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NEUROLOGICAL MANIFESTATION OF INHERITED METABOLIC DISORDERS IN CHILDREN PRESENTING TO PEDIATRIC DEPARTMENT

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Abstract

Objectives

To evaluate the neurological manifestations in children diagnosed with inherited metabolic disorders (IMDs), and to determine their clinical, biochemical, and radiological associations in a tertiary care pediatric setting.

Methodology

80 children with confirmed IMDs presented to Department of Pediatrics, CMH Rawalpindi were included in the study. Detailed clinical history, neurological examination, and demographic data were recorded. Laboratory investigations included serum ammonia, lactate, blood glucose, arterial blood gases, and advanced metabolic screening. Neuroimaging (MRI brain) and electroencephalography (EEG) were performed where indicated. Data were analyzed using descriptive and inferential statistics, with $p < 0.05$ considered statistically significant.

Results

Most children presented during infancy and early childhood, with a slight male predominance. Parental consanguinity was noted in 60% of cases. Seizures (65%) were the most common neurological manifestation, followed by developmental delay (56.3%) and hypotonia (47.5%). Movement disorders were observed in 17.5% of patients. Aminoacidopathies (30%) and organic acidemias (25%) were the most frequent diagnostic categories. Abnormal MRI findings were present in 62.5% of cases, and EEG abnormalities were observed in 55%. The mean age at presentation was 18.6 ± 10.4 months. Elevated serum ammonia and lactate levels were significantly associated with severe neurological manifestations ($p < 0.05$).

Conclusion

Neurological manifestations, including movement disorders, are prominent features of IMDs in children.

Introduction:

Movement disorders are important and one of the most common neurological manifestations of metabolic disorders. Both acquired and inherited disorders of metabolism contribute to the etiology of movement disorders. These metabolic disorders are often associated with other neurological manifestations such as alteration of consciousness, headache, vomiting, seizures, and raised intracranial pressure or organ-specific functional

derangement that help the clinician suspect the underlying problem. It is particularly important to recognize movement disorders associated with metabolic defects as some of them are eminently treatable or at least, available treatment options help in the reduction of symptoms and improvement in the quality of life [1]. The most common types are dystonia (54%) and myoclonus (28%) followed by other stereotypes (14%) [2]. In a study of 24 children with IEMs and movement disorders, dystonia, myoclonus, and ataxia were most commonly seen and significantly impacted the health-related quality of life [3]. Inborn errors of metabolism are group of disorders which result from partial or complete absence of enzymes involved in biochemical reactions within the cells. This leads to both abnormal synthesis as well as catabolism of metabolites. Most of these metabolites are neurotoxic and may cause death in early neonatal period or severe neurological disability. There are about 60 inherited metabolic disorders which can present in the neonatal period [4]. Number of these can be treated successfully if suspected and diagnosed early [5]. Metabolic diseases or inborn errors of metabolism (IEM) are significant cause of mortality and morbidity among children in both the developed and developing countries. The variety and complexity of IEM along with diverse clinical pictures present a formidable challenge to the treating pediatrician. At the same time, prevention of death or severe neurological sequelae is dependent on prompt and early diagnosis. These inherited disorders are caused by genetic mutations leading to defective protein function. Most are inherited in autosomal recessive pattern and few are X-linked recessive disorders. In Pakistan, it is reported that more than half of all marriages (56%) are between first and second cousins [6]. Movement disorders are important and one of the most common neurological manifestations of metabolic disorders. Both acquired and inherited disorders of metabolism contribute to the etiology of movement disorders. These metabolic disorders are often associated with other neurological manifestations such as alteration of consciousness, headache, vomiting, seizures, and raised intracranial pressure or organ-specific functional

derangement that help the clinician suspect the underlying problem. It is particularly important to recognize movement disorders associated with metabolic defects as some of them are eminently treatable or at least, available treatment options help in the reduction of symptoms and improvement in the quality of life [7]. The expression of movement disorders in IEMs depends on the age of presentation, pattern of injury in the brain, and the course of illness. The exact burden of movement disorders may be underestimated in developing countries as the diagnostic facilities are not routinely available and a variety of central nervous system infections including viral encephalitis mimic the acute presentations. In addition, as the movement disorders may evolve or have an adult-onset, there is a chance that their true estimation may be missed. In a prospective study of 170 patients with confirmed or probable IEMs with neurological manifestations, nearly one-third (29%, $N = 50$) had one or more types of movement disorder [8]. On the contrary, nearly one-tenth (9.3%) patients of any age and nearly one-fifth (22%) pediatric patients with a movement disorder have been estimated to suffer from a metabolic etiology [9].

