TREATABLE METABOLIC EPILEPSIES. DIAGNOSIS AND TREATMENT

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Abstract

Over 200 different metabolic disorders are prone to epileptic seizures, as the primary clinical manifestation or with other manifestations of their clinical condition.

Most of the metabolic disorders presenting with epilepsy are diagnosed and managed in childhood. Treatable metabolic diseases causing epilepsy are a well-defined group of all metabolic disorders, which are amenable to adequate management aiming directly at the primary cause of the seizures and at preventing or minimizing seizures' complications. Treatable metabolic epilepsies are clinically important to recognize and diagnose. Although some types of metabolic epilepsy require detailed testing for the diagnosis to be made, other types may be diagnosed on the basis of the clinical assessment, as is the case of pyridoxine-dependent epilepsy, with seizures cessation after pyridoxine administration.

The etiological mechanism of seizures in metabolic disorders is very complex. Cofactor deficiency, accumulation of toxic metabolites and energy deficiency are the main causes.

Administration of supplementation, early dietary interventions or other therapy options can treat metabolic disorders and control epileptic seizures or, at least, improve outcomes.

1. Introduction

Metabolic epilepsies are caused by an underlying distinct metabolic disorder, which is in turn associated to a high risk of developing epilepsy [1]. Over 200 different metabolic disorders are clinically prone to epileptic seizures as their main manifestation or with other manifestations of a complex phenotype [2].

Underlying etiology of epileptic seizures in metabolic disorders is diverse. Cofactor deficiency is a main underlying aetiology for seizures related to metabolic diseases, as is pyridoxal phosphate responsive epilepsy and pyridoxine - dependent epilepsy. Also, when toxic metabolites, such as ammonia, accumulate the occurrence of seizures may emerge. Several metabolic diseases present with hyperammonemia, as in urea cycle metabolic disorders and in metabolic acidemias. Furthermore, seizures may be related to disturbed neurotransmission, such as glycine accumulation in glycine encephalopathy. Seizures could also be caused by energy deficiency, as in disorders underlying hypoglycemia or impaired transport of glucose in the brain. Certain metabolic diseases are related to structural malformations of the brain that may provoke seizures. One classic example being polymicrogyria that is a prominent feature in peroxisomal disorders [1].

Treatable metabolic diseases causing epilepsy are a well-defined group of all metabolic disorders, which are amenable to adequate management aiming directly at the primary cause of the seizures and at preventing or minimizing seizures' complications. Treatable metabolic epilepsies are clinically important to recognize and diagnose, since early treatment optimizes the outcome. For a better understanding of early manifestations, diagnostic procedures and treatment options, these conditions are presented in detail.

2. Algorithm concerning metabolic epilepsies

It is worth stressing that epileptic manifestations per se, are not common ground in metabolic diseases. Consequently, seizures unrelated to systemic, neurologic and/or metabolic conditions do not, likely, underly metabolic diseases [3].

Most of the metabolic disorders associated with epilepsy are diagnosed and managed in childhood. Diagnosing epilepsy, early in its course, is essential because there are metabolic disorders potentially treatable. Immediate initiation of the appropriate therapy may lead to seizure control [1].

Metabolic epilepsies should be a potential diagnosis in neonatal and infancy seizures of unknown etiology, in refractory and/or long-lasting seizures, in seizures deteriorating with AEDs, in seizures deterioration either after fasting (related to GLUT1) or after

Table 1. Clinical presentations leading to the possible diagnosis of metabolic epilepsy

Aversion or intolerance to food
Developmental delay
Hypotonia
Developmental regression
Signs of encephalopathy (irritability, restlessness, crying, vomiting)
Abnormal head circumference (micro or macrocephaly)
Facial dysmorphia
Fluctuating course of illness
Abnormalities of lens or retina (cataracts, optic nerve atrophy, retinitis pigmentosa, cherry red spot)
Organomegaly
Movement disorders
Unusual body fluid odor
Metabolic acidosis with high-anion gap and metabolic derangements
Ketonuria
Severe epilepsy in a sibling
Parental consanguinity

protein rich meals (related to urea cycle defects), in neonatal myoclonic encephalopathy, in progressive myoclonic epilepsy in adolescence and in progressive myoclonic epilepsy in young adults (Table 1) [4, 5].

A good response to AEDs does not exclude metabolic epilepsies. Patients with GLUT1 deficiency are a paradigm of favorable response to commonly used AEDs [6], and pyridoxine-dependent epilepsy patients can have moderate seizure control, even absence of seizures, after the discontinuation of pyridoxine supplementation [7].

Any type of epileptic seizures may present in metabolic epilepsies. Myoclonic seizures are the main seizures in glycine encephalopathy and other cofactor metabolic disorders, infantile spasms are the main seizures in mitochondrial disorders, in disorders with serine biosynthesis defects, in phenylketonuria and biotinidase deficiency. Patients with metabolic disorders such as deficiency of GLUT-1, deficiency of creatine, deficiency of biotinidase, ~~syndromes~~ and mitochondrial diseases present generalized tonic-clonic seizures [1].

Additional features to lead to the possible diagnosis of metabolic epilepsies [4, 5] are presented below (Table 1).

If metabolic seizures are suspected, a comprehensive laboratory workup (Table 2) and an electroencephalogram (EEG) should be performed, alongside imaging of the brain, if indicated.

First line laboratory workup is likely to uncover common metabolic causes, such as hypoglycemia, electrolyte disequilibrium, and infections of the CNS. Blood gas analysis to investigate the presence of metabolic acidosis, hyperammonemia and/or hyperlactatemia is usually part of the initial laboratory evaluation [1, 4]. Using lactate as an example, it is known that seizures can give rise to lactate levels but the levels decrease quickly after seizure is over. A suspicion for metabolic diseases should be raised when lactate elevate 1 to 2 h after a seizure [8].When diagnosis remains unclear, a second line biochemical tests are carried out, based on clinical evidence, with plasma amino acids, as well as urine acylcarnitine and organic acids. Furthermore cerebrospinal fluid (CSF) is checked for glucose, amino acids, also urine sample should be sent for purines, pyrimidines, S-sulphocysteine, and guanidinoacetate [1]. Additional testing for the metabolomic profile can be considered, as well as, genotyping for potential gene mutations and variants, and whole exome and/or genome sequencing [2] (Table 2).

