Review Article

Actual Insights into Treatable Inborn Errors of Metabolism Causing Epilepsy

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This review offers an update on a group of inborn errors of metabolism causing severe epilepsy with the onset in pediatric age (but also other neurological manifestations such as developmental delay or movement disorders) with available effective or potentially effective treatments. The main pathogenic and clinical features and general recommendations for the diagnostic and therapeutic workup of the following disorders are discussed: vitamin B6-dependent epilepsies, cerebral folate deficiency, congenital disorders of serine metabolism, biotinidase deficiency, inborn errors of creatine metabolism, molybdenum cofactor deficiency, and glucose transporter 1 deficiency. Available treatments are more effective on epileptic manifestations (with the possibility of complete seizure control) and motor symptoms, whereas the benefits on cognitive outcome are usually minor.

Keywords: Cerebral folate deficiency, epileptic encephalopathies, inborn errors of creatine metabolism, metabolic epilepsy, pyridoxine-dependent seizures, serine metabolism disorders

INTRODUCTION

Inborn errors of metabolism are involved in different early-onset, drug-resistant epilepsies with a prevalence ranging from 0.1 to 300 per 100,000 live births.[1] In patients with suspected metabolic epilepsy, clinicians should pay a prominent attention to a group of severe but treatable or potentially treatable disorders.[2] An updated picture of the most important disorders of this group is provided here. Early diagnosis and treatment of these disorders can result in the prevention of a metabolic decompensation and in the possible subsequent improvement of clinical outcome.[1,2] Available treatments are more effective on epileptic manifestations and motor symptoms, whereas benefits on cognitive outcome are generally poor.[1,2]

Epilepsies Treatable with Pyridoxine or Pyridoxal-5′-Phosphate

ALDH7A1 deficiency

Alpha-aminoadipic semialdehyde dehydrogenase deficiency (antiquitin) is due to mutations on ALDH7A1 gene.[3,4] Antiquitin is an enzyme involved in lysine catabolism resulting in a pyridoxal-5′-phosphate (PLP) depletion [Figure 1] and in a subsequent activation of epileptogenic mechanisms (PLP is an essential cofactor for different enzymes involved in more than 140 neuronal intracellular process). ALDH7A1 deficiency is responsible for an autosomal-recessive pyridoxine-dependent epilepsy (OMIM 266100) with a prevalence ranging from 1:20,000 to 1:600,000.[5] The classical clinical presentation encompasses an early-onset epileptic encephalopathy with variable seizure types and with its onset in the neonatal period or in the first months of life.[4] More recently, milder epileptic phenotypes with later onset have been reported.[14] Other clinical manifestations of patients with ALDH7A1 deficiency include both neurological (abnormal fetal movements, signs of hypoxic ischemic encephalopathy, dystonia, increased startle response, irritability, and intellectual disability) and non-neurological (respiratory distress, abdominal distension, bilious vomiting, hepatomegaly, hypothermia, shock, and acidosis) symptoms.[6]

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Electroencephalographic patterns vary from suppression burst or hypersrhythmia to focal or multifocal epileptic discharges.[4] Possible structural brain abnormalities include hemispheric hypoplasia or atrophy, cerebellar or cortical dysplasia, intracerebral hemorrhage, or periventricular hyperintensity at magnetic resonance imaging (MRI).[5]

A therapeutic trial with an intravenous (100 mg) or an oral/enteral (30 mg/kg/day) administration of pyridoxine can be an important step also for the diagnosis.[4]

Intravenous administration of pyridoxine can induce a reduction of electroencephalographic abnormalities.[6] This response has no diagnostic value and if it is lacking, the diagnosis cannot be excluded.[6]

Increase of urinary \( \alpha \)-amino adipic semialdehyde (\( \alpha \)-AASA), urinary or plasma \( \alpha \)-AASA/\( \Delta \)-1-piperidine-6-carboxylate ratio, and plasma pipelicolic acid can be useful biomarkers to screen the candidate patients for \( \text{ALDH7A1} \) gene sequencing.[4] Other nonspecific metabolic abnormalities can be detected among plasma/cerebrospinal fluid amino acids (increase in threonine, glycine, taurine, histidine, 3-methyltyrosine, alanine, and glutamine) and neurotransmitter (decrease in gamma amino-butyric acid and increase in glutamate in cerebrospinal fluid).[4]

