ORIGINAL ARTICLE

Study of Inborn Errors of Metabolism among Children with Unexplained Encephalopathy at Al-Azhar University Hospitals

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Abstract

Background: ***CNS infections, toxins, hepatic or renal failure, hypoxia, and inborn metabolic abnormalities can all result in encephalopathy. One out of every 2,500 babies is born with an inborn error of metabolism (IEM), which disrupts metabolic processes. It is difficult to be diagnosed.***

Aim: ***The study aimed to determine the prevalence and classification of Inborn Errors of Metabolism (IEMs) in cases of unexplained encephalopathy in children.***

Methods: ***The research investigated children aged 1 to 18 with idiopathic encephalopathy, encompassing a thorough neurological evaluation, medical history review, physical examination, and laboratory analyses. Laboratory analyses encompassed complete blood count, electrolyte levels, and metabolic assessment. Statistical analysis examined correlations between IMEs and demographic factors, clinical symptoms, and investigation results.***

Results: ***The investigation evaluated 260 prospective patients from the Pediatric Neurology Unit of Al-Azhar University Hospitals, identifying 63 with a diagnosis of IEM. The median age was 3 years, with 63% male participants, 54% exhibiting consanguinity, and 21% possessing a familial history of IME. IME interferes with cerebral electrical activity, resulting in neurological manifestations such as seizures. Abnormal EEG and MRI findings were prevalent, with hepatic dysfunction observed in approximately fifty percent of the youngsters. Identified common IEMs include mitochondrial cytopathy and phenylketonuria, with no notable familial history correlation. Children exhibit clinical symptoms such as altered consciousness, convulsions, emesis, diarrhea, and respiratory distress.***

Conclusion: ***The study sheds insight into the high rate of encephalopathy in children caused by IEMs and offers helpful recommendations for doctors to identify and diagnose these conditions early.***

Keywords: Inborn Errors of Metabolism; Encephalopathy; Children; Metabolic Screen

1. Introduction

Encephalopathy is a medical disorder characterized by alterations in consciousness, behavior, and/or cognition.[1] "Inborn errors of metabolism" refers to a broad category that includes a wide range of conditions that can be passed down through generations or caused by random mutations. Proteins, carbohydrates, and fatty acids are all parts of the metabolic processes that might go wrong in certain diseases. Although inborn metabolic errors are rare in individuals, they occur in approximately 1 out of every 2500 births, making them a regular occurrence.[2] Although some metabolic abnormalities are inherited through an X-linked recessive pattern, autosomal recessive inheritance accounts for the vast majority of these cases. Autosomal dominant or maternal inheritance may occur under extremely unusual circumstances. Although some metabolic abnormalities are inherited through an X-linked recessive pattern, autosomal recessive inheritance accounts for the vast majority of these cases. Autosomal dominant or maternal inheritance may occur under extremely unusual circumstances.[3]

In progressive encephalopathy, brain and cognitive functions gradually decline over a period of three months or longer. Excessive agitation and disorientation are other possible symptoms, as are lethargy and drowsiness.[4]

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Multiple underlying causes can lead to extensive brain malfunction, which is known as encephalopathy. These include infections of the central nervous system (CNS), toxic exposure, liver or kidney failure, hypoxia, and inherited metabolic errors (IEM). When considering all of these factors, IEMs are the most neglected.[5,6] Around 80% of people with these illnesses have neurologic abnormalities as their primary symptoms. Seizures, hypotonia, metabolic encephalopathy, insufficient sucking reflexes, regression of milestones, and developmental delay were among the issues noted. Having gastrointestinal symptoms such as vomiting, enlarged liver, food intolerances, diarrhea, extreme aversions to specific meals, intolerances to physical exercise, and inadequate hydration is linked to the second most common occurrence. [2]

In order to ensure the most favorable outcome for children with IEM, it is crucial to swiftly recognize the symptoms of metabolic illnesses, conduct an assessment, and refer them to a specialized center that has experience managing these conditions. In order to avoid or lessen complications related to numerous metabolic diseases, it is essential to diagnose these conditions as soon as possible and start appropriate therapy.[7] However, how common are IEMs in children who come with encephalopathy? This information is scarce in the literature. However, only a handful of studies have shown a prevalence rate of 18% to 33.3%.[8,9] Thus, we aim in this research to determine the prevalence and classification of Inborn Errors of Metabolism (IEMs) in cases of unexplained encephalopathy in children.

