis and improve treatment.

Points to Remember

- *The two most common types of primary pediatric vasculitides are Henoch-Schonlein purpura and Kawasaki disease. The clinical expression and severity of the vasculitis are determined by the size of involved vessels, type of pathologic change, organs involved and systemic extent of the vascular injury.*

- *European League Against Rheumatism (EULAR)/ Pediatric Rheumatology European Society (PRES) classification criteria for childhood vasculitis are currently used to classify primary vasculitis in children.*

- *Advances in imaging techniques such as CT and MR angiography have revolutionized the imaging approach to large and medium vessel vasculitis.*

- *Controlled data are lacking to guide therapeutic decisions for children with systemic vasculitis, with the noticeable exception of Kawasaki disease.*

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CLIPPINGS

Safety and short-term outcomes of therapeutic hypothermia in preterm neonates 34-35 weeks gestational age with hypoxic-ischemic encephalopathy.

The clinicians aimed to determine the safety and short-term outcomes of preterm neonates born at 34-35 weeks gestation with hypoxic – ischemic encephalopathy (HIE) treated with therapeutic hypothermia. In findings, the therapeutic hypothermia in infants born at 34-45 weeks gestational age appears feasible. However, risks of mortality and side effects warrant caution with the use of therapeutic hypothermia in preterm infants.

Trivedi S, Vesoulis Z, Liao SM, Smyser CD, Mathur AM. Safety and short-term outcomes of therapeutic hypothermia in preterm neonates 34-35 weeks gestational age with hypoxic-ischemic encephalopathy. The Journal of Pediatrics Dec 2016.

NEWS AND NOTES

ISIEM 2017

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RHEUMATOLOGY

MACROPHAGE ACTIVATION SYNDROME

*Aruna Bhat

Abstract: *Macrophage activation syndrome (MAS) is a life threatening complication that may arise in chronic rheumatic diseases of childhood. It closely resembles hemophagocytic lymphohistiocytosis (HLH). Infections are common triggers. It is often a challenge to diagnose MAS as the features closely mimic sepsis and may rapidly progress to multiorgan dysfunction, unless prompt action is taken. Unremitting fever, cytopenia, liver dysfunction, coagulopathy, high levels of ferritin and hemophagocytosis in tissues are some of the cardinal features of this illness. MAS is associated with high mortality.*

Keywords: *Macrophage activation syndrome, Hemophagocytic lymphohistiocytosis, Sepsis mimic, Chronic rheumatic diseases of childhood.*

Macrophage activation syndrome (MAS) is a potentially fatal complication that occurs in systemic inflammatory disorders, particularly rheumatological conditions. It is a state of overwhelming inflammatory response due to dysregulated immune system. Central to the problem is the exaggerated, continuous activation of T-lymphocytes and well differentiated macrophages with hemophagocytic function.[1-4] The condition seems to be clinically heterogenous and bears very close resemblance to the group of conditions called hemophagocytic lymphohistiocytosis (HLH), but for the fact that it is seen in systemic inflammatory diseases. The resemblance to HLH has made the researchers wonder whether MAS should infact belong to the spectrum of HLH disorders and some even use the term MAS and reactive HLH interchangeably.

HLH encompasses spectrum of disorders which have similar clinical and histopathological manifestation. Primary or familial form and secondary or reactive form are two important sub-typesin HLH.[5,6] Primary HLH is of autosomal recessive inheritance and generally seen in young infants. It is often severe and may require hemopoietic stem cell transplantation. Secondary HLH is seen associated with infection or malignancy. Histologically the conditions are known to have characteristic hemophagocytic macrophages or histiocytes. MAS and the two forms of HLH share close similarities between them.

MAS has been reported to occur in variety of rheumatological conditions, systemic onset juvenile idiopathic arthritis (SoJIA) being the most frequent amongst them. It is believed that about 10% of children with SoJIA develop characteristic symptoms of life threatening MAS and even more, up to a third of the rest, may have milder symptoms on careful observation.[3,7] MAS may be seen in SoJIA even before the onset of arthritis in some cases. Kawasaki disease, systemic lupus erythematosus (SLE), various vasculitis syndromes, adult onset Still's disease (AOSD) and enthesitis related arthritis (ERA) are some of the other rheumatological conditions where MAS has been reported with varying frequencies.[8,9] MAS may occur in these conditions either at their initial presentation or at any time during the course of the illness.[10]

Etiopathogenesis

Etiopathogenesis of MAS is still not completely understood. Akin to reactive HLH, MAS can be triggered by various infections and potentially drugs.[11] It is believed that there is cytolytic dysfunction in conditions associated with hemophagocytic syndrome. NK cell function is greatly depressed in HLH and MAS.[12,13] Abnormal NK cell function is associated with abnormal perforin expression.[12] In health, virus infected cells and tumor cells are apoptosed in the body using perforin protein. Studies done in primary and secondary HLH patients show that perforin gene polymorphisms and/or mutations in MUNC13-4 genes (for producing essential protein in the intracellular trafficking and exocytosis of lytic granules) adversely affect the production and function of perforin protein.[14-16] This can result in defective clearance of virus infected cells or tumor cells. It can then lead to perpetual antigenic stimulation of the inflammatory cascade resulting in overproduction of Tcells, chemokines, cytokines and macrophages. Pathognomonic feature of hemophagocytosis is the result of cytokine excess and subsequent exaggerated activation of macrophages.[6]

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Clinical features

Clinical presentation may vary in patients. Some present typically with acute deterioration in clinical status and may rapidly progress to lifethreatening multisystem dysfunction. Those in whom the disease remains occult, symptoms may be fewer, milder and may resolve early. They may go undiagnosed or unreported.

The onset of typical MAS is heralded by change in the fever pattern to one that of high grade, unremittingfever with new onset lymphadenopathy, hepatosplenomegaly and rash. The triggers for the onset of MAS could be recent infection or highly active state of underlying disease. Although practically any infective agent can trigger MAS in predisposed individuals, viruses such as EBV, CMV, herpes, adenovirus, hepatitis, coxsackie and dengue, have been commonly reported.[3,16,17]

Liver dysfunction is common in MAS with elevation in serum transaminases, mild jaundice and hypofibrinogenemia. Worsening liver function will also result infall of erythrocyte sedimentation rate while C-reactive protein increases. With increasing severity of the illness, hemorrhagic syndrome resembling disseminated intravascular coagulopathy sets in along with abnormal clotting, respiratory distress, altered mental status, seizures and encephalopathy. Significant deterioration in renal function has been reported in some cases and carries poor prognosis.[3]

Clinical symptoms in life threatening MAS may be very similar to that seen in disseminated sepsis with multiorgan dysfunction. Cytopenia of at least two cell lines is common and there is elevation inserum LDH,
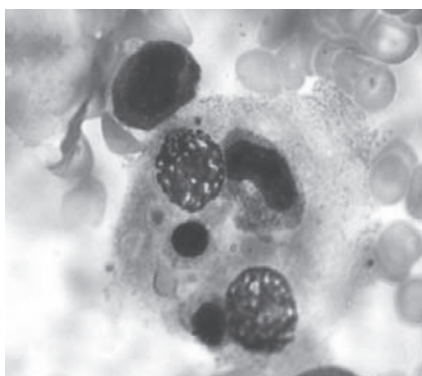

Fig. 1. Bone marrow aspirate cytomorphology Hemophagocyte with intracytoplasmic cells.

(Image courtesy: Dr Swasti Sinha, Consultant haematologist, Department of lab hematology, Narayana Health City, Bangalore.)

triglycerides, D-dimers and characteristically ferritin. Rise in ferritin particularly may be very marked, at times reaching to many folds of 10,000ng/mL and reflect the severity.[18] Hemophagocytosis demonstrated in samples obtained from bone marrow or other tissues is a hallmark of MAS (Fig.1). In patients in whom bone marrow does not reveal hemophagocytosis, or in subclinical cases, measurement of sIL2R alpha and sCD63 may help in suspecting early disease, but these lab tests are not routine.[19,20]

Diagnosis

Early diagnosis of MAS is often challenging as the symptoms and signs may be similar to those seen in underlying dysregulated systemic inflammatory disease. In a sick child, high index of suspicion with close monitoring and scrutiny of lab parameters will help suspect impending MAS. Hemophagocytosis which is considered a characteristic feature of MAS may often not be seen in the early stages,and in addition may escape detection due to errors in tissue sampling. Demonstration of hemophagocytosis is hence not made mandatory as per available diagnostic guidelines.[21,22]

In the absence of any validated diagnostic criteria for MAS, diagnostic criteria established for HLH by International Histiocyte Society has been utilized for many years (Box 1).[21]

Application of HLH diagnostic criteria to diagnose MAS in rheumatological illnesses is not without issues. Some of the symptoms which form the criteria for HLH are also symptoms found in common with different stages of the underlying inflammatory disease itself, thereby making the differentiation difficult. Other symptoms that appear in the criteria for HLH may appear at much later stages in systemic rheumatological illnesses, such as cytopenia, and may cause delay in the initiation of vital treatment. For example in SoJIA, leucocytosis and thrombocytosis are common findings and hence the stage of absolute cytopenia is reached much later. In search of a better criteria to suit MAS in rheumatological illnesses, European League Against Rheumatism, American College of Rheumatology and Paediatric Rheumatology International Trials Organisation collaborated to bring out the 2016 Classification criteria for MAS in systemic onset JIA (Box 2). The criteria has achieved preliminary evidence of its validity. It has been reported to have sensitivity of 0.73 and specificity of 0.99, positive predictive value of 97.4% and negative predictive value of 85.9%.[23] The expert panel considered fever as a prerequisite for the classification of MAS and concurred with HLH 2004 criteria in not considering demonstration of

Box. 1. HLH-2004 diagnostic criteria

Molecular diagnosis based on specific mutations found in either PF1 or MUNC13-4 genes

OR

The presence of at least 5 of 8 criteria:

1. Fever

2. Splenomegaly

3. Cytopenias (affecting at least 2 lineages in the peripheral blood) Hemoglobin levels <90 g/L (in infants <4 weeks old, haemoglobin <100 g/L) Platelets <100 x 10^9/L, Neutrophils <1.0 x 10^9/L

4. Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides $\geq$3.0 mmol/L (ie, >265 mg/dL) Fibrinogen <1.5 g/L

5. Documented hemophagocytosis in the bone marrow, spleen, or lymph nodes

6. Low or absent natural killer cell activity

7. Ferritin $\geq$500 µg/L

8. Soluble CD25(ie, soluble interleukin-2 receptor) $\geq$2,400 U/mL

Box. 2. 2016 Classification criteria of Macrophage Activation Syndrome in systemic juvenile idiopathic arthritis.[23]

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

Ferritin > 684 ng/mL

AND

Any 2 of the following:

1. Platelet count $\leq$ to 181 x 10^9/L

2. Aspartate aminotransferase > 48 units/L

3. Triglycerides > 156mg/dL

4. Fibrinogen $\leq$ 360 mg/dL.

Laboratory abnormalities should not be otherwise explained by patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis or familial hyperlipidemia.

hemophagocytosis as a mandatory criteria.[23] The expert panel hasalso suggested that this new criteria can be potentially extended to diagnose MAS which is not associated with underlying rheumatological conditions, such as in isolated infections.

Differential diagnosis

During the work up for MAS, it is important to carefully differentiate it from underlying disease flares or severe sepsis with disseminated intravascular coagulation.Other differentials to be considered and carefully eliminated in appropriate setting would be Reye syndrome, thrombotic thrombocytopenic purpura and severe drug reactions.

Treatment

Mild disease may often go undiagnosed and may remitearly if the triggers are eliminated. But in severe forms, early identification and aggressive treatment is essential to reduce mortality.

Till date there are no evidence-based guidelines available for treatment of MAS. Conventional practice in treatment of unresolving, severe MAS involves use of high dose of corticosteroids in conjunction with treatment

measures to resolve triggers such as infections. Initiation of treatmentis often with intravenous methylprednisolone pulses used in doses of up to 30 mg/kg/day for up to 3 consecutive days. This is generally followed by oral weaning doses of steroids starting from 1-2 mg/kg/day in divided doses and tapered down gradually as guided by clinical improvement.

If there is no adequate response noted within 24-48 hours of instituting steroids in severe MAS, addition of cyclosporine A is suggested at a dose of 2-5 mg/kg/day in two divided doses given as oral or IV, preferably oral.[24] Monitoring renal function and drug concentration levels are important aspects of cyclosporine treatment. Few patients may have ongoing MAS despite steroids and cyclosporine and need additional treatment. In such cases, since there are no specific treatment guidelines for MAS, HLH treatment recommendations may be considered with addition of Etoposide.[21] Etoposide is a podophyllatoxin derivative that inhibits DNA synthesis. Itcan potentially cause severe myelosuppression and merits caution when used in patients with hepatic and renal compromise. It is hence advisable to use this drug under expert guidance.

Other alternatives reportedly tried in resistant cases are antithymocyte globulin (ATG),[25] intravenous immunoglobulin and biological agents. Use of biologicals in MAS remains controversial. Some believe that agents

such as TNF alpha inhibitors can be therapeutic, whilst others have considered them as triggers in their cases. Anti-IL1 therapy (Anakinra, Canakinumab) has shown promising results in some, but the drugs are not available in India. There have been reports supporting the use of Rituximab in MAS associated with EBV.[26]

MAS is a potentially fatal disease with published mortality rates of up to 20%.[1] Those who have severe renal dysfunction or severe multiorgan dysfunction carry poor prognosis.[11] A subset of the patients may have recurring episodes of MAS requiring constant vigilance. Improving the outcomes in this disease is very much dependent upon early recognition and prompt treatment and to achieve this there is a need to have increase awareness among medical fraternity regarding this peculiar condition.

Points to Remember

- *Macrophage activation syndrome is a potentially fatal complication that occurs in rheumatological conditions due to overwhelming inflammatory response caused by dysregulated immune system*

- *A suspicion of MAS should be raised when there is a change in the fever pattern to high grade and unremittingwith new onset lymphadenopathy, hepatosplenomegaly and rash.*

- *Persistent fever, splenomegaly, bicytopenias, hypertriglyceridemia, and hemophagocytosis in the bone marrow are cardinal features of MAS.*

- *Various treatment options include intravenous methylprednisolone pulses, cyclosporine, etoposide, rituximab, anti-thymocytegloulin or TNF alpha inhibitors*

- *MAS is a potentially fatal disease with mortality rates of up to 20%. Severe renal dysfunction or multiorgan dysfunction carry poor prognosis.*

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CLIPPINGS

Does Thoracoscopy Have Advantages Over Open Surgery for Asymptomatic Congenital Lung Malformations?

The apparent incidence of antenatally diagnosed congenital lung malformations (CLM) is rising (1 in 3000), and the majority undergo elective resection even if asymptomatic. Thoracoscopy has been popularized, but early series report high conversion rates and significant complications.

A systematic review according to PRISMA guidelines was performed. Data were extracted for all relevant studies (2004-2015) and Rangel quality scores calculated. Analysis was on 'intention to treat' basis for thoracoscopy and asymptomatic lung lesions. Meta-analysis was performed using the addon package METAN of the statistical package STATA14™.

36 studies were eligible, describing 1626 CLM resections (904 thoracoscopic, 722 open). There were no randomized controlled trials. Median quality score was 14/45 (IQR 6.5) 'poor'. 92/904 (10%) thoracoscopic procedures were converted to open. No deaths were reported. Meta-analysis showed that regarding thoracoscopic procedures, the total number of complications was significantly less (OR 0.63, 95% CI 0.43, 0.92; p2 30%, p=0.15) and no publication bias seen.

A reduced total complication rate favors thoracoscopic excision over thoracotomy for asymptomatic antenatally diagnosed CLMs. Although operative time was longer, and open conversion may be anticipated in 1/10, the overall length of hospital stay was reduced by more than 1day.

Adams S, Jobson M, Sangnawakij P, Heetun A, Thaventhiran A, Johal N, et al. Does Thoracoscopy Have Advantages Over Open Surgery for Asymptomatic Congenital Lung Malformations? An Analysis of 1626 Resections. DOI: http://dx.doi.org/10.1016/j.jpedsurg. 2016.11.014

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RHEUMATOLOGY

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PITFALLS OF LABORATORY INVESTIGATIONS IN RHEUMATOLOGY

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Abstract: *Laboratory tests are important adjuncts to a thorough history and physical examination in pediatric rheumatology. The importance of frugal ordering and cautious interpretation of tests cannot be overemphasized. This review describes laboratory tests used to assist diagnosis and monitoring of various paediatric rheumatologic diseases and the common errors in their interpretation.*

Keywords: *Rheumatology, Acute Phase Reactants, Autoantibodies, HLA-B27, Synovial fluid*

Although pediatric rheumatology is predominantly a clinical field of medicine, judicious use of laboratory tests can be invaluable for diagnosis, exclusion and monitoring of many childhood rheumatologic diseases. On the other hand, indiscriminate ordering of complex laboratory tests to assist diagnosis of a suspected rheumatologic disease can confuse even the most astute clinician. This review aims to provide a framework to help physicians decide the usefulness and practical applicability of various basic and advanced laboratory tests in pediatric rheumatology, as also familiarize the reader with common errors in the interpretation of these tests. The various tests commonly employed are given in Table I.

A. Basic tests

1. Complete blood count (CBC)

Hemoglobin and RBC indices: Normocytic anemia on a routine screening blood test may be the first clue to an underlying inflammatory process. The pathophysiology is often driven by the underlying immune dysfunction;

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however other factors can contribute. Cytokine-mediated decreased red blood cell survival, impaired production of red blood cells in the bone marrow and blunted response to erythropoietin are the implicated mechanisms.[1] Autoimmune hemolytic anemia (AIHA) may be seen in systemic lupus erythematosus (SLE) and is diagnosed by a direct antiglobulin test.

Limitations in interpretation: Nutritional iron deficiency anemia can often co-exist, confusing the picture. In such a situation, relying on ferritin levels can be misleading as ferritin may be normal or even raised due to the inflammatory response. As such, the only reliable method of differentiating these two conditions on a blood test is transferrin levels and soluble transferrin receptor, both of which will be reduced in anemia of chronic disease, as opposed to iron deficiency anemia.

White cell count and differential count: Either an increase or a decrease in total white cell count may be a pointer towards an inflammatory process. For instance, the white cell count can be marginally to highly elevated in systemic juvenile idiopathic arthritis (15,000 - 50,000 per cubic mm), however, a decreasing trend in the same may be a red flag for macrophage activation syndrome (MAS). At the onset, a high white blood cell count, with clinical signs of inflammation (fever, joint/bone pains) should always alert the physician to suspect and look for an underlying malignancy. Acute lymphocytic leukemia is the most common differential diagnosis in a child suspected to have systemic JIA and the importance of a careful history, examination and special tests (bone marrow aspiration and biopsy) cannot be over emphasized. On the other hand, leukopenia with lymphopenia is often seen at diagnosis and during flares in patients with SLE.

Limitations in interpretation: Co-existence of an acute bacterial or viral infection, which is not an uncommon occurrence in our setting, can lead to difficulty in accurate interpretation of the white cell count. Signs and symptoms of a localising infection should be carefully looked for and treated concurrently with treatment of the inflammatory disorder.

Platelet count: As platelets are acute phase reactants, they can be elevated moderately to highly in many

Table I. Basic and advanced tests in rheumatological disorders

Basic tests	Specific tests (autoantibodies)	Adjuvant tests / organ specific	Genetic tests
Complete blood count and differential count	Antinuclear antibody (ANA)	Muscle enzymes: Creatine kinase (CK) Lactate dehydrogenase (LDH) Aspartate transaminase (AST) Aldolase	HLA B27
Inflammatory markers: Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Ferritin	Antibodies to specific nuclear antigens: - Anti-dsDNA - Anti-Sm - Anti-U1RNP - Anti-histone - Anti-SSA - Anti-SSB - Anti-centromere - Anti-Scl-70	Complements: C3 and C4	Genetic testing for periodic fever syndromes and other rare autoinflammatory diseases
Urinalysis	Direct antiglobulin test (DAT)	von Willebrand factor antigen (vWfAg)	
	Antiphospholipid antibodies	Synovial fluid analysis	
	Antineutrophilic cytoplasmic antibodies (ANCA)	Antistreptolysin O (ASO)	
	Rheumatoid factor		
	Anti-cyclic citrullinated peptide (CCP)		

rheumatological inflammatory conditions (systemic JIA, Takayasu arteritis, Kawasaki disease). Iron deficiency anemia is also associated with thrombocytosis and can lead to confusion. On the other hand, in SLE and the associated anti phospholipid antibody syndrome (APS), thrombocytopenia is a more common laboratory finding.

The clinical entity of macrophage activation syndrome deserves special mention owing to difficulty in diagnosis and a high mortality rate. In a clinical setting of MAS complicating systemic JIA, it is more valuable to look at the trend in white cell counts, rather than a single reading. A combination of unremitting fever, hepatosplenomegaly, decreasing hemoglobin, white cell count, platelet count and ESR in a child with established systemic JIA, is almost diagnostic of macrophage activation syndrome and warrants further investigations like ferritin, triglycerides, liver enzymes and coagulation parameters.

2. Inflammatory markers

The acute phase reactants ESR, CRP and ferritin are most widely used as inflammatory markers in a clinical setting of a rheumatological disease. However, they are not considered diagnostic of a rheumatological condition and by themselves do not warrant a rheumatological referral. Conversely, a borderline high or normal ESR, CRP or ferritin does not rule out JIA, particularly, if there are only a few joints involved at diagnosis. (e.g. oligoarticular JIA).

Erythrocyte sedimentation rate (ESR): ESR is a simple, inexpensive test and is a very widely ordered in clinical

pediatrics. ESR measures the rouleaux formation of red blood cells in millimetres in an hour. Increased rouleaux formation is seen in inflammatory conditions owing to increased fibrinogen levels. The utility of ESR in predicting the diagnosis or flare in a rheumatological condition is more complex than thought. ESR can be affected by several physiological and pathological conditions that need to be carefully considered before attributing a raised ESR to a rheumatological disease. However, if interpreted with caution, ESR is by far the simplest method of predicting flares and remission in systemic rheumatological conditions and is often used to monitor patients' response to medications in conjunction with careful clinical examination. Factors affecting ESR are listed in Box 1.