Acute intravenous administration of 100 mg of pyridoxine should be followed by a long-term oral/enteral administration at the dosage of 15–30 mg/kg/day in responding patients.[8] Lysine-restricted diet can represent a useful add-on therapeutic tool.[6] Its mechanism of action is based on a reduced production of potentially toxic lysine catabolites.[6] \( \text{l}\)-arginine supplementation has been recently proposed as an alternative to lysine-restricted diet to support neurocognitive functions.[7] The rational basis of this treatment includes a competitive inhibition of lysine transport and a subsequent reduction of accumulation of \( \alpha \)-AASA.[9] A successful \textit{ex vivo} antisense treatment of an aberrant m-RNA splicing in a lymphoblast cell line of a patient carrying the mutation c.75C>T opened an interesting, new perspective for the future.[7] Seizures with responsiveness to folinic acid have also been described in children with mutations in \( \text{ALDH7A1} \) gene.[9] The biochemical basis of this response are still unknown.[9]

**Pyridox(am)ine 5′-phosphate oxidase deficiency**

Pyridox(am)ine 5′-phosphate oxidase (PNPO) is the rate-limiting enzyme in the synthesis of PLP from dietary pyridoxine and pyridoxamine phosphate [Figure 1].[10] To date, PNPO-deficient activity has been associated with 17 disease-causing mutations in PNPO gene with an autosomal-recessive transmission.[10]

PNPO deficiency (OMIM 6032870) was originally reported as a severe life-threatening neonatal encephalopathy including neonatal pyridoxine-unresponsive seizures in the first hours after birth, suppression bursts on electroencephalogram, and perinatal respiratory distress resulting in intubation in five preterm infants from three families with parental consanguinity.[11] Seizures with variable semiology (prominently tonic and myoclonic) and onset (between prenatal period and the fifth month of life), dystonia, prematurity-related disorders, signs of metabolic derangement (including metabolic acidosis, hyperlactacidemia, hypoglycemia), anemia, and gastrointestinal symptoms (abdominal distension and hepatomegaly) completed the clinical presentation.[11] The initial paradigm of the exclusive PLP responsiveness of PNPO deficiency has been recently denied with the demonstration of a clinical or electroencephalographic response to pyridoxine in 12 patients (two of them suffered from status epilepticus after the switch from pyridoxine to PLP).[11,12] The best diagnostic issue for PNPO deficiency remains PNPO gene sequencing in children with a response to a therapeutic trial of PLP or pyridoxine.[11]

All children with PNPO deficiency should undergo sequential trials with PLP or, in case of unresponsiveness, pyridoxine.[11,12]

PLP can be administered orally or enterally at 30–60 mg/kg/day, even if some patients required higher dosages up to 100 mg/kg/day.[13] Pyridoxine can be administered as in \( \text{ALDH7A1} \) deficiency.[11-17]

**Hyperprolinemia type II**

Hyperprolinemia type II is a rare autosomal-recessive disorder that is caused by mutations in \( \text{ALDH4A1} \) gene resulting in a deficiency of \( \Delta \)-1-pyrroline-5-carboxylate dehydrogenase, a mitochondrial inner-membrane enzyme involved in the conversion of proline to glutamate [Figure 2]. This defect results in pyridoxine depletion and in subsequent seizures.[18]

Hyperprolinemia type II is a benign disorder with a high predisposition to recurrent seizures.[19] Seizures responsive to trials with intravenous pyridoxine without evidences of \( \text{ALDH7A1} \) or PNPO deficiency should suggest the diagnostic suspect of this disorder.[19] Biochemical markers include increased plasma proline, increased urinary \( \Delta \)-1-pyrroline-5-carboxylate, and reduced \( \Delta \)-1-pyrroline-5-carboxylate dehydrogenase activity in leukocytes and skin fibroblast.[19]

Seizures are commonly controlled with pyridoxine supplementation.[19] No specific dietary treatments are indicated.[19]
Cerebral Folate Deficiency

Cerebral folate deficiency (OMIM 613068) causing folinic-responsive epilepsy includes two disorders resulting from dysfunctions of cerebral folate receptor FOLR1: mutation of the FOLR1 encoding gene with an autosomal-recessive transmission or production of FOLR1 blocking/binding autoantibodies.\(^{[20]}\)

