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ORIGINAL ARTICLE

Neurometabolic Disorders-Related Early Childhood Epilepsy: A Single-Center Experience in Saudi Arabia

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Key Words
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Background: Data on the pattern of epilepsy caused by metabolic disorders in the first 2 years of life are limited in developing countries. We aimed to identify the metabolic causes of epilepsy presented in the first 2 years of life and to describe their clinical, radiological, molecular, and electroencephalographic characteristics.
Methods: This retrospective study was conducted between January 2010 and December 2011 at Saad Specialist Hospital (Al Khobar, Saudi Arabia). All patients younger than 2 years at the onset of epilepsy caused by metabolic disorders were reviewed. The International League Against Epilepsy definition was used, and febrile convulsion was excluded.
Results: Of 221 children diagnosed with epilepsy in the first 2 years of life at our hospital, 24 had metabolic diseases. The characteristics of these 24 children included the following: consanguinity in 18 patients (75%), developmental delay in 13 (54%), generalized tonic–clonic seizures in 10 (42%), infantile spasms in four (17%), myoclonic in seven (29%), and focal seizures in three. The diagnosis was confirmed by DNA studies in 17 patients (71%) and enzyme assay in seven (29%). The main diagnoses were peroxisomal disorders ($n = 3$), nonketotic hyperglycinemia ($n = 3$), Menkes disease ($n = 2$), neuronal ceroid lipofuscinosis ($n = 2$), biotinidase deficiency ($n = 2$), and mitochondrial disorder ($n = 2$). The remaining patients had lysosomal storage disease, aminoacidopathy, fatty acid oxidation defects, and organic aciduria. Seizure freedom was achieved in one third of patients in this cohort.

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Conclusion: Different metabolic disorders were identified in this cohort, which caused different types of epilepsy, especially myoclonic seizures and infantile spasms.

1. Introduction

The burden of epilepsy on children and their families is heavy. This situation becomes worse when devastating disorders such as metabolic diseases cause epilepsy. Epilepsy secondary to metabolic diseases was previously classified as symptomatic epilepsy and is currently part of the structural/metabolic group according to the recent International League Against Epilepsy (ILAE) classification.[1] Metabolic disorders are essentially caused by deficiency of an enzyme or a cofactor. Occasionally, these disorders are caused by a transport defect in which enzymes and cofactors are intact.[2,3] This metabolic derangement results in toxic accumulation of substrates before the enzyme block, defects in energy production, deficiency of products after the block, or a combination of all these metabolic deviations.[4] The biochemical composition of brain is distinct from that of other organs, and there is a complex relationship between the concentration of metabolites and neural function.[5,6] Thus, the brain is often affected by metabolic abnormalities, leading to epilepsy and other neurologic manifestations.[7,8] Some of these inborn errors of metabolism affect the brain cells directly, causing mitochondrial, lysosomal, and peroxisomal disorders. Others affect the brain indirectly by causing hypoglycemia, as in fatty acid oxidation defects.[9,10] During early life, the immature and developing brain often exhibits a greater sensitivity to these disorders compared with other age groups.[11,12] Epileptic seizures that are caused by inborn errors of metabolism may be nonspecific or can often take a typical clinical course.[13,14] Occasionally, specific electroencephalography (EEG) features may point toward the diagnosis early in the course of the disease.[15,16] Epileptic syndromes characterized by distinct seizure semiology and a characteristic EEG pattern may be caused by metabolic disorders, especially when presenting early in infancy.[15,16]

Although epilepsy is one of the leading chronic disorders in children, its metabolic etiology is often difficult to confirm and easy to miss. Therefore, we conducted this study to identify the metabolic causes of epilepsy presented in the first 2 years of life and to describe their clinical, radiological, molecular, and electroencephalographic characteristics.

2. Methods

This was a retrospective study conducted at Saad Specialist Hospital (Al Khobar, Saudi Arabia) from January 2010 to December 2011. This is a large private institute with 600 beds, 100 of which are allocated to children. All pediatric specialized services were available in this institute including services for neurologic and metabolic diseases. We reviewed all patients younger than 2 years who came to our institute with newly diagnosed epilepsy secondary to metabolic disorders. These patients were identified from the medical records of pediatric neurologic and metabolic clinics, pediatric wards, and neonatal and pediatric intensive care units. Data were extracted from medical records using a case report form. The clinical characteristics recorded in this form included the following: demographic information, consanguinity, age at first seizure, seizure type, developmental milestones, abnormal clinical findings, results of laboratory and radiological tests, EEG reports, and final diagnosis. The results of the following tests were also reviewed from the electronic laboratory records: serum glucose, lactate, ammonia, and amino acids; blood gas; acylcarnitine profile; urinary organic acids, ketones, and reducing substances; enzyme assays; and DNA studies. The following tests were reviewed as indicated by clinical features: transferrin isofocusing; lactate-to-pyruvate ratio; and skin and muscle biopsy for functional, biochemical, enzyme, DNA, and histopathological analysis, including electronic microscopy.