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┌─────────────────────────────────────────────┐
│ Box 1. Factors affecting ESR²               │
│                                             │
│   Low ESR                                   │
│                                             │
│     -  Congestive cardiac failure           │
│                                             │
│     -  Extreme leucocytosis                 │
│                                             │
│     -  Abnormalities of RBC shape example   │
│        spherocytosis, sickle cell disease   │
│                                             │
│     -  Polycythemia                         │
│                                             │
│     -  Hypofibrinogenemia                   │
│                                             │
│     -  Technical factors                    │
│                                             │
│   High ESR                                  │
│                                             │
│     -  Chronic infections (e.g. tuberculosis)│
│                                             │
│     -  Obesity / Hyperlipidemia             │
│                                             │
│     -  Anemia                               │
└─────────────────────────────────────────────┘
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C-reactive protein (CRP): CRP is a more complex and relatively expensive marker of inflammation. As opposed to ESR however, a rise in CRP is seen quickly with inflammation and normalizes at a faster rate. CRP should not be routinely ordered with ESR, especially in low resource setting except in special circumstances. For instance CRP can help distinguish a flare from infection in a patient with SLE. CRP is commonly raised with an infection, but remains normal in a flare.

Ferritin: Ferritin is an intracellular iron storage protein which can also be detected extracellularly in the serum and other body fluids. Serum ferritin levels are not just indicative of the body iron stores, but increased ferritin levels also reflect an inflammatory process. The mechanism of regulation of serum ferritin levels is complex. It is well known that oxidative stress, increased cytokine levels and decrease in serum iron lead to increased ferritin levels in inflammatory diseases. High ferritin levels predict disease

flare in systemic JIA and can be used to monitor disease activity in this subset of patients. Ferritin is also raised with flares in SLE, but is not a commonly used monitoring tool for the same. In MAS, ferritin level can be ominously high (in thousands)[3] and is an important tool to distinguish it from a flare of systemic JIA as also monitor response to treatment. Again, a rising ferritin level with other markers in a patient with systemic JIA should be thought to be MAS unless proved otherwise.

3. Urinalysis

A urine examination is the best and most non-invasive tool to determine inflammatory involvement of the kidney. In a patient with known or suspected SLE, a routine microscopic urine examination can yield insight into the extent of organ involvement. An active urinary sediment (raised RBCs, RBC casts, leukocytes) and increased urine protein levels are indicative of renal involvement of lupus and warrants further investigations like quantification of urinary protein and in some cases a kidney biopsy to help guide management. In patients with known renal lupus, urinalysis is used at frequent regular intervals to monitor progress and response to therapy. A sterile urine pyuria is an adjuvant test to help in the diagnosis of incomplete Kawasaki disease, where clinical criteria are not fulfilled.[4]

The limitations include falsely elevated urine protein often seen in ambulatory samples, which can misguide the clinician. As such, nephrologists recommend a first morning void sample for accurate interpretation of proteinuria.

B. Specific tests

Specific antibody tests are largely the domain of a pediatric rheumatologist; however, this section aims to briefly familiarize the pediatrician with some common antibody tests and interpretations of the same.

1. Antinuclear antibody (ANA): ANAs are a group of antibodies that target normal proteins in the nucleus of a cell. If present in large amounts, they can cause autoimmune diseases in an individual. Serum ANA levels can be elevated in a variety of rheumatological conditions like SLE, Sjogren's syndrome, mixed connective tissue diseases (MCTD), scleroderma, juvenile dermatomyositis (JDM) and can be associated with uveitis in a child with JIA. ANA finds place as a serological criterion in the American college of rheumatology (ACR) classification criteria for SLE and in an appropriate clinical setting with symptoms suggestive of lupus, ANA is an invaluable screening test for SLE. However, it is perhaps the most widely misinterpreted test in rheumatology and has many limitations that a clinician needs to be aware of.

Limitations in interpretation

(i) ANA can be positive 5%-18 %[5] of normal population, depending on the ethnicity and gender. Up to 15% - 20 % of Indian descent children can have a positive ANA, more so in females, not associated with any disease

(ii) ANA is also elevated in many non-rheumatological conditions like viral infections and use of certain medications notably isoniazid or minocycline. Hence unwarranted ordering of ANA without careful history taking can only lead to wrongful suspicion of a rheumatological condition with undue anxiety in the parent and physician.

(iii) ANA titre and pattern: ANA testing by indirect immunofluorescence (IIF) is the gold standard method of detection.[6] ELISA is a relatively newer method of detection of ANA and has lower sensitivity. ELISA is currently not recommended for purposes of screening for ANA.

(iv) The titre of ANA considered positive varies between laboratories. For IIF, titer cut off points of 1:80 or 1:160 are commonly used.[5] Generally, low positive ANA titres are seen in healthy children, whereas higher titres in the appropriate clinical setting may be associated with disease.

(v) The pattern produced by ANA in IIF assays is determined by the location of the target antigen within the cell and has known associations with certain diseases (for example: homogenous - SLE, fine speckled – Sjogren's etc.). However, these pattern associations lack specificity and their use in clinical practice is limited.

To summarize, ANA should not be ordered unless there are concerning symptoms and signs of a rheumatological disease and if positive, the interpretation should be done, purely considering the clinical setting.

Specific anti-nuclear antibodies: These are often ordered as a second step after a positive ANA, in a patient in whom there is a strong clinical suspicion of SLE or other connective tissue diseases.

Anti-double-stranded DNA: Anti-dsDNA is a specific subtype of anti-nuclear antibody which is often used to confirm the diagnosis of SLE. It is positive in about two thirds of children with SLE. As it is positive in less than 1% of the normal population, it is more useful in confirming the diagnosis of SLE, however, a negative test cannot rule out SLE with absolute certainty. Anti-dsDNA is also

associated with higher rates of renal involvement in SLE, and is commonly used to monitor progress and response to treatment in renal lupus.

Other specific anti-nuclear antibodies have known associations with certain rheumatological diseases and are used by rheumatologists as confirmatory tests for the same (Table II).[7] The presence of any of these antibodies associated with a clinical symptom complex certainly warrants specialist referral for further testing and guided management.

Table II. Disease association with specific anti-nuclear antibody

Specific antibody	Disease association
Double stranded DNA	SLE
SS-A (Ro)	Sjogren syndrome, SLE, NLE
SS-B (La)	Sjogren syndrome, SLE, NLE
Smith	SLE
Centromere	Limited cutaneous systemic sclerosis
Scl-70	Diffuse cutaneous systemic sclerosis
Ribonucleoprotein	MCTD
Histone	SLE

2. Direct antiglobulin test (DAT)

Also known as direct Coomb's test and is primarily used to diagnose autoimmune hemolytic anemia (AIHA), due to IgG antibodies to RBCs. As previously stated, the cause of anemia in rheumatological diseases is often multifactorial, with AIHA being a common association, especially in SLE. Although the overall prevalence of AIHA in SLE is only 5%-10%, the prevalence of positive DAT in SLE is much higher (18%-65%), alerting the physician to the possibility of false positive test results. The interpretation of a positive DAT should include careful history taking, examination as well as supportive evidence of hemolysis.

3. Anti-phospholipid antibodies (APLA)

Anti-phospholipid antibodies are antibodies directed against phospholipids found on the surface of all blood cells and lining of blood vessels. The commonly used laboratory tests to detect anti-phospholipid antibodies are:

lupus anticoagulant (LAC), ELISA for anticardiolipin (ACL) antibodies and ELISA for B2 microglobulin antibodies. The diagnosis of antiphospho lipid syndrome (APS) requires one or more episodes of vascular thrombosis and/or pregnancy morbidity (in adults) in addition to laboratory tests positive for APLA (LAC/ACL/B2 microglobulin), twice, at least 12 weeks apart.[5] The epidemiology of primary APS is largely unknown in the pediatric population; however secondary APS is commonly associated with SLE and must always be looked for in a newly diagnosed patient. A suspicion of secondary APS arises in a lupus patient when laboratory testing reveals a false positive VDRL or prolonged APTT. APS testing is often repeated annually in pediatric SLE with or without symptoms, as it can be an evolving diagnosis. On the other hand, it must be borne in mind that a large proportion of pediatric patients initially diagnosed with primary APS can go on to develop full blown SLE.

4. Antineutrophilic cytoplasmic antibodies (ANCA)

These antibodies have 2 main subtypes, depending on the specific protein target within the neutrophil. Anti-myeloperoxidase antibodies give rise to a perinuclear pattern (p-ANCA), whereas, anti-PR3 antibodies give rise to a cytoplasmic pattern (c-ANCA).

Although c-ANCA is generally associated with granulomatosis with polyangiitis (GPA previously called Wegener's), p-ANCA with microscopic polyangiitis (MPA) and eosinophilic GPA (e-GPA, previously called Churg Strauss), there are exceptions to the rule. Approximately 10%-20% of patients with GPA or MPA can test negative for ANCA and a negative test in the presence of a clinical symptom complex does not rule out suspicion for a small vessel vasculitis.

5. Rheumatoid factor (RF)

RF is a group of IgM antibodies directed against the Fc portion of an IgG molecule. The presence of IgM RF positivity on two occasions, at least 12 weeks apart in a child with more than 4 joints affected, is used for International League of Associations for Rheumatology (ILAR) classification of RF positive polyarticular JIA. RF positivity in JIA indicates worse disease, joint damage and resultant disability. Similarly, RF positivity in adults with rheumatoid arthritis (RA) indicates poor articular prognosis and worse extra articular disease. RF positivity may also be seen at high titres in Sjogren's syndrome. However, the incidence of RF positive polyarticular JIA is only <5 % of total JIA. A common error in interpretation of negative RF is that the child does not have JIA. This is

not true since the child could have RF negative polyarticular JIA. On the other hand, a false positive RF may be seen in younger children, due to chronic infections and hypergammaglobulinemic states.

6. Anticitrullinated peptide antibodies (ACCP)

These are a group of autoantibodies directed against protein epitopes containing citrulline. They are associated with RA in adults and polyarticular variety of JIA in children. They are highly specific in both these conditions but have a low sensitivity. Their association with these diseases implies more severe articular disease and bad prognosis. However, due to limited small sample studies, their use in diagnosis and management of JIA remains controversial.

C. Adjuvant tests

1. Muscle enzymes

Elevation of serum levels of muscle enzymes may have some broad differential diagnoses in the pediatric population, however, in a clinical setting of subacute symmetric proximal muscle weakness, with or without the associated pathognomonic rash, elevated levels of sarcoplasmic enzymes (creatinine kinase, aspartate transaminase, lactate dehydrogenase and aldolase) may help to clinch the diagnosis of juvenile dermatomyositis. Often the clue comes from a raised SGOT done as a part of a liver panel while evaluating a child with prolonged fever. However, there is considerable individual variation in the levels of these enzymes, hence it is recommended to test all four (if available) at the onset. Their levels do not always correlate with disease activity and therapeutic decisions need to be made in conjunction with the clinical and radiological picture. In long standing disease enzymes may be normal. Amongst the four enzymes, CK has the least and LDH has the best clinical correlation.

2. Complements

Complements are an integral part of the innate immune system and are involved in the pathogenesis of SLE. It is a well-known fact that C3 and C4 levels are used to assist in diagnosis of SLE, as also to monitor disease activity and response to treatment. However, homozygous deficiencies of the early proteins of the activation pathway are associated with susceptibility to SLE, and in such cases complements may not accurately reflect disease activity. CH50 (one CH50 unit is defined as the volume or dilution of serum that lyses 50% of erythrocytes in the reaction mixture) is a good screening test to detect complement deficiency. Low or absent CH50 implies the reduction or

absence of one of the components of the classic and terminal pathway. Individual complement components like C3, C4 and C1 esterase inhibitor can be measured by ELISA, however it must be remembered that C3 and C4 are also acute phase reactants and their levels may not always correlate with the clinical picture.

3. Synovial fluid analysis

Synovial fluid aspiration in pediatric practice is usually done in the suspicion of septic arthritis, or for therapeutic purposes in JIA (intraarticular steroid injection). When done to rule out or confirm the diagnosis of a septic joint, it is essential to look at the following components of the synovial fluid:[5] (a) White cell count (WCC): A synovial fluid WCC greater than 50,000/mm^3 with a predominance of polymorphonuclear leukocytes (i.e., greater than 90%) is likely to be associated with infection. (b) Gram stain and culture: The fastest method of proving infection is a Gram stain smear of synovial fluid after centrifugation, to look for evidence of causative organisms. The sensitivity of synovial Gram stains for a septic joint ranges from 50% to 70%. A positive culture, in the absence of prior antibiotics, has a high sensitivity in septic arthritis and is the confirmatory test.

4. Antistreptolysin O (ASO)

The inclusion of ASO titre as a supportive Jones criterion for diagnosis of suspected acute rheumatic fever (ARF) is based on the fact that ARF is a post-infectious, immunological reaction to group A streptococcal (GAS) antigens. There remains controversy as to whether post-streptococcal reactive arthritis (PSRA) is a distinct entity or along the same spectrum as ARF. However, ASO is a surrogate evidence of past GAS infection in patients presenting a few weeks after the initial infection, where a throat culture may have an extremely low yield. The interpretation of a single high ASO titre, however does not yield much useful information and can merely be an indication of past infection. Also, the timing of testing is crucial as ASO titres begin to rise approximately 1 week, and peak 3 to 6 weeks after the initial GAS infection. Thus, a two-fold rise in convalescent ASO titre is a useful supportive diagnostic tool for PSRA, in conjunction with a clinical picture of sore throat preceding arthritis by a few weeks.

D. Genetic tests

1. HLA B27

HLA B27 is a class I major histocompatibility complex (MHC) surface antigen located on chromosome 6 and presents antigenic peptides to T cells. HLA B27 has a pathogenetic role in adult ankylosing spondylitis (AS) and its pediatric counterpart, enthesitis related arthritis (ERA) subtype of JIA. Presence of HLA B 27 in the patient or a history of HLA B27 related disease in the family is a part of the ILAR classification criteria for ERA and may confer an increased risk of developing AS in the patient. However, absence of HLA B27 does not rule out the diagnosis of ERA, as some patients with ERA can be HLA B27 negative. Conversely, a small proportion of the normal population (2%-8%) may be positive for HLA B27 and never develop any disease manifestations. Thus, results of HLA B27 should be interpreted with caution and considering the clinical setting. Randomly asking for a HLA B27 may stigmatize the patient to a lifelong worry with no disease.

2. Genetic testing for periodic fevers and other newer autoinflammatory conditions

The hereditary periodic fever syndromes are a group of monogenic disorders, now described under the umbrella term hereditary autoinflammatory syndrome, of which, familial Mediterranean fever (FMF) is the most common. Since the discovery of MEFV gene associated with FMF, there has been a dramatic and ongoing increase in the numbers of well-defined clinical autoinflammatory syndromes associated with specific genetic abnormalities. As such, genetic testing in the appropriate clinical scenario has now become an integral part of laboratory testing in rheumatological diseases.

Points to Remember

- *Laboratory tests are not meant to replace a careful history and directed physical examination in pediatric rheumatology. They are valuable in assisting the physician in diagnosis and monitoring of complex rheumatological conditions.*

- *Extensive ordering of a 'Rheumatological Panel' can lead to confusion with regards to the diagnosis as well as unnecessary financial and emotional burden to the patient and family.*

- *Interpretation of the results must be done with extreme caution, bearing in mind normal physiological variations and contributory pathological conditions that can affect the test results. When in doubt, an expert consultation should be sought in the best interest of the patient.*

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CLIPPINGS

A retrospective study of the impact of rapid diagnostic testing on time to pathogen identification and antibiotic use for children with positive blood cultures.

Rapid identification of bloodstream pathogens provides crucial information that can improve the choice of antimicrobial therapy for children. Previous impact studies have primarily focused on adults. Our objective was to evaluate the impact of rapid testing in a children's hospital on time to organism identification and antibiotic use in the setting of an established antimicrobial stewardship program.

The authors conducted a retrospective study over three consecutive time periods (spanning January 2013-August 2015) as the hospital sequentially introduced two rapid testing methods for positive blood cultures. An antimicrobial stewardship program was active throughout the study. In the baseline period, no rapid diagnostic methods were routinely utilized. In the second period (PNAFISH), a fluorescent in situ hybridization test was implemented for gram-positive organisms and in the third a rapid multiplex PCR (rmPCR) test was employed. For children with positive blood cultures, time to organism identification use and duration of select antimicrobial therapies were compared between periods.

Positive blood cultures were analyzed. It was found that there was no difference in use or duration of broad-spectrum gram-negative therapy across the three time periods.

The study concluded that rapid diagnostic testing for children with positive blood cultures results in faster time to identification and can influence antibiotic prescribing in the setting of active antimicrobial stewardship particularly for gram-positive pathogens.

Veesenmeyer AF, Olson JA, Hersh AL, Stockmann C, Korgenski K, Thorell EA, et al. A Retrospective Study of the Impact of Rapid Diagnostic Testing on Time to Pathogen Identification and Antibiotic Use for Children with Positive Blood Cultures. Infect Dis Ther Nov 2016.

The Heidelberg appendicitis score predicts perforated appendicitis in children.

This study aimed to differentiate advanced from simple appendicitis and to predict perforated appendicitis among children with right–sided abdominal pain. The clinicians advised that perforated appendicitis can be ruled out by the Heidelberg appendicitis score (HAS). In children with right-sided abdominal pain, perforation should be considered with high C–reactive protein (CRP) levels and free fluids or abscess formation on ultrasound.

Michael Boettcher, PatrickGünther, ThomasBreil. The Heidelberg Appendicitis Score predicts perforated appendicitis in children. Clin Pediatr 11/23/2016.

<div style="border:1px solid black; text-align:center;">**RHEUMATOLOGY**</div>

BIOLOGIC DRUGS IN PEDIATRIC RHEUMATOLOGY

*Sathish Kumar T

Abstract: *The past decade has seen growing use of biologic drugs for the treatment of pediatric rheumatic diseases. The widest range of such treatments is used for juvenile idiopathic arthritis (JIA), although biologics are sometimes given in more refractory cases of juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM) and vasculitis. The discovery of biologic therapies, their efficacy and relative safety in treating multiple rheumatologic conditions, improve quality of life for the patients. This review summarizes the current state of biologic drugs, their clinical application and their efficacy and safety in the pediatric age group.*

Keywords: *Biologic drugs, Pediatric rheumatology, Efficacy, Safety*

Pediatric rheumatic diseases are systemic inflammatory conditions of unknown etiology for which no curative treatment still exists. Recent advances in understanding the pathophysiology of the inflammatory response have led to the development of a new class of medications that are capable of inhibiting selectively the principal mediators of inflammation and tissue damage. The introduction of these new molecules, which are collectively termed biologic agents, has opened a new era in the treatment of rheumatic diseases in children. Biologics are genetically engineered drugs targeting specific sites of the inflammatory cascade such as cytokines, cell surface molecules and adhesion molecules.[1] The biologic therapies that are currently available are divided into those that target cell surface molecules and those interacting with circulating molecules.

Cell surface molecules can serve as markers for specific cells and can be targeted and deleted by a monoclonal antibody, the first class of biologics.

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The second class of molecules interferes with cytokines. Cytokines, are the soluble mediators of inflammation, which bind to cell surface receptors. They may be divided in to proinflammatory ones, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) and anti-inflammatory, such asinterleukin-10 and interleukin-1 receptor antagonist (IL-1ra). Most biologics bind to the soluble cytokines or prevent their binding to specific receptors: They are fusion proteins with the extracellular domain of a cell surface receptor fused to the C region of an IgG1 in order to create a soluble form of the receptor. Various biological agents used to treat pediatric rheumatic diseases are mentioned in Table I and Box 1. The mechanism of action of biological agents is given in Table II.

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Box 1. Nomenclature used for biologic agents

Nomenclature-Abbreviations placed at the ends of the names of therapeutic agents convey specific information relating to their structure

- '-cept' refers to fusion of a receptor to the Fc part of human immunoglobulin G1 (IgG1)
- '-mab' indicates a monoclonal antibody (mAb)
- '-ximab' indicates a chimeric mAb
- '-zumab' indicates a humanized mAb

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Anti-tumor necrosis factor alpha agents

Knowledge of the role of TNF-α in inflammation, its over production in murine models of inflammation and in serum and synovial fluid in arthritis, has permitted the successful use of anti-TNF-α therapy: Anti-TNF-α agents have been used in pediatric rheumatology since 1990s and have radically changed the outcome of several diseases, especially in children with JIA who failed to respond adequately to methotrexate (MTX) or unable to tolerate due to side effects.

Anti-TNF-α drugs are also helpful in other autoimmune diseases like uveitis, Crohn's disease (CD), sarcoidosis, ophthalmologic manifestations of Behçet disease and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.[2] Three anti-TNF-α agents

Table I. Biologic agents used to treat pediatric rheumatic diseases

Agent	Mechanism	Major use(s)	Dose
Etanercept	TNF soluble receptor	Polyarticular-course JIA, enthesitis-related JIA	0.8 mg/kg weekly, 0.4 mg/kg twice weekly, to a maximum of 50 mg;administered by subcutaneous injection
Infliximab	Chimeric(mouse–human) anti-TNF antibody	Polyarticular-course JIA, enthesitis-related JIA, uveitis	6 mg/kg administered intravenously at weeks 0, 2 and 6 and every 8 weeks thereafter
Adalimumab	Humanizedanti-TNF antibody	Polyarticular-course JIA, enthesitis-related JIA, uveitis	If patients <30 kg, 20 mg by subcutaneous injection every other week; if patient $\geq$30 kg, 40 mg by subcutaneous injection every other week
Abatacept	T-cellco-stimulation inhibitor	Polyarticular-course JIA, in cases that do not respond to anti-TNF therapy	10 mg/kg (maximum 1,000 mg) administered intravenously at weeks 0, 2 and 4 and every 4 weeks thereafter
Anakinra	IL-1 receptor antagonist	Systemic JIA,cryopyrin-associated periodic syndrome (CAPS)	1–2 mg/kg daily (maximum 100 mg) administered by subcutaneous injection
Rilonacept	IL-1 soluble receptor	Systemic JIA, CAPS	2.2 mg/kg weekly (maximum 160 mg),with a loading dose of 4.4 mg/kg loadingdose at week 1, administered bysubcutaneous injection
Canakinumab	Humanizedanti-IL-1 antibody	Systemic JIA,CAPS	4 mg/kg (maximum 300 mg) administered by subcutaneous injection once monthly
Tocilizumab	Anti-IL-6-receptor antibody	Systemic JIA	If patient <20 kg, 12 mg/kg, administered intravenously every 2 weeks; if patient $\geq$20 kg, 8 mg/kg, administered intravenously every 2 weeks
Rituximab	Anti-CD20 antibody	Rheumatoid-factor positive polyarthritis JIA, cases that do not respond to anti-TNF therapy	Two doses of 750 mg/m^2 (maximum 1,000 mg) administered intravenously 2 weeks apart

Table II. Mechanism of action of biologic agents

Class of biologicals	Mechanism of action	Drugs
Soluble receptor antagonists	Acts by inhibiting the cytokine's ability to interact with its cell surface receptors	Etanercept
Monoclonal antibodies to cytokines or their receptors	-	Infliximab, adalimumab, certolizumab
Cell surface receptor antagonist proteins	Biologically inactive proteins that compete with a cytokine for binding to the cytokine's membrane receptor	Anakinra, rilonacept, recombinant antagonists of the interleukin (IL)-1 receptor

are currently approved for the use in the pediatric age: etanercept, infliximab and adalimumab.