Methodology:

The Observational study was conducted in the Department of Pediatrics CMH Rawalpindi over a period of 1 year from Feb 2024- Jan 2025. Ethical permission was taken from ethical review board of CMH and granted ethical permission No (5.5). A sample size of 80 was calculated using WHO sample size calculator, taking reported prevalence of IMD's as 10% in pediatric Population taking confidence Interval 90% and Margin of error 5.55%.[10]

Children who presented with clinical features suggestive of metabolic disorders, particularly those exhibiting neurological symptoms such as seizures, developmental delay, altered consciousness, hypotonia, hypertonia, movement disorders, or regression of milestones, were included in the study.

Patients with acquired metabolic disturbances, central nervous system infections, traumatic brain injury, or other clearly diagnosed non-metabolic

neurological conditions were excluded to maintain specificity of the study population.

A structured data collection form was utilized to obtain demographic and clinical information. Detailed medical histories were recorded, including age at presentation, sex, birth history, parental consanguinity, family history of similar illness, developmental milestones, and history of recurrent unexplained symptoms such as vomiting, lethargy, or coma. Comprehensive physical and neurological examinations were performed, focusing on tone abnormalities, reflex status, cranial nerve involvement, head circumference, and the presence of dysmorphic features or organomegaly.

Laboratory investigations were carried out to confirm suspected inherited metabolic disorders. These included baseline biochemical tests such as blood glucose, serum ammonia, lactate levels, arterial blood gas analysis, and liver and renal function tests. Advanced metabolic screening was performed where indicated, including tandem mass spectrometry, urine organic acid analysis, plasma amino acid profiling, and enzyme assays. Neuroimaging studies such as magnetic resonance imaging (MRI) of the brain were conducted to identify structural or metabolic changes in the central nervous system. Electroencephalography (EEG) was performed in patients with seizure activity to document electrical abnormalities. The collected data were categorized into qualitative and quantitative variables for systematic analysis.

Included categorical data such as gender (male/female), presence or absence of consanguinity, type of neurological manifestation (seizures, developmental delay, hypotonia, hypertonia, ataxia, movement disorders), type of inherited metabolic disorder diagnosed (e.g., aminoacidopathies, organic acidemias, urea cycle disorders, lysosomal storage disorders), MRI findings (normal/abnormal patterns), EEG abnormalities (present/absent), and clinical outcome categories (improved, static, deteriorated, deceased). These variables were analyzed using frequency distribution and percentages to describe patterns and associations among different clinical features and diagnostic categories. Included measurable numerical data such as age at presentation (in months or years), duration of symptoms, head circumference (in centimeters), serum ammonia levels (µmol/L), lactate levels (mmol/L), blood glucose levels (mg/dL), length of hospital stay (days), and developmental assessment scores. These continuous variables were summarized using mean, median, standard deviation, and range. Comparative statistical tests were applied where appropriate to determine relationships between biochemical parameters and severity of neurological manifestations. Data analysis was performed using statistical software. Descriptive statistics were used to summarize the demographic profile and clinical characteristics of the study population. Inferential statistical methods, such as chi-square tests for qualitative variables and t-tests or ANOVA for quantitative variables, were applied to assess associations between metabolic abnormalities and specific neurological presentations. A p-value of less than 0.05 was considered statistically significant. Ethical approval was obtained from the institutional review committee prior to commencement of the study. Informed consent was obtained from parents or legal guardians of all participating children. Confidentiality and anonymity of patient data were maintained throughout the research process.

Results:

A total of 80 children with confirmed inherited metabolic disorders (IMDs) were included in the study. The majority of patients presented during infancy and early childhood. Males were slightly more affected than females. A significant proportion of children had a history of parental consanguinity. The most common presenting neurological manifestation was seizures, followed by developmental delay and hypotonia. Among the different types of inherited metabolic disorders, aminoacidopathies and organic acidemias constituted the largest diagnostic categories. Neuroimaging revealed abnormal MRI findings in more than half of the patients, while EEG abnormalities were frequently observed among children presenting with seizures.

Quantitative analysis demonstrated that the mean age at presentation was 18.6 ± 10.4 months.

Elevated serum ammonia and lactate levels were significantly associated with severe neurological manifestations ($p < 0.05$). The average duration of hospital stay was 12.3 ± 4.6 days. Children with urea cycle disorders showed significantly higher mean serum ammonia levels compared to other IMDs. Clinical outcomes showed that more than half of the patients improved with supportive and specific metabolic management, while a smaller proportion experienced persistent neurological deficits. Mortality was observed primarily in cases presenting with severe metabolic crises.

