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Progressive myoclonic epilepsies: myth or reality?

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ABSTRACT – The progressive myoclonus epilepsies (PME) are rare diseases and many clinicians, who have only few opportunities to encounter such patients, may think of them as mythical. However, the category of PME has been retained by the latest classification scheme proposal of the International League Against Epilepsy. PMEs are defined by: 1) generalized epileptic seizures (focal seizures may also occur in certain etiologies), 2) a sometimes invalidating myoclonus, and 3) other neurological symptoms (ataxia, dementia, sensory deficits) that vary according to etiology. Indeed, PMEs are a heterogenous group of conditions, with diverse etiologies. Their prevalence varies according to the ethnic context, and PMEs may appear as fairly frequent in some settings, because of genetic factors (isolate and/or inbreeding, for instance, in PMEs with recessive inheritance). The genetic and biochemical mechanisms underlying PMEs are increasingly recognized. We must nowadays follow a logical diagnostic scheme that will take into account the ethnic and genetic context, the age at onset of symptoms and the respective weight of symptoms. New therapeutic approaches are under development, and the available purely symptomatic treatments can be used to best possible effect. It is thus possible to recognize PMEs as a group of conditions appearing either as epilepsy, or as a movement disorder, or still under the mask of various neurological or cognitive symptoms. It is also possible to organize a logical, comprehensive care for patients with PME.

Keywords: epilepsy, myoclonus, progressive myoclonic epilepsy

The relative infrequency of progressive myoclonic epilepsies (PMEs), which represent less than 1% of all forms of epilepsy, and their specific but often misleading clinical presentation (Berkovic *et al*. 1986, Serratosa 2001, Genton *et al*. 2005, Genton and Bureau 2003), explain their misdiagnosis, as well as the fact that they often go unrecognized and that a diagnosis of PME is always difficult to confirm. Although considerable literature is still devoted to PMEs, most epileptologists find it tempting to regard it as too much energy invested in a myth having little relation to practical reality.

However, the recent proposal for a new international classification scheme for the diagnosis of the epilepsies (Engel 2001) recognizes the group of PMEs as a distinctive diagnostic category to be added to the list of epileptic disorders. Moreover, the rarity of PMEs is relative, because in certain conditions these diseases can become fairly frequent: for instance, human isolates with consanguinity, for conditions with autosomal recessive inheritance. For example; in cases of Unverricht-Lundborg disease, we can retrace the introduction of the first mutated gene in such a population group about 1750, among families of French extraction in the Reunion Islands (Moulard *et al*. 2002, Moulard *et al*. 2003). This is also the case for certain diseases where a mutated gene can be frequent in some population groups, but extremely rare elsewhere: for ins-

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Table 1. The experience of the Centre Saint-Paul, Marseille, in the field of progressive myoclonic epilepsies.

Ceroid lipofuscinosis (Batten)		15
– late infantile (Jansky-Bielchowsky)	10	
– juvenile (Spielmeyer-Vogt)	2	
– adult (Kuf's)	3	
MERRF		2
Type III Gaucher		1
Lafora		40
Unverricht-Lundborg		63
DRPLA		2
Other/unclassified		10
Total		133

These patients were seen over a 45-year period, between 1960 and 2004. They represent less than 1% of evaluated patients (this, despite the concentration of PME cases, given the specific interest of the institution in these diseases). Undiagnosed cases represent old evaluations, which did not benefit from modern means of diagnostic assessment.

tance, this description was ap plied to dentate-rubro-pallido-luysian atrophy (DRPLA) in Japan because of its relatively frequent occurrence in that country, before the condition was identified elsewhere, especially in France (Iizuka *et al*. 1984, Destee *et al*. 2000).

The fact is that PMEs are a reality and our objective is to present a concise proposal for a logical diagnostic scheme applying to these conditions. *Table 1* presents the relative frequency of PMEs seen at the Centre Saint-Paul in Marseille; this prevalence is characteristic of a Mediterranean population; Scandinavian or Japanese centers are, of course, likely to present a different picture.