2. Patients and methods

Study Design and Setting:

This analytical cross-sectional study was conducted at the Pediatric Neurology Unit, encompassing both inpatient and outpatient services, as well as the Neurology and Pediatrics Departments at Al-Azhar University Hospitals (Al-Hussein & Bab-Al-Shaaria). The ethical committee of the Faculty of Medicine at Al-Azhar University in Cairo, Egypt, accepted the study protocol. Informed consent was secured from all patients or their guardians following an explanation of the study's objectives and procedures.

Eligibility Criteria:

This study encompassed children aged from 1 month to under 18 years with unexplained encephalopathy, whether acute or chronic. Acute encephalopathy is characterized as a swiftly advancing cerebral disorder in children, presenting as subsyndromal delirium, delirium, or coma within a duration of less than 4 weeks.[10] Progressive encephalopathy is characterized by a steady deterioration in cognitive and neurological functions over a period beyond three months. 4 Exclusion criteria included children who developed encephalopathy as a result of hypoxic-ischemic insult, renal or hepatic dysfunction, central nervous system infection, or head trauma.

Data Collection:

a) Pediatric Neurological Assessment:

A comprehensive medical history was gathered to ascertain any prenatal, perinatal, neonatal, infancy, and childhood variables that may contribute to the unexplained encephalopathy. The history encompassed, I) Pregnancy (prenatal): Hemorrhage, pyrexia, TORCH infection, trauma, pathologies (e.g., diabetes mellitus (DM), hypertension (HTN), and timing of pharmacotherapy. II) Delivery (Perinatal and Postnatal): Term, preterm, delivery method, difficulties associated with labor or the baby (cyanosis, jaundice, screaming, hemorrhage from orifices, seizures, trauma, congenital defects). III) Neonatal Period: Premature/full-term status, crying, feeding behaviors, motor activity, vomiting, epilepsy, trauma, fever, jaundice. IV) Infancy and Childhood: Epilepsy, fever, visual and social responsiveness, trauma, motor activity. V) Family History: Consanguinity, analogous situations, familial pedigree.

Examination: Comprehensive general assessment, dysmorphic characteristics, congenital anomalies, metrics (handedness, stature, mass, cranial circumference), integumentary system, oral cavity, auditory system, nasal structure, visual acuity, and other systems (cardiovascular, respiratory, gastrointestinal, genitourinary). CNS evaluation, conduct during assessment, focus, verbal communication, cranial nerve function, motor system (muscle tone, strength, reflexes), sensory perception (superficial, deep), coordination, involuntary movements, ambulation.

b) Laboratory Investigations:

Routine Laboratory Tests: Complete blood count (CBC), arterial blood gas,

electrolytes, blood urea nitrogen, creatinine, liver function tests, blood glucose level, serum ammonia, serum lactate, urine ketones, cerebrospinal fluid (CSF) examination, and toxicology screening were done.

II) Specific Metabolic Investigations:

Extended Metabolic Screen in Blood (Tandem Mass Spectrometry, MS/MS): Amino acids and acylcarnitine were analyzed using a triple quadrupole mass spectrometer.

Organic Acids in Urine: Urine samples were analyzed using gas chromatography/mass

spectrometry (GC/MS).

Whole Exome Sequencing Analysis: Conducted in selected cases.

III) Neuroimaging: including computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain, was performed to rule out intracranial pathology or trauma.

IV) Electroencephalography (EEG): EEG was conducted to identify subclinical status epilepticus.