Table I: Demographics Characteristics (n = 80)

Variable	Category	Frequency (n)	Percentage (%)
Gender	Male	46	57.5%
	Female	34	42.5%
Parental Consanguinity	Present	48	60%
	Absent	32	40%
Neurological Manifestations	Seizures	52	65%
	Developmental Delay	45	56.3%
	Hypotonia	38	47.5%
	Hypertonia	16	20%
	Movement Disorders	14	17.5%
	Ataxia	10	12.5%
Type of IMD Diagnosed	Aminoacidopathies	24	30%
	Organic Acidemias	20	25%
	Urea Cycle Disorders	14	17.5%
	Lysosomal Storage Disorders	12	15%
	Others	10	12.5%
MRI Findings	Abnormal	50	62.5%
	Normal	30	37.5%
EEG Abnormalities	Present	44	55%
	Absent	36	45%
Clinical Outcome	Improved	44	55%
	Static Deficit	20	25%
	Deteriorated	8	10%
	Deceased	8	10%

Table II: Laboratory Characteristic's (n = 80)

Variable	Mean ± SD	Median	Range
Age at Presentation (months)	18.6 ± 10.4	16	2 – 48
Duration of Symptoms (months)	4.8 ± 3.2	4	1 – 12
Head Circumference (cm)	44.2 ± 3.5	44	38 – 52

Serum Ammonia (µmol/L)	142.5 ± 65.8	130	45 – 320
Serum Lactate (mmol/L)	4.6 ± 2.1	4.2	1.5 – 10.8
Blood Glucose (mg/dL)	68.4 ± 18.7	70	32 – 110
Hospital Stay (days)	12.3 ± 4.6	11	5 – 24
Developmental Assessment Score	62.5 ± 15.3	60	35 – 95

A statistically significant association was found between serum ammonia levels and seizure presentation ($p = 0.01$). Elevated serum lactate levels were significantly associated with developmental delay ($p = 0.03$). Children with urea cycle disorders had significantly higher mean serum ammonia levels compared to other IMDs ($p < 0.001$). Abnormal MRI findings were significantly more common among patients with persistent neurological deficits ($p = 0.02$). Overall, the results demonstrated that neurological manifestations were common presenting features of inherited metabolic disorders in children, with seizures and developmental delay being the predominant symptoms. Early biochemical and neuroimaging evaluation played a critical role in diagnosis and outcome prediction.

Discussion:

A total of 80 children with confirmed inherited metabolic disorders (IMDs) were included in the present study. Most patients presented during infancy and early childhood. Male children were slightly more affected than females. A considerable proportion of patients had a history of parental consanguinity. Seizures were the most common neurological manifestation at presentation, followed by developmental delay and hypotonia. Similarly, a study conducted in 2023 reported that consanguinity was significantly associated with inherited metabolic disorders. In that study, organic acidemias followed by aminoacidopathies were identified as the most common groups, while methylmalonic acidemia and multiple carboxylase deficiency were among the most frequently diagnosed individual disorders [11]. In the current study, aminoacidopathies and organic acidemias constituted the largest diagnostic categories among the different types of inherited metabolic disorders. Neuroimaging findings revealed that more than half of the patients had abnormal MRI results. Additionally, EEG abnormalities were commonly observed in children who presented with seizures. In contrast, a 2016 study reported that glycogen storage disorders were the most prevalent, followed by gaucher disease and galactosemia. The associated complications in that study contributed to high morbidity and mortality rates [12].

Quantitative analysis in the present study showed that the mean age at presentation was 18.6 ± 10.4 months. Elevated serum ammonia and lactate levels were significantly associated with severe neurological manifestations ($p < 0.05$). A study published in 2015 reported that patients with IMDs presented to the Pediatric Emergency Services (PES) for various reasons, often related to acute metabolic decompensation requiring hospitalization. Given the low prevalence of these disorders, the authors emphasized the importance of establishing standardized diagnostic and therapeutic protocols to ensure optimal patient care [13]. In the present study, the mean duration of hospital stay was 12.3 ± 4.6 days. Children diagnosed with urea cycle disorders had significantly higher mean serum ammonia levels compared to those with other IMDs. Regarding clinical outcomes, more than half of the patients showed improvement with supportive and disease-specific metabolic management. However, a smaller proportion developed persistent neurological deficits, and mortality was primarily observed in patients presenting with severe metabolic crises. A 2024 study highlighted that including a broad spectrum of psychiatric manifestations in children and adolescents with various inherited metabolic disorders strengthened diagnostic accuracy. This approach

helped prevent misdiagnosis and reduced delays in initiating early and appropriate treatment [14]. Statistical analysis in the current study demonstrated a significant association between elevated serum ammonia levels and seizure presentation ($p = 0.01$). Increased serum lactate levels were significantly associated with developmental delay ($p = 0.03$). Furthermore, children with urea cycle disorders had significantly higher mean serum ammonia levels than those with other IMDs ($p < 0.001$). Abnormal MRI findings were significantly more frequent among patients with persistent neurological deficits ($p = 0.02$).