Cerebral folate deficiency presents as an encephalopathy including psychomotor retardation after an initial period of normal neuromotor development, autistic-like behavior or behavioral abnormalities, decelerated head growth, ataxia, hypotonia, spasticity, dyskinesia, and early-onset epilepsy with onset within the third year of life.\(^{[20]}\) Myoclonic seizures are the most common seizure type even though tonic and astatic seizures and episodes resembling infantile spasms have also been reported.\(^{[21]}\)

The main biochemical marker of a cerebral folate deficiency is represented by an extremely low 5-methyltetrahydrofolate concentration in the cerebrospinal fluid without evidences of peripheral folate depletion.\(^{[20,21]}\) If this abnormal value is detected, then FOLR1 gene sequencing and plasma FOLR1 blocking or binding autoantibodies measurement should be taken into account in the diagnostic workup.\(^{[20,21]}\)

Neuroradiological patterns in patients with cerebral folate deficiency include delayed myelination, cerebellar atrophy, bilateral calcifications in the basal ganglia, and decreased choline and inositol peaks on magnetic resonance spectroscopy.\(^{[20,21]}\)

Seizures respond to oral supplementation of folinic acid (1–5 mg/kg/day) with a subsequent possible improvement in the whole clinical outcome, whereas folic acid is found to be ineffective (in some cases, a worsening of seizures has been reported).\(^{[20,22]}\) A possible therapeutic role of milk-free diet has been advocated for cerebral folate deficiency due to FOLR1 blocking or binding autoantibodies.\(^{[22]}\) The rational basis for this approach has been provided by recent studies that demonstrated a downregulation in the production of FOLR1 autoantibodies.\(^{[23]}\)
Congenital Disorders of Serine Metabolism

Four clinically defined congenital disorders, with overlapping clinical features, of serine metabolism [Figure 3] have been reported: 3-phosphoglycerate dehydrogenase (3-PGDH; OMIM 601815), phosphoserine aminotransferase (PSAT; OMIM 610992), phosphoserine phosphatase (PSP; OMIM 172480), and serine transporter (OMIM 616657) deficiency.\textsuperscript{23,24} 3-PGDH deficiency is transmitted as an autosomal-recessive disorder.\textsuperscript{23} A compound heterozygous mutation in PSAT1 gene

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**Figure 2:** Metabolism of proline. Double black labels indicate the defect of Δ1-pyrroline-5-carboxylate dehydrogenase in hyperprolinemia type II. The enzyme defect results in an accumulation of proline and Δ1-pyrroline-5-carboxylate. Δ1-pyrroline-5-carboxylate induces inactivating adduct with pyridoxine with subsequent possible seizures resulting from pyridoxine depletion.

**Figure 3:** Schematic representation of serine metabolism
has been demonstrated in two index siblings with PSAT deficiency.\textsuperscript{[23]} PSP deficiency is inherited through an autosomal-recessive transmission.\textsuperscript{[23]} Serine transporter deficiency is caused by autosomal-recessive disorders following mutations in SLC1A4 gene and includes a phenotype with developmental delay, progressive microcephaly, hypomyelination, and seizures.\textsuperscript{[24]}

3-PGDH deficiency is the most common congenital disorder of serine metabolism and includes an infantile, a juvenile, and an adult phenotype.\textsuperscript{[23]} Infantile presentation includes congenital microcephaly, intrauterine growth retardation, intractable seizures, severe psychomotor retardation, spastic quadriplegia, congenital cataract, hypogonadism, and megaloblastic anemia.\textsuperscript{[23]} Seizure types include infantile spasms (75% of the affected patients), tonic–clonic seizures, tonic seizures, atomic seizures, absence seizures, gelastic seizures, and myoclonic seizures.\textsuperscript{[23]} After adolescence, the clinical pattern is characterized by mild or moderate intellectual deficiency, absence seizures, and behavioral problems.\textsuperscript{[23]} In adulthood, intellectual disability, peripheral polyneuropathy, cerebellar ataxia, and nystagmus have been described.\textsuperscript{[23]}

PSAT deficiency usually presents with acquired microcephaly, feeding difficulties, and intractable seizures.\textsuperscript{[23,25]} PSP deficiency has been reported in a single patient with Williams syndrome presenting with Intrauterine Growth Retardation (IUGR), congenital microcephaly, slow psychomotor development, and feeding difficulties.\textsuperscript{[23,26]}