Etanercept

The TNF-α inhibitor etanercept is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of a human IgG1. Etanercept effectively binds both TNF-α and lymphotoxin alpha and inhibits their activity. It is given by subcutaneous injection at a dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly; it is licensed and recommended by the Food and Drug Administration (FDA) in the USA in children over 2 years.

The efficacy of this drug was demonstrated for the first time on 69 children with polyarticular JIA, refractory or intolerant to methotrexate (MTX), in a double-blind, placebo-controlled trial.[3] Subsequent studies have demonstrated long-term safety and efficacy of etanercept up to 8 years of continuous treatment in patients with polyarticular course JIA.[4]

Unfortunately, these results are not applicable to all JIA sub-types; in particular, children with systemic onset JIA (SoJIA) do not respond to etanercept. Side effects of etanercept are generally mild and include injection site reactions, headaches and upper respiratory infections of mild to moderate severity, urticarial reactions, and gastrointestinal symptoms. A few cases of malignancy are reported in children treated with etanercept. Long-term data suggest that there is no increase in incidence of tumors, but the risk of malignancy in children remains undefined.

Infliximab

Infliximab is a chimeric human/murine monoclonal antibody directed against TNF-α. It possesses a human IgG1 C region and murine V regions effective in binding TNF-α. Due to the murine fragment, infliximab retains immunogenicity and can cause anaphylaxis, lack of efficacy and infusion reactions. Infliximab is given by intravenous infusion, at the dose of 3 to 6 mg/kg at 0, 2, and 6 weeks followed by maintenance every 8 weeks.[5] It has a longer half-life than etanercept.

Infliximab has been shown to be efficacious in children with juvenile enthesitis related arthritis (ERA) and in the management of refractory JIAuveitis.[5] It appears more effective than etanercept for JIA associated uveitis.[6] Furthermore, emerging data suggest efficacy of infliximab for the treatment of children with Kawasaki disease resistant to intravenous immunoglobulin.[7]

Infliximab is also approved for the use in pediatric Crohn's disease (CD)[8] as it has been demonstrated to induce clinical remission in patients with active luminal inflammatory CD in several studies. It is also effective in patients with abdominal or perianal fistulas, although pediatric studies on the use of anti-TNF-α in inflammatory bowel diseases are limited as well as the long-term outcome and safety have not yet been established.

Infliximab has been proven to be well tolerated in children. About 40% of treated patients can develop mild adverse effects, the most frequent being upper respiratory infections, which do not require the discontinuation of treatment; but such data suggest a need to promptly survey treated patients in order to prevent severe infections. Serious infusion reactions are reported in about 2.6% of children, the majority occurring in human antichimeric antibody (HACA) positive patients.[9]

Adalimumab

Adalimumab is a fully human IgG monoclonal anti-TNF-α antibody. It offers a higher binding activity, a role in cell lysis and in apoptosis and a less immunogenic effect based on its fully humanized structure. This latter property obviates the need of concomitant MTX administration. Adalimumab is licensed for the use in RA, ankylosing spondylitis, psoriatic arthritis and severe Crohn's disease. The dose is 24 mg/m^2 (maximum dose 40 mg), given subcutaneously every other week.[10] Adalimumab has been investigated also for the treatment of JIA-associated uveitis.[11] Based on the data of trials, in February 2008 the US FDA approved adalimumab for the treatment of active polyarticular JIA in children 4 years of age and above.

IL-1 antagonists

IL-1 is a proinflammatory cytokine secreted by monocytes and macrophages. It activates antigen-presenting cells and CD4+ lymphocytes and promotes lymphocyte differentiation;it increases prostaglandin E2, collagenases and neutral proteinases production. This cytokine plays a critical role in the maintenance of chronic inflammation. IL-1 blocking therapy is currently in use in children with JIA. It is particularly useful for the treatment of cryopyrin-associated periodic syndrome (CAPS), a rare disorder characterized by overproduction of IL-1.

Anakinra

Anakinra is a fully human IL-1ra which competitively binds to the IL-1 receptor, thus blocking endogenous IL-1 signalling. Anakinra is a short-acting agent that requires

daily subcutaneous administration at the dose of 1-2 mg/kg, maximum 100 mg/dose.[12] It can be combined with MTX or other disease-modifying antirheumatic drugs (DMARDs) and seems to be clinically and radiologically effective. The identification of the molecular basis of Muckle-Wells syndrome (MWS), familial cold-induced autoinflammatory syndrome (FCAS) and neonatal onset multisystemic inflammatory disease/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA), also known as CAPS, supported evidence for the role of IL-1β in the pathogenesis of these group of diseases. As a consequence, IL-1β blockade is an option for treatment of these syndromes.[13]

Adverse reactions during anakinra therapy are neutropenia, nausea, diarrhea, cardiopulmonary arrest, influenza-like symptoms, production of anti-anakinra antibodies and serious infections. However, the most frequent and common side effects are injection site reaction with burning and pain, and infections.

Rilonacept

Rilonacept is a recombinant fusion protein of IL-1 receptor protein components and the Fc portion of a human immunoglobulin. It is a longer IL-1α and IL-1β blocker and is administered once weekly by subcutaneous injection.[14] So far rilonacept is not approved for the treatment of JIA in children less than 12 years of age and there is a need for further controlled trials on larger patient cohorts with a longer follow-up.

Canakinumab

Canakinumab is a fully human anti-IL-1β monoclonal antibody that selectively blocks IL-1β. It is administered by subcutaneous injection at the dose of 2 mg/kg every 8 weeks. It was approved by the Food and Drug Administration (FDA) in the USA for the treatment of CAPS in 2009 and treatment of systemic JIA in 2013.

In a multicenter, randomized, double-blind, placebo-controlled trial, canakinumab showed rapid and sustained clinical efficacy in 45 patients, between the ages of 4-75 years with (cryopyrin associated periodic syndrome) CAPS syndrome.[15] The drug was administered for a total of 48 weeks. The use of canakinumab was not associated with life-threatening adverse effects other than an increased rate of infections. The prolonged duration of action and the low incidence of injection site reaction represent an advantage of this drug compared to rilonacept and anakinra in the treatment of CAPS syndrome.

In SoJIA, two sequential randomized double-blind,

placebo-controlled trials showed canakinumab to be effective in treating systemic features in SoJIA in patients 2-19 years old with active disease.[16] These studies showed canakinumab to be effective in treating systemic features in SoJIA. Pediatric ACR30 (Box 2) was reached in 84% of the patients on canakinumab at day 15 in the first trial vs. 10% in the placebo group (p < 0.001). At the end of the second trial, 73% had reached pediatric ACR50 and 31% had inactive disease. In the open-label phase, 74% of the patients on canakinumab had no flare vs. 25% in the placebo group. There were no reports of opportunistic infections, tuberculosis or malignancy in these two trials, but increased risk of infection, disease flare and MAS occurred.

IL-6 blockers

IL-6 is a proinflammatory cytokine synthetized by mononuclear cells, vascular endothelial cells and fibroblasts in response to stimulation by IL-1 and TNF-α. It stimulates B-cell growth, osteoclast activation and hepatocyte synthesis of acute phase reactants. IL-6 also plays an important role in the pathogenesis of anemia and growth failure of children with systemic JIA.[15] Furthermore, increased serum and synovial fluid levels of IL-6 have been found in children with systemic JIA and polyarticular JIA. For these reasons, the potential role for IL-6 as a therapeutic target was investigated in children with JIA.

Box 2. Pediatric ACR* 30 criteria

The pediatric ACR30 consists of 6 core criteria:

1) physician global assessment of disease activity
2) parent / patient assessment of overall well-being (each scored on a 10cm VAS$)
3) functional ability
4) number of joints with active arthritis
5) number of joints with limited range of motion
6) erythrocyte sedimentation rate

The definition of improvement is at least 30% improvement from baseline in 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by >30%.

Pediatric ACR50 and ACR70 improvement criteria are defined as above with improvements of 50% and 70% respectively.

*American College of Rheumatology; $Visual analog scale

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. It competes with natural soluble and membrane-bound IL-6 receptors. The TENDER trial showed tocilizumab was effective in treating SoJIA when compared to placebo. In the double-blind phase, at week 12, significantly more patients in tocilizumab group than in the placebo group (64 of 75 (85%) vs. 9 of 37 (24%), P < 0.001) had absence of fever and achieved ACR 30, and in the open-label extension phase at week 52, 80% of patients had at least 70% improvement and remained afebrile. Adverse events were more commonly seen in the tocilizumab group including serious infections, neutropenia and transaminitis.[17]

The CHERISH trial, a randomized, double-blind, placebo controlled withdrawal trial, of tocilizumab in polyarticular JIA, had three phases, including an open-label phase, where 89% of patients achieved pediatric ACR 30 response. Of the patients previously exposed to biologics, who had treatment failure prior to the study, 48% achieved pediatric ACR 70 with Tocilizumab.[18] Tocilizumab is approved in the USA by the FDA for the treatment of SoJIA in 2011 and for the treatment of polyarticular JIA in 2013.

Abatacept

Abatacept inhibits the activation of T cells by blocking the co-stimulatory signal required. Abatacept is given as intravenous infusion monthly at the dose of 10 mg/kg. It is a fully human soluble fusion protein, containing the extracellular portion of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and the Fc portion of IgG1. It was approved by the FDA in 2008 for the treatment of JIA based on the results of an international, multicenter, randomized, double-blind, placebo-controlled, withdrawal study. In the study, 53% of patients who went on to receive placebo after the initial phase had a flare vs.20% in the abatacept group. The end point was time at which the flare occurred. In the placebo group, the median time to flare was 6 months; insufficient events had occurred in the abatacept group for median time to flare to be assessed (p=0.0002).[19]

Golimumab

Golimumab is a fully human monoclonal antibody to soluble and transmembranous TNFα. It has been approved in adults for rheumatoid arthritis, psoriatic arthritis, and ankylosingspondylitis. In children with polyarticular disease, the GOKIDS trial, a placebo-controlled, three-phase withdrawal study, showed pediatric ACR 30 response in 87% of patients and 36% achieved inactive disease at the end of the first phase at 16 weeks. The study failed to meet its primary endpoint. Both groups had a sustained pediatric ACR 30 response (89%-95 %), and there was no difference in disease flare.[20] Further investigation in children is needed.

Certolizumab

Certolizumab pegol is a pegylated anti-TNFα inhibitor. Pegylation enhances the half-life of the drug and allows a 2- to 4-week dosing schedule. There is currently a clinical trial underway for the use of certolizumab in children with JIA.[21]

B-cell-targeted therapy

In recent years, a growing body of evidence suggested an important role of B lymphocytes in the pathogenesis of several autoimmune diseases: B cells are the precursors of immunoglobulin-secreting plasma cells and also produce cytokines that regulate the function of other cells.

Rituximab

Rituximab is a chimeric monoclonal antibody that binds to the CD20 receptor on the B cells. The CD20 receptor is in the pre-B cells and mature B cells. Due to its mechanism of action, it can potentially be used to treat conditions in which autoantibodies play a major role in the pathogenesis of disease. There are no randomized trials on rituximab, but there is some evidence of its benefits in ANCA-associated vasculitis, systemic lupus erythematosus (SLE), JIA and inflammatory central nervous system disease.[22,23,24] The most common protocol is 375 mg/m^2/week intravenously, for a total of four infusions; some patients need a second infusion cycle after a variable time.

Belimumab

Belimumab is a human monoclonal antibody against B lymphocyte stimulator (BLyS). It is expressed on macrophages and monocytes and it enhances the proliferation of B cells. It was approved in 2011 by the FDA to treat active SLE, making it the first medication to be approved in over 50 years. Although the data available is from adult studies, some of the newer studies have included a subset of pediatric patients. In 39 patients with childhood onset, 65% responded favorably at 6 months and 35% discontinued corticosteroids.[25]

Conclusion

With better understanding of the pathogenesis of rheumatologic diseases, newer and improved therapies are

increasingly available. Targeting specific areas of the immune response will aid in avoiding some unnecessary side effects. These newer therapies will allow for tailored, more individualized, treatment plans in the future.

Points to Remember

- *'Biologicals' is a name for a pharmacological group of specific proteins with high molecular weight specifically targeting pro-inflammatory cytokines or cell surface antigens.*

- *TNF α blockers now are approved for rheumatoid factor positive and negative polyarthritis, extended oligoarthritis, enthesitis related arthritis and psoriatic arthritis.*

- *Abatacept is approved for polyarticular JIA refractory to TNF inhibitors.*

- *Systemic onset JIA can be treated with tocilizumab or on an off label basis with the IL1 inhibitors anakinra or canakinumab.*

- *Biologicals are used in other pediatric rheumatic disease like periodic fever syndromes, refractory cases of SLE, juvenile dermatomyositis and vasculitis.*

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CLIPPINGS

Does the use of ibuprofen in children with extremity fractures increase their risk for bone healing complications?

Despite being an effective analgesic for children with fractures, some clinicians may avoid prescribing ibuprofen due to its potentially harmful effect on bone healing.

This study aimed to determine if exposure to ibuprofen is associated with an increased risk of bone healing complications in children with fractures.It was a retrospective study of children aged 6 months to 17 years who presented to the pediatric emergency department (PED) with a fracture of the tibia, femur, humerus, scaphoid, or fifth metatarsus and who followed up with the orthopedic service. These fractures were chosen due to their higher risk for complications. Patients were classified as exposed if they received ibuprofen in the PED or during hospitalization or were prescribed ibuprofen at discharge. The main outcome was a bone healing complication as evidenced by nonunion, delayed union, or re-displacement on follow-up radiographs.

Of the 808 patients included in the final analysis, 338 (42%) were exposed to ibuprofen. Overall, 27 (3%) patients had a bone healing complication; 8 (1%) developed nonunion, 3 (0.4%) developed delayed union, and 16 (2%) developed re-displacement. Ten (3%) patients who were exposed to ibuprofen, and 17 (4%) who were not, developed a bone healing complication (odds ratio 0.8, 95% confidence interval 0.4–1.8; $p = 0.61$). There was no significant association between ibuprofen exposure and the development of a bone healing complication despite adjustment for potential confounders.

The study concluded that children with extremity fractures who are exposed to ibuprofen do not seem to be at increased risk for clinically important bone healing complications.

DePeter KC, Blumberg SM, Dienstag Becker S, Meltzer JA. Does the Use of Ibuprofen in Children with Extremity Fractures Increase their Risk for Bone Healing Complications? J Emerg Med Nov 2016.

<div style="text-align:center">**GENERAL ARTICLE**</div>

MANAGEMENT OF ADOLESCENT ANXIETY DISORDERS

Venkateswaran R

Abstract: *Anxiety disorder is one of the most common mental health problemsamong adolescents. The types of anxiety disorders include generalized anxiety disorder, specific phobia, social phobia, selective mutism, panic disorder and agoraphobia. They commonly present with fear, worry, physical symptoms, avoidance and cognitive symptoms. It should be differentiated from developmentally normal fear. The varied presentation creates challenges in diagnosis and hence, a high index of suspicion is required to diagnose anxiety disorders. Early identification and treatment results in good clinical outcomes. Both psychotherapy and medications have been found to be beneficial in their management.*

Keywords: *Anxiety disorders, Adolescents, Child psychiatry.*

Anxiety disorders (AD) represent one of the most common psychological problems in adolescents.They often under-recognized and hence, misdiagnosed or missed, resulting in significant dysfunction. Early identification and appropriate management will improve overall functioning in these adolescents.[1] The major anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders V (DSM V) include separation anxiety disorder (SAD), selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder (GAD) and anxiety disorder due to another medical condition.[2] Anxiety disorders differ from one another in the types of objects or situations that induce anxiety symptoms. Previously obsessive-compulsive disorder was placed under anxiety disorder; however it is currently placed separately in view of distinct pathophysiology.

Epidemiology

Despite being the most common mental health concern, there is paucity of literature on anxiety disorders

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among the adolescent population in India. Most anxiety disorders develop in childhood and tend to persist if not treated. As per DSM V, anxiety disorders most commonly occur in females (2:1). According to a study done in the South Indian population, the prevalence of anxiety disorders using the standard criteria was 14.4%. Even symptom severity was higher in girls compared to boys.[3] Prevalence of specific AD was age and gender specific.[4]The most commonly encountered symptoms across the subtypes of anxiety disorders include anxious mood (12.6%), followed by cognitive symptoms (9.94%) and physical symptoms(9.22%).[3] Co-morbidities are quite prevalent among adolescents with anxiety disorders (23.7%) having another psychological condition (the most common being depression) and 14.2% having another anxiety disorder.[5] Co-morbidities increase the severity of anxiety symptoms and hence should be identified and appropriately managed.

Pathophysiology

The factors implicated in the pathophysiology of anxiety disorders are diverse and may be biological or environmental.

The biological factors include genetic factors and pre-morbid temperamental factors like behavioral inhibition. Various twin studies have implicated genetic factors in adolescents with anxiety disorder.[6] The presence of anxiety disorders in parents increases the likelihood of anxiety disorders in children. Children with behavioral inhibition (BI) have higher chances of developing anxiety disorders in adolescence. Behavioral signs of BI include long latencies in interacting with unfamiliar adults, retreat from unfamiliar objects or persons, cessation of play or vocalization, clinging to mother and fretting or crying.[7]

The environmental risk factors in the development of anxiety disorders include parental anxiety and parent-child interactions. Anxiousparents can model fear and anxiety, thus reinforcing anxiouscoping behaviour and maintaining avoidance,despite their desire to be of help to their child.[8] In terms of parent-child interaction, overprotectiveand overly critical parenting styles limit the development of autonomy and mastery, thereby contributing to the development of anxiety disorders in adolescents.[9] There is

also evidence stating that early separation from the mother leads to insecure attachment during infancy and toddlerhood, resulting in the development of anxiety at a later point of time in life.[10]

Physiological vs. pathological anxiety

Developmentally, normal fear and worries are common in children and adolescents, examples of which include fear of loud sounds and stranger anxiety experienced by infants; and fear of imaginary creatures, darkness and caregiver separation exhibited by toddlers. Adolescents also have worries about school performance, social approval and illness related anxiety.[11] Fears during childhood become problematic, if they do not subside with time causing significant dysfunction in adolescents. Anxiety disorders differ from the former by the presence of symptoms which appear out of proportion to or which persist beyond the developmentally appropriate period. They also differ from stress induced fear or worries, which are generally more transient (lasting for less than 6 months).[2] As clinicians, it is vital to differentiate between the anxiety disorders and normal fear and worriesthat exist in adolescents.

Clinical presentation

Adolescents with anxiety disorders typically present with fears,worries or behavioral disturbances. However, other presentations include somatic complaints like headaches or muscle aches and irritability or emotional outbursts, which result in this entity being misdiagnosed as medical condition or as oppositional behaviour of adolescents respectively.

Adolescents with SAD display excessive and developmentally inappropriate fear of separation from primary care givers. This distress can be exhibited even before transient separation, which children generally tend to cope well with and is a result of their increasing concerns regarding the safety and health of parents or themselves when separated. They have difficulty in sleeping alone, experience nightmares with themes of separation, frequently complain of physical symptoms and may often exhibit school refusal.

Specific phobia is fear of a particular object or situation, which is subsequently avoided, resulting in impairment.

Youth with GAD present with long standing excessive worries regarding a number of areas such as schoolwork, social interactions, health/safety and natural disasters. They also tend to have at least one physical symptom, not explained by medical condition. They have trouble controlling their worries. They often seek reassurance and may struggle with more internal distress than is evident to parents or teachers.[12]

Social phobia is characterized by patients experiencing fear or discomfort in one or more social settings or performance situations (e.g. music, sports). The discomfort is associated with social scrutiny and fear of embarrassing oneself in social settings. These adolescents often present with school refusal and may have difficulty in answering questions, reading aloud, initiating conversations and talking with unfamiliar people during school hours. They also have difficulty in attending parties and social events. Their cognitive ideation stems from concerns of being negatively evaluated by others. There is marked reduction in anxiety once they escape social situations.

Selective mutism is not common among adolescents. However, children with selective mutism present with difficulty in speaking during specific situations or at particular environments (e.g. school) despite being able to speak normally otherwise (e.g. with family and in the home environment). These children may communicate non-verbally with selected individuals. Selective mutism has been considered an early developmental manifestation of social phobia as most of these children also have symptoms of social phobia.[13]

Panic disorder is characterized by recurrent episodes of abrupt surge of intense fear that occur unexpectedly. The symptoms should include at least 4 of 13 symptoms from DSM-V such as pounding heart, chest pressure or pain, feeling of choking, sweating, shaking, difficulty in breathing, nausea, chills or dizziness. Adolescents with panic disorder fear recurrent panic attacks (anticipatory anxiety) and may develop avoidance of particular settings (agoraphobia). Most often, they present to medical casualty but evaluation is usually normal.

Agoraphobia presents with anxiety induced by two or more of the following situations: using public transport, being in open and closed spaces and being in a crowd. Individuals fear these environments because escape might not be possible in these situations if panic-like symptoms develop.

Course and prognosis

The long-term course of childhood anxiety disorders has not been well described. The sequelae of childhood anxiety disorders includesocial, family and academic impairments. Anxiety disorders disrupt the normal psychosocial development of the child. A longitudinal study

in New Zealand has observed that adolescents with anxiety disorders tend to develop elevated rates of anxiety, major depression, illicit drug-dependence and educational underachievement as young adults.[14] Suicidal behaviour can been countered in anxiety disorders, especially in severe cases and when there is co-morbid depression. An Indian study has observed 94.4% of adolescents with anxiety disorder to have impairments across various domains, which is very significant.[15]

Assessment

Comprehensive assessment is important in approaching adolescents with anxiety disorders. Adolescents usually present with varied symptom profile. They usually present with physical symptoms unexplained by medical conditions, behavioural problems, defiant behaviour, school refusal and decline in academic performance.

They usually present to primary care settings with above complaints and hence medical professionals need to have a high index of suspicion for identification of anxiety disorders. Information needs to be obtained about the anxiety symptoms from multiple informants including the adolescents and caregivers (parents and/or teachers).[16] Interviewing the adolescents often reveals subjective distress and the caregivers' report yields details about dysfunction. Although formal psychological testing or questionnaires are not required for the evaluation of anxiety disorders in routine clinics, there are several tools that may be helpful (Table I).

