INDIAN JOURNAL OF PRACTICAL PEDIATRICS

- **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**
- **Indexed in Excerpta Medica, CABI Publishing, Scopus**

Vol.20 No.3	**JUL.- SEP. 2018**
Dr.N.C.Gowrishankar Editor-in-Chief	**Dr.S.Thangavelu** Executive Editor

CONTENTS

Journal Office and address for communications: Dr. N.C.Gowrishankar, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

Published by Dr.N.C.Gowrishankar, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India and Printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai-14.

INSTRUCTIONS TO AUTHORS

General

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.

They are considered for publication on the understanding that they are contributed to this journal solely.

All pages are numbered at the top of the right corner, beginning with the title page.

All manuscripts should be sent to: The Editor-in-Chief, Indian Journal of Practical Pediatrics

Manuscript

1st Page –

Title

Name of the author and affiliation

Institution

Address for correspondence (Email, Phone, Fax if any)

Word count

No. of figures (colour / black and white)

No. of references

Authors contribution

2nd Page –

Abstract (unstructured, not exceeding 100 words) with key words (not exceeding 4)

3rd Page -

Acknowledgement

Points to remember (not more than 5 points)

Text

References

Tables

Legends

Figures – should be good quality, 4 copies black & white / colour,*

(4 x 6 inches – Maxi size) Glossy print

* Each colour image will be charged Rs. 1,000./- separately, with effect from January 2006 (Except for invited articles).

Text

Only generic names should be used

Measurements must be in metric units with System International (SI) Equivalents given in parentheses.

References

Recent and relevant references only

Strictly adhere to Vancouver style

Should be identified in the text by Arabic numerals as superscript.

Type double-space on separate sheets and number consecutively as they appear in the text.

Articles without references / defective references will entail rejection of article.

Tables

Numbered with Roman numerals and typed on separate sheets.

Title should be centered above the table and explanatory notes below the table.

Figures and legends

Unmounted and with figure number, first author's name and top location indicated on the back of each figure.

Legends typed double-space on separate sheet. No title on figure.

All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

Article Categories

Review article

Article should be informative covering the recent and practical aspects in that field. Main articles can be in 1500 – 2000 words with 12 – 15 recent references and abstract not exceeding 100 words.

Case report (covering practical importance)

250 – 600 words, 8 – 10 recent references

Clinical spotters section

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)

Letters to the Editor

200 – 250 words pertaining to the articles published in the journal or practical viewpoints with scientific backing and appropriate references in Vancouver style.

Check List

Covering letter by corresponding author

Declaration (as enclosed) signed by all authors **

Manuscript (4 copies)

Accompanied by a copy in CD / or submit as an email attachment in addition to hard copy.

Failing to comply with the requirement at the time of submission would lead to the rejection of the article.

Author's contribution / Authorship Criteria

All persons designated as authors should qualify for the authorship. Authorship credit should be based on substantial contributions to i) concept and design, or collection of data, or analysis and interpretation of data; ii) drafting the article or revising it critically for important intellectual content; and iii) final approval of the version to be published. All conditions 1, 2 and 3 must be met. Participation solely in the collection of data does not justify authorship and can be mentioned in the acknowledgement if wanted.

**** Declaration by authors**

I/We certify that the manuscript titled '…….' represents valid work and that neither this manuscript nor one with substantially similar content under my/our authorship has been published or is being considered for publication elsewhere. The author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership, including any and all rights incidental thereto, exclusively to the Indian Journal of Practical Pediatrics, in the event that such work is published in Indian Journal of Practical Pediatrics. I / we assume full responsibility for any infringement of copyright or plagiarism.

Authors' name(s) in order of appearance in the manuscript Signatures (date)

Selection procedures

All articles including invited articles will be peer reviewed by two masked reviewers. The decision of the Editorial Board based on the reviewer's comments is final. All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

GASTROENTEROLOGY - II

MANAGEMENT OF PERSISTENT AND CHRONIC DIARRHEA - PRACTICAL ISSUES

Sarath Gopalan

Abstract: *In the West, the term 'chronic diarrhea' applies to diarrheal illness that is 14 days or more in duration, irrespective of the underlying etiology. However, in developing countries, such as in the South Asian region with a high prevalence of infectious diarrhea, experts in the field recognized the need to differentiate chronic diarrhea of infective etiology from non-infectious causes of chronic diarrhea. Towards this objective, the World Health Organization has recognized the importance of coining a separate term for addressing chronic diarrhea of infective etiology. The currently accepted WHO definition of "Persistent Diarrhea" is any diarrheal illness lasting 14 days or more, abrupt in onset and due to infectious etiology. This is to be clearly distinguished from "Chronic non-infectious diarrhea" which is also 14 days or more in duration but insidious in onset and due to causes which are non- infective. This includes specific food allergy and intolerance, metabolic causes of osmotic and secretory diarrhea and intestinal disorders presenting as malabsorption due to associated villous atrophy of non-infective origin. This manuscript discusses the approach to management of persistent diarrhea in detail owing to the fact that this presentation of chronic diarrhea is very relevant to countries such as India and subsequently briefly addresses specific causes of non-infectious chronic diarrhea and approach to diagnosis and management.*

Keywords: *Diarrhea, Persistent, Chronic, Diagnosis, Management.*

The terms chronic diarrhea and persistent diarrhea have to be defined clearly for planning the practical approach to diagnosis and management in clinical settings. In the West, there has been considerable progress in diagnosis and management of chronic diarrhea appropriately owing to knowledge and the ready availability of advanced diagnostic tools. But in India, owing to the relative paucity of information and limited availability of diagnostic resources, the progress made in this regard has been comparatively much less. In order to bridge this gap, the Gastroenterology Chapter of the Indian Academy of Pediatrics (IAP) published a consensus statement in 2011.[1]

* Senior Pediatric Gastroenterologist and Hepatologist, Madhukar Rainbow Children's Hospital, New Delhi.
email: crnssindia@gmail.com

Epidemiology

Community studies from the South Asian region have brought out some very important observations. Approximately 20% of all acute diarrhea cases progresses beyond 14 days and 60 % of cases of persistent diarrhea occur before 6 months of age and 90 % before the age of one year.[2] Persistent diarrhea is responsible for about 30% - 50% of all diarrheal mortality in the South Asian region.[3,4,5]

Etiopathogenesis

There is a lack of clarity regarding the precise mechanisms causing persistence of diarrhea. It is believed to be attributable to a combination of effects such as those due to host factors, the effect of recurrent infections with many pathogenic organisms and persistence of mucosal injury caused by specific microorganisms such as Escherichia coli, Shigella, Campylobacter and Salmonella. About one fourth of infants and children with Shigella infection develop persistent diarrhea.[6] The risk of acute diarrhea becoming persistent is much higher in a setting of severe malnutrition and secondary lactose intolerance.[7] Furthermore, the most severe effects of persistent diarrhea are observed in the very young infants owing to a delayed intestinal maturation.[5] These effects are believed to result from chronic inflammation and villous atrophy leading to impaired absorption of nutrients from the lumen of the small intestine and a higher probability of bacterial translocation due to the resultant increased permeability to microbial and dietary pathogens. Persistent diarrhea is a very well-recognized clinical manifestation of both human immunodeficiency virus (HIV) and Cryptosporidium infection and micronutrient deficiency is likely to be an important factor contributing to an impaired immune response in affected infants and young children. [8,9,10]

Management

Absorption of nutrients from the lumen of the small intestine is invariably affected owing to significant damage to the intestinal brush border and therefore, nutritional intervention remains the mainstay of treatment in persistent diarrhea.[11,12,13] The dietary management of persistent diarrhea consists of 3 types of diets – Diet A, diet B and diet C. As these diets are mainly used in community settings in low socio-economic groups, they are inexpensive and prepared from natural ingredients. The main difference between these three diets is that diet A is a low lactose diet containing a mix of milk and cereal but does not involve complete elimination of milk from the diet. The addition of cereal (rice or semolina) to diet A helps to make it energy dense, provide quality proteins and also significantly increases palatability. However, it is important to limit the daily milk intake to 50-60 ml/kg/day in order to ensure that the daily lactose load does not exceed 2-2.5 g/kg/day. It has been observed that milk cereal mix are as efficacious as lactose-free diets in situations where the diarrhea is not severe and nutritional intervention is commenced early. Diet B is lactose-free with reduced starch and completely devoid of milk. The milk protein in diet B is replaced with chicken protein. Diet C is a monosaccharide -based diet with the main source of energy being glucose and protein source being chicken or egg protein hydrolysate.

When to change from diet A to B to C?

Each diet must be tried for at least 7 days before changing to the next dietary option. Nutritional intervention always must begin with diet A and changed to first diet B and subsequently to diet C only if there is an unsatisfactory response to sequential change. About two-thirds of infants and young children will respond well to diet A and will not require dietary modification and about 85% of infants can be effectively managed with either diet A or diet B and only a very small proportion will need to be shifted to diet C (Fig.1). Success with the specific dietary intervention and treatment failure is defined by any of the criteria given in Box 1.

Box 1. Criteria for the success and treatment failure of specific dietary intervention

Success of dietary intervention

- Less than 2 liquid stools for at least 2 successive days
- Weight gain on any 3 successive days
- Adequate food intake

Failure of dietary intervention

- Ten or more watery stools per day even after 48 hours following specific diet initiation
- Failure to establish weight gain even 7 days after initiation of diet
- Return of clinical signs of dehydration

A significant proportion of patients with persistent diarrhea are dehydrated and may have associated electrolyte imbalance. In these patients, correction of dehydration with low osmolarity oral rehydration solution (ORS) has been documented to be beneficial.[14,15]

There is clear evidence of a beneficial role of zinc even in patients with persistent diarrhea.[16] Table I illustrates details of energy and nutrient supplementation. Current evidence neither supports the routine use of antibiotics in patients with persistent diarrhea nor does it favour the use of probiotics, racecadotril or steroids in these patients.[17]

Management of persistent diarrhea - Challenges

Early infancy (less than 6 months of age) is a very challenging period in the management of persistent diarrhea as these infants respond best to an extensively hydrolysed formula (EHF). Although EHF have been introduced commercially and are now readily available in India, they still continue to be prohibitively expensive for communities

Diet A (Reduced lactose diet)

- Milk rice gruel
- Milk suji (Rava) gruel
- Rice with curd
- Dalia (Wheat rava)

Diet B (Lactose free - Reduced starch diet)

- Carbohydrates provided as mixture of cereals and glucose
- Milk replaced with chicken, egg or protein hydrolysate

Diet C (Monosaccharide based diet)

- Only glucose and protein source as egg white or chicken
- MCT oil added to feed to increase energy density

Fig.1. Dietary intervention in persistent diarrhea

Table I. Energy and nutrient requirements in persistent diarrhea

Food benefit	Dose	Duration
Energy	100 kcal/kg body weight (density 1 kcal/g)	After recovery to continue and subsequently provide according to RDA
Micronutrients		
Zinc	2mg /kg/day	2 weeks
Copper	0.3mg /kg/day	
Folic acid	5mg on day 1 and subsequently 1mg/day	
Oral vit. A	<6 months of age-50,000 IU >6 months to 1 year of age-100,000 IU 1 year to 5 years – 200,000 IU	Single stat dose
Inj vit. K	5mg intravenously	Single stat dose at admission
Inj magnesium sulfate (50%)	0.2ml/kg/day twice daily (Injection solution given orally)	3 days
Oral iron	3mg/kg/day	After recovery – for 2 weeks

Table II. Investigation in diagnosis of chronic diarrhea[1]

Type	Test	Availability in India	Diagnosis in India
Osmotic Vs Secretory diarrhea	Stool pH, reducing substance Stool electrolytes Stool osmotic gap Breath hydrogen tests	Good Poor-Fair Poor Poor	Based on stool pH, reducing substance and response to keeping nil orally
Fatty diarrhea	Sudan stain Acid steatocrit 72 hr stool fat	Good Poor Poor	Based on fat globules in normal microscopy and Sudan stain at some centres
Protein losing enteropathy	Fecal alpha-1 antitrypsin	Poor	Based on clinical picture, low serum albumin and by exclusion
Pancreatic insufficiency	Fecal elastase / chymotrypsin Secretin test	Poor Poor	Based on ruling out other causes of fatty diarrhea

with a low socio-economic background. Another challenge is the relative paucity of adequate and appropriate facilities to manage unresponsive infants at regional health care centres. In addition, the compliance with dietary regimens among the upper strata of society is poor. Many regional health centres are not adequately equipped to handle infants and young children requiring prolonged hospital stay and nutritional management.

Prevention of persistent diarrhea - Principles

Measures aimed at prevention of persistent diarrhea should be directed to achieve two main objectives - ensuring optimal nutritional status of the infant and young child with acute diarrhea and correcting undernutrition and appropriate treatment of acute diarrhea with avoidance of inappropriate antibiotic use. At the community level,

Fig.2. Etiology of chronic diarrhea

effective strategies before six months of age are promotion of exclusive breast feeding and after six months of age, timely introduction of age-appropriate complementary food along with meticulous attention to hand washing, food hygiene, use of low osmolarity ORS, oral zinc supplementation and avoiding unnecessary use of antibiotics.[18]

Chronic non-infectious diarrhea

The accurate incidence of chronic diarrhea of non-infectious etiology in India is not known. This is further complicated by the fact that there are multiple underlying etio-pathogenetic mechanisms causing chronic non-infectious diarrhea. The practical approach to confirmation of diagnosis and appropriate management depends on the underlying cause. In a study on 137 children with chronic diarrhea, 26% were due to celiac disease, 9% due to parasitic infections (giardiasis/amebiasis) and 5% attributable to tuberculosis.[19]

Fig.2 shows the specific etiology in chronic diarrhea and Table II summarizes the basic investigations useful in the diagnosis of chronic diarrhea.

It must be kept in mind, however, that a diagnosis confirmed by histopathological evaluation of gastrointestinal tissue obtained through upper gastrointestinal endoscopy or colonoscopy is an extremely valuable investigative modality in infants and children with chronic diarrhea. Management of chronic diarrhea is dependent on the specific etiology and confirmation of diagnosis. Limitation of diagnostic resources in developing countries such as India makes the diagnosis and management of chronic diarrhea a challenge.

Conclusion

The approach to the diagnosis and appropriate management of persistent diarrhea and chronic diarrhea of non-infectious etiology should always be planned from the practical standpoint of feasibility and affordability of investigative tools, diagnostic modalities and management options in countries of the South Asian region such as India. The crucial role of preventive public health strategies at community level in the overall management of persistent diarrhea need not be overemphasized and is an integral part of the overall management approach aimed at achieving a positive outcome. A systematic approach directed towards ascertaining the specific etiology in chronic diarrhea of non- infectious etiology is the first step in ensuring appropriate and effective management of the same.

Points to Remember

- ***Diarrhea lasting for more than 14 days is chronic diarrhea.***
- ***Persistent diarrhea is usually acute in onset, often infectious in etiology and curable unlike chronic which is often insidious in onset, non infectious in etiology and controllable.***
- ***Secondary lactose intolerance, persistence of gut or***

extra gut infections and malnutrition are the common causes of persistent diarrhea in our country.

- ***Management of persistent diarrhea include proper diet therapy and trace element supplementation in malnourished children.***
- ***Exclusive breastfeeding, introduction of complimentary feeding at proper time, measles vaccination, improvement in personal hygiene and supplementation of vitamin A are some of preventive strategies of persistent diarrhea in developing nations.***
- ***Etiological workup of chronic diarrhea should be meticulous.***

References

1. Mathai J, Raju B, Bavdekar A. Chronic and Persistent Diarrhea in Infants and Young Children – Status Statement. Pediatric Gastroenterology Chapter, Indian Academy of Pediatrics. Indian Pediatr 2011; 48:37-42.
2. Mittal SK. Chronic Diarrhea in tropics. Indian J Pediatr 1999; 66:S4-S15.
3. Alam S, Admed SH, Lamba LMS. Clinical profile of persistent diarrhea in a DTTU. Indian Pediatr 1997; 34:631-635.
4. Schorling JB, Wanke CA, Schorlling SK, McAullife JF, de Souza MA, Guerrat RL. A prospective study of persistent diarrhea among children in an urban Brazilian slum: patterns of occurrence and etiologic agents. Am J Epidemiol 1990; 132:144-156.
5. Fauveau V, Henry FJ, Briend A, Yunus M, ChakrabortyJ. Persistent diarrhea as a cause of childhood mortality in rural Bangladesh. Acta Paediatr 1992; 381:S 12–14.
6. Ahmed F, Ansaruzzaman M, Haque E, Rao MR, Clemen JD. Epidemiology of post shigellosis persistent diarrhea in young children. Pediatr Infect Dis J 2001; 20:525-530.
7. Sullivan PB. Studies of the small intestine in persistent diarrhea and malnutrition: the Gambian experience. J Pediatr Gastroenterol Nutr 2002; 34:S11-13.
8. Amadi B, Kelly P, Mwiya M, Mulwazi E, Sianongo S, Changwe F, et al. Intestinal and systemic infection, HIV and mortality in Zambian children with persistent diarrhea and malnutrition. J Pediatr Gastroenterol Nutr 2001; 32:550-554.
9. Adejuyigbe EA, Oyelami O, Onayemi O, Durosinmi MA. Paediatric HIV/AIDS in Ile-Ife, Nigeria. Cent Afr J Med 2003; 49:74-78.
10. Taniguchi K, Rikimaru T, Yartey JE, Akpedonu, P, Armar-Klemesu MA, Nkrumah FK, et al. Immunological background in children with persistent diarrhea in Ghana. Pediatr Int 1999; 4:162-167.
11. Bhan MK, Bhandari N, Bhatnagar S, Bahl R. Epidemiology and management of persistent diarrhoea in children of developing countries. Indian J Med Res 1996; 104:103-114.
12. International Working Group on Persistent Diarrhoea. Evaluation of an algorithm for the treatment of persistent diarrhoea: a multicentre study. Bull World Health Organ 1996; 74:479-489.
13. Bhutta ZA, Hendricks KH. Nutritional management of persistent diarrhea in childhood: a perspective from the developing world. J Pediatr Gastroenterol Nutr 1996; 22:17-37.
14. Dutta P, Mitra U, Dutta S, Manna B, Chatterjee MK, De A, et al. Hypo-osmolar oral rehydration salts solution in dehydrating persistent diarrhoea in children: double-blind randomized, controlled clinical trial. Acta Paediatr 2000; 89:411-416.
15. Sarker SA, Mahalanabis D, Alam NH, Sharmin S, Khan AM, Fuchs GJ. Reduced osmolarity oral rehydrationsolution for persistent diarrhea in infants: a randomizedcontrolled clinical trial. J Pediatr 2001; 138:532-538.
16. Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000; 72:1516-1522.
17. Bhatanagar S, Bhan MK, Singh KD, Srivastav R. Prognostic factors in hospitalized children with persistent diarrhea: Implications for diet therapy. J Pediatr Gastroenterol Nutr 1996; 23:151-158.
18. Sheth M, Obrah M. Diarrhea prevention through food safety education. Indian J Pediatr 2004; 71:879-882.
19. Yachha SK, Misra S, Malik AK, Nagi B, Mehta S. Spectrum of malabsorption in North Indian children. Indian J Gastroenterol 1993; 12:120-125.

NEWS AND NOTES

ISPGHAN

Date: October 26, 2018 – October 28, 2018

Venue: Mumbai

Contact:

Email: aabhanagral@gmail.com

GASTROENTEROLOGY - II

A REVIEW OF CONSTIPATION IN CHILDREN

***Sumit Kumar Singh**
****Surender K Yachha***

Abstract: *Childhood constipation is a common problem and functional constipation forms the major bulk. Careful history and examination is usually sufficient to diagnose functional constipation. Presence of red flags should raise a suspicion of underlying organic etiology. Polyethylene glycol, which is an osmotic laxative, is the first line agent for both disimpaction as well as maintenance therapy. Lactulose can be used in case of non-availability or intolerance to polyethylene glycol. Any precipitating factor needs to be identified and corrected. Prolonged treatment is necessary with gradual tapering before stopping. Proper counseling, timely follow-up and compliance to treatment results in good outcome.*

Keywords: *Constipation, Children, Polyethylene glycol*

Constipation is one of the common health related complaints in children seeking medical attention. Data from developed countries shows that prevalence of childhood constipation in the general population ranges from 0.7 to 29.6% and accounts for 3% of general pediatric visits and 30% of pediatric gastroenterologist office practice.[1] Functional constipation (FC) is the most common cause of constipation in children and is responsible for 90-95% of all cases of constipation in children.[2] Data from the developing countries on prevalence of constipation is not widely available.[3] In two studies published from our center, FC comprised of 77-85% of children with constipation.[4,5]

Normal stool frequency

Normal stool frequency varies from neonatal age group to childhood. Studies from Europe including infants and children up to 42 months of age showed that median stool frequency varies from 3 (0-9) per day at 1 month of age to 2 (0-6) per day at 3 months of age and also depends on whether the child is formula fed or breast fed.[6,7] There are very few studies on normal stool frequency and consistency in Indian children. Two studies from India described the average stool frequency which ranged from 3-4 times/day in less than 1 month; 1.5-2 times/day in 1 month - 1 year; 1-2 times/day in 1-2 years age, mostly formed and once a day in children older than 2 years of age.[8,9] Another recent study by Shava, et al including healthy Indian children with median age of 9 (range, 2.5-17) years documented the normal stool frequency as 7 (7-14) per week.[10] Thus, diagnosis of constipation should be made while keeping in mind the normal variations of stool frequency and consistency in healthy infants as well as variations based on their feeding pattern.

Definition

Constipation in children as defined by Rome IV is given in Box 1.[11,12] As normal stool frequency in Indian children older than 2 years of age is more than once a day, the diagnosis of FC should be guided by stool consistency and other features of FC rather than stool frequency alone.

Box 1. Constipation definition – Rome IV

Must include 2 or more of the following, occurring at least once per week for a minimum of 1 month

a) 2 or fewer defecations in the toilet per week

b) at least 1 episode of fecal incontinence per week after acquisition of toilet training

c) history of retentive posturing or excessive stool retention

d) history of painful or hard bowel movements

e) presence of a large fecal mass in the rectum or per abdomen

f) history of large diameter stools that can obstruct the toilet

* Scientific Pool officer

** Professor and Head,
Department of Pediatric Gastroenterology,
Sanjay Gandhi Postgraduate Institute of Medical Sciences,
Lucknow, Uttar Pradesh.
email: skyachha@yahoo.co.in

Pathophysiology

The pathophysiology of FC is multifactorial. The usual initiating event is a painful-frightening bowel movement as result of which child fears to pass stool leading to withholding of stool.[13] Prolonged stasis of stools in the rectum results in absorption of water making stool hard with further pain and difficulty in defecation. This leads to a vicious cycle of further retention and hardening of stool resulting in painful defecation and more withholding. This can lead to fecal impaction which sometimes may manifest as fecal incontinence.[14]

Evaluation

History and examination play an important role in making a diagnosis of constipation, differentiating functional and organic constipation and identifying the precipitants of FC. Presence of retentive posturing (hiding behind furniture or going to a corner and standing on toes with legs crossed, red faced) is seen characteristically in children with FC. This is often interpreted by parents as if the child is straining to pass the stool. Children with FC can also develop anal fissures and painful bleeding as a result of hard stool. Sometimes, children with long-standing FC may develop urinary symptoms like frequency, burning, crying during micturition, urinary retention /incontinence.[15] Identification and correction of precipitating factors of FC like faulty dietary intake, drugs, premature initiation of toilet training and change in local environment (start of schooling) form an integral part of management.[16]

Presence of red-flag signs in the form of early onset (<6 months of age), history of delayed passage of meconium, failure to thrive, abdominal distension, fever, diarrhea and vomiting should raise a suspicion of underlying organic etiology of constipation. Table I describes the various clinical features that point towards organic cause in a child with constipation. Hirschsprung disease is considered as one of the most common differential diagnosis of constipation by pediatricians. This can be distinguished from functional constipation based on history of onset in first month of life, delayed passage of meconium beyond 48 hours, presence of abdominal distension and occurrence of frequent enterocolitis.

Investigations

Functional constipation is the most common cause seen in 90-95% of children. A careful history and examination is all that is needed to confirm the diagnosis of FC without the need of any investigation. Children with red flag signs suggestive of an organic etiology or those with FC who fail to respond to therapy need diagnostic evaluation. X-ray abdomen can be done in a case of FC to assess disimpaction in obese children or those who refuse digital rectal examination (DRE) but is not required as a routine test.

Management

Management of children with FC includes a) medical therapy, b) toilet training, c) dietary modifications and d) parental counseling and follow-up.

Medical therapy

It comprises of 2 phases, first phase of disimpaction in patients with fecal impaction and second phase of maintenance therapy with laxatives.

Table I. Characteristics of organic etiology of constipation

Clinical feature	Suspected organic etiology
History of delayed passage of meconium, empty rectum on digital rectal examination with gush of air and liquid stool, abdominal distension, enterocolitis	Hirschsprung disease
Developmental delay, lethargy, cold intolerance, dry skin	Hypothyroidism
Frequent falls or abnormal gait beyond infancy, spinal dimple/ tuft of hair, abnormal neurological examination	Spinal cord abnormalities (tethered cord, spinal dysraphism)
Developmental delay, regression of mile stones, feeding difficulties	Cerebral palsy, neurodegenerative disorder
Abdominal pain, distension and bilious vomiting	Mechanical obstruction of bowel or pseudo-obstruction
Anemia and growth failure	Celiac disease
Pain abdomen, blue gum lines and pallor	Lead poisoning

Table II. Laxatives therapy for disimpaction in children with functional constipation

Oral agents	**Dosage**	**Side effect**
Polyethylene glycol (at home)	1-1.5 g/ kg/ day for 3-6 days (end point is either empty or a small amount of soft stool on rectal examination and resolution of any fecal impaction per abdomen if it was there)	Loose stools, bloating/ flatulence, nausea, vomiting
Polyethylene glycol solution (in hospital)	25 ml/ kg/ hour oral or by nasogastric tube in young children (end point is clear rectal effluent)	Nausea, vomiting, abdominal cramps, rarely electrolyte abnormality, pulmonary aspiration
Rectal agent (enema)	**Dosage**	**Side effects**
Phosphate soda (proctoclysis enema)	2-18 y: 2.5 mL/kg, max 133 mL/dose	Hyperphosphatemia Hypercalcemia

Disimpaction: The rationale behind disimpaction is to clear the colon completely in order to achieve the normal diameter and tone. This helps in attainment of proper anorectal reflexes and pelvic floor coordination to facilitate normal stool expulsion. Disimpaction can be either home based or hospital based with variable rate of success in the former (68-97%) while in the latter it is 100%.[17,18] Polyethylene glycol (PEG) is the first line agent for disimpaction and is given orally or through nasogastric tube in younger children after hospitalization.[19] Doses and duration of PEG for each method of disimpaction is given in Table II. Rectal enemas (Sodium phosphate) can also be used as an alternative therapy to clear the loaded colon if PEG is not available (Table II). Comparison of oral PEG and rectal enema in a randomized controlled trial did not prove the superiority of one over the other.[17] However, the re-impaction rate after initial disimpaction with enemas was higher than that with PEG as shown by two retrospective studies.[18,20] Oral route is preferred over enema because of the ease of administration, less invasive nature, patient friendly and socially acceptable. Manual evacuation of rectum is rarely required in patients failing oral and rectal disimpaction but it should be performed preferably under sedation. Glycerine suppositories are to be used for disimpaction in infants as PEG and enema are not advocated in them.[19]

Maintenance therapy: Maintenance therapy should only be started after effective disimpaction. Osmotic laxatives which include PEG and lactulose are the mainstay of maintenance therapy. Polyethylene glycol is recommended as the first choice.[19] The recommended dose of PEG for maintenance therapy is 0.2–0.8 g/kg/day.[19] In a Cochrane review in the treatment of constipation, PEG was found to be more effective in increasing stool frequency than placebo, lactulose and magnesium hydroxide.[21] A combination of PEG with electrolytes can be used to minimize the risk of electrolyte imbalance as it is iso-osmotic instead of hypo-osmotic PEG without electrolytes. Lactulose / lactitol can be used as a second line laxative agent in case of unavailability or intolerance to PEG. These undigestible disaccharides are fermented into hyperosmolar low molecular weight acids by intraluminal bacteria which results in intraluminal water retention and an increase in colonic peristalsis. The recommended dose of lactulose is 1-2g/kg once or twice a day and that of lactitol is 250 to 400 mg/kg/day. Both of them can be used across all age groups. Side effects of osmotic laxatives include fecal incontinence (in case of overdose) flatulence, abdominal pain and bloating, seen less commonly with PEG as compared to lactulose. In a recent study, lactulose was more often switched to PEG due to lack of adequate response compared to vice versa during maintenance therapy of children with FC.[5] The dose of laxative should be adjusted to have one or two soft stools/day without any pain or incontinence. It is important to continue maintenance treatment for at least 2 months but sometimes may need several months to years before discontinuation.[19] All symptoms of constipation should have been resolved for at least one month before discontinuation of treatment. Discontinuation of therapy should be done gradually.[19]

Stimulant laxatives act directly on the intestinal mucosa, stimulating intestinal motility and/or increasing water and electrolyte secretion. No randomized controlled trials are available in children regarding their efficacy. Thus, stimulant laxatives are usually required as rescue therapy (an acute or sudden episode of constipation while being

Table III. Stimulant laxatives as rescue therapy in treatment of functional constipation

Name	Dose	Side effects
Bisacodyl	Oral (effect in 6-8 hours), single bedtime dose 3-10 y: 5 mg/day >10 y: 5-10 mg/day Rectal (effect within 30-60 min) 2-10 y: 5 mg/day >10 y: 5-10 mg/day	No side effects on short term use. Abdominal cramps, diarrhea, hypokalemia
Sodium picosulphate	Given as single dose 1 month-4 years: 2.5-10 mg/day 4 to 18 years: 2.5-20 mg/day Available as liquid	abdominal pain, nausea and diarrhea

on regular compliant maintenance therapy). These are given for a short duration of 2-3 days to tide over the acute episode of constipation (Table III).

Toilet-training

It is as important as pharmacotherapy in treatment of children with FC. Toilet training should be started after 2 to 3 years of age. Child is made to sit in the toilet, 2-3 times a day for 5-10 minutes within 30 minutes of meals to take the advantage of gastro-colic reflex. The position of child while sitting in toilet is squatting in the Indian toilet or with foot rest in English toilet/potty seat to have appropriate angulation of knees and thighs to facilitate expulsion of stools. A reward system (positive reinforcement) helps in motivating the child and avoiding child-parent conflict. For toilet training it is advisable to follow the 'Rule of 1' (Box 2).[16]

Dietary modification

Most of the children with FC lacks adequate amount of fiber in their diet. Many of the young children are on predominant milk diet. There are no well-conducted randomized controlled studies of diet and treatment of constipation. Adequate intake of fiber-rich diet (cereals, whole pulses with bran, vegetables, salad and fruits) is recommended and parents should be provided with high fiber diet chart as per local practice. Younger children are encouraged to increase the intake of semi-solids and solid food with restriction of milk. Adequate intake of water and normal activity are advised.

Box 2. Toilet training – 'Rule of 1'

Toilet training to be done

- by one person
- one routine (5 min after each major meal)
- one place
- one word (e.g. pooh/potty, etc.)