The main biochemical marker of congenital disorders of serine metabolism is represented by low levels of serine in cerebrospinal fluid (under 13 μmol/L in 3-PGDH deficiency and up to 18 μmol/L in PSAT and PSP deficiency) and in plasma (the sample must be obtained in fasted state).\textsuperscript{[23,26,27]} Low levels of glycine can also be observed.\textsuperscript{[23]} Enzyme activity in skin fibroblast can be useful in the workup for 3-PGDH and PSP deficiency, whereas it was inconclusive in the index patient with PSAT deficiency.\textsuperscript{[23,26,27]} Molecular genetic confirmation is required for all the three abovementioned disorders.\textsuperscript{[23,26,27]}

Brain neuroimaging evidences hypomyelination or delayed myelination in 3-PGDH deficiency and cortical/subcortical atrophy associated with diffused white matter abnormalities in PSAT deficiency.\textsuperscript{[23,26]}

In infantile phenotype of 3-PGDH deficiency, an oral supplementation of serine (dosage range, 200–700 mg/kg/day) resulted in seizure control, normalization of serine levels in cerebrospinal fluid, and in the progression of head growth in most of the reported patients.\textsuperscript{[23]} A further supplementation of glycine (200 mg/kg/day) was often required to stabilize the clinical improvements.\textsuperscript{[23]} Similar results, with lower dosages of serine (100–150 mg/kg/day), were obtained in subjects with the juvenile phenotype.\textsuperscript{[23]} In the adult phenotype, an improvement in the daily activities was reported with the dosage of serine up to 80–120 mg/kg/day.\textsuperscript{[23]} Complete prevention of neurological manifestations has been obtained in a patient, whose mother received an oral supplementation of serine since the 27th week of gestation after a prenatal diagnosis of 3-PGDH, and in a female who was treated after a diagnosis of PSAT deficiency in the first day of life.\textsuperscript{[23]} No clinical trials were performed for serine transporter deficiency.\textsuperscript{[24]}

**BIOTINIDASE DEFICIENCY**

Biotinidase deficiency (OMIM 253260) is a congenital disorder with an autosomal-recessive inheritance resulting in an absence of recycling of biotin with subsequent impairments of the main biotin-dependent carboxylases [Figure 4] and accumulation of potentially neurotoxic and epileptogenic metabolites.\textsuperscript{[27]}

Patients with biotinidase deficiency present with seizures, hypotonia, nutritional or respiratory problems, skin rash, and alopecia.\textsuperscript{[28]} Seizure semiology is variable as well as electroencephalographic patterns (ranging from normality to hyspsarrhythmia).\textsuperscript{[28]} In the later ages, developmental delay, ataxia, optic neuropathy, and hearing loss are very frequent.\textsuperscript{[29]} Brain neuroimaging demonstrates normal findings or variable structural abnormalities such as cortical/subcortical atrophy, decreased white matter, ventricular enlargement, and abnormal signal in the basal ganglia (decrease or swelling of all the basal ganglia, hypointensity of the lentiform nuclei and caudate, or hyperintensity in the globus pallidus).\textsuperscript{[28]}

Biochemical markers of biotinidase deficiency include more- (increase in urinary organic acid, especially 3-hydroxyisovalerate, resulting from biotin-dependent carboxylase dysfunction) or less-specific abnormalities (lactic acidosis and moderate hyperammonemia).\textsuperscript{[28]} An assay to detect biotinidase enzyme activity on dried blood spot is available.\textsuperscript{[29]} Molecular genetic analysis is useful for the diagnostic confirmation, especially in the partial enzyme deficiency.\textsuperscript{[28,29]}

Seizures are promptly responsive to oral supplementation of biotin (5–10 mg/day).\textsuperscript{[28,29]} In this context, a trial with oral biotin is strongly recommended for diagnostic and therapeutic purposes in all early-onset drug-resistant seizures, if clinical phenotype is compatible.\textsuperscript{[28,29]} The administration of oral biotin in presymptomatic children, who are diagnosed early through specific newborn-screening programs, can prevent all clinical
and biochemical abnormalities.[28,29] Recommended dosage varies from 1–5 to 2.5–10 mg/day according to the severity of the enzyme activity deficiency.[28,29]

**INBORN ERRORS OF CREATINE METABOLISM**

Creatine metabolism [Figure 5] disorders include three rare diseases in which the intracellular transfer of energy, especially in muscle and brain, is impaired: guanidinoacetate methyltransferase (GAMT; OMIM 601240), arginine:glycine amidinotransferase (AGAT; OMIM 602360), and creatine transporter 1 (CT1; OMIM 300036) deficiency.[29] GAMT and AGAT deficiency are autosomal-recessive disorders, whereas CT1 deficiency is transmitted through an X-linked mechanism.[30]

