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The Most Common Treatable Neurometabolic Epilepsies in Children

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ABSTRACT

Epilepsy is a common neurological disorder in childhood with prominent neurological manifestations, signs, and symptoms in inherited neurometabolic disorders. Accurate diagnosis of neurometabolic disorders in epileptic patients increases the possibility of a specific treatment to improve epilepsy. Therefore, early diagnosis is essential in potentially treatable epileptic disorders. Various seizure types occur in neurometabolic disorders, which are often refractory to antiepileptic drugs (without the treatment of the underlying neurometabolic disorders). Patients with underlying disorders have severe clinical presentations, such as refractory seizures. In addition, they do not respond to antiepileptic drugs in many cases. In the epileptic patients with developmental delay and/or regression, neurometabolic disorders should be considered in the presence of abnormal neurological examination and brain imaging with specific patterns. Some of these disorders are potentially treatable. Therefore, neurologists should determine the etiology of epilepsy, especially in pediatric patients, and the treatment should not be restricted to symptomatic therapy. The present study aimed to introduce some of the treatable causes of epilepsy in pediatric patients.

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Introduction

Epilepsy is a common neurological disorder in childhood with the global prevalence rate of 0.5-1% (1). Inherited metabolic disorders are individually rare, with an estimated prevalence of 1:1000 (2), and are associated with significant morbidity. More than 100 inherited neurometabolic disorders are presented with epilepsy (3). Therefore, attempts should be made for the accurate diagnosis of these potentially treatable disorders.

Treatable inherited neurometabolic disorders are of 10-15 types (4). The present study aimed to identify the neurological diseases that meet three criteria: 1) eminently treatable diseases; 2) clinical presentation of prominent epilepsy and 3) association of prognosis with early diagnosis and treatment intervention. The current investigation focused on the most common treatable epilepsies and other conditions in which early diagnosis and intervention could lead to better prognosis in children. Of note, the emphasis has been placed on the conditions in which early detection and treatment are crucial.

This review was conducted based on literature search, clinical experience, and expert opinions.

Literature Review

1-*Pyridoxine-DependentSeizures/Pyridoxal Phosphate- and Folinic Acid-Responsive Seizures*

Pyridoxine-dependent or pyridoxal phosphate (PLP)-responsive epilepsies must be considered in the neonates with unexplained, refractory seizures, beginning before or shortly after birth (1,2).

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Pyridoxine-dependent epilepsy is caused by mutations in the ALDH7A1 gene encoding the antiquitin (ATQ) protein, which is involved in lysine catabolism in the central nervous system (CNS) (3,4). ATQ deficiency leads to increased alpha-aminoadipic semialdehyde (α-AASA) and piperideine-6-carboxylic acid (P6C) (4,5). P6C has been shown to inactivate PLP, thereby leading to a secondary deficiency (4,5). The final dysfunctional pathway is brain gamma-aminobutyric acid (GABA) deficiency, which causes an imbalance between excitatory and inhibitory activities, reducing the epileptic threshold.

Clinical Features

Classically, pyridoxal-dependent epilepsy is presented as neonatal seizures, which are refractory to some conventional antiepileptic drugs (7). ATQ deficiency is characterized by the early onset of epileptic encephalopathy. Despite seizure control, most of these patients develop intellectual disabilities (2). These prolonged seizures are a fracture of status epilepticus or early myoclonic encephalopathy (3). Folinic acid-responsive seizures have been reported in a few newborns with encephalopathy and apneas within five days after birth (8).

Diagnosis

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

Management

Intravenous administration of pyridoxine (100 mg) induces the cessation of epileptic seizures and electroencephalographic discharges within minutes. However, seizures may relapse, and pyridoxine administration may be repeated (total of 500 mg) within 24 hours or continued at 30/mg/kg for seven days in the case of a partial response (3).

Chronic therapy with oral PLP (30-50 mg/kg/day) may also induce seizure recovery (3). Furthermore, folinic acid-responsive seizures could be ceased with an additional dose of enteral folinic acid (3-5 mg/kg/day). Since mutations in the ALDH7A1 gene have been reported in these patients, administration of the adequate doses of pyridoxine has been proposed (6-8).

