The Most Common Treatable Neurometabolic Epilepsies in Children

Abstract

Epilepsy is one of the most common neurological disorders during childhood. Also, neurological manifestations are the prominent signs and symptoms in inherited neurometabolic disorders.

The proper diagnosis of neurometabolic disorder in a patient with epilepsy increases the possibility of a specific treatment, which leads to improve epilepsy .Thus, it is quite necessary to make an effort to diagnose potentially treatable epileptic disorders. We have different types of seizures in neurometabolic disorders, which are often (without treatment of underline neurometabolic disorders) refractory to antiepileptic drugs.

Patients with underlying disorders have severe clinical presentations, including refractory seizures, and do not usually respond to antiepileptic drugs.

In epileptic patients with developmental delay and/or regression, abnormal neurologic examination, and abnormal brain imaging with some specific patterns, neurometabolic disorders should be considered; some of these disorders are among treatable diseases.

Therefore, neurologist should consider the etiology of epilepsy, especially in pediatric patients and the treatment should not be restricted to symptomatic therapy. The present article aimed at introducing some treatable causes of epilepsy in pediatric patients.

Keywords: Pediatrics, Epilepsy, Treatment, Metabolic, Brain Disorders

Introduction*:*

Epilepsy is one of the most common neurological disorders in childhood and its prevalence is 0.5–1% (1). Inherited metabolic disorders are individually rare with the estimated prevalence of 1:1000 (2), which bring about significant morbidity. There are more than 100 inherited neurometabolic disorders presenting with epilepsy (3). Therefore, it is an important point to make an effort to diagnose these potentially treatable disorders. Inherited neurometabolic disorders, which are treatable, are about 10 to 15 types (4). The aim of the present study is to identify the neurological diseases that meet three criteria: the disease is eminently treatable, epilepsy may be prominent in the clinical presentation, and the prognosis is linked to early diagnosis and intervention of therapy. The current investigation is about the most common treatable epilepsies and other circumstances wherein early detection and intervention may be linked to better prognosis for children. Emphasis is given here to entities in which early recognition and treatment are crucial.

Methodology*:* Review based on Literature Search, Clinical Experience, Expert Opinion

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Literature Review

1- Pyridoxine or pyridoxal-phosphate / Folinic Acid dependent seizures

Pyridoxine or pyridoxal-phosphate (PLP) responsive epilepsies must be considered in neonates with unexplained and refractory seizures, with onset before or shortly after birth (1,2). The pyridoxine-responsive epilepsy is caused by mutation in the ALDH7A1 gene encoding for the antiquitin (ATQ) protein, which is involved in lysine catabolism in the CNS (3,4). Antiquitin deficiency results in increased alpha-aminoadipicsemialdhyde (α-AASA) and piperideine-6-carboxylic acid (P6C) (4,5). P6C has been shown to inactivate PLP leading to a secondary deficiency (4, 5). The final dysfunctional pathway is brain gamma-aminobutyric acid (GABA) deficiency leading to an imbalance between excitatory and inhibitory activity and reduced epileptic threshold.

Clinical Features

Classically, pyridoxal-dependent epilepsy is usually presented as neonatal seizures and these epileptic phenomena are refractory to some conventional antiepileptic drugs (7). ATQ deficiency is characterized by early onset of epileptic encephalopathy. Despite seizure control, most of these patients will have intellectual disability (2). Seizures are mainly prolonged, frature of status epilepticus or early myoclonic encephalopathy (EME) (3). Folinic-responsive seizures were reported in few newborns with encephalopathy and apneas within 5 days after birth (8).

Diagnosis

Both α-AASA and pipecolic acid are diagnostic markers of ATQ deficiency. An elevation rate of α-AASA in the urine, plasma and cerebrospinal fluid (CSF) is pathognomonic for this disorder (2).

Management

Intravenous administration of pyridoxine (100 mg) induces cessation of seizures and electroencephalographic discharges within minutes; however, seizures may relapse and pyridoxine may be repeated up to 500 mg total within 24 hours or continued at 30/mg/kg for seven days in case of partial response (3). Chronic therapy with oral PLP 30-50 mg/kg/d may induce seizures recovery (3). Folinic-responsive seizures ceased with adding 3-5mg/kg/d enterally of folinic acid. These patients were shown to have mutations in ALDH7A1 gene; thus, the administration of adequate doses of pyridoxine was proposed (6-8).