Clinical symptoms result from a decrease in cerebral creatine (in all the three disorders) and from the toxic effects of accumulated metabolites (guanidinoacetate in GAMT deficiency).[30]

GAMT, AGAT, and CT1 deficiency share a cluster of common symptoms including intellectual disability, language delay, and behavioral disorders.[30] Epileptic seizures (including myoclonic seizures, myoclonic astatic seizures, generalized tonic–clonic seizures, partial seizures with secondary generalization, drop attacks, and absences) are often the initial symptoms in GAMT deficiency.[30] GAMT deficiency results in a severe early-onset epileptic encephalopathy, developmental delay or neurological deterioration, intellectual disability, autistic-like behavior, and movement disorders (such as athetosis, chorea, choreoathetosis, ballism, and dystonia).[30]

In AGAT deficiency, seizures are uncommon (apart from febrile seizures).[30] In CT1 deficiency, epilepsy is drug responsive and less severe than in GAMT deficiency.[30]

None of the inborn errors of creatine metabolism has typical electroencephalographic patterns.[30] MRI of the brain demonstrates bilateral pallidal lesions in GAMT deficiency and a lack of creatine peak in the spectroscopy for all the three abovementioned disorders.[30]

Increased levels of guanidinoacetate in all body fluids (mainly cerebrospinal fluid and blood) are the main biochemical marker of GAMT deficiency.[30] Low levels of guanidinoacetate in plasma, urine, and cerebrospinal fluid can be observed in AGAT deficiency.[30] An increased urinary creatine/creatinine ratio is typical in CT1 deficiency.[30] Specifically oriented gene sequencing for GAMT, AGAT, or CT1 deficiency should always

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**Figure 4:** Schematic representation of biotin cycle

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**Figure 5:** Schematic representation of biotinylation cycle

**LEGEND:** ACC = acetyl-CoA carboxylase; MCC = 3-methylcrotonyl-CoA carboxylase; PC = pyruvate carboxylase; PCC = propionyl-CoA carboxylase;
be performed, if these biochemical abnormalities are recorded.\[30\]

In GAMT deficiency, an oral supplementation of creatine monohydrate (0.350–2 g/kg/day) results in the control of seizures and movement disorders, the regression of bilateral pallidal lesions, and in the restoration of creatine pools in the muscle (increased plasma creatine levels) and in the brain (reappearance of creatine peak in the magnetic resonance spectroscopy).\[30\] Additional dietary restriction of arginine (15 mg/kg/day) and supplementation of ornithine aspartate (350–800 mg/kg/day) provide further benefits for long-term outcome.\[30\] These treatments have generally no effects on neurocognitive, neuromotor, and behavioral development.\[30\]

In AGAT deficiency, creatine oral supplementation improves clinical outcome, whereas no effective treatment exists for CT1 deficiency.\[30\]

**Molybdenum Cofactor Deficiency**

Molybdenum cofactor deficiency (OMIM 252150) is an autosomal-recessive disorder resulting in the impairment of molybdenum-dependent enzymes including sulfite oxidase, xanthine oxidase, nitrate reductase, and nitrogenases.\[31\] More than 30 disease-causing mutations in genes encoding for the enzymes involved in the biosynthesis of molybdenum cofactor [Figure 6] have been reported in the literature.\[31\] Two-third of the patients with molybdenum cofactor deficiency are classified as having molybdenum cofactor type A deficiency (lack of cyclic pyranopterin monophosphate [cPMP]. Figure 6).\[31\]

The neurotoxic effects of accumulated sulfites resulting from the deficient activity of sulfite oxidase have been suggested as the main pathogenic mechanism for brain damage.\[31\]

Two phenotypes of molybdenum cofactor deficiency were reported in the literature: an early presentation with a severe epileptic encephalopathy (intractable neonatal seizures, tonus abnormalities, respiratory distress, and feeding difficulties) and an atypical later pattern with a global developmental delay.\[30\] Language, visual, and motor impairment with different degree of severity were present in all the reported patients.\[31\] Puffy cheeks and a small nose with a long philtrum represented distinctive facial features in some patients.\[32\]
Suppression burst pattern is often present in the electroencephalogram even if no pathognomonic traces have been characterized.\textsuperscript{[32]}

