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INBORN ERRORS OF METABOLISM - I

RECOGNIZING RED FLAGS IN INBORN ERRORS OF METABOLISM - CLINICAL PRESENTATION AND ALERTS

**** Ramaswamy Ganesh***

Abstract: *Inborn errors of metabolism are a heterogeneous group of rare genetic disorders that pose a significant diagnostic challenge due to their non-specific presentation, necessitating a high index of suspicion from healthcare providers. Early recognition of "red flags" is crucial for timely, life-saving intervention. This manuscript discusses the common clinical and laboratory red flags seen in inborn errors of metabolism.*

Keywords: *Inborn errors of metabolism, Children, Hypoglycemia, Hyperammonemia.*

* Head,
Department of Pediatrics,
Rainbow Children's Hospital,
Chennai.

email: ganeped@gmail.com

Points to Remember

- ***High index of suspicion in IEMs is crucial for timely intervention***
- ***Red flags in IEMs are categorized into three main areas - symptoms, signs and laboratory parameters.***
- ***The pattern of hypoglycemia with or without ketosis is a critical differentiator.***
- ***Hyperammonemia is a medical emergency***
- ***Unusual body odours and age-specific neurological symptoms are key clues***

References

1. Ficicioglu C, Bearden D. Isolated neonatal seizures: when to suspect inborn errors of metabolism. Pediatr Neurol. 2011 Nov; 45(5):283-91.
2. Bijarnia-Mahay S, Kapoor S. Testing Modalities for Inborn Errors of Metabolism - What a Clinician Needs to Know? Indian Pediatr. 2019 Sep 15; 56(9):757-766.
3. Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of neonatal cholestasis: consensus statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. Indian Pediatr. 2014 Mar; 51(3):203-10.
4. Sharma S, Prasad AN. Inborn Errors of Metabolism and Epilepsy: Current Understanding, Diagnosis, and Treatment Approaches. Int J Mol Sci. 2017 Jul 2; 18(7): 1384.
5. Bremova-Ertl T, Hofmann J, Stucki J, Vossenkaul A, Gautschi M. Inborn Errors of Metabolism with Ataxia: Current and Future Treatment Options. Cells. 2023 Sep 19; 12(18):2314.
6. Paj¹k R, Mendela E, Bêdkowska N, Paprocka J. Update on Neuropathies in Inborn Errors of Metabolism. Brain Sci. 2021 Jun 8; 11(6):763.
7. Das AM, Steuerwald U, Illsinger S. Inborn errors of energy metabolism associated with myopathies. J Biomed Biotechnol. 2010; 2010:340849.

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8. van de Burgt N, van Doesum W, Grevink M, van Niele S, de Koning T, Leibold N, et al. Psychiatric manifestations of inborn errors of metabolism: A systematic review. Neurosci Biobehav Rev. 2023 Jan; 144:104970.
9. Papadopoulou-Legbelou K, Gogou M, Evangeliou A. Cardiac Manifestations in Children with Inborn Errors of Metabolism. Indian Pediatr. 2017 Aug 15; 54(8): 667-673.
10. Bilgin H, Bozaci AE. The evaluation of inherited metabolic diseases presenting with rhabdomyolysis from Turkey: Single center experience. Mol Genet Metab Rep. 2024 Mar 15; 39:101070.
11. Clothier J, Hulton SA. Inherited metabolic renal disorders in children. Medicine. 2011 Jun 1; 39(6):350-2..
12. Saudubray JM, García-Cazorla Á. Clinical approach to inborn errors of metabolism in paediatrics. In Inborn metabolic diseases: diagnosis and treatment 2022 Jun 25 (pp. 3-123). Berlin, Heidelberg: Springer Berlin Heidelberg.
13. Alfadhel M, Mutairi FA, Makhseed N, Jasmi FA, Al-Thihli K, Al-Jishi E, et al. Guidelines for acute management of hyperammonemia in the Middle East region. Ther Clin Risk Manag. 2016 Mar 31; 12: 479-87.
14. Guerrero RB, Salazar D, Tanpaiboon P. Laboratory diagnostic approaches in metabolic disorders. Ann Transl Med. 2018 Dec; 6(24):470.
15. Belu A, Filip N, Trandafir LM, Spoialã EL, Tarcã E, Zamosteanu D, et al. Lactate, an Essential Metabolic Marker in the Diagnosis and Management of Pediatric Conditions. Diagnostics (Basel). 2025 Mar 23; 15(7): 816.
16. Ramsay J, Morton J, Norris M, Kanungo S. Organic acid disorders. Ann Transl Med. 2018 Dec; 6(24):472.

INBORN ERRORS OF METABOLISM - I

LABORATORY WORKUP IN SUSPECTED IEM - A STEPWISE APPROACH (BIOCHEMICAL TESTS, METABOLIC PANEL, INTERPRETATION PITFALLS)

***Anil Jalan**
****Ketki Kudalkar**

Abstract: *Inborn errors of metabolism are genetic disorders that disrupt normal intermediary metabolism. Early recognition and timely intervention are crucial to prevent severe complications, including disability and death. These conditions often present with variable and non-specific clinical symptoms, making accurate diagnosis challenging. Initial investigations such as blood glucose, ammonia, lactate levels, electrolytes and ketones may provide clues to the underlying metabolic disturbance. The findings of these investigation can guide the selection of more specific, advanced metabolic tests. Diagnostic confirmation typically relies on specialized investigations, including the analysis of acylcarnitines, organic acids, amino acids and specific enzyme assays. This article reviews both the foundational and advanced diagnostic tools, highlighting key biochemical markers used in the identification of Inborn errors of metabolism.*

Keywords: *Inborn errors of metabolism, Laboratory investigations, Acyl carnitines, Organic acids, Amino acids.*

* Consultant Pediatric Metabolic Specialist
email: jalananil12@gmail.com

** Biochemist,
Nirman Metabolic Clinic

Points to Remember

- ***Clinical presentation in IEMs can be very helpful in designing the tests in each case and always sharing the clinical details, discussing the possibilities with a metabolic expert can save time and expenses.***
- ***Sample collection should be done before starting any intervention or transfusion. Also, it is important that samples be collected at the right time in correct containers after discussing with the metabolic laboratory.***
- ***Guidelines of proper handling, storage and transport of samples to a metabolic laboratory must be followed.***
- ***Pre- and post- test counseling of parents is of utmost importance***

References

1. Saudubray JM, Ogier H, Bonnefont JP, Munnich A, Lombes A, Hervé F, et al. Clinical Approach to Inherited Metabolic Diseases in the Neonatal Period: A 20 year Survey, J Inher Metab Dis. 1986; 12 (1): 25-41.
2. Saudubray JM, GarciaCazorla A. Inborn errors of metabolism: diagnosis and treatment. Pediatr Clin North Am. 2006; 53(4):787-826.
3. Saudubray JM, Sedel F, Walter JH. Clinical approach to inborn errors of metabolism in infancy. J Inherit Metab Dis. 2006; 29(4):506-25.
4. Wanders RJ. Metabolic and molecular basis of peroxisomal disorders: a review. Am J Med Genet A 2004; 126A:355-75
5. Potter M, Hammond JW, Sim KG, Carpenter K, Christodoulou J, Wilcken B, et al. Ornithine carbamoyltransferase deficiency: improved sensitivity of testing for protein tolerance in the diagnosis of heterozygotes. J Inherit Metab Dis. 2001; 24(1):5-14.
6. Häberle J. Clinical and biochemical aspects of primary and secondary hyperammonemic disorders. Arch Biochem Biophys 2013; 536:101-8.
7. Walker V. Ammonia toxicity and its prevention in inherited defects of the urea cycle. Diabetes Obes Metab 2009; 11:823-35.