Statistical Analysis

All data were organized and statistically evaluated utilizing Jamovi software, the Jamovi Project (2024). jamovi (Version 2.5) [Software]. The statistical analysis comprised a descriptive analysis, wherein qualitative data is represented through frequency and percentage, while quantitative data is conveyed using mean and standard deviation (SD) or median and percentiles, contingent upon the Shapiro-Wilk test for normal distribution. Supplementary analytical methods were employed to examine the correlations between the IMEs and demographic variables, observed manifestations, and investigative results. The chi-square test was employed to examine the relationships. The flowchart was created using the Microsoft Word 365 desktop application.

3. Results

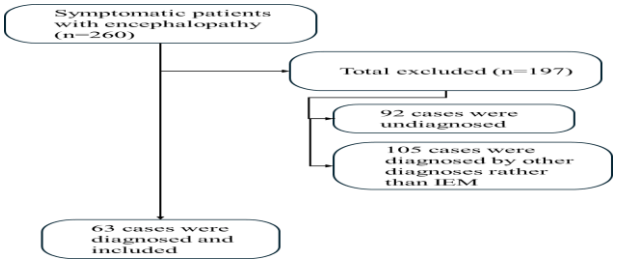

Figure 1. Flow chart summarizing the total selection process.

The study screened 260 potential symptomatic patients from Al-Azhar University Hospitals' Pediatric Neurology Unit from January 2023 to January 2024. Out of these, 63 were diagnosed with IEM, with only 17% using Whole Exome Sequencing (WES) in diagnosis, the total selection process is visualized in (Figure 1).

Table 1. Demographic Characteristics of included participants.

CHARACTERISTIC	N = 63
AGE, [YEARS] [1]	3.0 (1.08- 7.0)
SEX	
FEMALE	23 (37%)
MALE	40 (63%)
CONSANGUINITY	
NEGATIVE	29 (46%)
POSITIVE	34 (54%)
FAMILY HISTORY OF SIMILAR CONDITION	
NEGATIVE	50 (79%)
POSITIVE	13 (21%)
ENCEPHALOPATHY	
ACUTE ENCEPHALOPATHY	34 (54%)
CHRONIC (PROGRESSIVE) ENCEPHALOPATHY	29 (46%)
WES ANALYSIS	11 (17%)

[1] MEDIAN (IQR); N (%). WES; WHOLE SEQUENCING GENOME.

The median age of participants was 3 years, with 63% males, 56% consanguinity, 24% having a family history of IME, 54% diagnosed by encephalopathy, and 46% chronic and progressive encephalopathy, as shown in detail in (table 1).

Table 2. Manifestations of the included participants.

CHARACTERISTIC (N = 63)	YES	NO
NEUROLOGICAL MANIFESTATION		
SEIZURES	31 (49%)	32 (51%)
DISTURBED CONSCIOUS OF LEVEL	28 (44%)	35 (56%)
INTELLECTUAL DISABILITY	24 (38%)	39 (62%)
DELAYED MOTOR DEVELOPMENT	23 (37%)	40 (63%)
DELAYED SPEECH	23 (37%)	40 (63%)
MUSCLE WEAKNESS	9 (14%)	54 (86%)
HYPOTONIA	9 (14%)	54 (86%)
SPASTICITY	10 (16%)	53 (84%)
ATAXIA	6 (9.5%)	57 (90%)
MICROCEPHALY	5 (7.9%)	58 (92%)
HYPERACTIVITY	5 (7.9%)	58 (92%)
INVOLUNTARY MOVEMENTS	7 (11%)	56 (89%)
MACROCEPHALY	1 (1.6%)	62 (98%)
OTHER SYSTEM AFFECTION		
FAILURE TO THRIVE	32 (51%)	31 (49%)
POOR SUCKLING	27 (43%)	36 (57%)
RESPIRATORY DISTRESS	27 (43%)	36 (57%)
RECURRENT VOMITING	26 (41%)	37 (59%)
RECURRENT DIARRHEA	19 (30%)	44 (70%)
HISTORY OF NEONATAL JAUNDICE	14 (22%)	49 (78%)
HEPATOMEGALY	13 (21%)	50 (79%)
CATARACT	10 (16%)	53 (84%)
DYSMORPHIC FEATURES	9 (14%)	54 (86%)
CARDIOMYOPATHY	7 (11%)	56 (89%)
OPTIC ATROPHY	4 (6.3%)	59 (94%)
SPLENOMEGALY	2 (3.2%)	61 (97%)
SEPSIS	0	63 (100%)