Brain MRI pattern includes symmetrical pallidal or subthalamic lesions, areas of cerebral infarction, subcortical multicystic lesions, progressive cortical and subcortical atrophy, and diffused white matter abnormalities.\textsuperscript{[31]} Laboratory investigations in molybdenum cofactor deficiency evidence a decrease in serum and urinary uric acid, a positive urinary sulfite test, and an elevated urinary xanthine, hypoxanthine, and S-sulfocysteine.\textsuperscript{[31,32]}

One patient with molybdenum cofactor deficiency type A was treated with intravenous purified cPMP at a dosage of 80–160 μg/kg/day.\textsuperscript{[32]} The treatment resulted in a remarkable clinical and electroencephalographic improvement (including seizure control, improvement of alertness and twitching disappearance, reappearance of rhythmic elements, and reduction of epileptiform discharges) and in the normalization of the biochemical markers.\textsuperscript{[33]} A patient with a prenatally diagnosed molybdenum cofactor deficiency type A, treated with cPMP 80 μg/kg at 4h after birth and up to 240 μg/kg at 100 days of life, was also described.\textsuperscript{[30]} The patient did not experience seizures after the first day of life with the normalization of urinary sulfite, S-sulfocysteine, xanthine, and uric acid within 1–2 weeks.\textsuperscript{[30]} At the age of 21 months, a mild cognitive delay without motor deficits was observed.\textsuperscript{[30]} Comparable benefits were observed in 8 of the 11 patients with molybdenum cofactor deficiency type A, who became seizure-free with normal levels of urine S-sulfocysteine, xanthine, and urate after 5 years of treatment.\textsuperscript{[30]}

**GLUT1 Deficiency**

Glucose transporter 1 (GLUT1) is a facilitative glucose transporter with a prominent expression in brain, placenta, and erythrocytes.\textsuperscript{[34]} GLUT1 deficiency syndrome (OMIM 138140) is generally due to de novo SCL2A1 mutations or, in familial cases, due to mutations that are transmitted through an autosomal dominant mechanism.\textsuperscript{[34]}

GLUT1 deficiency syndrome includes a classical phenotype (early-onset epileptic encephalopathy,
acquired microcephaly, developmental delay, hypotonia, spasticity, and movement disorders including dystonia and ataxia) and various nonclassical phenotypes (early-onset absences, paroxysmal exercise-induced dystonia with or without seizures, choreoathetosis, alternating hemiplegia, intermittent ataxia, language delay, expressive language difficulties, learning difficulties, different degree of cognitive delay, and migraine).

Electroencephalogram can show various epileptic abnormalities. It has reported a typical reduction of some abnormalities, such as slow waves, after a meal. Magnetic resonance is usually nondiagnostic. Positron-emission tomography often demonstrates a decrease in cortical (prominently in the mesial temporal regions) and thalamic glucose uptake.

The main biochemical hallmark for GLUT1 deficiency syndrome is hypoglycorrachia. Cerebrospinal fluid-to-blood glucose ratio level lower than 0.35 is considered as strongly suggestive of GLUT1 deficiency (even if in milder phenotype, the ratio can be higher than 0.59). Clinicians should take into account that hypoglycorrachia can be also observed in meningitis, status epilepticus, mitochondrial diseases, hypoglycemic states, subarachnoid hemorrhage, and meningeal carcinomatosis. These disorders should be carefully excluded before performing second-level investigations for GLUT1 deficiency (test for uptake of 3-O-methylglucose into erythrocytes and SLC2A1 gene sequencing). The normal values of cells, proteins, and lactate, which are observed in GLUT1 deficiency, are useful in differential diagnosis of infectious, inflammatory, and mitochondrial diseases.

Ketogenic diet remains to be the gold standard for treatment of GLUT1 deficiency because it represents an alternative source of energy for the brain. It includes high proportion of fats and a restriction of carbohydrates and it mimics the metabolic state of fasting with an increased production of ketones.