In this study, epilepsy was classified according to the ILAE.[1] The diagnosis of metabolic disorder was based on biochemical, enzymatic, and molecular studies according to the clinical profile of each patient. The response to antiepileptic drugs (AEDs) was categorized into three groups according to the presence or absence of seizure freedom. The first group included seizure-free patients who became and remained seizure free within 6 months of starting AED. The AED regimen was defined as a monotherapy or a combination of two or more AEDs. The second group included patients who fluctuated between a period of seizure-free status and relapse within 6 months of starting AED. The third group includes patients who were never seizure free within 6 months of starting AED.

2.1. Statistical analysis

The data were analyzed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). Mean, median, and standard deviations were used for descriptive data.

3. Results

Of the 221 children diagnosed with epilepsy presenting in the first 2 years of life at our hospital, 24 had metabolic diseases. The clinical characteristics (Table 1) of these 24 patients were as follows: 13 (54%) male patients, positive family history of similar metabolic disease in a first-degree relative in eight (34%), and consanguinity in 18 (75%). The

Table 1 Characteristics of the 24 children with epilepsy secondary to metabolic disorders.*

Variables	No. of patients (%)
Total No.	24 (100)
Sex distribution	
Male	13 (54)
Female	11 (46)
Age at the onset of seizure (mo)	
0–12	16 (67)
13–24	8 (33)
Age at diagnosis (mo)	
0–12	10 (42)
13–24	8 (33)
25–30	6 (25)
Consanguinity	
Yes	18 (75)
No	6 (25)
Family history of metabolic disease	
Yes	8 (33)
No	16 (67)
Symptoms' duration before the first seizure (wk)	
<1	5 (21)
>1	19 (79)
Seizures type	
Focal seizures	3 (12)
Generalized seizures	
Tonic–clonic	10 (42)
Myoclonic	7 (29)
Infantile spasms	4 (17)
Hypotonia	9 (38)
Developmental delay	13 (54)
Abnormal MRI findings	12 (50)
Diagnosis confirmed by	
Enzyme study	7 (29)
Mutation analysis	17 (71)

MRI = magnetic resonance imaging.
* All children were younger than 2 years.

onset of seizures was in infancy in 16 (67%) patients and in the 2nd year of life in eight (33%) patients. The duration of other symptoms before the first seizure occurred was ≤1 week in five (21%) patients and >1 week in 19 (79%) patients. Developmental delay was observed in 13 patients (54%) and hypotonia in nine (38%) patients. The dominant type of seizures in these patients was found to be generalized tonic–clonic in 10 (42%), infantile spasms (Figure 1) in four (17%), myoclonic in seven (29%), and focal seizure in three (12%). These types of seizures led to a variety of EEG changes observed in our patients including generalized spikes and waves (Figure 2), generalized slowing, focal epileptogenic discharge, and hypsarrhythmia.

All patients were subjected to magnetic resonance imaging (MRI) of the brain, which revealed abnormal findings in half of the cases (Table 2; Figures 3 and 4), including an increased signal in cerebral white matter and basal ganglia, brain atrophy, demyelination, and subdural effusion.

The final diagnoses (Table 2) of this cohort were confirmed by DNA studies in 17 patients (71%) and enzyme assay in seven (29%) patients. Confirmed diagnoses included peroxisomal disorders ($n = 3$), nonketotic hyperglycinemia ($n = 3$), Menkes disease ($n = 2$), neuronal ceroid lipofuscinosis ($n = 2$), biotinidase deficiency ($n = 2$), mitochondrial disorder ($n = 2$), short-chain acyl-coenzyme A (CoA) dehydrogenase deficiency ($n = 2$), very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD; $n = 1$), carnitine acylcarnitine translocase deficiency ($n = 1$), carnitine palmitoyltransferase type II ($n = 1$), phenylketonuria ($n = 1$), glutaric aciduria type I ($n = 1$), citrullinemia ($n = 1$), congenital disorder of glycosylation type 1c ($n = 1$), Niemann–Pick disease type C ($n = 1$), and Sandhoff disease ($n = 1$).