Evaluation needs to be focused on differentiating AD from organic causes and other psychological problems presenting with anxiety (Fig.1). Physical conditions presenting with anxiety symptoms include hyperthyroidism, migraine, asthma, seizure disorders, lead intoxication and rarely hypoglycemia, pheochromocytoma and cardiac arrhythmias. Substance induced anxiety disorder is common with prescription drugs and psychoactive drugs. Commonly prescribed drugs that produce anxiety symptoms include anti-asthma

Table I. Rating scales and structures instruments

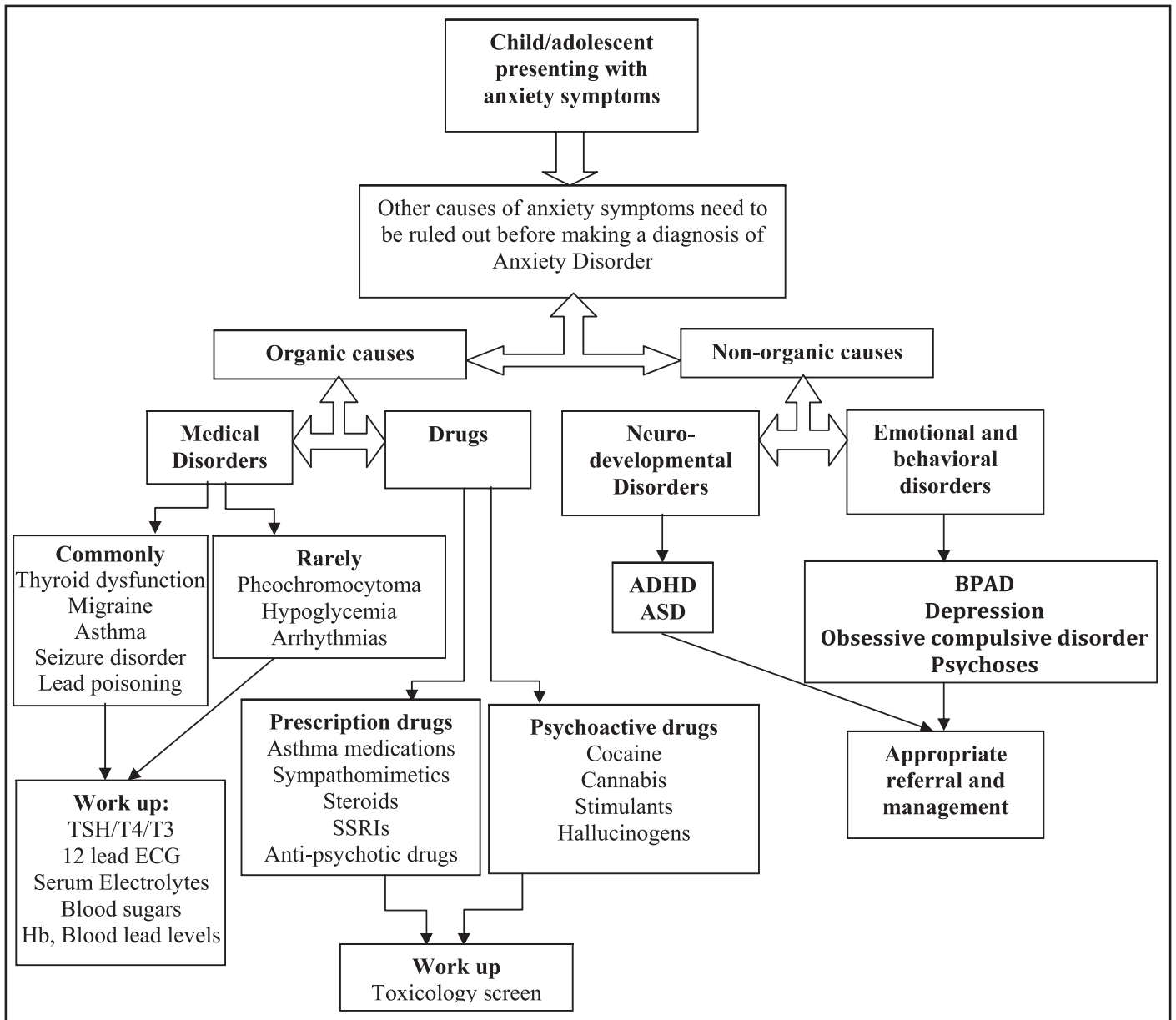| Instrument	Age range	Description
Schedule for affective disorders and schizophrenia for school age children (KSADS)	6-18 years	It's a semi structured clinical interview with good internal consistency. Different versions include present state, life time version and research version
Composite international diagnostic interview (CIDI)	Children, adolescent and adults	Standardized interview to access ICD-10 disorders with good inter-rater reliability and test retest reliability
Diagnostic interview for children and adolescents (DICA)	6-17 years	Semi structured, clinician rated interview
Multidimensional anxiety scale for children (MASC)	8-19 years	It's a self report instrument that measures symptoms in 4 point Likert scale with good internal consistency and inter rater reliability
Screen for childhood anxiety related emotional disorders (SCARED)	9-18 years	It's a 41 items self report tool that measures symptoms in 3 point Likert scale. Cutoff of 25 indicates the need for further evaluation. It has good internal consistency (a=0.9)
Revised children's manifest anxiety scale (RCMAS)	6-19 years	It's a self report-screening tool with good internal consistency. A short version (10 items) RCMAS-2 is also available
Child behavioralchecklist (CBCL) Teacher report form (TRF)	4-18 years	Assesses the range of internalizing and externalizing symptoms. TRF is a 120-item report rated by the teachers. It has an excellent internal consistency (a=0.9)
State trait anxiety inventory for children- parent report- Trait version (STAIC-P-T)	8-14 years	Assesses parent's perception of child's trait anxiety. There is an self-report tool for adolescents available (STAIC)

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│     Child/adolescent     │
│      presenting with     │
│     anxiety symptoms     │
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┌───────────────────────────────────┐
│  Other causes of anxiety symptoms  │
│   need to be ruled out before      │
│   making a diagnosis of            │
│   Anxiety Disorder                 │
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Organic causes ◄─► **Non-organic causes**

Medical Disorders ◄─► **Drugs**   **Neuro-developmental Disorders** ◄─► **Emotional and behavioral disorders**

Commonly
Thyroid dysfunction
Migraine
Asthma
Seizure disorder
Lead poisoning

Rarely
Pheochromocytoma
Hypoglycemia
Arrhythmias

**ADHD
ASD**

**BPAD
Depression
Obsessive compulsive disorder
Psychoses**

Prescription drugs
Asthma medications
Sympathomimetics
Steroids
SSRIs
Anti-psychotic drugs

Psychoactive drugs
Cocaine
Cannabis
Stimulants
Hallucinogens

Appropriate referral and management

Work up:
TSH/T4/T3
12 lead ECG
Serum Electrolytes
Blood sugars
Hb, Blood lead levels

Work up
Toxicology screen

Fig.1. Differential diagnosis and work up for anxiety disorders

medications (beta-agonists and methyl xanthines), sympathomimetic drugs, steroids, selective serotonin reuptakeinhibitors (SSRIs) and antipsychotics (Akathisia). Psychoactive agents like cannabis, cocaine, stimulants and hallucinogens also produce anxiety symptoms. Appropriate medical evaluation and toxicology screen is warranted when any of the above mentioned conditions is suspected.

Among the other psychiatric conditions that can present with anxiety symptoms, the following are common. Neurodevelopmental disorders like Attention Deficit Hyperactivity Disorder [(ADHD) (restlessness, poor concentration)] and Autism Spectrum Disorder[(ASD) (especially high functioning)], can present as social anxiety disorder. ASD in childhood can also present as selective mutism. Learning disability can present with school phobia. Anxiety symptoms are commonly seen in a depressive episode, along with low mood, decreased interest and biological symptoms.[1] Anxiety symptoms can be an early manifestation (prodromal symptoms) in major mental health conditions like Bipolar Affective Disorder (BPAD) and Psychotic Illnesses (especially in adolescents).[17]

Assessment of psychosocial stressors and family dynamics is of prime importance and helps in treatment planning.

Treatment

A multimodal approach is essential in the management of anxiety disorders, which usually begins with psycho-

Table II. SSRIs-Dose and side effects

S. No	Medications	Starting dose	Therapeutic dose range	Common side effects
1.	Sertraline	12.5 – 25 mg	50 – 200 mg	Nausea, sedation, headache
2.	Fluoxetine	5 – 10 mg	10 – 60 mg	Activation, nausea, Insomnia
3.	Fluvoxamine	12.5 – 25 mg	50 – 200 mg	Hyperactivity, abdominal discomfort
4.	Citalopram	5 – 10 mg	10 – 40 mg	Somnolence. Insomnia, diaphoresis
5.	Paroxetine	5 – 10 mg	10 – 40 mg	Sedation, nausea, dry mouth

educating the parents, adolescents and communicating the same to the school. An individualized treatment plan needs to be made considering the psycho social stressors, risk factors, severity of illness, impairment in functioning, co-morbid disorders, age and family functioning. The type of anxiety disorder and the cognitive maturity present, further helps in tailoring the treatment plan.

Psychotherapy: The first line of treatment for anxiety disordersis psychotherapy (of sole importance in milder cases). Cognitive behavioral therapy (CBT) involves cognitive restructuring and behavioral training. Coping skills are initially taught to help them develop control over anxiety symptoms or anxiety inducing situations. This is followed by relaxation training (deep abdominal breathing, Jacobson progressive muscle relaxation), cognitive restructuring (challenging negative thoughts) and graded exposure to fearful stimuli.

Treatment of specific phobia includes participant modeling (demonstrations of approaching feared objects or situations by the therapists or parents) and social skills training (in the treatment of social phobia).[18] A unique approach is used in panic disorder, where the patient is subjected to interceptive exposure [exposure to physical sensations associated with panic (such as dizziness, shortness of breath and sweating) by using exercises that induce these sensations], followed by education about the physiological processes that lead to these symptoms. Sara Dow proposed Dow's model for selective mutism, which is a school-based individualized treatment involving the combined efforts of teachers, clinicians and parents, with home and clinic-based behavioral interventions and medications if required.[19] The other schools of therapies that may be of use in these patients include psychodynamic psychotherapy, family therapy and interpersonal therapy. An eclectic approach, including components from the above mentioned schools of psychotherapy, is practiced routinely. The selection of psychotherapy also depends on the availability of resources and compliance to therapy.

Box.1 Signs and symptoms of serotonin syndrome

Agitation or restlessness

Confusion

Rapid heart rate and high blood pressure

Dilated pupils

Loss of muscle coordination or twitching muscles

Muscle rigidity

Heavy sweating

Diarrhea

Headache

Shivering

Goose bumps

Severe serotonin syndrome can be life-threatening. Signs and symptoms include:

High fever

Seizures

Irregular heartbeat

Unconsciousness

(Source:http://www.mayoclinic.org/diseases-conditions/ serotonin-syndrome/basics/ symptoms/ con-20028946 accessed on 22 Oct. 2016).

In a resource-limited country like India, the availability of appropriate intervention is limited.

Pharmacotherapy: Drugs are considered in the presence of moderate to severe symptoms, non-availability of resources for psychotherapy, poor compliance from the family for psychological approach or in the presence of co-morbidities.

Significant developmental differences exist between children and adults, in terms of metabolism and drug action, and this has definite implications in dosing, therapeutic benefits and toxicity. Therefore, it is recommended to start at a lower dose followed by gradual upward titration. Use of multiple drugs is usually avoided; but the presence of comorbid disorders may warrant a combination of drugs. It is also important to consider the fact that the developing brain is more sensitive to the effects of psychotropic medications and long-term implications have not been clearly understood in such patients who have been exposed to these medications from an early age. In the near future, with the advent of pharmacogenomics, it is hoped that therapy would be tailored to suit each individual, to improve efficacy and decrease adverse effects.

Drugs used as first line in the pharmacotherapy of anxiety disorders include selective serotonin reuptake inhibitors (SSRIs). The commonly used drugs arefluoxetine, escitalopram, sertraline, fluvoxamine and paroxetine. The dosing range and common side effects of these SSRIs are given in Table II. It is ideal to start with the minimum dose and then, gradually titrate once in 2-4 weeks depending on the need. FDA gives black box warning about the suicidal tendencies and the risk of serotonin syndrome (Box.1) associated with SSRIs. A history of bipolar disorder should be ruled out before the initiation of SSRI.

The other classes of medications used include serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclicsand bupropion. The commonly used SNRI is venlafaxine. The side effects include nausea, behavioral activation and hypertension. Tricyclic antidepressants include imipramine andclomipramine. It is not commonly used in view of its side effect profile which includes cardiac, anticholinergic, antihistaminergiceffects and postural hypotension. It is not advisable to combine tricyclics with SSRIs due to the risk of serotonin syndrome.

If there is no response to one SSRI, then a trial of another SSRI is given. If there is no improvement with trials of 2 distinct SSRIs, then SNRIs are considered. In case of poor treatment response, the presence of co-morbidities or organic causesneed to be evaluated. Institution of psychotherapy (along with medications) is to be considered in cases with poor treatment response, prior to switching agents.[20]

The first, large, randomized controlled study on the pharmacologic treatment of anxiety disorders in children, was published in 2001 (by the Research Unit on Pediatric Psychopharmacology [RUPP] Anxiety study group, 2001).

In this multisite NIMH-funded trial, 128 children (between the ages of 6 and 17) who met the criteria for social phobia, separation anxiety disorder or generalized anxiety disorder were randomly assigned to receive either fluvoxamine or placebo for eight weeks. By week 3 of the trial, significant differences between the treated and untreated groups were evident on the Pediatric Anxiety Rating Scale. Symptoms continued to improve through week 6, with little change during the final two weeks of the trial.[21] Another landmark trial, Child/adolescent Anxiety Multimodal Study (CAMS) has compared sertraline, cognitive behavioral therapy, combined treatment group and placebo among 488 adolescent patients. The outcome was assessed at 24 and 36 weeks. There was statistically significant improvement in all the treatment groups compared to placebo. There was however, no difference found between the sertraline (SSRI) the CBT groups. But, at 36 weeks, the combined treatment group was found to fare better than the individual treatment groups.[22] Evidence is week for SNRIs and tricyclic agents and this area needs further controlled studies.

Conclusion

Anxiety disorder is frequently encountered in adolescents, causing significant impairment at a productive age. The diagnostic challenges arise not only from its varied presentation, but also from the long list of differentials that need to be considered. Therefore, it is essential to maintaina very high index of suspicion and be thorough in evaluation. Timely identification will help in early initiation of treatment (for which, there are various options available, including psychotherapy and medications), whichhas been found to significantly improve the functioning and thereby the quality of life in adolescents.

Points to Remember

- *Anxiety disorder in adolescents is a common psychological problem, where high index of suspicion is required for early diagnosis and reduction of morbidity.*

- *It can present as unexplained physical symptoms, unnecessary worries, academic deterioration and school refusal.*

- *Diagnosis is mainly clinical though thyroid disorders, cardiac arrhythmias and complex partial seizures are to be considered in differential diagnosis.*

- *Cognitive behavioural therapy is the first line of treatment.*

- *Medications commonly used are SSRIs including sertraline, fluoxetine and escitalopram.*

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NEWS AND NOTES

Pediatric Endocrinology CME

Venue: Hotel Raintree (Anna Salai)   Date: 29th January, 2017

Conference Secretariat

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<div style="text-align:center">**GENERAL ARTICLE**</div>

DIAGNOSIS AND MANAGEMENT OF INFANTS LESS THAN SIX MONTHS OLD WITH SEVERE ACUTE MALNUTRITION

*Praveen Kumar
**Shivani Rohatgi

Abstract: *Severe acute malnutrition (SAM) is increasingly being recognized in infants who are less than 6 months of age with a higher risk of mortality and intellectual impairment compared to older children. There are fundamental differences in criteria for identification and admission due to physiological differences between young infants and older children. Principles of management essentially remain the same as for children more than 6 months with the exception of feeding management. All possible efforts should be directed towards establishment of exclusive breastfeeding by improving feeding practices and relactation by supplementary suckling techniques (SST) in these infants. If there are no prospects of breastfeeding, rehabilitation with diluted F-100 (F-100D) in place of F-100 should be done.*

Keywords: *Severe acute malnutrition, Infant less than six months, Supplementary suckling technique*

Malnutrition is an underlying problem in approximately 35%-45% of the estimated 10 million deaths in children who are under 5 years of age worldwide.[1] Besides increasing the risk of mortality, malnutrition, if untreated leads to growth retardation, impaired psychosocial and cognitive development. The first thousand days of life from conception is critical for brain development as this is the time of rapid brain growth.[2]

Most of the treatment guidelines on severe acute malnutrition (SAM) management focus on children aged 6-59 months. SAM is increasingly being recognized in infants who are less than 6 months of age[3], where there are no clear guidelines regarding optimal management.

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There are fundamental differences in criteria for identification, hospitalization and management protocol due to physiological differences between young infants and older children. These differences justify separate consideration of the management of severe acute malnutrition in infants less than 6 months old.

Prevalence of SAM in infants less than 6 months old

Approximately 4.7 million infants under 6 months of age worldwide are moderately wasted and 3.8 million are severely wasted.[4] Secondary data analysis of National Family Health Survey-3 revealed severe wasting in more than 13% of infants less than 6 months of age. Vulnerability for SAM in this age group was seen irrespective of their breastfeeding status.[5] It was observed that 35.9% of total SAM admissions were infants under 6 months.[6]

Risk factors

The development of SAM in this age group commonly reflects suboptimal feeding practices, especially breastfeeding practices. Other contributory factors include low birth weight, prematurity, perinatal insults, persistent diarrhea, recurrent illnesses, chronic underlying diseases or disability, poor maternal physical or mental health, social factors and exposure to HIV infection.

Diagnosis

An infant less than 6 months, if his/her weight for length is less than -3Z score or has bilateral pitting pedal edema without any other cause is diagnosed to have SAM. For infants whose length is less than 45cm, the presence of visible severe wasting makes him denotes SAM (Box 1).[7] Mid upper arm circumference which is used as one of the criteria for children between 6 months and 59 months is not recommended for this age group due to lack of consensus regarding optimal cut off in this group.[8]

Need for different treatment in infants less than 6 months with SAM

Infants less than 6 months have immature thermoregulation, renal and gastrointestinal functions as compared to older children. Clinical signs of infection and

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Box 1. Recommended criteria for identifying SAM in infants <6 months of age

- Weight/length < -3 Z score, using the WHO Growth Charts; OR

- Presence of visible severe wasting if length less than 45 cm; OR

- Presence of bipedal edema of nutritional origin

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(Source: WHO. Guideline: Updates on the management of severe acute malnutrition in infants and children. Geneva, World Health Organization; 2013).

hydration status may also be more difficult to assess in younger infants. As a result, criteria for admitting and discharging such infants with SAM have not been adequately defined and management protocol is different.

Admission criteria for inpatient care in infants less than 6 months

Ministry of Health & Family Welfare, GOI guidelines and earlier WHO guidelines recommended admission and in-patient care for all infants less than 6 months. However, risk of hospital infection, reluctance of mothers/caregivers for in-patient care has led to change in admission criteria in WHO 2013 update.[3]

Infants who are less than 6 months of age with SAM with the following criteria should be admitted for inpatient care[7]:

- Infant is too weak or feeble to suckle effectively (independently of his/her weight-for-length) or

- WfL (weight-for-length) <–3SD (in infants >45 cm) or

- Visible severe wasting in infants <45 cm or

- Presence of edema both feet.

Additional criteria for inpatient management[3]

- Any serious clinical condition or medical complication as outlined for infants who are 6 months of age or older with SAM

- Recent weight loss or failure to gain weight and who have not responded to nutrition counseling and support

- Any medical or social issue needing more detailed assessment or intensive support (e.g. disability, depression of the caregiver or other adverse social circumstances).

Components of care

During the last ten years, management of children aged 6-59 months with SAM, without medical complications and good appetite has seen major change in management with introduction of community based management for children. But this change in protocol is not applicable for infants less than 6 months as ready to use therapeutic food (RUTF) is the key intervention in this protocol which is not suitable for infants less than 6 months.[9,10] However, World Health Organization in its 2013 update recommended that uncomplicated severe acute malnutrition in infants less than 6 months should be recognized and outpatient treatment by supporting feeding by community workers should be offered as first line of treatment. This outpatient approach is believed to be more practical, more acceptable to families and would decrease not only the risk of nosocomial infections, but also the cost of treatment due to long hospital stay.[11]

The basic principles of management of infants less than 6 months with SAM who have medical complications or poor feeding history are similar to older children with medical complications or poor appetite. These children should receive same general medical care as older infants and children i.e., treatment of hypoglycemia, hypothermia, dehydration, electrolyte imbalance, infection, micronutrient supplementation, initiation of feeding, catch-up feeding, sensory stimulation and discharge. All admitted patients should be given parenteral antibiotics like ampicillin and gentamycin to treat sepsis and appropriate treatment for other specific diseases. Dietary management of children in this age group is labor-intensive and requires a different approach.

Management may be broadly divided into two categories - with prospects of breastfeeding and without prospects of breastfeeding.

(a) Feeding of infants with prospects of breastfeeding: Maternal factors influence the health of the infant in this phase and hence, it is essential to treat mother infant pair rather than infant alone. All possible efforts should be directed towards the establishment of exclusive breastfeeding by the mother. Mother and family members should be counseled about advantages of breastfeeding. Infants should be breastfed. Mother should be given support to relactate and also during breastfeeding. If it is not possible, wet nursing should be encouraged. Supplementary suckling technique (SST) stimulates breast milk production by stimulating prolactin (Box 2 and Table I and II). For supplementary feed, WHO 2013 update has recommended expressed breast milk (EBM) as the first

Box 2. Method for supplementary suckling technique (SST)

- The supplementation is given via a No-8 nasogastric tube.

- The tip is cut back beyond the side ports approximately 1cm

- Supplemented milk (expressed breast milk or diluted F-100) is put in a cup. The mother holds the cup with one hand initially 5-10 cms above the breast. The end of the tube is put in a cup.

- The tip of the tube is put on the breast at the nipple and the infant is offered the breast. Health staff can hold the cup/katori and support the mother. It may take one or two days for the infant to get used to the tube and it is important to continue this for few days.

- When the infant sucks on the breast with the tube in mouth, the milk from the cup is sucked up through the tube and taken by the infant.