Table 1: Proposed checklist for metabolic workup in epileptic children

| CLINICAL CONSIDERATIONS FOR DIFFERENTIAL DIAGNOSIS |
|-----------------------------------------------------|
| - Onset of epilepsy in the first months of life associated with developmental delay? (All the reported disease apart from defects of creatine metabolism); |
| - Epilepsy associated with microcephaly? (Exclude cerebral folate deficiency, inborn errors of serine deficiency or GLUT1 deficiency); |
| - Epilepsy associated with facial dismorphisms? (Exclude molybdenum cofactor deficiency); |
| - Epilepsy associated with Movement disorders? (Despite individual variability, prominent association of dystonia with pyridoxine dependent seizures and in GLUT1 deficiency, of choreo-athetosis or ballismus with creatine metabolism disorders and of ataxia with GLUT1 deficiency syndrome, biotinidase, cerebral folate deficiency and inborn errors of serine metabolism); |

| LABORATORY INVESTIGATIONS: DIAGNOSTIC STEPS |
|---------------------------------------------|
| - First level investigations (Complete blood count, arterial blood gases and electrolytes, blood glucose, liver functions tests, plasma ammonia, serum uric acid, thyroid functions tests); |
| - Second level investigations: |
| Newborns or infants with epilepsy and developmental delay |
| Therapeutic trials with pyridoxine, pyridoxal 5 phosphate or folinic acid; |
| • In patients with response to therapeutic trials: urinary vanillactic acid, serum pipercolic acid, CSF pipercolic acid, CSF alpha aminoacidic semialdehyde, CSF biogenic amine, CSF aminoacid; |
| • In patients without response to therapeutic trials: aminoacids, copper and ceruloplasmin in plasma, CSF aminoacids; |
| Patients with epilepsy and movement disorders |
| • Lactate, pyruvate, lactate/pyruvate ratio and guanidoacetate in blood; |
| • Urinary creatine/creatinine ratio and pterins; |
| • Lactate, pterins, biogenic amine and glycorrachia/glycemia ratio in CSF; |
| Patients with multiorgan involvement |
| • Lactate, pyruvate, lactate/pyruvate ratio, acylcarnitines, aminoacids, folic acids, homocysteine, sialotransferrin isoelectrining focusing in plasma; |
| • Ketones, organic acids, orotic acid, purine and pyrimidine in urine |
| - Third level investigations: skin (lysosomal storage disease) or muscle (mitochondrial diseases) biopsy, oriented molecular genetics investigations; |

NEUROIMAGING
- Bilateral pallidal lesions? (GAMT deficiency and molybdenum cofactor deficiency); |
- Areas of cerebral infarction or subcortical multicystic lesions? (molybdenum cofactor deficiency); |
- Absence of creatine peak at the magnetic resonance spectroscopy? (GAMT, AGAT or CT1 deficiency);
Ketogenic diet in patients with GLUT1 deficiency induces an optimal seizure control and it also results in a decrease in movement disorders (especially dystonia, paroxysmal exercise-induced dyskinesia, and ataxia).\(^{[34]}\)

The evaluation of its effects on the cognitive outcome requires further studies.\(^{[34]}\)

Alternative promising treatments for GLUT1 deficiency in the future will be represented by alpha-lipoic acid (an antioxidant that improves cellular glucose uptake and transport) and triheptanoin (a triglyceride that strengthens the function of common ketones).\(^{[34]}\)

**CONCLUDING REMARKS**

The expanding group of treatable metabolic epilepsy also includes Mabry syndrome (treatable with pyridoxine), milder forms of nonketotic hyperglycinemia (treatable with dextromethorphan and benzoate therapy), pyruvate dehydrogenase deficiency (that can be responsive to ketogenic diet and thiamine), congenital neurotransmitter deficiencies (pyruvate carboxylase deficiency can be responsive to tetrahydrobiopterin), holocarboxylase synthetase deficiency (treatable with biotin), and succinic semialdehyde dehydrogenase deficiency (that can be responsive to vigabatrin).\(^{[2]}\)

A detailed discussion of their features is beyond the scope of this review.

New next-generation sequencing techniques explore hundreds of genes in single experiment with relevant scope of this review.

Alternative promising treatments for GLUT1 deficiency in the future will be represented by alpha-lipoic acid (an antioxidant that improves cellular glucose uptake and transport) and triheptanoin (a triglyceride that strengthens the function of common ketones).\(^{[34]}\)

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A detailed discussion of their features is beyond the scope of this review.

New next-generation sequencing techniques explore hundreds of genes in single experiment with relevant gains in the most clinically ambiguous cases.\(^{[35]}\)

Despite these progresses, the diagnostic approach for treatable inborn errors of metabolism causing epilepsy should always be based on clinical evaluation and on the subsequent interpretation of a restricted group of biochemical markers in selected subjects [see Table 1].\(^{[1]}\)

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