Clinical setting

The term PME refers to a heterogeneous group of conditions, from a clinical as well as neurophysiological and etiological standpoint. The most characteristic attribute of all PMEs is a constellation of symptoms, particularly epileptic seizures and myoclonus that are progressive over time. Therefore, based on a consensus established over 10 years ago (Marseille Consensus Group 1990), PMEs can be defined as a group of progressive disorders characterized by the combination of epileptic seizures and a myoclonic syndrome.

The various components of PME could be described as follows:

In terms of etiology, epileptic seizures are typically generalized, with tonic-clonic convulsions and myoclonic seizures, as well as atypical absences and focal seizures (for example, the occipital seizures suggestive of Lafora disease).

Because myoclonic jerks are a permanent symptom, they can be detected clinically. This action myoclonus (triggered or aggravated by movement or preparation for movement) can be either massive (bilateral, generalized and symmetrical), or partial or fragmentary.

Seizures and myoclonus can be accompanied by neurological or sensory deficits that vary depending on etiology and contribute to the severity of the disease. Intellectual regression leading to dementia is present in all cases of PME characterized by diffuse damage to cortical neurons; in most cases, progression of the disease is rapid. Ataxia is also very frequent; in this context, it is not specific and is often masked by very intense myoclonia which renders standing or walking difficult. Sensory deficit is most often visual; it can be "functional" (like the occipital seizures in Lafora disease, with transient amaurosis) or "organic", as

Table 2. Genetic mechanisms in progressive myoclonic epilepsies.

Disease	Mode	Gene / Localisation	Known mechanism
Unverricht - Lundborg disease	AR	EPMI – 21q 22.3 (cystatin B)	CCCCGCCCCGCG expansion and point mutations
Lafora	AR	EPM2A – 6q23q25 (laforine)	Other possible gene 20% unlinked
MERRF	Mit.	Mitochondrial DNA	Most often, A8344G mutation
Sialidosis	AR	6p21.3a-N-acetylneuraminidase	Variable mutations
Galactosialidosis	AR	20q13 associated β-galactosidase deficit	Variable mutations
Late infantile ceroid lipofuscinosis	AR	CLN2 11p15.5	Numerous variations...
		CLN5 13q21.1 – q32	
		CLN6 15q21 – q23	
Juvenile ceroid lipofuscinosis		CLN3 – 165298	
Juvenile Huntington	AD	4p16 (huntingtin)	CAG expansion
DRPLA	AD	12p13 (atrophin)	CAG expansion
Type III Gaucher	AR	1eq21b – glucocerebrosidiase	Variable mutations

AR: autosomal recessive; **AD**: autosomal dominant; **Mit**.: mitochondrial.

in cases of retinal damage (ceroid lipofuscinoses), as well as cortical or mixed damage.

PMEs can also be classified in two main categories according to the nature of anatomo-pathological lesions:
– Metabolic storage disorders, where aberrant material, in terms of quantity and distribution, is present in nerve cells and sometimes in other tissues; such diseases are often diagnosed by cytologic or histologic investigations, as is the case for ceroid lipofuscinosis (CLF);
– What could be called "abiotrophic" diseases, characterized by progressive disappearance of certain neuronal networks due to apoptosis or cell death, not manifesting in anatomical overload, but rather in a functional deficit, as in Unverricht-Lundborg disease (ULD);
– Other PMEs seem to involve mixed mechanisms, because overload demonstrated by appropriate anatomopathological methods does not explain cellular degeneration; this is the case in Lafora, for example.

Finally, genetic transmission of these diseases is variable:
– In most cases, transmission is autosomal recessive;
– By contrast, other disorders are characterized by dominant or maternal transmission, associated with mitochondrial DNA;
– Finally, some very rare pathologies such as Kuf's disease can occur sporadically, either due to a *de novo* mutation or to another mechanism.
Table 2 summarizes the genetic characteristics of the best known PMEs.

Table 3. Diagnostic scheme for progressive myoclonus epilepsy (based on Genton and Bureau 2003).