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8. Iyer H, Sen M, Prasad C, Rupar CA, Lindsay RM. Coma, hyperammonemia, metabolic acidosis, and mutation: lessons learned in the acute management of late onset urea cycle disorders. Hemodial Int 2012;16:95-100. PMID: 22099885. DOI: 10.1111/j.1542-4758.2011.00591.x
9. Madigan T, Block DR, Carey WA, Kaemingk BD, Patel R. Proposed plasma ammonia reference intervals in a reference group of hospitalized term and preterm neonates. J Appl Lab Med. 2020 Mar 1; 5(2):363-9.
10. Gutierrez G, Williams JD. The riddle of hyperlactatemia. Crit Care. 2009;13(4):176. doi: 10.1186/cc7982. Epub 2009 Aug 12. PMID: 19691816; PMCID: PMC2750179.
11. Saudubray JM, Rabier D. Biomarkers identified in inborn errors for lysine, arginine and ornithine. J Nutr 2007; 137:1669S-72S.
12. Pasquali M, Monsen G, Richardson L, et al. Biochemical findings in common inborn errors of metabolism. Am J Med Genet C Semin Med Genet 2006; 142C:64-76.
13. Douillard C, Mention K, Dobbelaere D, Wemeau JL, Saudubray JM, Vantyghem MC. Hypoglycaemia related to inherited metabolic diseases in adults. Orphanet J Rare Dis 2012; 7:26.
14. Ogier de BH. Management and emergency treatments of neonates with a suspicion of inborn errors of metabolism. Semin Neonatol 2002; 7:17-26.
15. Vockley J, Singh RH, Whiteman DA. Diagnosis and management of defects of mitochondrial beta-oxidation. Curr Opin Clin Nutr Metab Care 2002; 5:601-9.
16. Wüst RC, Visser G, Wanders RJ, Houtkooper RH. Ketones and inborn errors of metabolism: old friends revisited. J Inherit Metab Dis 2017; 40:3-4.
17. Vaidyanathan K, Narayanan MP, Vasudevan DM. Organic acidurias: an updated review. Indian J Clin Biochem 2011; 26:319-25.
18. Forny P, Horster F, Ballhausen D, Chakrapani A, Chapman KA, Dionisi-Vici C, et al. Guidelines for the diagnosis and management of methylmalonic acidemia and propionic acidemia: first revision. J Inherit Metab Dis. 2021; 44: 566-592.
19. Pinto A, Daly E, Evans S, Almeida MF, Assoun M, Belanger-Quintana A, et al. Dietary practices in Isovaleric acidemia: a European survey. Mol Genet Metab Rep. 2017; 12: 16-22.
20. Kubota Y, Asakura K, Suzuki K. Hyperuricemia in Children and Adolescents: Present Knowledge and Future Directions. J Nutr Metab. 2019;2019:3480718. doi:10.1155/2019/3480718.
21. Yasha N, Suryawanshi N, Warbhe R, et al. Familial Hypercholesterolemia: A Literature Review of the Pathophysiology and Current and Novel Treatments. Cureus. 2023 Nov 20;15(11):e49121
22. Ertugrul G, Yankol Y, Mecit N, Kirimlioglu H, Kanmaz T, Acarli K, et al. Liver Transplant and Improvements in Cholesterol Biosynthesis Defects: A Case Report of SmithLemliOpitz Syndrome. Exp Clin Transplant, 2022 Jan; 20(1):104-107
23. Bozacý AE, Demirbaþ Ar F, Tekmenuray Ünal A, Taþ Ý, Bilgin H. The role of inborn errors of metabolism in the etiology of neonatal cholestasis: A single center experience. Trends in Pediatrics. 2023; 4(3):161172. DOI: 10.59213/TP.2023.38258
24. Jones PM, Bennett MJ. The changing face of new born screening: diagnosis of inborn errors of metabolism by tandem mass spectrometry. Clin Chim Acta 324 (2002) 121-128.
25. Villani GR, Gallo G, Scolamiero E, Salvatore F, Ruoppolo M. "Classical organic acidurias": diagnosis and pathogenesis. Clin Exp Med. 2017; 17(3):305-23.
26. Frank MP, Powers RW. Simple and rapid quantitative high-performance liquid chromatographic analysis of plasma amino acids. J Chromatogr B Analyt Technol Biomed Life Sci. 2007 Jun 1; 852(1-2):646-9.
27. Hoffmann GF, Kolker S. Defects in amino acid catabolism and the urea cycle. Handb Clin Neurol 113(2013)1755-1773
28. Vernon HJ. Inborn Errors of Metabolism - Advances in Diagnosis and Therapy. JAMA Pediatrics. June 2015
29. Froissart R, Piraud M, Boudjemline AM, Ianey-Saban C, Petit F, Hubert-Buron A, et al. Glucose-6- Phosphatase Deficiency. Orphaned J Rare Dis. 20(2011)27.
30. Lee H, Deignan JL, Dorrani N, Strom SP, Kantarci S, Quintero-Rivera F, et al. Clinical exome sequencing for genetic identification of rare mendelian disorders. JAMA, 2014; 312 (18): 1880-1887.
31. Yang Y, Munzy DM, Xia F, Goldstein BA, Bernstein JA, Chaib H, et al. Molecular findings among patients referred for clinical whole - exome sequencing. JAMA. 2014; 312(18): 1870-1879.
32. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol, 2014; 76(4): 473-483.
33. Dewey FE, Grove ME, Pan C, Goldstein BA, Bernstein JA, Chaib H, et al. Clinical interpretation and implications of whole genome sequencing. JAMA. 2014; 311(10):1035-1045.
34. Waikar SS, Sabbisetti VS, Bonventre JV. Normalization of urinary biomarkers to creatinine during changes in glomerular filtration rate. Kidney Int. 2010 Sep; 78(5): 486-94.
35. Singh S, Rawat A, Aggarwal J. Cerebrospinal fluid (CSF) analysis and role in clinical neurology. Int J Clin Biochem Res. 2021; 8(2):73-78.

INBORN ERRORS OF METABOLISM - I

GENETIC TESTING IN INBORN ERRORS OF METABOLISM

***Sankar VH**
****Vinitha AO**

Abstract: *Inherited metabolic disorders are a diverse group of genetic disorders that result from disrupted metabolic pathways in the body. Early identification of these disorders is of foremost importance to provide appropriate treatment in time to prevent progression of the disease. Genetic testing panels which include, targeted gene panels, whole exome sequencing and whole genome sequencing help in identifying both pathogenic or likely pathogenic variants, to make a precise molecular diagnosis. A comprehensive combination of clinical and preliminary biochemical evaluations and genetic testing enhances diagnostic accuracy and guides specific interventions. Further, confirming the genetic condition facilitates family screening and genetic counselling. This article highlights the impact of genetic testing on making a definitive diagnosis and helps in managing inherited metabolic disorders.*

Keywords: *Metabolic disorder, Genetic testing, Whole exome sequencing, Whole genome sequencing, Genetic counselling*

* Professor and Head,
Department of Medical Genetics
email : sankarvh@gmail.com

** Assistant Professor of Pediatrics,
SAT Hospital,
Government Medical College, Thiruvananthapuram.

Points to Remember

- ***Inherited metabolic disorders are primarily monogenic conditions, most of which follow an autosomal recessive inheritance pattern.***
- ***Genetic testing plays a crucial role in confirmation of diagnosis, and helps in understanding the disease progression as well as in guiding specific therapies.***
- ***A solid understanding of the genetic mechanisms is essential for selecting the appropriate tests in individual conditions since, several tests are available for diagnosis including Sanger sequencing, next generation sequencing (gene panels, WES, WGS) and MLPA.***
- ***Variants identified in genetic testing are classified into five categories: Pathogenic, likely pathogenic, benign, likely benign and variant of unknown significance. Accurate interpretation of these results requires correlation with the patient's clinical phenotype and metabolic findings.***
- ***Genetic counselling is essential before and after testing. It helps in predicting recurrence risk and facilitates family screening.***

References

1. Shchelochkov OA, Venditti C P. An approach to inborn errors of metabolism. In: Kliegman RM, St. Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM, editors. Nelson Textbook of Pediatrics. 22nd ed. Philadelphia (PA): Elsevier, 2024; pp 803-806.
2. Gospe SM Jr. Pyridoxine-dependent epilepsy - ALDH7A1 [Internet]. In: Adam MP, Feldman J, Mirzaa GM, et al. editors. Gene Reviews®. Seattle (WA): University of Washington, Seattle; 1993-2025 [updated 2022 Sep 22]. Available from: https://www.ncbi.nlm.nih.gov/books.
3. Oder D, Liu D, Hu K, Üçeyler N, Salinger T, Müntze J, et al. α-Galactosidase A genotype N215S induces a specific cardiac variant of Fabry disease. Circ. Cardiovasc. Genet. 2017 Oct; 10(5): e001691.

Cite as: Sankar VH, Vinitha AO. Genetic testing in inborn errors of metabolism, Indian J Pract Pediatr. 2025; 27(3): 218-226.

4. Eren K, Taktakoðlu N, Pirim I. DNA sequencing methods: from past to present. Eurasian J Med. 2022 Dec; 54(Suppl1):47-56. doi: 10.5152/eurasianjmed. 2022.22280. PMID: 36655445; PMCID: PMC11163357.
5. Huang WJ, Zhang X, Chen WW. Gaucher disease: a lysosomal neurodegenerative disorder. Eur Rev Med Pharmacol Sci. 2015 Apr 1; 19(7):1219-1226.
6. Qin D. Next-generation sequencing and its clinical application. Cancer Biol Med 2019. Feb; 16(1) :4-10. doi: 10.20892/j.issn.2095-3941.2018.0055. PMID: 31119042; PMCID: PMC6528456.
7. Yohe S, Thyagarajan B; Review of clinical next-generation sequencing. Arch Pathol Lab Med.2017 Nov 1; 141 (11): 1544-1557. doi: 10.5858/arpa.2016-0501-RA. Epub 2017 Aug 7. PMID 28782984.
8. Ko A, Youn SE, Kim SH, Lee JS, Kim S, Choi JR, et al. Targeted gene panel and genotype-phenotype correlation in children with developmental and epileptic encephalopathy. Epilepsy Res. 2018;141:48-55. doi:10.1016/j.eplepsyres.2018.02.003.
9. Grody WW, Deignan JL. Diagnostic molecular genetics. In: Rimoin DL, Pyeritz RE, Korf BR, editors. Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics. 7th ed. London: Academic Press; 2020. Chapter 6, p 449 - 453.
10. Stuppia L, Antonucci I, Palka G, Gatta V. Use of the MLPA assay in the molecular diagnosis of gene copy number alterations in human genetic diseases. Int J Mol Sci. 2012;13(3):3245-3276. doi: 10.3390/ijms13033245. Epub 2012 Mar 8. PMID: 22489151; PMCID: PMC3317712.
11. Jahic A, Günther S, Muschol N, Fossøy Stadheim B, Braaten Ø, Kjensli Hyldebrandt H, Kuiper GA, Tylee K, Wijburg FA, Beetz C. "Missing mutations" in MPS I: Identification of two novel copy number variations by an IDUA-specific in house MLPA assay. Mol Genet Genomic Med. 2019 Sep; 7(9):e00615. doi: 10.1002/mgg3.615. Epub 2019 Jul 18. PMID: 31319022; PMCID: PMC6732313.
12. Madry J, Hoffman-Zacharska D, Królicki L, Jakuciñski M, Friedman A. PLP1 gene duplication as a cause of the classic form of Pelizaeus-Merzbacher disease - case report. Neurol Neurochir Pol. 2010 Sep-Oct; 44(5):511-5. doi: 10.1016/s0028-3843(14) 60142-0. PMID: 21082496.
13. Touati G, Mochel F, Rabier D. Diagnostic procedures In: Saudubray JM, Baumgartner MR, Walter J, editors. Inborn Metabolic Diseases: Diagnosis and Treatment. 7th ed. Berlin: Springer; 2022;pp 92-107.
14. He M, Gibson KM. Biochemical studies. In: Hoffmann GF, Nyhan WL, editors. Inherited metabolic diseases: a clinical approach. 2nd ed. Oxford: Oxford University Press; 2017. 2022; pp439-460.
15. Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, et al. Sequence and organization of the human mitochondrial genome. Nature. 1981; 290: 457-65.
16. Mavraki E, Labrum R, Sergeant K, Alston CL, Woodward C, Smith C, et al. Genetic testing for mitochondrial disease: the United Kingdom best practice guidelines. Eur. J. Hum. Genet. 2023 Feb 1; 31(2):148-63.
17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May; 17(5):405-424. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID:25741868; PMCID: PMC4544753.