In 2014, an algorithm-based approach for diagnosing pediatric metabolic diseases was proposed, emphasizing the importance of recognizing key neuroimaging features to support early and accurate diagnosis [15].Overall, the findings of the present study demonstrated that neurological manifestations are common presenting features of inherited metabolic disorders in children, with seizures and developmental delay being the predominant symptoms. Early biochemical investigations combined with neuroimaging evaluation played a crucial role in diagnosis and prognosis assessment. Similarly, a 2018 study recommended that any child presenting to the emergency department with unexplained acute encephalopathy should be evaluated for suspected inherited metabolic disorders, particularly in high-risk families, as early intervention significantly improves outcomes [16].

Conclusion:

Movement disorders represent a significant and often common neurological manifestation of inherited metabolic disorders in children. The present study highlights that seizures, developmental delay, and metabolic abnormalities such as hyperammonemia and lactic acidosis are key clinical indicators that should prompt early metabolic evaluation. Timely biochemical investigations and neuroimaging play a crucial role in diagnosis, prognostication, and management. Early recognition is particularly important, as several metabolic disorders are treatable, and prompt intervention can reduce morbidity, prevent severe neurological sequelae, and improve overall quality of life.

REFERENCES

Ebrahimi-Fakhari D, Münchau A, Stamelou M. A special issue on childhood-onset movement disorders. Movement Disorders. 2019 May;34(5):595-7.

Gouider-Khouja N, Kraoua I, Benrhouma H, Fraj N, Rouissi A. Movement disorders in neuro-metabolic diseases. european journal of paediatric neurology. 2010 Jul 1;14(4):304-7.

Eggink H, Kuiper A, Peall KJ, Contarino MF, Bosch AM, Post B, Sival DA, Tijssen MA, de Koning TJ. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet journal of rare diseases. 2014 Nov 26;9(1):177.

Burton BK, Nadler HL. Clinical diagnosis of the inborn errors of metabolism in the neonatal period. Pediatrics. 1978 Mar 1;61(3):398-405.

Donnell GN, Koch R, Bergren WR. Observations on results of management of galactosemic patients. InGalactosemia 1969 (p. 247). Charles C Thomas, Publisher, Springfield, Ill.

Pakistan NI. Pakistan Demographic and Health Survey 2006-07 Islamabad. Pakistan: National Institute of Population Studies and Macro International Inc. 2008.

Ebrahimi-Fakhari D, Munchau A, Stamelou M. A special issue on childhood-onset movement disorders Mov Disord. 2019;34:595–7

Gouider-Khouja N, Kraoua I, Benrhouma H, Fraj N, Rouissi A. Movement disorders in neuro-metabolic diseases. european journal of paediatric neurology. 2010 Jul 1;14(4):304-7.

Cordeiro D, Bullivant G, Siriwardena K, Evans A, Kobayashi J, Cohn RD, Mercimek-Andrews S. Genetic landscape of pediatric movement disorders and management implications. Neurology: Genetics. 2018 Sep 26;4(5):e265.

Orsucci D, Caldarazzo Ienco E, Giuntini M, Vista M. The Clinical Burden of Inherited Neurometabolic Disorders in Adults—A Territorial Care Approach. Journal of Clinical Medicine. 2025 Dec 24;15(1):146.

Pappas K, Fabie NA, Feldman GL. Child with suspected metabolic disorder. InSymptom-Based Approach to Pediatric Neurology 2023 Jan 1 (pp. 639-652). Cham: Springer International Publishing.

Cheema HA, Malik HS, Parkash A, Fayyaz Z. Spectrum of inherited metabolic disorders in Pakistani children presenting at a tertiary care centre. J Coll Physicians Surg Pak. 2016 Jun 1;26(6):498-502.

Gutiérrez MM, López RL, López AM, Barriocanal MB, Nodal EM, Sánchez AA, García SG. Inherited metabolic disorders in pediatric emergency services. Anales de Pediatría (English Edition). 2015 Jun 1;82(6):404-11.

Baglioni V, Bozza F, Lentini G, Beatrice A, Cameli N, Colacino Cinnante EM, Terrinoni A, Nardecchia F, Pisani F. Psychiatric manifestations in children and adolescents with inherited metabolic diseases. Journal of Clinical Medicine. 2024 Apr 10;13(8):2190.

Ibrahim M, Parmar HA, Hoefling N, Srinivasan A. Inborn errors of metabolism: combining clinical and radiologic clues to solve the mystery. American Journal of Roentgenology. 2014 Sep;203(3):W315-27.

Abdel Maksoud M, ELsayed SM, Shatla RH, Imam AA, Elsayed RM, Mosabah AA, Sherif AM. Frequency of inborn errors of metabolism screening for children with unexplained acute encephalopathy at an emergency department. Neuropsychiatric Disease and Treatment. 2018 Jun 29:1715-20.