Epilepsy and inborn errors of metabolism: clinical and electroencephalographic features

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Abstract
Clinical and electroencephalographic phenotypes of the epilepsy in patients with inborn errors of metabolism are increasingly reported in the literature. The attempt to define several disease-specific syndromes is crucial in order to recognize the correct syndrome, which could be a valuable clue in the treatment of the underlying IEM (inborn errors of metabolism). In this paper, a classification of inborn errors of metabolism is proposed, according to their clinical and EEG features. Different epileptic syndromes and epileptiform patterns are reported in association with IEMs, however, very few of them show typical disease-specific electroencephalographic (EEG) features. Epilepsy occurring in patients with an IEM may be classified according to clinical or etiopathogenetical criteria. They can be clinically distinguished by the age of onset, seizures' semiology, EEG findings and epileptic syndromes. From a pathogenetic point of view they may be divided into two main classes: 1) disturbances of energy metabolism 2) intoxication-type disorders of intermediary metabolism 3) storage disorders with impaired neuronal function 4) disorders of neurotransmitter synthesis. Epilepsy syndromes mainly associated to IEMs are summarized in table 1. Here we reviewed the main epilepsy syndromes associated with IEM according to their clinical and EEG features.

IEM presenting with West Syndrome
Epileptic encephalopathy encompasses a group of severe, drug-resistant epileptic syndromes in which neurocognitive impairment results to be caused by seizures themselves. They usually show a neonatal or early-infantile onset within the first months of life and a deleterious outcome. Several metabolic disorders present with epileptic encephalopathy which can be diagnosed by clinical investigations. Clinical characteristics of 62 patients with WS and PKU out of 503 PKU patients only (12.3%) were reported. No patients who started the diet therapy before the age of 3 months had WS. The incidence of West syndrome in PKU patients results to be higher than in the general population (0.24-0.42%)17. However, prognosis of West syndrome merely rely on the underlying cause as symptomatic patients can improve after treatment of the idiopathic ones 18. The most severe and refractory epileptic encephalopathy occurring few hours after birth characterized by lethargy, hypotonia, apneaic attacks and weak Moro response leading to deep coma without biochemical evidence of ketosis or acidosis. A typical suppression-burst pattern is observed at the EEG recording (fig 1). Diagnosis is supported by determination of high plasma glycine levels in absence of biochemical markers of an organic acidemia (mainly propionic and methylmalonic acidemias) with a simultaneously elevated CSF glycine. Some of these patients may present brain malformations as dysgenesis of corpus callosum and gyral abnormalities. West syndrome is the most common epileptic encephalopathy occurring within the first year of life with an incidence peak around the age of 5 months. It is characterized by infantile spasms, hypsarrhythmia and psychomotor delay and shows a poor outcome in most cases. However, prognosis of West syndrome merely rely on the underlying cause as symptomatic patients can improve after treatment of the idiopathic ones and improves with antiepileptic treatment as the epilepsy and EEG patterns are cause themselves of the psychomotor impairment. The early identification of the underlying cause of WS is a crucial point to allow early diagnostic and treatment as the cerebral development can be partially restored. The clinical manifestations of untreated patients are now rarely observed since the extensive screening program was applied. The incidence of West syndrome in PKU patients results to be higher than in the general population (12.3%) than that of West syndrome in the general population. The incidence of WS in PKU patients is 68%17. However, the identification of the underlying cause of WS is crucial in order to recognize the correct syndrome, which could be a valuable clue in the treatment of the underlying IEM.