2-Glucose Transporter Type-1 Deficiency

Glucose is the most essential substrate for brain energy metabolism (10,11). At rest, the brain of infants and children consumes up to 80% of the total glucose supply in the body (12). Transport of glucose from the blood-brain barrier is performed by glucose transporter 1 (GLUT1), which is encoded by the GLUT1 gene on chromosome 1p34.2 (SLC2A1 gene) (13).

Clinical Features

Classically, patients with GLUT1 deficiency syndrome (Glut1-DS) present with epileptic encephalopathy, as well as various seizure types, developmental delay, acquired microcephaly, and movement disorders (14). Seizures are myoclonic (involuntary limb jerking with head bobbing), hypotonic, and unresponsive, along with eye-rolling and staring (14). The spectrum of epilepsy syndromes includes juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, early-onset absence epilepsy, and focal epilepsy (15).

Diagnosis

In the patients with Glut1-DS, CSF glucose concentration is extremely low (16). Moreover, hypoglycorrhachia is observed in meningitis, meningeal carcinomatosis, subarachnoid hemorrhage, prolonged seizures or status epilepticus, and mitochondrial diseases (17,18). In suspected cases, the CSF/serum ratio of 0.33 to 0.37 is considered diagnostic for Glut1-DS (19). CSF lactate level of less than 1.4 mmol/l is another marker of Glut1-DS (20,21), and the results of a study in this regard showed that CSF lactate never elevates in Glut1-DS (22).

Management

Epilepsy in the patients with Glut1-DS could be effectively treated with a ketogenic diet (22). This syndrome mimics the metabolic state of fasting, while maintaining ketosis and utilizing nutritional fat rather than the body fat. Prolonged hypoglycorrhachia may lead to irreversible brain damage (15). Ketones serve as an alternative fuel to the brain in the presence of hypoglycorrhachia (22). A ketogenic diet could improve myelination and prevent brain damage in these patients (23). Additionally, alpha lipoic acid and triheptanoin are among the potential supplementary Glut1-DS therapies (23).

3-Hyperinsulinism/Ammonemia (HI/HA)

This syndrome presents as serum hypoglycemia and hyperammonemia. With autosomal dominant inheritance, this syndrome is provoked by fasting or high-protein diets (24,25). The disorder is caused by the mutations in glutamate dehydrogenase (GDH), which is a mitochondrial enzyme (26).

Clinical Features

One of the major clinical manifestations of HI/HA in recurrent hypoglycemia, which could be ac-

companied by hyperammonemia (27,28). Fasting causes hypoglycemic attacks, and the most common neurological manifestations in the patients include cognitive decline and seizures due to hypoglycemia or its complications (29,30).

Diagnosis

Elevated plasma ammonia concentrations (>35 µmol/lL) and glycemic response to glucagon in the presence of hypoglycemia (29,31,32) are noted in the patients with HI/HA. Genetic or enzyme assays are essential to confirming the diagnosis of the hyperinsulinism/hyperammonemia syndrome. Biochemical studies have included the evaluation of GDH activity and GTP inhibition of GDH activity in lymphoblast homogenates (31).

Management

HI/HA could be controlled by diazoxide treatment at the dosage of 10-15 mg/kg/day (33).

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

Potassium channels are important regulators of tissue excitation, and their activation damps down electrical activity and causes neuron membrane repolarization (34). Mutations in the KATP channel are associated with several metabolic syndromes (35). Severe gain-of-function mutations lead to developmental delay, epilepsy, and neonatal diabetes, also known as the DEND syndrome.

Clinical Features

Neonatal diabetes mellitus (NDM) is defined as insulin-requiring hyperglycemia, which is often diagnosed within the first three months of life. NDM is a rare disorder with an incidence of 1:300,000-500,000 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 the activated mutations in the KATP channel subunit Kir6.2 (potassium inverse rectifying channel 6.2, encoded by KCNJ11) or SUR1 gene (sulfonylurea receptor1, encoded by ABCC8) located on chromosome 11 (38). Some of the dysmorphic features in DEND include prominent metopic suture, bilateral ptosis, downturned mouth, and contractures (39).