- The cup/katori is placed **at least 10 cm below** the level of the breast so the milk does not flow too quickly and distress the infant.

choice. For infants without edema if EBM is not available, commercial infant formula or diluted F-100 (volume of 100mL diluted to 135mL by adding 35mL of plain water) or F-75 is given. This recommendation is based on possible adverse effect of high solute load on infant kidney.[12] However, there are no studies that examined feeding approach in the transition and rehabilitation phase of treatment of SAM less than 6 months. Once child is on SST, infant weight should be monitored and gradually stopped after satisfactory weight gain (Fig.1).[13] Infants with SAM and edema should be given infant formula or F-75 in a situation where breast milk is not available.

(b)Feeding of infants without prospects of breastfeeding: One of the biggest challenges is how to support infants who have no option to be breastfed. If there are no realistic prospects of being breastfed, they should be given appropriate and adequate replacement feeds. WHO recommends different formulation of F-75 (75 kcal/100mL) during initiation of treatment /stabilization phase and therapeutic F-100 diluted during transition and rehabilitation phase by cup (Table II). Indications for nasogastric feeding, routine supplements and treatment of complications are similar to those for older children.

Feeding of infants who do not require inpatient care or whose caregivers decline for admission

The mother or the other caregiver must be counselled and supported for optimal infant and young child feeding, based on general recommendations for feeding infants and young children, including for low-birth-weight infants.[14] It is important to monitor weight gain weekly to observe

Table I. Amounts of EBM/F100 diluted for infants put on SST

Class of Weight (kg)	Total mL of EBM/F100 diluted	Quantity of EBM/F100 diluted (F-100 D) per feed in mL (8 feeds/day)
>=1.2	200	25
1.3 to 1.5	240	30
1.6 – 1.7	280	35
1.8 - 2.1	320	40
2.2 – 2.4	360	45
2.5 – 2.7	400	50
2.8 – 2.9	440	55
3.0 – 3.4	480	60
3.5 – 3.9	520	65
4.0 – 4.4	560	70

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│              Starting quantity of milk for SST as per Table I  │
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│  Weight Gain at 20 g per day irrespective of admission weight │
│                    for 3 consecutive days                     │
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                              ▼
┌──────────────────┐   ┌──────────────────┐   ┌──────────────────┐
│ Weight gain 10 g │◄──│  Milk quantity   │──►│ Weight gain not  │
│ per day          │   │     halved       │   │   maintained     │
│ irrespective of  │   │                  │   │                  │
│ actual weight    │   │                  │   │                  │
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         │                                              │
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┌──────────────────┐                   ┌──────────────────────────┐
│    Stop SST      │                   │ Continue SST with 75% of │
│                  │◄──────────────────│ starting quantity of milk│
└──────────────────┘                   └──────────────────────────┘
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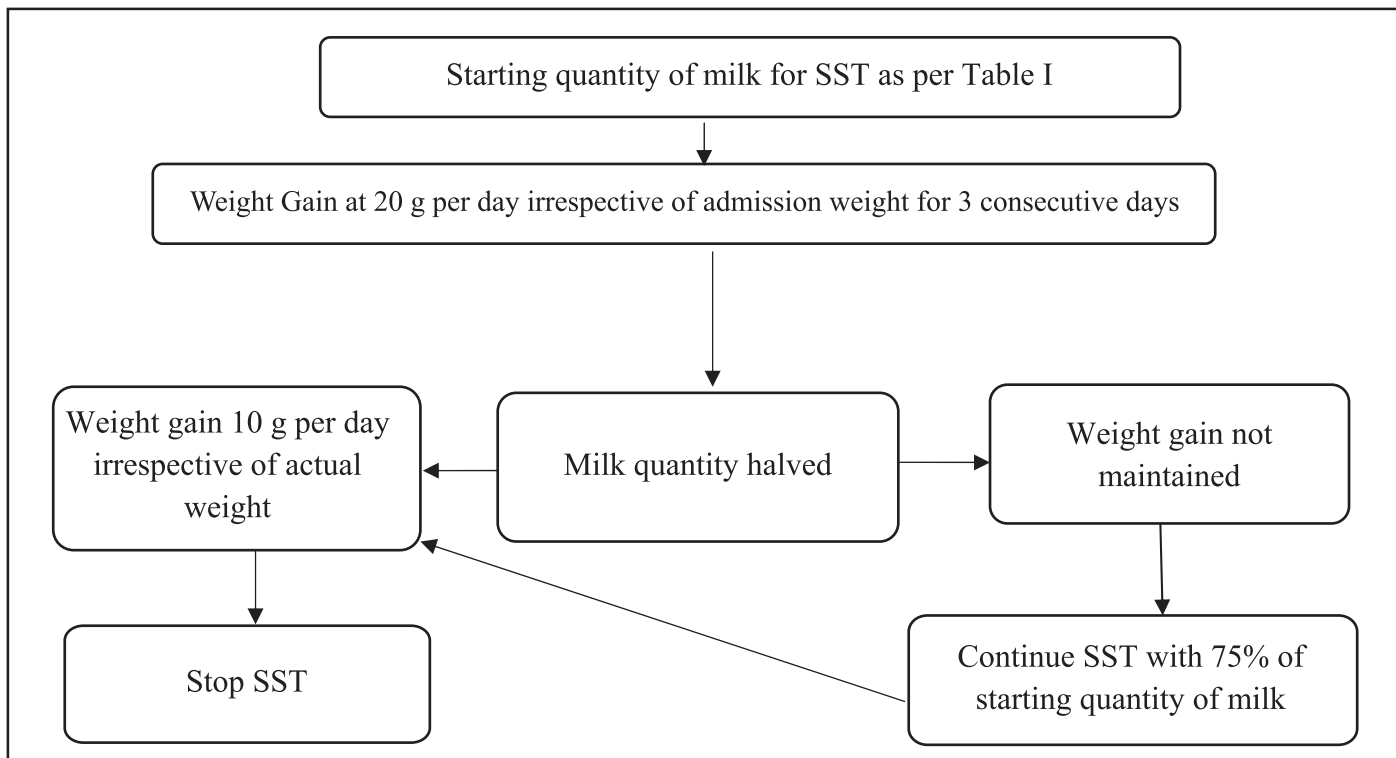
Fig.1. Decision flow for infants <6 months on supplementary suckling technique

Table II. Amount of feed to be offered to infants without prospects of breastfeeds

Class of Weight (in kg)	Stabilization Phase F-75 (Non cereal) in mL	Transition Phase F-100 D in mL	Rehabilitation Phase F-100 D in mL
≤1.5	30	30	40 - 50
1.6- 1.8	35	35	45 - 60
1.9- 2.1	40	40	50 - 70
2.2- 2.4	45	45	60 - 80
2.5- 2.7	50	50	70 - 90
2.8- 2.9	55	55	80 -100
3.0- 3.4	60	60	90 -110
3.5- 3.9	65	65	100 -120
4.0- 4.4	70	70	110 - 130
4.5-4.9	80	80	120 - 140

changes. The infant should be referred to inpatient care in case of weight loss or static weight while the mother or caregiver is receiving support for breastfeeding, it is recommended that assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided.

Sensory stimulation

Due to lack of interaction and play, children with SAM may have delayed mental and behavioral development. Play therapy is intended to develop language and motor skills aided by simple, inexpensive toys made with commonly

available household objects. It should take place in a loving, relaxed and stimulating environment. Physical activity should be stimulated as soon as the child improves.

Heath education of mothers

All mothers should be educated about feeding and infant care practices before discharge. They should be motivated and supported so that they can sustain exclusive breastfeeding till six months of age. Mothers should be counselled also, to start appropriate complementary foods when the baby completes 180 days of life, the importance of timely immunization and care during common illnesses.

Discharge criteria in infants less than 6 months

WHO 2013 guidelines suggest that infants who have been admitted to inpatient care can be transferred to outpatient care when:

a. all clinical conditions or medical complications, including edema, are resolved, 5

b. the infant has good appetite, is clinically well and alert,

c. weight gain on either exclusive breastfeeding or replacement feeding is satisfactory, more than 5g/kg/day for at least 3 successive days,

d. the infant has been checked for immunizations and other routine interventions,

e. the mothers or caregivers are linked with needed community-based follow-up and support.

Discharge criteria from all care when infants show:

a. breastfeeding effectively or are feeding well with replacement feeds,

b. adequate weight gain of 15-20% after edema disappears,

c. weight-for-length $\geq$ 1SD.

Conclusions

Treating malnourished infants less than 6 months of age is important to avoid malnutrition-associated morbidity and mortality in the short term and to improve health and development in the long term. Scientific evidence for recommendations is weak. Focus of treatment is on establishing and sustaining exclusive breastfeeding during first six months.

Points to Remember

- *Severe acute malnutrition (SAM) is increasingly being recognized in infants who are less than 6 months of age.*

- *Infants less than 6 months with SAM are identified by their W/L $\leq$ - 3SD score and or presence of bilateral pitting edema. MUAC cut off is not well defined for this age group.*

- *Basic principles of management (Ten steps) remain same as for more than 6 months old age, however focus is on establishing exclusive breastfeeding unless there is no prospect of breastfeeding.*

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CLIPPINGS

Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians.

Zika virus infection can be prenatally passed from a pregnant woman to her fetus. There is sufficient evidence to conclude that intrauterine Zika virus infection is a cause of microcephaly and serious brain anomalies, but the full spectrum of anomalies has not been delineated.

A comprehensive search of the English literature using Medline and EMBASE for Zika from inception through September 30, 2016 was done. Congenital anomalies were considered in the context of the presumed pathogenetic mechanism related to the neurotropic properties of the virus. Congenital Zika syndrome has a recognizable pattern of structural anomalies and functional disabilities secondary to central and, perhaps, peripheral nervous system damage. Although many of the components of this syndrome, such as cognitive, sensory, and motor disabilities, are shared by other congenital infections, there are 5 features that are rarely seen with other congenital infections or are unique to congenital Zika virus infection: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia and symptoms of extrapyramidal involvement.

Although the full spectrum of adverse reproductive outcomes caused by Zika virus infection is not yet determined, a distinctive phenotype—the congenital Zika syndrome—has emerged. Recognition of this phenotype by clinicians for infants and children can help ensure appropriate etiologic evaluation and comprehensive clinical investigation to define the range of anomalies in an affected infant as well as determine essential follow-up and ongoing care.

Moore CA, Staples JE, Dobyns WB, Pessoa A, Ventura CV, Borges da Fonseca E, et al.Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. JAMA Pediatr. doi:10.1001/jamapediatrics.2016.3982 Published online November 3, 2016.

NEWS AND NOTES

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<div style="text-align:center">**DRUG PROFILE**</div>

VITAMINS AND MINERALS SUPPLEMENTATION IN PEDIATRICS

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Abstract: *Deficiency of vitamins and minerals is common in children in India. Pediatricians tend to use vitamin and mineral supplement empirically and these medications are available over the counter without prescription. There are no definite guidelines regarding the dose of many of the vitamins required and different preparations come with different composition which makes it difficult to standardise. This article reviews the evidence for use of vitamins and minerals in children, a survey of preparations available in the Indian market and their relevance in regular supplementation.*

Keywords: *Multivitamins, Minerals, RDA*

Vitamins and minerals are essential for the survival of every cell in the human body. Evidence suggests that they have definite biochemical roles, especially as co-factors for various enzymes and as integral ingredients of bone and blood. Lack of vitamins could cause deficiency diseases, such as scurvy, rickets and anemia; chronic conditions of the cardiovascular and ocular systems; and poor immune function. Dietary requirements of vitamins and minerals may be obtained from a balanced diet. It is difficult to exactly the Indian diet calculate the vitamin and mineral content in due to the cultural diversity and varied geographical factors in different parts of the country. However, the Indian diet largely comprises of cereals, pulses, vegetables, fats, milk and milk products that offer all essential nutrients required for proper growth and development. Yet, more than 50% of the Indian population is under nourished. In fact, India ranks number one in terms of low birth weight (BW) infants at an estimated 7.4 million

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LBW babies born every year. While nutritional deficiencies prevail in rural areas, changes in lifestyle and the dramatic shift to unhealthy eating habits and physical inactivity have caused nutritional deficiencies to spread like an epidemic in urban areas as well. Even after sixty six years of independence, India has still to battle against these top seven nutritional deficiencies namely, iron, vitamin D, calcium, vitamin B complex, zinc, vitamin A and iodine.[1,2] UNICEF has estimated that India has 1/3rd of global 2 billion people suffering from vitamin and micronutrient deficiency.[3] The recommended dietary allowance (RDA) by Indian council of Medical Research (ICMR) is given in Table I.

Iron

Many surveys estimate iron deficiency anemia as a major public health problem in India. Low intake - half of recommended dietary allowance (RDA) and poor bioavailability of iron due to presence of phytates and low ascorbic acid/iron ratios in Indian diets have been identified as probable causes[5]. Inadequate intake of vitamins and infections also contribute to iron deficiency.

According to National Family Health Survey (NFHS) III data, the prevalence of anemia among children less than five years of age is around 70%; largely believed to be due to iron deficiency.[6]

Oral iron medication:[7] Bivalent ferrous iron (e.g. ferrous sulphate, ferrous gluconate, ferrous ascorbate, ferrous lactate, ferrous succinate and ferrous fumarate) is preferred over ferric iron which has poor oral bioavailability. Heme iron is better absorbed than ferrous, which is better absorbed than ferric iron. Avoid administration of iron with meals, tea, milk and calcium which interfere with absorption.

Dose: 3 mg/kg/day of elemental iron in 2 divided doses, to be taken on an empty stomach. Duration: 6-8 weeks after hemoglobin level is restored to normal.

Newer preparations include iron amino acid conjugates (ferrous bisglycinate, ferrous trisglycinate and ferrous glycine sulphate) and carbonyl iron that do not alter the colour and taste of the food and have high oral bioavailability even in the presence of dietary inhibitors.

Table I. RDA of vitamins and minerals for Indian children[4]

Group	Age	Ca mg/d	Fe mg/d	Mg mg/d	Zn mg/d	Vit. A mcg/d		B1 mg/d	B2 mg/d	B3 mg/d	B6 mg/d	Vit.C mg/d	Folate mcg/d	B12 mcg/d
						Retinol	B carotene							
Infants	0-6mo	500	46mcg/kg/d	30	---	350	2800	0.2	0.3	710 mcg/kg	0.1	25	25	0.2
	6-12mo		5	45	---			0.3	0.4	650 mcg/kg	0.4			
Children	1-3y	600	9	50	5	400	3200	0.5	0.6	8	0.9	40	80	0.2-1
	4-6y		13	70	7			0.7	0.8	11	0.9		100	
	7-9y		16	100	8	600	4800	0.8	1.0	13	1.6		120	
Boys	10-12y	800	21	120	9	600	4800	1.1	1.3	15	1.6	40	140	0.2-1
Girls	10-12y	800	27	160	9			1.0	1.2	13	1.6			
Boys	13-15y	800	32	165	11			1.4	1.6	16	2.0	40	150	0.2-1
Girls	13-15y	800	27	210	11			1.2	1.4	14	2.0			
Boys	16-17y	800	28	195	12			1.5	1.8	17	2.0	40	200	0.2-1
Girls	16-17y	800	26	35	12			1.0	1.2	14	2.0			

Carbonyl iron is a small particle preparation (<5 microns) of highly purified metallic iron produced from pentacarbonyl gas. It does not alter the taste or colour of food and undergoes slow and sustained absorption. It is available in the form of 100 mg capsules. Treatment is monitored by peak reticulocyte count on days 5-10 following initiation of therapy.

Parenteral therapy: Iron dextran complex (injection) contains 50 mg/mL of elemental iron. The indications for parenteral therapy includes: a) noncompliance with oral administration of iron, b) severe bowel disease (e.g. inflammatory bowel disease) as use of oral iron might aggravate the underlying disease of the gut, c) chronic hemorrhage (e.g. hereditary telangiectasia, menorrhagia, chronic hemoglobinuria from prosthetic valves), d) acute diarrheal disorder in underprivileged populations with iron deficiency anaemia.[8]

Dose:[7] Hb deficit 0.0476 + 1mL/5kg. Max: <5kg= 25mg, 5-10 kg=50 mg, >10 kg= 100mg. Or it may be given as 4 x wt. in kg x Hb deficit. Blood transfusion: Packed red cell transfusion is (10ml/kg/transfusion) reserved for debilitated children with infection, especially if cardiac dysfunction is present and the hemoglobin level is 4g/dL or less.

Partial exchange transfusion if anemia is associated with cardiac failure, in which case it may be sufficient to raise the hemoglobin to 4-5mg/dL to correct immediate anoxia. The usual formula to give packed cells in such a situation is to multiply the actual Hb by two and this will give the amount of packed cells in mL to be given per Kg of body weight.

Vitamin D

It has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.[9] Though majority of population in India live in areas receiving ample sunlight throughout the year, vitamin D deficiency is very common in all age groups and both sexes across the country.[10,11] Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70%-100% in the general population.[12]

Treatment is necessary for all individuals with deficiency whether symptomatic or not consists of vitamin D supplementation as Stoss therapy (single IM injection

of 6 lakh units) or daily or weekly oral regimens with equal efficacy and safety, combined with calcium supplements.[13] Routine supplementation starting from new-born period is being increasingly endorsed.[14] Prevention by sensible sunlight exposure, food fortification and routine supplementation are the currently available options for tackling this nutritional deficiency.

Vitamin D in therapeutics for 1. Rickets 2. Intestinal malabsorption 3. Hyperparathyroidism[15]

Dosage: Oral < 6 month 3000 units, 6 month - 12 year 6000 units and 12-18 year 10,000 units as single dose.

In renal insufficiency, all patients receiving pharmacological doses of vitamin D should have their plasma calcium concentration checked regularly and when nausea and vomiting are present.

Overdose

Excessive doses may give rise to anorexia, nausea, vomiting, diarrhea, loss of weight, headache, polyuria, thirst and vertigo. If hypervitaminosis occurs discontinue treatment with ergocalciferol, reduce dietary calcium intake and correct dehydration and electrolyte disturbance. Hypercalcemia may be corrected by the administration of hydrocortisone or calcitonin.

Drug interactions: Ergocalciferol is inactivated, probably through enzyme systems, by the long term administration of anticonvulsants.

Calcium

Calcium deficiency is not uncommon in Indian children.[16] Daily calcium intake in India, both the reality and the recommendations, are far lower than the Western data.[17] Children usually tolerate calcium supplements with citrates and maleate better than calcium carbonate. However, any inexpensive calcium supplement that the child tolerates will do. Approximately, 40% of any calcium supplement is the elemental calcium. Calcium citrate: 21% elemental calcium; best absorbed form of calcium supplement, does not require gastric acidity for absorption (can be given without food). Calcium carbonate: 40% elemental calcium, requires gastric acid for absorption, has to be given with food.

B complex

Vitamin B complex consists of eight water soluble vitamins that have important role in metabolism in the body. It includes vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (Niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), folic acid and vitamin B12.

Thiamine

Thiamine strengthens the immune system and improves the body's ability to withstand stressful conditions. In children, the overall clinical picture of thiamine deficiency is not easy to recognize, mimicking or being confused with other diseases. Not surprisingly, the likelihood of this condition not being recognised is even greater in resource-limited settings.[18] Despite being easily treatable, thiamine deficiency continues to be seen in all age groups in both developed and underdeveloped countries with potentially severe and life-threatening consequences.[20, 21] A high level of clinical suspicion in the following situations should help in diagnosis: suspicion of infantile beriberi; unexplained neurological signs, encephalitis and cardiac failure; early clinical deterioration after initiation of feeds in malnutrition; sepsis (including in severe acute malnutrition - SAM) severe burns; major trauma; hypoxia; and lactic acidosis unresponsive despite correction of shock. However, in the absence of specific diagnostic tests, the only way to diagnose thiamine deficiency is to demonstrate a rapid clinical improvement (within hours or days) of a therapeutic slow IV thiamine challenge given over 30 min. Evidence-based pediatric thiamine dosage recommendations for severe acute illness are lacking. Doses found in this literature vary from 50 to 1500mg depending on the clinical condition, with neurological presentations potentially requiring higher doses and having a longer recovery time (a few days). Prevention of thiamine deficiency during the early refeeding phase in complicated SAM initially requires 10-30mg of thiamine daily followed by 5-10mg daily for a month.[22] Thiamine supplementation has been effective in populations with high prevalence of thiamine deficiency.[23] Daily requirement ranges from 2-8 mg in children less than 8 years and 12-14 mg in older children. No known toxicity is known with high dose of vitamin B1.

Other B complex vitamins

Folic acid or vitamin B-12 supplementation did not reduce the burden of common childhood infections[24] but seems to improve gross motor and problem solving functioning.[25] Supplementation of folic acid and vitamin B12 may be required during induction chemotherapy in children with acute lymphoblastic leukemia.[26] The reports of increasing recognition of megaloblastic anemia in India due to deficiency of folic acid and vitamin B12 also need consideration when reviewing the need for supplementation of these vitamins, particularly in those high risk populations.[27] Persistence of biochemical riboflavin deficiency in rural Indian children despite adequate dietary intake in the 80's suggested that the exact requirement of

Table II. Comparison of constituents in some commonly used vitamins

Product	B1 (mg)	B2	B3 (mg)	B5 (mg)	B6 (mg)	B12 (mcg)	A (IU)	C (mg)	D (IU)	E (IU)	Ca (mg)	I (mcg)	Zn (mg)
Abidec	0.7	-	9	3	1	-	1320	60	100	7.4	-	-	-
A to Z	2.25	2.5	22.5	2.5	1	2.5	2500	40	200	7.5	1.25	50	1
Vi syneral	2	1	15	2.5	1	1	2500	50	200	-	-	-	5
Zincovit	0.75	0.75	7.5	1.25	0.6	0.5	1250	-	100	2.5	-38	5	
Polybion SF	2	2.5	15	3	0.75	2	-	-	-	-	-	-	-
Becosules	2	2.5	20	6	2	-	-	75	-	-	-	-	-

communities living in unfavourable environmental conditions is yet to be determined. However, there are no recent reports of riboflavin deficiency as public health problem in India. There is little data on deficiency of the remaining B complex vitamins.

Vitamin K

Vitamin K is another essential fat soluble vitamin which plays a pivotal role in blood clotting. It is important to supplement vitamin K in new-borns especially who are exclusively breast fed. Conditions requiring vitamin K administration include, hemorrhagic disease of newborn, malabsorption syndrome, cystic fibrosis, biliary atresia, hepatic failure and as antidote to anticoagulant drug.