Neuroimaging findings (Table 2) are usually normal or nonspecific, and include cerebellum dysplasia, neuronal dysplasia, leukodystrophy or hypomyelination, hypoplasia and agenesis of the corpus callosum [9, 10]. Certain signal abnormalities are more frequently found in certain types of metabolic disorders [9]. For example, pyridoxine-dependent epilepsy and glycine encephalopathy are associated with hypoplasia or agenesis of corpus callosum [2], glycine encephalopa-

Table 2. Laboratory, EEG and imaging workup in possible metabolic epilepsy

Initial laboratory tests
– Glucose
– Electrolytes
– Blood gases
– CNS infections
– Ammonia
– Lactate
Additional biochemical tests in plasma
– Amino acids
– Acylcarnitine profile
– α-aminoadipic semialdehyde
– Homocysteine
– S-sulfocysteine
– Ammonia
– Guanidinoacetate
CSF laboratory tests
– Glucose
– Amino acids
– Folate
– 5-methyltetrahydrofolate (MTHF)
– α-aminoadipicsemialdehyde
– Pyridoxal phosphate
Urine laboratory tests
– Organic acids
– Aminoadipicsemialdehyde
– Homocysteine
– S-sulphocysteine
– Guanidinoacetate
Metabolomic profiling
Genotyping
– PCR product sequencing
– Allele specific PCR (ARMS)
– Allele specific probes
– PCR amplification coupled with restriction enzyme analysis
– Single Strand Conformation Polymorphism
– Denaturing Gradient Gel Electrophoresis
Whole sequencing
– Exome
– Genome
EEG findings
– Generalized slowing
– Burst suppression
– Spike-wave, polyspike-wave complexes
– Status epilepticus in sleep
– Comp-like rhythm
Neuroimaging findings
– Normal
– Cerebellum dysplasia
– Neuronal dysplasia
– Leukodystrophy
– Hypomyelination
– Hemispheric hypoplasia
– Brain atrophy
– Corpus callosum hypoplasia
– Corpus callosum agenesis

Table 3. Treatable metabolic epilepsies

Cofactor metabolic disorders with epileptic seizures
– Pyridoxine dependent epilepsy
– Pyridoxal 5' - phosphate responsive epilepsy
– Early onset vitamin B6-dependent epilepsy
– Cerebral folate deficiency
– Methylene tetrahydrofolate reductase (MTHFR) deficiency
– Molybdenum cofactor deficiency type A
– Biotinidase deficiency and holocarboxylase synthetase deficiency
Epilepsy as a result of energy deficiency disorders
– Glucose transporter (GLUT-1) deficiency type 1
– Guanidinoacetate methyltransferase (GAMT) deficiency
Amino acid metabolic disorders associated with epilepsy
– Glycine encephalopathy
– Maple syrup urine disease
– Serine biosynthesis defect
– Urea cycle disorders
– Phenylketonuria

thy can be associated with delayed myelination and dilated ventricles [9], and folate deficiency are associated with hypomyelination or leukodystrophy [11].

Regarding electroencephalogram (EEG) findings, there are various EEG abnormalities (Table 2). For example, ~~a~~ patients with pyridoxine dependent and pyridoxal phosphate responsive epilepsy as well as glycine related encephalopathy may present a burst-suppression pattern in EEG while those affected by urine maple syrup disease may present a comb-like rhythm [12, 13].

The term treatable metabolic epilepsy reflects disorders in the spectrum of inborn errors of metabolism that may develop epileptic seizures, resolved with the appropriate treatment. Clinicians and investigators should investigate and diagnose these treatable but otherwise catastrophic encephalopathies.

Types of treatable metabolic epilepsy are shown in Table 3.

3. Treatable metabolic epilepsies

A. Epilepsy related to cofactor metabolic disorders

EPILEPSY DEPENDENT ON PYRIDOXINE (PDE)

PDE is an epileptic encephalopathy, inherited through the autosomal recessive (AR) way. A marked benefit to adequate therapeutic dosages of vitamin B6 coupled with non-responsive treatment with AEDs characterize the disorder [4]. Pathogenic variations in the antiquitin gene (ALDH7A1) are underlying PDE and its prevalence is 1 in 20,000 to 600,000. This epileptic encephalopathy is an example of severe but efficiently treatable disorders than clinicians do not want to miss [4, 14].

Although seizures respond to adequate therapeutic dosages of vitamin B6, PDE patients do not have B6 deficiency. PDE is manifested as a result of the deficient enzyme antiquitin in the metabolic pathway of lysine. Antiquitin is the dehydrogenase of piperideine-6-carboxylate (P6C) and a-aminoadipic semialdehyde (aAASA), and the defect results in high concentrations of αAASA and P6C, which inactivate pyridoxal-5-phosphate (PLP), a cofactor in neurotransmitter metabolism. Due to its reactive properties as a semialdehyde, αAASA also convey a pathogenetic effect, undergoing multiple reactions in the cells and interacting with diverse metabolic pathways [4]. Furthermore, pipecolic acid is a GABA modulator and its accumulation may contribute to seizure pathophysiology [15].

Presentation

PDE presents, in most cases, within the first week of life, with neonatal seizures presenting within hours of birth in 70% of affected children; atypical cases can present later, but no later than the age of 3 years [16].

Seizures of unknown etiology, mainly of myoclonic type, in the absence of any gestational complication and perinatal abnormality, unresponsive to treatment, raise flag to the suspicion for PDE. Patients with classical PDE present a spectrum of clinical features such as abnormal fetal movements or dystonic movements, respiratory distress, birth asphyxia or hypoxic-ischaemic encephalopathy, abnormal cry, irritability, vomiting, startle response, hepatomegaly, hypothermia, shock and acidosis [4].

