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Manifestations and treatment of epilepsy in children with neurometabolic disorders: A series from Jordan

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ABSTRACT

Purpose: To examine the characteristics of epilepsy in children with neurometabolic disorders to reveal co morbidities and optimal treatment.
Methods: We retrospectively reviewed the files of children diagnosed with a neurometabolic disorder and treated at Jordan University Hospital between 2001 and 2012. We examined the incidence, age at onset, clinical characteristics, and medical control of epilepsy.
Results: Cases treated (40 boys, 30 girls) included the different categories of neurometabolic diseases. Twenty-nine patients (41.4%) were also diagnosed with epilepsy, with age at seizure onset ranging from 3 days to 7 years. All types of seizures were reported, but generalized tonic–clonic and mixed types were most common (16/29 patients, 55.2%). Patients were on either a single antiepileptic drug (16/29, 55.2%) or multiple drugs (13/29, 44.7%), and most drugs prescribed were older generation anticonvulsants. Complete seizure control was achieved in 19/29 patients (65.5%), partial control in 7/29 (24.1%), and poor or no control in 3/29 (10.3%). EEG recordings were missing from the medical files of 10/29 patients. The first EEG revealed epileptiform activity in 12/19 patients (63.2%) and was normal in 7/19 patients (36.8%).
Conclusions: Epilepsy was diagnosed in about half of pediatric neurometabolic disease patients, with the majority of seizure cases well controlled.

1. Introduction

Hereditary neurometabolic disorders are rare in the general population but relatively common in Jordan due to the high rate of consanguineous marriage.[1] Neurometabolic disorders are a major risk factor for global developmental delay (GDD) in Jordanian children, accounting for 13% of all GDD cases,[2] a Figure 10 times higher than reported in other countries.[3]

Neurometabolic disorders are not a frequent cause of epilepsy, but epilepsy is a frequent comorbidity in many neurometabolic disorders.[4–6] However, a previous study from Jordan on the causes of neonatal seizures concluded that neurometabolic disorders account for 28.6% of all neonatal seizure cases[7] compared to 9% in previous studies on other populations.[8,9]

Most previous studies on epilepsies associated with neurometabolic disorders addressed seizure characteristics in specific neurometabolic disease entities,[10–12] while few studies have examined the incidence and clinical characteristics of epilepsy in neurometabolic disorders as a group.[13,14] To our knowledge, no such study has been conducted in Jordan.

2. Objectives of the study

To examine the characteristics of epilepsy in children with neurometabolic disorders to reveal co morbidities and optimal treatment.

3. Patients and methods

This retrospective study was conducted at Jordan University Hospital, a tertiary care referral hospital located in Amman, from January 2001 until December 2012. All children aged one day to 18 years and presenting to the child neurology clinic with a neurometabolic disorder were included. The medical files were reviewed to collect data on the type of neurometabolic disorder, the presence of epilepsy, age at seizure onset, seizure features, and responses to anticonvulsant treatment.

3.1. Definitions

The diagnosis of neurometabolic disorder was based on the clinical and biochemical findings. The diagnosis of mitochondrial disorders was based on clinical features, brain MRI, serum lactate levels, and in some cases on the results of muscle biopsy examinations using light microscopy, electron microscopy, or

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biochemical analyses of respiratory chain enzymes. The diagnosis of mucopolysaccharidosis was based solely on a positive urine test for mucopolysaccharides as specific lysosomal enzyme essays were not available at the time of study. Diagnosis of pyridoxine dependency was based on the clinical picture, failure of seizures to respond to antiepileptic treatments, and normalization of the EEG with suppression of seizures in response to pyridoxine.

We defined complete control of seizures as the disappearance of all seizures for at least 3 months. Although this is not a widely accepted definition, we used it in this study as an indicator of epilepsy control. We defined partial control of seizures as a decrease in seizures frequency of at least 25% from baseline as reported by parents. We defined "no response" as a reduction in seizure frequency of less than 25% as reported by parents.

4. Results

4.1. Patients' characteristics

During the study period, 70 patients were diagnosed with a neurometabolic disorder (40 boys and 30 girls). The total duration of follow-up ranged from 3 months to 5.5 years. The neurometabolic disorders encountered included: mitochondrial disorders (18 patients) lysosomal disorders (22 patients), peroxysomal disorders (4 patients) amino acid disorders (10 patients), organic acid disorders (5 patients) Canavan disease (2 patients), vitamins and trace element disorders (8 patients), and urea cycle defect (one patient). The specific disorders in each group are presented in Table 1.

Table 1
The various types of neurometabolic disorders and their association with epilepsy.