Patient counseling and follow-up

It is worth explaining the parents about the basic pathophysiology of FC. It helps in establishment of the faith in treating physician, facilitates them to understand the goal of treatment and therefore improves the compliance to the therapy. Any precipitating factors identified should be eliminated or modified by appropriate advice. A close and regular follow-up is essential to ensure and reinforce the compliance and assess the response to treatment. At each follow-up, stool history, associated symptoms, compliance with diet, medications and toilet-training should be recorded. It is advisable for parents to maintain a stool diary for objective assessment of treatment response. First follow-up is advised at 2 weeks to assess compliance and subsequently at 1-2 months interval till normal bowel habit is attained. Further, three monthly follow up for a minimum period of one year should be done. Once normal bowel habit is achieved with disappearance of all symptoms of constipation for at least 6 months, laxative therapy can be gradually tapered over a period of 3 months and stopped.[16]

Outcome

Data from the Western countries have shown that 50% of children with FC recover and are off laxative therapy within 6-12 months.[22, 23] A small but significant proportion

which is around 25% continues to experience symptoms up to adult age.[24] Data from India shows that 95% respond over a follow-up duration of 15.0 ± 16.7 months.[4] On follow-up, 18.4% patients have recurrence of symptoms and 10.5% of them require rescue disimpaction.[4]

Refractory constipation

Diagnosis of refractory constipation is made when there is no response to therapy despite sustained conventional treatment with optimal dose and duration of at least 3 months.[19] The prevalence of refractory constipation is estimated to be 20-30%.[19] Children with refractory constipation should be investigated for hypothyroidism, celiac disease, Hirschprung disease, cow's milk protein allergy in young children, lead poisoning and spinal abnormalities. In case the above causes are ruled out, the child should be referred to a higher centre for evaluation of slow transit constipation, pseudoobstruction and pelvic dyssynergia.[16]

Conclusion

Constipation is a common medical condition seen in children. FC is the most common cause and can be diagnosed on the basis of careful history and examination. It is important to identify fecal impaction as disimpaction is necessary before starting maintenance therapy. PEG, an osmotic laxative, is the first line therapy for FC. Lactulose can be used in case of non-availability or intolerance to PEG. Parent counseling along with dietary modification and toilet training are equally important. Treatment needs to be given for prolonged period with gradual tapering before stoppage. Refractory cases need to be evaluated at referral centre.

Points to Remember

- ***Functional constipation is the most common cause of chronic constipation in children.***
- ***Presence of red flag signs should raise the suspicion of organic etiology.***
- ***Polyethylene glycol, an osmotic laxative is the first line of treatment for children with functional constipation.***
- ***Lactulose can be used in case of non-availability or intolerance to polyethylene glycol.***
- ***Treatment needs to be continued for long period with tapering before stoppage.***

References

1. Van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006; 101:2401- 2409.
2. Rubin G, Dale A. Chronic constipation in children. Br Med J 2006; 333:1051-1055.
3. Rajindrajith S, Devanaryana NM, Adhikari C, Pannala W, Benninga MA. Constipation in children: An epidemiological study in Sri Lanka using Rome III criteria. Arch Dis Child 2012; 97:43-45.
4. Khanna V, Poddar U, Yachha SK. Etiology and clinical spectrum of constipation in Indian children. Indian Pediatr 2010; 47:1025-1030.
5. Poddar U, Singh S, Pawaria A, Srivastava A, Yachha SK. Aetiological spectrum, clinical differentiation and efficacy of polyethylene glycol over lactulose in children with constipation: Experience of 316 cases. J Paediatr Child Health 2018. doi: 10.1111/jpc.14099. [Epub ahead of print] accessed on 31st August, 2018.
6. Steer CD, Emond AM, Golding J, Sandhu B. The variation in stool patterns from 1 to 42 months: a population bases observational study. Arch Dis Child 2009; 94:231-234.
7. denHertog J, van Leengoed E, Kolk F, van den Broek L, Kramer E, Bakker E, et al. The defecation pattern of healthy term infants up to the age of 3 months. Arch Dis Child Fetal Neonatal Ed 2012; 97:F465-F470.
8. Yadav M, Singh PK, Mittal SK. Variation in bowel habits of healthy Indian children aged up to two years. Indian J Pediatr 2014; 81:446-449.
9. Sujatha B, Velayutham DR, Deivamani N, Bavanandam S. Normal Bowel Pattern in Children and Dietary and Other Precipitating Factors in Functional Constipation. J Clin Diagn Res 2015; 9:SC12-SC15.
10. Shava U, Yachha SK, Srivastava A, Poddar U, Sensarma M. Assessment of stool frequency and colonic transit time in Indian healthy children and functional constipation: a difference from the West. Indian J Gastroenterol 2018 (in Press).
11. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood Functional Gastrointestinal Disorders: Child/ Adolescent. Gastroenterology 2016; 150:1456-1468.
12. Benninga MA, Nurko S, Faure C, Hyman PE, Roberts J, Schechter NL. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology 2016; 150:1443-1455.
13. Mugie SM, Di Lorenzo C, Benninga MA. Constipation in childhood. Nature Rev Gastroenterol Hepatol 2011; 8(9):502-511.
14. Rajindrajith S, Devanarayana NM. Constipation in children: novel insight into epidemiology, pathophysiology and management. J Neuro gastroenterol Motil 2011; 17(1):35-47.

15. Loening-Baucke V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics 1997; 100:228-232.
16. Yachha SK Srivastava A, Mohan N, Bharadia L, Sensarma M. Management of Childhood Functional Constipation: Consensus Practice Guidelines of Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. Indian pediatr 2018; June 13 pii: S097475591600121 [e-pub ahead of print].
17. Bekkali NLH, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O, et al. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. Pediatrics 2009; 124:e1108-1115.
18. Guest JF, Candy DC, Clegg JP, Edwards D, Helter MT, Dale AK, et al. Clinical and economic impact of using macrogol 3350 plus electrolytes in an outpatient setting compared to enemas and suppositories and manual evacuation to treat paediatric faecal impaction based on actual clinical practice in England and Wales. Curr Med Res Opin 2007; 23:2213-2225.
19. Tabbers MM, Di Lorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatmentof functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014; 58: 258-274.
20. Freedman SB, Thull-Freedman J, Rumantir M, Eltorki M, Schuh S. Pediatric constipation in the emergency department: evaluation, treatment and outcomes. J Pediatr Gastroenterol Nutr 2014; 59:327-333.
21. Gordon M, Naidoo K, Akobeng AK, Thomas AG. Cochrane review: osmotic and stimulant laxatives for the management of childhood constipation. Evid Based Child Health 2013; 8:57-109.
22. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. J Pediatr 2005; 146:359-363.
23. Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: A systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr 2010; 50:256-268.
24. Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics. 2010; 126:e 156-162.

CLIPPINGS

Antacid therapy for gastroesophageal reflux in preterm infants: a systematic review

Gastro-oesophageal reflux is prevalent in preterm infants. Despite widespread use in clinical practice, there is still much controversy over the efficacy and safety of drug interventions, particularly antacid therapy. The objective was to systematically review the effects of antacid therapy on preterm infants with symptoms of gastro-oesophageal reflux, and to assess the safety of these interventions.

An electronic search of the Cochrane central register of controlled trials (CENTRAL, The Cochrane Library), MEDLINE (1966–present), EMBASE (1980–present) and CINAHL (1982–present) as well as other online sources was carried out. Participants were preterm infants (<37 weeks gestation) with gastro-oesophageal reflux disease who were receiving care on a neonatal unit. The effects of histamine-2 receptor antagonists, proton pump inhibitors and alginates against placebo, primarily to see if they reduced the symptoms of reflux was assessed.

Six studies were included in this review. Meta-analysis could not be carried out due to a lack of studies assessing the same intervention with the same outcomes. Omeprazole therapy significantly reduced the oesophageal acid exposure percentage time with pH<4 ($p<0.01$) and sodium alginate significantly decreased gastro-oesophageal reflux episodes ($p=0.024$). Metoclopramide and ranitidine showed a significant increase in gastro-oesophageal reflux disease symptoms versus placebo ($p<0.04$). No significant results were found for the use of esomeprazole or lansoprazole versus placebo.

Conclusion: There is insufficient evidence available to conclude whether antacid therapy is effective or safe when treating gastro-oesophageal reflux disease in preterm infants. Further research is needed into this topic and caution should be taken when administering antacids to preterm infants.

Dermyshi E, Mackie C, Kigozi P, et al., Antacid therapy for gastroesophageal reflux in preterm infants: a systematic review. BMJ Pediatr Open 2018; 2:e000287. doi: 10.1136/bmjpo-2018-000287

GASTROENTEROLOGY - II

AUTOIMMUNE HEPATITIS

***Geetha M**
****Sreerekha KB**

Abstract: *Autoimmune hepatitis is one of the common causes of acute and chronic liver disease in children and adolescents. It has a varied presentation and if detected early, can be treated effectively. Early diagnosis is the most important which may not be easy in many cases. This article outlines the clinical presentations, scores for diagnosis and outlines the treatment aspects of this condition. When medical management fails, liver transplantation is the only option.*

Keywords: *Liver diseases, Autoimmune, Simplistic scoring.*

Autoimmune liver disease includes autoimmune hepatitis, autoimmune sclerosing cholangitis (ASC) and de novo autoimmune hepatitis after liver transplantation.

A. Autoimmune hepatitis

Autoimmune hepatitis (AIH) a progressive, inflammatory, immunological disease. AIH is more commonly seen in females. It was first described by Jan Waldenstorm in a patient with chronic hepatitis. The disease is characterised by chronic hepatitis, circulating autoantibodies and raised immunoglobulins with no known etiology.[1] Just like any other autoimmune disease, this involves formation of antibodies against antigens in the liver resulting in a progressive inflammation followed by liver cell damage which if left unchecked can cause fibrosis, cirrhosis and end stage liver disease, necessitating liver transplantation. However, if diagnosed early and if proper treatment is initiated, mortality or need for liver transplant may be avoided. In children, the disease is known to have a more aggressive course than adults, requiring early recognition and treatment to have a favourable outcome.[2]

* Pediatric Gastroenterologist

** Senior Specialist,
Department of Pediatrics,
Aster Medcity, Cochin.

email: drgeethasanil@gmail.com

Epidemiology

Though it was earlier considered rare in children, there are now increasing reports about cases in children predominantly females. It is not known whether this represents an actual increase in incidence or a greater identification of the disease due to increased awareness and greater availability of diagnostic tests.

Genetics

The strongest associations are found in the HLA-DRB1 locus of the major histocompatibility complex (MHC) which presents the antigen to the immune system and stimulates a response. Children who are DRB1*03 gene positive tend to have a higher incidence of mortality and are more likely to require liver transplantation.[3,4]

Pathogenesis

The exact etiology in still unknown. Genetic susceptibility both within and outside the MHC complex, deficient cellular regulators and molecular mimicry are some of the pathogenic mechanisms described. Environmental triggers, have been suspected to be the triggers, but there is no conclusive evidence to prove this theory. The principle of molecular mimicry may account for the mechanism of liver injury by various environmental triggers, viruses, drugs, etc.[5]

Types

AIH has been classified into two subtypes based on the antibody profile (Table I).[6] In both types of AIH, approximately 20% of patients have other autoimmune disorders like autoimmune thyroiditis, vitiligo, type I diabetes mellitus, Grave's disease, inflammatory bowel disease, nephrotic syndrome, etc. A small proportion of patients with autoimmune hepatitis may be negative for all presently known antibodies and termed "seronegative"AIH.[7-9]

Clinical presentation

Autoimmune hepatitis can present in the following ways:

i) Acute hepatitis: 40% of the patients present in this manner and the clinical features of the disease are indistinguishable

Table I. Autoimmune hepatitis – Classification

Variables	Type I AIH	Type II AIH
Characteristic autoantibodies	Antinuclear antibody Smooth muscle antibody Anti-actin antibody Autoantibodies against soluble liver antigen and liver pancreas antigen Atypical perinuclear anti-neutrophil cytoplasmic antibody.	Antibody against liver-kidney microsome-1 (LKM-1) Antibody against liver cytosol 1(LC-1)
Geographic variation	Worldwide	Worldwide, rare in North America
Age at presentation	Any age	Childhood and young adults
Sex	Female in 75% of cases	Female in approximately 95% cases
Association with other autoimmune diseases	Common	Common
Clinical severity	Varied	Generally severe
Histopathology features at presentation	Variable	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long term maintenance	Variable	Approximately 100%

from acute viral hepatitis. A few also present as fulminant hepatic failure wherein liver transplantation may be the only treatment option. This is more common in type II AIH. A common presentation is persistence of raised transaminases after an attack of viral hepatitis A, EBV, non A-E, etc. The child remains asymptomatic but the enzymes fail to normalize. This warrants a complete evaluation for other conditions like Wilson's disease and AIH.

ii) Chronic hepatitis: The presentation is insidious with symptoms of fatigue, arthralgia, relapsing jaundice, headache, anorexia, amenorhea and weight loss which can last for months to years in 25%-40% of patients. This is common in Type I AIH.

iii) Cirrhosis with portal hypertension: Some patients present for the first time with variceal bleeding, encephalopathy and end -stage liver disease.

iv) Asymptomatic/Incidental finding: This condition is often made by USG abdomen which may pick up findings like hepatomegaly, hepatosplenomegaly or even cirrhosis in an asymptomatic child.

v) Complications: Sometimes children present for the first time with complications like end-stage liver disease, GI bleed, hepatic encephalopathy with or without ascites.

Though the diagnosis can be established, these patients generally do not respond to standard treatment and will need liver transplantation.

Diagnosis

The diagnostic criteria for AIH involves positive serology and characteristic findings in liver biopsy. Autoantibody positivity alone is not diagnostic of AIH, though it is strongly suggestive. This is because, there may be non-specific autoantibody positivity in patients with other conditions, especially in the adult population. For this reason, the cut-off for the antibody titer is different in adults and children. In adults, a titer of 1:40 is the cut-off, while it is 1:20 for anti nuclear antibody (ANA) and smooth muscle antibody (SMA) and 1:10 for liver kidney and microsomal type 1 (LKM 1) antibody in children. It is also interesting that in the acute or fulminant forms of hepatitis, the antibodies are often found to be negative, but they become positive during follow up.

Autoantibodies: It forms an important aspect of the diagnostic armamentarium for AIH. They aid in differentiating type I and Type II. However, they are not pathognomonic for AIH. The conventional autoantibodies associated with AIH are ANA, SMA and LKM-1antibodies. Other non-standard antibodies described in AIH are anti-liver cytosol antibody type -1 (LC-1), pANCA, anti-asialoglycoprotein receptor (ASGPR) and [Sep (O-Phosphoserine) TRNA: Sec (Selenocysteine) TRNA Synthase] a protein coding gene (SEPSECS), soluble liver antigen/liver-pancreas (SLA/LP) autoantibodies.

Antinuclear antibody (ANA): It is one of the most non-specific antibodies and can be seen in other conditions too. In the liver, the staining pattern may be homogeneous or speckled. The speckled pattern is more commonly seen in younger children.[10]

Smooth muscle antibody (SMA): SMA may be seen alone or in conjunction with ANA in type I AIH. They are directed against the components of cytoskeleton like actin, tubulin, vimentin, desmin and skeletin.

Liver kidney microsomal type 1 antibody: LKM antibody is the main serological marker for Type II AIH. The target antigen is in the endoplasmic reticulum. They are further sub-classified as LKM 1, 2 and 3.[11]

Seronegative autoimmune hepatitis: In some patients, the above antibodies are all negative but the total immunoglobulin level is very high, signifying an underlying autoimmune pathology. Such patients were found to respond to immunosuppressive agents and were termed "sero-negative autoimmune hepatitis". However, the exact prevalence is unknown and many authors believe that these patients, later on, develop antibody positivity on follow up.

Imaging

Imaging helps in identifying the presence of a chronic liver disease and portal hypertension and its complications. However, its role in the diagnosis is limited.

Liver biopsy

In all cases of suspected AIH, a liver biopsy is recommended and should be done unless there is significant contraindication.[12] Biopsy helps not only in establishing the diagnosis but also to rule out other pathology in liver, guiding the treatment and long term follow up of these patients. In seronegative hepatitis, the liver biopsy picture helps to make a diagnosis. In situations where liver biopsy is contraindicated, if all the other tests strongly point to diagnosis of AIH, treatment should not be withheld for want of tissue diagnosis.

The characteristic feature in biopsy is mononuclear cell infiltrate invading the limiting plate- called interface hepatitis or piecemeal necrosis. There can be spillover of inflammatory cells into the hepatic lobule and hepatic regeneration with "rosette" formation.[13] An abundance of plasma cells along with large number of eosinophils is usually seen.

In many situations, a few of the above tests may be suggestive of AIH but the biopsy may not be typical and vice-versa. Since the treatment involves the use of steroids and other immunosuppressive agents and also life-long medications, it is only wise to be sure of the diagnosis before starting the child on life-long medication. To help in such situations, a "Simplified diagnostic criteria" was put forward (Table II).

Simplified diagnostic criteria for AIH

In 2008 a simplified scoring system was introduced by Hennes, et al. for clinical practice.[14] Four criteria were included - autoantibody detection, IgG levels, liver histology and exclusion of viral hepatitis. Negative scoring for infections like hepatitis B, C and Wilson's disease were also taken into account. The maximum score is 8. Probable AIH is when score is 6 and definite AIH is when score is ≥ 7.

Table II. Simplified diagnostic criteria of AIH

Category	Parameter	Score
Autoantibodies*	ANA / SMA 1:40	1
	ANA / SMA $\geq$ 1:80 or LKM $\geq$1:40 or SLA positive	2*
IgG	> Upper limit of normal	1
	>1.1 Upper limit of normal	2
Histology	Compatible with AIH	1
	Typical of AIH	2
Absence of Viral hepatitis	Yes	2

**Addition of points achieved for all autoantibodies (maximum, 2 points).*

Treatment

Anti-inflammatory or immunosuppressive therapy is the standard treatment for both types of AIH in children. The goals of treatment are to reduce hepatic inflammation and induce remission, improve symptoms and prolong survival.[15] Children tend to have more aggressive disease and it is recommended to start treatment in all cases.[16-18]

Standard treatment: Initial treatment with prednisolone alone or in combination with azathioprine is mandatory in all children with histological evidence of hepatitis with or without fibrosis or cirrhosis. Prednisolone is started at a dose of 2 mg/kg/day (max 60 mg/day). Once adequate response is seen, it can be gradually decreased by 5-10 mg every 2 weeks, with weekly monitoring and maintained at the minimum possible dose. After two weeks of initiation of steroids azathioprine in a dose of 2 mg/kg/day should be started (0.5mg/kg/day to begin with) and continued. Although transaminases may start decreasing with treatment, complete normalisation takes approximately six months in AIH-1 and nine months in AIH -2.[16] Once a patient goes into remission, (characterized by normalization of transaminases and decrease in titer of antibodies), steroids are gradually tapered till a minimum of 2.5 to 5 mg daily which is continued indefinitely along with maintenance dose of azathioprine. Some centres advocate single agent maintenance with azathioprine alone. However, patients with AIH type II tend to relapse on this single agent regimen and have to be maintained on combination of low dose steroids and azathioprine. In patients who do not respond, rescue treatment with mycophenolate mofetil (MMF), or calcineurin inhibitors like tacrolimus or cyclosporine should be considered, failing which liver transplantation is the only option.

Monitoring: In the first 4-8 weeks, weekly LFT are required to titrate the medication. Thereafter, it can be done once in 4-6 weeks. Monitoring for side effects of azathioprine must also be done in the appropriate setting. Monitoring of antibody titers is not recommended in adults, but in children, IgG levels and antibody levels seem to correlate with disease activity and are useful indices to monitor.[19]

Relapse or flares: While on treatment, a rise in transaminases is termed as a “flare”. The cause is most commonly due to poor compliance, improper dosage of medication or a concurrent infection. This is usually treated with an increase in the dose of prednisolone which is then tapered after remission is established

Rescue therapy: This was resorted to if there is no response to the steroid therapy. Medications used are biological agents like rituximab, infliximab and anti-thymocyte globulin.

Remission: This is said to have been achieved when the following criteria are met:

a) Transaminases within the normal range, b) normalisation of IgG levels, c) negative or low titre antibodies (<1:20 for ANA and ASMA and < 1:10 for Anti - LKM and Anti-SLA) and d) histological resolution of inflammation by biopsy. Since repeated biopsy is not feasible, the first three criteria are enough to call it a remission. However, in the event of long term remission when stoppage of medication is planned, a liver biopsy is essential to establish histological remission. Only then withdrawal of medication can be considered. In Type II AIH, there have been no reported cases wherein medication has been stopped successfully.

B. Autoimmune sclerosing cholangitis

Sclerosing cholangitis refers to an inflammatory process (most likely autoimmune), in the intrahepatic or extrahepatic bile ducts resulting in damage and fibrosis. The diagnosis is made on the basis of the cholangiographic appearance in magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). It occurs in a number of conditions like severe MDR3 gege defects, immunodeficiencies, Langerhan’s cell histiocytosis, cystic fibrosis, etc. When no such etiology is identified, the name primary sclerosing cholangitis (PSC) is given.

Inflammatory bowel disease (IBD) is found to be associated in 45% of patients with ASC and 20% of AIH. Most of these patients are positive for ANA +/- SMA antibodies. Treatment is similar to the treatment for AIH along with ursodeoxycholic acid (UDCA) in a dose not more than 15 mg/kg/day. Remission is however difficult to achieve and the disease progresses in about 50% of cases.

C. De novo autoimmune hepatitis after liver transplantation

AIH can occur in any patient who has undergone liver transplantation irrespective of the indication for transplant. The incidence of is reported to be 2%-6%.[20] The clinical and biochemical pattern is similar to autoimmune hepatitis and they respond to standard treatment.

Prognosis

The prognosis of children who respond to immunosuppresive treatment is good. Immunosuppresion

has vastly improved the survival and decreased the morbidity for AIH and is definitely indicated once a diagnosis is established. The disease has a fluctuating course with flares and spontaneous remissions. Despite good disease control, about 8.5% of patients develop end-stage liver disease and require liver transplantation.[16] All patients with AIH should receive vaccination for hepatitis B and hepatitis A and this must be done preferably before the start of immunosupression to ensure better response.[21]

Liver transplantation

Indications for liver transplantation in AIH are:

1. Fulminant or acute liver failure not responding to treatment.
2. End stage liver disease
3. AIH + ASC refractory to treatment
4. Hepatic malignancy

However, patients who undergo liver transplantation must be made aware that in 30%-80% of cases, the disease can recur in the transplanted liver.[22,23] It manifests as recurrence of symptoms and reappearance of antibodies. They respond to standard treatment for AIH.

Conclusion

Autoimmune hepatitis is probably underdiagnosed in children due to the insidious symptoms and lack of standardised laboratory test. However, it should be looked for and excluded in all cases of transaminitis or liver dysfunction so as to enable early diagnosis and prompt institution of treatment, which can prevent and to a certain extent reverse damage to the liver. In the future, better immunosupressants with targeted action may produce more sustained remission with lesser side effects, thereby improving the morbidity and mortality associated with this disease.

Points to Remember

- ***Autoimmune hepatitis is seen more in girls.***
- ***This condition is suspected whenever transaminases are fluctuating.***
- ***Clinical features can mimic any form of hepatitis.***
- ***Autoantibodies form an important part of the work up but they are not diagnostic.***
- ***Liver biopsy should be done.***
- ***If treated appropriately, it can be life saving.***
- ***Without proper treatment decompensation can occur in few requiring liver transplant.***

References

1. Vergani D, Mieli-Vergani G. Autoimmune hepatitis. In: Rodes J, Benhamou JP, Dufour JF. Textbook of hepatology: from basic science to clinical practicde. 3rd ed. London: Blackwell publishing, 2007:1089-1101.
2. Mieli-Vergani G, Vergani D. Autoimmune liver diseases in children- what is different from adulthood? Best Pract Res Clin Gastroenterol 2011; 25(6):783-795.
3. Czaja AJ, Strettell MD, Thomson LJ, Santrach PJ, Moore SB, Donaldson PT, et al. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. Hepatology 1997; 25(2):317-323.
4. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Significance of HLA DR4 IN type 1 autoimmune hepatitis. Gastroenterology 1993; 105(5):1502-1507.
5. Vergani D, Choudhuri K, Bogdanos DP, Mieli-Vergani G. Pathogenesis of autoimmune hepatits. Clin Liver Dis 2002; 6(3):727-737.
6. Krawitt EL. Autoimmune Hepatitis. N Eng J Med 2006; 354:54-66.
7. Johnson PJ, Mc Farlane IG. Meeting point: Intenational Autoimmune Hepatitis group. Hepatology 1993; 18(4):998-1005.
8. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. INternational Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatits. J Hepatol 1993; 31(5):929-938.
9. Gassert DJ, Garcia H, Tanaka K, Reinus JF. Corticosteroid responsive crytopgenic chronic hepatitis: evidence for seronegative autoimmune hepatitis. Dig Dis Sci 2007; 52(9):2433-2437.
10. Czaja AJ, Nishioka M, Morshed SA, Hachiya T. Patterns of nuclear immunoflorescence and reactivities to recombinant nuclear antigens in autoimmune hepatitis. Gastroenterology 1994; 107(1):200-207.
11. Manns MP, Obermayer- Straub P. Cytochromes P450 and uridine triphosphate-glucuronosyltransferases: model autoantigens to study drug -induced, virus induced and autoimmune liver disease. Hepatology 1997; 26(4):1054-1066.
12. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and Management of autoimmune hepatitis. Lancet 1984;(2)8409:954-956.
13. Ferreira AR, Roquete ML, Toppa NH, de Castro LP, Fagundes ED, Penna FJ. Effect of treatment of hepatic histopathology in children and adolescents with autoimmune hepatitis. J Pediatr Gastroenterol Nutr 2008; 46(1):65-70.

14. Hennes M, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of Autoimmune hepatitis. Hepatology 2008; 48:1540-1548.
15. Alvarez F. Autoimmune hepatitis and primary sclerosing cholangitis. Clin Liver Dis 2006; 10(1):89-107.
16. Gregorio GV, Portman B, Reid F, Donaldson PT, Doherty DG, McCartney M, et al. Autoimmune hepatitis in childhood: a 20 year experience. Hepatology 1997; 25(3):541-547.
17. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/ sclerosing cholangitis overlap syndrome in childhood: a 16 year prospective study. Hepatology 2001;33(3): 544-553.
18. Maggiore G, Bernard O, Hadchouel M, Hadchouel P, Odievre M, Alagille D. Treatment of autoimmune chronic active hepatitis in childhood. J Pediatr 1984; 104(6): 839-844.
19. Gregorio GV, McFarlane B, Bracken P, Vergani D, Mieli-Vergani G, et al. Organ and non-organ specific autoantibody titres and IgF levels as markers of disease activity: a longitudinal study in childhood autoimmune disease. Autoimmunity 2002;35(8):515-519.
20. Kerkar N, Yanni G. Denovo and recurrent autoimmune hepatitis after liver transplantation : A comprehensive review. J Autoimmun 2016;66:17-24.
21. Worns MA, Teufel A, Kanzler S, Shrestha A, Victor A, Otto G, et al. Incidence of HAV and HBV infections and vaccination rates in patients with autoimmune liver diseases. Am J Gastroenterol 2008; 103(1):138-146.
22. Seaberg EC, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in United States from 1987-1998: updated results from the Pitt-UNOS Liver Transplant registry. Clin Transpl 1998; pp17-37.
23. Wiesner RH, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, et al. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. Hepatology 1998; 28(3):638-645.

CLIPPINGS

Association of Whole-Body Computed Tomography With Mortality Risk in Children With Blunt Trauma JAMA Pediatr. 2018;172(6):542_549. doi:10.1001/jamapediatrics.2018.0109

Although several studies have demonstrated an improvement in mortality for injured adults who receive whole-body computed tomography (WBCT), it is unclear whether children experience the same benefit. The objective was to determine whether emergent WBCT is associated with lower mortality among children with blunt trauma compared with a selective CT approach.

A retrospective, multicenter cohort study was conducted from January 1, 2010, to December 31, 2014, using data from the National Trauma Data Bank on children aged 6 months to 14 years with blunt trauma who received an emergent CT scan in the first 2 hours after emergency department arrival. Data analysis was conducted from February 2 to December 29, 2017. Patients were classified as having WBCT if they received CT head, CT chest, and CT abdomen/pelvis scans in the first 2 hours and as having a selective CT if they did not receive all 3 scans. The primary outcome was in-hospital mortality in the 7 days after ED arrival. To adjust for potential confounding, propensity score weighting was used. Subgroup analyses were performed for those with the highest mortality risk (ie, occupants and pedestrians involved in motor vehicle crashes, children with a Glasgow Coma Scale score lower than 9, children with hypotension, and those admitted to the intensive care unit).

Of the 42,912 children included in the study (median age [interquartile range], 9 [5_12] years; 27,861 [64.9%] boys), 8757 (20.4%) received a WBCT. Overall, 405 (0.9%) children died within 7 days. After adjusting for the propensity score, children who received WBCT had no significant difference in mortality compared with those who received selective CT (absolute risk difference, -0.2%; 95% CI,-0.6% to 0.1%). All subgroup analyses similarly showed no significant association between WBCT and mortality.

Conclusion: Among children with blunt trauma, WBCT, compared with a selective CT approach, was not associated with lower mortality. These findings do not support the routine use of WBCT for children with blunt trauma.

Meltzer JA, Stone ME, Reddy SH, Silver EJ. Association of Whole-Body Computed Tomography With Mortality Risk in Children With Blunt Trauma. JAMA Pediatr. 2018;172(6):542–549. doi:10.1001/ jamapediatrics.2018.0109.

GASTROENTEROLOGY - II

PORTAL HYPERTENSION

***Sumathi Bavanandam**

Abstract: *Portal hypertension is the commonest cause of recurrent significant upper gastrointestinal bleed in children. Extra-hepatic portal venous obstruction followed by cirrhosis are the common causes of portal hypertension. Bleed is well tolerated in non-cirrhotic portal obstruction unlike cirrhosis, where features of hepatic decompensation like ascites and encephalopathy are common following variceal bleed. Good history and physical examination are important in identifying the level of portal hypertension. Effective management of acute variceal bleed is essential to prevent bleed related mortality. Endoscopy after hemodynamic stabilisation has both diagnostic and therapeutic role in managing children with portal hypertensive bleeds.*

Keywords: *Portal hypertension, Variceal bleed, Endotherapy, Children.*

Portal hypertension refers to increased pressure in the portal system and is defined as portal venous pressure above 10 mm Hg.[1] Portal hypertension (PHT) is not uncommon in children. In the developing countries, the common cause of portal hypertension is extra-hepatic portal venous obstruction (EHPVO) followed by cirrhosis.[2] Gastrointestinal bleed is the common clinical presentation in EHPVO and often they are well tolerated bleeds without signs of decompensation unlike variceal bleed due to cirrhosis. Outcome of the bleed depends upon the effective management of acute variceal bleed and underlying liver status.

Portal vein is formed by union of splenic vein and superior mesenteric vein at the level of L1 vertebra. Varices represent abnormal venous communications between portal and systemic circulation that develop to decompress the portal venous system in portal hypertension. The most common sites of varices are the lower oesophagus, stomach and rectum. Less common sites are peribiliary, retroperitoneal and bare area of liver. Gastroesophageal varices are clinically important as they are more prone to bleeding due to their position and exposure to food and acid, unlike varices in other sites like splenorenal or in the retroperitoneal region where chances of bleed are less but symptoms due to compression of adjacent organs can occur rarely. Functional classification of portal hypertension is based on the presence or absence of cirrhosis (Fig.1).