Seizures
Myoclonic syndrome

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Clinical assessment: age, progression, associated symptoms, ethnic and genetic context
EEG studies: wakefulness, sleep, polygraphy with surface electromyogram, IPS

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Differential diagnosis

Child	
- with mental retardation/dementia	- non specific epileptic encephalopathy (± aggravation due to inappropriate AED)
	- specific encephalopathy, metabolic diseases
- without mental retardation	- aggravation of IGE due to inappropriate treatment
Adolescent/adult	
- without mental retardation/dementia	- aggravated IGE (particularly JME)
- with mental retardation/dementia	- Alzheimer, dialysis encephalopathy…

↓

Schematic orientation of diagnostic tests

Child between two and eight years	Older child/adolescent
Ceroid lipofuscinosis: EEG and IPS Fundoscopy Skin or digestive mucosa biopsy Brain biopsy (adult form)	Unverricht-Lundborg disease Search for gene mutation
Juvenile Huntingdon: Search for mutation	Lafora disease EEG occipital anomalies Axillary skin biopsy
Sialidosis: Fundoscopy Neuraminidase dosage	MEERF Muscular biopsy Search for gene mutation
	DRPLA Search for gene mutation

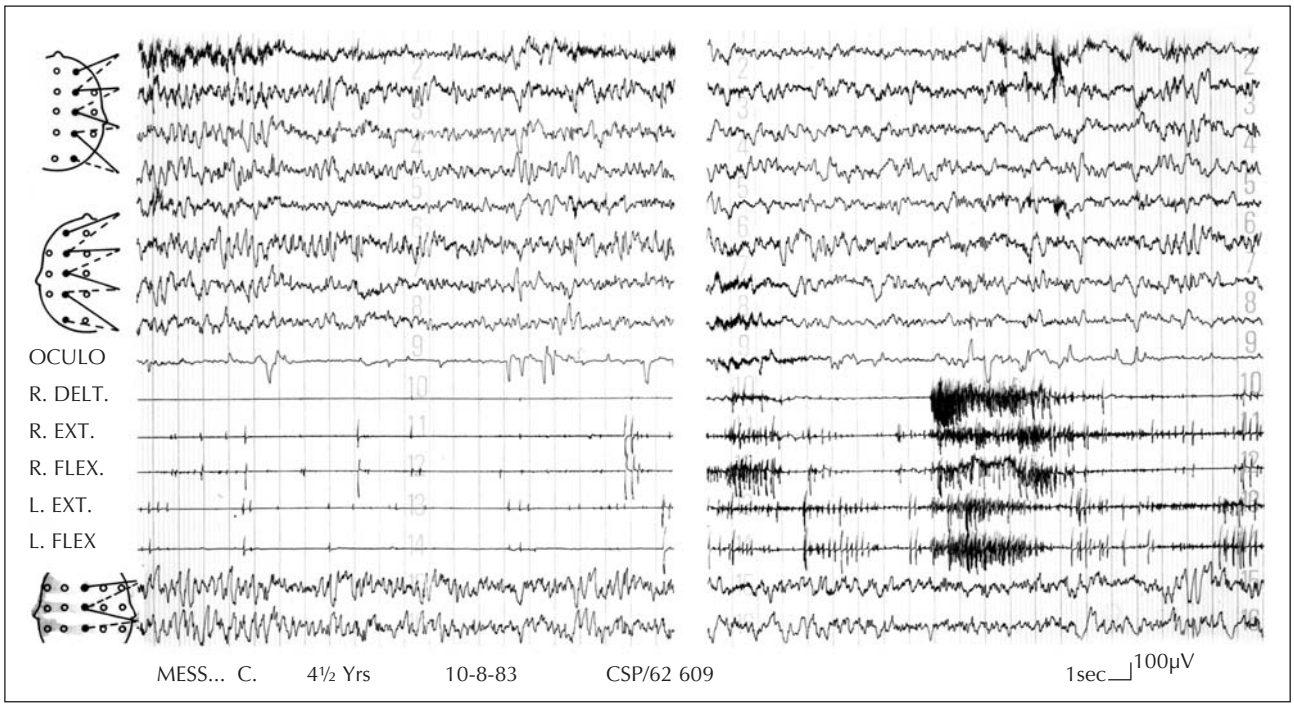

Figure 1. Four and a half years old girl, presenting a late infantile form of ceroid lipofuscinosis. Left: EEG at rest showing overall slow background activity and rare spikes waves in the central regions and the vertex. Polygraphy shows the presence of segmental myocloni, asynchronous involving the upper limbs; some myocloni were preceded by spike wave activity. Right: action myoclonus triggered by movement of both upper limbs.