Diagnosis

Increased αAASA (specific) and pipecolic acid (non-

specific) levels in urine, plasma and CSF, multiple folds over the higher normal values, are found, even with treatment [17, 18] (Table 4). The mutation, the age, pyridoxine treatment and possibly nutritional lysine intake have an impact on αAASA levels [4].

Urinary and plasma αAASA, together with plasma pipecolic acid are useful biomarkers to untreated as well as treated patients. Pipecolic acid is the primary biomarker used, which is complemented with αAASA determination in patients with unclear pipecolic acid results and high clinical probability to have PDE. Due to the fact that αAASA testing is limited to few laboratories worldwide it is advisable to test pipecolic acid before proceed to αAASA testing [4].

The identification of causative mutations in the antiquitin gene (ALDH7A1, chromosome 5q31) support the diagnosis. Identified mutations in the gene exons 4, 6, 9, 11 represent 60% of the pathogenic mutations reported in patients of Caucasian origin and those are the exons initially screened for mutations [19]. If sequencing is negative for point mutations, deletions may be the cause and further molecular testing is required. Point mutations may be of unknown significance and functional studies could serve to ascertain the impact of the mutation.

Treatment

The need for PDE diagnosis is inappropriate to delay the administration of pyridoxine. In cases with epileptic seizures developing within the first month of life, seizures are controlled within an hour with 50-100 mg of intravenous pyridoxine (Table 5). Seizures remain controlled with 5-30 mg/kg/d of pyridoxine given orally (Table 5) but when pyridoxine is stopped, seizures may present again [10]. When treatment is restarted, seizures are rapidly controlled [19]. In atypical (late-onset) PDE, seizure response may require up to seven days of pyridoxine therapy [10]. Pyridoxine should not exceed 500 mg daily because peripheral neuropathy may develop [20].

In some patients with unclear response to pyridoxine, initiation of folinic acid may have a beneficial effect. The mechanism underlying folinic acid responsive epilepsy is not clearly understood. The disorder is a condition similar to pyridoxine-dependent epilepsy, having comparable diagnostic laboratory markers. Regarding CSF biogenic amines, an unknown peak (peak X) is emerging [1]. In neonates, 3-5 mg/kg folinic acid daily may control the seizures [4], while folinic acid at a daily dose of 10-30 mg could be beneficial for children [2] (Table 5), although it is not well established whether long-term folinic acid may help after the stabilization of seizures. Furthermore, a high dose of folinic acid could exacerbate seizures, and the clinical benefit for this intervention should be intensively monitored and established [4].

Subsequent pregnancies have a recurrence risk of 25% and supplemental pyridoxine should be given to any pregnant with an at-risk fetus, to prevent intrauterine seizures and improve neurodevelopmental outcomes [4].

EPILEPSY DEPENDENT ON PYRIDOXAL 5´ - PHOSPHATE

Pyridoxal phosphate responsive metabolic epilepsy is an extremely rare epilepsy, inherited by the autosomal recessive disorder and only a few cases reported. This condition is due to pathogenic variations in the pyridoxamine 5'-phosphate oxidase gene (PNPO), leading to deficiency of pyridoxine phosphate oxidase, an enzyme that oxidizes both pyridoxine phosphate and pyridoxamine phosphate into pyridoxal phosphate [22]. Pyridoxal phosphate is the drastic conformation of pyridoxine [22].

Presentation

Pyridoxal phosphate responsive metabolic epilepsy is a neonatal epileptic encephalopathy with lethargy, hypotonia and refractory seizures that presents very early in life, with more than 80%of of affected neonates to present seizures in the first week of life [9]. Infantile spasms, myoclonic seizures, focal seizures, generalized tonicoclonical seizures, atonic seizures and status epilepticus may develop [23]. A range of neurological and systemic manifestations may also present, such as movement disorders and pigmentary retinopathy [24]. EEG may show, among others, electrical status epilepticus during sleep [23].

Diagnosis

The clinical diagnosis is supported by seizure control and EEG changes when pyridoxal phosphate supplementation of 50 mg is administered orally, frequently within an hour from onset (Table 5), while a percentage of neonates may have seizure cessation with pyridoxine [25].

Low pyridoxal phosphate in CSF supports further the diagnosis. Additional findings include the diminished enzyme activities related to cofactor pyridoxal phosphate, the increase of the glycine and threonine amino acids in plasma, also the increase of the glycine, threonine and of 3- methoxytyrosine amino acids, and the decrease of 5-hydroxy indolacetic acid and homovanillic acid in CSF [1] (Table 4).

Molecular analysis of the responsible gene PNPO may establish the diagnosis. Several pathogenic variants have been identified with many missense mutations corresponding to the active arginine residues in the protein sequence [26, 27].