Diagnosis

Diagnosis of DEND could be confirmed by genetic mutation testing (38).

Management

Glibenclamide treatment could enhance the mental function, motor function, and glucose homeostasis of the patients with DEND (40).

5-Hyperekplexia, Startle Disease, and Stiff Infant Syndrome

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

Clinical Features

Symptoms may occur due to severe opisthotonic posturing and hypertonia in the neonatal period. In addition, head retraction may be observed in older children (44). The stiffness disappears spontaneously during infancy, and most children become normal by the age of three. In adolescence, stiffness attacks may recur in response to cold exposure and startle reactions (45).

Diagnosis

Family history of startle disease is considered essential to diagnosis. Unlike startle-provoked epilepsy, electroencephalography is normal in stiff infant syndrome (45). The disorder is associated with mutations in the α-1 subunit of the glycine receptor (46).

Management

Clonazepam, levetiracetam, and sodium valproate are the most effective agent to reduce these attacks (45). In addition, the combination of clonazepam and clobazam could be effective in the ambulation and elimination of the falls (47).

6-Creatine Synthesis Disorders

Creatine kinase converts creatine into creatine phosphate (48). Creatine is an essential material for the brain. In this regard, one syndrome is focused on creatine transport, and two other syndromes are focused on creatine synthesis. Creatine synthesis disorders are caused by the defects in the guanidinoacetic acid methyltransferase (GAMT) or arginine glycine acyl transferase (AGAT) enzymes (48,49). Creatine deficiency in the brain is caused by the deficiency in creatine transporter gene (SLC6A8) (50).

Clinical Features

Seizures, mental retardation, and speech delay are the main symptoms associated with this syndrome (49). Moreover, global developmental delay is observed prior to 12 months of age. Speech delay and receptive language deficiencies are the other severe symptoms in this syndrome (48). Severe types of this syndrome are associated with complications such as the abnormal signal changes of the basal ganglia, extrapyramidal movement

disorders, early global developmental delay, and refractory seizures (49).

Diagnosis

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

Management

Cerebral creatine deficiency syndrome responds to the supplementations of creatine and ornithine with arginine restriction (51). Creatine doses in the patients diagnosed with AGAT deficiency have been determined at 100-800 mg/kg/day (3-4 doses daily) (53). Early treatment with 100-800 mg/kg/day creatine supplementation could prevent the cognitive deficits associated with GAMT disorder (48,54). In addition, sodium benzoate (100 mg/kg/day) and ornithine (100-700 mg/kg/day) are recommended for GAA reduction (54,55).

7-Serine Biosynthesis Defects

Serine is an amino acid that is absorbed from dietary protein (56). It is synthesized by serine hydroxymethyltransferase from the conversion of glycine (57-59).

Clinical Features

Patients with serine deficiency present with severe neurological symptoms, including intractable seizures, psychomotor retardation, and congenital microcephaly (56). Furthermore, serine deficient children have neurodevelopmental delay and variable clinical seizure patterns (60). Seizures begin as flexor spasms with West syndrome or generalized tonic-clonic seizures (61). In some cases, bursts of inappropriate laughing suggest that gelastic seizures are present as well (62).

Diagnosis

Low plasma level of serine and low CSF concentrations of serine, glycine, and 5-methyltetrahydrofolate (5-MTHF) are the diagnostic markers for this type of seizures (60,63).

Management

High doses of serine (200-600 mg/kg/day) are recommended for the patients with serine deficiency (64). Serine has been shown to prevent epilepsy and cause normal neurodevelopment in the siblings of these patients (60). Moreover, treatment with serine (500 mg/kg/d) and glycine (200 mg/kg/d) could normalize the plasma and CSF concentrations (64).

8-Biotinidase Deficiency

Biotinidase deficiency is an autosomal recessive disease with the prevalence of 1:60,000 in normal populations (65,66). The main cause of biotinidase deficiency is problematic biotin absorption, which was previously known as late-onset multiple holocarboxylase deficiency (67,68).