* Professor,
Department of Gastroenterology,
Govt. Mohan Kumaramangalam Medical College and Hospital, Salem.
email: drbsumathi@rediffmail.com

Etiology

EHPVO refers to the development of portal cavernoma in the absence of associated liver disease and is defined by the obstruction of the extrahepatic portal vein, with or without involvement of the intrahepatic portal veins or other segments of the splanchnic venous axis. EHPVO is the most common cause of PHT in Indian children. Among the intrahepatic causes biliary atresia, metabolic liver diseases, congenital hepatic fibrosis, autoimmune liver disease are important causes unlike the west where cirrhosis is more common.[3] EHPVO in children has phlebosclerosis as initial component with thrombosis as a secondary event due to infection or a primary thrombotic disorder.[4] Omphalitis, neonatal umbilical sepsis, umbilical vein cannulation, repeated abdominal infections, sepsis, dehydration, abdominal surgery and trauma are some of the predisposing factors.[5] Less commonly, congenital anomalies of left and right vitelline veins (from which the portal vein develops) can result in obstruction and may be associated with other congenital defects.[6] Prothrombotic states remains a less common cause.[7] Cirrhosis due to biliary atresia, metabolic liver diseases, autoimmune hepatitis, chronic hepatitis B, C, vascular obstructions and less commonly drugs can lead to portal HT. Studies in Indian children have shown extra-hepatic (68%-76%), intra-hepatic (24%-28%), non-cirrhotic portal fibrosis (NCPF) (4%), congenital hepatic fibrosis (3%) and Budd-Chiari syndrome (3%) as the causes of portal HT.[8,9]

Clinical presentation

Clinical presentation of portal HT in Indian children is based on the underlying etiology. Gastrointestinal bleed can present as hematemesis or melena and less commonly as hematochezia either alone or in combination. Upper

CHF-congenital hepatic fibrosis, NCPF-Non cirrhotic portal fibrosis

Fig.1. Portal hypertension - Functional classification

gastrointestinal bleeding was observed in 85% of children with EHPVO and often in the first or second decade of life and well tolerated due to normal functioning liver.[10] In children with biliary atresia, oesophageal varices are found between 30% to 50% by 10 years of age with their native liver.[11] Following a variceal bleed, encephalopathy and spontaneous bacterial peritonitis occur in children with cirrhosis. Ascites in EHPVO mostly occurs following an acute episode of bleeding and resolves within 1-2 weeks.[3,9] Non bleeding manifestations of EHPVO are splenomegaly (95.8%), anemia (91.6%), transient ascites (10.4%), epistaxis (6.25%), hypersplenism (37.5%).[12]

History should include umbilical sepsis, catheterisation, recurrent diarrhea, trauma and abdominal surgery for EHPVO. History for chronic liver disease include maternal history of B, C related viral hepatitis during pregnancy, drug abuse, tattooing in older children, consanguinity, family history of liver disease, Wilson disease (WD) and progressive familial intrahepatic cholestasis (PFIC). History of recurrent jaundice, high coloured urine, pale stool, itching and steatorrhea are seen in chronic cholestatic liver diseases like progressive familial intrahepatic cholestasis, Alagille syndrome, non syndromic bile duct paucity, cholangitic type of congenital hepatic fibrosis, rarely untreated choledochal cyst and biliary strictures which can progress to cirrhosis and portal hypertension.

Sine qua non in portal hypertension is splenomegaly. Presence of small liver, splenomegaly without ascites and anterior abdominal veins is suggestive of EHPVO whereas firm liver, splenomegaly, anterior abdominal veins, with or without ascites, point towards cirrhosis of liver. Dysmorphic facies is seen in Alagille syndrome. Pruritogenic skin marks, thick hyperpigmented skin over extremities often occur in chronic cholestasis. Children with congenital hepatic fibrosis are young and present with firm liver well appreciated below xiphisternum with moderate splenomegaly whereas similar clinical features in young adults or older patients without decompensation suggest non-cirrhotic portal fibrosis. Tender hepatomegaly, ascites, dilated abdominal wall veins and presence of veins over the back are seen in Budd Chiari syndrome. Elevated jugular venous pulsations and tender hepatomegaly indicate cardiac cirrhosis.

Investigations

The investigations include a) baseline test, b) tests to diagnose portal hypertension and c) tests to find etiology.

a) Tests-Baseline

Blood tests: Complete hemogram: Low hemoglobin indicates anemia either due to acute variceal bleed or chronic blood loss but less commonly due to impaired absorption of iron in portal hypertension. Anemia is most often microcytic, hypochromic and less often normocytic, normochromic due to chronic systemic disease as in cirrhosis. Pancytopenia or bicytopenia indicate hypersplenism.

Liver function tests (LFT): LFT is usually normal in non-cirrhotic portal hypertension but 10% can have deranged liver function tests. Reversal of albumin globulin ratio indicates chronic liver disease.

b) Tests - Portal hypertension diagnosis

Imaging: Ultrasound with Doppler study of portal venous system: Conventional two-dimensional (2D) and Doppler ultrasound (US) in the evaluation of PHT is a very good tool to assess the size of the liver, spleen, parenchymal

abnormalities, presence of free fluid in the abdomen, anatomy of the portal venous system, hepatic veins, hepatic artery, inferior vena cava and collaterals and to select cases for transjugular intra-hepatic portosystemic shunt (TIPS). Splenomegaly, omental thickening and splenorenal collaterals are indicators of portal hypertension.

Apart from this, the following will help the clinician to identify the underlying level of portal hypertension - Normal liver echoes, non visualization of portal vein but replaced by portal cavernoma, collaterals and splenomegaly indicate EHPVO. Altered or increased liver echoes, splenomegaly, dilated portal vein, with or without ascites is suggestive of cirrhosis. Presence of liver cyst, renal cyst and collaterals suggest congenital hepatic fibrosis (CHF). In cholangitic type of CHF there may be biliary dilatation. Presence of hepatic venous outflow tract obstruction with or without IVC obstruction, comma shaped collaterals suggest Budd-Chiari syndrome. Altered liver echoes and dilated hepatic veins will be seen in cardiac cirrhosis.

Contrast enhanced computed tomography (CECT) abdomen and magnetic resonance imaging (MRI): CT scan is not routinely indicated in portal hypertension but required prior to liver transplant. In contrast-enhanced CT scan, thrombus may be seen as a nonenhanced intraluminal filling defect. CECT has the advantage of displaying varices and parenchymal hepatic abnormalities also. Magnetic resonance cholangiopancreatography (MRCP) is done in children with portal biliopathy, cholangitic type of portal hypertension and also to look for vascular anomaly.

c) Tests-Etiology of PHT

Estimation of protein C, protein S and anti-thrombin III is required for prothrombotic work up, especially in familial cases of EHPVO. Serum ceruloplasmin, Kayser–Fleischer ring (KF ring) by slit lamp examination, 24 hours urinary copper after D-penicillamine challenge are required for diagnosis of Wilson disease. Viral markers for hepatitis B, C are needed not only to diagnose chronic liver disease due to B, C and if negative to vaccinate them against hepatitis B infection, as children with portal hypertension may require repeated blood transfusions. Anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-liver kidney microsomal (LKM) antibody and liver biopsy will help in suspected autoimmune liver disease. Serum bile acids, gamma glutamyl transpeptidase (GGT), cholesterol and liver biopsy with immunohistochemistry will help to diagnose PFIC.

Liver biopsy: Liver biopsy is indicated for auto-immune liver disease, ductal paucity, Wilson disease and PFIC. In presence of ascites and coagulopathy, transjugular route is ideal.

Management

This consists of managing acute variceal hemorrhage, prevention of further bleed and treatment of complications with regular follow up. The first step in a child with variceal bleed is to stabilise them hemodynamically taking care of airway, breathing and circulation. Control of bleed may be achieved with pharmacological agents, therapeutic endoscopy, interventional radiology or surgery. In children with EHPVO with variceal bleed, Hb should be maintained at 8 gm / dL. Transfusion of blood products depend upon the amount of bleed and hemodynamic status of the child. Injection vitamin K and fresh frozen plasma is required in chronic liver disease with coagulopathy.

Primary prophylaxis

Primary prophylaxis involves treatment before the first GI bleed using endoscopy or with non-selective beta blockers and is an accepted modality of management in adults with portal HT.[13] However, a recent international survey at pediatric liver units showed that 70% of pediatric centres would perform surveillance endoscopy and instigate primary prophylaxis.[14] According to current recommendations for children with portal HT, based on the Baveno VI consensus, children 'would be considered' for surveillance esophagogastroduodenoscopy on the basis of hypersplenism with intention to treat depending on endoscopy findings.[15]

Pharmacotherapy - Acute variceal bleeding

Pharmacotherapy should be started even before endoscopy and continued for 2-5 days. Octreotide has been shown to be effective and safe with early control of active bleeding in most cases. The most common dosage regimen is 1µg/kg as slow bolus followed by 1-3µg/kg /hour. An alternative is terlipressin, a synthetic analogue of vasopressin, but not much data is available about its use in children. Endoscopy has to be done after hemodynamic stabilisation. Fig.2a and 2b shows esophageal varices and gastric varices on endoscopy.

Endotherapy

This is to be done only after hemodynamic stabilisation. Endoscopy has both diagnostic and therapeutic role in children with portal hypertension.

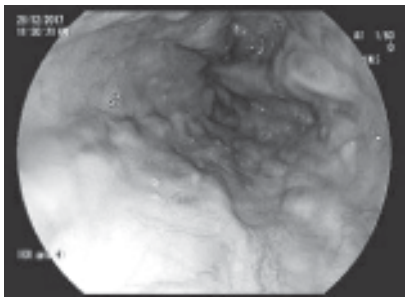

Fig.2a. Esophageal varices

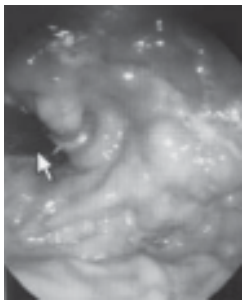

Fig.2b. Gastric varices

Endoscopic sclerotherapy (EST) and endoscopic variceal ligation (EVL) are the two modalities in endoscopic treatment. EST involves intravariceal or perivariceal injection with a sclerosing agent causing it to stop bleeding and shrink over a period of time. EVL involves cutting off the blood flow to the varix by applying a rubber band tightly around it with subsequent thrombosis of the varices. EVL is the preferred technique in children with esophageal varices but may not be feasible in small children usually under 10 kg of body weight. Both EST and EVL have been shown to obliterate varices with a 90% success rate. Fundal varices should be managed by endoscopic injection of tissue adhesive (cyanoacrylate).[16]

Following endoscopic therapy, child should fast for at least 2 hours. Feeding of solid are withheld until liquids are tolerated. Sucralfate or antacid drugs should be given for 5-7 days. Balloon tamponade should only be used in an intubated and sedated child where there is failure to control active bleeding. It serves as a bridge to definitive treatment or to facilitate transfer to a specialist centre.[17] Other method like hemospray can be useful in gastric erosions or oozing portal gastropathy but cannot substitute the need for EVL or EST. In those with intractable bleeding recombinant factor VIIa may be considered in addition to conventional treatment.[18] Approach to variceal bleed is given in Fig.3.

Fig.3. Acute variceal bleed - Approach

Secondary prophylaxis

Following a variceal bleed, recurrence is likely with subsequent bleeding rates as high as 80%. Hence, all children should receive secondary prophylaxis. A number of techniques are available including endoscopy, pharmacotherapy, TIPS and surgery. Non-selective beta blockers like propranolol can be used though the results are conflicting. For children with compensated cirrhosis, EVL is the treatment of choice and repeated every 2-4 weeks following the first variceal bleed to obliterate the gastroesophageal varices. These children require regular surveillance at 6-12 monthly intervals and when varices reappear, endotherapy is needed. Interventional radiology may be helpful in selected cases of failed endotherapy, portal biliopathy for TIPS and to relieve biliary obstruction.

Surgery

Decompressive shunt surgery should be considered in cases with failed endotherapy. In general, hypersplenism is not an indication for surgical intervention, but profound thrombocytopenia with bleeding, repeated infections or physical discomfort that is caused by massive splenomegaly may require splenectomy. In patients who have left-sided portal hypertension, splenectomy alone is curative. Rex shunts (mesenterico-left portal bypass) in children who have EHPVO are effective and are considered to be more physiologic because they restore normal portal flow to the liver.[19]

Management of portal biliopathy

Symptomatic portal biliopathy is predominantly due to compression of bile ducts due to varices around common bile duct, ischemia induced biliary strictures with or without stone in common bile duct resulting in obstructive jaundice and cholangitis. These children can be treated by endoscopic sphincterotomy / stent placement or rarely by surgery.

Complications

The major life-threatening complication of portal HT is GI bleeding. Other complications include massive splenomegaly, thrombocytopenia, ascites, increased intestinal permeability, hepatic encephalopathy, hepatopulmonary syndrome and portopulmonary hypertension, growth failure, vascular coagulation, portal biliopathy and overall poorer quality of life.

Points to Remember

- ***Portal hypertension is the commonest cause of recurrent major gastrointestinal bleed.***
- ***Good history and thorough physical examination is an essential step in evaluation of portal hypertension.***
- ***EHPVO is the commonest type of portal hypertension followed by cirrhosis and bleed due to EHPVO is well tolerated unlike cirrhosis.***
- ***Endoscopy is to be done after hemodynamic stabilisation and has diagnostic and therapeutic role.***
- ***Effective management of acute variceal bleed is important to avoid bleed related mortality.***
- ***Outcome of portal hypertension is dependent upon underlying liver status and regular follow up is a must.***

References

1. Gugig R, Rosenthal P. Management of portal hypertension in children. World J Gastroenterol 2012; 18:1176-1184.
2. Arora NK, Ganguly S, Mathur P, Ahuja A, Patwari A. Upper Gastrointestinal bleeding: Etiology and Management. Indian J Pediatr 2002; 69:155-168.
3. Yachha SK. Portal hypertension in children: An Indian perspective J Gastroenterol Hepatol 2002; 17:S228-S231.
4. Yadav S, Dutta AK, Sarin SK. Do umbilical vein catheterization and sepsis lead to portal vein thrombosis? A prospective, clinical and sonographic evaluation. J Pediatr Gastroenterol Nutr 1993; 17:392-396.
5. Stringer MD, Heaton ND, Karani J, Olliff S, Mr Howard ER. Patterns of portal vein occlusion and their etiological significance. Br J Surg 1994; 81:1328–1331.
6. Odievre M, Pige G, Alagille D. Congenital abnormalities associated with extraheptic portal hypertension. Arch Dis Child 1977; 52:383-385.
7. Yachha SK, Aggarwal R, Sharma BC, Misra RN, Aggarwal A, Naik SR. Functional protein C and anticardiolipin antibody in children with portal vein thrombosis. Indian J Gastroenterol 2001; 20:47-49.
8. Poddar U, Thapa BR, Vashishta RK, Girish CS, Singh K. Congenital hepatic fibrosis in Indian children. J Gastroenterol Hepatol 1999; 14:11921196.
9. Poddar U, Thapa BR, Puri P, Girish CS, Vaiphei K, Vasishta RK, et al. Non-cirrhotic portal fibrosis in children. Indian J Gastroenterol 2000; 19:12-13.
10. Poddar U, Thapa BR, Rao KL, Singh K. Etiologyical spectrum of Oesophageal varices due to portal hypertension in Indian children. J Gastroenterol hepatol 2008; 23(9):1354-1357.
11. Grammatikopoulos T, McKiernan PJ, Dhawan A. Portal hypertension and its management in children. Arch Dis Child 2018; 103:186-191.
12. Karthikeyan P, Sumathi B, Nirmala D, Bhaskar Raju, Nedunchelian K, Sekar P. Non bleeding manifestations in

children with extrahepatic portalvein obstruction. Int J Contemp Pediatr 2016; 3(1):206-209.

13. de Franchis R. Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63:743-752.
14. Antiga L. Medical management of esophageal varices and portal hypertension in children. Semin Pediatr Surg 2012; 21:211-218.
15. Shneider BL, de Ville de Goyet J, Leung DH, Srivastava A, Ling SC, Duché M, et al. Primary prophylaxis of variceal bleeding in children and the role of MesoRex Bypass: summary of the Baveno VI Pediatric Satellite Symposium. Hepatology 2016; 63:1368-1380.
16. McKiernan P, Abdel-Hady M. Advances in the management of childhood portal hypertension. Expert Rev Gastroenterol Hepatol 2015; 9:575-583.
17. Shneider BL, Bosch J, de Franchis R, Emre SH, Groszmann RJ, Ling SC, et al. Portal hypertension in children: expert pediatric opinion on the report of the Baveno v Consensus Workshop on Methodology of diagnosis and therapy in Portal hypertension. Pediatr Transplant 2012; 16:426-437.
18. Leblebisatan G, Sasmaz I, Antmen B, Yildizdas D, Kilinc Y. Management of life-threatening hemorrhages and unsafe interventions in nonhemophiliac children by recombinant factor VIIa. Clin Appl Thromb Hemost 2010; 16:77-82.
19. Bombini DA, Superina A, Almond PS, Whitington PF, Alonso E. Experience with the Rex shunt in children with extrahepatic portal hypertension. J Pediatr Surg 2000; 35:13-18.

CLIPPINGS

Pediatric post streptococcal glomerulonephritis: Clinical and laboratory data

Acute post streptococcal glomerulonephritis (APSGN) is the most common post infectious glomerulonephritis in childhood. The aim of this study was therefore to identify the possible risk factor(s) responsible for decreased glomerular filtration rate (GFR) in APSGN.

The data of patients followed up with a diagnosis of APSGN in the Pediatric Nephrology Clinic of Gaziantep University Hospital between October 2014 and October 2016 were retrospectively evaluated.

The total number of subjects was 75 (male/female, 42/33) with a mean age of 8.20 ± 3.25 years. The most common presentations were edema (86.7%), macroscopic hematuria (82.7%) and hypertension (73.3%, n = 55). On laboratory examination, 28 children (37.3%) had hypoalbuminemia, 58 (77.3%) had proteinuria, 20 (26.7%) had increased C reactive protein (CRP), while 74 (98.7%) and 12 (16%) had decreased complement (C)3 and C4, respectively. The number of children with GFR <90 mL/min/1.73 m2 was 22 (29.3%). The risk of decreased GFR was significantly higher in patients with increased CRP (P = 0.001; OR, 3.58), hypoalbuminemia (P = 0.006; OR, 4.83), and decreased C4 (P = 0.010; OR, 11.53). Additionally, white blood cell (WBC) count, neutrophil count, and neutrophil/lymphocyte ratio (NLR) were significantly higher (P = 0.02, P = 0.006, P = 0.004, respectively) in patients with low GFR.

Conclusion: Although the prognosis of APSGN in children is good, severe systemic complications and renal failure may develop during the follow up period. Decreased C4, presence of hypoalbuminemia and increased inflammatory markers (WBC, CRP, neutrophil count and NLR) might be possible risk factors for severity of renal involvement. Decreased C4, in particular, may be a risk factor for decreased GFR in those children.

Demircioglu Kýlýc B, Akbalýk Kara M, Buyukcelik M, Balat A. Pediatric post streptococcal glomerulonephritis: Clinical and laboratory data. Pediatr Int 2018;60:645-650. doi:10.1111/ped.13587.

NEWS AND NOTES

The 29th International Pediatric Association (IPA) Congress 2019

Date: March 17-21, 2019

Venue: Panama City, Panama, Central America

GASTROENTEROLOGY - II

UPPER GASTROINTESTINAL BLEEDING IN CHILDREN

***SK Mittal**
****Malobika Bhattacharya**

Abstract: *Upper gastrointestinal bleeding in children may be life threatening. Frequent causes of upper gastrointestinal bleeding in children include variceal hemorrhage (most commonly extra-hepatic portal venous obstruction in Indian setting) and mucosal lesions (gastric erosion and ulcer secondary to drug intake). All patients should be evaluated for the source, degree and possible cause of the bleeding. A complete and thorough history and physical examination is therefore vital. Upper gastrointestinal endoscopy is the first line diagnostic procedure. The goals of therapy in a child with gastrointestinal bleeding should be directed towards hemodynamic resuscitation, cessation of bleeding from source and prevention of future episodes. Proton pump inhibitor and H2 receptor antagonists (both oral and parenteral) are the mainstay in the treatment of bleeding from mucosal lesion. Variceal bleeds are managed by infusion of vasoactive agents like octreotide and therapeutic emergency endoscopy after initial hemodynamic stabilization of the patient.*

Keywords: *Varices, Endoscopy, Proton pump inhibitor, H2 receptor antagonists, Octreotide.*

Upper gastrointestinal bleeding (UGI) is defined as bleeding arising from a source proximal to the ligament of Trietz in the distal duodenum. It usually presents with hematemesis and/or melena. In contrast, hematochezia is usually a sign of a lower gastrointestinal (LGI) bleeding distal to the ligament of Treitz. However, in some infants with UGI bleeding, there may be passage of fresh blood per rectum because of the rapid gastrointestinal transit time in a profusely bleeding child.

* Senior Consultant Pediatric Gastroenterologist, Max Super Speciality Hospital

** Associate Professor and Head, Department of Pediatrics, Government Institute of Medical Sciences, Greater Noida.

email: skmittal44@yahoo.com

Epidemiology

The incidence of UGI bleeding is not well established in the pediatric age group. As much as 20% of all cases of gastrointestinal bleeding in children originate from an UGI source.[1] A population-based study from France estimated that UGI bleeding occurred in 1 to 2 per 10,000 children per year (77% of whom required hospitalization) and that 36% were consequent to the administration of non-steroidal anti-inflammatory drugs (NSAIDs).[2] In one of the largest prospective studies, UGI bleeding (defined for this study as hematemesis or any amount of blood from the nasogastric tube) was observed in 63 of 984 (6.4%) pediatric intensive care unit (PICU) admissions wherein factors such as high pediatric risk mortality score, coagulopathy, pneumonia and multiple trauma were associated with high risk of bleeding.[3,4]

Etiology

The etiology of UGI bleed varies with age but considerable overlap exists between the different age groups. The severity of bleeding mainly depends on the etiology of UGI bleed. In Indian studies, portal hypertension has been reported to be the commonest cause (95%) in contrast to the developed countries where bleeding from non-variceal causes like peptic ulcer and esophagitis are more common (66%). Extra-hepatic portal vein obstruction was the common cause of portal hypertension in Indian children (Table I).[5,6] While evaluating a child with UGI bleed, it is important to consider age specific etiologies (Table II).

Neonates

Although upper GI bleeding is a rare condition in the first month of life, it may arise from a variety of causes. True upper GI bleeding in a neonate must be differentiated from swallowed maternal blood. Hemorrhagic disease of new born usually presents with lower GI bleed but can occasionally present as hematemesis. It is more likely to occur in neonates who did not receive vitamin K injection at birth. Stress gastritis and ulcers are associated with critical illnesses but may rarely occur spontaneously in neonates. Certain congenital malformations such as intestinal duplication and vascular anomalies may also give

Table I. Upper GI bleed–Causes

Etiology	Yachha, et al (1996)	Mittal, et al (1994)
Varices	95%	39.4%
Esophagitis	-	23.7%
Gastritis	1.3%	7.2%
Gastric ulcer	-	1.2%
Duodenal ulcer	-	0.42%
Esophageal ulcer	-	0.42%
Henoch-Schonlein purpura	1.3%	-
Idiopathic thrombocytopenic purpura	1.3%	-
Gastroduodenal artery aneurysm	1.3%	-
Unknown	-	27.5%

Table II. Upper GI bleed - Age-wise etiology

Neonate	Infant	Child or adolescent
Swallowed maternal blood	Stress gastritis	Mallory-Weiss tear
Vitamin K deficient bleeding	Acid-peptic disease	Acid-peptic disease
Stress gastritis	Mallory-Weiss tear	Gastric or esophageal varices
Esophagitis Trauma	Esophagitis	Esophagitis
Vascular anomalies	Vascular anomalies	Foreign body
Gastrointestinal duplications	Gastrointestinal duplications	Caustic ingestion
Coagulopathy	Gastric or esophageal varices	Vasculitis (e.g. Henoch-Schonlein purpura)
Milk protein intolerance	Duodenal or gastric webs	Crohn's disease
Congenital coagulation factor deficiency	Bowel obstruction	Bowel obstruction
		Dieulafoy lesion (large tortuous arteriole in the stomach wall that erodes and bleeds)
		Hemobilia

rise to upper GI bleed. Coagulopathy in a neonate may be caused by sepsis, hepatic failure or (congenital) individual clotting factor deficiency. GI bleeding due to underlying coagulopathy in neonates is rare as they present more commonly with large cephalhematoma, persistent bleed from umbilical cord stump and IV sites and/or as intracranial bleeds. Milk protein intolerance mostly presents as lower GI bleed although it may rarely present with upper GI bleed also.

Infants and toddlers

Stress ulcers in sick infant and toddler, peptic ulcer disease, variceal bleed in patients of portal hypertension and vascular malformations are the major causes of bleed in this age group. Reflux esophagitis is an important cause of GI bleeding in this age group but it more often presents as occult blood in stool and persistent anemia. Esophageal or gastrointestinal foreign body, communicating duplication cysts, NSAID usage and corrosive ingestion can also cause significant upper GI bleeding.

Older children and adolescents

The spectrum of upper GI bleeding in this age group

is similar to that in adults. In Mallory Weiss syndrome there are longitudinal mucosal tears caused by bouts of forceful vomiting. The bleeding is usually small in quantity and resolves spontaneously, but may occasionally be life threatening. GI foreign bodies can cause bleeding if they are sharp (pins, blades), contain caustic substances (e.g. batteries) and lodged in the esophagus. Suggestive history of foreign body includes choking episode, which may have occurred days to weeks before the onset of bleed. Rarely a leaking ingested button battery may lead to aorto-esophageal fistula and life threatening bleeding.

Esophagitis in this age group is usually caused by gastroesophageal reflux disease, eosinophilic esophagitis or occasionally by corrosive ingestion. Peptic esophagitis may be caused by recurrent vomiting due to other causes. Gastric ulcerations can occur in all age groups especially in the setting of critical illnesses or NSAID usage. Binge drinking of alcohol is an important cause of gastritis in adolescents. Peptic ulcer disease and gastritis may also occur in association with Helicobacter pylori infection and occasionally other infections such as cytomegalovirus. In these disorders, hematemesis is usually small volume and preceded by epigastric pain and/or discomfort for weeks or months.

Pill esophagitis is caused by direct esophageal mucosal injury from prolonged contact with certain drugs such as tetracycline used to treat acne (doxycycline and minocycline), NSAID and bisphosphonates. It usually presents with odynophagia and may progress to hematemesis. Similar presentation may also be seen in infectious esophagitis caused by candida, cytomegalovirus or herpes simplex.

Esophageal variceal bleeding is the most frequent cause of severe acute upper GI bleeding in children seen in referral pediatric gastroenterology setup. Esophageal varices are due to portal hypertension, the clues to which include presence of splenomegaly, ascites and/or abnormally enlarged liver. Also recurrent episodes of hematemesis is usually due to underlying portal hypertension. It may develop secondary to cirrhosis, portal vein thrombosis or occlusive disease of the hepatic vein and inferior vena cava. Rarely, severe acute upper GI bleeding may occur from a peptic ulcer that has eroded into an underlying artery or a from a Dieulafoy lesion.

UGI bleeding characteristically presents with either hematemesis and/or melena. Hematemesis can be bright red blood indicating brisk or fresh bleeding or coffee ground material that indicates relatively slower rate of bleeding allowing gastric acid to alter the appearance of blood. Almost all significant upper GI bleeds are followed by melena.

Although upper GI bleed is typically associated with melena and lower GI bleed with passage of fresh blood in stools (hematochezia), these distinctions are not absolute because melena may be associated with proximal lower GI bleeding and hematochezia may be seen in massive upper GI bleeding. Due to shorter transit time of the intestine, neonates and infants with upper GI bleeding are more likely than adults, to present with hematochezia.

Differential diagnosis

It includes vomited blood originating from non-GI structures and ingested blood and blood-like substances. Neonates and infants may swallow maternal blood during delivery or breast feeding and this can resemble upper GI bleed. The two can be distinguished by the Apt-Downey test which is based on the principle that fetal hemoglobin is resistant to alkali denaturation and remains red or pink while adult hemoglobin denatures to a brownish yellow hue. This test is applicable only in the first few months of life as the concentration of fetal hemoglobin falls sharply thereafter.

Swallowed blood from the patient's respiratory tract is difficult to differentiate from upper GI bleeding. This should be considered in a child with history of recurrent epistaxis. The nares should be examined for signs of injury. Occasionally endoscopic examination of the respiratory passages may be required to adequately evaluate the nasopharynx, larynx and respiratory tract.

Red colored drinks, medications and food colors may also be confused with blood. This can be suspected from suggestive history of ingestion and confirmed by tests for occult blood. These tests are based on color changes that indicate presence of hemoglobin. However, some of these tests [e.g. Hemoccult (simple test checks for the presence of hidden blood in a patient's stool)] may give false negative results in acidic specimens. Other kits that are designed specifically to detect blood in gastric secretions by incorporating an alkali to neutralize gastric acid [e.g. Gastroccult (qualitative screening method for detecting the presence of occult blood and determining the pH of gastric aspirate)] are preferable in suspected upper GI bleed.

Factitious illness (formerly known as Munchausen syndrome by proxy) caused by intentional mixing of blood or blood like substances to mimic upper GI bleeding should be considered in patients with unexplained bleeding from an indeterminate source. The patient or siblings may have

history of recurrent illnesses without an obvious cause and frequent hospital visits.

History

The clinical history should include information concerning the time course of the bleeding episode, estimated blood loss and any associated symptoms (Table III). The presence of hematemesis, melena or hematochezia should be documented. Particular attention should be given to GI symptoms including dyspepsia, heartburn, abdominal pain, dysphagia and weight loss. In infants, these features may be reflected in poor feeding and irritability.

History of jaundice (present or past), easy bruising or change in stool color may suggest underlying liver disease. In recent or recurrent epistaxis, a nasopharyngeal source of bleeding should be looked for. History of easy bruising or bleeding suggests a disorder of coagulation, platelet dysfunction or thrombocytopenia. Personal or family history of liver, kidney or heart disease, or coagulation disorders should be obtained.

Drug history is elicited to detect intake of drugs that may induce ulceration (such as NSAIDs and corticosteroid). Some medications such as NSAID also affect coagulation and can exacerbate bleeding from another cause. Alcohol ingestion (in particular, binge drinking) and tobacco use can contribute to peptic ulcer disease and large intakes of caffeine (e.g. caffeinated sodas) can promote acid secretion and dyspepsia.