Table 4. Treatable metabolic epilepsies

Sample	Volume	Tube	Collection/Storage
Plasma*			
A-aminoadipic semialdehyde	2.5-5 mL	Heparin	Freeze, store at -20^{0}C
Pipecolic acid	0.5 mL	Heparin or EDTA	Freeze immediately at -20^{0}C stable for 1 month
Lactate (Lactic Acid)	>0.3mL	Fluoride-oxalate tube	Collect and send to lab on ice, test performed immediately
Folate	0.5-1 mL	Heparin	Freeze, stable 72 hours at -20^{0}C, indefinitely at -80^{0}C
Homocysteine	2.5-5 mL	Heparin	Stable for 72 hours when stored on gel at 28°C
S-sulfocysteine	2.5-5mL	Heparin	Freeze, store at -20^{0}C
Ammonia	2.5-5mL	Lithium heparin	Centrifuged and analyzed within 30 min
Glucose	>0.5ml	Lithium heparin	Samples are drawn during fasting, send immediately to lab
Guanidinoacetate	2.5-5mL	Heparin	Stored frozen at -20^{0}C for up to 7 days
Amino acids	2.5-5mL	Heparin	Samples are drawn during fasting Deproteinize and buffer, PH 2.2, freeze, storage at -20^{0}C
Acylcarnitine profile	2.5-5mL	Heparin	Freeze and store at -80^{0}C
CSF*			
A-aminoadipic semialdehyde	0.5-1 mL	Sterile vial	Freeze, stable 72 hours at -20^{0}C, indefinitely at -80^{0}C
Pyridoxal phosphate	0.5-1 mL	Sterile vial	Freeze immediately stable 72h at -20^{0}C, store indefinitely at -80^{0}C
5-methyltetrahydrofolate (MTHF)	0.5-1 mL	Sterile vial	Freeze, stable for 72 hours at -20^{0}C, indefinitely at -80^{0}C
Glucose	0.25mL	Fluoride-oxalate tube	CSF samples are drawn during fasting, send immediately to lab
Amino acids	0.2-0.5mL	Sterile vial	Samples are drawn during fasting Collect in ice, immediately to lab
Urine*			
A-aminoadipic semialdehyde	> 1mL	Sterile collection tube	Freeze, store at -20^0 C
Pipecolic acid	0.5-1mL	Sterile collection tube	Freeze immediately at -20^{0}C, stable for 1 month
Glycine	0.2mL	Sterile collection tube	Collect in ice, immediately to lab
Vanillactic acid	5-10 mL	Sterile collection tube	Random urine specimen Freeze immediately at -20^{0}C
Homocystein	5 mL	Sterile collection tube	Random urine specimen frozen at -20^{0}C within 30 min of collection
S-sulphocysteine	2-3 mL	Sterile collection tube	Random urine specimen, frozen at -20^{0}C stable for 90 days
Cystine	4 mL	Sterile collection tube	Specimen from 24-hour urine collection, freeze immediately
Organic acids	10 mL	Sterile collection tube	First morning urine before food or drink is suggested. No apples, grapes, pears, cranberries 48 hours prior to collection
Guanidinoacetate	0.5-1mL	Sterile collection tube	Freeze immediately at -20^{0}C, stable indefinitely
Phenylpyruvate	>3mL	Sterile collection tube	Freeze immediately at -20^{0}C

Presented in order of appearance in the text. Data collected from: A) https://mnglabs.labcorp.com/, B) NHS UKAS website HEFT, C) https://ltd.aruplab.com/, D) https://www.mayocliniclabs.com/, E) https://www.albertahealthservices.ca/, F) https://ltd.aruplab.com/

Table 5. Treatment of metabolic epilepsies

Pyridoxine-dependent epilepsy
50-100 mg intravenous pyridoxine, followed by of oral administration of pyridoxine at a daily dose of 5-30 mg/kg (Not exceeding 500 mg/d)
If no response to pyridoxine, oral administration of a daily dose of 3-5 mg/kg folic acid in neonates and a daily dose of 10-30 mg in children
Pyridoxal 5'-phosphate-responsive epilepsy
Oral administration of 50 mg pyridoxal phosphate, followed by 30-50 mg/kg/d
Early onset vitamin B6-dependent epilepsy
Administration of pyridoxine or pyridoxal phosphate (as previously)
Cerebral folate deficiency
Oral administration of a daily dose of 3-5 mg/kg folic acid in neonates and a daily dose of 10-30 mg in children
Methylenetetrahydrofolate reductase (MTHFR) deficiency
Oral administration of a daily dose of 100 mg/kg betain, with increments up to a daily dose of 20 g
Molybdenum cofactor deficiency type A
Intravenous cyclic pyranopterin monophosphate at a daily dose of 80-320 μg/kg, followed by a daily dose of 240 μg/kg
Biotinidase and holocarboxylase synthetase deficiency
Oral administration of 5-10 mg/d biotin
GLUT-1 deficiency
Ketogenic diet
GAMT deficiency
Oral administration of a daily dose of 400-800 mg/kg creatine and 400-800 mg/kg L-ornithine
Protein-restricted diet
Glycine encephalopathy
Sodium benzoate, dextromethorphan, felbamate, and ketamine
Branched-chain α-ketoacid dehydrogenase deficiency (Maple syrup urine disease)
BCAAs-restricted diet, and administration of a BCAA-free amino acid supplementation
Serine biosynthesis defect
Oral administration of a daily dose of 500-700 mg/kg L-serine and 200-300 mg/kg glycine for severe forms
Oral administration of 100-150 mg/kg/d L-serine for milder forms
Urea cycle disorders
Hemodialysis
Amino acids L-citrulline or L-arginine supplementation
Protein restricted diet
Liver transplantation
Phenylketonuria
Dietary therapy. Selenium, copper, magnesium, and zinc supplementation may be required
Oral administration of sapropterindihydrochloride

Treatment

Although seizures are unresponsive to AEDs in pyridoxal phosphate responsive epilepsy, they are controlled by 30-50 mg/kg/d pyridoxal phosphate [28] (Table 5). Due to the high doses of pyridoxal phosphate, hepatic function is closely inspected in children treatment, as abnormal liver function may emerge [27].

EARLY-ONSET VITAMIN B6-DEPENDENT EPILEPSY

This type of epilepsy is due to in trans pathogenic variants in both *PLPBP* gene alleles, as was recently discovered [29]. It is suggested that PLPBP affects vitamin B_6 homeostasis, by supplying PLP to apo-enzymes, and minimizes toxicity due to excessive unbound PLP [30, 31].

Presentation

Seizures in the neonates are the most characteristic feature of biallelic *PLPBP* gene mutations, although first seizure may occur later, delaying treatment with vitamin B6. Generalized tonic-clonic seizures and myoclonic seizures are predominantly observed, as well as intellectual disability is common [32].

Diagnosis

Biochemical findings are not consistent. The most common findings include elevated lactate in plasma with associated metabolic acidosis and elevated glycine in urine. Raised vanillactic acid is the most common finding in urine [29]. Molecular diagnosis is made by identifying missense, nonsense, frameshift, or splice site pathogenic PLPBP variants [29, 32] (Table 4).

Treatment

Treatment with pyridoxine or pyridoxal phosphate or both, as early as possible, is highly important (Table 5). Two inconclusive reports, one by Darin et al. states that pyridoxal phosphate is more effective than pyridoxine in controlling seizures, while in the study by Plecko et al. patients with good seizure control and normal intelligence were treated with pyridoxine [30, 33].