INBORN ERRORS OF METABOLISM - I

RECOGNISING TREATABLE INBORN ERRORS OF METABOLISM IN CHILDREN WITH DEVELOPMENTAL DELAY, AUTISM, EPILEPSY, MOVEMENT DISORDER OR CEREBRAL PALSY MIMICS

***Umamaheswari Balakrishnan**
****Rabindran Chandran**

Abstract: *Inborn errors of metabolism may present with neurological dysfunctions like developmental delay, autism, epilepsy and movement disorders. Due to overlapping clinical features and non-specific systemic features, these conditions may be missed leading to delayed diagnosis, treatment and poor outcomes. Advances in expanded newborn screening methodology, biochemical diagnostics and genomic sequencing help in precise diagnosis of these treatable inborn errors of metabolism. Many inborn errors of metabolism can be treated with dietary modifications, cofactor supplementation, enzyme replacement, organ transplantation and supportive measures. Early appropriate treatment results in better developmental outcomes. This review proposes a practical diagnostic approach to identify metabolic red flags and provides an evidence-based summary of therapeutic strategies.*

Keywords: *Treatable inborn errors of metabolism, Developmental delay, Autism, Epilepsy, Movement disorders, Cerebral palsy mimic.*

* Professor and Head of Neonatology
email: drumarajakumar@gmail.com

** Assistant Professor of Neonatology
Sri Ramachandra Medical College and Research Institute, Chennai

Points to Remember

- ***Treatable inborn errors of metabolism often masquerade as common neurodevelopmental disorders, leading to missed diagnostic opportunities.***
- ***Clinical red flags-such as developmental regression, episodic encephalopathy, refractory seizures or multisystem involvement-should prompt metabolic evaluation.***
- ***A tiered biochemical workup with genetic testing provides a cost-effective strategy in most clinical settings.***
- ***Early treatments like dietary therapy, cofactor supplementation and targeted metabolic treatments can improve outcomes.***

Note : Readers are requested to refer to standard text books for abbreviation - expansion (of metabolic disorders).

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References

1. Saudubray JM, Cazorla AG. Clinical approach to inborn errors of metabolism in pediatrics. In: Saudubray JM, Baumgartner MR, Walter J, editors. Inborn Metabolic Diseases - Diagnosis and Treatment. Springer.Germany 2016; pp3-70.
2. Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, et al., NDD Exome Scoping Review Work Group. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019 Nov; 21(11):2413-2421.

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doi: 10.1038/s41436-019-0554-6. Epub 2019 Jun 11. Erratum in: Genet Med. 2020 Oct; 22(10):1731-1732. doi: 10.1038/s41436-020-0913-3. PMID: 31182824; PMCID: PMC6831729.

3. Choudhry S, Khan M, Rao HA, Jalan A, Khan EA. Etiology and outcome of inborn errors of metabolism. J Pak Med Assoc. 2013 63(9):1112-6. PMID: 24601187.
4. Horvath GA, Blau N, Ferreira CR. Clinical and biochemical footprints of inherited metabolic disease. V. Cerebral palsy phenotypes. Mol Genet Metab. 2022; 137(4):445-448. doi: 10.1016/j.ymgme.2021.03.008.
5. Leach EL, Shevell M, Bowden K, Stockler-Ipsiroglu S, van Karnebeek CD. Treatable inborn errors of metabolism presenting as cerebral palsy mimics: systematic literature review. Orphanet J Rare Dis. 2014; 9:197. doi: 10.1186/s13023-014-0197-2.
6. Friedman JM, van Essen P, van Karnebeek CDM. Cerebral palsy and related neuromotor disorders: Overview of genetic and genomic studies. Mol Genet Metab. 2022; 137(4):399-419. doi: 10.1016/j.ymgme. 2021.11.001.
7. Hoytema van Konijnenburg EMM, Wortmann SB, Koelewijn M, Tseng LA, Houben R, et al. Treatable inherited metabolic disorders causing intellectual disability: 2021 review and digital app. Orphanet J Rare Dis 16, 170 (2021). https://doi.org/10.1186/s13023-021-01727-2.
8. den Hollander B, Hoytema van Konijnenburg EMM, Hewitson B, van der Meijden JC, Balfoort BM, Winter B, et al. The Metabolic Treatabolome and Inborn Errors of Metabolism Knowledgebase therapy tool: Do not miss the opportunity to treat! J Inherit Metab Dis. 2025 Jan;48(1):e12835. doi: 10.1002/jimd.12835. PMID: 39777714; PMCID: PMC11707409.
9. Therrell BL, Padilla CD, Borrajo GJC, Khneisser I, Schielen PCJI, Knight-Madden J, et al. Current Status of Newborn Bloodspot Screening Worldwide 2024: A Comprehensive Review of Recent Activities (2020-2023). Int J Neonatal Screen. 2024 May 23; 10(2):38. doi: 10.3390/ijns10020038.
10. •igman T, Petkoviæ Ramad•a D, Šimiæ G, Bariæ I. Inborn Errors of Metabolism Associated With Autism Spectrum Disorders: Approaches to Intervention. Front Neurosci. 2021 May 28; 15:673600. doi: 10.3389/fnins. 2021.673600.
11. Sharma S, Prasad AN. Inborn Errors of Metabolism and Epilepsy: Current Understanding, Diagnosis, and Treatment Approaches. Int J Mol Sci. 2017 Jul 2;18(7): 1384. doi: 10.3390/ijms18071384.
12. Lipiñski P. Autism spectrum disorder and inherited metabolic diseases: are there any common features?. Pediatr Endocrinol Diabetes Metab. 2025; 31(1):30-34. doi:10.5114/pedm.2025.148397
13. Takezawa Y, Kikuchi A, Haginoya K, Niihori T, Numata-Uematsu Y, Inui T,et al . Genomic analysis identifies masqueraders of full-term cerebral palsy. Ann Clin Transl Neurol. 2018 Mar 26;5(5):538-551. doi: 10.1002/ acn3.551. PMID: 29761117; PMCID: PMC5945967.
14. van Eyk CL, Webber DL, Minoche AE, Pérez-Jurado LA, Corbett MA, Gardner AE, Berry JG, Harper K, MacLennan AH, Gecz J. Yield of clinically reportable genetic variants in unselected cerebral palsy by whole genome sequencing. NPJ Genom Med. 2021 Sep 16; 6(1):74. doi: 10.1038/s41525-021-00238-0
15. Saini AG, Sharma S. Movement Disorders in Inherited Metabolic Diseases in Children. Ann Indian Acad Neurol. 2020 May-Jun; 23(3):332-337. doi: 10.4103/aian. AIAN_ 612_19.
16. Koens LH, Klamer MR, Sival DA, Balint B, Bhatia KP, Contarino MF,et al. A Screening Tool to Quickly Identify Movement Disorders in Patients with Inborn Errors of Metabolism. Mov Disord. 2023 Apr; 38(4):646-653. doi: 10.1002/mds.29332.
17. Ortigoza-Escobar JD. A proposed diagnostic algorithm for inborn errors of metabolism presenting with movement disorders. Front Neurol.2020; 11:582160.
18. Schulze A, Bauman M, Tsai AC, Reynolds A, Roberts W, Anagnostou E,et al. Prevalence of Creatine Deficiency Syndromes in Children With Nonsyndromic Autism. Pediatrics. 2016 Jan; 137(1). doi: 10.1542/peds. 2015-2672.
19. Ýnci A, Özaslan A, Okur Ý, Biberoðlu G, Güney E, et al. Autism: Screening of inborn errors of metabolism and unexpected results. Autism Res 2021; 14: 887-896. doi: 10.1002/aur.2486.
20. Falsaperla R, Sciuto L, La Spina L, Sciuto S, Praticò AD, Ruggieri M. Neonatal seizures as onset of Inborn Errors of Metabolism (IEMs): from diagnosis to treatment. A systematic review. Metab Brain Dis. 2021 Dec;36(8): 2195-2203. doi: 10.1007/s11011-021-00798-1.
21. Rahman S, Footitt EJ, Varadkar S, Clayton PT. Inborn errors of metabolism causing epilepsy. Dev Med Child Neurol. 2013; 55(1):23-36. doi: 10.1111/j.1469-8749. 2012.04406.x.
22. Ismayilova N, Leung MA, Kumar R, Smith M, Williams RE. Ketogenic diet therapy in infants less than two years of age for medically refractory epilepsy. Seizure. 2018 Apr; 57:5-7. doi: 10.1016/j.seizure. 2018.02.014. Epub 2018 Mar 2. PMID: 29524777.
23. Brimble E, Ruzhnikov MRZ. Metabolic Disorders Presenting with Seizures in the Neonatal Period. Semin Neurol. 2020 Apr; 40(2):219-235. doi: 10.1055/s-0040-1705119. Epub 2020 Mar 17. PMID: 32185789.
24. Balakrishnan U. Inborn Errors of Metabolism-Approach to Diagnosis and Management in Neonates. Indian J Pediatr. 2021 Jul; 88(7):679-689. doi: 10.1007/s12098-021-03759-9.