Dose in prophylaxis: In all newborn term babies 1mg IM and 0.5 mg IM for preterm (birth weight <1500 grams). It may be given to patients on long-term broad-spectrum antibiotics. Oral dose is 5mg daily.[28]

Zinc (sulphate, acetate or gluconate)

Zinc (Zn) is an essential metallic element for animal and human health as it is important for epithelial regeneration. Zinc is conceptually essential to reduce childhood illness especially infections, enhance physical growth and decrease morbidity and mortality in children.[29] Symptoms attributable to severe zinc depletion include growth failure, primary hypogonadism, skin disease, impaired taste and smell, and impaired immunity and resistance to infection. In developing countries, supplementation with Zinc was found to lower frequency and severity of infections like diarrhea and pneumonia and reduce mortality. It is estimated that globally 2 billion people are at risk of zinc deficiency.[30] Adequate zinc was shown to increase linear growth and weight gain in stunted

and underweight young age Indian children.[31] In fact, WHO recommends zinc supplementation during diarrheal infection and for treatment of severe malnutrition.[32] Zinc is a component of many multivitamins and iron syrup.

Uses:[33]

1. Acute diarrhea: Along with ORS, zinc is the mainstay of treatment and this is the most important indication for its use. Zinc supplementation in diarrheal disease is an intervention that could reduce morbidity due to this killer disease as it not only reduces severity and duration of episodes but also reduces incidence of new episodes in the 2-3months following the full course

2. Acrodermatitis enteropathica

3. Wilson disease

4. Zinc deficiency

Dosage: As zinc base. Acute watery diarrhea - <6months 10mg/day as single dose, >6months 20mg/day as single dose for 14 days. Acrodermatitis enteropathica - Oral 0.5mg - 1mg/kg/dose twice daily. Wilson disease - Oral 2-12 years 25-37.5mg/dose 12-18yr 50mg/dose 2-4 times daily. Do not give at the same time as penicillamine. Zinc deficiency - Oral therapy: newborn 1mg/kg once daily, 10 - 30kg 22.5mg once or twice daily. More than 30kg, 45mg 1-3 times daily. Adjust according to response. Oral: Take 1 hour after food, dissolved in water. The tablet may be dissolved in breast milk, ORS or water.

Vitamin A

Though Vitamin A supplementation program is being aggressively implemented in India, a recent Cochrane review suggests that there is no convincing evidence that

either maternal postpartum or infant vitamin A supplementation results in a reduction in infant mortality or morbidity in low and middle income countries.[34]

Recommended daily allowance is as follows.

Infants: 300-400mcg

Children: 400-600mcg

Adolescents: 750mcg

1mcg Retinol=3.3IU of vitamin A

Dosage for treatment of vitamin A deficiency: Oral <6 months of age 50,000 IU; 6-12 months 100,000

IU, >1year 200,000 IU. The same dose is repeated next day and 4 weeks later.

National program: Prophylaxis of vitamin A deficiency 1 lakh IU at 9months with measles vaccine, 2 lakh IV at 16-18 months with DPT booster and after that 2 lakh IV every 6 months upto 5 years of age.

Dose in measles and malnutrition:

<1 year: 100,000 IU and >1 year: 200,000 IU

Iodine

Iodine is a trace element that is essential for skeletal growth and neurodevelopment, mainly as it forms an essential component of thyroid hormones thyroxine (T4) and triiodothyronine (T3). Iodine is naturally present in some foods, added to others and available as a dietary supplement. Inadequate thyroid hormone production due to iodine deficiency leads to multiple adverse effects on growth and development, and is the most common cause of preventable mental retardation in the world.

The RDA for iodine is as follows[35]

<6 years: 90mg

6-12 years: 120mg

>12 years: 150mg

Dosage: Thyrotoxicosis - neonatal - 1 drop 3 times daily Thyrotoxicosis (preoperative) - 0.1 - 0.3 mL 3 times daily.

Indian scenario

Vitamins and their combinations are often self-prescribed by the people and there are no definite guidelines regarding the dose of individual vitamins. There are about 1223 vitamin preparations available in Indian market.[36] They are available as single vitamins (83 brands), combination of 2 or more vitamins (161) or with combinations like minerals (831), antioxidants and other nutritional supplements (148). Majority of them are incorporated with minerals like iron, calcium, etc. There is a huge disparity among the constituents of individual brands and their strengths.

In a large number of products, the amount of the constituents are not clearly specified, which leads to great concern. High and prolonged use of certain vitamins can cause to hypervitaminosis and other systemic manifestations.

Composition of the some of the commonly used multivitamins syrup brands in India (per 5ml) are also compared Table II. Most of the medicines contained various vitamins above the ideal RDA. However, there are no studies to support the assumption that a child could receive vitamins in toxic doses by available vitamin preparations.

Conclusion

Multivitamins and minerals are as essential as the macronutrients for the proper growth and development of children. It should be supplemented as and when required. There should be definite guidelines and standardisation of constituents of medicines so that issues pertaining to both overdose and under dose can be eliminated to a certain extent.

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DERMATOLOGY

CUTANEOUS MANIFESTATIONS OF CONNECTIVE TISSUE DISORDERS

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Abstract: *Connective tissue disorders or collagen vascular disorders are inflammatory disorders of the connective tissue with multisystem involvement. They are characterized by the presence of specific and non-specific cutaneous manifestations. These disorders which may present with vague symptoms like prolonged fever and fatigue, tend to have a chronic course with remissions and exacerbations. Specific dermatological findings pave the way for early diagnosis and prompt treatment. This article focuses on the dermatological manifestations and treatment of the most common rheumatic diseasesof childhood namely lupus erythematosus, systemic sclerosis, dermatomyositis and juvenile idiopathic arthritis.*

Keywords: *Childhood lupus erythematosus, Juvenile systemic sclerosis, Dermatomyositis, Juvenile idiopathic arthritis, Cutaneous manifestations*

Connective tissue disorders or collagen vascular disorders are inflammatory disorders of connective tissue with multisystemic involvement. This group of disorders comprise of systemic lupus erythematosus (SLE), dermatomyositis, localized and systemic forms of scleroderma, juvenile idiopathic arthritis, mixed connective tissue disease, eosinophilic fasciitis, Sjögren syndrome and antiphos-pholipid antibody syndrome which present with specific cutaneous manifestations. Of these disorders, childhood lupus erythematosus is one of the most common systemic autoimmune connective disorders seen in children. This article focuses on the dermatological manifestations and treatment of the most common rheumatic diseases in children namely systemic lupus erythematosus, systemic sclerosis, dermatomyositis and juvenile idiopathic arthritis. [1]

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Juvenile systemic lupus erythematosus (JSLE)

Childhood onsetlupus erythematosusor JSLE is a chronic multisystem autoimmune disorder that occurs as a result of immune dysregulation and formation of auto-antibodies with an onset before 18 years. The course is marked by remissions and relapses.[2] It is more common in native Americans, African Americans and Asians.[3] Worldwide incidence varies between 0.28 to 0.48 per 1,00,000 children per year, while the prevalence ranges from 6.3 to 24 per 1,00,000. In India, a study from north India reports a point prevalence of 3.2 per 1,00,000. About 18 % of patients with SLE present during childhood and adolescence.[1] Onset of this disorder is seen in 5% of children before 5 years, 35% between 5 and 10 years with the majority of about 60% presenting between 11 and 15 years.[4] Mean age of onset has been reported to be lower in Caucasians than non-Caucasians.[5] Sex ratio (girls:boys) before puberty is 4:3, which increases to 4:1 after puberty.[3]

Childhood LE is more severe than the adult form with the involvement of renal and central nervous systems. The American College of Rheumatology (ACR) criteria for classification of SLE includes mucocutaneous lesions such as the malar rash, discoid rash, photosensitivity and oral ulcers as four criteria out of the total eleven. Mucocutaneous lesions may be classified as LE specific lesions associated with classical histological features of LE and non-specific LE lesions without classical histology. Specific LE lesions are categorized into 3 forms namely acute cutaneous lupus erythematosus (ACLE-localized malar rash, generalized erythematous rash), subacute cutaneous lupus erythematosus (SCLE - annular/ polycyclic and psoriasiform) and chronic cutaneous lupus erythematosus (CCLE-localized and generalized discoid LE, lupus profundus, lupus panniculitis, chill blain LE and mucosal LE). SCLE and CCLE lesions may occur less frequently or rarely in childhood LE.[1]

Malar rash

This is the most common specific LE lesion that occurs in 60%–85% of children withLE.[6-10] It presents as symmetrical, erythematous, well defined rash over the malar eminences, sparing the nasolabial folds and may heal with hypo or hyperpigmentation. Sometimes, diffuse

erythematous rash may occur over the sunlight non-exposed areas of the body. Presence of these two lesions indicates the presence of systemic disease activity in JSLE.

Discoid rash

This is characterized by the presence of erythematous, well defined plaques with adherent scales, telangiectasia, follicular plugging and scarring. Removal of the adherent scale will exhibit the follicular projections that resemble the carpet tacks. This is termed as the 'Carpet tacks sign' which is considered to be characteristic of discoid LE. SCLE lesions which are less common in JLE, present as erythematous, annular, polycyclic or psoriasiform lesions with easily detachable scales predominantly over the upper trunk, extensor aspect of arms and dorsum of hands. These lesions heal without scarring. Involvement of the lower extremities is more common in children than adults.[1,4,6]

Photosensitivity

Photosensitivity occurs with history of burning sensation over the lesions on exposure to sunlight. Erythema will be accentuated after sun exposure. This photosensitive rash occurs on the face, neckline and upper arms.

Painless oral ulcers

These are seen on the hard palate, which begin as erythematous patches are characteristic features of SLE. Other mucosal lesions that may present are painful ulcers on the buccal mucosa and lips, erosions, gingivitis and mucosal hemorrhages. Presence of oral ulcers signifies the active phase of the disease in JSLE.

Hair loss

Hair loss in JSLE may present as diffuse non-scarring alopecia, lupus hair (thin, fragile, unruly broken hair), scarring alopecia, telogen effluvium or alopecia areata.[4,6,8]

Non-specific LE lesions

These include Raynaud's phenomenon, livedo reticularis, telangiectasia of the palms and fingers, linear telangiectasia of the cuticles and periungual skin, calcinosis cutis, acanthosis nigricans and urticarial vasculitis. Livedo reticularis presents as persistent erythema in a reticulate pattern which is exacerbated by exposure to cold.[1,4,6] This is more often seen on the lower extremities. In a study done at a pediatric dermatology referral centre, US, 38 children were found to have childhood LE (CLE) and 15 had neonatal LE out of the 53 children enrolled. Out of the 38 children with CLE, 13 had ACLE, 6 had SCLE and 17 had CCLE. Non-specific LE lesions such as small vessel vasculitis, Degos like vasculopathy, periungual telangiectasia, livedo reticularis, Raynaud's phenomenon, nonscarring alopecia, urticaria, erythema multiforme and bullous SLE were present in 15 children.[9]

Neonatal lupus erythematosus (NLE)

NLE occurs in babies born to mothers with LE or who have a tendency to develop systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome or undifferentiated connective tissue disorder due to the placental transfer of maternal anti Anti-Sjögren's-syndrome-related antigen A (SSA/Ro) and anti Sjögren syndrome type B antigen/ Lupus La protein (SSB/La) IgG antibodies. These mothers are found to have anti-Ro antibodies, anti-La or anti–U1 ribonucleoprotein (U_1RNP) antibodies. About 23% of the babies with NLE present at birth with mostly cardiac manifestations and occasionally cutaneous lesions. Onset of skin lesions may start within the first few weeks of life. Characteristic dermatological features are erythematous macules or patches and annular plaques over the scalp, face, neck and extensor aspects of the arms. Rarely lesions may occur on the palms, soles and vulva. Periorbital erythema termed as Raccoon eyes,owl eyes or eye mask is considered characteristic of NLE. Sometimes, discoid rash, scaly atrophic macules/patches, telangiectasia and petechiae, may also be present. Lesions may heal by 6-12 months of age coinciding with the waning of maternal antibodies mostly without scarring, but may leave a transient hypo or hyperpigmentation, telangiectasia, atrophy or scarring.[2,4,6,7]

Drug induced LE

Drug induced LE is less common in children compared to adults. Drugs that could trigger LE are minocycline, INH, hydralazine, procainamide and tumour necrosis factor alpha (TNFα) TNF alpha antagonists. Classical cutaneous lesions of LE such as malar/discoid rash, mucosal lesions as well asRaynaud's phenomenon are conspicuous by their absence. Instead, patients present with photosensitivity, palpable purpura, urticaria, urticarial vasculitis, bullae, ulcers and erythema nodosum. However, malar or discoid rash may occur in LE induced by TNF alpha antagonists. Drugs like NSAID, griseofulvin and terbinafine could cause SCLE which differs from the classic picture by the presence of the lesions on the legs. Drug induced LE is characterized by increased titres of antihistone antibodies.[6]

Treatment

The most important step in the management of cutaneous lesions in LE is sun protection which could be

achieved by the use of broad spectrum sunscreens, protective clothing, wide brimmed hats and umbrellas. Topical corticosteroids and topical immunomodulators such as tacrolimus and pimecrolimus are effective in the treatment of localized lesions. Oral hydroxychloroquine has been found to be useful in the prevention of flares. Extensive lesions with multisystem involvement could be managed by the use of systemic corticosteroids, azathioprine, cyclophosphamide and mycophenolate mofetil.[4,5]

Juvenile systemic sclerosis

Juvenile systemic sclerosis (JSSc), earlier known as progressive systemic sclerosis in children or scleroderma is a chronic connective disease characterized by fibrosis of the skin and multiple internal organs, in children aged 16 years or younger. It is rare in childhood, accounting for about 10% of all patients with systemic sclerosis.[2] JSSc is more common in females with a female: male sex ratio of 2.1-10.5:1.[6] A study from Lucknow reported an incidence of JSSc as 9% with a female preponderance of 82% giving a female to male sex ratio of 4.75:1.[11] Scleroderma is classified as localized scleroderma (which encompasses localized morphea, linear morphea, circumscribed morphea, generalized and pansclerotic morphea), systemic scleroderma and overlap syndromes. Localized scleroderma which is characterized by absence of involvement of internal organs, is10 times more common than systemic scleroderma in children.[12] Systemic scleroderma (SSc) is classified as diffuse cutaneous systemic sclerosis and limited cutaneous systemic sclerosis, with the diffuse disease being more common than the limited type in children.[13] Another study reported 60.9% of patients with diffuse SSc and 39.1% with limited SSc.[11]

Diffuse cutaneous SSc

This is characterized by rapidly progressive, widespread thickening of the skin spreading to the elbows and knees, associated with early visceral involvement of lungs, heart and kidney.

Limited cutaneous SSc

This presents with non-progressive skin thickening restricted to distal extremities associated with late visceral disease (pulmonary hypertension, malabsorption).

Diagnostic criteria for JSSc include one major criteria and 2 out of the 20 minor criteria pertaining to various systems such as skin, vascular, cardiac, respiratory, gastrointestinal, neurologic, musculoskeletal, and serologic evidence.Major criteria is sclerosis/induration of skin proximal to metacarpal or metatarsal phalangeal joints. Minor criteria with regard to skin and vascular system are sclerodactyly, Raynaud's phenomenon, nailfold capillary abnormalities and digital tip ulcers.[2,14,15]

Cutaneous lesions

In JSSc, cutaneous lesions have an insidious onset and hence, there is often a delay in the diagnosis. Edema which is the earliest cutaneous manifestation may be present before the onset or along with induration of skin before the sclerosis. About one third of children with JSSc present with edema in association with arthralgia and myositis. Induration of the skin begins in the distal extremities and then progresses to the proximal part of the extremities, trunk and the face. Skin becomes thickened, shiny, tightly bound to the underlying structures and is not pinchable. Distal tapering of the fingers termed as sclerodactyly with painful restriction of movements may occur. Characteristic features of face involvement that result due to the tight skin are absence of forehead creases resulting in expressionless face, pinched nose, small mouth, pursed lips and prominent teeth. Hypopigmentation and hyperpigmentation occur giving rise to the typical 'salt and pepper appearance' in skin. Sometimes, calcification and fingertip ulceration are seen.[4,6,16]

Vascular lesions

Raynaud's phenomenon,a vasospastic response which occurs in 75% of patients with JSSc is precipitated by cold and emotional stress.[6,13,16,17] It is characterized by pallor, cyanosis and hyperemia of the fingers or toes and may be associated with swelling, pain, tingling or burning sensation. Rarely, Raynaud's phenomenon may also affect the ears, nose, cheeks and lips. An Indian study observed Raynaud's phenomenon in 83% of children with JSSc.[11]

Nailfold abnormalities

These are seen in 74% and digital ulcers in 65% of children with JSSc.[18]Nailfold capillary abnormalities which are due to the endothelial cell damage, can be observed after placing a drop of mineral oil on the nailfold, using a dermatoscope, opthalmoscope or otoscope. Dilated, giant capillary loops and avascular areas are considered to be the characteristic patterns in systemic sclerosis. Other patterns that have been reported are megacapillaries, drop outs, irregular loops, hemorrhages, tortuosities and arborization.[6,15,19]

Treatment

Early diagnosis and prompt effective treatment will help to reduce the morbidity. Care must be taken to avoid

trauma, exposure to cold weather and other factors that may produce vasospasm such as stress, tension, fatigue and smoking. Regular use of emollients is advocated. Ulcers have to be attended to at the earliest on a daily basis. Nifedepine and pentoxifylline are used to treat Raynaud's phenomenon. Methotrexate, mycophenolate mofetil and cyclophosphamide have been found to be useful in the treatment of extensive lesions.

Juvenile dermatomyositis

Juvenile dermatomyositis(JDM) is a rare childhood, chronic, idiopathic, autoimmune, inflammatory vasculopathic disorder, which mainly affects the skin and muscle, but may also affect the joints, heart, lungs, gut and other systems. It is the most common idiopathic inflammatory myopathy that occur in children and adolescents. Incidence has been reported as 3.2/ million children in the western literature. JDM is more common in females with a sex ratio of 2.3:1 and a mean age of onset of 7 years. It is estimated that about 25% of all patients with dermatomyositis present before 18 years, while 18% of them, have their onset before 4 years.[4,6]

Diagnostic criteria defined by Bohan and Peter in 1975, which is still widely used includes the presence of characteristic cutaneous findings (Gottron's papules, heliotrope rash)combined with symmetric proximal muscle weakness, raised serum muscle enzymes (creatine kinase, lactate dehydrogenase, transaminase and aldolase), muscle biopsy evidence of myositis and necrosis and evidence of myopathy on electromyography (EMG). A definitive diagnosis of JDM is made based on the presence of typical skin lesions and 3 of the above mentioned criteria. A probable diagnosis of JDM is considered with the presence of the rash and 2 of the above criteria.[6,20,21]

Cutaneous manifestations

In JDM approximately 50% of the children with JDM present with an insidious onset of skin lesions, weakness, fatigue and abdominal pain, while about 30% have a fulminant onset associated with fever, profound weakness and systemic involvement. Dermatomyositis sine myositis or amyopathic dermatomyositis, a clinical variant of dermatomyositis characterized by the presence of cutaneous manifestations in the absence of clinical signs of muscle involvement, is rare in children.[21] JDM differs from adult dermatomyositis in that there is an increased incidence of calcinosis and less risk of malignancy.[22,23] Approximately 75% of children with JDM present with cutaneous manifestations during the initial visit.[2,6] Skin lesions that occur in JDM are the characteristic

heliotrope rash, Gottron's papules, periungual erythema, nailfold capillary abnormalities, calcinosis, malar rash, vasculitic ulcers, lipodystrophy, oral ulcers, poikiloderma and limb edema. In a study from Melbourne Gottron's papules were observed in 91%, malar rash in 79%, heliotrope rash in 73%, nailfold changes in 68% and poikiloderma in 53% of children with JDM at the initial presentation.[24]

Heliotrope rash is pathognomonic of JDM, occurs as a pink to violet or purplish rash over the upper eyelids. This rash may be associated with skin induration and edema of the face involving especially the periorbital area and cheeks. Less often, edema of the extremities and trunk may occur. Anasarca when present is an indicator of severe disease activity. Erythema may also occur over the forehead, temples, ears and cheek. Malar rash in JDE which is not well delineated as in SLE, may involve the nasolabial folds. Presence of violaceous, telangiectatic erythema associated with fine scaling over the nape of neck, scalp hairline, extensor aspects of shoulders and arms, elbows, knees and knuckles is known as 'Gottron's sign'. **'Shawl sign'** refers to the presence of erythema over the shoulders, 'v' area of the neckand upper portion of the chest wall. Sun exposure has been reported to trigger the onset of lesions and exacerbate the existing skin lesions. Photosensitivity has been reported in about 50% of the patients. Linear, erythematous lesions may be seen over the extensor surfaces of the extremities. Symmetrical, erythematous, shiny, scaly plaques and papules that mainly occur over the proximal interphalangeal joints and less often over the metacarpophalangeal and distal interphalangeal joints are known as Gottron's papules, which are one of the characteristic manifestations of DM. Other sites that may be involved are elbows, knees and malleoli. Sometimes, these lesions may become crusted and ulcerated. Painful oral ulcers over the gingiva and buccal mucosa and sometimes, throughout the gastrointestinal tract may occur.Patients may present with scarring or non-scarring alopecia.[2,4,6,21,25]

Vasculopathy

This is an important feature of JDM. Periungual erythema and nailfold capillary abnormalities have been observed in 50% to 100% of children with JDM. Capillary nailfold abnormalities such as dilated loops, hemorrhages, drop outs, tortuosity, bushy capillaries, arborized clusters of giant capillary loops and thrombosis, though not specific only to JDM, are considered to be characteristically present in JDM. Though these changes may be visualized by naked eye examination, they are best observed with dermoscope,

opthalmoscope or otoscope. Periungual erythema, hyperkeratotic and ragged cuticles are typically seen, the latter being considered to denote active disease. Nailfold abnormalities signify the long duration of symptoms before treatment, chronicity, severity, calcinosis and cutaneous ulceration. Other manifestations of vasculopathy include livedo reticularis, cutaneous vasculitic ulcers, capillary dilatation and erythema over the gingiva. Cutaneous ulcers have been reported in about 30% of patients and are associated with poor prognosis. Lesions may occur over the extensor surfaces, elbows, pressure points, outer canthi of the eyes, axillae and stretch marks.[2,4,6,21]

Calcinosis cutis

This occurs in 12% to 43% of patients with JDM, usually occurs 1-3 years after the onset, but may occur at the time of initial presentation. A study from Mumbai reported calcinosis in 18.1% of patients, while another study from north Indiaobserved 27.3% of patients to have calcinosis.[26,27] Four forms have been described namely cutaneous or subcutaneous plaques and nodules, deep tumoral deposits in the muscles, calcinosis along the fascial planes and the severe, reticular exoskeleton like deposits. Calcinosis commonly occurs at sites which are more prone for trauma such as elbows, knees, fingers, buttocks and shoulders. Chalky white material extrudes from the surface of the nodules, which are painful. These lesions may ulcerate or result in sinus formation or cellulitis. Contractures have been reported to occur in about 17%- 30% of patients with JDM. Calcinosis is said to reflect the duration of disease before initiation of treatment, duration of active disease, inadequate therapy and underlying cardiac or pulmonary disease.