CEREBRAL FOLATE DEFICIENCY

Cerebral folate deficiency is rare, inherited as AR disorder and is due to defects in the folate receptor alpha gene (FOLR1) [1]. The alpha type of folate receptor is the main carrier of folate through the blood-brain barrier. Molecular defects of this carrier may lead to diminished levels of 5-methyltetrahydrofolate (MTHF) in cerebrospinal fluid. MTHF is the crucial folate metabolite and is taking part in myelin biogenesis and neurotransmitter biosynthesis [34].

Other syndromes, such as Rett and Aicardi-Goutieres, have been recognized as clinically resembling conditions of cerebral folate deficiency, as they are responding to anti-folate treatment.

Presentation

Typical features usually present from the age of 4 months to early childhood, presenting with severe developmental delay, cerebellar ataxia, spastic paraplegia, ataxia, movement disorders, irritability, sleep disturbance, progressive hearing and visual impairment, and also generalized tonic-clonic, tonic, atonic, and myoclonic seizures [2, 34]. Neuroimaging findings include cerebellar atrophy and hypomyelination or leukodystrophy [11].

Diagnosis

Diagnosis is established by abnormal levels of MTHF in the CSF, accompanied by normal levels of folates in plasma. Molecular testing of the underlying FOLR1 gene, can identify variants, which may be missense (the most common mutation), nonsense, splice mutations, or even duplication [35] (Table 4).

Treatment

Early administration of folinic acid (Table 5) can improve clinical presentation and consequently restore folate CSF levels [11, 34].

DEFICIENCY OF METHYLENETETRAHYDROFOLATE REDUCTASE

The severe form of methylenetetrahydrofolate reductase (MTHFR) deficiency is a rare (1 in 200,000) AR disorder, due to pathogenic variations of the MTHFR gene [36]. MTHFR is the reductase of 5, 10 methylene tetrahydrofolate to 5-methyltetrahydrofolate (MTHF). MTHF circulates as the abundant folate in blood, CSF and other tissues. Its deficiency increases total plasma homocysteine and reduces methionine [37]. In turn, reduced methionine leads to the deficiency of the crucial methyl donor, that takes part in multiple methylation processes, namely S-adenosylmethionine [1].

Presentation

Clinical MTHFR deficiency in infancy is characterized by lethargy, hypotonia, feeding difficulties, apnea, with seizures, including myoclonic, tonic-clonic, and infantile spasms [1, 2]. Those seizures may advance to Lennox-Gastaut syndrome [38]. Later onset forms usually present with higher MTHFR and therefore present different symptoms, such as psychiatric conditions and gait abnormalities [39] and may be asymptomatic until the late thirties [40].

Diagnosis

As expected, total homocysteine in the plasma is high, methyl donor amino acid methionine is decreased, also MTHF in CSF and blood folate may also decrease [39]. Homocysteine elevation is accompanied by homocysteinuria [38]. Conclusive evidence for this deficiency comes by the enzyme assay and alternatively by testing of the causative gene for mutations. If this particular disorder is not recognized on time, severe consequences to normal development emerge with subsequent coma, and early death [2] (Table 4).

Treatment

The treatment goal is reducing homocysteine levels through chemical conversion of homocysteine to

methionine with betaine methyltransferase [1]. The outcome can improve upon early treatment with betaine [38]. Treatment usually begins with 100 mg/kg, with increments up to 20 g/d [38] (Table 5).

MOLYDBENUM COFACTOR DEFICIENCY TYPE A

Molybdenum serves as cofactor for three different oxidases, in alphabetical order aldehyde oxidase, sulfite oxidase and xanthine oxidase. The deficiencies of the cofactor or of the sulfite oxidase, are very rare AR disorders that result in toxic concentrations of sulfites [2]. Only type A of molybdenum cofactor deficiency (with molecular defects in gene MOCS1) are treatable.

Presentation

Affected neonates have feeding disorders in a short period after birth, marked hypotonia, uncontrollable seizures and response to startle [2]. In addition, developmental delay and other clinical features, as spasticity, and lens dislocation emerge [1]. The clinical and radiological findings may resemble those of hypoxic-ischemic encephalopathy [41].

Diagnosis

Biochemical tests show reduction of plasma homocysteine and urine cystine coupled with increase in plasma and urinary S-sulfocysteine (Table 4). Diagnosis is also established by the DNA analysis of the MOCS1 gene.

Treatment

Neonates affected by molybdenum cofactor deficiency type A are administered with cyclic pyranopterin monophosphate intravenously (Table 5), which is a precursor of the molybdenum cofactor biosynthesis, is advised to be given the earliest possible before establishment of any neurologic damage [42].

BIOTINIDASE AND HOLOCARBOXYLASE SYNTHETASE DEFICIENCIES

Biotinidase and holocarboxylase synthetase deficiencies are AR disorders, induced by mutations in two genes, BTD and HLCS respectively. Biotin, which is recycled through the enzyme biotinidase, is indispensable cofactor for many carboxylases. The enzyme holocarboxylase synthetase is responsible for attracting biotin to carboxylases, subsequently activating them to function properly. Both disorders are related to multiple carboxylase deficiencies, with an estimated overall l1:60,000 incidence of biotinidase deficiencies. The later deficiency of holocarboxylase synthetase is rare with much lower incidence [43].

Presentation

Both deficiencies of biotinidase and holocarboxylase synthetase, share common clinical presentations. The deficiency of holocarboxylase synthetase presents mostly earlier, during the first 3 months, while the age of onset of biotinidase deficiency varies according to the enzyme activity, with a typical early age of presentation at 3 and a half months.

Biotinidase deficiency presents with developmental regression, ataxia, hypotonia, hearing and vision abnormalities, feeding problems, seizures, and breathing difficulties [2, 43]. Feeding problems, according to the literature, include vomiting and gagging, breathing difficulties, apnea or hyperventilation [43].