Physical examination

After the initial hemodynamic assessment, the rest of the physical examination should focus on finding the source of bleed. Presence of skin and mucus membrane bleeds suggests a bleeding disorder, coagulopathy, trauma or liver disease. The presence of cutaneous hemangiomas raises the possibility of gastrointestinal hemangiomatosis. Hereditary hemorrhagic telangiectasia (Osler-Weber-

Table III. Upper GI bleed - Clinical clues to etiology

History	Probable etiology
Sudden onset massive hematemesis	Vascular bleed (variceal or AV malformations)
Vomiting preceding hematemesis	Mallory-Weiss tear, gastritis, esophagitis
Melena	Moderate or brisk upper GI bleed
Hematochezia in infants	Very brisk upper GI bleed
Epigastric pain or heartburn	Gastritis, peptic ulcer, esophagitis (peptic, eosinophilic or pill)
Odynophagia	Pill esophagitis, esophageal foreign body, infectious esophagitis (candida, CMV, HSV)
Jaundice	Underlying liver disease
Epistaxis	Ingested blood from nasopharynx, bleeding disorder
Easy bruising or bleeding	Bleeding disorder, coagulopathy
Critical illness	Peptic gastritis, esophagitis, ulcer disease, bleeding from non-GI source (e.g. traumatic NG or ET tube placement)
Medications: NSAIDS, bisphosphonates, tetracyclines	Pill esophagitis, peptic disease
Breast-fed infant	Swallowed maternal blood
History of choking episodes	Esophageal foreign body
Binge alcohol intake	Gastritis, esophagitis

Rendu syndrome) is characterized by mucocutaneous hemangiomas and usually presents with recurrent epistaxis and/or GI bleeding. Hepatomegaly or reduced liver span, splenomegaly, prominent abdominal wall veins or free fluid in abdomen can be suggestive of chronic liver disease. Epigastric tenderness might be due to gastritis or acid peptic disease.

Laboratory evaluation

This includes complete blood count, coagulation studies, liver function tests, blood urea nitrogen (BUN) and serum creatinine. The BUN result can be helpful for confirming the source of bleeding. An increase in BUN in the absence of renal disease is consistent with an UGI rather than a lower GI source of blood loss because blood in the proximal GI tract has relatively more time to be absorbed, leading to a rise in the BUN. However, a normal or low BUN does not rule out an UGI bleed. For patients with clinically significant bleeding or known varices, a specimen should be drawn to type and cross-match blood in case transfusion is required. Less extensive laboratory evaluation may be appropriate for patients with small amounts of blood in the vomitus and a likely explanation.

Radiological investigations: Plain X-rays are helpful to detect foreign bodies in patients with suggestive history. They are also useful for diagnosing bowel obstruction or perforation in patients with abdominal tenderness and distension. Ultrasonography of the whole abdomen is useful to assess liver and spleen size, hepatic echotexture and large AV malformations. Doppler studies elucidate the hemodynamics of portal hypertension in patients with acute variceal bleed.

Endoscopy: Upper gastrointestinal endoscopy is the procedure of choice for diagnosis as well as treatment for most patients with UGI blood. In the hands of an experienced endoscopist, the etiology in 85%-90% of cases can now be determined. It can identify the site of bleeding, diagnose the specific cause of bleeding and can be used to perform therapeutic interventions where feasible. In case of esophagitis, gastritis or duodenitis, the affected site should be biopsied. In suspected peptic ulcer disease, antral biopsies for H. pylori work up (histological examination, rapid urease test and culture) should be taken.

Though there is no definite time frame given, in all cases of major upper GI bleed, an early endoscopy (with in first 24 hour, as soon as the patient is hemodynamically stable) is recommended as mucosal lesions tend to heal very fast and may be missed if the endoscopy is delayed. Endoscopy is contraindicated in hemodynamically unstable patients.

Angiography: CT or MR angiography may help to delineate vascular malformations distal to the duodenum, in areas not accessed by routine upper GI endoscope. The preferred modality depends on institutional preference. For therapeutic purposes, conventional celiac or superior mesenteric angiography may be useful in treating some patients with massive non-variceal bleed due to splenic artery aneurysms and other vascular anomalies, hemobilia or ulcers that are not amenable to endoscopic procedures. The amount of bleed must be more than 0.5 ml/min to be detectable by angiography. Angiography is helpful in making the diagnosis as well as in allowing embolic (coil/fibrin/glue) occlusion of the arterial branches supplying the lesion in cases of vascular malformation.

Nuclear scintigraphy: In patients with persistent bleeding in whom endoscopy fails to detect the site of bleeding, radioisotope-tagged RBC scans using technetium 99 m-sulfur colloid may be successful. This modality is helpful only if the rate of bleeding exceeds 0.1 ml/min. However, it has significant false localization and false-negative rates.

Management

Initial assessment and resuscitation: While doing clinical assessment in cases of hematemesis, it should be remembered that the vomited blood usually represents only a tip of the iceberg as most of the blood is propelled forwards by GI movements.

The initial evaluation of a patient presenting with upper GI bleed consists of assessment of hemodynamic status and if required, resuscitation. Vital signs, including the heart rate, blood pressure, presence of orthostatic changes and capillary refill time should be monitored. Patients with impaired peripheral perfusion (shock, orthostatic hypotension) should be managed in an ICU setting for resuscitation and close observation and stabilized prior to endoscopy. Both gastroenterology and surgical opinion should be sought promptly for all patients with severe acute UGI bleeding. Clinical signs suggestive of severe acute UGI bleeding include melena or hematochezia, heart rate >20 beats per minute above the mean heart rate for age, prolonged capillary refill time, decrease in hemoglobin of more than 2 g/dL, need for fluid bolus and the need for blood transfusion to maintain hemoglobin between 8-10 g/dL.[7-9]

On initial assessment, if patient is found to have signs of shock or decreased responsiveness, his/her airway should be maintained and breathing and circulation supported. The patient should have two large bore patent IV cannula

in situ. In severely volume depleted individuals in whom iv access cannot be obtained, an intraosseous or central line should be placed. Blood should be sent for grouping and cross matching, complete blood count and coagulation profile. The vital signs and oxygen saturation should be continuously monitored. Intravascular volume replenishment should be started immediately with crystalloids initially, followed by colloids/blood products as indicated. Any coagulopathy should be corrected with parenteral vitamin K administration and fresh frozen plasma transfusion. A nasogastric tube should be inserted at the earliest for gastric lavage and to detect ongoing bleed. Colour of gastric aspirate is a good indicator of status of ongoing bleeding. All patients should be started on empiric acid suppression therapy and kept nil per oral. Detailed assessment should be done while ensuring hemodynamic stability.

After initial assessment and resuscitation, for hemodynamically stable patients with small amounts of blood in the vomitus with a likely explanation (e.g. Mallory-Weiss tear), supportive care with observation generally is sufficient, usually with acid suppression to treat any peptic component and reduce the risk for rebleeding. For patients with larger amounts of blood in vomitus or hemodynamic instability, the management is different.

Nasogastric tube and gastric lavage: In patients presenting with unexplained clinically significant upper GI bleeding, nasogastric or orogastric tube lavage is sometimes used to confirm the diagnosis and to determine if the bleeding is ongoing. This approach is particularly helpful if the bleeding is suspected to be a vascular bleed (e.g. variceal). The lavage will also remove particulate matter, fresh blood and clots to facilitate endoscopy and decrease the risk of aspiration and prevent progression to encephalopathy in patients with cirrhosis. The lavage may be performed with either water or normal saline, at room temperature. Ice water lavage is not recommended as this practice does not slow bleeding, may induce iatrogenic hypothermia, particularly in infants and small children and in case of lavage done with fluid at 32^{o}C, may induce local coagulation defect.

If the lavage returns fresh blood or blood with the appearance of coffee ground, it confirms an UGI (or nasopharyngeal) source of bleeding. However, lavage may not be positive if the bleeding has ceased or arises beyond a closed pylorus.

Pharmacotherapy (Table IV)

Variceal Bleed[7]: Pharmacological therapy has the advantages of being applicable in most patients and capable of being started as soon as a diagnosis of variceal hemorrhage is suspected. Studies comparing pharmacotherapy and endoscopic sclerotherapy report similar efficacy but fewer side effects with pharmacotherapy thereby highlighting the fact that it should be the first line therapy in variceal bleeding.

Octreotide is a somatostatin analog that decreases splanchnic blood flow and has fewer hemodynamic adverse effects than vasopressin. Pediatric studies have shown that it controls UGI bleed in up to 70% of children. It is the drug of choice for variceal bleeds and is initiated as a bolus injection of 1 mcg/kg(up to a maximum of 50 mcg) followed by continuous infusion of 1 mcg/kg per hour, which may be increased hourly by1 mcg/kg per hour upto 4 mcg/kg per hour. Infusion should be continued for atleast 24-48 hours after the bleeding has stopped to prevent recurrence. The major adverse effect of octreotide is hyperglycemia.

Vasopressin and terlipressin: Vasopressin use has been largely replaced by octreotide and now by terlipressin. The usual dose is 0.002 to 0.005 units/kg/min for 12 hours and then tapered over 24 to 48 hours (maximum - 0.2 units/min). Its use is limited by the side effect vasoconstriction. Nitroglycerin has also been used to decrease portal pressure and when used in conjunction with vasopressin, may ameliorate some of its adverse effects. Vasopressin has been replaced by its longer acting and safer analogue terlipressin, which has been found to be as effective as octreotide in adults. Experience with terlipressin in children is limited though it is expected to be equally effective with an advantage of intermittent (4-6 hourly) dosing.

Somatostatin is also used for control of active bleed, in a dose of 250 mcg/kg IV bolus followed by 250 mcg/kg/hour continuous infusion. In case of response, the infusion can be continued for 2 to 5 days, while frequently monitoring for hyperglycemia. Side effects include abdominal discomfort, flushing, nausea, bradycardia, steatorrhoea and dyspepsia.

Prokinetic agents: Erythromycin has been used as a prokinetic agent to clear the stomach of blood prior to emergency endoscopy. Metoclopramide has also been used as a prokinetic and as a 'pharmacologic tamponade' as it increases the lower esophageal sphincter tone.

Mucosal bleed: Mucosal bleeding is the most frequent upper GI bleed in critically ill children. Therapy is directed at neutralizing and/or preventing the release of acid. The various agents used are proton pump inhibitors (PPI) and H2 receptor antagonists.

Table IV. Pharmacologic options in children with upper GI bleed

Mode of Action	Category	Agent	Dose
Acid Suppression (IV)	Proton Pump inhibitor	Esomeprazole	Intermittent dosing: Infants: 0.5 to 1 mg/kg/dose IV once daily Children 1 to 17 years: <55 kg: 10 mg IV once or twice daily ≥55 kg: 20 mg IV once or twice daily Continuous IV infusion: 1 mg/kg IV bolus (maximum 80 mg), followed by infusion of 0.1 mg/kg/hour (maximum 8 mg/hour)
		Omeprazole	Children and adolescents: 0.5 to 3 mg/kg IV daily, in one or two divided doses (maximum 80 mg daily)
		Pantoprazole	Intermittent dosing: Children and adolescents: <40 kg: 0.5 to 1 mg/kg IV once or twice daily >40 kg: 20 to 40 mg IV once or twice daily Continuous IV infusion: 1 mg/kg IV bolus (maximum 80 mg), followed by an infusion of 0.1 mg/kg/hour (maximum 8 mg/hour)
	H1 blocker	Ranitidine	Intermittent dosing: Infants, children and adolescents: 2 to 5 mg/kg/day IV divided every six to eight hours; maximum dose 200 mg/day. Continuous IV infusion: Children and adults: 1 mg/kg IV bolus (maximum 50 mg), followed by infusion of 2 to 4 mg/kg/day (maximum 6.25 mg/hour)
Acid suppression (oral)	Proton pump inhibitor	Omeprazole	Children and adolescents: 1 to 3 mg/kg daily (maximum 80 mg daily), in one or two divided doses
		Esomeprazole	Infants one month to one year (daily): 3 to 5 kg: 2.5 mg; 5 to 7.5 kg: 5 mg; 7.5 to 12 kg: 10 mg Children 1 to 11 years (daily): <20 kg: 10 mg; ≥20 kg: 10 mg or 20 mg Children ≥12 years and adults: 40 mg twice daily initially, followed by 20 to 40 mg once daily (as a maintenance dose, once risk of recurrent bleeding is low)
		Pantoprazole	Children 5 to 11 years: 15 to 40 kg: 20 mg once daily; > 40 kg: Use adult dose Children ≥12 years and adults: 40 mg twice daily initially, followed by 20 to 40 mg once daily (as a maintenance dose, once risk of recurrent bleeding is low)
Vasoactive	Somato-statin analogue	Octreotide	Children: 1 to 2 microgram/kg IV bolus (maximum agent 50 micrograms), followed by 1 to 2 microgram/kg/hour as a continuous IV infusion (maximum 50 micrograms per hour). Initial bolus may be repeated once in the first hour if needed.

Proton pump inhibitors (PPIs) are more efficacious than H2 receptor antagonists. Pantoprazole is used for control of active bleed. Dosage in children are: for bodyweight <40 kg: 0.5 to 1 mg/kg per day IV once daily; >40 kg: 20 to 40 mg once daily (maximum : 40 mg/d). These can be started empirically as it is important to raise the gastroduodenal pH to maintain clot stability. High dose PPI infusion has been found to decrease the need for endoscopic therapy.

H2 receptor antagonists are used for control of active bleed and prevention of rebleeds. Ranitidine can be used as either continuous or bolus infusion; in the former 1 mg/kg is given initially followed by infusion of 2 to 4 mg/kg per day while in the latter 3 to 5 mg/kg per day is divided into every 8 hourly infusions.

Treatment for H. pylori infection with a H2 blockers or PPIs plus any two antibiotics (mainly nitroimidazoles-metronidazole/tinidazole, macrolides- clarithromycin, amoxicillin and beta-lactams) for 10-14 days is recommended in patients with peptic ulcer disease positive for H. pylori or with no identifiable cause. American College of Gastroenterology recommends four specific drug regimens that use above referred combination of three medications or Bismuth- containing quadruple therapy - Bismuth subsalicylate, metronidazole, tetracycline all in 4 daily doses and ranitidine or PPI twice a day for 10-14 days. These combinations are expected to cure 70% to 85% of infections.

Endoscopic procedures

Variceal bleed: Upper gastrointestinal endoscopy should be performed as soon as possible after initial stabilization. Endoscopic therapy should be done if variceal source of hemorrhage is confirmed. A meta-analysis has shown that endoscopic variceal ligation (EVL) is superior to sclerotherapy in the initial control of bleeding. However EVL cannot be performed in infants and toddlers due to the large size of available devices; endoscopic sclerotherapy (EST) is the mainstay of therapy in this group. Combination of pharmacological and endoscopic therapy is the most rational approach in the treatment of acute variceal hemorrhage. Endoscopic injection of 'tissue glue' is effective for controlling bleeding gastric varices. Argon plasma coagulation can be used for bleeding portal hypertensive gastropathy lesions e.g., GAVE- Gastric Antral Vascular Ectasias.

Non-variceal ulcer bleeds: In case of peptic ulcers with stigmata indicating high risk of rebleed (spurting or oozing vessel in ulcer base/adherent clot), any of the following endoscopic therapy may be given: Injection therapy with adrenaline and saline, mechanical hemostasis (Endoclip devices) with or without adrenaline, or thermocoagulation with or without adrenaline.

Balloon tamponade: In patients with variceal bleed who continue to bleed despite pharmacologic and endoscopic methods, a Sengstaken-Blakemore tube can be placed to stop hemorrhage by mechanically compressing esophageal and gastric varices. However, its use is associated with potentially lethal complications such as aspiration and necrosis/perforation of the esophagus with mortality rates as high as 20%.[10] The tube should never be kept inflated beyond 12 hours in children. Since the advent of safe pharmacotherapeutic agents and endoscopic therapeutic procedures, balloon tamponade has almost been abandoned as a tool to control variceal bleeding.

Surgical treatment

Consultation with a pediatric surgeon and interventional radiologist is necessary for children with massive bleeding, ongoing significant blood loss (replacement required is equal to or more than the estimated blood volume of the child) and failed endoscopic procedure. Approaches to manage refractory variceal hemorrhage include insertion of transjugular intrahepatic porto-systemic stents (TIPS) in sinusoidal and post-sinusoidal portal hypertension, selective or non-selective surgically created portosystemic shunts and nonshunt procedures aimed at interrupting and ligating varices directly (devascularization). Non-variceal bleed can be tackled by transcatheter embolization by an interventional radiologist. If this is not technically feasible or expertise is unavailable, surgical ligation / resection can be resorted to.

Points to Remember

- ***Upper gastrointestinal (UGI) bleeding can present with hematemesis and/or melena.***
- ***Although melena suggests UGI bleeding, it may also occur in patients with a proximal lower GI source.***
- ***Patients with brisk UGI bleeding and rapid intestinal transit time may present with hematochezia, particularly if they are infants or toddlers.***
- ***The initial evaluation of the patient with UGI bleeding involves an assessment of hemodynamic stability and resuscitation, if indicated.***
- ***Mucosal bleeds are more common in developed countries while variceal bleeds are more common in developing ones.***

- ***Nasogastric or orogastric lavage may be performed in patients with clinically significant UGI bleeding to confirm the location and to remove fresh blood or particulate matter from the stomach to facilitate endoscopy.***
- ***Hemodynamically unstable children or those with large volume bleeding should be given parenteral proton pump inhibitors.***
- ***Patients with documented variceal bleed should be given infusion of vasoactive agents like octreotide.***
- ***Endoscopy usually permits identification of the bleeding source, allows for risk stratification regarding the likelihood of continued bleeding, and in some cases permits therapeutic intervention.***

References

1. Rodgers BM. Upper gastrointestinal hemorrhage. Pediatr Rev 1999; 20:171.
2. Grimaldi-Bensouda L, Abenhaim L, Michaud L, Mouterde O, Jonville-Béra AP, Giraudeau B, et al. Clinical features and risk factors for upper gastrointestinal bleeding in children: a case-crossoverstudy. Eur J ClinPharmacol 2010; 66:831-837.
3. Lacroix J, Nadeau D, Laberge S, Gauthier M, Lapierre G, Farrell CA. Frequency of upper gastrointestinal bleeding in a pediatric intensive care unit. Crit Care Med 1992; 20:35-42.
4. Cochran EB, Phelps SJ, Tolley EA, Stidham GL. Prevalence of and risk factors for, upper gastrointestinal tract bleeding in critically ill pediatricpatients. Crit Care Med 1992; 20:1519-1523.
5. Yachha SK, Khanduri A, Sharma BC, Kumar M. Gastrointestinal bleeding in children. J Gastroenterol Hepatol 1996;11:903-907.
6. Mittal SK, Kalra KK, Aggarwal N. Diagnostic upper gastrointestinal endoscopy for hematemesis in children: experience from a pediatric gastroenterology centre in north India. Indian J Pediatr1994;61:651-654.
7. Shneider BL, Bosch J, de Franchis R, Emre SH, Groszmann RJ, Ling SC, et al. Portal hypertension in children: expert pediatric opinion on the report of the Baveno v ConsensusWorkshop on Methodology of Diagnosis and Therapy in Portal Hypertension. Pediatr Transplant 2012; 16:426-437.
8. Thomson MA, Leton N, Belsha D. Acute upper gastrointestinal bleeding in childhood: development of the Sheffield scoring system to predict need for endoscopic therapy. J Pediat rGastroenterol Nutr 2015; 60:632-636.
9. Freedman SB, Stewart C, Rumantir M, Thull-Freedman JD. Predictors of clinically significant upper gastrointestinal hemorrhage among children with hematemesis. J Pediatr Gastroenterol Nutr 2012; 54: 737-743.
10. Jaramillo JL, de la Mata M, Mino G, Costan G, Gomez-Camacho F. Somatostatin versus Sengs taken balloon tamponade for primary haemostasia of bleeding esophageal varices: a randomized pilot study. J Hepatol 1991; 12: 100–105.

NEWS AND NOTES

MADRAS PEDICON 2019

44th Annual Conference of Indian Academy of Pediatrics - Tamilnadu State Chapter

Organised by Indian Academy of Pediatrics – Chennai City Branch

Date: 15th to 18th August, 2019

Contact

Dr.Janani Sankar, Organising Secretary, MADRAS PEDICON 2019

Dr.N.Suresh, Treasurer, Chennai Pedicon 2019

IAP-CCB House, Third Floor, Flat No.9, Halls Towers,

56, Halls Road, Egmore, Chennai-600 008. Tamilnadu. India.

Mobile: 9841078101, 9444288174

Email: madraspedicon2019@gmail.com

GASTROENTEROLOGY - II

LIVER TRANSPLANTATION - CURRENT TRENDS

***Vidyut Bhatia**
***Akshay Kapoor**
***Smita Malhotra**
****Anupam Sibal***

Abstract: *Liver is now the second most commonly transplanted organ. Published data from across the world have consistently shown 10-year survival figures of above 90% and 20 year survival close to 85%. Recent published data from India has mirrored similar success and results of programs worldwide. As of today, the expected survival from a liver transplantation is close to 95%. This has largely been possible because of improvements in immunosuppression, intensive care, better surgical techniques and timely referral for transplant due to enhanced acceptability amongst the medical fraternity. Indications include acute and chronic liver failure resulting in end stage liver disease and certain metabolic disorders with or without intact liver function. Newer surgical innovations including split and monosegmental grafts have helped expand the available donor pool. Exhaustive pretransplant donor assessments are mandatory to ensure donor safety and successful outcome. Pretransplant recipient optimization includes immunization, addressing micro and macronutrient deficiencies and eradication of any infections. Postoperative optimal intensive care forms the cornerstone for good outcomes. Sepsis continues to be one of the leading complications in the post transplant period. Acute rejection is frequent though chronic rejection and biliary leaks are relatively fewer in children. Triple immunosuppression with steroids, calcineurine inhibitors and mycophenolate mofetil has greatly reduced the incidence of rejection. Feasibility of weaning patients completely off immunosuppression is an area of active research.*

Keywords: *Liver Transplantation, Children, Immunosuppression.*

* Consultant-Pediatric Gastroenterology and Hepatology

** Senior Consultant Pediatric Gastroenterologist and Hepatologist, Indraprastha Apollo Hospital, New Delhi.

email: drvidyut@gmail.com

The liver has now become the second most commonly transplanted organ. Liver transplantation (LT) has evolved from being a novelty that was in the domain of specialized research centers in the West to a procedure with comparable results readily available at select centers in our country. The evolution of the procedure over the last four decades from an experimental desperate attempt to a streamlined surgery has radically changed the treatment of children with end stage liver disease (ESLD), acute liver failure (ALF) and other chronic liver illnesses. Newer surgical innovations have made it the paradigm of surgical expertise and excellence.

Long-term data from centers across the world have shown encouraging survival figures. Published data across the world, especially the Japanese and Korean registries (which are predominantly living related programs) have consistently shown 10-year survival figures of above 90% and 20 year survival close to 85%.[1,2] Recently published data from India has mirrored similar success and results of programs worldwide.[3] Pediatric patients account for approximately 10% of all LTs performed at any center. The aim of the present article is to bring to the fore evolving indications, outcomes and recent changes in the management of post transplant patients.

Historical aspects

After Starzl performed the first human LT in 1963, it took almost 20 years for the LT program to be fully established in the West.[4] The need for a LT program in India was felt way back in the early 1990s. During that period, little was being offered to patients with ALF or end-stage liver disease and as a result the mortality was high. LT, the only hope for these patients was available in the West at a considerable cost along with long waiting periods. Taking cognizance of this need, the Indian Parliament in 1994 passed "The Transplantation Of Human Organs Act" which became a law in 1995. Initial transplants were unsuccessful. The first successful transplant was performed at the Indraprastha Apollo hospitals, New Delhi in a small boy with biliary atresia (BA) in 1998.[5] This milestone provided a much-needed momentum to establish LT in India. The boy is now a healthy adult studying medicine aiming to become a surgeon himself.

The first decade was full of challenges. Initially, the surgery was regarded as experimental and many pediatricians were not too keen to recommend this treatment modality for their patients who required LT. Many children requiring LT were often referred late, as guidelines regarding referral were not available. Most of the children who merited a LT belonged to the economically deprived strata of the society and were financially incapable of affording it. Lack of cadavers minimized the number of transplants. With the passage of time and increasing success rates of the transplant programs, acceptability of this treatment modality has increased. Both the medical fraternity and the public at large recognized LT as an important modality that had the potential to save otherwise unsalvageable children with end stage liver disease. The year 2007 was a watershed after which the numbers have steadily picked up. Many new centers offering LT also came up thereafter. The transplant act was also amended and later notified in 2014 bringing about significant changes in the certification of brain death, simplifying procedures required for certification and allowing organ retrieval.

As of today, the expected survival from a LT is close to 95%.[6,7] This has largely been possible because of improvements in immunosuppression, intensive care, better surgical techniques and experience and in general, a positive view of the procedure amongst medical professionals.

Indications

LT should only be offered if the life expectancy is less than a year or if there is an unacceptable quality of life. It is not indicated if an acceptable alternative is available. The commonest indication for pediatric LT in India and across the world is biliary atresia. It is useful to classify indications of pediatric LT depending on the locus of the defect.

1. Locus within the liver

LT is indicated in patients with both chronic liver failure (CLF) and acute liver failure (ALF).

Acute liver failure: ALF is a rapidly evolving, dynamic illness characterized by massive hepatic necrosis leading to an incapacitated liver that is incapable of performing its functions. LT is the only definitive therapy for ALF. It has revolutionized the management of ALF. The prognosis has improved from a meager 10%-20% survival to 75%-80% at 1-year. It is however, the timing of LT in the setting of ALF, which is a topic of debate. Numerous prognostic and scoring systems are available for deciding the timing of LT in children with ALF. The King's College criteria and the Clichy's criteria have been accepted and validated as the most useful tools to establish the requirement for LT among patients with ALF.[8] The IAP consensus statement endorses international normalised ratio (>4) or factor V concentration (<25%) as acceptable criteria for deciding the need for LT in children.[8]

Chronic liver failure: Children with CLF can have well compensated liver function till very late in the illness. For some of these children a viral illness, bleeding or a hepatotoxic drug tilts the scale in favor of a transplant. Specific transplant criteria for conditions producing CLF have not been developed fully. Many of these criteria exist for individual diseases and not for the group as a whole.

In children with BA, the clinical course of the patient post-portoenterostomy must be taken into account. LT is indicated when the surgery fails to restore sufficient bile flow by 3 months post procedure (as evidenced by elevated bilirubin) or when life-threatening complications such as hypoalbuminemia, recurrent variceal bleeding and coagulopathy occur. Early groundwork for LT should begin as soon as failure of the Kasai surgery is established. This includes, preparing the donor, optimizing weight, treating any micronutrient deficiencies and immunization.

This group also includes patients with metabolic illnesses (Wilson's disease, tyrosinemia, galactosemia, etc) in whom the primary defect is in the liver and LT is performed primarily for hepatic complications. LT in such cases replaces the cirrhotic liver and also corrects the underlying metabolic defect.

2. Locus outside the liver with intact liver function

It is the diseases in this subgroup that have expanded the ambit of indications for pediatric LT. This category includes diseases wherein the liver is the source of the metabolic defect, but is structurally unaffected i.e. there is absence of cirrhosis (e.g. Primary hyperoxaluria type 1, hypercholesterolemia, Criggler Najjar syndrome). LT prevents kernicterus in infants with Criggler Najjar syndrome and prevents atherosclerosis and risk of sudden cardiac death in patients with hypercholesterolemia. LT also prevents metabolic crises in babies and children with urea cycle defects and organic acidemias. LT in such cases is done to correct the underlying gene defect. Combined liver and kidney transplantation (CLKT) is standard therapy for patients suffering from hyperoxaluria and atypical hemolytic uremic syndrome.

Assessment

The aims of assessment for LT are to confirm the diagnosis and severity of disease, define the patient's general medical status, determine eligibility and priority for transplant and also arrange interim supportive care. It is essential to make sure that routine immunizations are complete. Early routine immunization should be ensured prior to transplantation and should be given at least one month before LT to ensure seroconversion. This is important as the risk of infections increase significantly in the post transplant period due to immune suppressants. Children with CLF can have complex multisystem problems that need to be addressed prior to undergoing LT. This usually includes nutritional rehabilitation and management of complications arising from liver failure (varices, ascites, hepatorenal and hepatopulmonary syndromes).

Various studies have shown that pretransplant nutritional status has a direct bearing on the success of LT, especially in children. Modular feeds allowing protein (3 g/kg/day), carbohydrate (using glucose polymers) and fat (50% medium and 50% long chain triglycerides) contents to provide calories up to 150 kcal/kg/day along with fat-soluble vitamin supplementation is recommended. Water-soluble vitamin requirement is usually twice the recommended dietary allowance. Management of complications like varices and ascites include endoscopic ligation and adding diuretics. Coagulopathy is treated by giving enteral/parenteral vitamin K; while active bleeding can be managed by giving fresh frozen plasma.

Transplant surgery

The liver graft can be obtained from either a cadaver or from a living donor. The donor and recipient should preferably have compatible ABO blood groups, though incompatible ABO transplants are also now feasible. HLA matching is not necessary. Living related liver transplant (LRLT) is the technique of choice in countries (including India) that do not have easy access to cadavers. This has benefitted pediatric LT programs immensely, as the left lateral segment can be safely taken from the parents without significant morbidity.

The donor for LRLT must be a relative of the child and preferably have a compatible blood group. ABO incompatible LTs have also been performed successfully by using pre-transplant conditioning with Rituximab and/or plasmapheresis. In addition, newer surgical innovations have been developed to expand the available donor pool and overcome shortage. The following technical variants are in existence:

Split LT: Split LT from a cadaveric donor provides two grafts. The left lateral segment is utilized in a child and the right lobe is used for an adult.

Monosegmental LT: Reduced left lateral segment grafts and hyper-reduced left lateral segment grafts can be used in cases where the graft is too large to fit into the abdominal cavity without compromising its vascular pedicle.

Auxiliary partial LT: The graft is placed with the diseased native liver in situ in cases where there is a possibility of native liver regeneration and immunosuppression withdrawal as is the case in ALF. Careful, serial and meticulous follow up with radiological screening and tapering of immunosuppression is required while the transplanted liver shrinks and degenerates and the native liver regenerates.

Postoperative care

The cornerstones of postoperative management include appropriate ventilation, adequate tissue perfusion, prevention and management of sepsis and immunosuppression. Elective ventilation with adequate analgesia during the first 12-24 hours post transplant helps the child as well as the intensivist to tide over the metabolic derangements arising out of prolonged surgery. It also enables reliable radiological assessment of the new graft. Fluid imbalance commonly occurs in LT. Children usually become hypovolemic during surgery, as they lose ascitic fluid. They may also vasoconstrict due to intra-operative hypothermia and inotropes. Fluid replacement with colloids/crystalloids may be necessary to maintain a central venous pressure between 6-7 cm of water and an adequate urine output. Prophylactic antibiotics with an adequate gram positive, gram negative and antifungal cover are started 24 hours pre-operatively.

Immunosuppression: The availability of potent immune suppressants has contributed greatly to the success story of pediatric LT. While the initial treatment regimen of LT consisted of corticosteroids and azathioprine (AZA) with a graft survival of only 30%, the introduction of cyclosporin A (CSA) in the early 1980s and tacrolimus (TAC) in the early 90s, revolutionized solid organ transplantation. There are 2 main phases of immunosuppression.