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2- Glucose transporter I deficiency

Glucose is the most essential substrate for brain energy metabolism (10,11). In the resting, the infants and children brain can consume up to 80% of the body's total glucose supply (12). Transport of glucose from blood brain barrier is performed by glucose transporter 1, which is encoded by the GLUT1 gene at chromosome1p34.2 (SLC2A1 gene) (13).

Clinical Features

Classically, patients with GLUT1 deficiency syndrome (GLUT1DS) present with epileptic encephalopathy and different seizure types, developmental delay, acquired microcephaly, and movement disorders (14). Seizures are observed as myoclonic limb jerking with head bobbing, hypotonia, unresponsiveness, eye-rolling, and staring (14). The spectrum of epilepsy syndrome included juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, early-onset absence epilepsy, and also focal epilepsy (15).

Diagnosis

In patients with GLUT1DS, CSF glucose concentration is very low (16). Also hypoglycorrhachia is observed in meningitis, meningeal carcinomatosis, subarachnoid hemorrhage, prolonged seizures or status epilepticus, and mitochondrial diseases (17,18). In suspected cases, the CSF/blood ratio of 0.33 to 0.37 is diagnostic for GLU1 deficiency (19). CSF lactate below 1.4 mmol/l is another marker of GLUT1DS (20 ,21). The results of a study showed that CSF lactate is never elevated in GLUT1DS (22).

Management

Epilepsy in GLUT1 deficiency patients can be effectively treated with the ketogenic diet (22). This syndrome mimics the metabolic state of fasting, but maintains ketosis utilizing nutritional fat rather than body fat. Long-lasting hypoglycorrhachia can be result in irreversible brain damage (15). Ketones serve as an alternative fuel to the brain when hypoglycorrhachia occurs (22). Ketogenic diet may lead to improvement in myelination and prevention of brain damage in these patients (23). Also, alpha lipoic acid and triheptanoinare are the potential supplementary treatment of GLUT1DS (23).

3- HI/HA (Hyperinsulinism/ammonemia)

This syndrome is presented as hypoglycemia and hyperammonemia in serum. Also, this syndrome with autosomal dominant inheritance is provoked by fasting or high-protein meals (24,25). The disorder is caused by mutations of a mitochondrial enzyme of glutamate dehydrogenase (GDH) (26).

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Clinical Features

The clinical manifestation includes recurrent hypoglycemia, which could be in combination with hyperammonemia (27,28). Fasting causes the attack of hypoglycemia in these patients. Common neurological manifestations are cognitive decline and seizures that are the result of hypoglycemia and/or the complications of it (29, 30).

Diagnosis

Elevated plasma ammonia concentrations (>35µmol/lL), and a glycemic response to glucagon at times of hypoglycemia (29, 31, 32) is noted in these patients. Genetic or enzyme assay is necessary to confirm the diagnosis of Hyperinsulinism/hyperammonia syndrome (HHS). Biochemical researches included evaluation of GDH activity and GTP inhibition of GDH activity in lymphoblast homogenates (31).

Management

Diazoxide (10-15 mg/kg/day) can control the affected patients of HI/HA (33).

4- DEND (Developmental Delay, Epilepsy, Neonatal Diabetes)

Potassium channels are important regulators of excitation in tissues with their activation damping down electrical activity and causing neuron membrane repolarization (34). Mutations in the K_{ATP} channel are associated with several metabolic syndromes (35). The most severe gain-of-function mutations lead to developmental delay, epilepsy and neonatal diabetes, a condition known as DEND syndrome.