Seizure freedom was achieved in eight patients with fatty acid oxidation disorders, phenylketonuria, citrullinemia, and biotinidase deficiency. By contrast, seizure freedom was not achieved in patients with peroxisomal disorders, nonketotic hyperglycinemia, Menkes disease, and neuronal ceroid lipofuscinosis (Table 2). Furthermore, response to AED fluctuated between seizure-free periods and relapse in patients with mitochondrial disorders, lipid storage diseases, glutaric aciduria type I, and congenital disorder of glycosylation.

4. Discussion

Although individually rare, inherited metabolic diseases collectively affect a significant percentage of children presenting with acute and life-threatening conditions.[2] Seizures are often caused by metabolic disturbances, some of which are due to inborn errors of metabolism.[17,18] When presenting with seizures, the diagnosis of these disorders can be challenging, and therefore, a high index of suspicion is needed to make the right diagnosis and to start the proper management that can sometimes be life-saving.[3,4] Proper history taking, especially detailed family history, may point toward the diagnosis of inherited metabolic disease. Most of our patients were the product of consanguineous marriage and one third had a history of an affected person with the same metabolic disease in the family. This was not surprising because the prevalence of consanguinity in Saudi Arabia is high compared with other countries.[19] It is well-known that consanguinity increases the risk of inherited diseases in the offspring because it brings the recessive genes together to manifest as a disease entity. It is interesting that a vast majority of our patients, who had their mutations detected, showed a homozygous mutation compared with the double heterozygous mutations usually observed in other countries.[2,19] This can be explained by the fact that the community in Saudi Arabia is mostly tribal and tends to live in clusters and practice intermarriage, which increases the chance of individuals to carry homozygous mutation.[19]

According to the clinical practice guidelines developed by our hospital, basic metabolic screening including analysis of serum ammonia, lactate, and amino acids in addition to urine organic acids is recommended for all infants presenting with recurrent unexplained seizures. Detailed metabolic investigations including enzymes assay and molecular studies were guided by other clinical manifestations and the likelihood of specific metabolic disorders. This approach is thought to be cost effective and likely to pick

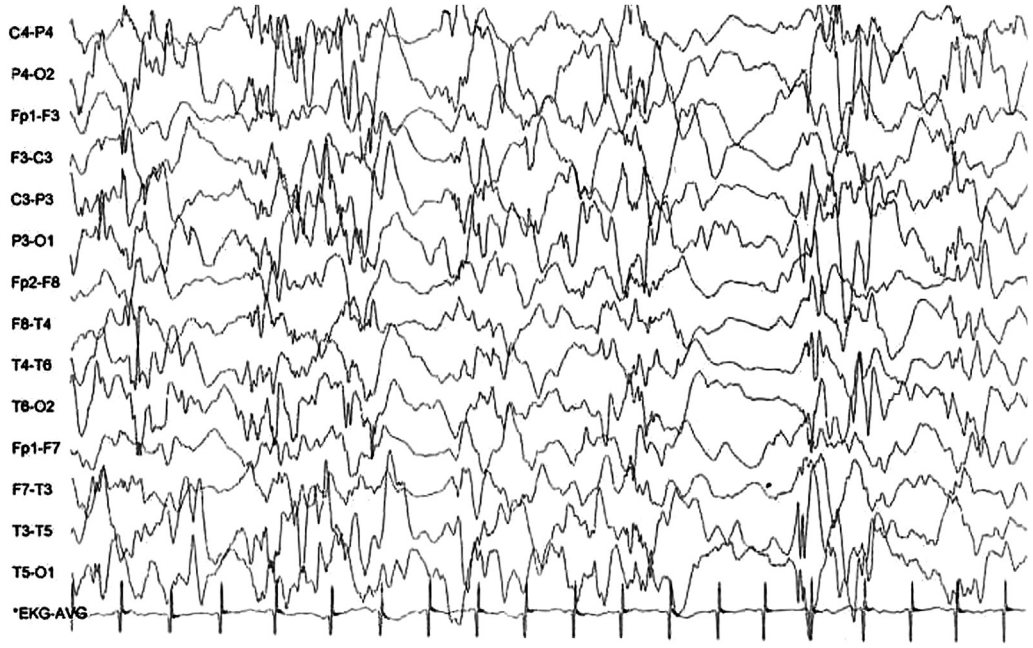

Figure 1 Electroencephalogram showing hypsarrhythmia in a 9-month-old infant (patient number 4) with nonketotic hyperglycinemia.

out the relatively small number of children with metabolic disorders among those presenting with epilepsy.[3,17,18] By implementing this diagnostic strategy, we identified a variety of disorders causing seizures in young children.