The deficiency of holocarboxylase synthetase also exhibits metabolic derangements with acidosis and hyperammonemia and also hypotonia, lethargy, vomiting, hypothermia, and tachypnea [1].Typical seizure types in this condition, include infantile spasms, generalized tonic-clonic and myoclonic seizures [1]. Both disorders are complicated by alopecia and skin rash [43]. Affected persons with biotinidase deficiency may also present neuromuscular symptoms including paresis, muscular atrophy and prominent peripheral muscle denervation [44].

Diagnosis

The typical metobolicl findings in this condition are hyperammonemia, lactic acidemia, and acidosis [1]. The most prominentl biochemical imbalances indicating the confirmation of biotinidase deficiency are the abnormal high organic acids, such as 3- methyl crotonyl glycine, propionyl glycine, 3-hydroxy isovalerate, methyl citrate, and hydroxy propionate [43] (Table 4).

The deficiency of biotinidase is established either by the assay measuring biotinidase activity or molecular testing for causative pathogenic variations in the BTD gene [43]. In contrast, only pathogenic variations corresponding to the HLCS gene, can confirm holocarboxylase synthetase deficiency [43].

Treatment

Excellent results are achieved as both deficiencies of biotinidase and holocarboxylase synthetase adequately clinically respond to administration of oral biotin [43] (Table 5).

B. Epilepsy as a result of energy deficiency disorders

GLUCOSE TRANSPORTER 1 (GLUT1) DEFICIENCY

De Vivo et al. were first to describe, in 1991, in the literature Glut1 deficiency, also termed De Vivo disease. Pathogenic variations in the solute carrier family 2, facilitated glucose transporter member 1

(*SLC2A1*) gene underly Glut1 deficiency. In the majority of cases, these are *de novo* mutations, while in familiar cases it is inherited with an autosomal dominant pattern and rarely with an autosomal recessive pattern and a rare (1:100,000) estimated incidence [45].

The disease is characterized by the deficiency of GLUT, which is indespensable for glucose to pass the blood-brain and other barriers. When this important molecular transporter of glucose gene is affected by mutation reduces the brain main energy substrate, glucose.

Presentation

Although cases with missense mutations characterize mostly moderate to mild disease, straight phenotype-genotype correlation is not yet established. Patients diagnosed with the same pathogenic variations do not typically have the same clinical presentation [46]. This implies that confounding factors, and disease-modifying genes interplay to modify the phenotype and give rise to the complexity of this condition [46].

Developmental regression is common in this condition with refractory seizures, microcephaly and a complex movement disorder consisting of ataxia and dystonia. The most common symptom is epilepsy, which usually begins within 2 years from birth and more frequently within the first few months of life, and is resistant to traditional seizure medications [47]. Seizures may be of various types. Only 10% of cases with early GLUT-1, have absence of seizures, while in contrast only 5% of those having epilepsy with myoclonic-atonic seizures are GLUT-1 deficiency patients [47].

However, other clinical manifestations may develop later in life, such as dystonia induced by paroxysmal exertion, choreoathetosis, alternating hemiplegia, and other paroxysmal events, such as intermittent ataxia, dystonia, and migraine [47].

Diagnosis

GLUT-1 deficiency syndrome should be included in the differential diagnosis of pharmacoresistant epilepsy in the clinical practice. The mutations of SLC2A1 have been reported to be responsible for approximately 1% of all idiopathic generalized epilepsies [48]. A strong clue for the diagnosis is the presence of induced dyskinesia by paroxysmal exercise in the affected individual or in the family, which may worsen after a period of fasting. All features can relapse or even worsen with fasting. EEG findings after fasting are typically related with slow activity and coexisting multifocal or generalized high-amplitude spikes.

CSF samples in GLUT-1 deficiency is recommended to be obtained during fasting as CSF glucose and CSF-to-blood glucose ratio are expected to be low (Table 4). The diagnosis can be confirmed by looking for reduced glucose transport across the erythrocyte membrane (which carries the same glucose transporter), and molecularly, by identifying mutations of SLC2A1 gene that encodes GLUT-1 [47].

Treatment

A ketogenic diet is part of the management aiming to deviate glucose, providing in turn, ketone bodies as brain energy alternative source [1]. The efficient ketogenic management may result in adequate control on seizures, while the ameliorating effect on the patients developmental evolution is less profound [49].

GUANIDINOACETATE METHYLTRANSFERASE (GAMT) DEFICIENCY

GAMT deficiency is a rare AR condition (1 in 500,000) of creatine biosynthesis, due to mutations in the GAMT gene [11]. GAMT supports guanidinoacetate (GAA) methylation, producing creatin and consequently, GAMT deficiency results in deficiency of creatine. Creatine is an energy storage and transmission substrate, crucial for brain development, having also functional properties as a neurotransmitter and a neuromodulator [1].

Presentation

The clinical GAMT deficiency present in affected infants up to the third year [50]. GAMT deficiency causes global developmental regression and cognitive dysfunction, immediately and markedly affecting the development of speech and language ability. Additional clinical presentations are hypotonia, epilepsy, autism, hyperactivity, movement disabilities and other related problems [51, 52].

Affected children with a high probability (2/3) have seizures with generalized tonic-clonic, myoclonic, partial complex and drop attacks [52].

Diagnosis

Blood and urine exhibit elevated GAA (Table 4) and spectroscopy by magnetic resonance do not display a marked creatine peak or display a severely reduced peak. To confirm diagnosis genotyping is implemented, with more than 50 different GAMT gene pathogenic variations identified, the most common of which are missense variants [11, 53].

Treatment

GAMT is treated with high-dose (400-800 mg/kg/d) creatine administration, while GAA toxic concentrations are decreased by administration of L-ornithine

(400-800 mg/kg/d) and restriction of arginine, when a diet restricted to proteins is applied [50, 52, 54].