Clinical Features

Neonatal diabetes mellitus (NDM) is defined as insulin requiring hyperglycemia, diagnosed within the first three months of life. NDM is a rare disorder with an incidence of 1 in 300,000 to 500,000 live births (36). DEND syndrome is a form of permanent-NDM (PNDM) associated with developmental delay, epilepsy, and muscle weakness (37). It is an autosomal recessive disorder caused by activating mutations in the K_{ATP} channel subunit Kir6.2 (potassium inverse rectifying channel 6.2; encoded by KCNJ11) or SUR1 (sulfonylurea receptor1; encoded by ABCC8) genes located on chromosome 11 (38). Dysmorphic features including prominent metopic suture, bilateral ptosis, downturned mouth, and contractures, have been noted in this disorder (39).

Diagnosis

Diagnosis can be confirmed by genetic mutation testing (38).

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Management

Treatment with glibenclamide leads to improvement in mental, motor function, and glucose homeostasis (40).

5- Hyperekplexia, Startle disease , Stiff Infant Syndrome

Hyperekplexia is an autosomal-dominant disorder defined by an exaggerated startle reaction in response to unexpected, sudden tactile or auditory stimulation. (41-43).

Clinical Features

Symptoms may begin with severe opisthotonic posturing and hypertonia, in the neonatal period. Head retraction may appear in older children (44). The stiffness disappears spontaneously during infantile period, and most children are normal by three years of age. In adolescence period, stiffness attacks may recur in response to cold exposure and startle reaction (45).

Diagnosis

A family history of startle disease is important to diagnosis. Unlike startle-provoked epilepsy, in stiff infant syndrome, the Electroencephalography (EEG) is always normal (45). The disorder is associated with mutations in the α-1 subunit of the glycine receptor (46).

Management

The most useful agent to reduce the attack is Clonazepam. Levetiracetam or sodium valproate are also useful. (45). Combination of clonazepam and clobazam was effective in ambulation and eliminating the falls (47).

6- Creatine synthesis disorders

Creatine kinase converts the creatine to creatine phosphate (48). Creatine is an essential material for brain.

One syndrome is focused on creatine transport and two other syndromes focused on creatine synthesis. The creatine synthesis disorders are due to either a defect in the guanidinoacetic acid methyltransferase (GAMT) or arginine glycine acyl transferase (AGAT) enzymes (48, 49). Creatine deficiency in the brain is as a result of deficiency in creatine transporter gene (SLC6A8) (50).

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Clinical Features

Seizures, mental retardation, and speech delay are the main symptoms observed in these syndromes (49). Global developmental delay is observed prior to 12 months of age. Speech delay is severe symptom as are the receptive language deficiencies (48). Abnormal signal changes of the basal ganglia and also extrapyramidal movement disorder, early global developmental delay and refractory seizures are observed in the patient with severe type (49).

Diagnosis

Cerebral creatine deficiency syndrome may be diagnosed with abnormal guanidine-acetic acid (GAA) levels in urine or plasma (51, 55). Magnetic resonance spectroscopy (MRS) reveals severely reduced creatine peak (52).

Management

Cerebral creatine deficiency syndrome responds to supplementation of creatine and ornithine with arginine restriction (51). The doses of creatine in patients with the diagnosis of AGAT deficiency are 100–800 mg/kg/day administered three or four doses daily (53). Treatment in early life with 100–800 mg/kg/day supplementation of creatine causes prevention of the cognitive deficits in the GAMT disorder (48,54). Sodium benzoate (100 mg/kg/day) and Ornithine (100-700 mg/kg/day) is also recommended for reducing GAA (54,55).

7- Serine biosynthesis defects

Serine is an amino acid, which is absorbed from dietary protein (56). It is synthetized by hydroxyl methyl transferase from the conversion of glycine (57- 59).

Clinical Features

Serine deficient patients have severe neurological symptoms including intractable seizures, psychomotor retardation, and congenital microcephaly (56).Children shows neurodevelopmental delay and also different patterns of clinical seizures (60). Seizures start as flexor spasms with West syndrome or as generalized tonic clonic seizures (61). In some patients, bursts of inappropriate laughing suggest that gelastic seizures are also present (62).

Diagnosis

Low level of serine in plasma and low cerebrospinal fluid concentrations of serine, glycine, and 5-methyltetrahydrofolate (5-MTHF) are diagnostic markers for this type of seizure (60, 63).