The spectrum of metabolic disorders in our cohort was wide and included peroxisomal disorders, mitochondrial diseases, lysosomal storage diseases, organic aciduria, urea cycle defects, and fatty acid oxidation defects. Some of these disorders tend to affect the central nervous system primarily and cause chronic encephalopathy, and hence, they were more prevalent in our patients. This group included peroxisomal biogenesis disorders, nonketotic hyperglycinemia, neuronal ceroid lipofuscinosis, mitochondrial disease, and Menkes disease. Most of these metabolic disorders present in a progressive manner with developmental delay, hypotonia, and epilepsy, as observed in our patients.[5,6] The exception to this pattern of presentation is nonketotic hyperglycinemia, which usually presents with

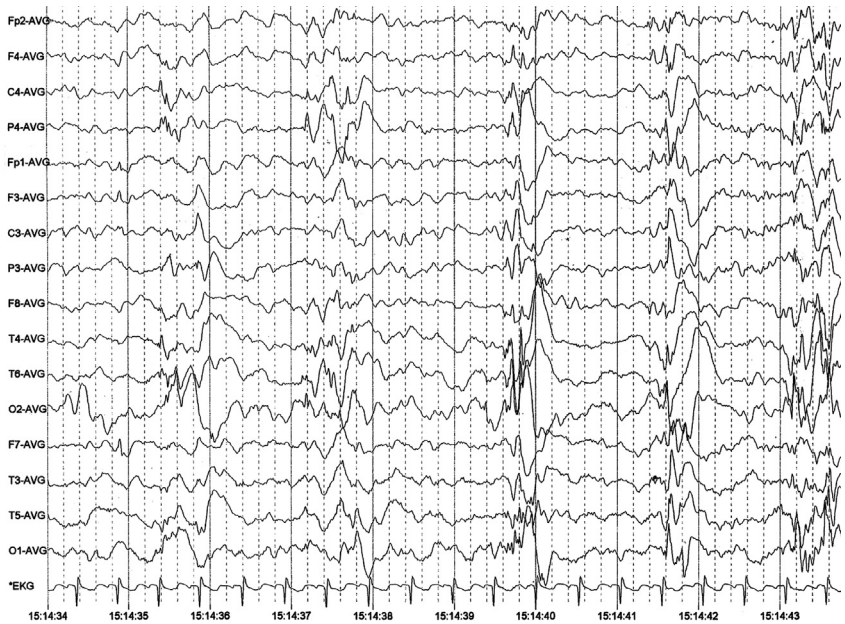

Figure 2 Electroencephalogram showing generalized spikes and waves in addition to bilateral posterior quadrant epileptiform discharges in a 1-year-old (patient number 1) with peroxisomal biogenesis disorder.

Table 2 Clinical, laboratory, radiological, and electroencephalographic findings in the 24 children with epilepsy secondary to metabolic disorders.