Other skin lesions that may occur as the disease becomes chronic are panniculitis, acanthosis nigricans, lipodystrophy and poikiloderma. Poikiloderma is characterized by the presence of hypo or hyperpigmentation with atrophy and telangiectasia. Lipodystrophy, which may be localized, partial or generalized, occurs in 40% of patients. Palmar erythema and thickening may occur, which at times becomes severe and result in hyperkeratosis, fissuring and hyperpigmentation resembling a 'mechanic's hand'. Generalised erythema with scaling (erythroderma) has also been observed. Scaling of scalp associated with itching may be present.[2,4,6,21]

Treatment

Strict avoidance of sunlight is mandatory and use of broad spectrum sunscreens should be practiced. Topical corticosteroids and immunomodulators have not been found to be much effective when used alone. Hydroxychloroquine is useful in the treatment of cutaneous lesions. Emollients will help to combat the dry skin. Pressure points or sites more prone for trauma should be properly protected with padding. Various treatment options available for calcinosis include diphosphonates, colchicine, aluminum hydroxide, diltiazem, probenecid and alendronate.

Secondary bacterial infections warrant the use of appropriate systemic antibiotics.[6,21]

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA), earlier termed as juvenile rheumatoid arthritis refers to a group of arthritidesof unknown etiology, characterized by chronic inflammation of the synovium of peripheral joints that lasts for more than 6 weeks in children younger than 16 years. JIA is considered to be the most common rheumatic disease in children, which occurs with a prevalence that ranges from 0.07 to 4.1 per 1000 children.It encompasssystemic onset JIA(Still's disease), oligoarthritis, rheumatoid factor (RF) positive polyarthritis, RF-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis. Oligoarthritis is the most common JIA found to occur in 52% followed by 13% RF- negative polyarthritis, 12% enthesitis related arthritis, 8% each of psoriatic arthritis and undifferentiated arthritis, 6% systemic onset arthritis and 2% RF-positive polyarticular arthritis.Among these conditions, systemic arthritis differs from the others by the presence of cutaneous manifestations. A studyfrom Tumkur observed that out of 112 children with JIA,8.93% had systemic onset arthritis.[28]

Systemic onset JIA

Systemic onset JIA (SoJIA) is also known as Still's disease, after Still who first described this disease in 1897. Systemic onset arthritis is defined by the presence of arthritis in one or more joints with or preceded by fever that lasts for at least 2 weeks duration, in addition to one of the following criteria namely evanescent, non-fixed erythematous eruption, serositis, generalized lymphadenopathy and hepatosplenomegaly. Sex incidence is equal. Erythematous, evanescent, asymptomatic blanching macules and at times papules or plaquesoccur during the fever episodes. These lesions are present on the trunk, extremities and at times on the face. Fever may be 39°C or higher and may spike twice daily. Extraarticular manifestations that may be present include lymphadenopathy, hepatosplenomegaly, pericarditis, pleuritis and abdominal pain.[4,6,28]

Conclusion

Collagen vascular disorders are known for their chronic course, increased morbidity and at times mortality due to the complications. Disorders like systemic lupus erythematosus, systemic sclerosis, dermatomyositis and juvenile idiopathic arthritis focused in this article are characterized by specific cutaneous manifestations. Hence, it is important for us to be well aware of the specific and the non-specific dermatological features of these conditions as "Eyes do not see what the mind does not know".An early diagnosis and prompt treatment will definitely have a huge impact on reduction of morbidity and improvement of quality of life of the children with collagen vascular disorders.

Points to Remember

- *Systemic lupus erythematosus, systemic sclerosis, dermatomyositis and juvenile idiopathic arthritis are connective disorders which have many specific cutaneous manifestations.*

- *Malar rash, discoid rash and photosensitivity reaction are specific for systemic lupus erythematosus.*

- *Induration of the skin, morphea and vascular lesions are pathognomonic of juvenilesystemic sclerosis.*

- *Gottron's papules and heliotrope rashare characteristic skin lesions of juvenile dermatomyositis.*

- *Awareness of the specific and non-specific dermatological features of these conditions will enable the pediatrician to refer the child early for prompt diagnosis and treatment.*

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CLIPPINGS

Twenty-five years of RENHIS: a history of histopathological studies within EUVAS.

In the early 1990s, an international working group of experienced renal pathologists, the Renal Histology group, set up a scoring system for biopsies with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis. This scoring system subdivided glomerular, interstitial and vascular lesions and served as a tool for the evaluation of all renal biopsies from studies of the European Vasculitis Study Group (EUVAS). Histopathological studies gave new insights into the prediction of renal outcome in patients with ANCA-associated glomerulonephritis. Percentage of normal glomeruli and a selected number of interstitial parameters were reliable predictors of long-term follow-up glomerular filtration rate in all studies. Out of these results, a histopathological classification distinguishing focal, crescentic, mixed and sclerotic classes of ANCA-associated glomerulonephritis was developed. Until today, 13 studies have validated this classification system. Future studies will try to determine if and how renal histology could be helpful in guiding treatment of ANCA-associated glomerulonephritis.

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NEWS AND NOTES

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SURGERY

LOCAL ANESTHETICS FOR BEDSIDE PEDIATRIC SURGICAL PROCEDURES

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Abstract: *Pain control is an important part in the management of children with injuries. Proper understanding of the commonly available local anesthetic drugs, their common complications, early detection of toxicity and safe management are essential. The purpose of the present review is to discussand to inform non-anesthesiologist physicians and other medical persons who may be using local anesthetic drugs for childrento alleviate pain for minor procedures.*

Keywords: *Local anesthesia, Lignocaine, Bupivacaine, Intra lipids, Toxicity.*

Local anesthetics (LA) are commonly used for nerve blocks or for simple suturing of small injuries in children by pediatricians and general practitioners. This article provides some basic knowledge about the safe use of local anesthetic agents.

Classification of local anesthetics

There are two classes of clinically useful local anesthetics, the amino-amides (amides) and the amino-esters (esters). The amides are degraded in the liver by cytochrome P450 enzymes, whereas the esters are hydrolyzed primarily by plasma cholinesterases. Amide local anesthetics are commonly used in pediatric practice, e.g. lignocaine,bupivacaine, levobupivacaine and ropivacaine.

Bupivacaine

Bupivacaineis the most commonly used amide local anesthetic agent for regional blockade in infants and children. After a single administration, analgesia may be

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expected for up to 4 hours, although its duration of action is somewhat less in young infants. The most commonly used concentration for peripheral nerve blocks is 0.25%, with reduced concentrations of 0.0625% to 0.1% used for continuous epidural administration. The 0.5% concentration is less commonly used in children. Bupivacaine is highly bound to plasma proteins, particularly to α1-acid glycoprotein. It is a racemic mixture of the levo and dextroenantiomers; the *l*-isoform is the bioactive one with regard to clinical effect and the *d*-isoform contributes more to toxicity. The major advantage of levobupivacaine, the enantiomer of bupivacaine, over the racemic preparation is the reduced cardiac and central nervous system (CNS) toxicities.

Ropivacaine

Ropivacaineis an amide local anesthetic. Like levobupivacaine, it is an *l*-enantiomer that has reduced risks of cardiac and neurologic toxicities compared with bupivacaine. Ropivacaine is also reputed to have a lesser degree of motor blockade for equianalgesic potency. The decreased potential for toxicity makes ropivacaine an attractive agent in this age group.

EMLA cream

EMLA cream (Eutectic mixture of local anesthetics), is a commonly employed transdermal local anesthetic. Prilocaine an ester derivative is one of the components in EMLA. EMLA should only be applied to normal intact skin in appropriate dose. It should be applied and kept in place for 1 to 2 hours and thenthe cream is removed before the procedure. Adverse reactions include skin blanching, erythema, itching, rash, and methemoglobinemia.

Complications during local anesthetic administration

Many toxic reactions are self-limited because the local anesthetic redistributes throughout the body and plasma concentrations rapidly decrease.

Local complications

These are usually the result of injection technique,which include pain, ecchymosis, hematoma, infection and nerve laceration.

Local anesthetic systemic toxicity (LAST)

Systemic toxicity resulting from excessive blood levels of anesthetic is clinically manifested as adverse reactions in the CNS and cardiovascular system. Local anesthetics readily cross the blood-brain barrier to cause alterations in CNS function. A consistent sequence of symptoms can be observed as plasma local anesthetic concentrations progressively increase, although this may not be readily apparent in infants and small children. Because of the lower threshold for cardiac toxicity with bupivacaine, cardiac and CNS toxicity may occur virtually simultaneously in infants and children or cardiac toxicity may even precede CNS toxicity.

The earliest symptom of local anesthetic toxicity is circumoral paresthesia, which is due to the high tissue concentrations of local anesthetic rather than CNS effects. The developmentof circumoral paresthesia is followed by the prodromal CNS symptoms of lightheadedness and dizziness, which progress to both visual and auditory disturbances, such as difficulty in focusing and tinnitus. Objective signs of CNS toxicity during this time are shivering, slurred speech and muscle twitching. As the plasma concentration of local anesthetic continues to increase, CNS excitation occurs, resulting in generalized seizures. Further increases in the local anesthetic concentration depresses the CNS, with respiratory depression leading to a respiratory arrest.

The cardiovascular toxicity usually follows CNS toxicity.Systemic blood pressure decreases because of peripheral vasodilatation and myocardial depression.There is progressive bradycardia. These effects culminate in a cardiac arrest. In large doses, bupivacaine produces ventricular dysrhythmias, including ventricular tachycardia and ST segment changes suggestive of myocardial ischemia, especially when epinephrine containing solutions are used. Bupivacaine has a particularly strong affinity for the fast sodium channels as well as the calcium and slow potassium channels in the myocardium. These effects explain why it is frequently so difficult to resuscitate children from a toxic dose of bupivacaine. The cardio pulmonary resuscitation (CPR) should be continued for a longer period.With an intravascular injection of bupivacaine with epinephrine, characteristic ECG changes occursuch as peaked T waves and ST segment elevation, particularly in the lateral chest leads. Tachycardia is not a reliable indicator of an intravascular injection of bupivacaine. Signs of severe toxicity are given in Box 1.

Plasma protein binding is the most important pharmacologic factor that determines the toxicity of local

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Box 1.Signs of severe toxicity

- Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions
- Sinus bradycardia, conduction blocks, ventricular tachyarrhythmiasand asystole.

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anesthetics, particularly for amides, because it is the free (unbound) fraction of the drug that produces toxicity. The neonatal liver has limited enzymatic activity to metabolize and biotransform these drugs. Concentrations of both albumin and α1-acid glycoprotein are less in neonates and infants producing significantly greater concentrations of free lidocaine and bupivacaine in infants and neonates.

Hypersensitivity to local anesthetics

Hypersensitivity reactions to local anesthetics are rare.Ester local anesthetics are metabolized to p-aminobenzoic acid, which is usually responsible for allergic reactions in this group.

Prevention of toxicity

Always be aware of the maximum dose of local anesthetics in children. Dose of local anesthetic should be determined according to the child's age, weight, physical status andthe area to be anesthetized. Concentration, maximum dose and duration of action are given in Table I.

Doses should be reduced by 30% in infants younger than 6 months of age.Toxic reactions from the administration of local anesthetics are a function of the total dose administered, the site of administration, the technique of administration and the rate of degradation, metabolism and excretion of local anesthetic.

Technique of administration

Whenever regional anesthesia is performed, the operator must be prepared for an adverse reaction; and resuscitation supplies, including drugs, suction, and airway equipment, must be immediately available.

The needle or catheter must always be inspected for blood as soon as it is positioned, but before injecting the local anesthetic, to determine if the tip is within an artery or vein. Aspirate slowly before injecting. Do not aspirate forcefully because the blood vessels which are thin walled can collapse readily when too much negative pressure is applied. Slow incremental injection of the therapeutic blocking dose of local anesthetic (over several minutes) may further increase the safety of regional blockade.

Table I. Local anesthetics - Pharmacology

Sl. no.	Local anesthetic	Concentration	Maximum dose (mg/kg)	Duration of action
1	Lignocaine 2%	20 mg/mL	3	90 min
2	Lignocaine 2% with adrenaline 1:200000	20 mg/mL	7	120 min
3	Bupivacaine 0.25%	2.5 mg/mL	2.0	180-600 min
4	(Levo)Bupivacaine 0.25%	2.5 mg/mL	2.0	200-300 min
5	Ropivacaine 0.2%	2.0 mg/mL	3	120-240 min

For this reason, a small volume of local anesthetic with a marker for intravascular injection such as epinephrine in a concentration of 1: 200,000, is employed whenever possible. Epinephrine is contraindicated in blocks in which vasoconstriction of an end artery could lead to tissue necrosis, such as for digital and penile blocks.

Treatment of toxic reactions

- Stop injecting the LA

- Call for help

- The initial management should consist of establishing and maintaining a patent airway and providing supplemental oxygen

- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)

- Establish intravenous access.

If seizures occur, they should be managed appropriately. If seizure activity is present, the use of succinylcholine or other relaxant may facilitate tracheal intubation but does not prevent seizure activity. It should be remembered, however, that the acute morbidity from seizures is the result of airway complications (hypoxia and aspiration) and that securing the airway takes precedence over the actual control of the electrical activity of the seizure. CNS excitability is exacerbated in the presence of hypercarbia; it is, therefore, important to mildly hyperventilate children who have seizures.

Because the initial stage of cardiovascular toxicity consists of peripheral vasodilation, supportive treatment should include intravenous fluid loading (10 to 20 mL/kg of isotonic crystalloid) and, if necessary, vasopressor such as dopamine, norepinephrine may be administered to maintain vascular tone and systemic blood pressure. As toxicity progresses to cardiovascular collapse, profound decreases in myocardial contractility occur, followed by dysrhythmias.

It is necessary to assess cardiovascular status continuously. Arrhythmias should be managed using standard protocol and it should be remembered that arrhythmias in LA toxicity are more resistant to treatment. In circulatory arrest, CPR is initiated using standard protocol.

Intravenous lipid emulsion

All current data strongly suggest that lipid infusion is the most successful therapy for local anesthetic cardiotoxicity and immediate administration of this agent should be the first line of therapy. The lipid treatment promotes the elution of bupivacaine from the myocardium. This non-specific, observed extraction of local anesthetics from aqueous plasma or cardiac tissues is termed a 'lipid sink'. Another proposed mechanism is that lipids counteract local anesthetic inhibition of myocardial fatty acid oxidation, thereby enabling energy production and reversing cardiac depressionas well as accelerating the recovery from bupivacaine-induced asystole.

20% Intralipid is to be administered in the dose of 1.5 mL/kg as an initial bolus; the bolus can be repeated 1- 2 times for persistent asystole. This is followed by an infusion at 0.25 mL/kg/min for 30-60 minutes; increase

Box.2 Management of cardiac arrest in LA toxicity

- Continue CPR throughout treatment with lipid emulsion

- Recovery from LA-induced cardiac arrest may take >1 hr

- Propofol is not a suitable substitute for lipid emulsion.

- Arrange for safe transport to a higher centre.

infusion rate up to 0.50 mL/kg/min for refractory hypotension.The management principles of cardiac arrest are given in Box 2.

Points to Remember

- *Calculate the maximal dose of local anesthetic that you are going to use before starting the procedure.*

- *Always aspirate very slowly before injecting*

- *Keep resuscitating equipments like ambu bag, drugs ready before even small procedure.*

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CLIPPINGS

The brain adapts to dishonesty.

Dishonesty is an integral part of our social world, influencing domains ranging from finance and politics to personal relationships. Anecdotally, digressions from a moral code are often described as a series of small breaches that grow over time. Here we provide empirical evidence for a gradual escalation of self-serving dishonesty and reveal a neural mechanism supporting it. Behaviorally, we show that the extent to which participants engage in self-serving dishonesty increases with repetition. Using functional MRI, we show that signal reduction in the amygdala is sensitive to the history of dishonest behavior, consistent with adaptation. Critically, the extent of reduced amygdala sensitivity to dishonesty on a present decision relative to the previous one predicts the magnitude of escalation of self-serving dishonesty on the next decision. The findings uncover a biological mechanism that supports a 'slippery slope': what begins as small acts of dishonesty can escalate into larger transgressions.

Neil Garrett, Lazzaro SC, Ariely D, Sharot T. The brain adapts to dishonesty.

Nature Neuroscience 19, 1727–1732 (2016) doi:10.1038/nn.4426

New aspects in the management of pneumonia.

Despite improvements in the management of community-acquired pneumonia (CAP), morbidity and mortality are still high, especially in patients with more severe disease. Early and appropriate antibiotics remain the cornerstone in the treatment of CAP. However, two aspects seem to contribute to a worse outcome: an uncontrolled inflammatory reaction and an inadequate immune response. Adjuvant treatments, such as corticosteroids and intravenous immunoglobulins, have been proposed to counterbalance these effects. The use of corticosteroids in patients with severe CAP and a strong inflammatory reaction can reduce the time to clinical stability, the risk of treatment failure, and the risk of progression to acute respiratory distress syndrome. The administration of intravenous immunoglobulins seems to reinforce the immune response to the infection in particular in patients with inadequate levels of antibodies and when an enriched IgM preparation has been used; however, more studies are needed to determinate their impact on outcome and to define the population that will receive more benefit.

Prina E , Adrian Ceccato, Torres A. New aspects in the management of pneumonia.

Critical Care (2016) 20:267 DOI 10.1186/s13054-016-1442-y

<div style="text-align:center">**RADIOLOGY**</div>

OSTEOMYELITIS 2

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In this issue we continue with osteomyelitis focussing on cross sectional imaging. Since CT also uses the same X-radiation as conventional radiography, bone appears white just as in plain films. Fig.1 shows thickened cortex on the left side compared to the normal right femur. This is the sclerosis associated with chronic osteomyelitis. Fig.2 is the bone window of the same section showing the cause of the sclerosis due to the persistence of dead bone or sequestrum seen as the inner white ring and the new bone or involucrum seen as the outer white ring.The high kV and computer technology used in CT are able to produce more details of soft tissue. Hence, you can also see some inflammatory changes on the lateral aspect of the femur (black arrow in Fig.1) and the sinus tract in the sub-cutaneous fat tissue (white arrow). Fig. 3 shows breaks in the cortex that signify the cloacae (white arrows). All the features of chronic osteomyelitis are therefore seen in greater detail in CT.
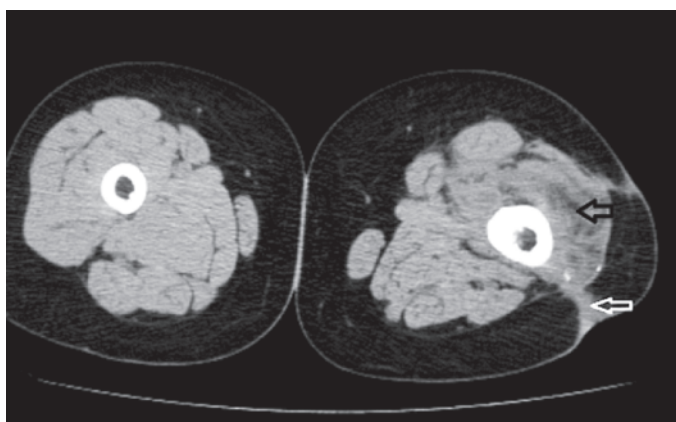
Fig.1.Sclerosis of left femur in chronic ostyeomyelitis

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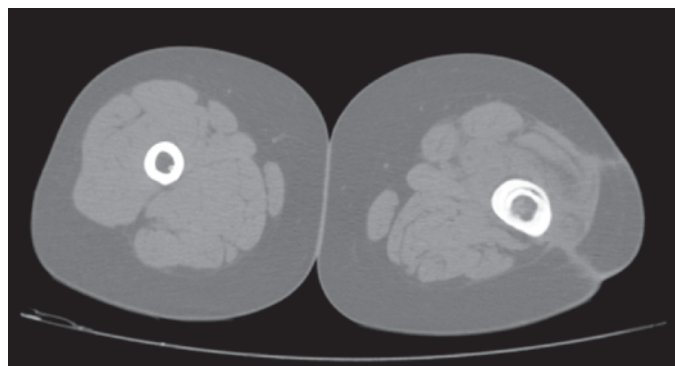
Fig.2.Sequestrum(inner white ring) and involucrum(outer white ring)
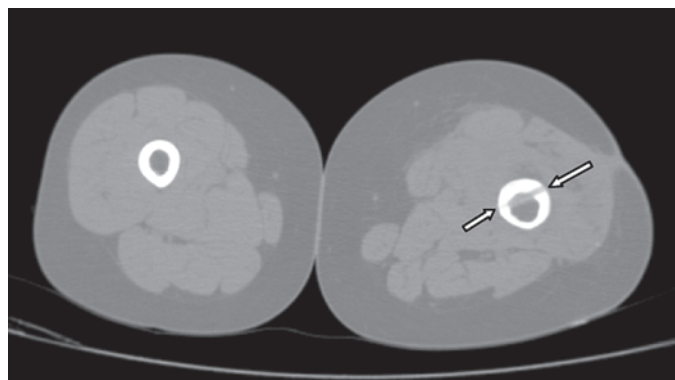
Fig.3.Cloacae in chronic ostyeomyelitis

Timely diagnosis of acute osteomyelitis and the use of newer and more potent antibiotics prevent the morbidity associated with chronic osteomyelitis. Yet, as we saw in the previous issue, presentation can be vague, history is intentionally or unwittingly not authentic, the X-ray is not helpful or the findings are too subtle. While CT shows excellent detail of extent in chronic osteomyelitis, it is not suitable for the crucial acute phase. In this situation MRI is very helpful. Of late we have been using MRI more often for the musculoskeletal system in children. The earliest finding of acute osteomyelitis on MRI is alteration of normal marrow signal intensity as early as 2 days after the onset of infection. While MRI may not be considered an option by the clinician at first, it is usually requested a little later if there is a clinical suspicion or if there is a search for something unexpected. The girl in Fig.4 came with a clinical diagnosis of doubtful tarsal coalition because she complained of chronic midfoot pain and examination

Fig.4.Osteomyelitis of metatarsal
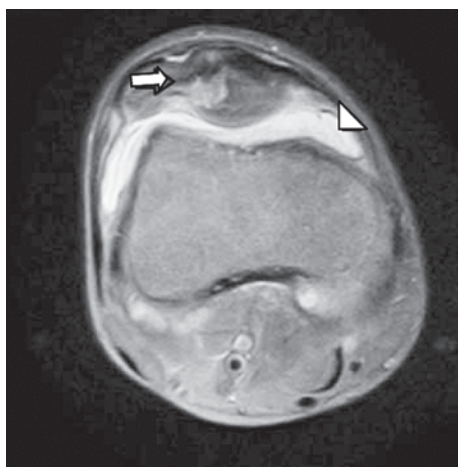
Fig.5.Osteomyelitis of patella(arrow) and joint fluid(arrowhead)

Fig.6.Septic arthritis

showed mild flat foot. There was no external swelling. The plain X-ray was normal. MRI unveiled a diagnosis of osteomyelitis of left second metatarsal bone (Fig.4). There was white marrow edema in the whole length of the 2nd metatarsal, mild periosteal reaction in the medial cortex and periosseous bright inflammatory changes pointing to a diagnosis of osteomyelitis. This could be compared with the marrow signal of the other bones. Similarly the seven year old in Fig.5 continued to have joint swelling after falling on his knee a few months back. MRI reveals irregularity of the ossification centre of the patella, inhomogeneity of the unossified cartilage and white joint fluid between the femur and patella. All these indicate partial destruction due to infection following the injury. MRI is thus helpful in some situations in assessing the extent of actual disease. Its sensitivity is more than 80%. Disadvantages are the long scanning times and the inability to use it near metallic implants like fixation devices.