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Management

High dose of serine (200–600 mg/kg/day) is recommended (64). It is shown that serine prevents epilepsy and causes normal neurodevelopment in the sibling of the patients (60). Treatment with serine (500 mg/kg/d) and glycine (200 mg/kg/d) normalizes plasma and CSF concentrations (64).

8- Biotinidase deficiency

Biotinidase deficiency is an autosomal recessive disease with prevalence of 1/60000 in normal population (65, 66). The main cause of biotinidase deficiency is the problem in biotin absorption, which previously called as late-onset multiple (holo) carboxylase deficiency (67,68).

Clinical Features

Major clinical phenotypes of biotinidase deficiency include developmental delay, hypotonia, seizures, ataxia, alopecia, perioral rash, sensorineural hearing loss, vision loss, optic atrophy, lactic academia (65, 66,69), myopathy/peripheral neuropathy, and cellular immunity problems (66).

Diagnosis

Patients show ketosis, lactic acidosis, hypoglycemia, and hyperammonia in biothinidase deficiency (70). In severe biothinidase deficiency, the activity of enzyme is less than 10% and in partial enzyme deficiency the activity of biothinidase is 10-30 % (71).

Management

Children with severe form of biotinidase deficiency are treated with pharmacologic doses of biotin (5–20 mg daily) (72). Early diagnosis and therapy can significantly reduce their complications, and prognosis is excellent (65).

9- Cerebral folate deficiency

Infants with cerebral folate deficiency usually presents between 4-6 months with a progressive neurological regression (73,74).

Clinical Features

Cerebral folate deficiency presents with severe irritability, decreasing of head circumference, and developmental regression, leading to profound cognitive decline, blindness, ataxia, and spastic quadriplegia (75).

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Diagnosis

Diagnosis of cerebral folate deficiency is confirmed by low level of folate metabolite and methylentetrahydrofolate (5MTHF) in CSF despite of normal serum folate (73-76).

Management

Treatment with oral folinic acid (0.5-1 mg/kg/day), for at least a year, has been shown to normalize 5MTHF levels in the CSF and produces neurologic recovery (75, 77).

10- Biopterin synthesis disorders

Tetrahydrobiopterin (BH4) synthesis deficiency is one of the malignant types of hyperphenylalaninemia (78). BH4 deficiency is associated with hyperphenylalaninemia in 1–3 percent of patients (79). BH4 is known as cofactor of phenylalanine hydroxylase (80).

Clinical Features

Major phenotype of BH4 disorders include intellectual disability, myoclonic seizures, muscular rigidity, dystonia, and microcephaly (81).

Diagnosis

This condition can be identified in neonatal period by an elevated phenylalanine level in serum (78-80). By measuring dihydropteridine reductase in blood dried spots, neurotransmitters and pterins in the CSF, pterin metabolites in urine, and reduced enzyme activity, the disease can be diagnosed (80).

Management

A 5–10 mg/kg dose of BH4is the significant dose for correction of peripheral hyperphenylalaninemia, and 10–20 mg/kg per day is needed for correction of classic phenylketonuria (78, 79). Lifelong supplementation with L-DOPA, 5-hydroxytryptophan, and carbidopa is necessary for the treatment of hyperphenylalaninemia (79, 82-85). Intracranial calcifications in these patients may be reversible with folinic acid (81).

11- Methylmalonic acidemia (MMA)

Neonatal form of methylmalonic acidemia presents with rapid deterioration of newborn after a short symptom-free interval (86, 87). Seizures may complicate acute metabolic decompensation (88).

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Clinical Features

Children with methylmalonic acidemia may appear normal at birth. The symptoms during the first week after birth appear in 80% of those with complete mutase deficiency (89). After the protein feeding, the child shows recurrent vomiting, dehydration, hypotonia, lethargy, respiratory distress, and failure to thrive. More than 50% of patients are presented with anemia, leukopenia, and thrombocytopenia (89, 90) .Also intracranial hemorrhage is reported in MMA (91).

Diagnosis

Analysis of urine organic acids is needed for the diagnosis of MMA (90). Neuroimaging in MMA may show swelling, delay in myelin maturation, focal necrosis of the globus pallidum, calcification of the basal ganglia, and volume loss (88).