C. Epilepsy related to various amino acid metabolic disorders

GLYCINE ENCEPHALOPATHY

Glycine encephalopathy is an autosomal recessive metabolic disorder caused by pathogenic variations in the genes named glycine dehydrogenase (GLDC), amino methyltransferase (AMT), and glycine cleavage system protein H (GCSH), that encode the necessary subunits to form the cleavage enzyme for glycine, with an incidence of 1:60.000 [55]. The condition is characterized by the toxic accumulation of glycine. Glycine also functions as agonist to the NMDA glutamate receptor and neurotransmitter in the brainstem and spinal cord with inhibitory activity. Consequently, excitatory NMDA glutamate receptors are overstimulated causing epileptic seizures, while the inhibitory activity of glycine in the brain and the cerebrospinal cord is causing muscular dysfunction with apnea and hypotonia [1].

Presentation

Glycine excess encephalopathy is clinically classified by the age at symptoms onset in three types: neonatal, infantile and late-onset [55, 56]. The vast majority of patients fall into the neonatal category, which involves a stereotypic presentation with severe hypotonia, apnea requiring assisted ventilation, and intractable seizures, with approximately 30% of such patients dying in the neonatal period [56]. Patients with the infantile type have mild to moderate psychomotor retardation, behavioral problems, seizures, and chorea [56]. The clinical presentations of late-onset are heterogeneous with a better prognosis [57]. Myoclonic and generalized seizures in this disorder, including, are often difficult to treat [2].

Diagnosis

Glycine levels are elevated to a much greater extent in CSF than in plasma; hence, an abnormally high value for the CSF/plasma glycine ratio is observed [56] (Collection and storage conditions in Table 4).

Diagnosis can be confirmed by finding mutations, large deletions or duplications in the genes coding for GLDC, AMT, and GCSH [56].

Treatment

Severe glycine excess encephalopathy is characterized by a poor outcome even when early treatment is initiated, while milder forms usually have improved outcomes with early treatment initiatives [58]. Sodium benzoate, dextromethorphan, felbamate, and ketamine, can reduce high concentrations of plasma glycine and consequently NMDA receptor antagonism, which can assist in seizure control [1].

MAPLE SYRUP URINE DISEASE

Branched-chain α-ketoacid dehydrogenase (BCKD) deficiency, more commonly known as maple syrup urine disease (MSUD), is an AR disorder with a prevalence of 1:185,000 [59]. It is caused by trans pathogenic variations in both alleles, in each of the *BCKDHA*, *BCKDHB*, *DBT* genes that are necessary for the subunits of the mitochondrial complex that decarboxylates α-ketoacid derivatives (BCKAs) of the branched-chain amino acids (BCAAs) leucine, isoleucine and valine, leading to the accumulation of BCAAs. Amino acid leucine is neurotoxic and when accumulated is responsible for the neurological presentation of this disease [1].

Presentation

Clinical features of MSUD include maple syrup odor, irritability, feeding disorder, lethargy, apnea, opisthotonus, stereotyped movements like fencing and bicycling, and ketonuria [59]. They present during the neonatal period or later in life in milder cases. Infections, surgeries, injuries or other stressors may cause acute episodes of metabolic instability and neurologic deterioration observed at any age. During these episodes, the affected patients develop seizures, nausea, vomiting, dystonia, ataxia, decreased consciousness that may even advance to coma and subsequently death [59]. An intermittent type of MSUD is characterized by normal growth and development. However, affected children with this type of MSUD may progress to clinical features and biochemical abnormalities resembling the typical type of MSUD with catabolic stressors [59].

Diagnosis

Plasma amino acid analysis shows high levels of alloisoleucine and biochemical derangement of the normal 1:2:3 proportion of amino acids isoleucine/leucine/valine (Table 4). Diagnosis is further established based on pathogenic variations of the responsible genes BCKDHA, BCKDHB, and DBT, or alternatively by evaluating deficient enzyme activity (BCKD) in propagated leukocytes or liver biopsies [59].

Treatment

Diet has two primary measure taken, first to reduce BCAAs and second to supplement the nutrients to reduce BCAAs catabolic process [60]. Long-term treatment requires careful manipulation of calories, restriction of dietary BCAAs, and supplementation

using a BCAA-free amino acid mixture to provide non-BCAAs and other nutrients for protein synthesis [61].

SERINE BIOSYNTHESIS DEFECT

Amino acid L-serine biosynthesis by the enzyme phosphoglycerate dehydrogenase (PGDH), phosphoserine Aminotransferase (PSAT1), and phosphoserine phosphatase (PSPH). The deficiency of L-serine is caused by molecular alterations in any of these three enzymes, while phosphoglycerate dehydrogenase (PGDH) is the one with the most common defects [2]. Serine biosynthesis defects are rare, inherited in an AR mode, as a result of pathogenic variations in the corresponding genes PHGDH, PSAT1, and PSPH respectively. L-serine function as the basic molecule for the biosynthesis of more complex compounds [62]. Also L-serine and the products of its metabolism have been recognized to be essential for cell proliferation and specific functions in the central nervous system [63].

Presentation

In most patients, the onset of symptoms is present before birth, as intrauterine growth

retardation and microcephaly. Epileptic seizures develop at the first weeks to months of life. Later during the first year of life, hypertonia becomes evident, evolving into spastic tetraplegia [64].

More clinical presentations are related to hypogonadism, feeding difficulties and congenital cataracts [63].

A mild deficiency has been described infrequently in older children including absences and tonic clonic seizures [65].

Diagnosis

Aminoacid serine and, to a lesser extent, glycine is low in CSF and plasma, although they can be normal in a nonfasting state [64] (Table 4). Diagnosis can be confirmed by demonstarting the enzymes' defective activity in skin fibroblast cultures or by pathogenic variations in the three causative genes PHGDH, PSAT1, and PSPH [2].

Treatment

Administration of a higher dose of L-serine (500-700mg/kg/d) in severe forms and glycine (200-300 mg/kg/d) for infants with the severe infantile form or a lower dose of L-serine (100-150 mg/kg/d) in mild forms have a beneficial effect on seizures, irritability and spasticity [62, 65].