Patient	Metabolic disorder	Clinical manifestations	Type of seizures	EEG	Brain MRI	Result of confirmatory test	Response to AED
1.	Peroxisomal biogenesis disorder (*PEX19*)	Hypotonia, developmental delay, liver dysfunction	Myoclonic	Generalized spikes and waves	Brain atrophy, demyelination	c.320delA homozygous mutation in the *PEX* gene	Never seizure free
2.	Zellweger syndrome (*PEX1*)	Hypotonia, developmental delay	GTC	Generalized slowing	Brain atrophy	c.2528 G>A homozygous mutation in the *PEX1* gene	Never seizure free
3.	Zellweger syndrome (*PEX1*)	Hypotonia, developmental delay, dysmorphism	Infantile spasm	Hypsarrhythmia	Brain atrophy	c.2528 G>A homozygous mutation in the *PEX1* gene	Never seizure free
4.	Nonketotic hyperglycinemia	Acute encephalopathy, hypotonia	Infantile spasm	Hypsarrhythmia	Brain atrophy	Homozygous 5′ UTR deletion of the *GLDC* gene	Never seizure free
5.	Nonketotic hyperglycinemia	Acute encephalopathy, microcephaly	Infantile spasm	Hypsarrhythmia	Bilateral subcortical heterotopia	Homozygous 5′ UTR deletion of the *GLDC* gene	Never seizure free
6.	Nonketotic hyperglycinemia	Hypotonia	Infantile spasm	Hypsarrhythmia	Brain atrophy	Homozygous 5′ UTR deletion of the *GLDC* gene	Never seizure free
7.	Menkes disease	Macrocephaly, hypopigmented brittle hair, fractures	Myoclonic	Generalized slowing	Bilateral subdural effusion	c.1933C>T hemizygous mutation in the *ATP7A* gene	Never seizure free
8.	Menkes disease	Hypopigmented brittle hair, hypotonia	Myoclonic	Generalized slowing	Normal	c.1933C>T hemizygous mutation in the *ATP7* gene	Never seizure free
9.	Neuronal ceroid lipofuscinosis-2	Microcephaly, developmental delay	Myoclonic	Generalized slowing	Cerebellar and vermian atrophy	p.G514 R; g.5837 A>T heterozygous mutation in the *CLN2* gene	Never seizure free
10.	Neuronal ceroid lipofuscinosis-3	Developmental delay	GTC	Generalized slowing	Increased T_2 signal in cerebral white matter	IVS2−3C>T homozygous mutation in the *CLN3* gene	Never seizure free
11.	Biotinidase deficiency	Alopecia, hypopigmented skin, developmental regression	GTC	Generalized slowing	Normal	p.C33F homozygous mutation in exon 2 of the *BTD* gene, also low serum biotinidase	Seizure free
12.	Biotinidase deficiency	Developmental delay	GTC	Generalized slowing	Normal	Low serum biotinidase	Seizure free
13.	Complex 1 respiratory chain deficiency	Failure to thrive, developmental delay, cardiomyopathy	GTC	Generalized slowing	Increased signal in basal ganglia	Low muscle NADH-Q oxyreductase	Fluctuating seizure free and relapse
14.	Mitochondrial DNA depletion syndrome	Hypotonia, liver failure	Focal	Focal temporoparietal epileptogenic discharge	Normal	c.766_767insGATT insertion homoplasmy mutation in the *DGUOK* gene	Fluctuating seizure free and relapse
15.	SCAD	Hypotonia, developmental delay	GTC	Generalized slowing	Normal	Low SCAD enzyme in skin	Seizure free
16.	SCAD	Hypotonia, developmental delay	GTC	Generalized slowing	Normal	Low SCAD enzyme in skin	Seizure free

(*continued on next page*)

Table 2 (*continued*)

Patient	Metabolic disorder	Clinical manifestations	Type of seizures	EEG	Brain MRI	Result of confirmatory test	Response to AED
17.	Phenylketonuria	Microcephaly, craniosynostosis, features of Antley—Bixler syndrome	GTC	Generalized slowing	Normal	p.R261 homozygous mutation in exon 7 of *PAH*	Seizure free
18.	Glutaric aciduria type 1	Developmental delay, choreoathetosis	Myoclonic	Generalized slowing Focal temporoparietal epileptogenic discharge	Wide Sylvian fissures	Low glutaryl-CoA dehydrogenase in skin	Fluctuating seizure free and relapse
19.	Citrullinemia	Acute encephalopathy	GTC	Generalized slowing	Normal	p.R363W homozygous mutation in the *ASS1* gene	Seizure free
20.	Congenital disorder of glycosylation Type 1c	Developmental delay	Focal	Focal temporoparietal epileptogenic discharge	Normal	c.482A>G (p.Y161C) homozygous mutation in the *ALG6-CDG* gene	Fluctuating seizure free and relapse
21.	Niemann—Pick disease type C	Hepatosplenomegaly, cherry red spot	Focal	Focal temporoparietal epileptogenic discharge	Normal	Low leukocyte sphingomyelinase enzyme	Fluctuating seizure free and relapse
22.	Sandhoff disease	Cherry red spot, developmental regression	Myoclonic	Generalized slowing, focal temporoparietal epileptogenic discharge	Demyelination	Low leukocyte galactosidase A enzyme	Fluctuating seizure free and relapse
23.	Carnitine acylcarnitine translocase deficiency	Acute encephalopathy	Myoclonic	Generalized slowing, focal temporoparietal epileptogenic discharge	Normal	IVS2-10T>G homozygous mutation in the *CACT* gene	Seizure free
24.	VLCAD	Acute encephalopathy, hepatomegaly, raised CPK	GTC	Generalized slowing	Normal	Intron 16 IVS 16 + 6 GC deletion homozygous for the *VLCAD* gene	Seizure free

AED = antiepileptic drugs; CoA = coenzyme A; CPK = creatinine phosphokinase; EEG = electroencephalogram; GTC = generalized tonic—clonic; MRI = magnetic resonance imaging; NADH = nicotinamide adenine dinucleotide (reduced); *PEX* = peroxi; SCAD = short-chain acyl CoA dehydrogenase deficiency; UTR = untranslated region; VLCAD = very-long-chain acyl CoA dehydrogenase deficiency.