25. Tusié-Luna MT, Aguilar-Salinas CA. Precision medicine for metabolic disorders in low and middle-income countries: areas of opportunity and challenges for the future. Rev Invest Clin. 2021; 73(5):316-320. doi: 10.24875/RIC.21000344.
26. Zhou M, Deng L, Huang Y, Xiao Y, Wen J, et al. Application of the Artificial Intelligence Algorithm Model for Screening of Inborn Errors of Metabolism. Front Pediatr. 2022; 10:855943.
27. Mani Urmila N, Kewalramani D, Balakrishnan U, Manokaran RK. A case of carbonic anhydrase type VA deficiency presenting as West syndrome in an infant with a novel mutation in the CA-VA gene. Epilepsy Behav Rep. 2022; 20:100573. doi: 10.1016/j.ebr.2022.100573.

INBORN ERRORS OF METABOLISM - I

GLYCOGEN STORAGE DISORDERS - DIAGNOSTIC APPROACH, MANAGEMENT AND RECENT ADVANCES

***Rajkali Rajendiran**
***Jagadeesh Menon**
****Naresh Shanmugam**

Abstract: *Glycogen storage disorders are a group of heterogeneous inherited enzymopathies affecting glycogen metabolism, primarily in the liver and muscle. The clinical spectrum ranges from severe neonatal hypoglycemia to late-onset liver, muscle and cardiac disease. Advances in molecular genetics, including newborn screening, enable earlier and more precise diagnosis and improved genotype-phenotype correlations. Metabolic profiles (e.g. hypoglycemia with ketosis, lactic acidosis) and genetic testing guide diagnosis. Management has traditionally been primarily dietary (frequent feeding, uncooked cornstarch), but therapeutic options have now expanded considerably. Enzyme replacement (e.g. acid alpha-glucosidase for Pompe disease) and novel small-molecule or substrate-based therapies improve disease control. Emerging gene therapies and targeted agents (e.g. SGLT2 inhibitors in GSD-Ib) are transforming care. Supportive care, transplantation and emerging therapies ensure better long-term outcomes in patients with glycogen storage disorders.*

* Consultant (Associate)
Department of Pediatric Gastroenterology,
Hepatology and Transplantation,
Dr Rela Institute and Medical Centre, Chennai

** Director - Woman and Child Health,
Consultant Pediatric Hepatologist and
Gastroenterologist,
Institute of Advanced Pediatrics
Dr Rela Institute and Medical Centre, Chennai
email: drnareshps@gmail.com

Keywords: *Glycogen storage disorder, Diagnosis, Enzyme replacement, Gene therapy, SGLT2 inhibitor, Newborn screening.*

Points to Remember

- ***GSDs are a heterogeneous group of inherited disorders affecting glycogen metabolism. The organs involved primarily are liver and muscle, however, the metabolic effect is seen in multiple systems of the body.***
- ***Hepatic forms cause fasting intolerance, hypoglycemia, hepatomegaly and growth failure; muscular forms cause exercise intolerance, cramps, rhabdomyolysis; whereas multisystemic forms (e.g., Pompe) carry cardiac and respiratory morbidity.***
- ***Advances in molecular genetics allow precise genotype-phenotype correlation, serving as the gold standard for the diagnosis of most GSDs. Biopsy is less often needed.***
- ***Core strategies for management include frequent feeds, avoidance of fasting, dietetic modification with consumption of uncooked cornstarch for sustained glucose release, high-protein diets for gluconeogenesis and complication targeted care.***
- ***Therapeutic advances include enzyme replacement therapy (ERT) for Pompe disease, novel pharmacologic options like empagliflozin for neutropenia in GSD-Ib and experimental strategies like recombinant adeno-associated viral vector (rAAV)-mediated gene therapy, genome editing, autophagy activators and glycogen synthase inhibitors.***
- ***Early diagnosis and metabolic control prevent acute crises and long-term complications such as hepatic adenomas/carcinoma, hepatic failure, renal disease, myopathy and cardiomyopathy.***

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References

1. Orho M, Bosshard NU, Buist NR, Gitzelmann R, Aynsley-Green A, Blümel P, et al. Mutations in the liver glycogen synthase gene in children with hypoglycemia due to glycogen storage disease type 0. J Clin Invest. 1998 Aug 1;102(3):507-15.
2. Hicks J, Wartchow E, Mierau G. Glycogen storage diseases: a brief review and update on clinical features, genetic abnormalities, pathologic features, and treatment. Ultrastruct Pathol. 2011 Oct; 35(5):183-96.
3. Laberge AM, Mitchell GA, van de Werve G, Lambert M. Long-term follow-up of a new case of liver glycogen synthase deficiency. Am J Med Genet A. 2003 Jul 1;120A(1):19-22.
4. Kollberg G, Tulinius M, Gilljam T, Ostman-Smith I, Forsander G, Jotorp P, et al. Cardiomyopathy and exercise intolerance in muscle glycogen storage disease 0. N Engl J Med. 2007 Oct 11; 357(15):1507-14.
5. Roach PJ, Depaoli-Roach AA, Hurley TD, Tagliabracci VS. Glycogen and its metabolism: some new developments and old themes. Biochem J. 2012 Feb 1; 441(3):763-87.
6. Bachrach BE, Weinstein DA, Orho-Melander M, Burgess A, Wolfsdorf JI. Glycogen synthase deficiency (glycogen storage disease type 0) presenting with hyperglycemia and glucosuria: report of three new mutations. J Pediatr. 2002 Jun;140(6):781-3.
7. Tagliaferri F, Massese M, Russo L, Commone A, Gasperini S, Pretese R, et al. Hepatic glycogen storage diseases type 0, VI and IX: description of an italian cohort. Orphanet J Rare Dis. 2022 Jul 19; 17(1):285.
8. Ekstein J, Rubin BY, Anderson SL, Weinstein DA, Bach G, Abeliovich D, et al. Mutation frequencies for glycogen storage disease Ia in the Ashkenazi Jewish population. Am J Med Genet A. 2004 Aug 30;129A(2): 162-4.
9. Chou JY, Jun HS, Mansfield BC. Type I glycogen storage diseases: disorders of the glucose-6-phosphatase/ glucose-6-phosphate transporter complexes. J Inherit Metab Dis. 2015 May; 38(3):511-9.
10. Gümüº E, Özen H. Glycogen storage diseases: An update. World J Gastroenterol. 2023 Jul 7;29(25):3932-63.
11. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GPA. Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type I (ESGSD I). Eur J Pediatr. 2002 Oct;161 Suppl 1:S20-34.
12. Derks TGJ, Rodriguez-Buritica DF, Ahmad A, de Boer F, Couce ML, Grünert SC, et al. Glycogen Storage Disease Type Ia: Current Management Options, Burden and Unmet Needs. Nutrients. 2021 Oct 27; 13(11):3828.
13. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. Genet Med Off J Am Coll Med Genet. 2014 Nov; 16(11):e1.
14. Visser G, Rake JP, Fernandes J, Labrune P, Leonard JV, Moses S, et al. Neutropenia, neutrophil dysfunction and inflammatory bowel disease in glycogen storage disease type Ib: results of the European Study on Glycogen Storage Disease type I. J Pediatr. 2000 Aug; 137(2):187-91.
15. Bali DS, El-Gharbawy A, Austin S, Pendyal S, Kishnani PS. Glycogen Storage Disease Type I. 2006 Apr 19 [updated 2021 Oct 14]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. PMID: 20301489.
16. Visser G, Rake JP, Labrune P, Leonard JV, Moses S, Ullrich K, et al. Granulocyte colony-stimulating factor in glycogen storage disease type 1b. Results of the European Study on Glycogen Storage Disease Type 1. Eur J Pediatr. 2002 Oct;161 Suppl 1:S83-87.
17. Menon J, Vij M, Sachan D, Rammohan A, Shanmugam N, Kaliamoorthy I, et al. Pediatric metabolic liver diseases: Evolving role of liver transplantation. World J Transplant. 2021 Jun 18; 11(6):161-79.
18. Kasahara M, Horikawa R, Sakamoto S, Shigeta T, Tanaka H, Fukuda A, et al. Living donor liver transplantation for glycogen storage disease type Ib. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2009 Dec;15(12):1867-71.
19. Wortmann SB, Van Hove JLK, Derks TGJ, Chevalier N, Knight V, Koller A, et al. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. Blood. 2020 Aug 27;136(9):1033–43.
20. Makrilakis K, Barmpagianni A, Veiga-da-Cunha M. Repurposing of Empagliflozin as a Possible Treatment for Neutropenia and Inflammatory Bowel Disease in Glycogen Storage Disease Type Ib: A Case Report. Cureus. 2022 Jul; 14(7):e27264.
21. Shimizu S, Sakamoto S, Horikawa R, Fukuda A, Uchida H, Takeda M, Yanagi Y, Irie R, Yoshioka T, Kasahara M. Longterm Outcomes of Living Donor Liver Transplantation for Glycogen Storage Disease Type 1b. Liver Transpl. 2020 Jan; 26(1):57-67. doi: 10.1002/ lt.25649. Epub 2019 Nov 26. PMID: 31587472.22.
22. Talente GM, Coleman RA, Alter C, Baker L, Brown BI, Cannon RA, et al. Glycogen storage disease in adults. Ann Intern Med. 1994 Feb 1; 120(3):218-26.
23. Derks TGJ, van Rijn M. Lipids in hepatic glycogen storage diseases: pathophysiology, monitoring of dietary management and future directions. J Inherit Metab Dis. 2015; 38(3):537-43.