[1] N (%)

The IME causes a variety of clinical manifestations, primarily neurological and neuromuscular, affecting overall growth and development. A large proportion of children (40-48%) experience neurological symptoms such as seizures, disturbed consciousness, intellectual disability, delayed motor development, and speech. Neuromuscular symptoms include muscle weakness, hypotonia, and spasticity. Other manifestations include ataxia, microcephaly, hyperactivity, involuntary movements, and macrocephaly. Over 30% of children have multiple system affection, with failure to thrive being the most common. Other manifestations include poor suckling, respiratory distress, recurrent vomiting and diarrhea, potential liver dysfunction, and ophthalmic manifestations like cataract and optic atrophy, as shown in detail in (table 2).

Table 3. frequency of Inborn metabolic errors among participants.

DIAGNOSIS	N = 63
POSSIBLE MITOCHONDRIAL CYTOPATHY	10 (16%)
PHENYLKETONURIA	8 (12.7%)
GLUTARIC ACIDURIA TYPE 1	6 (9.5%)
MAPLE SYRUP URINE DISEASE (MUSD)	5 (7.9%)
POSSIBLE MALONIC ACIDURIA	5 (7.9%)
UREA CYCLE DEFECT	5 (7.9%)

NEURONAL CEROID LIPOFUSCINOSIS	4 (6.3%)
MUCOPOLYSACCHARIDOSIS II	3 (4.8%)
NIEMANN-PICK C	3 (4.8%)
WILSON'S DISEASE	3 (4.8%)
LESCH-NYHAN SYNDROME	2 (3.2%)
METACHROMATIC LEUKODYSTROPHY	2 (3.2%)
PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION (PKAN)	2 (3.2%)
PHOSPHOGLYCERATE KINASE DEFICIENCY	1 (1.6%)
TAY-SACHS DISEASE	1 (1.6%)
POSSIBLE FATTY ACID OXIDATION DEFECT (FAOD)	1 (1.6%)
KRABBE'S DISEASE	1 (1.6%)
POSSIBLE NON KETOTIC HYPERGLYCINEMIA	1 (1.6%)

IMEs were detected in a total of 24.23% of children, with the most common diagnosis being possible mitochondrial cytopathy (16%), as shown in (table 3). The study found that all children presented with metabolic acidosis, increased serum lactate, and hyperglycemia, as well as phenylketonuria, a type of inflammatory bowel disease (IBD). All children had chronic and progressive encephalopathy, seizures, delayed motor development, and speech delays. Hyperactivity was significantly associated with phenylketonuria within the sample size. Four children had cataract, and dysmorphic features were most observed in children diagnosed with phenylketonuria. Glutaric aciduria type 1 was detected in six children, none of whom had a family history, and three reported consanguinities. The most observed investigations in all children were metabolic acidosis, hyperammonemia, hypoglycemia, and ketones. Brain atrophy was observed in three children, and basal ganglia abnormalities were observed in two children. MUSD was detected in five children, with fewer manifestations and risk factors. All children were associated with failure to thrive, and four had cataracts. Possible malonic aciduria was detected in five children, all significantly associated with encephalopathy, disturbed conscious level, recurrent vomiting, diarrhea, failure to thrive, respiratory distress, and poor suckling. The only significant investigational finding was hyperammonemia in four children and brain atrophy in one child.

Table 4. associations between the Inborn Metabolic Errors and Demographic data.