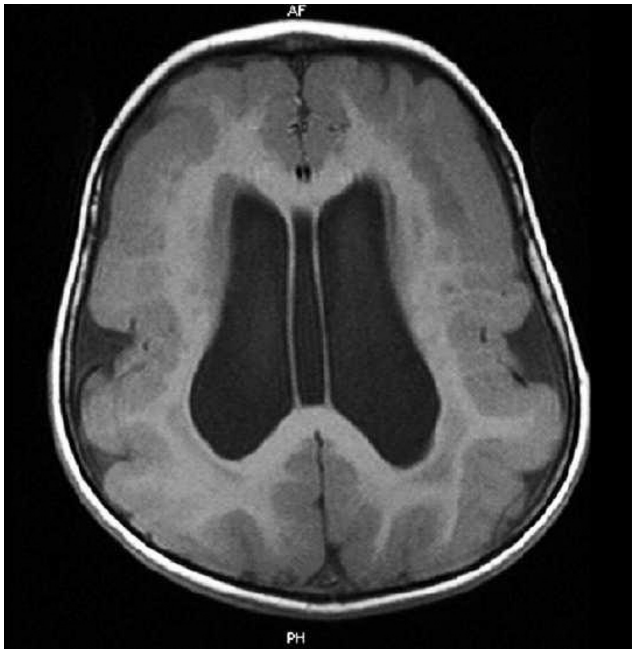

Figure 3 T_1-weighted brain magnetic resonance imaging of a 1-year-old child (patient number 18) with glutaric aciduria type 1 showing thick cerebral cortex with poorly developed sulcal and gyral formation. Wide Sylvian fissure is partially visualized.

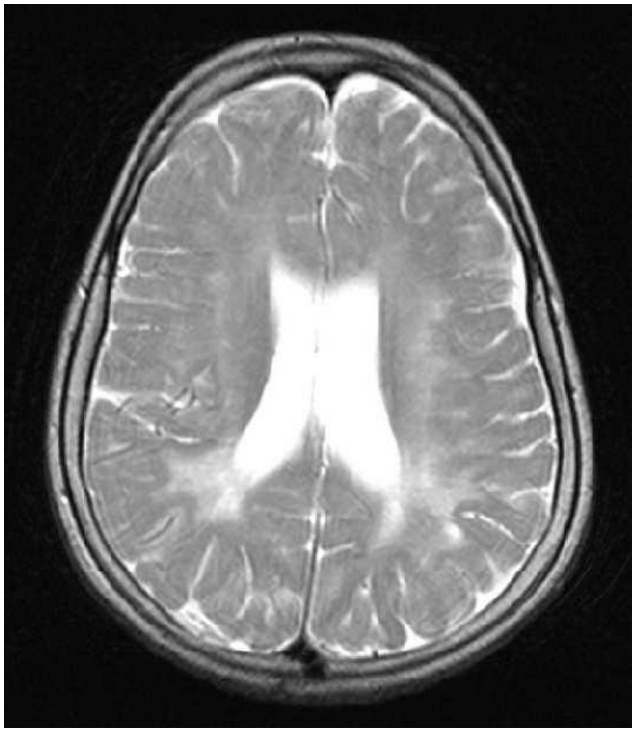

Figure 4 Brain magnetic resonance imaging of a 10-month-old infant (patient number 10) with neuronal ceroid lipofuscinosis-3 showing diffusely increased T_2-weighted signal in cerebral white matter bilaterally, which is more pronounced in the posterior portions.

acute epileptic encephalopathy, as observed in three of our patients with this disorder. This disorder often presents with infantile spasms that are difficult to control and carry a poor prognosis.[7,20] Some of our patients presented with acute decompensation, as in citrullinemia, due to the toxic effect of the associated hyperammonemia. If diagnosed early, this particular disorder is potentially treatable by detoxifying medication and dialysis.[3,4] Thus, early diagnosis and treatment of the underlying metabolic derangement are likely to prevent epilepsy in these patients. Similarly, patients with fatty acid oxidation defects, especially those with VLCAD and carnitine cycle disorders, develop encephalopathy and epilepsy secondary to hypoglycemia, which cause energy deficiency. Therefore, treating the underlying pathology of these patients by providing optimum calories, avoiding fasting, and supplementing them with carnitine when needed will result in a favorable outcome.[8,9] Furthermore, patients with biotinidase deficiency can benefit from early diagnosis and replacement therapy with oral biotin, which is an efficient and affordable medication.[4,10] The prognosis for these patients is good if biotin replacement commences in the neonatal period. By contrast, treatment of patients with peroxisomal biogenesis disorders, nonketotic hyperglycinemia, neuronal ceroid lipofuscinosis, mitochondrial disease, and Menkes disease is supportive, and their prognosis is largely unfavorable.[4,10] New treatment strategies including enzyme replacement therapy are emerging for other inborn errors of metabolism such as mucopolysaccharidoses, Gaucher disease, and Fabry disease.[4] In addition, gene therapy is a promising modality but it is still experimental.[4,10]