24. Bao Y, Dawson TL, Chen YT. Human glycogen debranching enzyme gene (AGL): complete structural organization and characterization of the 5' flanking region. Genomics. 1996 Dec 1;38(2):155–65.
25. Demo E, Frush D, Gottfried M, Koepke J, Boney A, Bali D, et al. Glycogen storage disease type III-hepatocellular carcinoma a long-term complication? J Hepatol. 2007 Mar; 46(3):492-8.
26. Coleman RA, Winter HS, Wolf B, Chen YT. Glycogen debranching enzyme deficiency: long-term study of serum enzyme activities and clinical features. J Inherit Metab Dis. 1992; 15(6):869-81.
27. Vertilus SM, Austin SL, Foster KS, Boyette KE, Bali DS, Li JS, et al. Echocardiographic manifestations of Glycogen Storage Disease III: increase in wall thickness and left ventricular mass over time. Genet Med Off J Am Coll Med Genet. 2010 Jul;12(7):413-23.
28. Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, et al. Glycogen storage disease type III diagnosis and management guidelines. Genet Med Off J Am Coll Med Genet. 2010 Jul; 12(7):446–63.
29. Ross KM, Brown LM, Corrado MM, Chengsupanimit T, Curry LM, Ferrecchia IA, et al. Safety and Efficacy of Chronic Extended Release Cornstarch Therapy for Glycogen Storage Disease Type I. JIMD Rep. 2016; 26:85-90.
30. Davis MK, Weinstein DA. Liver transplantation in children with glycogen storage disease: controversies and evaluation of the risk/benefit of this procedure. Pediatr Transplant. 2008 Mar; 12(2):137-45.
31. Rossiaud L, Miagoux Q, Benabides M, Reiss O, Jauze L, Jarrige M, et al. Galectin-3: a novel biomarker of glycogen storage disease type III. Cell Death Discov. 2025 Apr 14; 11(1):173.
32. Derks TGJ, Peeks F, de Boer F, Fokkert-Wilts M, van der Doef HPJ, van den Heuvel MC, et al. The potential of dietary treatment in patients with glycogen storage disease type IV. J Inherit Metab Dis. 2021 May; 44(3):693-704.
33. Andersen DH. Familial cirrhosis of the liver with storage of abnormal glycogen. Lab Investig J Tech Methods Pathol. 1956; 5(1):11-20.
34. Greene HL, Brown BI, McClenathan DT, Agostini RM, Taylor SR. A new variant of type IV glycogenosis: deficiency of branching enzyme activity without apparent progressive liver disease. Hepatol Baltim Md. 1988;8(2): 302-6.
35. Akman HO, Karadimas C, Gyftodimou Y, Grigoriadou M, Kokotas H, Konstantinidou A, et al. Prenatal diagnosis of glycogen storage disease type IV. Prenat Diagn. 2006 Oct; 26(10):951-5.
36. Shin YS, Steigüber H, Klemm P, Endres W, Schwab O, Wolff G. Branching enzyme in erythrocytes. Detection of type IV glycogenosis homozygotes and heterozygotes. J Inherit Metab Dis. 1988; 11 Suppl 2:252-4.
37. Ferguson IT, Mahon M, Cumming WJ. An adult case of Andersen's disease-Type IV glycogenosis. A clinical, histochemical, ultrastructural and biochemical study. J Neurol Sci. 1983; 60(3):337-51.
38. Li SC, Chen CM, Goldstein JL, Wu JY, Lemyre E, Burrow TA, et al. Glycogen storage disease type IV: novel mutations and molecular characterization of a heterogeneous disorder. J Inherit Metab Dis. 2010 Dec; 33 Suppl 3:S83-90.
39. Goldberg T, Slonim AE. Nutrition therapy for hepatic glycogen storage diseases. J Am Diet Assoc. 1993 Dec; 93(12):1423-30.
40. Liu M, Sun LY. Liver Transplantation for Glycogen Storage Disease Type IV. Front Pediatr. 2021; 9:633822.
41. Kakhlon O, Ferreira I, Solmesky LJ, Khazanov N, Lossos A, Alvarez R, et al. Guaiacol as a drug candidate for treating adult polyglucosan body disease. JCI Insight. 2018 Sep 6; 3(17):e99694, 99694.
42. Kakhlon O, Vaknin H, Mishra K, D'Souza J, Marisat M, Sprecher U, et al. Alleviation of a polyglucosan storage disorder by enhancement of autophagic glycogen catabolism. EMBO Mol Med. 2021 Oct 7;13(10): e14554.
43. Newgard CB, Fletterick RJ, Anderson LA, Lebo RV. The polymorphic locus for glycogen storage disease VI (liver glycogen phosphorylase) maps to chromosome 14. Am J Hum Genet. 1987 Apr; 40(4):351–64.
44. Grünert SC, Hannibal L, Spiekerkoetter U. The Phenotypic and Genetic Spectrum of Glycogen Storage Disease Type VI. Genes. 2021 Aug 3;12(8):1205.
45. HERS HG. Etudes enzymatiques sur fragments hépatiques; application à la classification des glycogénoses [Enzymatic studies of hepatic fragments; application to the classification of glycogenoses]. Rev Int Hepatol. 1959; 9(1):35-55. French. PMID: 13646331.
46. Manzia TM, Angelico R, Toti L, Cillis A, Ciano P, Orlando G, et al. Glycogen storage disease type Ia and VI associated with hepatocellular carcinoma: two case reports. Transplant Proc. 2011 May; 43(4):1181-3.
47. Wolfsdorf JI, Weinstein DA. Glycogen storage diseases. Rev Endocr Metab Disord. 2003 Mar; 4(1):95-102.
48. Burwinkel B, Amat L, Gray RG, Matsuo N, Muroya K, Narisawa K, et al. Variability of biochemical and clinical phenotype in X-linked liver glycogenosis with mutations in the phosphorylase kinase PHKA2 gene. Hum Genet. 1998 Apr;102(4):423-9.
49. Roscher A, Patel J, Hewson S, Nagy L, Feigenbaum A, Kronick J, et al. The natural history of glycogen storage disease types VI and IX: Long-term outcome from the largest metabolic center in Canada. Mol Genet Metab. 2014 Nov; 113(3):171-6.

50. Burwinkel B, Shiomi S, Al Zaben A, Kilimann MW. Liver glycogenosis due to phosphorylase kinase deficiency: PHKG2 gene structure and mutations associated with cirrhosis. Hum Mol Genet. 1998 Jan;7(1):149-54.
51. Willems PJ, Gerver WJ, Berger R, Fernandes J. The natural history of liver glycogenosis due to phosphorylase kinase deficiency: a longitudinal study of 41 patients. Eur J Pediatr. 1990 Jan;149(4):268-71.
52. Manz F, Bickel H, Brodehl J, Feist D, Gellissen K, Geschöll-Bauer B, et al. Fanconi-Bickel syndrome. Pediatr Nephrol Berl Ger. 1987 Jul; 1(3):509-18.
53. Saltik-Temizel IN, Coºkun T, Yüce A, Koçak N. Fanconi-Bickel syndrome in three Turkish patients with different homozygous mutations. Turk J Pediatr. 2005; 47(2): 167-9.
54. Lee PJ, Van't Hoff WG, Leonard JV. Catch-up growth in Fanconi-Bickel syndrome with uncooked cornstarch. J Inherit Metab Dis. 1995;18(2):153–6.
55. Gümüs E, Özen H. Glycogen storage diseases: An update. World J Gastroenterol. 2023 Jul 7; 29(25):3932–63.
56. Sperry E, Leslie N, Berry L, Pena L. Pompe Disease. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2025 Sep 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1261/
57. Amalfitano A, Bengur AR, Morse RP, Majure JM, Case LE, Veerling DL, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. Genet Med Off J Am Coll Med Genet. 2001; 3(2):132-8.
58. Dhillon S. Avalglucosidase alfa: First Approval. Drugs. 2021 Oct; 81(15):1803-9.
59. Blair HA. Cipaglucosidase Alfa: First Approval. Drugs. 2023 Jun; 83(8):739-45.
60. Zhou Z, Austin GL, Shaffer R, Armstrong DD, Gentry MS. Antibody-Mediated Enzyme Therapeutics and Applications in Glycogen Storage Diseases. Trends Mol Med. 2019 Dec; 25(12):1094-109.
61. Nascimbeni AC, Fanin M, Angelini C, Sandri M. Autophagy dysregulation in Danon disease. Cell Death Dis. 2017 Jan 19; 8(1):e2565.
62. Cenacchi G, Papa V, Pegoraro V, Marozzo R, Fanin M, Angelini C. Review: Danon disease: Review of natural history and recent advances. Neuropathol Appl Neurobiol. 2020 Jun; 46(4):303-22.
63. Komurcu-Bayrak E, Kalkan MA, Coban N, Ozsait-Selcuk B, Bayrak F. Identification of the pathogenic effects of missense variants causing PRKAG2 cardiomyopathy. Arch Biochem Biophys. 2022 Sep 30; 727:109340.
64. Lebo RV, Anderson LA, DiMauro S, Lynch E, Hwang P, Fletterick R. Rare McArdle disease locus polymorphic site on 11q13 contains CpG sequence. Hum Genet. 1990 Nov; 86(1):17-24.
65. Lucia A, Martinuzzi A, Nogales-Gadea G, Quinlivan R, Reason S, International Association for Muscle Glycogen Storage Disease study group. Clinical practice guidelines for glycogen storage disease V & VII (McArdle disease and Tarui disease) from an international study group. Neuromuscul Disord NMD. 2021 Dec; 31(12):1296-310.
66. Lam JR, Anastasopoulou C, Khattak ZE, Ashraf M. McArdle Disease (Glycogen Storage Disease Type 5). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Sep 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560785/
67. Nayab A, Alam Q, Alzahrani OR, Khan R, Sarfaraz S, Albaz AA, et al. Targeted exome sequencing identified a novel frameshift variant in the PGAM2 gene causing glycogen storage disease type X. Eur J Med Genet. 2021 Sep; 64(9):104283.
68. Santoro L, Pjetraj D, Velmishi V, Campana C, Catassi C, Dionisi-Vici C, et al. A new phenotype of aldolase a deficiency in a 14 year-old boy with epilepsy and rhabdomyolysis - case report. Ital J Pediatr. 2022 Mar 4; 48(1):39.
69. Comi GP, Fortunato F, Lucchiari S, Bordoni A, Prelle A, Jann S, et al. Beta-enolase deficiency, a new metabolic myopathy of distal glycolysis. Ann Neurol. 2001 Aug; 50(2):202-7.
70. Moslemi AR, Lindberg C, Nilsson J, Tajsharghi H, Andersson B, Oldfors A. Glycogenin-1 deficiency and inactivated priming of glycogen synthesis. N Engl J Med. 2010 Apr 1; 362(13):1203-10.