		POSSIBLE MITOCHONDRIAL CYTOPATHY	PHENYLKETONURIA	MUSD	GLUTARIC ACIDURIA TYPE 1	POSSIBLE MALONIC ACIDURIA	UERA CYCLE DEFECT
CONSANGUINITY	Positive	4.0 (11.4%)	3.0 (37.5%)	3.0	3.0	2.0	3.0
	(N=34)			(60%)	(50.0%)	(40.0%)	(60.0%)
	Total	10.0 (15.9%)	8.0 (12.7%)	5.0	6.0	5.0 (7.9%)	5.0
	(N=63)			(7.9%)	(16.67%)		(7.9%)
	p value	0.334	0.317	0.778	0.838	0.514	0.778
FAMILY	positive	0.0 (0.0%)	2.0 (25%)	0.0	0.0 (0.0%)	0.0 (0.0%)	1.0
HISTORY	(N=13)			(0.0%)			(20.0%)
	Total	10.0 (15.9%)	8.0 (12.7%)	5.0	6.0	5.0 (7.9%)	5.0
	(N=63)			(7.9%)	(16.67%)		(7.9%)
	P VALUE	0.079	0.744	0.235	0.189	0.235	0.971

The table displays information regarding the prevalence of several metabolic illnesses in connection with consanguinity and familial history. The analysis reveals differing frequencies of various disorders, with consanguinity exhibiting elevated percentages in certain instances; however, the statistical evaluation (p-values) demonstrates no significant association between consanguinity or family history and the occurrence of these disorders within this particular sample.

4. Discussion

IMEs are a heterogeneous collection of disorders defined by either complete or partial enzyme deficiency due to genetic or spontaneous mutations. These deficiencies impede the metabolism of carbohydrates, proteins, and fatty acids, leading to substrate accumulation, a deficit of subsequent products, and potentially the activation of alternative metabolic pathways that produce substances not typically present in the body, which may result in toxicity. [11,12] Neonatal birth screening can detect up to 50 conditions, yet thousands remain unexamined, resulting in numerous missed cases that may present late with severe complications, including neurological injury and potential mortality. Early and accurate diagnosis, dependent on heightened clinical suspicion and the use of laboratory, radiological, and genetic tests, is essential to initiate appropriate treatment and improve prognosis. [13]

IEM was identified in 24.2% of patients. The study comprised individuals with a mean age of 3.0 years, with a male preponderance of 63%, a consanguinity rate of 56%, and a familial history of IME. Encephalopathy was the predominant symptom in 54% of instances. The majority of children displayed neurological symptoms, with seizures, altered awareness, and cognitive impairment being the most prevalent. More than 30% had several systemic afflictions, with failure to flourish being the most common. Abnormal EEG and MRI findings were identified in 38.09% of patients.

The male predominance is justifiable due to the

inheritance of these diseases through X-linked recessive genes. The elevated consanguinity rate is readily attributed to the prevalence of consanguineous marriages in Arabian and Middle Eastern countries, facilitating the transmission of autosomal recessive genes, which is the primary mechanism for the inheritance of inherited metabolic disorders. The robust link with various types renders it a significant determinant in the development of IMEs. Moreover, the occurrence of several cases within the same family is noted, potentially attributable to the scarcity of skilled physicians knowledgeable about these diseases outside university institutions, as well as the absence of genetic follow-up and counseling in instances of prior affected offspring.[14] A variety of systemic factors, including toxins, hypoxia, infection, intracranial hemorrhage (IME), and hepatic or renal failure, can contribute to the altered consciousness, behavior, and cognition that characterize encephalopathy. Primary neurological factors, such as tumors or hemorrhages, also play a role. In children with IMEs, metabolic encephalopathy can manifest as acute or persistent symptoms. Our results corroborate this, showing that 54 percent of patients presented with acute encephalopathy and 46 percent with chronic progressive encephalopathy. Seizures(48%), disturbed conscious level(44%), Intellectual disability(40%), delayed motor development(40%), and delayed speech(40%) were among the many other neurological signs that were commonly reported. The second most common symptom was a variety of neuromuscular abnormalities, including delayed motor development (37% of cases), weak muscles (14% of cases), ataxia (11% of cases), microcephaly (7.9% of cases), hyperactivity (including involuntary movements), and macrocephaly (1.6%). There were also signs of systemic affection, such as a higher prevalence of failure to thrive (51%), poor suckling (43%), and respiratory distress (43%). Recurrent vomiting (41% of cases) and diarrhea (30%) were the gastrointestinal symptoms that were observed. An increased risk of hepatomegaly(21%), dysmorphic features(14%), and splenomegaly (3.2% of infants) was associated with a history of neonatal jaundice (22% of children). Cardiomyopathy, a cardiac symptom, affects 11% of patients, while cataracts and optic atrophy, two eye conditions, affect 16% and 6.3% of patients, respectively, without a single episode of sepsis.