Management

The aim of treatment is limiting catabolism and restricting protein intake (0.5–l.5g/kg/day) in the acute crises. Intramuscular hydroxocobalamin (1 mg/ weekly), L-carnitine, betaine, and folate are typically used for the treatment of MMA (90, 93-95).

12- Glutaric aciduria type 1 (GA1)

Glutaric aciduria type 1 (GA1) is an inborn error of lysine, hydroxylysine, and tryptophan catabolism (96, 97).

Clinical Features

In later infancy, GA1 mainly presents as an acute encephalopathy with predominant dyskinesia and dystonia due to necrosis of the basal ganglia, particularly the putamina (98). In GA1, neonates present with jitteriness, irritability, macrocephaly, and hypotonia. Seizures usually occur within the context of acute decompensation in association with symptoms of rapid deterioration. Dyskinetic movements may be often misdiagnosed for seizures (99).

Diagnosis

Urine organic acids profile shows increased 3-OH- glutaric acid and glutaryl -carnitine as the major peak (100). Neuroimaging typically shows enlarged frontotemporal CSF spaces, wide Sylvian fissures, and sometimes subdural hematoma (Figure 1) (101, 102).

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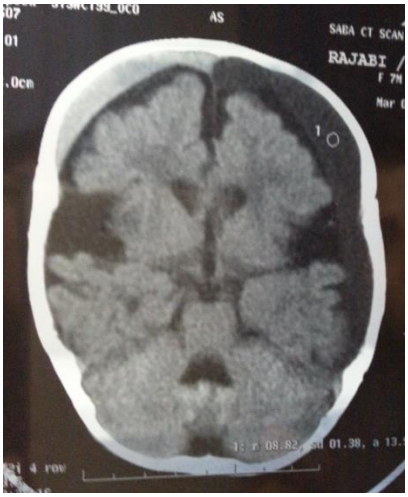

Figure 1: A patient with glutaric aciduria type 1. Axial T1WI MRI shows frontotemporal atrophy, resulting in wide sylvian fissures with right subdural hematoma

Management

The basic treatments include dietary protein and lysine restriction, carnitine and riboflavin supplementation (100,103).

13- Homocystinuria

The increased excretion of homocysteine is noted in several inborn errors of methionine metabolism. The deficiency of cystathionine β synthase is responsible for this disorder(104).

Clinical Features

Clinical features of homocystinuria include vascular occlusive disease, malar flush, osteoporosis, genu valgum, pes cavus, marfanoid appearance, mental retardation, seizure, typical strokes, dystonia, and psychiatric abnormalities (105).

Diagnosis

Diagnosis is based on accumulation of Homocysthine and methionine in serum (105,106).

Management

All the patients need pyridoxine (vitamin B6) prior to starting the treatment (106). Pyridoxine, folic acid, and vitamin B12 have been used in pyridoxine non-responders as cofactors of methionine metabolism (107). Concentrations of homocysteine may also be reduced in B6-unresponsive patients by treatment with betaine (86 to 280 mg/kg) (105).

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14- Ketogenic diet responsive epilepsies

Glucose transporter-1 deficiency was described in details in the previous paragraphs (11 -23).

Pyruvate dehydrogenase complex deficiency

Clinical signs associated with pyruvate dehydrogenase complex (PDC) deficiency include hypotonia/hypertonia, seizures, microcephaly, ataxia, respiratory distress, facial dysmorphism, spasticity, peripheral neuropathy, optic atrophy, nystagmus, ptosis, and strabismus (108-111). Patients are usually treated with a high-fat (>55%), low-carbohydrate (Ketogenic) diet and thiamine (100–600mg/day) (112).

Conclusion

Epilepsy is one of the most clinical features of different neurogenetic and neurometabolic disorders. Finding of etiology, especially in pediatric epileptic patients is very important for treating epilepsy. In the present article, some treatable causes of epilepsy in pediatric patients were mentioned. In most of these epileptic disorders, by treating the underlying causes of diseases, we can stop epilepsy and control it appropriately. Therefore, the pediatric neurologist should find the etiology in pediatric epileptic patients and symptomatic therapy is not acceptable in this field.

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