Induction phase: This phase occurs in the immediate post transplant period when the recipient is flooded with antigens from the donor graft. Although associated with several side effects, corticosteroids continue to be the mainstay of this phase. Several steroid free regimens using thymoglobulin and basiliximab have been attempted but are associated with increased incidence of acute rejection.[9]

Maintenance phase: The usual immunosuppressive regimen consists of TAC and prednisolone, with or without AZA or mycophenolate mofetil (MMF). TAC based immunosuppression is preferred over CSA because it has been associated with less rejection and fewer cosmetic side effects. However, TAC is associated with a greater incidence of de-novo diabetes and gastrointestinal side effects as compared to CSA. Sirolimus is a newer immunosuppressant, which prevents T-cell proliferation by inhibiting cytokine production by interfering with the post receptor signaling. It has a significant steroid sparing effect and considerably less nephro and neurotoxicity. Interleukin-2 receptor (IL-2R) antibodies are monoclonal antibodies, which selectively target the IL-2Rs on activated T-cells. Basiliximab and daclizumab are two such drugs used in combination with a calcineurin inhibitor (CNI). Long-term use including their incorporation into CNI sparing regimens in liver graft recipients with emerging nephrotoxicity or neurotoxicity has been validated.

Complications

Primary non-function of the graft and early hepatic artery thrombosis (HAT) are rare but catastrophic complications of LT. The causes include poor donor status, faulty organ preservation, retrieval and technical or immunological complications in the recipient. Early HAT has an estimated incidence of less than 10%. Prompt recognition by judicious use of Doppler followed by thrombectomy and revision of arterial anastomosis might be life saving. Portal vein thrombosis (PVT) has an incidence of 5% and is common in children with small hypoplastic veins. It can present as graft dysfunction or unexplained gastro-intestinal hemorrhage. A physiological shunt like the Meso-Rex may be performed if technically feasible.

Sepsis continues to be one of the leading complications in the post transplant period. Preexisting significant sepsis, insertion of central venous catheters, prolonged ventilation and poor graft function can all contribute to its increased incidence.

Acute rejection is characterized by fever, irritability and vague abdominal pain. Since, the symptoms are non-specific, intensivists have to rely on the biochemistry, which shows an increased bilirubin level with transaminitis. Treatment is with pulse methylprednisolone (20-40 mg/kg/day) intravenously over 2 or 3 days. Chronic rejection (<5%) is an uncommon complication in the pediatric setting. It can cause an insidious onset of graft fibrosis, ductopenia and eventual graft loss. Biochemical findings include an increasing bilirubin level and a raised gamma-glutamyl transferase (GGT) in excess of ALT/AST. Treatment modalities include intensifying or changing the immunosuppressant regimen.

Biliary complications are the commonest structural post LT complications in adults but are rare in children. The strictures can be anastomotic or non-anastomotic. Anastomotic strictures can occur at the hepatico-jejunostomy site or at the ductal confluence. Non-anastomotic strictures are often the result of late HAT. Anastomotic strictures are short and respond well to endoscopic stenting, while non-anastomotic strictures are harder to manage. They can lead to progressive graft dysfunction.

EBV infection should be suspected in post transplant patients with prolonged fever and unexplained lymphadenopathy [post-transplant lymphoproliferative disorder (PTLD)]. A tissue biopsy should be performed for all cases in which the lesion can be identified on physical examination or CT/MRI scanning. EBV loads should also be monitored closely in such patients. Reducing immunosuppression is the first step in treating PTLD. Use of monoclonal antibodies like CD20 antibody rituximab in conjunction with low dose corticosteroid therapy has been tried with variable success in EBV positive PTLD.[10]

Advances in management

Tolerance: With the capability of latest immunosuppressive regimens to diminish the incidence of acute rejection, the side effects occurring over long-term use have become a major challenge for LT recipients. The emphasis is now to reduce immunosuppression to the least possible degree at the earliest. Most centres advocate early steroid withdrawal by 3-6 months though this is debatable. Most recipients preserve stable graft function with either TAC or CSA.

Liver is a more immunologically privileged organ. Weaning a patient completely off immunosuppression may rarely be possible. Experience in LT recipients who have been poorly compliant with therapy or in whom immunosuppression was temporarily suspended due to adverse effects suggests that it may be possible in some cases to withdraw immunosuppression completely without precipitating graft rejection or loss.[11] This is an area of active research.

Liver cell therapy (LCT)

Liver cell therapy is a newer technique where different types of cells found in the liver (hepatocytes, stem cells, macrophages) are extracted and infused in recipients to treat certain disorders. This technique is still in a nascent

stage in its development and the indications are few. It has been attempted successfully for certain metabolic liver diseases (congenital errors of metabolism, Criggler Najjar syndrome, acute liver failure, urea cycle defects and cholestatic disorders) and pediatric liver failure. The advantages of LCT are that it is a simpler technique as compared to surgery; that a single donor may be able to benefit multiple recipients, the cost is lower with the ability to give multiple infusions and use in a non-emergent setting.

The technique involves infusing ABO compatible cryopreserved hepatocytes/other liver cells manually into the recipient.[12] The portal vein or splenic artery is usually chosen for children with metabolic disorders. Approximately 10% of the recipient's estimated liver cell mass is transfused. The portal pressure needs to be monitored consistently to prevent side effects. The recipients require immunosuppression similar to the ones used for conventional LT.

Growth and quality of life

Most studies have shown an improvement in the health related quality of life (HRQOL) of the children post LT. However, the HRQOL is lower when compared to the general population. Children (<7 years) who received hepatic grafts have progressed to puberty normally with normal linear growth and sexual maturation. Pre-pubertal children who underwent LT had impaired height velocities and sexual maturation. Parents of transplanted children have reported low scores for social interaction and scholastic performance, which picked up with time. Sexual maturation and fertility are achieved normally in pediatric liver recipients.

Liver transplant in India: Improving outcomes

In the West, approximately 2-3 pediatric LTs per million population are performed annually. At that rate, around 2000-3000 children will need LTs in India every year. This estimate is likely to be representative, since the incidence of extra hepatic biliary atresia (EHBA) (1/12,000 to 1/18,000), which is the commonest indication for LT, is similar throughout the world.[7]

Evaluation of a child for LT not only involves a detailed clinical and surgical assessment; it also involves a detailed socio economic assessment. Families need to be committed to the cause, as a young child will need the support of a caregiver for the greater part of his childhood.

Pediatric LT is also changing the social milieu, as was evidenced by fathers coming forward in greater numbers as donors. Pediatric LT costs about rupees 12-15 lakhs in India, which is 1/10th of that being offered worldwide. The last 7 years have shown a rapid growth in the number of pediatric LT recipients in India. About 120 pediatric LTs are performed in India each year.

Conclusion

Pediatric LT is a well-established life saving procedure for children with pre-terminal liver failure, metabolic liver disease and chronic liver diseases. With increasing expertise, concerns have shifted away from procedure related mortality to moderating and rationalizing immunosuppression and inducing a state of functional tolerance. There is also a burgeoning growing need to identify lacunae in the long term post transplant care, including prevention of kidney dysfunction, post transplant metabolic syndrome and de novo malignancies. It is incumbent on the treating pediatricians to ensure proper communication with the recipient and his/her family to achieve compliance with the treatment protocol.

Points to Remember

- ***Liver transplantation is now routinely performed in many centres across India.***
- ***Most liver transplants in India are from living related donors.***
- ***The most common indication for liver transplant is biliary atresia.***
- ***Current 1-year survival following living related transplant is close to 95%.***
- ***Triple immunosuppression with steroids, calcineurine inhibitors and immunomodulators have greatly reduced the incidence of rejection.***

References

1. Byun J, Nam-Joon Yi, Jeong-Moo Lee, Suk-won Suh, Tae Yoo, YoungRok Choi, et al, Long term outcomes of pediatric liver transplantation according to age. J Korean Med Sci 2014; 29(3):320-327.
2. Kasahara M, Umeshita K, Inomata Y, Uemoto S. Long-term outcomes of pediatric living donor liver transplantation in Japan: an analysis of more than 2200 cases listed in the registry of the Japanese Liver Transplantation Society. Am J Transplant 2013; 13(7):1830-1839.
3. Sibal A, V Bhatia, S Gupta. Fifteen years of liver transplantation in India. Indian Pediatr 2013; 50(11):999-1000.
4. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117:659-676.

5. Poonacha P, Sibal A, Soin AS, Rajashekar MR, Rajakumari DV. India's first successful pediatric liver transplant. Indian Pediatr 2001; 38(3):287-291.
6. Mohan N, Karkra S, Rastogi A, Dhaliwal MS, Raghunathan V, Goyal D, et al. Outcome of 200 Pediatric Living Donor Liver Transplantations in India. Indian Pediatr 2017; 54(11):913-918.
7. Sibal A, Malhotra S, Guru FR, Bhatia V, Kapoor A, Seth S, et al. Experience of 100 solid organ transplants over a five-yr period from the first successful pediatric multi-organ transplant program in India. Pediatr Transplant 2014; 18(7):740-745.
8. Bhatia V, Bavdekar A, Yachha SK. Management of acute liver failure in infants and children: consensus statement of the pediatric gastroenterology chapter, Indian academy of pediatrics. Indian Pediatr 2013; 50(5):477-482.
9. Turner AP, Knechtle SJ , Induction immunosuppression in liver transplantation: a review. Transpl Int 2013; 26(7): 673-683.
10. Kelly DA, Bucuvalas JC, Alonso Em, Karpen SJ, Allen U, Green M, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013; 19(8):798-825.
11. Liu XQ, Hu Z-Q, Pei YF, Tao R. Clinical operational tolerance in liver transplantation: state-of-the-art perspective and future prospects. Hepatobiliary Pancreat Dis Int 2013; 12(1):12-33.
12. Soin AS, Raut V, Mohanka R, Rastogi A, Goja S, Balachandran M, et al. Use of ABO-incompatible grafts in living donor liver transplantation-first report from India. Indian J Gastroenterol 2014; 33(1):72-76.

CLIPPINGS

Ultrasound-guided placement of long peripheral cannulas in children over the age of 10 years admitted to the emergency department: a pilot study

Most children admitted to the emergency department (ED) require peripheral venous access (PVA), which is often difficult to perform or is unsuccessful. Ultrasound guidance helps with the placement of peripheral short cannulas (SC), but it has a limited cannula duration and a high risk of developing complications. The aim of this study was to compare success rates, dwell times and complications of peripheral venous long cannulas (LCs) inserted under ultrasound guidance with those of SCs in children.

All children older than 10 years of age admitted to paediatric ED requiring PVA for an expected therapy of more than 5 days were studied. In children with difficult intravenous access (DIVA), after two unsuccessful attempts of 'blind' placement of SCs, LCs (20 G, 8 cm) were inserted in the deep veins of arms using ultrasound guidance and the direct Seldinger technique.

LC placement (n=20) was successful in 100% of the cases. LC dwell time was 9.2±6.0 days, and most catheters were electively removed because they were no longer indicated. SC (n=20) placement showed a shorter dwell time duration, 3.2±2.1 days ($p<0.0001$), with complications occurring in 70% of the cases compared with 25% of cases in patients with LC ($p=0.002$). No local or major infectious complications were reported with LC placement.

Conclusion: Ultrasound-guided placement of LC was associated with a low risk of catheter failure and complications compared with the 'blind' placement of SC. LC placement may be considered a valid option in patients with DIVA requiring PVA in paediatric ED or in children who are candidates for infusion therapy expected to last longer than 5 days.

Paladini A, Chiaretti A, Sellasie KW, Pittiruti M, Vento G. Ultrasound-guided placement of long peripheral cannulas in children over the age of 10 years admitted to the emergency department: a pilot study. BMJ Paediatr Open. 2018;2(1):e000244.


Docowize

GASTROENTEROLOGY - II

WILSON DISEASE

Dhanasekhar Kesavelu

Abstract: *Wilson disease is an autosomal recessive disorder due to a defect of copper transport by the hepatic lysosomes affecting most commonly children or young adults. Excess copper deposition in the liver, brain, kidneys and the skeletal system runs an invariably fatal course and needs to be managed effectively. Multiple modalities are now available in the diagnosis, genetics, neuroimaging and management. Novel mutations have been increasingly reported in Wilson both in Indian subcontinent and abroad. Treatment choices includes zinc, trientin, penicilamine and liver transplant. Penicillamine once a 'gold standard' for treatment, has been debated by experts and lacks a general consensus globally.*

Keywords: *Ceruloplasmin, Copper, Penicillamine, Zinc.*

Wilson disease (WD) is an autosomal recessive condition characterized by inability of the liver to transport and store normally absorbed dietary copper resulting in abnormal deposition of copper in the basal ganglia, eyes, liver and other tissues. The first ever clinical and pathological description of about 200 cases published in the brain now bears the name of the condition that S.A.Kinnier Wilson described.[1] The clinical manifestations and the pathology of Wilson disease have been described by various clinicians during different periods. In 1902, Kayser and in 1903, Fleischer described the corneal pigmentation of Wilson disease.[2,3] In 1913 the hepatic copper content in Wilson disease was described by Rumpel.[4] Not until 1948 the copper metabolism in Wilson was ever described till the work of Mandelbrote and Cumings. Ceruloplasmin deficiency was described in 1952 (Scheinberg and Gitlin& Bearn and Kunkel). In 1974, Frommer described the impaired biliary excretion of copper.

* Consultant Pediatric Gastroenterologist, Department of Pediatric Gastroenterology, Apollo Childrens Hospital, Chennai.
email: drdskgastro@gmail.com

Epidemiology

The prevalence rate of Wilson disease is 1 in 30000. A mutation in the ATP7B gene located on chromosome 13 is responsible for Wilson disease. Genetic analyses from India have been reported mainly from three centers: Chandigarh, Kolkata and Vellore. The commonest mutations in these studies are variable and include: (a) Chandigarh group: T3305C, C2975A, 2977insA and 3031insC-6% each (b) Kolkata group: C813A-19% and (c) Vellore group: G3182A-16% and C813A-12%. Till date, a total of 51 mutations of ATP7B have been documented in India including 34 novel mutations (Chandigarh-18, Kolkata-5 and Vellore-11).[5,6,7] Of the mutations documented in India, C813A is the common mutation. There is no single predominant mutation noted in the Indian population unlike the studies in other countries: PH1069Q in 60% of central European population and pR778L in 45% of Chinese population, thus suggesting genetic heterogeneity in India.

Commercial testing of all mutations is practically impossible due to the wide range of mutations that are found in India.The H1069Q mutation which is the most frequent mutation in the United States and the northern Europe has been reported to correlate with the late onset of symptoms and less severe disruption of copper metabolism. Variable mutations have various clinical presentations and vary from one region to another.

Pathophysiology

Copper is very important for cellular function. Free copper is extremely toxic and can cause irreversible cellular damage. Complicated intrinsic mechanisms handle copper very well in the transport of copper to intracellular sites and the excess is eliminated through the biliary system. Ceruloplasmin and ATP7B are involved in the copper transport. The hepatocyte trans-golgi network are very important in the copper metabolism as it mediates the incorporation of six copper molecules into apoceruloplasmin forming ceruloplasmin. In individuals with Wilon disease, mutation in the ATP7B gene results in defective ATP7B protein that cannot perform these functions. Consequently, copper accumulation happens in the hepatocytes. Excessive copper accumulation not only exceeds the storage capacity of the cells but also causes

cell damage. The spill over of copper causes urinary excretion and also deposited in other organs and tissues leading to dysfunction and damage. The cellular damage is caused directly due to the toxic effects of copper. Recent reviews have shown that caspase 3 initiated apoptosis with resultant cell death accelerated due to excess copper is directly related to XIAP (X linked inhibitor of apoptosis).[8]

Clinical features

The presentation can be multisystemic and may cause diagnostic dilemma.[9] The manifestations of Wilson disease can be hepatic, neurological, psychiatric, ophthalmologic, skeletal or other manifestations.

Hepatic manifestations

Data shows that 40-50% of all patients present with hepatic manifestation. The average age of presentation is 11.5 years.[10] Majority of children present over the age of 5 years. It is unusual to present beyond the age of 40 years. Rare case reports of children presenting as early as 2 years have been reported.[11] The hepatic presentation can be asymptomatic hepatomegaly or splenomegaly or both, elevation of liver enzymes, acute transient hepatitis or any of the above with hepatic dysfunction, hemolytic anemia and elevation of unconjugated bilirubin. Wilson disease may mimic autoimmune hepatitis. Rare occurrence of Wilson disease as acute fulminant hepatitis has also been reported with acute liver failure in about 5% of cases. Coombs negative hemolytic anemia due to massive release of copper into the blood stream triggering intravascular hemolysis, progressive cirrhosis and unexplained liver disease (under the age of 5 years) can also be rarer presentations.

Neurological manifestations

The neurological manifestation in Wilson can occur in 40-60% of patients. The average age of symptom onset is documented at 18.9 years although it may appear as early as 6 years. The manifestations are given in Box 1.

Psychiatric manifestations

The frequency with which Wilson disease present with psychiatric manifestations in children is unknown but is well documented to present in around 20% of adults. Poor scholastic performance and change in handwriting are often observed in children. Personality changes, disturbances in mood particularly depression, psychosis (unusual), anti-social behavior or criminal behavior, sexual preoccupation and disinhibition and cognitive impairment are the reported psychiatric symptoms in adults.

Box 1. Wilson disease – Neurological manifestations

- Tremors [resting, postural or kinetic may involve the upper extremity (coarse) or may be distal (small in amplitude)]
- Dysarthria
- Dystonia (involving tongue, face and pharynx may be present in 40%)
- Cerebellar dysfunction (25%)
- Gait abnormalities
- Chorea, tics, myoclonus
- Painful legs and restless leg syndrome
- Autonomic dysfunction (25 to 30%)
- Seizures (Generalized, partial, benign epilepsy of childhood, rarely status epilepticus)
- Headache and seizures (10%)
- Peripheral sensorimotor polyneuropathy
- Pseudo-bulbar palsy. emotional lability, hypersomnia, altered rapid eye movement sleep function, priapism and muscle cramp]

Ophthalmic manifestations

Interestingly Kayser and Fleischer described pigmented corneal rings about 10 years before the description of Wilson disease by Wilson. Deposition of copper in the descemet membrane causes Kayser-Fleischer (KF) rings. Excess copper is deposited throughout the cornea but it is only in the Descemet's membrane that the sulphur-copper complexes are formed.[12]

K-F rings are usually bilateral, colour may vary from gold to brown to green (hence difficult to see in individuals with brown iris) and typically appears in the superior part of cornea, then inferior, later medially and laterally. It may not be seen in pre-symptomatic stage. Absence of KF rings in some individuals with established liver disease has also been reported. A slit lamp examination is mandatory in any child with suspected Wilson disease. Corneal deposition of copper may also occur in other conditions like chronic lymphocytic leukemia, multiple myeloma, etc.

Sunflower cataract: It is the other ophthalmic presentation of Wilson disease first described by Siemerling and Oloff in 1922. It consists of copper deposition in the lens that

assumes a 'sunflower appearance' with a central disc and radiating petal like spokes.

Other manifestations

Bone and joint involvement of Wilson disease are under recognized components, although osteoporosis has been reported in 88% patients. In about 10%-15% of patients, hemolytic anemia may be the presenting feature.[13] This is due to erythrocytes that undergo oxidative damage due to copper. Thrombocytopenia has also been reportedly concomitantly in some cases. Hypokalemia, muscle weakness, renal tubular dysfunction, hypercalciuria, hyperphosphaturia have been reported in Wilson disease. Occasionally, gynecological problems such as menstrual irregularity and delayed puberty in girls and gynecomastia in boys have been reported. Rare occurrences like glucose intolerance and parathyroid insufficiency have been reported.[14]

Diagnosis

The genetic testing of Wilson disease is challenging due to the existence of multiple documented mutations which makes commercial testing impractical. Specific tests may be needed depending on clinical presentation.[15] Hepatic copper content by liver biopsy remains the most sensitive and specific test for Wilson disease. Elevation of more than 250 micrograms per gram of dry tissue (normal 15 to 55 microgram/gram) is typically present. It is elevated even in those who are clinically asymptomatic. The use of liver biopsy in the diagnosis of Wilson disease supercedes the risks associated with it. A scoring system used for diagnosis of Wilson disease is given in Table I.[16]

Slit lamp examination: A slit lamp examination is mandatory in suspicious cases.[3] The presence of K-F ring should strongly raise the suspicion of Wilson disease though the absence of it does not rule out Wilson disease.

Ceruloplasmin: Measuring ceruloplasmin in the serum is a safe, simple and practical method of screening for Wilson disease. It is used in combination with other tests to diagnose Wilson. Certain conditions like Menkes disease, aceruloplasminemia, sprue, nephritic syndrome, protein losing enteropathy and chronic liver disease have low ceruloplasmin.[4]

Measurement of 24-hour urinary copper: This may be the best screening test for Wilson disease especially in individuals with neurological or psychiatric dysfunction.[5] Urine copper levels in symptomatic Wilson disease patients typically exceed 100 micrograms/day. Urine copper may be elevated in obstructive liver disease. It is important that patients collect urine in copper free container to avoid spurious elevations.[6] The penicillamine challenge is performed by giving a 500 mg dose of penicillamine (regardless of the patient's weight) at the beginning of the 24-hour urine collection and then again at 12 hours. Urinary copper excretion greater than 1600 mcg per 24 hours (>25 micromol) is much more likely in Wilson disease compared with other types of liver disease.

Table I. Scoring system for Wilson disease[16]

**If no quantitative liver copper available, ** or typical abnormalities at brain maganetic resonance imaging. KF, Kayser-Fleischer; ULN, upper limit of normal.*

Serum copper and serum free (Non-ceruloplasmin bound) copper: In Wilson disease serum copper is reduced. Labs measure only total copper. Non-ceruloplasmin bound copper is calculated. The normal range of non-ceruloplasmin bound copper 10-15 microgram/dL.[7] The reduction in serum copper is an indication of the reduced ceruloplasmin.

Neuroimaging studies

MRI of the brain of children with Wilson disease who have neurological dysfunction is most likely to be 100% abnormal.[17] The most common finding in the MRI that is well recognized is the increased signal intensity in the T2 weighted images in the basal ganglia. Other findings have been noted and generalized brain atrophy is a common finding.

Treatment

Although liver transplantation is the definitive treatment in Wilson disease, medicines offer palliation and they intend to maintain and restore copper balance.[18,19] Modification in diet includes avoidance of copper containing diet like organ meat, shell fish, oyster, lobster, chocolates, nuts and mushroom.

Zinc

The most popular and safe drug that is used in the management of Wilson disease is Zinc in the form of acetate, gluconate or sulfate. It reduces the absorption of dietary copper in the intestinal enterocytes. The increased metallothionein binds the copper and zinc trapping within the intestinal mucosal cells which are initially sloughed off and excreted in the feces. Zinc may be used as a monotherapy and some consistent success has been reported. Dose is 50 mg thrice daily (elemental zinc). Zinc is well tolerated but gastric discomfort may occur.[20]

Penicillamine

An active metabolic byproduct of penicillin, it chelates the copper. Functional improvement is seen 2 weeks after commencing therapy. The initial dose of 250-500 mg four times daily is advised to be taken on an empty stomach. Penicillamine does have adverse effects which are skin rash, fever, eosinophilia, thrombocytopenia and lymphadenopathy in 20-30% of children.[21,22]

Trientine

Trientine is a copper chelating agent action similar to penicillamine, hence this must also be taken on an empty stomach. The usual dose is 750 to 2000 mg, divided into three doses. Experience in Trientine is lesser in children when compared to penicillamine.

Conclusion

Wilson disease has evolved both historically and scientifically over the past few decades. The progress has shown the multifaceted presentations of the disease with predisposition to affect any part of the body. Medical management is of paramount importance. Liver transplant aims to cure the disease completely. Genetic testing is useful for screening family members especially siblings when the mutations in the proband are known.

Points to Remember

- ***Wilson disease is a conundrum and has a multi faceted presentation.***
- ***Jaundice is a common hepatic manifestation, but may be associated with a variety of neurological symptoms.***
- ***One should look for other system involvements such as ophthalmological, hematological and renal manifestations.***
- ***Early diagnosis and treatment will slow the progression of the disease and may reduce morbidity.The treatment is generally well tolerated and 'compliance' is the key factor.***
- ***Screening of sbilings is a must for all children with Wilson disease.***
- ***Liver transplant aims to be curative.***

References

1. Walshe JM. History of Wilson's disease: 1912 to 2000. Mov Disord 2006; 21:142-147.
2. Wilson SAK. Progressive lenticular degeneration: a familialnervous disease associated with cirrhosis of the liver. Brain1912; 34:295-507.
3. Kayser B. Ubereinen Fall von angeborenergrunlicher Verfarbung der Kornea. Klin Monatsbl Augenheilkd 1902; 40:22-25.
4. Fleischer B. Zweiweiterer Falle von gru nlicher Verfarbungder Kornea. Klin Monatsbl Augenheilkd 1903; 41:489-491.
5. Kumar S, Thapa BR, Kaur G, Prasad R. Identification and molecular characterization of 18 novel mutations in the ATP7B gene from Indian Wilson disease patients: Genotype. Clin Genet 2005; 67:443-5. 20.
6. Gupta A, Aikath D, Neogi R, Datta S, Basu K, Maity B, et al. Molecular pathogenesis of Wilson disease: Haplotype analysis, detection of prevalent mutations and genotype-

phenotype correlation in Indian patients. Hum Genet 2005; 118:49-57.

7. Santhosh S, Shaji RV, Eapen CE, Jayanthi V, Malathi S, Chandy M, et al. ATP7B mutations in families in a predominantly Southern Indian cohort of Wilson's disease patients. Indian J Gastroenterol 2006; 25:277-82
8. Cumings JN. The copper and iron content of brain and liverin the normal and in hepato-lenticular degeneration. Brain1948; 71:410-415.
9. Scheinberg IH, Gitlin D. Deficiency of ceruloplasmin inpatients with hepatolenticular degeneration (Wilson's disease). Science 1952; 116:484-485.
10. Bearn AG, Kunkel HG. Biochemical abnormalities inWilson's disease. J Clin Invest 1952; 31:616.
11. Frommer DJ. Defective biliary excretion of copper in Wilson's disease. Gut 1974; 15:125 -129.
12. Saito T. An assessment of efficiency in potential screeningfor Wilson's disease. J Epidemiol Community Health 1981; 35:274-280.
13. Scheinberg IH. Sternlieb I. Wilson's disease. Philadelphia: WB Saunders. 1984; 112.
14. Brewer GJ. Wilson's Disease: A Clinician's Guide to Recognition, Diagnosis, and Management. Boston: Kluwer Academic Publishers; 2001.
15. Olivarez L, Caggana M, Pass KA, Ferguson P, Brewer GJ. Estimate of the frequency of Wilson's disease in the US Caucasian population: a mutation analysis approach. Ann Hum Genet 2001; 65:459-463.
16. Clinical Practice Guidelines. In: EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol 2012; 56: 671-685.
17. Sinha S, Taly AB, Ravishankar S, Prashanth LK, Venugopal KS, Arunodaya GR, et al. Wilson's disease: cranial MRI observations and clinical correlation. Neuroradiology 2006; 48:613-621.
18. Wang XH, Cheng F, Zhang F, Li XC, Kong LB, Li GQ, et al. Living-related liver transplantation for Wilson's disease. Transpl Int 2005; 18:651-656.
19. Tamura S, Sugawara Y, Kishi Y, Akamatsu N, Kaneko J, Makuuchi M. Living-related liver trasplantation for Wilson's disease. Clin Transplant 2005; 19:483-486.
20. Hoogenraad TU. Paradigm shift in the treatment of Wilson's disease: zinc therapy now treatment of choice, Brain Dev 2006; 28:141-146.
21. Walshe JM. Penicillamine: the treatment of first choice for patients with Wilson's disease. Mov Disord1999; 14:545-550.
22. Sternlieb I, Scheinberg IH. Penicillamine therapy for hepatolenticular degeneration. JAMA 1964; 189:748-754.

NEWS AND NOTES

South Neocon, 2018

12th Annual South Zone Neonatology Conference and

15th Annual Convention of National Neonatology Forum, Tamilnadu State Chapter

Date: 5th, 6th & 7th October, 2018

Venue: Chettinad Hospital & Research Institute, Kelambakkam

Contact

Dr.S.Giridhar

Joint organising secretary of conference

Chettinad Hospital & Research Institute, Chettinad Health City, Rajiv Gandhi Salai, OMR,

Kelambakkam, Kanchipuram Dist., Tamilnadu – 603103.

Mobile: +91 9841027228 / +91979791055189

Landline: 044 47428284 / 8287

Website: www.nnftn.org

Life at War: Series 4 - The Immunology of Human Tuberculosis – Mendelian Susceptibility to Mycobacterial Disease (MSMD) and Beyond, Mumbai, India.

Date: 14-15 October, 2018

Contact

Mr.Prasad Taur: 9702915451, 022 24197239

Mrs.Shital: 9699242517

Email: lifeatwarseries@gmail.com

DRUG PROFILE

PHARMACOTHERAPY IN AUTISM

***Jeeson C Unni**
****Ranjit Baby Joseph**
*****Susan Mary Zachariah**
*****Fathima Jafna**

Abstract: *Autism spectrum disorder is a heterogeneous neurodevelopmental disorder affecting social communication and behaviour. Though symptoms can be seen from as early as 6 months of age, most are picked up between 2-3 years of age. Even today, there is no clarity regarding the use of medications in autism spectrum disorder. Research is yet to narrow in on drugs that target the core symptoms of this multifaceted illness.*

Keywords: *Autism spectrum disorder, Core symptoms, Medications.*

In the United States, more than half the children with autism spectrum disorder (ASD) receive medication and its use increases with age. Since no drug has proven effect on the core symptoms of autism, drugs are used to treat associated symptoms.[1] ASD is commonly associated with challenging behavior such as irritability, aggression, self-injury, hyperactivity and inattention, seizures and sleep disorders that may benefit from pharmacotherapy. The atypical antipsychotics aripiprazole (>6 yrs age) and risperidone (> 5 yrs age), clinically indicated for autism in children, are Food and Drug Administration (FDA) approved for the treatment of irritability only.[2,3] Other pharmacologic treatments commonly used for challenging behavior include other atypical antipsychotics, alpha-2 agonists, mood stabilizers, stimulants, atomoxetine and naltrexone. Within the core symptoms, repetitive behaviors have been most frequently targeted by pharmacologic treatments.

* Editor-in-chief,
IAP Drug Formulary

** Senior Lead Consultant in Pediatrics

*** Developmental Pediatrician

*** Specialist, Dept of Child Health
Aster Medcity, Kochi.

email: jeeson1955@gmail.com

Repetitive behavior, along with irritability and aggression, considered the positive symptoms have been studied more extensively than the largely negative core symptoms of impairments in social communication. The American Academy of Pediatrics (AAP) suggests targeting the main one or two behavioral problems in a given child when considering medicines in ASD.[4]

The drugs may be i) those that have been shown to be not efficacious and should probably be abandoned as potential treatments, ii) those that are possibly efficacious and deserve more research and iii) those that are currently proposed as new lines of treatment.

Studies on pharmacotherapy - Limitation

Autism is an extraordinarily heterogeneous disorder and manifestation is influenced by any number of variables such as language level, age and cognitive ability. A drug with a specific mechanism may not produce the same result in two individuals with the same diagnosis but divergent presentation or etiology. A study can be designed on effect of a drug on a prominent symptom, e.g. irritability but its effectiveness in reducing core symptoms of autism due to the positive effect on irritability cannot be assessed by parents or researcher. Many studies had limited statistical power (the ability of a study to capture a treatment effect) because of small sample size, design issues such as lack of control, heterogeneous samples and imprecise measurement of effect.

There is no gold-standard for the measurement of effect on autism symptoms in clinical trials. The gold-standard diagnostic instruments, the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) were not created to measure severity or improvement of the disorder. Clinical trials of pharmacotherapy of autism is awaiting the advent of biomarkers of autism to dramatically increase power through study design that measures mechanism as was made possible in Fragile X and tuberous sclerosis.