UREA CYCLE DISORDERS

Urea cycle disorders (UCDs) are metabolic disorders caused by molecular aberrations in the transporter enzymes collaborating in the removal of ammonia from the liver, leading to hyperammonemia. Eight disorders are considered as UCDs: N-acetylglutamate synthase deficiency (NAGSD), Carbamyl phosphatesynthetase 1 deficiency (CPS1), Ornithine transcarbamylase deficiency (OTCD), Argininosuccinatesynthetase deficiency (ASSD) (Citrullinemia), Argininosuccinatelyase deficiency (ASLD) (Argininosuccinic aciduria), Arginase deficiency (ARGD, Argininemia), Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome (or mitochondrial ornithine transporter 1 deficiency (ORNT1D) and Citrullinemia type II (mitochondrial aspartate/glutamate carrier deficiency (CITRIN).Except for ornithine transcarbamylase deficiency (OTCD) which is an X-linked UCD, the rest are inherited as autosomal recessive disorders [66]. The population incidence of urea cycle disorders is found to be 1 in 35,000 births according to screening studies [67].

Presentation

An infant with a complete defect in a urea cycle enzyme (other than ARG) commonly presents with hyperammonemia coma. If not treated, hyperammonemia coma may progress to death, because ammonia is extremely toxic in the developing brain and the CNS.

The reversibility of the toxic effects of hyperammonemia depends on how long the exposure took place, on the levels of excess ammonia in the blood and the developmental stage of the brain [67]. During neonatal life, excessive ammonia causes brain edema and results in neurological disorders including epileptic seizures, cognition decline, motor deficits and coma.

Patients with mild defects of the urea cycle can manifest hyperammonemia at any age and have a significant risk for developmental disabilities and even death. In these cases, hyperammonemia and even coma may be induced by a number of complications and interventions such as illness and surgery [66].

Diagnosis

Hyperammonemia without a high anion difference and with non-excessive plasma glucose levels is the diagnostic biomarker [67]. Other laboratory findings include, high glutamine and alanine in plasma, low plasma arginine, with the exception of arginase deficiency) and increased or decreased citrulline in plasma [68] (Table 4). Genotyping may confirm the diagnosis.

Treatment

Neonates with hyperammonemia, should be subjected to urgent treatment for the immediate reduc-

tion of ammonia. Hemodialysis as an urgent measure, is very effective and should be initiated if high levels of ammonia are observed [68]. Conventional therapy includes pharmacological intervention, so-called Nitrogen (N) scavenger therapy, supplementation with the amino acids L-citrulline or L-arginine and low-protein diet that balances N restriction with growth requirements. The only known "cure" for UCD is liver transplantation [66].

PHENYLKETONURIA/MAINKA STONE

Phenylketonuria (PKU) is a rare, inborn error of metabolism, most often caused by missense mutations in the gene encoding phenylalanine hydroxylase (PAH), which catalyzes the hydroxylation of phenylalanine (Phe) to generate tyrosine (Tyr) [69]. The incidence of PKU is about 1/15,000 [70]. High levels of Phe and its metabolites (for ex. keto acid and phenylpyruvate), cause increased oxidative stress, altered neurotransmitter metabolism and decreased cerebral protein synthesis. Low Tyr levels could have an additional role in the pathophysiology of the disorder [70].

Presentation

Signs and symptoms include delayed cognitive/motor development, epileptic seizures, a characteristic smell in urine and skin, microcephaly, hypopigmentation, hyperactivity, behavioral problems, and movement disorders. Neonates with mild forms of PKU are mostly normal as neonates and develop the clinical PKU after several months.

Affected newborns appropriately treated are less likely to develop symptoms. Still, insufficiently treated individuals may have symptoms. Neuropsychiatric characteristics include obsessive-compulsive disorders, depression and features compatible with those observed in individuals with an autism spectrum disorder.

Diagnosis

Standard newborn tests usually identify PKU at birth screening in many countries, including Greece. Commercial microarray genotyping for nucleotide variations are capable to determine predisposition for PKU. As in all AR disorders both parents should carry of a PKU pathogenic variation, in order to have a child with PKU with a probability of 25%.

Treatment

PKU is treatable by dietary intervention for a lifetime, to maintain low Phe amounts of and supportive amounts of Tyr. Life-long dietary treatment is coupled with adequate monitoring of Phe and Tyr blood levels, and assessment of the cognitive condition [70]. Deficiencies in trace elements (selenium, copper, magnesium, and zinc) also complicate the dietary intervention for PKU and supplementation may be required.

Oral sapropterindi hydrochloride (common name KUVAN), is a synthetic form of BH4, which can decrease Phe in PKU patients. A 30-day trial is required to assess BH4 responders among PKU patients. Encouragingly, KUVAN supports brain well-beeing in a proportion of PKU cases [71]. An enzyme substitution treatment has recently been approved by the FDA for use in this disorder [71].

Conclusion

In newborns, infants or young children that appear normal at birth and present nonspecific manifestations such as epileptic seizures, developmental regression or delay, hypotony, lethargy, vomiting, irritability, dysmorphic features, movement disorders and organomegaly, metabolic disorders should be included in the differential diagnosis.

Treatable metabolic epilepsy is an uncommon entity and may not have an obvious vertical transition depicted in the family tree. The differential diagnosis should include treatable metabolic epilepsies in clinical phenotypes and an initial approach involves combined diagnostic and therapeutic strategies. Typical etiologies, like infection, should be examined, along with metabolic screens.

Upon the potential diagnosis of metabolic epilepsies, an emergency EEG with a pyridoxine trial (100 mg intravenously) is the appropriate management [20]. Other vitamins and cofactors can be administered, such as pyridoxal phosphate, folinic acid, and biotin, if no therapeutic response is present [2, 3]. A ketogenic diet can have a beneficial effect in children suffering from GLUT-1 deficiency.

The underlying cause of metabolic eoileosy should also be considered for the right antiepileptic drugs to be consindered. Phenobarbitone, which inhibits glucose transport, is an example of an antiepileptic drug not to be used in children with GLUT-1 deficiency [72].

Reaching an accurate diagnosis is of high importance for the right treatment and care, so as to achieve immediate cessation of seizures, and for family counseling regarding prognosis and recurrence risk [3, 20].

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