Clues for a clinical diagnosis

Good assessment of the clinical picture presented by a given patient can point to a specific diagnosis from the start. Age at onset, family context and especially ethnic or geographic origin are essential elements that can orientate a diagnosis (*table 3*). For a detailed description of PMEs, the reader can refer to a recent work (Genton *et al*. 2005) and to the references quoted therein.

The *myoclonic syndrome* dominates the clinical picture in most cases, but can be overshadowed by epileptic seizures (in the early stages), or by signs of cognitive deterioration or sensory symptoms, particularly visual, as in Lafora disease (Tassinari *et al*. 1978) or ceroid lipofuscinoses. Myoclonic jerks are often most intense in the morning on awakening, inhibiting all ordinary daily activities (since they are triggered by movement) as well as speech, which can become choppy and explosive. Myoclonus is massive (sometimes resulting in falls), or segmental (*figure 1*) and focal, arrhythmic, asynchronous and asymmetrical, facilitated by stress and by movement or preparation for movement, especially rising up and beginning to walk. Preferential facial location is seen in cases of sialidosis. Myoclonus disappears or is greatly reduced during sleep, and intensify upon arousal. It is chiefly responsible for invalidity in ULD (Unverricht-Lundborg disease), where it constitutes practically the only residual symptom in advanced cases.

Tonic-clonic and clono-tonicoclonic seizures are constant. Most PMEs also present atypical absences and clonic seizures. Unilateral seizures can occur; focal seizures, particularly occipital, are characteristic of Lafora disease (Roger *et al*. 1983).

Severe and progressive *dementia* is characteristic of some etiologies. It is absent or moderate in ULD and in adult benign myoclonic epilepsy (Okino 1997) (disorder in which cortical damage is minimal or absent); variable in myoclonic epilepsy associated with ragged-red fibers (MERRF) (Fukuhara *et al*. 1980), in sialidosis and Gaucher's disease; a major symptom in Lafora (Van Heycop Ten Ham and Jager, 1963; Rapin *et al*., 1978) disease and in most cases of ceroid lipofuscinoses.

Neurological and sensorial symptoms are variable depending on etiology and on stage of evolution of the disease. Ataxia, often difficult to evaluate due to the intensity of the myoclonus, is almost constant. Sensory deficits are more specific: episodes of cortical blindness in Lafora disease often associated with occipital seizures; progressive blindness in most cases of ceroid lipofuscinosis due to retinal deposits; deafness or multisensorial deficit in MERRF. A muscular deficit can also be seen in MERRF.

Specific anomalies indicate particular etiologies: possible hepatosplenomegaly in Gaucher's disease (type III),