INBORN ERRORS OF METABOLISM - I

NEUROIMAGING IN INBORN ERRORS OF METABOLISM - DIAGNOSTIC PATTERN AND CLINICAL IMPLICATIONS

***Gopinathan K**
****Nikshita Jain**
*****Jyotsna**

Abstract: *Inborn errors of metabolism often produce characteristic, symmetric brain injury patterns that can be recognized on Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy. A systematic, pattern-based approach-integrating patient age, clinical evolution, and tissue predilection-enables early and accurate diagnosis. Distinct imaging signatures such as elevated N-acetylaspartate in Canavan disease or restricted diffusion in Maple syrup urine disease directly warrant urgent management and prognostication. Advances in neuroimaging now guide gene and transplant-based therapies, underscoring its pivotal role in the early recognition and treatment of paediatric neurometabolic disorders.*

Keywords: *Pediatric neuroimaging, Inborn errors of metabolism, Magnetic resonance spectroscopy, Pattern recognition.*

Points to Remember

- ***Selective vulnerability of brain structures helps to record specific images which point towards specific metabolic disorders.***
- ***Typical MRI patterns can predict certain specific white matter disorders.***
- ***Patterns do not always confirm to specific disorders, since at early stages / subclinical and burnt-out stages of the disorders, patterns are not typical on MRI.***
- ***MR Spectroscopy is useful for the confirmation of some of the metabolic disorders.***

Bibliography

1. Liserre R, Pinelli L, Gasparotti R. MR spectroscopy in pediatric neuroradiology. Transl Pediatr. 2021 Apr;10(4):1169-1200. doi: 10.21037/tp-20-445. PMID: 34012861; PMCID: PMC8107850. https://pubmed.ncbi.nlm.nih.gov/34012861/
2. Gaillard F, Knipe H, Buemi F, et al. Canavan disease. Radiopaedia.org. Accessed 24 Oct 2025. https://doi.org/10.53347/rID-1045
3. Barkovich AJ, Raybaud C. Pediatric neuroimaging. 6th ed. New York: Thieme; 2019. https://hsrc.himmelfarb.gwu.edu/books/121
4. Wolf NI, Engelen M, van der Knaap MS. MRI pattern recognition in white matter disease. Handb Clin Neurol. 2024;204:37-50. doi: 10.1016/B978-0-323-99209-1.00019-3. PMID: 39322391. https://pubmed.ncbi.nlm.nih.gov/39322391/
5. Aida N. 1H-MR spectroscopy of the early developmental brain, neonatal encephalopathies, and neurometabolic disorders. Magn Reson Med Sci. 2022 Mar 1; 21(1): 9-28. doi: 10.2463/mrms.rev.2021-0055. Epub 2021 Aug 21. PMID: 34421092; PMCID: PMC9199977. https://pubmed.ncbi.nlm.nih.gov/34421092/

* Professor of Radio Diagnosis,
Government Kilpauk Medical College and Hospital, Chennai.
email : drgopinathanmdrd@gmail.com

** Consultant Pediatric Radiologist,
BJ Wadia Children's Hospital, Mumbai

*** Consultant Radiologist,
Mithra Scans, Salem.

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6. Cornelius LP, Kannan B, Saravanan V, Venkatesan EP. Intramyelinic edema in maple syrup urine disease. Ann Indian Acad Neurol. 2014 Apr; 17(2):211-3. doi: 10.4103/0972-2327.132638. PMID: 25024577; PMCID: PMC4090852. https://pubmed.ncbi.nlm.nih.gov/25024577/
7. La Piana R, Uggetti C, Roncarolo F, Vanderver A, Olivieri I, Tonduti D, et al. Neuroradiologic patterns and novel imaging findings in Aicardi-Goutières syndrome. Neurology. 2016 Jan 5; 86(1):28-35. doi: 10.1212/WNL.0000000000002228. Epub 2015 Nov 18. PMID: 26581299; PMCID: PMC4731289. https://pubmed.ncbi.nlm.nih.gov/26581299/
8. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. Neurology. 2009 Feb 24; 72(8):750-9. doi: 10.1212/01.wnl.0000343049.00540.c8. PMID: 19237705; PMCID: PMC2677542. https://pubmed.ncbi.nlm.nih.gov/19237705/
9. Jha P, Elfeky M, Fortin F, et al. Leopard skin sign (white matter). Radiopaedia.org. Accessed 24 Oct 2025. https://doi.org/10.53347/rID-17588
10. Reis E, Coolen T, Lolli V. MRI findings in acute hyperammonemic encephalopathy: three cases of different etiologies. J Belg Soc Radiol. 2020 Jan 30;104(1):9. doi: 10.5334/jbsr.2017. PMID: 32025625; PMCID: PMC6993592. https://pubmed.ncbi.nlm.nih.gov/32025625/
11. Sehgal R, Sharma S, Sankhyan N, Kumar A, Gulati S. Selective corticospinal tract involvement in late-onset Krabbe disease. Neurology. 2011 Jul 19;77(3):e20. doi: 10.1212/WNL.0b013e318225aaf5. PMID: 21768595. https://pubmed.ncbi.nlm.nih.gov/21768595/
12. Twomey EL, Naughten ER, Donoghue VB, Ryan S. Neuroimaging findings in glutaric aciduria type 1. Pediatr Radiol. 2003 Dec;33(12):823-30. doi: 10.1007/s00247-003-0956-z. Epub 2003 Oct 8. PMID: 14534757. https://pubmed.ncbi.nlm.nih.gov/14534757/
13. Loes DJ, Hite S, Moser H, Stillman AE, Shapiro E, Lockman L, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol. 1994 Oct;15(9):1761-6. PMID: 7847225; PMCID: PMC8333737. https://pubmed.ncbi.nlm.nih.gov/7847225/
14. Bonfante E, Koenig MK, Adejumo RB, Perinjelil V, Riascos RF. The neuroimaging of Leigh syndrome: case series and review of the literature. Pediatr Radiol. 2016 Apr;46(4):443-51. doi: 10.1007/s00247-015-3523-5. Epub 2016 Jan 6. PMID: 26739140. https://pubmed.ncbi.nlm.nih.gov/26739140/
15. Kilicarslan R, Alkan A, Demirkol D, Toprak H, Sharifov R. Maple syrup urine disease: diffusion-weighted MRI findings during acute metabolic encephalopathic crisis. Jpn J Radiol. 2012 Jul; 30(6):522-5. doi: 10.1007/s11604-012-0079-2. Epub 2012 Apr 3. PMID: 22476847. https://pubmed.ncbi.nlm.nih.gov/22476847/
16. Kim JH, Lim MK, Jeon TY, Rha JH, Eo H, Yoo SY, et al. Diffusion and perfusion characteristics of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episode) in thirteen patients. Korean J Radiol. 2011 Jan-Feb;12(1):15-24. doi: 10.3348/kjr.2011.12.1.15. Epub 2011 Jan 3. Erratum in: Korean J Radiol. 2011 Mar;12(2):268. PMID: 21228936; PMCID: PMC3017880. https://pubmed.ncbi.nlm.nih.gov/21228936/
17. Takanashi J, Barkovich AJ, et al. Nonketotic hyperglycinemia: diffusion-weighted MRI pattern and glycine peak at 3.55 ppm on MR spectroscopy. AJNR Am J Neuroradiol. 2001 May; 22(5):872-7. doi: 10.3174/ajnr.A1383. PMID: 11309371. https://pubmed.ncbi.nlm.nih.gov/11309371/

DRUG PROFILE

APPLICATION OF THERAPEUTIC MONOCLONAL ANTIBODIES AND FC FUSION PROTEINS IN PEDIATRICS

Jeeson C Unni

Abstract: *The experience with the use of monoclonal antibodies and Fc fusion proteins in the pediatric age group is limited. The objective of this article is to review those factors impacting the clinical efficacy and safety of monoclonal antibodies and Fc fusion proteins in pediatric patients during drug development. Of the 68 monoclonal antibodies and Fc-fusion protein products, 20 products have approved indications in children. The number of children studied was approximately 2% to 70% of the sample size of adult studies carried out for the same indication. In general, pediatric dosing regimens were often based on body weight and weight tiered than the adult-dosing regimen. In conclusion, most monoclonal antibody and Fc-fusion protein products use weight-based dosing regimens for pediatric patients that differ from adult dosing.*

Keywords: *Pediatric dosing, Drug development, Fc-fusion proteins, Immunogenicity, Modelling and simulation, Monoclonal antibodies.*

Points to Remember

- ***Fewer studies in children as compared to adults mean that the last is not yet said regarding recommendations on drug dosing, side effects and safe use of mAb/Fc products in children.***
- ***The use of mAb/Fc products in lower-middle-income countries, including India, is low***
- ***Pediatricians need to be aware of newer mAb/Fc products licensed for use in pediatrics.***

References

1. US Food and Drug Administration. Immunogenicity Assessment for Therapeutic Protein Products. https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf. Accessed September 17, 2025.
2. US Food and Drug Administration. Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products-Developing and Validating Assays for AntiDrug Antibody Dectection. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm629728.pdf. Accessed September 17, 2025.
3. Levy G. Pharmacologic targetmediated drug disposition. Clin Pharmacol Ther. 1994; 56:248252.
4. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting targetmediated drug disposition. J Pharmacokin Pharmacodyn. 2001; 28: 507532.
5. US Food and Drug Administration. Guidance for Industry: Pediatric Rare Diseases-A Collaborative Approach for Drug Development Using Gaucher Disease as a Model. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM587660.pdf Published 2017. Accessed September 17, 2025.