Medications that have been tried but later found to be not effective

Fenfluramine: Because of its serotonin lowering effect was tried and found effective in treating probably core

symptoms of ASD. Later studies did not confirm this effect and seemed to adversely affect learning and have cardiovascular side effects.[5]

Naltrexone : An opioid receptor antagonist (Opioid dysregulation has been proposed as a cause of autism) was tried, but found to only have some effect on hyperactivity and none for control of core symptoms of ASD.[6]

Anticonvulsants like divalproex, lamotrigine and levetiracetam used frequently in this population, have been shown to be ineffective for repetitive behavior and social symptoms.[7]

Medications that may be effective in ASD

Atypical antipsychotics: Atypical antipsychotics have not been studied for its effect on the core symptoms of autism. However, their use in improving symptoms such as social withdrawal and stereotypic behaviors have been analysed.

Risperidone: Found effective on the irritability subscale of the Aberrant Behavior Checklist [ABC], stereotypy and aggression in autistic children.[8-10] Somnolence and daytime drowsiness are the common side effects. Metabolic adverse events including weight gain and dyslipidemia are common. Excessive drooling and extrapyramidal symptoms like tremor, dyskinesia and rigidity are not uncommon. Paliperidone, an active metabolite of risperidone, approved for use in the US for schizophrenia and schizoaffective disorder, may ameliorate symptoms of irritability associated with autism.[11]

Aripiprazole: Evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication intervention for some behavioural aspects of ASD in children/adolescents with less irritability and hyperactivity and fewer stereotypies (repetitive, purposeless actions).[12] However, notable side effects, such as weight gain, sedation, drooling and tremor, must be considered. One long-term study found no difference in relapse rates in those on aripiprazole versus children on placebo. They suggest that a re-evaluation of aripiprazole effect must be done after irritability is controlled. The studies suggest that the atypical antipsychotics may have a modest effect on the core symptoms of autism.

Antidepressants: Most studies of antidepressants have focused upon primarily repetitive behavior.

Fluoxetine: When compared to placebo, fluoxetine resulted in significantly greater improvement in repetitive behavior in adults.[13] In a small study of 45 children with ASD, by the same group, treatment with fluoxetine resulted in significantly greater improvement in repetitive behavior than placebo.[14]

Fluvoxamine: Found to be effective in reducing repetitive thoughts and actions in a small group of adults with autism.[15]

Systematic reviews however report evidence that selective serotonin reuptake inhibitors (SSRIs) have no effect in children and limited positive effect in adults.[16,17] Further, the SSRI-induced activation and agitation in this population needs to be factored.

Pharmacotherapy for co-morbid Attention-deficit/hyperactivity disorder (ADHD)

Methylphenidate (MPH): Early studies of MPH in children with ADHD and ASD reported significant negative side effects (e.g. irritability, self-injury, stereotypy) and limited therapeutic benefit when compared to expected outcomes based on MPH in treating ADHD without ASD.[18,19] RCT by pediatric psychopharmacology autism network however demonstrated that MPH was effective at reducing hyperactivity and impulsivity in approximately 50% of autistic children studied in comparison to 70% to 80% response to MPH for isolated ADHD.[20-22] More adverse effects were reported in children with ASD and the highest tolerated dose was lower than that tolerated in children without ASD.[20] The positive effect was only in the area of hyperactivity and impulsivity and none of the other symptoms of ASD. Secondary analysis examined the effects of MPH on social communication skills and self-regulation skills. The improvements noted in ability to initiate and respond to bids for joint attention, in self-regulation and in attaining a better regulated affective state need to be studied in future.[23]

Atomoxetine: There are very few controlled clinical trials studying the efficacy of atomoxetine for ADHD in autism. Since evidence for its use in this scenario is not conclusive, it may be tried in mild ADHD associated with ASD and in high functioning autism.[24]

Drugs with potential for treating core symptoms of ASD

Several classes of drugs not previously used in children for behavioral purposes have been tried as possible treatments for the core symptoms of autism including acetylcholinesterase inhibitors, glutamatergic drugs and oxytocin.[25]

Cholinergic agents: Acetylcholinesterase inhibitors are FDA-approved for the treatment of dementia associated

Table I. Symptom-wise pharmacotherapy in ASD

Symptoms	Drugs	Remarks
Irritability and aggression	Risperidone, aripiprazole	Both are FDA approved (Clozapine and haloperidol have been tried but not recommended due to significant side effects[34,35])
Aberrant social behaviour	Risperidone, oxytocin nasal spray	(Secretin, an endogenous hormone which acts as a neuropeptide in CNS was investigated extensively but showed no significant clinical benefit.[36])
Hyperactivity and inattention	Methylphenidate, atomoxetine, venlafaxine	Methylphenidate is superior. Low dose venlafaxine is found to improve inattention and self-injurious behaviours. [37]
Repetitive behaviours	Fluoxetine, fluvoxamine	Fluoxetine has shown to have atleast 50% improvement in repetitive behaviours
Cognition	Memantine, rivastigmine	Rivastigmine has shown promising results for cognitive improvement compared to memantine[38,39]
Insomnia	Melatonin, mirtazapine,	Controlled-release formulation of melatonin, in addition to cognitive-behavioral therapy, improved sleep latency as early as one week in a 14-week study [40]

with Alzheimer's disease and studies suggest that cholinergic abnormalities may be implicated in autism. Donepezil may be useful for irritability and hyperactivity, but not for language and social symptoms, rivastigmine for some improvement on the childhood autism rating scale (CARS) and a scale of expressive language ability and galantamine for improving both core and associated symptoms of ASD.[26]

Glutamatergic drugs: It has been hypothesized that autism may result from an imbalance between excitatory glutamatergic and inhibitory GABAergic pathways. N-methyl-D-aspartate (NMDA) glutamate receptor antagonists were studied. D-Cycloserine enhanced the durability of social skills training in ASD[27] and amantadine demonstrated improvement in hyperactivity and irritability when used as adjunctive drug with risperidone.[28] Memantine, a different glutamatergic antagonist, approved by FDA for dementia of Alzheimer's disease, was found to be effective in treating ASD symptoms - language function, social behavior, and self-stimulatory behaviors to a lesser degree.[26,29] Acamprosate[30] and N-acetylcysteine[31] are also being studied.

Oxytocin: Being a neuropeptide that influences development of emotional and social affiliative behaviors, there has been much excitement and expectation for the role of this molecule in the treatment of ASD. Effective administration was an issue till intranasal route was identified. The hype created by this drug has been dampened by more recent studies.[32] Despite the limitations, oxytocin is expected to be a game changer in the management of the severe social impairments of ASD. In the meanwhile, studies recommend intranasal oxytocin as well tolerated and safe for long term use in the ASD.[33]

Symptom-wise pharmacotherapy in ASD is given in Table I.

Other medications under study

Balovaptan, a selective vasopressin V1a receptor antagonist which is currently under phase II trial is the first agent expected to improve core social interaction and communication. FDA has now granted breakthrough therapy designation for balovaptan in individuals with ASD.[41] An antilymphoma drug, romidepsin which acts by histone deacetylase (HDAC) inhibition is expected to be useful especially in patients with SHANK3 mutation which accounts for around 2%.[42] Nitrosynapsin, related to the FDA approved memantine acts by modulating the excitatory-inhibitory imbalance in brain by modulating transcription factor MEF2C which regulates multiple genes linked to ASD and human MEF2C haplo insufficiency results in ASD, intellectual disability, and epilepsy.[43] After the recent demonstration of cholinergic abnormalities in autism, there is a growing interest in cholinergic modulation in targeting autistic symptoms. DMXB-A is a

nicotinic drug which is proposed to be effective in ASD. The neuronal nicotinic acetylcholine receptor (nAChR) alterations are proposed as biomarkers for ASD and specific nAChRs subtypes are likely to be useful therapeutic targets for the treatment of core deficits.[44]

Conclusion

Till date there is no pharmacological intervention that effectively ameliorates the core symptoms of autism. Drugs may be used judiciously by experts to treat the irritability, repetitive behaviour, and to some extent aggression and social relatedness. Various methodology issues in studies targeting pharmacotherapy in ASD is cited for lack of evidence based conclusions. Biomarkers of Fragile X and tuberous sclerosis have been useful in providing strong evidence for effect of pharmacotherapy in these conditions and research in the field is awaiting the detection of biomarkers of autism for achieving similar results.

References

1. Siegel M, Beaulieu AA. Psychotropic medications in children with autism spectrum disorders: a systematic review and synthesis for evidence-based practice. J Autism Dev Disord 2012; 42(8):1592-1605.
2. Farmer CA, Aman MG. Aripiprazole for the treatment of irritability associated with autism. Expert Opin Pharmacother 2011; 12(4):635-640.
3. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. Paediatric Drugs 2007; 9(5):343-354.
4. Myers SM, Johnson CP. American Academy of Pediatrics Council on Children With Disabilities. American Academy of Pediatrics clinical report: Management of children with autism spectrum disorders. Pediatrics 2007; 120(5):1162-1182.
5. Campbell M, Adams P, Small AM, Curren EL, Overall JE, Anderson LT, et al. Efficacy and safety of fenfluramine in autistic children. J Am Acad Child Adolesc Psychiatr 1988; 27(4):434-439.
6. Bouvard MP, Leboyer M, Launay JM, Recasens C, Plumet MH, Waller-Perotte D, et al. Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study. Psychiatr Res 1995; 58(3):191-201.
7. Wasserman S, Iyengar R, Chaplin WF, Watner D, Waldoks SE, Anagnostou E, et al. Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. Int Clin Psychopharmacol 2006; 21(6):363-367.
8. Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. Pediatrics 2016; 137 Suppl 2:S124-135.
9. Sharma A, Shaw SR. Efficacy of risperidone in managing maladaptive behaviors for children with autistic spectrum disorder: a meta-analysis. Efficacy of risperidone in managing maladaptive behaviors for children with autistic spectrum disorder: a meta-analysis. J Pediatr Health Care 2012; 26(4): 291-299.
10. Chavez B, Chavez-Brown M, Rey JA. Role of risperidone in children with autism spectrum disorder. Ann Pharmacother 2006; 40(5): 909-916.
11. Stigler KA, Mullett JE, Erickson CA, Posey DJ, Mc Dougle CJ. Paliperidone for irritability in adolescents and young adults with autistic disorder. Psychopharmacology (Berl) 2012; 223(2): 237-245.
12. Hirsch LE, PringsheimT. Aripiprazole for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2016; (6):CD009043. doi: 10.1002/14651858. CD009043.pub3.
13. Hollander E, Soorya L, Chaplin W, Anagnostou E, Taylor BP, Ferretti CJ, et al . A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. Am J Psychiatry 2012; 169(3): 292-299. doi: 10.1176/appi.ajp.2011.10050764.
14. Hollander E, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. Neuropsychopharmacology 2005; 30(3):582-589.
15. McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996; 53(11): 1001-1008.
16. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2013 Aug 20; (8):CD004677. doi: 10.1002/14651858. CD004677.pub3.
17. Kolevzon A, Mathewson KA, Hollander E. Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. J Clin Psychiatry 2006; 67(3): 407-414.
18. Scahill L, Pachler M. Treatment of hyperactivity in children with pervasive developmental disorders. J Child Adolesc Psychiatr Nurs 2007; 20:59-62.
19. Aman MG, Farmer CA, Hollway J, Arnold LE. Treatment of inattention, overactivity, and impulsiveness in autism spectrum disorders. Child Adolesc Psychiatr Clin N Am. 2008; 17: 713-738.
20. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of

methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry 2005; 62:1266-1274.

21. Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 2006; 45:1284-1293.
22. Greenhill LL, Abikoff HB, Arnold LE, Cantwell DP, Conners CK, Elliott G, et al. Medication treatment strategies in the MTA Study: relevance to clinicians and researchers. J Am Acad Child Adolesc Psychiatry 1996; 35:1304-1313.
23. Jahromi LB, Kasari CL, McCracken JT, Lee LS, Aman MG, McDougle CJ, et al. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. J Autism Dev Disord 2009; 39:395-404.
24. Ghanizadeh A. Atomoxetine for treating ADHD symptoms in autism: a systematic review. J Atten Disord 2013; 17(8):635-640.
25. Posey DJ, Erickson CA, McDougle CJ. Developing drugs for core social and communication impairment in autism. Child Adolesc Psychiatr Clin N Am 2008; 17(4):787-801.
26. Rossignol DA, Frye RE. The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review. Front Pediatr 2014 Aug 22; 2:87. doi: 10.3389/fped.2014.00087. eCollection 2014.
27. Wink LK, Minshawi NF, Shaffer RC, Plawecki MH, Posey DJ, Horn PS, et al. d-Cycloserine enhances durability of social skills training in autism spectrum disorder. Mol Autism 2017; 8: 2. doi: 10.1186/s13229-017-0116-1. eCollection 2017.
28. Mohammadi MR, Yadegari N, Hassanzadeh E, Farokhnia M, Yekehtaz H, Mirshafiee O, et al. Double-blind, placebo-controlled trial of risperidone plus amantadine in children with autism: a 10-week randomized study. Clin Neuro pharmacol. 2013; 36(6):179-184.
29. Chez MG, Burton Q, Dowling T, Chang M, Khanna P, Kramer C. Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. J Child Neurol 2007 May; 22(5):574-579.
30. Erickson CA, Ray B, Maloney B, Wink LK, Bowers K, Schaefer TL, et al. Impact of acamprosate on plasma amyloid-â precursor protein in youth: a pilot analysis in fragile X syndrome-associated and idiopathic autism spectrum disorder suggests a pharmacodynamic protein marker. J Psychiatr Res 2014; 59:220-228.
31. Deepmala, Slattery J, Kumar N, Delhey L, Berk M, Dean O, et al. Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neurosci Biobehav Rev 2015;55:294-321.
32. Alvares GA, Quintana DS, Whitehouse AJ. Beyond the hype and hope: Critical considerations for intranasal oxytocin research in autism spectrum disorder. Autism Res 2017; 10(1): 25-41.
33. Cai Q, Feng L, Yap KZ. Systematic review and meta-analysis of reported adverse events of long-term intranasal oxytocin treatment for autism spectrum disorder. Psychiatry Clin Neurosci 2018; 72(3):140-151.
34. Posey DJ, McDougle CJ. Use of atypical antipsychotics in autism. In: Hollander E, (ed). Autism Spectrum Disorders. New York, New York: Marcel Dekker, Inc; 2003; 247-264.
35. Faretra G, Dooher L, Dowling J. Comparison of haloperidol and fluphenazine in disturbed children. Am J Psychiatry 1970; 126(11):1670-1673.
36. Williams K, Wray JA, Wheeler DM. Intravenous secretin for autism spectrum disorders (ASD). Cochrane Database Syst Rev. 2012;(4):CD003495. [PubMed] [Ref list]
37. Carminati GG, Deriaz N, Bertschy G. Low-dose venlafaxine in three adolescents and young adults with autistic disorder improves self-injurious behavior and attention deficit/hyperactivity disorders (ADHD)-like symptoms. Prog Neuropsychopharmacol Biol Psychiatry. 2006; 30(2):312-315.
38. Owley T, Salt J, Guter S, Grieve A, Walton L, Ayuyao N, et al. A prospective, open-label trial of memantine in the treatment of cognitive, behavioral, and memory dysfunction in pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2006; 16(5):517-524.
39. Exelon (rivastigmine) prescribing information. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; Oct, 2013. Available at: https://www.pharma.us.novartis.com/product/pi/pdf/exelon.pdf. Accessed February 3, 2015.
40. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012; 21(6):700-709.
41. Keown A. FDA Calls Roche's Autism Drug a Breakthrough; January 2018. Available at https://www.biospace.com/article/unique-fda-calls-roche-s-autism-drug-a-breakthrough/ accessed on 18th June, 2018.
42. Qin L, Ma K, Wang ZJ, Hu Z, Matas E, Wei J, et al. Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition. Nat Neurosci 2018; 21(4):564-575. doi. org/10.1038/s41593-018-0110-8.
43. Tu S, Akhtar MW, Escorihuela RM, Amador-Arjona A, Swarup V, Parker J, et al. NitroSynapsin therapy for a mouse MEF2C haploinsufficiency model of human autism. Nat Commun 2017; 8(1):1488. doi: 10.1038/s41467-017-01563-8.

44. Anand R, Amici SA, Ponath G, Robson J, Nasir M, McKay SB. Nicotinic Acetylcholine Receptor Alterations in Autism Spectrum Disorders – Biomarkers and Therapeutic Targets. Available at https://www.intechopen.com/books/autism-a neurodevelopmental-journey-from-genes-to-behaviour/nicotinic-acetylcholine-receptor-alterations-in-autism-spectrum-disorders-biomarkers-and-therapeutic. Accessed on 18th June, 2018.

CLIPPINGS

Effect of Needle Aspiration of Pneumothorax on Subsequent Chest Drain Insertion in Newborns: A Randomized Clinical Trial.

Treatment options for a symptomatic pneumothorax in newborns include needle aspiration (NA) and chest drain (CD) insertion. There is little consensus as to the preferred treatment, reflecting a lack of evidence from clinical trials. The objective was to investigate whether treating pneumothoraces diagnosed on chest radiography (CXR) in newborns receiving respiratory support with NA results in fewer infants having CDs inserted within 6 hours of diagnosis.

This randomized clinical trial was conducted from October 7, 2013, to December 21, 2016. The setting was 5 tertiary European neonatal intensive care units. Infants receiving respiratory support (endotracheal ventilation, continuous positive airway pressure, or supplemental oxygen >40%) who had a pneumothorax on CXR that clinicians deemed needed treatment were eligible for inclusion.

Infants were randomly assigned (1:1) to drainage using NA or CD insertion, stratified by center and gestation at birth (<32 vs e”32 weeks). Caregivers were not masked to group assignment. For NA, a needle was inserted between the ribs to aspirate air and was removed once air was no longer aspirated. A CD was inserted if clinicians deemed that the response was inadequate. For CD insertion, a drain was inserted between the ribs and was left in situ.The primary outcome was whether a CD was inserted on the side of the pneumothorax within 6 hours of diagnosis.

A total of 76 infants were randomly assigned, and 6 (4 assigned to NA and 2 to CD) were excluded because they met exclusion criteria at enrollment. Of the 70 remaining infants, 33 (16 male [48%]) were assigned to NA and 37 (22 male [59%]) to CD insertion. Their median (interquartile range [IQR]) gestational age was 31 (27-38) vs 31 (27-35) weeks, and their median (IQR) birth weight was 1385 (1110-3365) vs 1690 (1060-2025) g, respectively. Fewer infants assigned to NA had a CD inserted within 6 hours (55% [18 of 33] vs 100% [37 of 37]; relative risk, 0.55; 95% CI, 0.40-0.75) and during hospitalization (70% [23 of 33] vs 100% [37 of 37]; relative risk, 0.70, 95% CI, 0.56-0.87).

Needle aspiration reduced the rate of CD insertion in symptomatic newborns with pneumothorax on CXR. It should be used as the initial method of draining radiologically confirmed pneumothorax in symptomatic infants.

Murphy MC, Heiring C, Doglioni N, et al. Effect of Needle Aspiration of Pneumothorax on Subsequent Chest Drain Insertion in Newborns - A Randomized Clinical Trial. JAMA Pediatr. 2018;172(7):664–669. doi:10.1001/jamapediatrics.2018.0623.

NEWS AND NOTES

Certificate Course in Pediatric Pulmonology and Flexible Bronchoscopy, Chennai, India.

Date: 25th February – 3rd March, 2019

Contact

Tel. No.: 044-42001800

E-mail: kkcth@kkcth.org; md@kkcth.org

DERMATOLOGY

CHILDHOOD DERMATOPHYTOSIS

Madhu R

Abstract: *Dermatophytosis is a superficial fungal infection of the keratinized tissues of skin, hair and nail caused by dermatophytes belonging to the three genera Trichophyton, Microsporum and Epidermophyton. There has been an increase in the prevalence of chronic and recurrent dermatophytosis in India over the last few years. This scenario which is predominantly seen in adults has resulted in the simultaneous increase in the frequency of Tinea corporis and Tinea cruris among children affecting even infants and neonates. This change in the trend has been mainly limited to the glabrous skin. Counseling regarding the general measures and the compliance to treatment forms the cornerstone for management of dermatophytosis. Localised lesions are treated with topical antifungal agents. Indications for systemic therapy include the presence of extensive lesions and involvement of hair and nail.*

Keywords: *Tinea corporis, Tinea capitis, Tinea unguium, Children, Treatment, Resistance*

Dermatophytosis is a superficial fungal infection of the keratinized tissues of skin, hair and nail caused by dermatophytes belonging to the three genera Trichophyton, Microsporum and Epidermophyton.[1,2] Dermatophytes are classified based on the nature of habitat into anthropophilic (human) which are the most common, zoophilic (animal) and geophilic (soil). Infection is transmitted to human beings through either direct contact with an infected person or animal or soil or through contact with desquamated keratinocytes or hair shed from infected patients present on fomites, floor, swimming pool, etc. Tinea capitis is the most common clinical form of dermatophytosis in children aged less than 12 years worldwide including India.[3-6] There has been an increase in the prevalence of dermatophytosis among adults in India over the last 5-7 years.[7] This has resulted in concomitant increase in the occurrence of dermatophytosis of the glabrous skin (surface without hairs or projections) namely Tinea corporis, Tinea cruris and Tinea faciei in the children. Multiple family members being affected by this infection, like scabies has become a regular phenomenon.[7] Chronic dermatophytosis which refers to the presence of infection for more than six months with or without recurrences in spite of treatment is being increasingly seen.[1] There are various factors related to the environment, host, etiological agent, antifungal resistance and drugs considered responsible for the change and rising scenario of dermatophytosis in India. The most important factor is the rampant abuse of the topical steroid, antifungal and antibacterial combination creams either prescribed by the practitioners or purchased over the counter (OTC) by the parents of children or dispensed by the pharmacists themselves.[2]

Factors - Environment, host, etiological agent and antifungals

Environment - Global warming has resulted in a change in the climatic conditions in India resulting in a hotter and more humid climate, less but intense rainfall, both of which predispose individuals to either increased sweating or damp weather. This results in a favorable atmosphere for the dermatophytes which thrive in the presence of moisture. Overcrowding, poor hygiene, scarcity of water and poor living conditions are the constraints faced by the migratory population making them more vulnerable to chronic and recurrent dermatophytosis.[8]

Host factors- In the past, dermatophytosis was considered as an infection that was prevalent only in the lower socioeconomic population. But in recent years, it is not uncommon to see children belonging to the affluent strata being affected by dermatophytosis. Studies have shown that students in the age group between 11-20 years were commonly affected.[9,10] This preponderance could be explained by the fact that the children in this age group are more predisposed to sweating by virtue of increased physical activity and the present fashion of wearing of tight clothing like leggings, jeans and jeggings, not to undermine the role of synthetic uniforms and track pants, which are definitely not the type of clothing that would suit the hot and humid climate in India. Failure to follow the general

* Senior Assistant Professor,
Department of Dermatology (Mycology),
Madras Medical College, Chennai.
email: renmadhu08@gmail.com

measures, poor compliance with regard to usage of medicine for the appropriate duration, sharing of soaps, towels, clothing and bed linen, sharing of prescriptions resulting in incomplete treatment and neglected hair and nail infection are the factors that result in perpetuation of the infection in the family. Immunosuppressive states predispose children to develop extensive and chronic dermatophytosis. In the studies on chronic and recurrent dermatophytosis done by Meriya, et al and Sharma, R et al, students comprised 18% and 33.3% of the study population.[11,12]

Etiological agent - dermatophytes such as Trichophyton rubrum , Trichophyton memtagrophytes var. interdigitale, Epidermophyton floccosum and Microsporum canis are present worldwide, of which Trichophyton rubrum is the most common organism causing Tinea corporis. Various studies done in India have shown Trichophyton rubrum to be the commonest organism, however with a lesser prevalence compared to the past, followed by Trichophyton mentagrophytes which is on the rise.[13-18] Some studies done in the recent years have reported Trichophyton mentagrophytes to be the predominant isolate.[19-21] Exact reasons for change in the trend of the dermatophytes and the impact of this change on the increased prevalence of dermatophytosis of the glabrous skin need scientific evaluation.

Antifungal drugs - Griseofulvin, fluconazole, itraconazole and terbinafine are the systemic antifungal agents available in the armamentarium for the treatment of dermatophytosis, of which the latter two drugs are more in vogue in office practice. In the current scenario of chronic, recurrent and recalcitrant dermatophytosis in India, treatment duration mentioned in the standard textbooks of dermatology has ceased to be sufficient and effective to result in clinical cure. In addition, itraconazole, the only broad spectrum, cost effective drug available for our patients with deep mycoses is being injudiciously prescribed, sometimes even in patients with clinical suspicion of dermatophytosis. There are numerous brands of itraconazole available in the market today, many of which are products of inaccurate manufacturing technology, thereby compromising the efficacy of the drug that already has a low bioavailability. Suboptimal dose and duration of treatment often predicts clinical failure. In immunocompromised children on poly pharmacy, drug-drug interactions that may interfere with the absorption or increase the metabolism of the antifungal drugs should be kept in mind.

Topical steroid/antifungal/antibacterial combination creams: Few years back, with the price regulation of steroids, low potent molecules were replaced by potent steroids such as clobetasol and mometasone in the combination creams. These combination creams which contain a potent steroid, antifungal and 2 antibacterial agents have 2-5 components and are the highest selling and rampantly abused products either as OTC or by practitioners.[22,23] In the study on "Over-the-counter topical medications in dermatophytosis" by Dabas, et al, there were 12 children below 18 years and steroid was the chief constituent in 77.94% of the preparations used by the study population.[24] Steroid component in these preparations causes local immunosuppression creating an atmosphere conducive for fungal multiplication and deeper penetration. It takes around 3 weeks for the immune system to recover and this explains the non-response to treatment in the initial phase and the need for extended duration of treatment.[24, 25] Antibiotics in the combination creams interfere with the normal microflora of the skin and result in barrier dysfunction. Thus, it becomes important to understand that topical steroid alone or in combination does not have any role in the treatment of dermatophytosis.

Clinical types

Tinea corporis – Tinea corporis refers to dermatophytic infection of the skin of the body excluding the face, scalp, groin, palms and feet. After an incubation period of 1-3 weeks, arthroconidia invade the skin by adhesion, germination, penetration and subsequent prolongation of the hyphae in a centrifugal pattern.[26] In contrast to the studies done in the past which reported Tinea capitis to be the most common clinical presentation of dermatophytosis in children, Tinea corporis has evolved as the commonest clinical type in the current scenario.[4-6] In a recent study done by Reddy VS, et al in 500 children in Kerala, Tinea corporis was observed in 53.1% of children followed by Tinea cruris and Tinea capitis.[27] Characteristic lesion of Tinea corporis is a well defined, scaly plaque with papules in the active periphery and central clearing, the latter resulting from the elimination of the hyphae by the host immunity. In this era of rampant abuse of topical steroids, it has become a regular phenomenon to see steroid modified lesion to be still identified as Tinea or Tinea incognita in which the dermatophytic lesion cannot be made out clinically. Pseudo imbricata or ring within ring appearance has been observed in the patients who have used topical steroids.[2] Atypical forms resembling eczematous dermatitis, psoriasis or erythema multiforme are not uncommon.[7] Multisite involvement, especially combination of Tinea corporis and Tinea cruris is more often seen. Differential diagnosis of Tinea corporis includes nummular eczema, psoriasis, herald patch of pityriasis rosea and lichen simplex chronicus when lesions are lichenified.

Tinea cruris: This refers to dermatophytosis of the groins. Lesions may extend to the thighs and the back. While obese children are understandably more prone to develop Tinea cruris, it is indeed common to see thin adolescents suffering from Tinea cruris, obviously due to the habit of wearing synthetic undergarments and tight occlusive clothes.[2] Differential diagnosis includes candidial intertrigo and flexural psoriasis.

Tinea faciei: Dermatophytic infection of the face is known as Tinea faciei. At times, extension of lesions over the forehead or near the ear, may extend to the scalp and cause glabrous type of Tinea capitis. There is an increased occurrence of Tinea faciei in the current era of recalcitrant dermatophytosis. Astute examination for a distinct border will aid in diagnosis. Psoriasis, pityriasis versicolor, seborrheic dermatitis and rosacea are mimics of Tinea faciei.

Tinea manuum which involves the palms and Tinea pedis that involves the feet are less common in children. Various types of Tinea pedis are intertriginous type, hyperkeratotic type or the Mocassin's foot, vesiculobullous and ulcerative types.

Tinea capitis: It is a fungal infection of the scalp and scalp hair caused by dermatophytes belonging to the genera Microsporum and Trichophyton and was the most common dermatophytosis of childhood. The incidence in India varies from 0.5% to 10% and is common in the prepubertal children in the age group between 5 -15 years.[28] This infection usually occurs following tonsuring or hair cut with infected blades or due to sharing of fomites with infected siblings or playmates or by playing with infected pet animals. The clinical presentation of Tinea capitis depends on the type of hair invasion and the host immune response and may be non-inflammatory, inflammatory or mixed type of Tinea capitis. Mixed type may comprise of either two types of non-inflammatory or inflammatory or may be a combination of non-inflammatory and inflammatory types.[26, 29] Clinical types of Tinea capitis are given in Table I.

Table I. Clinical types of Tinea capitis

Non-inflammatory types	Inflammatory types
Grey patch	Kerion
Black dot	Abscess
Smooth patch of baldness	Favus
Seborrheic	Pustular
Glabrous type (adult type)	Agminate follicultis

Grey patch is characterized by patches of partial hair loss with dull grey, lusterless broken off hairs and fine scaling. Black dot pattern results due to infection by endothrix organisms, wherein arthroconidia present inside the hair shaft makes the hair brittle and break at the level of the scalp with the remnant of hair left behind in the infected follicle appearing as a black dot on clinical examination. Smooth patch of baldness or alopecia areata like lesions presents with almost total loss of hair and minimal scaling. In the glabrous type, lesion usually extends from the nape of neck to occiput or from the face, forehead and cheek to the temporal or frontal areas and is the common type seen in adolescents. Seborrhoeic type is more commonly caused by Trichophyton tonsurans and is characterised by diffuse scaling. Among the inflammatory types, kerion which occurs as a painful, inflammatory boggy mass studded with broken hairs and oozing purulent material from the follicular orifices is the most common type. Regional lymphadenopathy and id reactions are common in the kerion and abscess types. Mimics include psoriasis, atopic dermatitis and seborrhoeic dermatitis in which there would be diffuse scaling, but no hair loss. Smooth patch of baldness type has to be differentiated from alopecia areata which is a non-scaly patch with characteristic exclamation mark (!) hair. Only a potassium hydroxide examination of the scraping of the scalp and hair root examination will help to solve the clinical diagnostic dilemma. Trichotillomania characterized by hair loss in accessible area with varying lengths of hair and traction alopecia are other conditions considered as DD for hair loss in Tinea capitis.[26, 28]

Onychomycosis - Fungal infection of the nails in children is relatively uncommon. This can be explained by the fact that children have a faster rate of growth of nails, smaller surface area of nails and are less prone for trauma or susceptibility to develop Tinea pedis or other pre-existing skin conditions. Children with AIDS and Down syndrome are more prone to develop onychomycosis. Onychomycosis refers to fungal infection of the nails caused by

Table II. Onychomycosis - Clinical types

Distal and lateral subungual onychomycosis (DLSO)
Superficial white onychomycosis
Proximal subungual onychomycosis
Endonyx
Total dystrophic onychomycosis
Mixed type of onychomycosis

dermatophytes, non - dermatophytic moulds and yeasts. Nail infection caused by dermatophytes is termed as Tinea unguium. Dermatophytes most commonly associated with Tinea unguium are Trichophyton rubrum, Trichophyton mentagrophytes var interdigitale, Epidermophyton floccosum and Trichophyton tonsurans. Various clinical types of onychomycosis are given in Table II, of which distal and lateral subungual onychomycosis (DLSO) is the most common clinical type in children as is in the adults.[26, 30, 31] In the study done by Jeelani S at Kashmir on onychomycosis in children in the age group between 6 months to 18 years, it was found that onychomycosis was more common in children from rural areas than their urban counterparts and that toe nails are infected more than the finger nails.[31]

Investigations

Dermatophytosis of the glabrous skin is essentially a clinical diagnosis. Potassium hydroxide (KOH) mount examination of the scales from the suspected lesion can be done which will show the characteristic hyaline, long branching, septate hyphae in dermatophytosis. Similarly, KOH examination of the nail and hair root will help to confirm the diagnosis.