enzyme involved in the two-step process of creatine metabolism. Creatine is a crucial compound for energy metabolism and is carried to the brain and muscle by a specific transporter. Patients with creatine deficiency present with WS as well as recurrent episodes of nonconvulsive status epilepticus. Bilirubin deficiency frequently presents with WS as well as an adrenoleukodystrophy gene with onset within the first months of life. Patients may show hypotonia, psychomotor delay, alopexia and dermatitis. Supplementation with 5-10 mg/kg of bilirubin stops the seizures and prevents the occurrence of a brain disease or "linky-hair disease" commonly characterized by polypolymeric seizures that include partial clonic status epilepticus, infantile spasms, multifocal seizures and myoclonus. The EEG usually shows hypersynchrony or multifocal spike. It is an X-linked recessive disorder due to mutation of ATP1A1 encoding a copper-transport protein. CuZn-transporting ATPase-alpha polypeptide leading to reduced plasma ceruloplasmin and copper levels. Treatment with copper-histidine might be effective if started before the age of 6 weeks. Other than PKU, WS can occur in patients with several aminoacidopathies. WS has been reported in association with branched-chain organic acidurias. The latter belongs to the "intoxication-type" group of IEM characterized by recurrent episodes of severe metabolic acidosis and long-term complications including renal failure and brain toxicity. Five patients with methylmalonic aciduria (MMA) and WS were reported. Two Vietnamese patients with "myoclonic convulsions, psychomotor retardation and hypsarrhythmia"23, a Japanese patient with MMA showing brief tonic seizures and polyspike bursts on EEG24, and a patient with vitamin B12 deficiency and secondary MMA were described25. Moreover, Campeau et al (2006) reported on a 4, 5 months old baby with MMA that presented with infantile spasms, psychomotor impairment and hypsarhythmia at the EEG recording. In this child urine MMA excretion increased after starting steroid treatment for WS and was managed by dietary protein restriction and metronidazole therapy26. Patients with propionic acidemia and maple syrup disease in association to WS were reported27. We diagnosed hyperprolinemia type 1 (HP1) in a patient with WS (Di RosAl Torrellia unpublished data). HP1 is an autosomal recessive disorder due to mutations of proline-dehydrogenase (PRODH) gene involved in proline metabolism whose deficiency leads to high plasma proline levels and high urine excretion28. Proline seems to play a neuromodulator role on specific glutamatergic synapses in CNS and its accumulation results in an increase of excitatory neurotransmission probably favouring epileptogenesis29. Despite different mutations on PRODH gene have been reported with mild to severe reduction of the residual enzyme activity, a clear genotype/phenotype correlation in this peculiar disorder was not done. Mitochondrial disorders can be the underlying cause of infantile spasms (IS). They are defined as that group of disorders due to defects of the respiratory chain complexes (OXPHOS)30. Epilepsy has been associated to 26-60% of all mitochondrial disorders31-32, however few studies have been published about the epileptic phenotypes. Leigh syndrome is a severe, early-onset mitochondrial subacute necrotizing encephalomyelopathy characterized by psychomotor delay, hypotonia, feeding difficulties, failure to thrive, oculomotor disturbances, apnic spells, breath disturbances. Patients usually have severe lactic acidosis in plasma and CSF. Symmetric lesions of the basal ganglia, brainstem and thalami are usually detected by the MRI scan30. The genes involved into Leih syndrome encode one of the subunits of the pyruvate dehydrogenase complex (PDH), one of the subunits of the respiratory chain complexes or proteins involved into assembly components of respiratory complexes I and IV32. From 10-30% of patients with Leih syndrome shows a mutation of the subunits of ATP synthase 632. Epilepsy is a common manifestation of Leigh syndrome usually presenting with drug-resistant seizures and some peculiar EEG patterns. Infantile spasms are reported in patients with Leigh syndrome32. The EEG pattern of a patient with a mitochondrial encephalopathy due to a ATPase 6 deficiency is shown in fig 2.

**Aminoacidopathies (PKU, MMA, PA)**

**Biotin deficiency**

**Meknes disease**

**Creatine deficiency**

**Mitochondrial disorders (complex I, II, IV, V deficiency)**

**Molybdenum cofactor deficiency**

**Methylene tetrahydrofolate reductase (MTHFR) deficiency**

## IE Ms associated to status epilepticus

A dramatic mitochondrial encephalopathy associated to acute liver failure is Alpers’ syndrome, an autosomal recessive disorder due to mutations of POLG1 gene encoding DNA polymerase γ1 characterized by frequent onset with status epilepticus and acute liver failure in a previously healthy child. Severe lactic acidosis in plasma and CSF is a striking feature34. The EEG pattern typically associated to Alpers’ syndrome is characterized by posterior rhythmic high-amplitude delta with superimposed (polyspikes) (RHADS). When clinical features present with RHADS at the EEG recording diagnosis is strongly suspected33. What clinicians must keep in mind is to avoid treatment with sodium valproate in patients with suspicion of Alpers’ syndrome as it may dramatically worsen liver failure33.