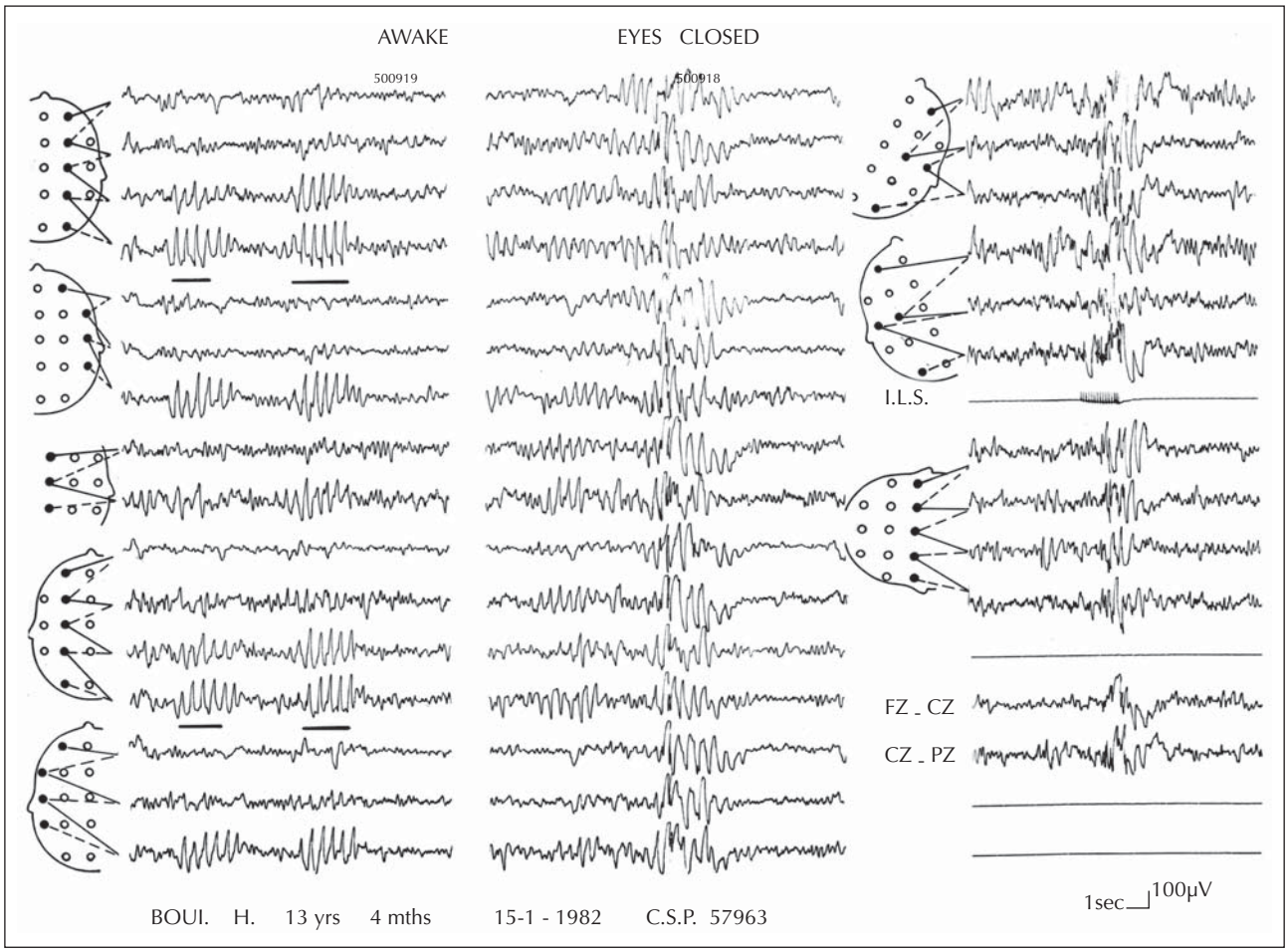

Figure 2. 13 years 4 months-old girl, presenting with Lafora disease. Left: awake, discharges of spikes in the posterior regions of both hemispheres. Centre: eyes closed, discharge of diffuse, spike waves. Right: posterior polyspike waves discharge induced by photic stimulation.

cherry-red spot in the fundus oculi (Rapin *et al.*, 1978) in sialidosis. The patient's general appearance can offer an indication. Shortness and gross facies are associated with galactosialidosis. Serious worsening of the patient's general state of health, with thinness, is often seen in MERRF. Renal failure (often at the dialysis stage when PME is diagnosed) is characteristic of renal failure PME syndrome.

In most cases of PME, at least early in the progression, the *neurophysiological studies* reveal large somatosensory potential which can decrease with evolution. The EEG shows major progressive alteration of background activity in clinically progressive diseases. Some anomalies, in a posterior location, indicate Lafora disease *(figure 2)*, while others are located at the vertex and have been described by Tassinari et al. 1974 in Unverricht-Lundborg disease *(figure 3)*; but they are also seen in other types of action myocloni. Photosensitivity is present in many forms of PME and manifests as spikes sharp wave discharges or polyspikes sharp wave generalized discharges at intermittent photic stimulation (IPS), associated with massive myocloni; or as stimulus-by-stimulus responses to slow frequencies, highly characteristic of ceroid lipofuscinoses, from late infantile to adult forms.

Hierarchy of diagnostic tests

Diagnosing a form of PME requires obtaining a complete clinical picture; having adequate knowledge of the genetic, ethnic and geographic context; and taking into account the progression of symptoms. Of course, the various diagnostic procedures can be used for genetic counseling or for prenatal testing.