Clinical Features

Major clinical phenotypes of biotinidase deficiency include developmental delay, hypotonia, seizures, ataxia, alopecia, perioral rashes, sensorineural hearing loss, vision loss, optic atrophy, lactic academia (51,65,66), myopathy/peripheral neuropathy, and cell immunity disorders (66).

Diagnosis

Patients with biotinidase deficiency present with ketosis, lactic acidosis, hypoglycemia, and hyperammonia (69). In severe cases, enzyme activity is less than 10%, and in partial enzyme deficiency, biothinidase activity is 10-30% (70).

Management

Children with severe biotinidase deficiency are treated with the pharmacologic doses of biotin (5-20 mg/day) (71). Early diagnosis and treatment could significantly reduce the associated complications, resulting in excellent prognosis (65).

9-Cerebral Folate Deficiency

Infants with cerebral folate deficiency normally present with progressive neurological regression at the age of 4-6 months (72,73).

Clinical Features

Cerebral folate deficiency is associated with severe irritability, reduction of the head circumference, and developmental regression, which lead to profound cognitive decline, blindness, ataxia, and spastic quadriplegia (69).

Diagnosis

Diagnosis of cerebral folate deficiency is confirmed by the low levels of folate metabolite and methyltetrahydrofolate (5 MTHF) in the CSF despite normal serum folate (72-74).

Management

Treatment with oral folinic acid (0.5-1 mg/kg/day) for a minimum of one year has been shown to normalize the levels of 5 MTHF in the CSF and result in neurological recovery (69,75).

10-Biopterin Synthesis Disorders

Tetrahydrobiopterin (BH4) synthesis deficiency is a malignant type of hyperphenylalaninemia

(76). BH4 deficiency is associated with hyperphenylalaninemia in 1-3% of the patients (69). In addition, BH4 is known as the phenylalanine-hydroxylase cofactor (77).

Clinical Features

Major phenotypes of BH4 disorders include intellectual disability, myoclonic seizures, muscular rigidity, dystonia, and microcephaly (51).

Diagnosis

This condition could be diagnosed in the neonatal period based on the elevated serum phenylalanine level (69,76,77). Other diagnostic measures in this regard include the measurement of dihydropteridine reductase in dried blood spots, neurotransmitters and pterins in the CSF, pterin metabolites in urine, and reduced enzyme activity (77).

Management

BH4 does of 5-10 mg/kg is the significant dose for the correction of peripheral hyperphenylalaninemia, and 10-20 mg/kg/day is the required dose for the correction of classical phenylketonuria (69,76). Furthermore, lifelong supplementation with L-DOPA, 5-hydroxytryptophan, and carbidopa is considered essential for the treatment of hyperphenylalaninemia (69,78-81). Intracranial calcifications in these patients may be reversible with folinic acid treatment (51).

11-Methylmalonic Acidemia (MMA)

Methylmalonic acidemia (MMA) in neonates is presented with the rapid deterioration of the newborn after a short symptom-free interval (8,82). In such cases, seizures may complicate acute metabolic decompensation (83).

Clinical Features

Children with MMA may appear normal at birth. The symptoms often manifest during the first week of birth in 80% of the cases with complete mutase deficiency (67). After protein feeding, the infant may have recurrent vomiting, dehydration, hypotonia, lethargy, respiratory distress, and failure to thrive. More than 50% of the patients with MMA present with anemia, leukopenia, and thrombocytopenia (67, 69). In addition, intracranial hemorrhage has been reported in MMA (84).

Diagnosis

Analysis of urinary organic acids is essential to the diagnosis of MMA (69). Neuroimaging in MMA may show swelling, delayed myelin maturation, focal necrosis of the globus pallidus, calcification of the basal ganglia, and volume loss (83).

Management

The aim of MMA treatment is to limit catabolism and restrict protein intake (0.5-l.5 g/kg/day) in the acute cases. Moreover, intramuscular hydroxocobalamin (1 mg/week), L-carnitine, betaine, and folate are typically used in the treatment of MMA (69,86-88).