Management

Counseling the parents and the adolescents regarding the general measures is the most important step in the management of dermatophytosis (Table III).

Table III. General measures[2]

- To strictly avoid use of topical steroid combination creams
- Infected patients should take bath in cold water twice a day and wipe dry after taking bath
- Infected clothes should be washed separately, in hot water at 60° C and dried in good sunlight inside out
- Cotton clothing to be preferred; to avoid wearing synthetic undergarments with elastic bands and synthetic tight clothing
- To avoid sharing of clothes, towel, soap with others
- Obese patients to wear boxer type inner garments and avoid V type garments
- To avoid wearing waist bands
- Regular washing of towels, bed linen and wet mopping of the floor

Table IV. Topical antifungal agents[32]

Topical antifungal creams	Frequency of application every day
1% Clotrimazole	twice
2% Ketoconazole	once
2% Miconazole	twice
1% Bifonazole	once
1% Oxiconazole	once
2% Sertaconazole*	twice
1% Luliconazole*	once
1% Eberconazole	twice
1% Terbinafine	once/twice
1% Butanefine	twice
1% Ciclopirox Olamine	twice
0.25% Amorolfine	twice
2% Whitfield's ointment	twice

** Luliconazole is FDA approved for use > 18 years and Sertaconazole >12 years.*

Treatment of dermatophytosis

Topical antifungals alone would suffice to treat localized lesions without topical steroid abuse. In the current scenario, it is a common practice to combine topical and systemic antifungal agents, preferably belonging to different classes for the treatment of extensive lesions. Topical antifungal agents provide high concentration of the drug at the site of action, Which are to be applied following the "Rule of Two" - Twice daily (except bifonazole, oxiconazole and luliconazole) over the lesion and 2 cms beyond the margins for 2 weeks beyond complete resolution.[2] Topical antifungal agents are given in Table IV.

8% Ciclopirox Olamine and 5% Amorolfine nail lacquers are used in the treatment of onychomycosis along with the systemic antifungal agents. 5% Tavaborole and 10% Efinaconazole are newer topical agents approved by FDA for the treatment of onychomycosis, but are yet to be available in India

Indications for systemic therapy include failure of topical antifungal therapy, extensive, chronic and recurrent,

Table V. Systemic antifungal drugs in childhood dermatophytosis[31.33,34]

		Duration of treatment		
Drug/Age limit	**Dosage**	**Skin**	**Hair**	**Nails**
Griseofulvin > 6 months	10 - 20 mg/day	6-8 weeks	-	-
Fluconazole from newborn period	15 - 20 mg/day	-	8-12 weeks	-
	3 mg/kg weekly twice	6-8 weeks	-	Finger - 6 months Toe - 12 months
	5mg/kg daily	-	4 weeks	-
Terbinafine >2 years	5mg/kg daily <20 kg - 62.5 mg 20-40 kg - 125 mg >40 Kg - 250 mg	4-6 weeks	4-6 weeks	Finger - 6 wks Toe - 12 weeks
Itraconazole > 6months	3-5 mg/ kg	2-4 weeks	4 weeks	Continuous therapy for 2- 4 months
	Pulse therapy - 3-7 mg/kg/ day in 2 divided doses x 1 week/ month	-	-	Finger - 2 pulses Toe - 3 pulses

multiple site involvement, Tinea faciei, Tinea manuum, Tinea pedis, Tinea capitis and onychomycosis. Treatment duration of systemic antifungal drugs is more experience based than evidence based, as the regimens given in the standard textbooks have been found to be ineffective in the current scenario.[2] Steroid modified and extensive or chronic, recurrent dermatophytosis may warrant longer duration of treatment. A recommended treatment regimen of systemic antifungal agents is given in Table V. Antihistamines can be given for a week if itching is troublesome.

Points to Remember

- ***There has been an increase in the incidence of dermatophytosis in infants and children over the last few years in India, concomitant with a rising scenario of dermatophytosis in adults.***
- ***Abuse of topical steroid, steroid and antibacterial combination creams and self treatment by caretakers are the multiple factors responsible for this rise.***
- ***It is imperative to educate the parents against the use of over the counter steroid creams for Tinea infection and ensuring the compliance to the general measures and duration of appropriate antifungal medication.***
- ***Avoidance of tight clothing, sharing of towels and soaps may reduce the incidence of these infections.***

References

1. Dogra S, Uprety S. The menace of chronic and recurrent dermatophytosis in India: Is the problem deeper than we perceive? Indian Dermatol Online 2016; 7:73-76.
2. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: An appraisal. Indian J Dermatol 2017; 62:227-236.
3. Cortez AC, de Souza JV, Sadahiro A, de Oliveira JA. Frequency and aetiology of dermatophytosis in children age 12 and under in the state of Amazonas, Brazil Rev Iberoam Micol 2012; 29(4):223-226.
4. Balai M, Khare AK, Gupta LK, Mittal A, Kuldeep CM. Pattern of pediatric dermatoses in a tertiary care centre of South West Rajasthan. Indian J Dermatol 2012; 57: 275-278.
5. Hassan I, Ahmad K, Yaseen A. Pattern of pediatric dermatoses in Kashmir valley: A study from a tertiary care centre. Indian J Dermatol Venereol Leprol 2014; 80: 448-451.
6. Jawade SA, Chugh VS, Gohil SK, Mistry AS, Umrigar DD. A clinico-etiological study of dermatoses in pediatric age group in tertiary health care center in South Gujarat region. Indian J Dermatol 2015; 60:635.
7. Dogra S, Narang T. Emerging atypical and unusual presentations of dermatophytosis in India. Clin Dermatol Rev 2017; 1:S12-18.
8. Madhu R, Janaki Chellam, Sentamilselvi Ganapati. Changing and rising Scenario of dermatophytosis in India:

Causes and solutions. Rashmi Sarkar, Seemal R Desai, Eds. World Clin Dermatol 2016; 3(1):pp220-250.

9. Abida Malik, Nazish Fatima, Parvez Anwar Khan. A Clinico-Mycological Study of Superficial Mycoses from a Tertiary Care Hospital of a North Indian Town. Virol-mycol 2014; 3:135.
10. Penmetcha U, Myneni RB, Yarlagadda P, Simgamsetty S. A Study of Prevalence of Dermatophytosis in and around Guntur District, Andhra Pradesh, South India. Int J Curr Microbiol App Sci 2016; 5(9):702-717.
11. Zacharia1 M, Kunjukunju BP. Clinical Profile of Patients with Chronic Dermatophytosis- A Descriptive Study from A Tertiary Care Centre In Kerala.

    J Evid Based Med Healthc 2017; 4(47):2866-2869.
12. Sharma R, Adhikari L, Sharma RL. Recurrent dermatophytosis: A rising problem in Sikkim, a Himalayan state of India. Indian J Pathol Microbiol 2017; 60:541-545.
13. Bhagra S, Ganju SA, Kanga A, Guleria BC. Mycological pattern of dermatophytosis in and around Shimla hills.Indian J Dermatol 2014; 59: 268-270.
14. Kaur I, Thakur K, Sood A, Mahajan V, Gupta PK, Chuhan, et al. Clinicomycological profile of clinically diagnosed cases of dermatophytosis in North India: a prospective cross-sectional study. Int J Health Sci Res 2016; 6(8): 54-60.
15. Chudasama V, Solanki H, Vadasmiya M, Jayadekar T. A study of superficial mycosis in tertiary care hospital. IJSR 2014; 3(3): 222-224.
16. Mankodi RC, Kanvinde MS. Incidence of dermatophytosis in Ahmedabad, Gujarat. Indian J Pathol Bacteriol 1969; 12(3):114-117.
17. Kumar K, Kindo AJ, Kalyani J, Anandan S. Clinico-mycological profile of dermatophytic skin infections in a tertiary care center-A cross sectional study. Sri Ramachandra Journal of Medicine 2007; 1(2):12-15.
18. Ramaraj V, Vijayaraman RS, Rangarajan S, Kindo AJ. Incidence and prevalence of dermatophytosis in and around Chennai, Tamilnadu, India. Int J Res Med Sci 2016; 4:695-700.
19. Kumaran G, Jeya M. Clinico-mycological profile of dermatophytic infections. Int J Pharm Bio Sci 2014; 5(2):(B)1-5.
20. Shikha Jain and Vishal Sharma. Clinicomycological Study of Dermatophytes in Solan Int J Curr Microbiol App Sci 2015; 4(12):190-193.
21. Kansra S. Prevalence of dermatophytoses and their Antifungal Susceptibility in a tertiary care hospital of North India. Int J Sci Res 2016; 5(3):450-453.
22. Panda S, Verma S. The menace of dermatophytosis in India: The evidence that we need. Indian J Dermatol Venereol Leprol 2017; 83:281-284.
23. Bishnoi A, Vinay K, Dogra S. Emergence of recalcitrant dermatophytosis in India. Lancet 2018; 18(3):250.
24. Dabas R, Janney MS, Subramaniyan R, Arora S, Lal VS, Donaparthi N. Use of over-the-counter topical medications in dermatophytosis: A cross-sectional single- center, pilot study from a tertiary care hospital. Indian J Drug Dermatol 2018; 4:13-17.
25. Sardana K, Khurana A. Overview of causes and treatment of recalcitrant dermatophytoses. In: Sardana K, Khurana A, Garg S, Poojary S, eds. IADVL Manual on Management of dermatophytoses.1st edn, New delhi: CBS Publishers & distributors; 2018; pp80-104.
26. Hay RJ, Ashbee HR. Fungal infections. Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D (eds). Rook's Textbook of Dermatology. 9th edn. West Sussex: Wiley Blackwell; 2016; pp932-935.
27. Reddy VS, Anoop T, Ajayakumar S, Bindurani S, Rajiv S, Bifi J. Study of clinical spectrum of pediatric dermatoses in patients attending a Tertiary Care Center in North Kerala. Indian J Paediatr Dermatol 2016; 17:267-272.
28. Pai VV, Hanumanthayya K, Tophakhane RS, Nandihal NW, Kikkeri NN. Clinical study of Tinea capitis in Northern Karnataka: A three-year experience at a single institute. Indian Dermatol Online J 2013; 4:22-26.
29. Jahangir M, Hussain I, Khurshid K, Haroon TS. A clinic-etiological correlation in tinea capitis. Int J Dermatol 1999; 38: 275-278.
30. Jeelani S, Lanker AM, Jeelani N, Ahmed QM, Fazili T, Bashir H. Clinico-mycological study of onychomycosis in children from a tertiary care center. Indian J Paediatr Dermatol 2016; 17:95-100.
31. Khurana A. Treatment of fungal infections in Special conditions. In: Sardana K, Khurana A, Garg S, Poojary S, eds. IADVL Manual on Management of dermatophytoses.1st edn, New delhi: CBS Publishers &distributors; 2018; pp121-135.
32. Poojary SA. Topical antifungals: A review and their role in current management of dermatophytoses. Clin Dermatol Rev 2017; 1:S24-29.
33. Garg T, Sharma S, Rathi SK. Treatment of dermatophytic infection of hair. In: Sardana K, Khurana A, Garg S, Poojary S, eds. IADVL Manual on Management of dermatophytoses. 1st edn, New delhi: CBS Publishers &distributors; 2018; pp105-111.
34. Rengasamy M, Chellam J, Ganapati S. Systemic therapy of dermatophytosis: Practical and systematic approach. Clin Dermatol Rev 2017; 1:S19-23.

DENTAL

DEVELOPMENT AND DEVELOPMENTAL ANOMALIES OF TEETH

***Narendra J Chandraneee**
****Aditi Kapur**
*****Rahul Morankar**
******Indira MD**
*******Vaibhav V Patni**
********Kaushik N Chandranee**

Abstract: *Development of tooth starts in the fifth week of intrauterine life and characterized by an interaction between oral epithelium and ectomesenchyme. Tooth eruption is a unique phenomenon characterized by eruption sequences and timings. The chronology of tooth eruption shows a variation in different populations. Developmental anomalies of teeth can be classified according to variation in their number, size, shape and hereditary disturbances. Knowledge regarding tooth development, eruption and developmental dental anomalies are very important for Pediatricians who monitor the process of growth and development in children. Early diagnosis of developmental dental anomalies can be significant in preventing the onset of dental problems.*

Keywords: *Tooth development, Eruption, Sequence of eruption, Developmental anomalies.*

* Professor and Head,
Department of Pedodontics and Preventive Dentistry,
R R Kambe Dental College and Hospital,
At Kanheri Sarap, Tq Barshitakli, Dist Akola,
Maharashtra.
email: isppdpresident2015@gmail.com

** Associate Professor,

*** Senior Resident,
Pediatric Dentistry Unit,
Oral Health Sciences Centre,
Post-graduate Institute of Medical Education and
Research, Chandigarh.

**** Ph D Scholar,
Dept. of Pedodontics,
Jagadguru Sri Shivarathreeshwara University,
Mysore, Karnataka.

***** Patni Dental Clinic,
Malgujaripura, Wardha, Maharashtra.

*******Senior Lecturer,
Department of Pedodontics and Preventive Dentistry,
R R Kambe Dental College and Hospital,
At Kanheri Sarap, Tq Barshitakli, Dist Akola,
Maharashtra.

Tooth development

Initiation: The initiation of tooth development includes molecular interactions between dental epithelium and underlying ectomesenchymal cells.[1] In tooth development, the first signal-inducing differentiation comes from epithelium, whereas it comes from mesenchyme in all other ectodermal organs.[2] The interaction between epithelium and ectomesenchymal cells lead to the formation of bud, cap and bell morphological stages of tooth development.[3-7]

Eruption of teeth

It has been shown that, under normal circumstances, tooth eruption begins when 3/4 of its final root length is established.[8] When tooth erupts in the mouth its root is not fully developed and is termed young primary/permanent tooth. It takes about one and three years for the root apex to close in primary and permanent tooth respectively. The young primary/permanent tooth needs extra care as any treatment at this stage is complicated owing to open root apex.

The eruption of primary and permanent teeth are the important milestone in an individual's maxillofacial growth and development and has significant application in forensic odontology as well. The studies related to the chronology of teeth comprised of eruption timings during which a tooth might erupt into the oral cavity and the sequence of eruption in maxillary and mandibular arches. Although, most of the data is from cross-sectional studies, there are longitudinal studies as well that explain the chronology of eruption in primary and permanent dentition.[9]

Palmer tooth numbering system is the most commonly used system in India (Fig.1a & b). Tooth eruption shows variations amongst different population groups, individuals, and tooth pairs (Table I & II).[9-19] The knowledge of eruption sequence can be an asset in diagnosis and treatment planning during growth and development of child.

Fig.1a. Palmer tooth numbering system (primary dentition)

Fig.1b. Palmer tooth numbering system (permanent dentition)

Table I. Timing of eruption of primary teeth (in months) at different states of India

Table II. Timing of eruption of permanent teeth (in years) at different states of India

The eruption sequence too varies in primary and permanent dentition.[20] In this regard norms of polymorphism in the sequence of eruption can be more useful. When such norms are available it enables the pediatrician / pedodontist to assess the normality of eruption of a given teeth in the child and help in planning the treatment. [12, 16]

Though, there is a particular sequence and timing of eruption in primary and permanent dentition, prematurely erupted teeth can be sometimes present in newborns. Teeth present at birth are known as natal teeth whereas neonatal teeth erupt within the first 30 days of life. Natal teeth are three times more common compared to neonatal teeth[21] and the incidence ranges from 1: 2,000 to 1: 3,500.[22]

Delayed tooth eruption can be defined as the eruption of a tooth beyond the normal time established for a race, gender and ethnicity. Tooth eruption can get delayed due to local, systemic and genetic conditions. Local factors include the presence of supernumerary teeth, odontoma, gingival fibromatosis and trauma. Systemic conditions include vitamin D-resistant rickets, endocrine disorders like hypothyroidism, hypopituitarism and hypoparathyroidism, long-term chemotherapy, renal failure, radiation damage, celiac disease, anemia, HIV infection and heavy metal intoxication. Genetic disorders which can lead to delayed eruption include amelogenesis imperfecta, Hurler's syndrome, mucopolysaccharidosis VI, cleidocranial dysplasia and osteopetrosis.[23]

Table III. Eruption age (in months) of primary teeth in Central India Population[12]

Early and late eruption of teeth

True and significant deviations from the accepted norms of eruption time are often observed in clinical practice. From pediatric dentistry practice point of view, it will be appropriate to define the early and late eruption of tooth to quench the anxiety of health-conscious parents who are worried about very early or non-eruption of tooth in their child. Rasmussen P and Kotsaki A (1997)[24] suggested; that, when the emergence of tooth is more than 2 standard deviations (SD) from the mean of the established norms for eruption times, it should be considered as delayed eruption. Suri L (2004)[25] defined delayed tooth eruption as the emergence of a tooth into the oral cavity at a time that deviated significantly from norms established for different races, ethnicities, and sexes. The mean ± 2 SD range covers 95.7% of the populations as per the standard normal distribution curve (Table III and IV). Eruption age below 5th percentile and eruption age above 95th percentile respectively may be termed as early and late eruption age for that population group. [12, 16]

It may be noted that early and late eruptions are less frequent in primary dentition than in permanent dentition and most early and late eruptions do not have a significant clinical effect. The early and late eruption of permanent teeth may cause disturbances in the establishment of normal development of permanent dentition occlusion.

Table IV. Eruption age (in years) of permanent teeth in Central India Population[16]

Developmental anomalies of teeth

The developmental anomalies of teeth can be classified according to variation in their number, size, shape and hereditary disturbances.

1. Developmental anomalies related to number of teeth

a) Hypodontia[26]: Overall prevalence is 3.5-8% with female predominance (Female: Male ratio 1.5:1) but the condition is rare in primary dentition (less than 1%). Missing teeth can be complete (anodontia), more than 6 teeth (oligodontia) or single or more (hypodontia). Missing the third molar is the most common followed by second premolar and lateral incisor (Fig.2a and 2b). It has been found to be associated with ectodermal dysplasia, progeria, Down syndrome, chondroectodermal dysplasia, Hallermann-Streiff syndrome, Rieger syndrome, Crouzons syndrome and osteodystrophy.

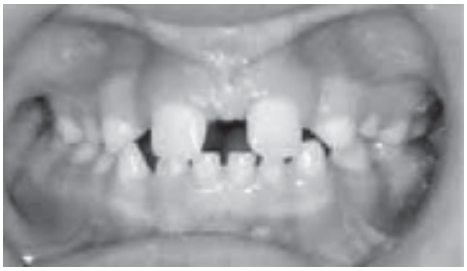

Fig.2a.Missing maxillary lateral incisors causing diastema

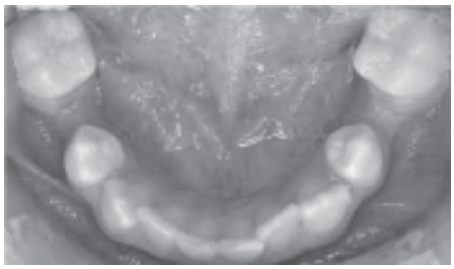

Fig.2b.Missing mandibular premolars

b) Hyperdontia (Supernumerary teeth)[27]: Overall prevalence is about 1-3% and more common in Asians. In Indian population the prevalence is 3% with single tooth hyperdontia being the most common. It is common in permanent dentition and majority occurs in the maxilla (Fig.3a). Mesiodens is a supernumery tooth present in the midline between the two central incisors. Mesiodens between maxillary central incisors is most common followed by distomolars, para-premolars and canines (Fig.3b and 3c). It is associated with syndromes like cranio-metaphyseal dysplasia, oral-facial-digital syndrome, cleidocranial dysplasia and Apert syndrome.

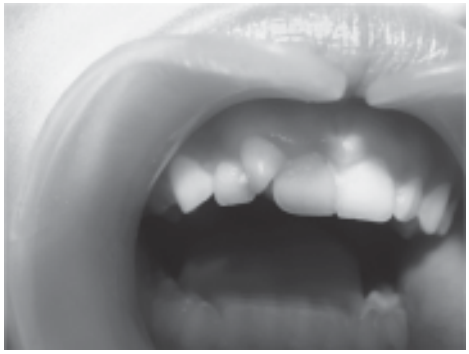

Fig.3a.Supernumerary tooth between maxillary right central and lateral incisors

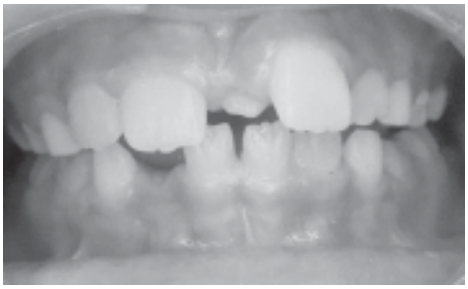

Fig.3b. Mesiodens causing diastema and protrusion of permanent maxillary left central incisor.

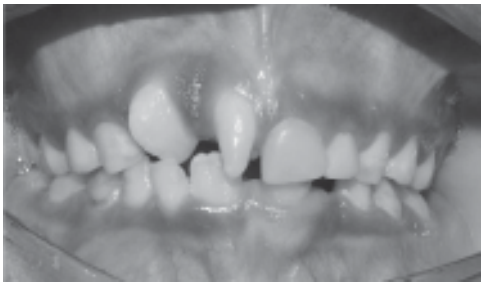

Fig.3c. Mesiodens causing diastema and rotation of right central incisor

2. Developmental anomalies related to size of teeth

a) Microdontia[28]: Teeth are smaller than normal with a prevalence of isolated microdontia between 1%-8% and the most frequently affected tooth is maxillary lateral incisors (Fig.4).[26] Relative microdontia is seen in macrognathia. True generalized microdontia although rare can be seen in pituitary dwarfism and Down syndrome.

b) Macrodontia[29]: It is characterized by greater than normal tooth size (Fig.5). Micrognathia leads to relative macrodontia. Generalized involvement is rare and found to be associated with conditions like gigantism and hemifacial hyperplasia.

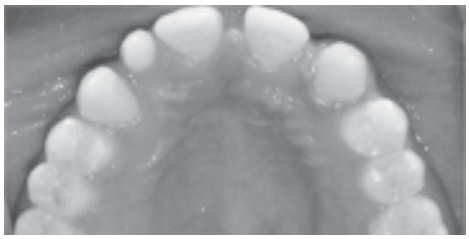

Fig.4.Microdontia and (peg shaped permanent maxillary right lateral incisor) and hypodontia (missing permanent maxillary left lateral incisor)

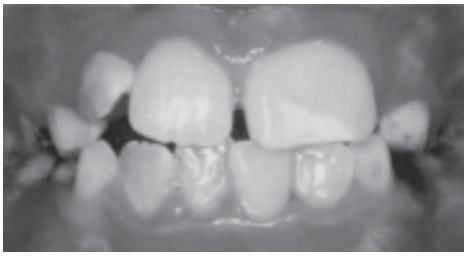

Fig.5.Macrodontia – Maxillary left central incisor

3. Developmental anomalies related to shape of teeth

a) Double teeth[26, 28]: Gemination-division of tooth germ occurs by invagination. The total tooth count is more than normal.

Fusion: Union/fusion of tooth germs where the tooth count is less than normal (Fig.6a, 6b and 6c). Clinical appearance is similar in gemination and fusion with unknown etiology and is most common in maxillary incisor region. Its prevalence in primary and permanent dentition is 0.5% and 0.1% respectively.

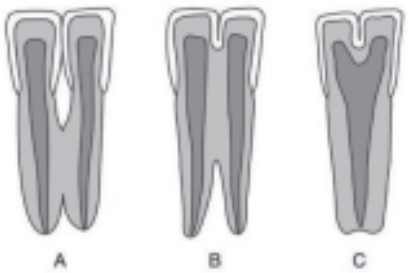

Fig.6a. Diagrammatic representation of concrescence (A), fusion (B) and gemination (C)

b) Concrescence[30]: Two adjacent teeth is by joined by cementum and is most common in maxillary posterior region. It can be associated with trauma or overcrowding.

c) Talon cusp[28]: An additional cusp is seen on palatal surface of anterior tooth and its prevalence varies from 1% - 8%. This condition is common in permanent dentition

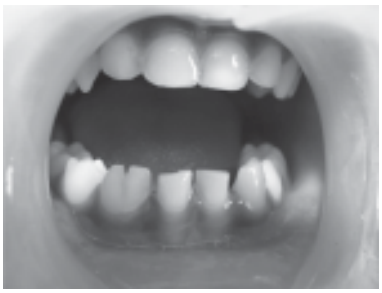

Fig.6b. Fusion-Mandibular right lateral incisor with canine

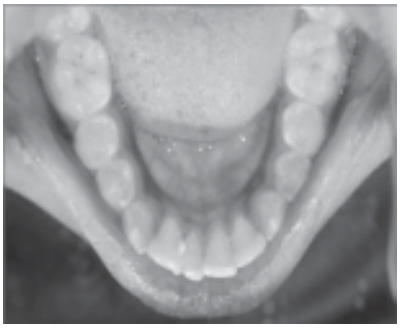

Fig.6c.Fusion of permanent mandibular right central and lateral incisor

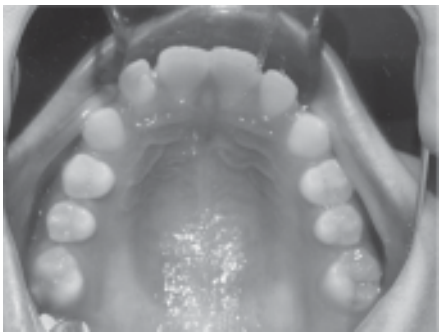

Fig.6d. Talon cusp in permanent maxillary right lateral incisor

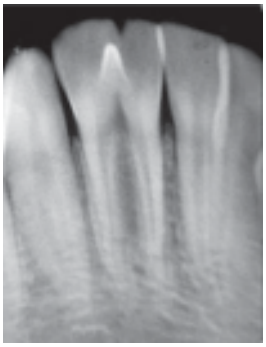

Fig.6e. IOPA X-ray - Talon cusp at fusion line of permanent mandibular right central and lateral incisor

Fig.6f.Dens evaginatus (mandibular second premolar)

and is most common in maxillary lateral incisor followed by maxillary central incisor (Fig.6d and 6e).

d) Dens evaginatus[31]: A cusp like projection present in the central groove and is most common in mandibular premolars with bilateral involvement (Fig.6f). A higher prevalence has been reported amongst Asians, native Americans, and Alaskans.

e) Dens invaginatus/ Dens in Dente[32]: An accentuation of the lingual pit with deep invagination of crown is seen and is composed of enamel and dentin with or without pulp projections (Fig.6g). Its revalence ranges from less than 1% to 10%. The condition is generally bilateral with permanent lateral incisor being the most commonly affected tooth.

f) Dilaceration[26,28]: An angulation in root portion of tooth is seen. Trauma during root development is the most common cause and is most commonly associated with permanent maxillary incisor followed by mandibular incisors.

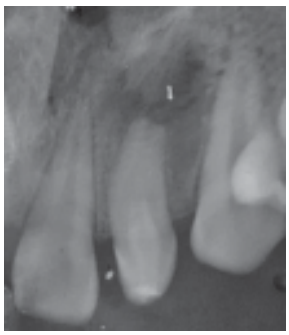

Fig.6g. Dens invaginatus / Dens in Dente: IOPA X-ray showing Dens in Dente in permanent maxillary left lateral incisor

4. Hereditary developmental alterations

a) Amelogenesis imperfecta[26, 28]

A hereditary developmental disorder that demonstrates developmental alterations in the structure of enamel without any systemic disorder (Fig.7). The condition involves both primary and permanent dentitions and frequency varies between 1:718 and 1:14,000.

The formation of enamel include synthesis of enamel matrix, its mineralization and maturation. They are classified into: a) hypoplastic b) hypocalcified c) hypomaturative types

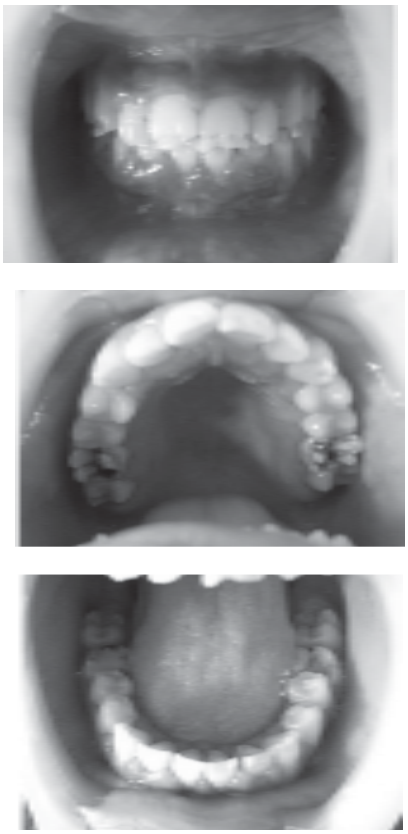

Fig.7. Amelognesis imperfecta

(Picture courtesy: Dr.Sneha Tulsani)

i) Hypoplastic: Defect related to enamel matrix formation. Enamel present is mineralized appropriately and can easily be differentiated from dentin on radiographs and is characterized by an abnormal shape of teeth and open contacts.

ii) Hypocalcified: Defect is associated with mineralization although enamel matrix synthesis is normal. The shape of the tooth is normal but enamel is soft and lost easily.

Erupted teeth show yellow-brown enamel which further becomes brown to black.

iii) Hypomaturative: Enamel matrix synthesis and mineralization is normal but enamel's crystal structure show defect in maturation. Tooth shape becomes normal and enamel become mottled in appearance-white, brown or yellow. The radiodensity of enamel is similar to dentin.

b. Dentinogenesis imperfecta[26, 28]

A hereditary developmental disorder affecting dentin also known as opalescent dentin. It is an autosomal dominant disorder with a prevalence of 1:8000. Both primary and permanent dentitions are involved. More severe involvement of primary teeth is followed by permanent incisors and first molars. The affected teeth become opalescent with yellow-brown to blue-gray discoloration. Enamel easily can get separated from underlying dentin which exhibits rapid attrition. Crowns become bulbous with cervical constriction whereas roots become thin with obliteration of pulp chambers and root canals.

c. Dentin dysplasia[26, 28]

The reported prevalence is 1:100,000 and disorder show autosomal dominant inheritance. In Type I Dentin dysplasia (Radicular type or 'rootless teeth') roots are short and pulp canals are obliterated. Enamel and coronal dentin are the asset. Color is normal in both dentitions and periapical radiolucencies may be present. The dentinal disorganization leads to a wide variation in root formation.