Brain MRI is occasionally performed in children with epilepsy. This modality can delineate the anatomical distribution of the pathological insult, as well as give a reasonable prediction of the possible etiology. In patients with epilepsy secondary to metabolic disorders, brain MRI may occasionally give an insight into the possible cause and effect of the disease.[5,7] Moreover, certain metabolic disorders may result in typical radiological findings such as enlarged perisylvian fissures and subdural effusion as observed in the patient with glutaric aciduria type 1 in this study.[8,10] Subdural effusion can also be caused by Menkes disease as observed in one patient. This patient was initially missed as a case of nonaccidental injury. Interestingly, both diagnoses can also lead to subconjunctival hemorrhage. In this study, 50% of patients had abnormal brain MRI. Most of these radiological changes were nonspecific, apart from the abnormal findings in the two patients with Menkes disease and glutaric aciduria type 1, which suggested the diagnosis before the molecular and enzyme results were available.

In most cases, epilepsy secondary to inherited metabolic disorders presents with polymorphic clinical and EEG findings that are difficult to classify into a precise epileptic syndrome.[6,8]

Some of these rare epileptic syndromes with specific seizure semiology and electroclinical pattern such as Ohtahara syndrome and early myoclonic encephalopathy start early in the neonatal period and mimic metabolic disorders with epilepsy. Nevertheless, no patient in this series fitted in any of the described epilepsy syndromes. The majority of our patients presented with generalized

tonic–clonic seizures with generalized slowing of EEG. However, all three patients with nonketotic hyperglycinemia had infantile spasms with typical hypsarrhythmia. A further seven patients in this cohort, with different metabolic disorders, had myoclonic epilepsy. It seems that specific types of seizures, such as myoclonic seizures, or distinctive electroencephalographic patterns, such as burst suppression patterns as in our cohort, may suggest an underlying metabolic disease.[20–24] Similar to our findings, previous studies indicated that early myoclonic encephalopathy may be an early sign of metabolic disease.[20–24] Therefore, the correlation between the phenotype, mode of presentation, and EEG recordings reminds physicians about the importance of making an accurate diagnosis earlier in cases with neurometabolic disorders-related early childhood epilepsy.[25] Furthermore, timing prediction of seizures is often associated with inborn errors of metabolism, depending on the mechanism by which seizures are produced.[13,26]

Management of patients with inherited metabolic disorders and seizure can be challenging. In addition to adequate general and resuscitation care including ventilation, correction of fluid and electrolyte imbalance, and starting medications and special formula as indicated, patients with inborn errors of metabolism require early selective use of antiepileptic medications if presenting with recurrent seizures. However, some of these medications may be harmful by, for example, increasing the risk of hepatotoxicity in patients with mitochondrial diseases already receiving sodium valproate.[25] One third of patients in this study achieved seizure freedom, whereas the rest failed to achieved this or fluctuated with an occasional relapse. Most of those who responded to AED had treatable metabolic diseases such as citrullinemia and biotinidase deficiency. By contrast, patients who failed to respond to AEDs had metabolic disorders with no specific available treatment such as peroxisomal disorders and lysosomal storage diseases. It is worth noting that some patients may need multiple antiepileptic medications to show clinical response. Others may show changes in the pattern and type of seizures during treatment.[25]

The introduction of the expanded newborn screening for treatable metabolic disorders has increased the early detection rate and improved management and outcome of many patients.[3,4] However, the management and prognosis of some of the untreatable metabolic disorders causing epilepsy, such as peroxisomal and mitochondrial disorders, have not improved significantly in the past few decades despite the advances in technology and diagnostic facilities.[6,14]

In addition to being a retrospective review, this study has other limitations including the patient referral system, which was based on private and insurance schemes, and thus, may not necessarily represent the pattern of diseases in the wider community.