Fig.7. Chronic recurrent multifocal osteomyelitis. Note periosteal reaction.

Ultrasound is extremely good for identifying fluid collections. Therefore it can localize periosseous abscesses and joint fluid and is useful for diagnosing septic arthritis. The unossified head of femur in infants enables a good view of the joint. Fluid in the joint space causing dislocation of the femur can be seen. Similarly joint fluid in the shoulder or in the bursae surrounding the knee joint can be diagnosed. Fig.6 is a two year old child with knee swelling. Ultrasound showed joint fluid. X-ray was normal apart from the soft tissue swelling. MRI was done to exclude osteomyelitis. The cortex of normal bone in MRI is black due to the lack of hydrogen atoms. The black cortex in the picture is regular. The marrow intensity is normal. But, there is fluid in the suprapatellar bursa with synovial thickening and perisynovial altered intensity due to edema. These features suggest septic arthritis.
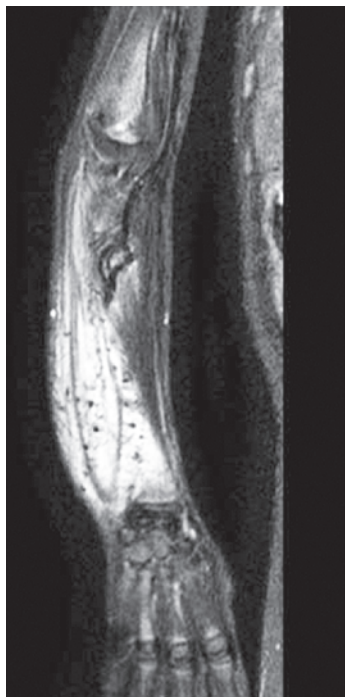
Fig.8.Chronic recurrent multifocal osteomyelitis. Note marrow edema and increased vascularity.

Chronic recurrent multifocal osteomyelitis is a rare disease of children where there are areas of marrow inflammation mostly in the metaphyses with lysis of bones. It is not an infection but an immune mediated response. There is periosteal reaction, but no abscess formation, no sequestra or sinuses. The disease runs a protracted course over many years with recurrent lesions. The lysed areas heal with sclerosis. There is increased vascularity which brings in a differential diagnosis of Ewing's sarcoma. But the clinical course and multiple lesions help in the diagnosis. Fig.7 shows discontinuity of the cortex of both ulnar bones with exuberant periosteal reaction. Fig.8 is the MRI showing hyperintensities within the medulla of both bones in the forearm. In addition, there are multiple tubular shadows denoting increased vascularity.

Conventional imaging is definitely the first modality in suspected childhood osteomyelitis. However, normal X-rays do not exclude osteomyelitis especially in the first week of symptoms. The next modality of choice is MRI which shows not only osseous involvement but also soft tissue extension and joint anatomy. CT is more useful in chronic osteomyelitis for assessing the full extent of bone destruction. Ultrasound has its limitations and helps only in identifying fluid in some joints.

NEWS AND NOTES

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A RARE CASE OF VIRGINAL BREAST HYPERTROPHY IN A 12-YEAR-CHILD TREATED WITH REDUCTION MAMMOPLASTY

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Abstract: *Virginal breast hypertrophy is an idiopathic rare condition found in peri-pubertal period and is characterized by massive breast hypertrophy without any hormonal or CNS cause.*

Virginal breast hypertrophy should be one of differential diagnosis of massive breast hypertrophy. Both physical, psychological symptoms and growth phase should be the basis of consideration in management.

Keywords: *Virginal breast hypertrophy, Reduction mammoplasty, Gigantomastia*

Virginal breast hypertrophy (VBH) often termed as puberty-induced or juvenile gigantomastia, is a rare benign disease. It is characterized by rapid and excessive growth of one or two breasts during peri-pubertal period, usually 1-2 years before menarche without hormonal imbalance.[1] Breast growth becomes out of proportion to the growth of the child. Durston first reported VBH in 1669.[2] Breast enlargement is due to unusual end organ sensitivity to normal hormone levels.[3] The development of gigantomastia in peripubertal period causes psychological stress and other problems. Reduction mammoplasty is the first line treatment followed by breast reduction, mastectomy and reconstruction with or without hormonal therapy.[4] Very few cases have been reported in children in India.

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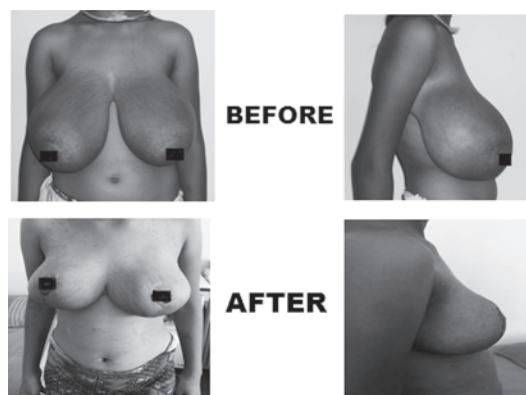
Fig.1. Virginal breast hypertrophy with massive breast enlargement before and after surgery

Case report

A 12-year-old female child presented with bilateral excessive increase of breast size since 5 months before consultation. Stating from one year ago there was normal increase in breast size, but in last 5 months there was bilateral excessive increase in the size reaching the present size (Fig.1). Child had mild pain over the breast area after 2 months of onset of enlargement. It was associated with refusal to go to school and low self-esteem. There was no history of any discharge, redness, localized lump, ulceration, infection or postural problems. There was no history of any other significant illness, drug intake, excessive growth of hair over the body or any other glandular swelling. Child has attained thelarche but not attained menarche. Child was born to non-consanguineous parents, with no similar complaints in the family. Antenatal and developmental history were normal.

On examination the vitals were normal. SMR staging was, pubic hair - stage 2 and breast - stage 4. On local examination the breasts were enlarged on both sides. From suprasternal notch to the right nipple the measurement was 31cm, to the left nipple 32 cm and to the umbilicus 32cm. Both breasts were symmetrical and hyperpigmented. There were striae present over the surface with no visible sinus or enlarged veins. The right nipple was more retracted than the left and there was no discharge from the nipples. There was no discoloration of breast, areola or nipple and no rise of local temperature. (It was

soft and movable through retro mammary space). There was no discharge on palpating the areola, no puckering/peaud'orange, no cysts, masses or movable lump (there was diffuse mild tenderness over the breasts). Systemic examination was normal.

Routine blood investigations including, peripheral smear were normal. USG abdomen and pelvis, MRI brain andbone age were normal. Hormone levels (LH 1.8mIU/mL, E2 estradiol 30.3pg/mL, prolactin 21.7ng/mL, testosterone 34ng/dL, beta HCG 1.2 IU/L) were normal and appropriate for age.

After obtaining plastic surgeon and obstetric consultations reduction mammoplasty was done and 2.5kg of breast tissue was removed (Fig.1). Histo-pathological examination of excised breast sample from both sides revealed stromal hyperplasia, hypertrophy of cellular connective tissue and ductal epithelium, without any malignant changes, suggestive of virginal breast hypertrophy. The child was followed up till 8 months after surgery and so far there is no recurrence or enlargement of breast or any other morbidity. Psychological issues, attention span and school performance also improved drastically.

Discussion

Patients with VBH usually present with rapid growth of one or both breasts to massive proportions, usually during the peripubertal period. Patients will have symptoms due to massively enlarged breast i.e. breast pain, back and neck pain, abnormal posture, hygienic difculties, intertriginous lesions at the inframammary folds, orthopnea and skin necrosis. They can also havepsychological problems, low self-esteem, refusal to school and lack of confidence. Etiology of VBH is unknown. Normal levels of estrogen, progesterone, gonadotropins and growth hormone during this rapid growth phase have been reported previously.[5] Drug-induced gigantomastiaafter exposure to penicillamine, neothetazone, cyclosporine and protease inhibitors have been reported.[6]

Familial cases of VBH associated with Cowden syndrome, have been reported. Cowden syndrome is an autosomal dominant disorder caused by a mutation of the PTEN (phosphatase and tensin homologue) tumor suppressor gene located on the long(q) armofchromosome-10 and is characterized by multiple hamartomatous lesions and increased risk of breast, endometrial, gastrointestinal and thyroid cancer.[7]

Surgery with or without hormonal therapy has been proposed as treatment. Surgical options for VBH include reduction mammoplasty with or without free nipple graft or in extreme cases, subcutaneous mastectomy and breast reconstruction may be required.[8] If breast enlargement is not excessive, surgery may be delayed till completion of breast development. Reduction mammoplasty following a period of observation to conrm breast growth stabilization is recommended in the majority of cases and may occasionally be sufcient to result in successful and complete relief of this distressing condition. If breast growth is rapid and massive, multiple sequential reduction mammoplasty may be requiredspecially if operated in active growth phase of the disease. Recurrence is also common and it may require reoperations, that is associated with signicant morbidity, including both physical and psychological.[9] If subcutaneous mastectomy is selected as the surgical treatmentofchoice, properpre-operative counseling regarding future issues and thorough documentation are required. Hormonal treatment including, tamoxifen, medroxyprogesterone, danazol and bromocriptine have been used in past for several cases.[10] These treatments may lead to breast growth arrest, without observation of size reduction or symptom alleviation. There is no data on the safety and efficacy of hormonal therapy and success rate also varied from case to case. Literature suggests that hormonal therapy is effective in recurrence of gigantomastia. Case reports of post-operative prevention of breast growth as well as recurrence with tamoxifen have been published previously with dose varying from 20-40mg per day for 4-6 months. Higher doses of these medications should be used carefully as they are known to have side effects like endometrial hyperplasia, hot ushes, venous thromboembolism and bone density changes.

Conclusion

VBH should be kept in mind in peripubertal period, especially when hormonal and other radiological investigations are normal. Histopathological diagnosis is confirmatory and mandatory. Other differential diagnosis of breast hypertrophy should be ruled out. Surgery should be performed at the appropriate time, with consideration of both physical and psychological symptoms. The role of hormonal therapy is controversial in adolescents as they are in growth phase during this period.

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CLIPPINGS

Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

Limiting the duration of antimicrobial treatment constitutes a potential strategy to reduce the risk of antimicrobial resistance among children with acute otitis media.

In this trial, 520 children, 6 to 23 months of age, with acute otitis media received amoxicillin–clavulanate either for a standard duration of 10 days or for a reduced duration of 5 days followed by placebo for 5 days. Rates of clinical response (in a systematic fashion, on the basis of signs and symptomatic response), recurrence, and nasopharyngeal colonization were measure and episode outcomes using a noninferiority approach was analyzed. Symptom scores ranged from 0 to 14, with higher numbers indicating more severe symptoms. Children who were treated with amoxicillin–clavulanate for 5 days were more likely than those who were treated for 10 days to have clinical failure (77 of 229 children [34%] vs. 39 of 238 [16%]; difference, 17 percentage points [based on unrounded data]; 95% confidence interval, 9 to 25). The mean symptom scores over the period from day 6 to day 14 were 1.61 in the 5day group and 1.34 in the 10 day group ($P=0.07$); the mean scores at the day 12 to 14 assessment were 1.89 versus 1.20 ($P=0.001$). The percentage of children whose symptom scores decreased more than 50% (indicating less severe symptoms) from baseline to the end of treatment was lower in the 5day group than in the 10day group (181 of 227 children [80%] vs. 211 of 233 [91%], $P=0.003$). No significant betweengroup differences in rates of recurrence, adverse events, or nasopharyngeal colonization with penicillin nonsusceptible pathogens were noted. Clinical failure rates were greater among children who had been exposed to three or more children for 10 or more hours per week than among those with less exposure ($P=0.02$) and were also greater among children with infection in both ears than among those with infection in one ear ($P<0.001$).

Alejandro Hoberman, Jack L. Paradise, Howard E. Rockette, Diana H. Kearney, Sonika Bhatnagar, Timothy R. Shope, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. N Engl J Med 2016; 375:24462456, December 22, 2016 DOI: 10.1056/NEJMoa1606043.

Getting the balance right: adverse events of therapy in anti-neutrophil cytoplasm antibody vasculitis.

Antineutrophil cytoplasm antibody associated systemic vasculitides (AASV) have traditionally been managed with a combination of cyclophosphamide and glucocorticoids during the induction phase, followed by azathioprine in the maintenance phase. Whilst these therapies have markedly improved the prognosis in AASV, treatment related adverse events remain a major challenge and include complications such as infection, glucocorticoid related side effects, malignancy, cardiovascular disease, infertility and death. Newer biologic therapies have been shown to demonstrate equivalent efficacy as cyclophosphamide for remission but the hoped for reduction in adverse events has yet to be realised. More recent efforts have been focused on refining existing therapeutic regimens and strategies, tailoring individual treatment to disease severity, patient age and kidney function to derive maximum treatment efficacy while minimising treatment toxicity. In particular, current interventional trials are targeting a reduction in corticosteroid exposure in an effort to make induction and maintenance regimens safer.

Wong L, Harper L, Little MA. Getting the balance right: adverse events of therapy in anti-neutrophil cytoplasm antibody vasculitis. Nephrol Dial Transplant (2015) 30 (suppl 1): i164-i170. doi: 10.1093/ndt/gfu406

CASE REPORT

SEXUALLY TRANSMITTED IN TEENS - REPORT OF THREE CASES

*Kumar Parimalam
**Hemamalini R

Abstract: *Teenagers have special health related vulnerabilities and the recognition of adolescent healthcare has been growing in the recent years. According to WHO, sexual and reproductive ill health is one of the major causes of morbidity and mortality among this age group. Many adolescents are sexually active and at risk of contracting sexually transmitted infection [STI]. STIs are associated with an increased risk of acquiring HIV infection. Awareness about STIs will help detect and treat them early to prevent complications and spread of infection to the society. We report three adolescent school boys with STI in whom early diagnosis was missed.*

Keywords: *Adolescent, STI, Wart, Chancre*

STIs spread primarily through person to person by sexual contact. The most common diseases include, syphilis, gonorrhoea, chlamydial infections, chancroid and warts. There is an increase in the prevalence of STIs among teenagers. STIs can manifest as ulcers, urethral or vaginal discharge, bubo or papules as in warts and HIV infection has to be ruled out in all.

Case Report

Case 1: Thirteen year old boy with painless penile ulcer (Fig.1.) of 7 days duration. There was no other systemic or skin manifestation. VDRL was positive in 1:8 dilution.

Case 2: Seventeen year old boy with painless perianal ulcer (Fig.2) of unknown duration. No other systemic or skin manifestation. VDRL was positive in 1:16 dilution and Treponema pallidum hemagglutination (TPHA) test also was positive.

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Fig.1. Chancre over glans penis - well defined oval ulcer with indurated base

Fig.2. Chancre in the perianal skin - well defined ulcer with indurated base

Fig.3. Perianal wart - Multiple small skin coloured keratotic papules

Case 3: Thirteen year old boy presenting as pruritus ani of three weeks' duration showed painless papules in the perianal area (Fig.3.). There was no other systemic or skin manifestation. He was negative for VDRL.

Rapid test for HIV was negative in all three.

All the three teenagers were brought by their parents after failure of treatment from private practitioners. Only on repeated interrogation did the boys come out with the history that they had unprotected, anal, homosexual

practice, case no 1 being active and the other two receptive. All three were counselled and treated adequately including the partners.

Discussion

The primary chancre of syphilis caused by Treponema pallidum presents as painless ulcers with an incubation period of 9-90 days and heals within 3-6 weeks. In adolescents, chancre is exclusively transmitted through sexual contact. The estimated rate of transmission of infection is 30% associated with an increased risk of HIV acquisition[1] as ulcerative STIs serve as portal of entry or exit for HIV. Chancre usually affects the penile and labial skin, but rarely the oral and perianal region. It should be differentiated from other common causes of genital ulcers like herpes, chancroid and drug eruption. Though the prevalence of syphilis has decreased in the recent years there have been significant outbreaks in many areas. According to Silber, diagnosis is missed nearly in one third of the cases with syphilis.[2] Diagnosis in a teen who normally denies history of exposure can be established by dark field microscopy and serological tests for syphilis. Single dose of deep intramuscular benzathine penicillin, 50,000 units/kg (maximum, 2.4 million units) after test dose is the treatment of choice.

Anogenital warts, another common STI, is caused by up to sixty different strains of human papilloma virus [HPV]. HPV 16 and 18 may lead to squamous cell carcinoma.[3] The incubation period ranges from two weeks to eight months.[4] The incidence of genital warts is higher in boys which is attributable to the result of homosexual contact with an infected partner. Though asymptomatic, patients may complain of pruritus ani like in our case. Bleeding during defecation may be the presenting complaint in few. Rarely these warts may show spontaneous regression.[5] However, the risk of re-infection is high in homosexuals. Prevalence of high risk HPV infection is high among adolescents which may lead to an increased risk of malignancy.[6,7,8] It has also been observed that HIV infected persons are more prone to develop genital warts than HIV negative counterparts. Anogenital warts should be differentiated from condylomalata which is a manifestation of syphilis that is highly contagious. Reactive VDRL and other tests will confirm the syphilitic aetiology. Podophylin application with adequate precaution is the best and most cost effective treatment for perianal warts.

It is important to rule out sexual abuse in all children with unexplained ano-genital lesions. Child sexual abuse as defined by WHO is "inappropriate sexual behaviour with a child and involving a child in sexual activity that he or she does not fully comprehend, is unable to give informed consent to, or that violates the laws and social taboos of society". Many factors make children vulnerable to sexual abuse, key determinant being the female sex. However, in developing countries male children do constitute a large portion of child victims. Though an alarming 53.22% of children in India are reported to be sexually abused based on the report of the Ministry of Women and Child Development, in the absence of an allegation, investigation of child sexual abuse is difficult for law enforcement. All three cases discussed here were boys and none had physical or behavioural indicators of child sexual abuse.

Conclusion

STIs are not uncommon in school children. Through updated knowledge and a high index of suspicion will aid in early diagnosis and treatment, as teenagers do not disclose correct history during their first visit to the doctor. Proper counselling of patient and partner is as important as medical treatment. Timely and appropriate treatment of patient and contacts will avert complication and spread of STI in community. There is a need for sex education, and prevention of STI, including vaccination against HPV.

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<div style="text-align:center">**LETTER TO THE EDITOR**</div>

ACUTE PANCREATITIS: A RARE COMPLICATION IN AN EPILEPTIC CHILD ON VALPROATE THERAPY

Valproic acid (VPA) is one of the most commonly used anticonvulsant in children. VPA-related side effects may be dose-dependent or idiosyncratic. Hepatitis, hemostatic abnormalities, bone marrow suppression, hyperammonemic encephalopathy and pancreatitis are the dreaded adverse effects associated with VPA therapy. We describe a thirteen-year-old boy with neuromigrational disorder and symptomatic generalized epilepsy who presented with history of abdominal pain following a fatty meal and multiple episodes of non-bilious vomiting of three days duration. He was on long-term treatment with valproate and the dose of valproate was increased from 1500 mg per day to 1600 mg per day, about two months prior to presentation with abdominal pain. He was also on treatment with 1500 mg per day of vigabatrin and 20 mg per day of clobazam. There was no fever, abdominal distension or altered bowel habit. Epigastric tenderness was observed. Neurological examination had revealed signs of incordination. Blood counts, electrolytes, lipid profile and liver enzymes were normal. Serum amylase was 391 U/L (reference range, 28-100 U/L) and lipase was 444 U/L (reference range, 13-60 U/L). Serum valproic acid level was 134ìg/mL (therapeutic range, 50-100 µg/mL).Ultrasound abdomen was normal. Computerized tomography of abdomen had shown mild peripancreatic fat stranding. He was managed with intravenous fluids, withdrawal of valproate and initiation of levetiracetam. Follow-up ultrasound abdomen, serum amylase and lipase after six weeks were normal.

VPA-related pancreatitis is a rare entity with an estimated incidence of 1:40,000.[1]There is paucity of reports on VPA-related pancreatitis from India. Diagnosis is established by the clinical symptomatology, hyperamylasemia or hyperlipasemia or imaging evidence of pancreatitis. Pancreatitis may result from free radicals mediated injury or effect of VPA on beta oxidation. VPA-related pancreatitis is common in young patients, patients with encephalopathy or chronic renal failure, patients on polytherapy or during first year of therapy.[2]Another study had found no association between dose, duration, VPA level or polytherapy.[3]Asymptomatic elevation of amylase, hemorrhagic or chronic pancreatitis, pseudocyst or endocrine insufficiency may be encountered in patients with VPA-induced pancreatitis.[4,5] Discontinuation of VPA is the pivotal step in the management of patients with VPA- related pancreatitis. Restarting VPA should be avoided as there is a high risk of relapse. Children on VPA therapy with acute abdominal symptoms must be evaluated appropriately to diagnose acute pancreatitis, as it carries a high risk for morbidity and mortality.

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SUBJECT INDEX

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