12-Glutaric Aciduria Type 1 (GA1)

Glutaric aciduria type 1 (GA1) is an inborn error of lysine, hydroxylysine, and tryptophan catabolism (8,89).

Clinical Features

In late infancy, GA1 is mainly presented as acute encephalopathy with predominant dyskinesia and dystonia due to the necrosis of the basal ganglia, particularly the putamina (90). In GA1, neonates present with agitation, irritability, macrocephaly, and hypotonia. Seizures normally occur within the context of acute decompensation in association with the symptoms of rapid deterioration. Dyskinetic movements may often be misdiagnosed for seizures (91).

Diagnosis

Urinary organic acids profile shows increased 3-OH-glutaric acid and glutarylcarnitine as the major peak in GA1 (92). Neuroimaging typically shows enlarged frontotemporal CSF spaces, wide Sylvian fissures, and occasional subdural hematoma (Figure 1) (93,94).

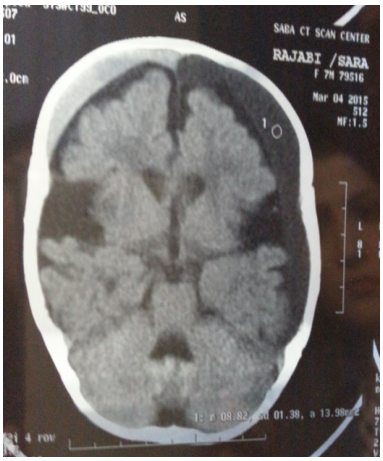

Figure 1. A patient with glutaric aciduria type 1. Axial T1WI MRI shows frontotemporal atrophy, resulting in wide sylvian fissures with right subdural hematoma.

Management

The basic treatments for GA1 involve dietary protein supplementation, lysine restriction, and carnitine and riboflavin supplementation (69,92).

13-Homocystinuria

Increased excretion of homocysteine is noted in several inborn errors of methionine metabolism, which is mainly caused by cystathionine β synthase deficiency (95).

Clinical Features

Clinical features of homocystinuria include vascular occlusive disease, malar flush, osteoporosis, genu valgum, pes cavus, marfanoid appearance, mental retardation, seizures, typical strokes, dystonia, and psychiatric abnormalities (96).

Diagnosis

Diagnosis of homocystinuria is based on the accumulation of serum homocysteine and methionine (67,96).

Management

All the patients with homocystinuria need pyridoxine (vitamin B6) prior to treatment (67). Pyridoxine, folic acid, and vitamin B12 have been used in pyridoxine non-responders as the cofactors of methionine metabolism (69). Homocysteine concentrations may also decrease in B6-unresponsive patients through betaine treatment (86-280 mg/kg) (96).

14-Ketogenic Diet-Responsive Epilepsies

GLUT1 deficiency has been described in detail in the previous sections of the article (11-23).

Pyruvate Dehydrogenase Complex Deficiency

The clinical signs associated with pyruvate dehydrogenase complex deficiency include hypotonia/hypertonia, seizures, microcephaly, ataxia, respiratory distress, facial dysmorphism, spasticity, peripheral neuropathy, optic atrophy, nystagmus, ptosis, and strabismus (97-100). Patients are normally treated with a high-fat (>55%), low-carbohydrate (ketogenic) diet and thiamine administration (100-600 mg/day) (67).

Conclusion

Epilepsy is among the most common clinical features in various neurogenetic and neurometabolic disorders. Etiological findings play a pivotal role in the treatment of epilepsy, especially in pediatric epileptic patients. In the present study, some treatable causes of epilepsy in pediatric patients were explored. In the majority of these epileptic disorders, treatment of the underlying causes of the disease could effectively control epilepsy. Therefore, it is recommended that pediatric neurologists investigate the etiologies in pediatric epileptic patients, while symptomatic therapy is not considered to be a viable option in this regard.

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Conflict of Interest

The authors declare no conflict of interest.

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