5. Conclusion

In this cohort of young children, different metabolic disorders were identified, which caused different types of epilepsy, especially myoclonic seizures and infantile spasms.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

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References

1. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;**51**:676–85.
2. Beaudet AL, Scriver CR, Sly WS, Valle D. Genetics, biochemistry, and molecular bases of variant human phenotypes. In: Scriver CR, Beaudet AL, Valle D, Sly WS, editors. *The metabolic and molecular bases of inherited diseases*. 8th ed. New York: McGraw-Hill; 2001. p. 3–45.
3. Mohamed S. Recognition and diagnostic approach to acute metabolic disorders in the neonatal period. *Sudan J Paediatr* 2011;**11**:20–8.
4. Mohamed S. Treatment strategies for acute metabolic disorders in neonates. *Sudan J Paediatr* 2011;**11**:6–13.
5. Panagariya A, Agarwal V. Neurometabolic disorders. *Indian J Clin Biochem* 2007;**22**:1–2.
6. Poll-The BT. Disorders of metabolism and neurodegenerative disorders associated with epilepsy. In: Walla SJ, Farrell K, editors. *Epilepsy in children*. 2nd ed. London: Arnold Publishers; 2004. p. 65–75.
7. Vigevano F, Bartuli A. Infantile epileptic syndromes and metabolic etiologies. *J Child Neurol* 2002;**17**:3S9–13.
8. Pascual JM, Campistol J, Gil-Nagel A. Epilepsy in inherited metabolic disorders. *Neurologist* 2008;**14**:S2–14.
9. Pearl PL, Bennett HD, Khademian Z. Seizures and metabolic diseases. *Curr Neurol Neurosci Rep* 2005;**5**:127–33.
10. Wolf NI, Bast T, Surtees R. Epilepsy in inborn errors of metabolism. *Epileptic Disord* 2005;**7**:67–81.
11. Naviaux RK, Nguyen KV. POLG mutations associated with Alpers' syndrome and mitochondrial DNA depletion. *Ann Neurol* 2004;**55**:706–12.
12. Iizuka T, Sakai F, Kan S, Suzuki N. Slowly progressive spread of the stroke-like lesions in MELAS. *Neurology* 2003;**61**:1238–44.
13. Bahi-Buisson N, Dulac O. Epilepsy in inborn errors of metabolism. *Handb Clin Neurol* 2013;**111**:533–41.
14. Cesaroni E, Scarpelli M, Zamponi N, Polonara G, Zeviani M. Mitochondrial encephalomyopathy lactic acidosis and strokelike episodes mimicking occipital idiopathic epilepsy. *Pediatr Neurol* 2009;**41**:131–4.
15. Waldbaum S, Patel M. Mitochondria, oxidative stress, and temporal lobe epilepsy. *Epilepsy Res* 2010;**88**:23–45.
16. Yanling Y, Qiang G, Zhixiang Z, Chunlan M, Lide W, Xiru W. A clinical investigation of 228 patients with phenylketonuria in Mainland China. *Southeast Asian J Trop Med Public Health* 1999;**30**:58–60.
17. Kroczka S, Skowronek-Bala B, Zajac A. Causes of symptomatic epilepsy in two first years of life children hospitalized in 2006-2007 years. *Przegl Lek* 2008;**65**:745–50. [Article in Polish].
18. Khreisat WH. Clinical profile of epilepsy during the first two years of life. *Pak J Med Sci* 2006;**22**:5–59.

19. Mohamed S. Sanfilippo syndrome, glucose-6-phosphate dehydrogenase deficiency and sickle cell/β+ thalassemia in a child: the burden of consanguinity. *Am J Med Genet A* 2014;**164A**:267—9.
20. Rossi S, Daniele I, Bastrenta P, Mastrangelo M, Lista G. Early myoclonic encephalopathy and nonketotic hyperglycinemia. *Pediatr Neurol* 2009;**41**:371—4.
21. Dravet C, Malafosse A. Progressive myoclonus epilepsies. In: Wallace SJ, Farrell K, editors. *Epilepsy in children*. 2nd ed. London: Arnold Publishers; 2004. p. 257—67.
22. Nabbout R, Dulac O. Epileptic syndromes in infancy and childhood. *Curr Opin Neurol* 2008;**21**:161—6.
23. Wolf NI, Rahman S, Schmitt B, Taanman JW, Duncan AJ, Harting I, et al. Status epilepticus in children with Alpers disease caused by POLG1 mutations: EEG and MRI features. *Epilepsia* 2009;**50**:1596—607.
24. Kassaï B, Chiron C, Augier S, Cucherat M, Rey E, Gueyffier F, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. *Epilepsia* 2008;**49**:343—8.
25. Papetti L, Parisi P, Leuzzi V, Nardecchia F, Nicita F, Ursitti F, et al. Metabolic epilepsy: an update. *Brain Dev* 2013;**35**:827—41.
26. Pal DK, Pong AW, Chung WK. Genetic evaluation and counseling for epilepsy. *Nat Rev Neurol* 2010;**6**:445—53.