Type of neurometabolic disorder	No. of patients	No. of patients with seizure (%)
Mitochondrial disorders	18	7/18 (38.9%)
Lysosomal disorders	22	8/22 (36.4%)
Mucopolysacharidosis	9	0/9 (0%)
Disorders of sphingolipid metabolism	13	8/13 (61.5%)
Gaucher disease	1	0/1 (0%)
Neimann pick disease type c	1	0/1 (0%)
Metachromatic leukodystrophy	7	4/7 (57.1%)
Neuronal ceroid lipofucinosis	4	4/4 (100%)
Peroxysomal disorders	4	0/4 (0%)
X-linked adrenoleukody strophy	2	0/2 (0%)
Zellweger syndrome	2	0/2 (0%)
Amino acid disorder	10	6/10 (60%)
Homocystinurea	4	3/4 (75%)
Phenylketonuria	3	1/3 (33.3%)
Maple syrup	2	1/2 (50%)
Non ketotic hyperglycinemia	1	1/1 (100%)
Organic acid disorder	5	1/5 (20.0%)
Isovaleric academia	1	0 (0%)
Propionic acidemia	1	0 (0%)
Methylmalonic academia	3	1/3 (33.3%)
Canavan disease	2	1/2 (50%)
Vitamins and trace elements	8	5/8 (62.5%)
Pyridoxine dependency	4	4/4 (100%)
Biotinidase deficiency	1	1/1 (100%)
Wilson disease	3	0/3 (0%)
Urea cycle defect	1	1/1 (100%)
Ornithine transcarbamylase deficiency	1	1/1 (100%)

Twenty-nine of these patients (41.4%) were also diagnosed with epilepsy. The frequency of concurrent epilepsy varied among the different disorders and ranged from 0% to 100%. The frequency of epilepsy among the different disorders included: 1/1 patient or 100% in the urea cycle defect, 5/8 patients or 62.5% in the vitamins and trace element group, 6/10 patients or 60% in the amino acid disorders, 1/2 patients or 50% in Canavan disease, 7/18 patients or 38.9% in the mitochondrial disorders, 8/22 patients or 36.4% in the lysosomal disorders, 1/5 patients or 20% in the organic acid disorders and 0/4 patients or 0% in the peroxysomal disorders (Table 1). In the lysosomal disorders, disorders of sphingolipid metabolism were most frequently associated with epilepsy (8/13 patients or 61.5%), notably neuronal ceroid lipofuscinosis (4/4patients or 100%) and metachromatic leukodystrophy (4/7 patients or 57.1%), while mucopolysacharidosis, Neimann pick disease type c and Gaucher disease were not associated with epilepsy (0%). In the amino acid disorders, nonketotic hyperglycinemia (1/1 patient or 100%) and homocystinurea (3/7 patients or 75%) were most frequently associated with epilepsy. In the vitamin related disorders all patients had associated epilepsy (100%) while none of the patients with Wilson disease had epilepsy (Table 1).

4.2. Epilepsy characteristics

The age at onset of epilepsy ranged from 3 days to 7 years. Onset of seizures occurred in the first year of life in 15/29 patients (51.7%), between 13 months and 4 years of age in 8/29 patients (27.6%), and after age 4 years in 6/29 patients (20.6%). Seizures were the first presenting symptom of the disease in 12 patients (41.4%); this included all patients with pyridoxine dependency, all patients with neuronal ceroid lipofuscinosis, one patient with non ketotic hyperglycinemia, one patient with biotinidase deficiency and two patients with mitochondrial disorders. All types of seizures were reported; however, generalized tonic–clonic and mixed types were the most common (16/29 patients, 55.2%) and each occurred with approximately equal frequency. Other types of seizures observed in neurometabolic disease patients included myoclonic in 6 patients (20.6%), tonic in 4 patients (13.8%), simple focal in one patient (3.4%), partial complex in one patient (3.4%), and infantile spasms in one patient (3.4%) (Table 2). Status epilepticus was reported in only 3/29 epilepsy patients (10.3%). Classification of seizures into epileptic syndromes was possible in only 6/29 patients (20.7%). All four patients with neuronal ceroid lipofuscinosis were classified into progressive myoclonic epilepsy, one patient with pyridoxine dependency and one patient with methylmalonic academia were classified into west syndrome, and one patient with non ketotic hyperglycinemia was classified into early myoclonic encephalopathy.

All 29 comorbid patients were taking either a single antiepileptic drug (16/29 patients, 55.2%) or multiple drugs (13/29 patients, 44.7%). The most common antiepileptic drugs used as monotherapy or in combination were the older generation anticonvulsants phenobarbital, clonazepam, valproic acid, and carbamazepine (22/29 patients, 75.8%). The newer antiepileptic drugs lamotragine, topiramate, and levetiracetam were prescribed to 7/29 patients (24.1%). In our clinic the old antiepileptic drugs are tried first; newer antiepileptic drugs are usually started as add on drugs only if older drugs were tried and failed to suppress seizures. The newer antiepileptic drugs are usually tapered and stopped if they did not control seizures after titration to maximal dose. None of our patients received non-pharmaceutical treatments such as surgery, ketogenic diet, or vagal nerve stimulation. Complete control of seizures was achieved in 19/29 patients (65.5%) and partial control in 7/29 patients (24.1%), while 3/29 patients (10.3%) exhibited poor or no response to both older and newer generation antiepileptic drugs.