Type II Dentin dysplasia (Coronal type) is characterized by normal root length in both primary and permanent dentition and shows a clinical resemblance to dentinogenesis imperfecta. Tooth color is normal. Pulp chambers are enlarged with apical extension giving a thistle-tube shaped or flame-shaped appearance.

d. Regional odontodysplasia (Ghost teeth) [26, 28]

A localized developmental non-hereditary abnormality of teeth characterized by a defective formation of enamel, dentin, and pulp. It may involve a region, a quadrant or complete arch. Etiology is unknown and can be seen in both dentitions. This condition show maxillary predominance with 2.5:1 ratio and majority of affected teeth fail to erupt and those erupted show small yellow-brown irregular crowns. The roots are short with enlarged pulp and open apices.

Points to Remember

- ***Development of tooth is a genetically guided unique process that begins in intrauterine period and continues for several years after birth.***
- ***Chronology of tooth eruption follows a sequence which shows variation according to gender, jaws, and quadrant in the type of population studied.***
- ***The eruption process can also get affected by various syndromes, systemic conditions, numerous external factors and genetic conditions.***
- ***The developmental anomalies of teeth can be related to their number, size, shape and hereditary disturbances which show a variation in prevalence and severity.***
- ***Eruption time of teeth has huge variation compared to standard eruption charts. Therefore pediatrician's knowledge about tooth development, eruption, and developmental disturbances has a considerable significance.***

References

1. Jernvall J, Keränen SV, Thesleff I. Evolutionary modification of development in mammalian teeth: quantifying gene expression patterns and topography. Proc Natl Acad Sci U S A 2000; 97(26):144–148.
2. Pispa J, Thesleff I. Mechanisms of ectodermal organogenesis. Dev Biol 2003; 262(2):195–205.
3. Tucker A, Sharpe P. The cutting-edge of mammalian development; how the embryo makes teeth. Nat Rev Genet 2004;5(7):499–508.
4. Nanci A. In: Ten Cate's oral histology - Development, structure, and function. 8th Edn Mosby Elsevier, St Louis. 2008;pp 80-82.
5. Koussoulakou DS, Margaritis LH, Koussoulakos SL. A curriculum vitae of teeth: evolution, generation, regeneration. Int J Biol Sci 2009; 5(3):226–243.
6. Marson A, Foreman R, Chevalier B, Bilodeau S, Kahn M, Young RA, et al. Wnt signaling promotes reprogramming of somatic cells to pluripotency. Cell Stem Cell 2008; 3(2):132–135.
7. D'Souza R. Development of the pulpodentinal complex. In: Hargreaves K (ed) Seltzer and Bender's dental pulp. Quintessence Books, Chicago, 2002;pp63-94.
8. Gron AM. Prediction of tooth emergence. J Dent Res 1962; 41:573-585.
9. Guna Shekhar M, Tenny J. Longitudinal study of age and order of eruption of primary teeth in Indian children. J Clin Exp Dent 2010; 3(2):e113-116.
10. Vinod K, Singh R, Suryavanshi R, Ashok Kumar, Singh RK, Ranjan R. Eruption chronology of Primary Teeth in Garhwa district, Jharkhand, India. IAIM 2016; 3(5): 81-84.
11. Kaul SS, Pathak RK, Santosh. Emergence of deciduous teeth in Punjabi children, North India. Zeitschriftfür Morphologie und Anthropologie 1992; 79(1): 25-34.

12. Minal Niswade, Chandranee NJ. "A cross sectional analysis of time and sequence of eruption of deciduous teeth in children of a municipal city in maharashtra state." Thesis submitted to Maharashtra University of Health Sciences, Nashik, Maharashtra. December 2016 (unpublished).
13. Banerjee P, Mukherjee S. Eruption of deciduous teeth among Bengalee children. Am J Phys Anthropol 1967; 26(3):357-358.
14. Tewari A, Chawla HS. Study of sequence and eruption age of permanent teeth in North Indian children: Chandigarh. J Indian Dent Assoc 1979; 51(1):7-13.
15. Lakshmappa A, Guledgud MV, Patil K. Eruption times and patterns of permanent teeth in school children of India. Indian J Dent Res 2011; 22(6):755-763.
16. Sonam Gupta, Chandranee NJ – "Eruption pattern of permanent teeth in children of a municipal city in Maharashtra state - A cross sectional study". Thesis submitted to Maharashtra University of Health Sciences, Nashik Maharashtra December 2016 (unpublished).
17. Gaur R, Singh, NY. Emergence of permanent teeth among the meiteis of Manipur, India. Am J Hum Biol 1994; 6:321–328.
18. Kumar CL, Sridhar MS. Estimation of the age of an individual based on times of eruption of permanent teeth. Forensic Sci Int 1990; 48(1):1-7.
19. KK Aggarwal, Amandeep Kaur, Rakesh Kumar. Chronological pattern of eruption of permanent teeth in the adolescent age group in Patiala district, Punjab. J Punjab Acad Forensic Med Toxicol 2011; 11(1):12-19.
20. Nelson SJ. Wheeler's Dental Anatomy, Physiology and Occlusion. 9th edn. 2009.
21. Shubhangi Mhaske, Monal B. Yuwanati, Ashok Mhaske, Raju Ragavendra, Kavitha Kamath, and Swati Saawarn, "Natal and Neonatal Teeth: An Overview of the Literature," ISRN Pediatrics, vol. 2013, Article ID 956269, 11 pages, 2013. https://doi.org/10.1155/2013/956269.
22. El Khatib K, Abouchadi A, Nassih M, Rzin A, Jidal B, Danino A, et al., "Natal teeth: apropos of five cases." Revue de Stomatologieet de ChirurgieMaxillo-Faciale. 2005; 106:6:325–327.
23. Faizal C Peedikayil. Delayed Tooth Eruption. e-Journal of Dentistry 2011; 1(4):81-86.
24. Rasmussen P, Kotsaki A. Inherited retarded eruption in the permanent dentition. J Clin Pediatr Dent 1997; 21:205-211.
25. Suri L, Gagari E, Vastardis H. Delayed tooth eruption: pathogenesis, diagnosis, and treatment A literature review. Am J Orthod Dentofacial Orthop 2004; 126(4):432-445.
26. Neville, Damm, Allen and Bouquot. Oral & Maxillofacial Pathology- Saunders Elsevier, St. Louis. 3rd Edition. 2008. pp 54-99.
27. Kaur N, Kumar K, Rastogi P, Juneja S, Narwal N. Prevalence and distribution of oral developmental anamolies amongst population of Ghaziabad. J dental specialities 2014; 2(1):25-29.
28. Shafer, Hine, Levy. Developmental disturbances of oral and paraoral structures. In Textbook of Oral Pathology-Elsevier, India. 6th edn, 2009; pp3-62.
29. Namdar F, Atasu M. Macrodontia in association with a contrasting character microdontia. J Clin Pediatr Dent.1999; 23:271-274.
30. Romito LM, Omaha. Concrescence: Report of a rare case. Oral Med Oral Pathol Oral Radiol Endod. 2004.97: 325-327.
31. Dankner E, Harari D, Rotstein I. Dens evaginatus of anterior teeth – literature review and radiographic survey of 15,000 teeth, Oral Surg Oral Med Oral Pathol Oral Radiol Endod.1996; 81: 472-476.
32. Chen YH, Tseng CC, Harn WM. Dens invagininatus. Review of formation and morphology with 2 case reports. Oral Surg Oral Med Oral Pathol Oral Radiot Endod. 1998; 86: 347-352.

NEWS AND NOTES

ISIEM 2019: 5th National Conference of the Indian Society For Inborn Errors In Metabolism (ISIEM), Pune, Maharashtra

Date: 18-20 January, 2019

Contact

Dr.Chaitanya Datar

Mobile: 09763301410

Email: isiempune2019@gmail.com

Website: www.isiem.org

RADIOLOGY

PRECOCIOUS PUBERTY

***Vijayalakshmi G**
****Natarajan B**
****Kasi Visalakshi KP**
****Abirami K**
*****Thangalakshmi A**
*****Raveendran J**

Precocious puberty is a disturbing condition that has to be promptly evaluated. The central type is gonadotropin dependent due to early activation of the hypothalamic-pituitary-gonadal axis. Peripheral or precocious pseudopuberty is due to increased sex steroid production from ovarian, adrenal and testicular tumors which is gonadotropin independent. Radiological assessment plays an important part and occupies a crucial position in the algorithm for the evaluation of precocious puberty.

Bone age estimation with X-rays gives an objective evidence for skeletal maturation and can also be used for follow-up of patients on treatment. There are atlases, like that of Gruelich and Pyle, Tanner and Whitehouse from where one can compare the hand X-ray of the child with standards that will help one to arrive at the age of the child. There are websites (like boneXpert) which will give the answer within seconds of uploading the X-ray of the hand. One can also use the old method of timing of appearance of epiphyses (Table I). All the phalangeal centres are present by the age of two years. The lateral X-ray of knee helps in the age group of 3 to 5 years. The AP and lateral films of elbow help in resolving age between six and fourteen.

If bone age is advanced by more than two years precocity has set in. In premature thelarche that occurs in girls less than 3 years, bone age is not advanced. Similarly children with premature pubarche may show slightly advanced bone age but not more than a difference of 2 years. So, final adult height is not significantly affected in these children.

Table I. Age and appearance of epiphyses

Age	Appearance of epiphyses
1 year and 6 months	Lower end of the radius
2 years	Phalangeal centres
2 years and 6 months	Base of the first metacarpal
4 years	Patella
6 to 7 years	Radial head
8 years	Medial epicondyle of humerus
10 to 11 years	Olecranon
10 years in girls and 12 in boys	Pisiform
12 to 14 years	Lateral epicondyle of humerus

Ultrasound is useful to evaluate the uterus and ovaries in girls and the testes in boys. In premature thelarche and pubarche, there is no increase in size or change in contour of the uterus. The uterus is still infantile i.e. the cervix is longer than the uterus. At puberty the uterus becomes longer than the cervix in the ratio of 2:1. Premature pubarche in girls is now viewed as a forerunner of the metabolic syndrome and polycystic ovarian disease. Follow-up is necessary. Ultrasound features of ovarian hyperandrogenism include bilaterally enlarged ovaries, presence of five or more small follicles, about 5 mm each, without a dominant follicle and increased stromal echogenicity relative to the myometrium. However, these features may not be present always. Ultrasound and other cross-sectional imaging will also detect granulosa cell tumors or germ cell tumors of ovary that may be the cause of peripheral precocious puberty where estradiol levels are high with low FSH and LH.

Testicular growth is the first sign of male puberty when the testes reach a volume of 4 ml or a length of 2.5 cm. In premature pubarche or adrenarche (includes pubarche

* Professor
** Associate Professor
*** Assistant Professor,
Department of Pediatric Radiology,
Institute of Child Health and Hospital for Children,
Chennai.
email: drviji.rad@gmail.com

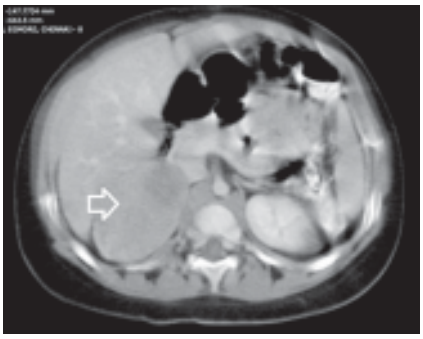

Fig.1. Adrenal tumor on right (arrow)

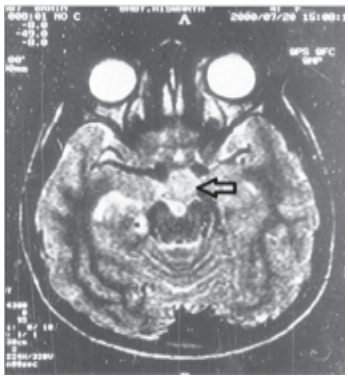

Fig.2. Hypothalamic hamartoma (arrow)

and appearance of axillary hair, body odour and acne) the testicular size is prepubertal. Testicular size depends on the pituitary hormones-FSH and LH. When testicular size is normal and there are signs of androgen excess like penile enlargement and pubic hair, peripheral precocious puberty due to testicular or adrenal tumor is the probable etiology. Androgen levels are increased while FSH and LH may be normal initially and drop later. Fig.1 shows an adrenal tumor in the right renal fossa in a four year old boy. The normal kidney has been displaced down and outwards.

In central precocious puberty FSH and LH are raised. With GnRH stimulation both are raised further. The commonest is idiopathic type especially in girls. Other secondary causes are hamartomas, astrocytomas, pineal gland tumors and HCG secreting germ cell tumors. Fig.2 is that of a child who had precocious puberty with gelastic seizures. There is a round lesion in the midline just below the level of the thalamus near the midbrain. This is a hypothalamic hamartoma. As the name suggests it is a hamartomatous collection of cells arising from the hypothalamus at the floor of the third ventricle. It has the same intensity as the brain and does not enhance. A germ cell tumor can also arise at the same site but will show enhancement with contrast. MRI is definitely indicated even in the absence of CNS symptoms. Children with shunt surgery for hydrocephalus are also known to have

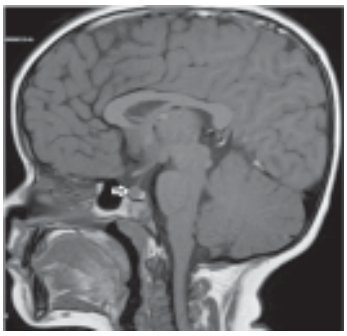

Fig.3. Hypothyroidism. Note the enlarged pituitary (arrow)

precocious puberty because of early activation of the hypothalamic- pituitary- gonadal axis.

Fig.3 is the CT brain of a 7 year old girl who had developmental delay now presenting with progressive breast enlargement and menstruation. Uterus showed increased size and pubertal contour. However, bone age was grossly delayed. The pelvic epiphyses were small and dysgenic pointing to a diagnosis of hypothyroidism. Thyroid levels were low while TSH was high. This is a case of Van Wyk-Grumbach syndrome. TSH acts on peripheral FSH receptors. The anterior pituitary can be very much enlarged (Fig.3) and should not be mistaken for tumor. Delayed bone age with precocious puberty is a clue for this condition.

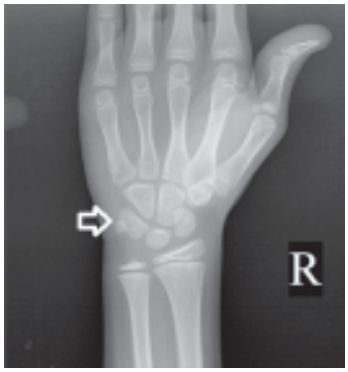

Fig.4. Pisiform appears at 10 years in girls and by 12 in boys

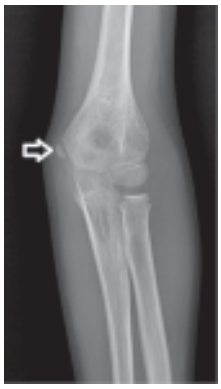

Fig.5. Elbow - Epiphysis of epicondyle is seen (arrow)

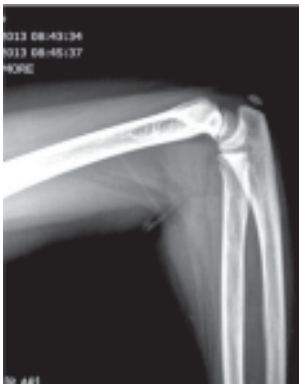

Fig.6. Note the site for the epiphysis of the olecranon (11 years)

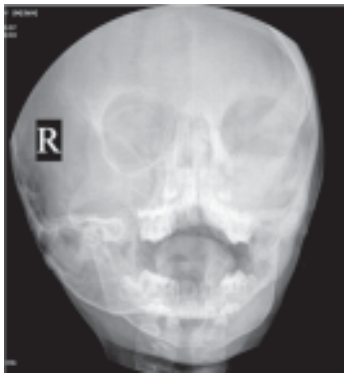

Fig.7. McCune Albright syndrome

Fig.4, 5, 6 belong to a 7 year old child with precocious puberty. Bone age is advanced to 11 years. The pisiform has appeared and the olecranon is seen. The child also had facial asymmetry with a prominent malar bone on the left. Fig.7 is an X-ray PNS which shows thickened left maxilla and hazy sinus. This is a case of fibrous dysplasia with precocious puberty or McCune Albright syndrome. It is gonadotropin independent. There may also be other endocrinopathies like increased thyroid, parathyroid or growth hormones. History, physical examination, hormonal levels and radiological assessment are all the various components of the evaluation of precocious puberty.

CLIPPINGS

Rate of Recurrence of Adverse Events Following Immunization: Results of 19 Years of Surveillance Ii Quebec, Canada.

While adverse events following immunization (AEFI) are frequent, there are limited data on the safety of reimmunizing patients who had a prior AEFI. The objective was to estimate the rate and severity of AEFI recurrences.

Data from the AEFI passive surveillance system in Quebec, Canada that collects information on reimmunization of patients who had a prior AEFI was analysed. Patients with an initial AEFI reported to the surveillance system between 1998 and 2016 were included. Rate of AEFI recurrence was calculated as: number of patients with recurrence/ total number of patients reimmunized.

Overall, 1350 patients were reimmunized, of which 59% were less than 2 years old. The AEFI recurred in 16% (215/1350) of patients, of whom 18% (42/215) rated the recurrence as more severe than the initial AEFI. Large local reactions extending beyond the nearest joint and lasting 4 days or more had the highest recurrence rate (67%, 6/9). Patients with hypotonic hyporesponsive episodes had the lowest rate of recurrence (2%, 1/50). Allergic-like events recurred in 12% (76/659) of patients but none developed anaphylaxis. Of 33 patients with seizures following measles mumps rubella with/without varicella vaccine, none had a recurrence. Compared with patients with non-serious AEFIs, those with serious AEFIs were less often reimmunized (60% versus 80%, rate ratio: 0.8, 95% confidence interval 0.66 to 0.86).

Conclusion: Most patients with a history of mild or moderate AEFI can be safely reimmunized. Additional studies are needed in patients with serious AEFIs who are less likely to be reimmunized.

Zafack JG, Toth E, Landry M, Drolet JP, Top KA, Serres GD. Pediatr Infect Dis J September 10, 2018. doi: 10.1097/INF.0000000000002162.

CASE REPORT

A RARE CASE OF DROP ATTACKS - L 2 HYDROXY GLUTARIC ACIDURIA

***Harish GV**
***Sandeep Reddy**
****Tejaswi G**

Abstract: *L-2-hydroxyglutaric aciduria is a neurometabolic disorder caused by mutations in the L-2 hydroxyglutarate dehydrogenase gene. The disease has an insidious onset with slow progression and diagnosis is commonly made in late childhood to early adolescence. Initial clinical features are developmental delay, learning difficulties and in later years cerebellar signs become the dominant clinical manifestation. Drop attacks present as sudden and spontaneous falls without loss of consciousness and followed by rapid recovery can occur in epilepsies, movement disorders, cataplexy, psychiatric disorders and rarely in leukodystrophies. We report a case with drop attacks with elevated urinary 2 hydroxyglutaric acid.*

Keywords: *L-2 hydroxyglutaric aciduria, Drop attacks, Dysgraphia , Symmetrical confluent hyperintensities.*

L2-hydroxyglutaric aciduria (L-2-HGA) is a rare neurometabolic disorder of organic acid metabolism. Exact incidence and prevalence are not known. The disorder appears to be pan-ethnic with cases reported worldwide.[1,2] It is an autosomal recessive encephalopathy, a "disorder of metabolite repair".[3] L-2-hydroxyglutarate is normally metabolized to alpha-ketoglutarate and the pathologic findings in this metabolic disorder are due to a toxic effect of L-2-hydroxyglutarate on the central nervous system. L-2-hydroxyglutarate has no known physiological function and its accumulation is toxic to the human brain, causing a leukoencephalopathy and increasing the susceptibility for tumours.[3] The diagnosis of L-2-HGA can be made based on magnetic resonance imaging (MRI), biochemical analysis and mutational analysis of L-2-HGDH gene.[4] Chalmers et al and Duran et al. first described patients with D-2-hydroxyglutaric aciduria (D-2-HGA) and L-2-HGA respectively.[5,1] Muntau et al. described a case of combined L-2-HGA and D-2-HGA.[6]

* Associate Professor,

** Post graduate,
Department of Pediatrics,
Prathima Institute of Medical Sciences,
Karimnagar, Telangana.
email: drharish82@gmail.com

Case report

A 7 year old boy born to second degree consanguineous parents, first in birth order, with an uneventful perinatal period was brought with delay in the development of higher mental function and poor scholastic performance. Since 3 years of age he had recurrent drop attacks while walking, running and playing. The frequency of attacks was once a week initially which has progressively increased to 3-4 episodes/week. There was no aura, palpitations or hyperventilation. Each episode lasted for less than 15sec with no loss of consciousness, postictal confusion or drowsiness. There was no history of headache, involuntary movements, seizures, prior traumatic brain injuries, anxiety, mood swings or disruptive behavior. He had normal sleep wake cycle. Visual and hearing abilities were normal without any tinnitus or vertigo. There was no significant family history. Initially parents thought that child was a bit lazy and ignored, but as the frequency of episodes were increasing, child was brought for medical attention. Over the past two years, he was treated symptomatically on OPD basis, with multivitamin medications and calcium supplements.

Vitals were normal. He had macrocephaly, with head circumference 54 cm (more than 97th percentile). Spine was normal. Child had difficulty in reading simple words (dyslexia), writing alphabets, drawing a circle or triangle (dysgraphia) and was also hyperactive. Cranial nerves examination, sensory system and motor system examination were normal. There was no hypertonia, dystonia, involuntary movements or abnormal posturing. Cerebellar signs were absent. Other systems were normal. Ophthalmological examination including fundoscopy and slit lamp examination was normal. Pure tone audiometry was normal.

Complete hemogram, blood sugar, electrolytes, renal and liver function tests were normal. Thyroid profile, serum lead levels, ECG, 2D-ECHO and EEG were normal. CT brain showed diffuse symmetrical hypodensities in

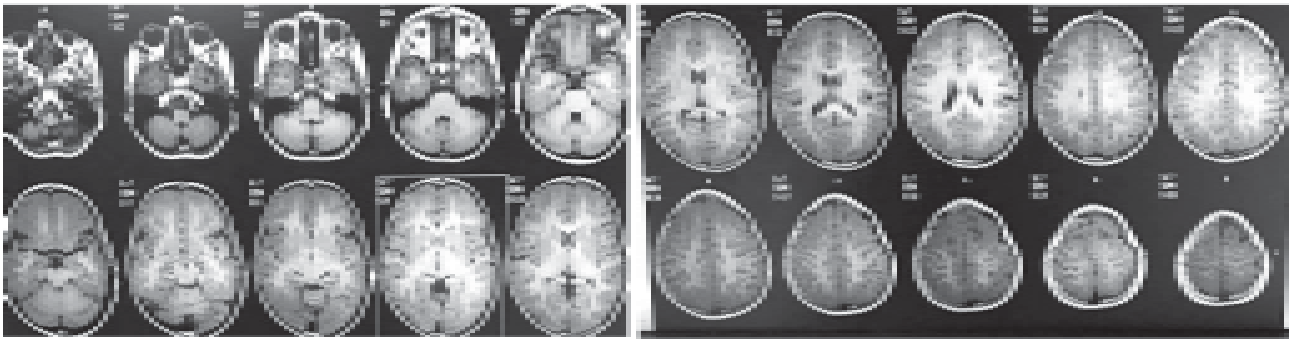

Fig.1. MRI Brain contrast (T2/FLAIR) - Symmetrical confluent hyperintensities involving bilateral periventricular regions in frontal and occipital regions and T2 hypodensity in bilateral thalami

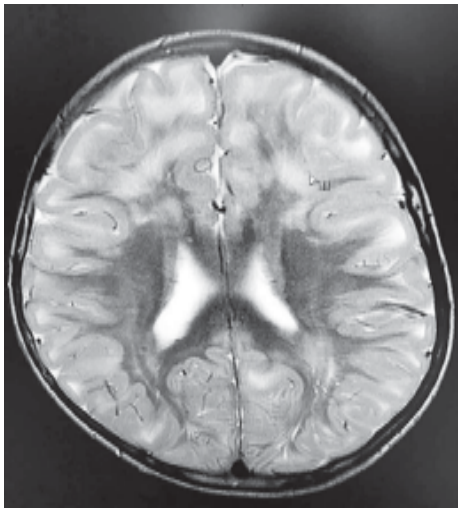

Fig.2. T2/FLAIR non enhancing symmetrical confluent hyperintensities involving bilateral periventricular regions

white matter of bilateral frontal and occipital regions suggestive of leukodystrophy. MRI brain with contrast revealed symmetrical confluent hyperintensities involving bilateral periventricular regions in frontal and occipital regions in T2/FLAIR, showing no enhancement on contrast and T2 hypodensity noted in bilateral thalami (Fig.1 and 2). This narrowed down the possibilities to Canavan's disease, Alexander's disease and metachromatic leukodystrophy, as child had macrocephaly, progressive declined in neurological function with MRI white matter abnormalities.

Further investigations like gas chromatography (GC), tandem mass spectrometric analysis, ferric chloride levels, very long chain fatty acid (VLCFA) levels were done. The urine organic acid profile showed elevated levels of 2-OH-glutaric acid (159.54%), a 27 fold elevation which was significant with other metabolites ($FeCl_3$, VLCFA levels) being normal. Thus the diagnosis of L-2 hydroxyglutaric aciduria was made. His parents were counseled regarding the disease course and prognosis. He was empirically started on L-carnitine and on follow up showed a decrease in the number of drop attacks with improved scholastic performance.

Discussion

L-2 hydroxyglutaric aciduria has an insidious onset starting in childhood, with developmental delay, epilepsy and cerebellar ataxia as cardinal clinical signs.[4] The course of the disease is slowly progressive. Affected children are often initially normal, which can lead to a delay in diagnosis.[7,8] Therefore, mild L-2-HGA patients often remain undiagnosed until adolescence or even adulthood. Virtually all patients display delayed mental and motor development and about two-third of them have epilepsy and cerebellar dysfunction. In about half of the patients, macrocephaly and extra pyramidal symptoms are observed. Hypotonia was most prevalent in the earlier stages which explained the drop attack in our patient and spasticity in the later stages of disease. Neurological decompensation (e.g. loss of milestones, such as unassisted walking and the development of speech deficits) were also present in a quarter of the patients. Balaji et al reported two siblings with dystonia diagnosed by classical neuroimaging findings with elevated urinary 2 hydroxyglutaric acid.[9] They had macrocephaly with slow progression of disease similar to the present case, but with extrapyramidal signs predominantly dystonia which was not seen in the present case.

A highly characteristic pattern of MRI abnormalities in L-2-HGA are involvement of subcortical cerebral white matter, dentate nucleus, globus pallidus, putamen and caudate nucleus.[2] This was not seen in the present case but there was involvement of periventricular white matter and T2 hypodensities in bilateral thalami. Differential diagnosis for these MRI findings are Canavan's and Kearns-Sayre syndrome. These conditions show diffuse bilateral

involvement of subcortical U fibres, periventricular and deep white matter, thalami and globus pallidus. Similar picture is seen in Kearns-Sayre syndrome. In MR spectroscopy there was notable absence of elevated N-acetyl aspartate (NAA) peak to suggest Canavan's disease or increased lactate and low NAA in Kearns-Sayre syndrome. Accumulation of 2 hydroxyglutaric acid in urine is detected by gas chromatography (GC) mass spectrometric analysis. Gregerson et al. (1977) first identified D-2 and L-2-hydroxyglutaric acids (D-2HG and L-2HG) in human urine.[10] Accumulation of 2-HG in urine is detected by gas chromatography (GC) mass spectrometric analysis. Normally there are 2 isomers of 2 hydroxyglutaric acid. They are with L and D configurations which are found in equal amounts in urine. Among these, D2-HGA presents with grave neurological symptom in neonatal period. L2-HGA is slowly developing neurometabolic disorder. Lesson learnt from this case report is to suspect organic acidemia in any child presenting with macrocephaly, neurological deterioration, hypotonia, abnormal movements and MRI changes in white matter. L2 hydroxy glutaric aciduria is one of the rare metabolic disorders. There had been no case of leukodystrophy presenting predominantly with drop attacks as seen in present case report which might be an atypical presentation.

References

1. Duran M, Kamerling JP, Bakker HD, van Gennip AH, Wadman SK. L-2-Hydroxyglutaric aciduria: an inborn error of metabolism? J Inherit Metab Dis 1980; 3(4):109-112.
2. Steenweg ME, Salomons GS, Yapici Z, Uziel G, Scalais E, Zafeiriou DI, et al. L-2-Hydroxyglutaricaciduria: pattern of MR imaging abnormalities in 56 patients. Radiology 2009; 251:856–865.
3. Van Schaftingen E, Rzem R, Veiga-da-Cunha M. L-2-Hydroxyglutaric aciduria, a disorder of metabolite repair. J Inherit Metab Dis 2009; 32:135–142.
4. Steenweg ME, Jakobs C, Errami A, van Dooren SJ, Adeva Bartolomé MT, Aerssens P, et al. An overview of L-2-hydroxyglutarate dehydrogenase gene (L2HGDH) variants: a genotype-phenotype study. Hum Mutat 2010; 31:380–390.
5. Chalmers RA, Lawson AM, Watts RWE, Tavill AS, Kamerling JP, Hey E, et al. D-2-hydroxyglutaric aciduria: Case report and biochemical studies. J Inherited Metab Dis1980; 3:11-15.
6. Muntau AC, Röschinger W, Merkenschlager A, van der Knaap MS, Jakobs C, Duran M, et al, Combined D-2- and L-2-hydroxyglutaric aciduria with neonatal onset encephalopathy: a third biochemical variant of 2-hydroxyglutaric aciduria? Neuropediatrs 2000; 31:p137-140.
7. Tortori-Donati P, Rossi A. Pediatric Neuroradiology, brain. head, neck and spine. Springer 2005; ISBN: 3540410775.
8. Larnaout A, Hentati F, Belal S, Ben Hamida C, Kaabachi N, Ben Hamida M. Clinical and pathological study of three Tunisian siblings with L-2-hydroxyglutaric aciduria. Acta Neuropathol 1994; 88(4)367-370.
9. Balaji P, Viswanathan V, Chellathurai A, Panigrahi D. An interesting case of metabolic dystonia: L-2 Hydroxylglutaric aciduria. Ann Indian Acad Neurol 2014; 17:97-99.
10. Gregersen N, Ingerslev J, Rasmussen K. Low molecular weight organic acids in the urine of the newborn Acta Paediatr 1977; 66: 85-89.

NEWS AND NOTES

Financial Acumen and Corporate Entrepreneurship (FACE)

Date: 13th & 14th October, 2018

Time: Saturday 1pm to Sunday 1pm

Venue: Five Falls Resorts, 35/31 Five Falls Main Road,
Opposite to Vivekanantha Ashram, Courtallam, Tamilnadu.

Contact details

Dr.A.Somasundaram

Hon.Secretary, IAP TNSC

IAP TNSC House, Ground Floor, F Block, 56, Halls Road

Egmore, Chennai 600 008.

Ph.No.044 28191524