* Editor-in-Chief,
IAP Drug Formulary,
Senior Lead Consultant,
Department of Pediatrics and Neonatology,
Aster Medcity, Kochi.
email : jeeson1955@gmail.com

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6. Liu XI, Dallmann A, Wang YM, Green DJ, Burnham JM, Chiang B, Wu P, Sheng M, Lu K, van den Anker JN, Burckart GJ. Monoclonal Antibodies and Fc-Fusion Proteins for Pediatric Use: Dosing, Immunogenicity, and Modeling and Simulation in Data Submitted to the US Food and Drug Administration. J Clin Pharmacol. 2019 Aug;59(8):1130-1143. doi: 10.1002/jcph.1406.
7. Bai S, Jorga K, Xin Y, Jin D, Zheng Y, Damico-Beyer LA, Gupta M, Tang M, Allison DE, Lu D, Zhang Y, Joshi A, Dresser MJ. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet. 2012 Feb 1; 51(2):119-35.
8. BNF for children 2019-20. British Medical Association, Royal Pharmaceutical Society of Great Britain, Royal College of Paediatrics and Child Health, Neonatal and Paediatric Pharmacists Group. BMJ Group, Tavistock Square, London, WC1H 9JP, UK and Pharmaceutical Press Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society. 66-68 East Smithfield, London E1W1AW, UK. 2019.
9. IAP Drug Formulary 2024 with IAP Recommendations on Drug Therapy for Pediatric Illness. 6th ed. Eds Jeeson C Unni, Pallab Chatterjee. A project of IAP CMIC, Pixel Studio, Cochin, 2014.
10. Wang YM, Wang J, Hon YY, Zhou L, Fang L, Ahn HY. Evaluating and reporting the immunogenicity impacts for biological products-a clinical pharmacology perspective. AAPS J. 2016; 18:395403.

GENERAL ARTICLE

RECENT UPDATES IN DELIVERY ROOM PRACTICES

***Anitha M**

Abstract: *Neonatal resuscitation programme has continuously been updated for our country, incorporating guidelines from American Heart Association and the European Resuscitation Council. Delayed cord clamping is now recommended for stable term and preterm newborns who do not require immediate resuscitation, as it improves hemodynamic stability and survival. It reduces the need for blood transfusions and also reduces intra-ventricular hemorrhage in preterm infants. Umbilical cord milking is an alternative option to delayed cord clamping, only in situations where delayed cord clamping cannot be performed (both term and preterm infants). Umbilical cord milking is contraindicated in preterm infants less than 28 weeks gestation. A physiological approach to cord clamping involves clamping when the respiration has started and lung aeration and pulmonary blood flow are established. This approach presents technical challenges for resuscitating the neonates near the introitus or maternal incision site, using specially designed trolleys currently undergoing validation. T-piece resuscitators are the recommended devices and supra-glottic airways may also be considered as the primary interface to administer positive pressure ventilation instead of a face mask for newborn infants.*

Keywords: *Delayed cord clamping, Umbilical cord milking, Positive pressure ventilation, T-piece resuscitator, Supraglottic airway.*

* Associate Professor of Neonatology, Institute of Obstetrics and Gynaecology, Centre of Excellence for Newborn Care and Hospital for Women and Children, Madras Medical College, Chennai.
email : drmanithamd@gmail.com

Points to Remember

- ***Delayed Cord Clamping (DCC) for at least 120 seconds is the choice in vigorous neonates (34-42 weeks) and gives the maximum benefit even in preterm infants.***
- ***Milking intact umblical cord may be beneficial in 34-28weeks non-vigorous neonates and also in vigorous neonates when DCC is not possible.***
- ***Umbilical cord milking is contraindicated in infants less than 28 weeks.***
- ***T-Piece resuscitator is the preferred device for administering PPV at birth and self-inflating bags should always be available for backup.***
- ***Supra glottic airways are better than face masks for PPV delivery and nasal interfaces are comparable alternatives to face masks for respiratory support in DR.***

References

1. Yamada NK, Szyld E, Strand ML, Finan E, Illuzzi JL, Kamath-Rayne BD, et al. American Heart Association and American Academy of Pediatrics. 2023 American Heart Association and American Academy of Pediatrics Focused Update on Neonatal Resuscitation: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2024 Jan 2; 149(1): e157-e166. doi: 10.1161/CIR.0000000000001181. Epub 2023 Nov 16. PMID: 37970724.
2. Lu J, Yue G, Wang Q, Zhou X, Ju R. A review on development of placental transfusion in term and preterm infants. Front Pediatr. 2022 Sep 15;10:890988. doi: 10.3389/fped.2022.890988. PMID: 36186636; PMCID: PMC9520323.
3. Rabe H, Mercer J, Erickson-Owens D. What does the evidence tell us? Revisiting optimal cord management at the time of birth. Eur J Pediatr. 2022 May;181(5):1797-1807. doi: 10.1007/s00431-022-04395-x. Epub 2022 Feb 2. Erratum in: Eur J Pediatr. 2022 May;181(5):1809. doi: 10.1007/s00431-022-04414-x. PMID: 35112135; PMCID: PMC9056455.

Cite as: Anitha M, Recent updates in delivery room practices, Indian J Pract Pediatr. 2025; 27(3):281-284.

4. Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, et al. iCOMP Collaborators. Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis. Lancet. 2023 Dec 9; 402(10418):2209-2222. doi: 10.1016/S0140-6736(23)02468-6. Epub 2023 Nov 14. PMID: 37977169.

5. Seidler AL, Libesman S, Hunter KE, Barba A, Aberoumand M, Williams JG, et al. iCOMP Collaborators. Short, medium and long deferral of umbilical cord clamping compared with umbilical cord milking and immediate clamping at preterm birth: a systematic review and network meta-analysis with individual participant data. Lancet. 2023 Dec 9; 402(10418):2223-2234. doi: 10.1016/S0140-6736(23)02469-8. Epub 2023 Nov 14. Erratum in: Lancet. 2023 Dec 9; 402(10418):2196. doi: 10.1016/S0140-6736(23)02710-1. PMID: 37977170.

6. Koo J, Kilicdag H, Katheria A. Umbilical cord milking-benefits and risks. Front Pediatr. 2023 Apr 18; 11: 1146057. doi: 10.3389/fped.2023.1146057. PMID: 37144151; PMCID: PMC10151786.

7. Koo J, Aghai ZH, Katheria A. Cord management in non-vigorous newborns. Seminars in Perinatology. 2023 Jun 1;47(4):151742.

8. Ditai J, Barry A, Burgoine K, Mbonye AK, Wandabwa JN, Watt P, et al. The Baby Saver: Design of a New Device for Neonatal Resuscitation at Birth with Intact Placental Circulation. Children (Basel). 2021 Jun 21; 8(6):526. doi: 10.3390/children8060526. PMID: 34205496; PMCID: PMC8235222.

9. Aziz K, Chadwick M, Baker M, Andrews W. Ante- and intra-partum factors that predict increased need for neonatal resuscitation. Resuscitation. 2008 Dec; 79(3): 444-52. doi: 10.1016/j.resuscitation.2008.08.004. Epub 2008 Oct 25. PMID: 18952348.

10. Diggikar S, Ramaswamy VV, Koo J, Prasath A, Schmölzer GM. Positive Pressure Ventilation in Preterm Infants in the Delivery Room: A Review of Current Practices, Challenges, and Emerging Technologies. Neonatology. 2024; 121(3):288-297.

11. Roehr CC, Davis PG, Weiner GM, Jonathan Wyllie J, Wyckoff MH, Trevisanuto D. T- piece resuscitator or self-inflating bag during neonatal resuscitation: a scoping review. Pediatr Res. 2021 Mar; 89(4):760-766. doi: 10.1038/s41390-020-1005-4. Epub 2020 Jun 11. PMID: 32526766.

12. Yamada NK, McKinlay CJ, Quek BH, Schmölzer GM, Wyckoff MH, Liley HG, et al. Supraglottic Airways Compared with Face Masks for Neonatal Resuscitation: A Systematic Review. Pediatrics. 2022 Sep 1; 150(3): e2022056568. doi: 10.1542/peds.2022-056568. PMID: 35948789.

13. Ni Chathasaigh CM, Davis PG, O'Donnell CP, McCarthy LK. Nasal interfaces for neonatal resuscitation. Cochrane Database Syst Rev. 2023 Oct 3; 10(10): CD009102. doi: 10.1002/14651858.CD009102.pub2. PMID: 37787113; PMCID: PMC10546484.

14. Blank DA, Zhou L, Malhotra A, Bhatia R, Badurdeen S, Davies-Tuck M, Duthie K, Tuttle Z, Gilby DM, Polglase GR, Hooper SB, Roberts CT. Face mask versus nasal mask device use for initial resuscitation in extremely and very preterm infants (FONDUE): An open-label, single-centre, randomised, controlled trial. Lancet Child Adolesc Health. 2025 Oct; 9(10):715-723. doi: 10.1016/S2352-4642(25)00193-2. PMID: 40908053.