Recourse to *neuropathologic exams* for diagnostic purposes has been greatly reduced; this is especially true of the most invasive procedures (particularly brain biopsies). In Lafora disease, amylaceous bodies are revealed by a skin biopsy performed in the axillary region, which is rich in sweat glands (anomalies are particularly apparent in the cells of the excretory canals) (Carpenter 1981). Vacuolized lymphocytes can be identified in cases of Ceroid lipofus-

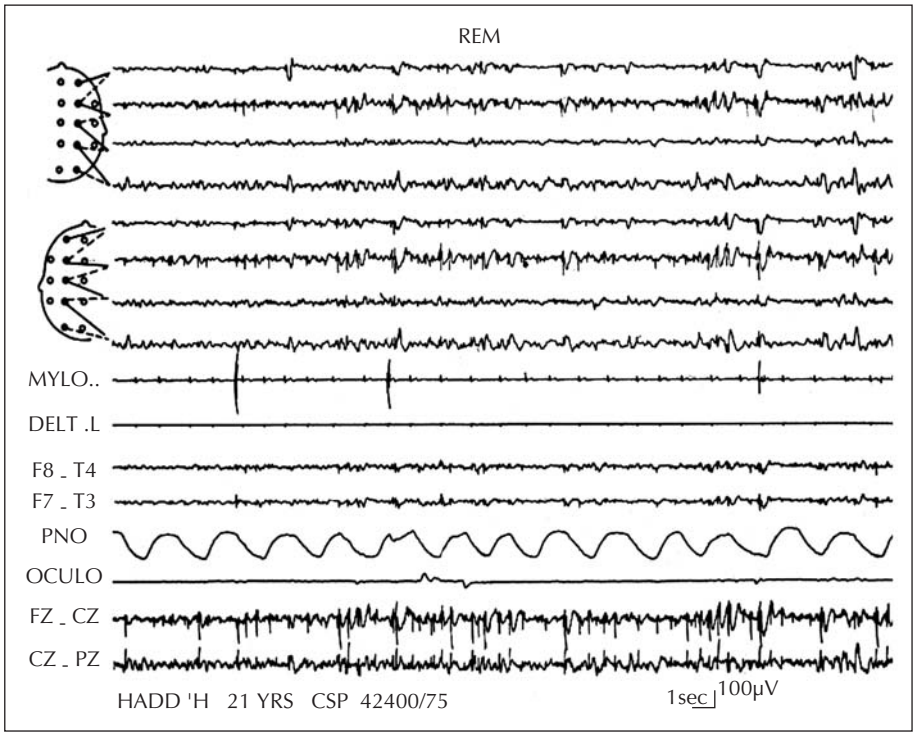

Figure 3. 21 years-old man, with Unverricht-Lundborg disease. During REM, appearance of rapid spikes and polyspikes waves around vertex and central regions.

cinosis. As for MERRF, detecting "ragged" muscle fibres requires a muscular biopsy, that can, however, show little changes or give false-negative findings. The adult form of ceroid lipofuscinosis (Kuf's disease), is very particular in the way that it appears sporadically, with histological damage limited to the CNS. A brain biopsy is often inevitable for the diagnosis.

Biochemical studies remain useful for detecting enzyme deficits. However, these tests are difficult and often misleading in mitochondrial pathologies such as MERRF (Bindoff *et al*. 1991).

Genetic studies are essential because they confirm the diagnosis rather easily in cases of Unverricht-Lundborg, DRPLA, juvenile Huntington's chorea, MERFF (Wallace *et al*. 1991) (and the other mitochondriopathies), adult benign familial myoclonic epilepsy (Mikami *et al*. 1999), and certain other disorders. We have made great advances in the field, particularly in respect to Lafora disease (Serratosa *et al*. 1995, Minassian *et al*. 1998), but 20% of patients do not present identifiable mutations in the two known locations, and diagnosis can remain clinical and neuropathological in these cases.

Conclusion

PMEs are a reality. Moreover, due to their rarity and overall seriousness, they present both a diagnostic and a therapeutic challenge. They are a heterogeneous group of disorders whose clinical presentation can be considered typical, often spectacular, and sometimes misleading. A certain knowledge, as well as common sense, is needed to establish a rational hierarchy of complementary studies: *table 3* summarizes the practical clinical steps to carry out in order to diagnose PMEs in children and adolescents. Arriving at a precise etiological diagnosis makes it possible to establish prognosis, develop a general treatment plan, and provide familial genetic counseling. □

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