The prevalence of IEM in patients exhibiting encephalopathy in our investigation corresponds with prior literature. Abdel Maksoud and colleagues performed a prospective observational study including 30 children in Egypt who were hospitalized with unexplained encephalopathy. The findings, published in 2018, indicated that 33.3% of the children had positive initial screening tests for inborn errors of metabolism (IEMs).[15] A research by Singhal et al. (2022) in Indian children with noninfectious encephalopathy identified inborn errors of metabolism as a prominent cause of noninfectious encephalopathy. The research discovered metabolic reasons in 18% of the 50 pediatric subjects.[16] Our sample exhibited a male predominance of 63%, akin to the 60% observed by Abdel Maksoud and colleagues.15 A positive family history does not invariably signify inborn errors of metabolism (IEMs) due to the possibility of asymptomatic carriers; however, a history of mortality among preceding siblings should prompt inquiries into probable IEMs. Conversely, Singhal et al. (2022) reported a female majority in India.16 These variances may indicate geographical or population-specific disparities in the epidemiology or genetic predispositions associated with the illness.

The majority of neurological presentations in the present study were seizures. In line with this, the 2018 study by Abdel Maksoud et al. Seizures were common in the group studied by Singhal et al. (2022), with 77% of participants reporting them.[15,16]

Our results indicated that 51% of the study cohort exhibited failure to thrive. The significant prevalence of the following symptoms in this study—insufficient suckling (43%), respiratory distress (43%), recurrent vomiting (41%), and diarrhea (30%)—is likely a major contributing factor to the frequent occurrence of failure to thrive. These results align with the findings of Abdel Maksoud et al. (2018), who reported a 40% incidence[15], and Debray et al. (2007), who observed that failure to thrive occurred in 52% of instances.[17]

Mitochondrial cytopathies constituted the most prevalent metabolic condition, representing 16% of the cases. Mitochondrial illnesses are among the most common inborn errors of metabolism, with an estimated prevalence of approximately 1 in 5,000 individuals.[18] This conclusion corroborates prior research, which has indicated that mitochondrial abnormalities occur in 13% of pediatric populations exhibiting neurologic symptoms.15 A study investigating the epidemiology of mitochondrial abnormalities in children experiencing gradual intellectual and neurological decline revealed that 4.5% of the sample group was identified with mitochondrial illnesses.[19] In this study, phenylketonuria (PKU) was detected in 12.7% of cases, making it the second most frequent IEM. One of the more common IEMs, PKU, has a lot written about it. [20] Our cohort's high PKU prevalence highlights the

urgent need to enhance Egypt's screening systems and implement early intervention strategies to prevent permanent brain damage. Within this investigation, 9.5% of the cases were associated with glutaric aciduria type 1 (GA1). Although this metabolic illness is uncommon, it is known to induce encephalopathy in newborns and young children. [21,22]

Our study's main merit is that it fills a notable informational void about the frequency and clinical manifestation of IEMs causing encephalopathy in youngsters. This study's results can help doctors identify the unique demographic and clinical features of IEM patients, which can aid in their early discovery and diagnosis.

4. Conclusion

The study sheds insight into the high rate of encephalopathy in children caused by IEMs and offers helpful recommendations for doctors to identify and diagnose these conditions early. If there is a history of IEM in the family or if a kid has symptoms of GIT, intellectual disability, or unexplained developmental delay, then screening for IEM is essential. Diagnosing IEM requires a high level of clinical suspicion and laboratories that are well-equipped.

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Authorship

All authors have a substantial contribution to the article

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