NEO CAPSULE

GROWTH CHARTS

***Sindhu Sivanandan**
****Lakshmi V**

Abstract: *Growth monitoring in preterm infants is crucial to neonatal care, guiding nutritional decisions and predicting long-term health. Traditional growth references, such as the Fenton charts, reflect observed populations but are limited by methodological variability. Prescriptive standards, particularly the INTERGROWTH-21st project, provide an international standard for optimal growth. The newborn size at birth standard is used for comparing weight, length and head circumference at birth, while the preterm postnatal growth standards are used for monitoring the postnatal growth trajectories of preterm infants up to six months corrected age. Recent advances emphasize the use of z-score changes and individualized growth trajectories rather than cross-sectional percentiles to identify extrauterine growth restriction (EUGR). Preferably incorporating proportional indices and body composition measures offer a more complete assessment of growth rather than taking weight alone into consideration.*

Keywords: *Growth references, Prescriptive standards, INTERGROWTH 21st project, Optimal growth.*

Points to Remember

- ***Reference vs Standard growth charts - References describe observed growth in specific populations; standards prescribe how infants should grow under optimal conditions.***
- ***Size at birth vs postnatal growth - Size at birth charts classify infants at delivery, while postnatal growth charts track growth trajectories; they should not be used interchangeably.***
- ***Identifying extra-uterine growth restriction should be based on longitudinal monitoring using z-score rather than one-time assessment at discharge based on weight falling below 10th centile.***
- ***Preterm infants have a period of postnatal adaptation and growth at a trajectory that is-0.8 SD below fetal growth. Sicker preterm infants with postnatal morbidities have greater deviation from this trajectory. (Delta z score, growth velocity and weight gain ratio have to be included).***
- ***INTERGROWTH-21st standards are the first prescriptive postnatal growth standards for preterm infants, endorsed by WHO and CDC. These curves merge with WHO growth standards at 6 months corrected age.***
- ***Beyond weight indicators - Comprehensive growth monitoring should include length, head circumference, proportional indices (BMI, ponderal index, MUAC/HC ratio) and body composition measures for a complete(fuller) picture of growth and nutrition.***

* Senior Consultant Neonatologist
Kauvery Hospital, Chennai

** Senior Consultant Neonatologist and Head
Mehta Multi-Speciality Hospital, Chennai

email: drsindhusivanandan@gmail.com

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References

1. American Academy of Pediatrics. Nutritional needs of preterm infants. Pediatrics. 1985; 75(5):976-986.
2. Spiegler J, Preuss M, Gebauer C, Bendiks M, Herting E, Göpel W; German Neonatal Network. Does breastmilk influence the development of bronchopulmonary dysplasia? J Pediatr. 2016; 169:76-80.e4.
3. Embleton ND, Korada M, Wood CL, Pearce MS, Swamy R, Cheetham TD. Catch-up growth and metabolic outcomes in adolescents born preterm. Arch Dis Child. 2016; 101(11):1026-1031.
4. Belfort MB, Ehrenkranz RA. Neurodevelopmental outcomes and nutritional strategies in very low birth weight infants. Semin Fetal Neonatal Med. 2017; 22(1):42-48.
5. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet. 2004; 363(9421):1642-1645.
6. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013; 13:59. doi: 10.1186/1471-2431-13-59. PMID: 23601190; PMCID: PMC3637477.
7. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics. 2010; 125(2):e214-e224.
8. Villar J, Papageorghiou AT, Pang R, Ohuma EO, Cheikh Ismail L, Barros FC et al. International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study. Lancet Diabetes Endocrinol. 2014 Oct;2(10):781-92. doi: 10.1016/S2213-8587(14)70121-4. Epub 2014 Jul 6. PMID: 25009082
9. WHO Expert Committee. Physical status: the use and interpretation of anthropometry. World Health Organ Tech Rep Ser. 1995;854:i–xii, 1-452.
10. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG et al. International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6; 384(9946):857-68. doi: 10.1016/S0140-6736(14)60932-6. PMID: 25209487.
11. Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC et al. International Fetal and Newborn Growth Consortium for the 21(st) Century (INTERGROWTH-21(st)). Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21(st) Project. Lancet Glob Health. 2015 Nov;3(11):e681-91. doi: 10.1016/S2214-109X(15)00163-1. PMID: 26475015.13.
12. Rochow N, Raja P, Liu K, Fenton T, Landau-Crangle E, Göttler S, Jahn A, Lee S, Seigel S, Campbell D, Heckmann M, Pöschl J, Fusch C. Physiological adjustment to postnatal growth trajectories in healthy preterm infants. Pediatr Res. 2016 Jun;79(6):870-9. doi: 10.1038/pr.2016.15. Epub 2016 Feb 9. PMID: 26859363.
13. Landau-Crangle E, Rochow N, Fenton TR, Liu K, Ali A, So HY,et al. Individualized Postnatal Growth Trajectories for Preterm Infants. JPEN J Parenter Enteral Nutr. 2018 Aug;42(6):1084-1092. doi: 10.1002/jpen.1138. Epub 2018 Feb 8. PMID: 29419902
14. Cole TJ, Statnikov Y, Santhakumaran S, Pan H, Modi N; Neonatal Data Analysis Unit and the Preterm Growth Investigator Group. Birth weight and longitudinal growth in infants born below 32 weeks' gestation: a UK population study. Arch Dis Child Fetal Neonatal Ed 2014; 99:F34-40.
15. Ehrenkranz RA. Nutrition, growth and clinical outcomes. World Rev Nutr Diet 2014;110:11–26
16. Starc M, Giangreco M, Centomo G, Travan L, Bua J. Extrauterine growth restriction in very low birth weight infants according to different growth charts: A retrospective 10 years observational study. PLoS One. 2023; 18(4):e0283367.
17. Gidi NW, Goldenberg RL, Nigussie AK, McClure E, Mekasha A, Worku B, et al. Incidence and associated factors of extrauterine growth restriction (EUGR) in preterm infants, a cross-sectional study in selected NICUs in Ethiopia. BMJ Pediatr Open. 2020; 4(1):e000765.
18. Bagga N, Panigrahi N, Germain A, Namazova I, Rahman MM, Saugstad OD, et al. Extrauterine Growth Restriction: Need for an Accurate Definition. Newborn (Clarksville). 2023; 2(3):198-202.
19. Silveira RC, Procianoy RS. Preterm newborn's postnatal growth patterns: how to evaluate them. J Pediatr (Rio J). 2019; 95 Suppl 1:42-48.
20. Sung TH, Lin CS, Jeng MJ, Tsao PC, Chen WY, Lee YS. Weight growth velocity and growth outcomes in very-low-birth-weight infants developing major morbidities. Pediatr Neonatol. 2024; 65(2):177-182.

CASE REPORT

INFANTILE SYSTEMIC HYALINOSIS DUE TO HOMOZYGOUS DELETION MUTATION (C.1074DELT) IN ANTHRAX TOXIN RECEPTOR2

***Janani Sankar**
****Venkateswari Ramesh**
*****Ramkumar Ramamoorthy**

Abstract: *Infantile systemic hyalinosis is an autosomal recessive disorder characterized by hyaline deposits in the papillary dermis and other tissues leading to a progressive and fatal clinical course. The diagnosis is usually based on characteristic clinical findings, followed by confirmation with molecular genetic testing. We report two infants with inherited systemic hyalinosis, one had the diagnosis confirmed by molecular genetic testing identifying the homozygous c.1074delT mutation in the ANTXR2 gene, highlighting the importance of genetic confirmation even in resource-limited settings.*

* Senior Consultant Pediatrician and Medical Director
email: janani.sankar@yahoo.com

** Consultant Pediatrician

*** Consultant Pediatric Dermatologist,
Kanchi Kamakoti CHILDS Trust Hospital and
CHILDS Trust Medical Research Foundation

References

1. Landing BH, Nadorra R. Infantile systemic hyalinosis: report of four cases of a disease fatal in infancy, apparently different from juvenile systemic hyalinosis. Pediatr Pathol 1986; 6:55-79.
2. Hanks S, Adams S, Douglas J, Arbour L, Atherton DJ, Balci S, et al. Mutations in the Gene Encoding Capillary Morphogenesis Protein 2 Cause Juvenile Hyaline Fibromatosis and Infantile Systemic Hyalinosis. Am J Human Gen2003; 73(4): 791-800.
3. Madke B, Kharkar V, Mahajan S, Cikhalkar S, Khopkar U. Infantile systemic hyalinosis: A case report and review of literature. Indian Dermatol Online J 2010; 1(1): 10-13.
4. Urbina F, Sazunic I, Murray G. Infantile Systemic Hyalinosis or Juvenile Hyaline Fibromatosis? Pediatr Dermatol 2004; 21:154-9.
5. Dowling O, Difeo A, Ramirez MC, Tukel T, Narla G, Bonafe L, et al. Mutations in Capillary Morphogenesis Gene-2 Result in the Allelic Disorders Juvenile Hyaline Fibromatosis and Infantile Systemic Hyalinosis.Am J Human Gen2003; 73(4): 957-66.
6. El-Kamah GY, Mostafa MI. Heterogenicity and atypical presentation in infantile systemic hyalinosis with severe labio-gingival enlargement: First Egyptian Report. Dermatol Online J 2009; 15(5): 6.
7. Rahman N, Dunstan M, Teare MD, Hanks S, Edkins SJ, Hughes J, et al. The Gene for Juvenile Hyaline Fibromatosis Maps to Chromosome 4q21.Am J Human Gen 2002; 71(4): 975-80.
8. Urbina F, Sazunic I, Murray G. Infantile systemic hyalinosis or juvenile hyaline fibromatosis? Pediatr Dermatol. 2004; 21:154-9.
9. Stucki U, Spycher MA, Eich G, Rossi A, Sacher P, Steinmann B, et al. Infantile systemic hyalinosis in siblings: clinical report, biochemical and ultrastructural findings and review of the literature. Am J Med Genet2001; 100:122-129.
10. Quintal D, Jackson R. Juvenile Hyaline fibromatosis: A 15 year follow up. Arch Dermatol 1985. 121(8): 1062-3.

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