### IE Ms presenting with progressive myoclonic epilepsy

A group of IEMs producing relatively typical progressive myoclonic epilepsies (PMEs) include Unverricht-Lundborg disease, MERRF, Lafora disease, neuronal ceroid lipofuscinosis (NCL), juvenile neuronopathic Gaucher diseases and sialidoses35. PMEs are a group of neurodegenerative disorders characterized by intractable epileptic myoclonic and generalized tonic-clonic seizures, myoclonic jerks, and progressive and extrapyramidal manifestations. The longitudinal EEG progression shows an initial slowing of the background activity and the appearance of isolated focal discharges36. Moreover a reduction of the EEG discharges during sleep was reported. The photoparoxysmal response is commonly evoked by photic stimulation at the lower rates (1 Hz) in patients with Unverricht-Lundborg disease, Lafora disease, MERRF and NCLs37-39.

**Epilepsy with predominant myoclonic seizures occurring in IEMs**

Myoclonic seizures may be the prominent manifestation of several mitochondrial disorders (complex I, IV and V deficiency, Alpers’ syndrome)32, 34, NKKH, storage disorders35. GLUT-1 deficiency40. GLUT-1 deficiency is a mitochondrial encephalopathy characterized by persistent hypoglycaemia in the absence of hypoglycaemia and with normal or low lactate in the CSF. Patients shows microcephaly, psychomotor delay, pyramidial signs, movement disorders. Epilepsy in GLUT-1 deficiency is usually drug-resistant with an expanding phenotype spectrum40, 41.

Leen et al (2010) distinguished three main forms 1) the classical phenotype (84% of patients) 2) the nonclassical phenotype characterized by mental retardation and atypical movement disorders (complex I, IV and V deficiency, Alpers’ syndrome). One additional phenotypically characterized by persistent hypoglycaemia in the absence of hypoglycaemia and with normal or low lactate in the CSF. Patients shows microcephaly, psychomotor delay, pyramidial signs, movement disorders. Epilepsy in GLUT-1 deficiency is usually drug-resistant with an expanding phenotype spectrum40, 41.

Roulet-Perrez et al (2008) reported on a 10.5-year-old girl initially diagnosed with IGE that turned out to have a mild form of GLUT-1 deficiency. This patient presented early-onset absence seizures with myoclonic jerks at the upper limbs or trunk related to an EEG pattern characterized by polymorphic and irregular spontaneous bursts of generalized 2-4 Hz SW shorter than the one observed in typical absence seizures42. Differently from the typical absences, seizures were only partially responding to the antiepileptic therapy with valproate, ethosuximide and clobazam. Togther to the clear epileptiform manifestations, the patients presented prolonged episodes of mild confusion and unsteadiness mainly in concomitance with fasting or stressful situations.

The EEG recording showed a dramatic change of diffuse slowing of the background activity with interposed irregular spikes that disappeared after meal28. Other patients with apparent disappearance of absence epilepsy were reported as having mild form of GLUT-1 deficiency43,45. Absence seizures are mainly refractory or partially-responsive to the AEDs.

Patients with GLUT-1 deficiency could be effectively treated by ketogenic diet. Unfortunately, the identification of the mild forms of GLUT-1 deficiency is a challenge as the lumbar puncture is not useful procedure in a patient with diagnosis of IGE. The main IEMs presenting with GTCS are shown in table 4.

**GTCS occur in several metabolic disorders together with other seizures’ types.**

They can be part of the constellation of signs and symptoms of PMEs (as previously discussed).

Epileptic seizures associated to GLUT-1 deficiency also include GTCS. The main IEMs presenting with GTCS are shown in table 4.
GLUT-1 deficiency

NCL2, NCL3

Storage disorders

Mitochondrial disorders

References


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