Chapter 16

Unverricht–Lundborg disease

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The causal disease

Progressive myoclonus epilepsy of the Unverricht–Lundborg type (EPM1) is an autosomal recessive neurodegenerative disorder that has the highest incidence among the progressive myoclonus epilepsies worldwide (Berkovic *et al.* 1986; Marseille Consensus Group 1990). It is characterized by stimulus-sensitive myoclonus, and tonic–clonic epileptic seizures. As EPM1 progresses, patients develop additional neurological symptoms including ataxia, dysarthria, intentional tremor, and decreased coordination, together reflecting widespread neuronal degeneration in the brain (Koskiniemi *et al.* 1974a, Norio and Koskiniemi 1979). Some patients become wheelchair-bound. Patients may experience emotional lability, depression, and a mild intellectual decline over time, but overall their cognitive functions are less impaired than their motor functions (Koskiniemi *et al.* 1974a; Lehesjoki and Kälviäinen 2007; Kälviäinen *et al.* 2008). Loss-of-function mutations in the gene encoding CYSTATIN B (*CSTB*) are the primary genetic cause of EPM1 (Lalioti *et al.* 1997; Pennacchio *et al.* 1998; Joensuu *et al.*, 2008).

Previously EPM1 has been known by the following names: Baltic myoclonus, Baltic myoclonic epilepsy, and Mediterranean myoclonus. With advances in genetic testing, these disorders are now collectively classified as EPM1 (Kälviäinen *et al.* 2008).

Epilepsy in the disease

At disease onset (6–16 years), EPM1 patients present primarily with myoclonic jerks and/or generalized tonic–clonic seizures. Involuntary action-activated or stimulus-sensitive myoclonus (i.e., triggered by light, physical activity, noise, cognitive stimulus, and/or stress) is observed in the majority of patients (Koskiniemi *et al.* 1974a; Norio and Koskiniemi 1979). This asynchronized myoclonus occurs primarily in the proximal muscles of the extremities; it may be focal or multifocal, and it may generalize to myoclonic seizures or status myoclonicus (Koskiniemi *et al.* 1974a).

The most prevalent type of epileptic seizures that EPM1 patients present with is generalized tonic–clonic seizures, which can combine with simple motor or complex partial seizures (Koskiniemi *et al.* 1974a; Norio and Koskiniemi 1979). However, tonic–clonic seizures are not necessarily observed in all cases, as they may be obscured in part by myoclonic jerks. In rare cases, tonic–clonic seizures are not observed at all. The seizures can be controlled with antiepileptic drugs, which in many cases eliminate them altogether. In the final stages of the disease, care should be taken to distinguish between generalized tonic–clonic seizures and continuous myoclonic and possibly subcortically generated jerks or status myoclonicus (Lehesjoki and Kälviäinen 2007; Kälviäinen *et al.* 2008).

Diagnostic tests for the disease

Diagnosis should be considered for any previously healthy child who between the ages of 6 and 16 presents with at least one of the following symptoms: (1) involuntary, stimulus and/or action activated myoclonic jerks, (2) generalized tonic–clonic seizures, (3) mild neurological signs in motor function or coordination, (4) photosensitivity, generalized spike-and-wave and polyspike-and-wave paroxysms, and background slowing in the electroencephalogram (EEG), and (5) worsening of neurological symptoms (myoclonus and ataxia) (Koskiniemi *et al.* 1974b; Kälviäinen *et al.* 2008). At disease onset, the magnetic resonance imaging (MRI) scan is typically normal; however, cerebral atrophy and neuronal loss in the pons, medulla, and cerebellum have been observed in some patients at later stages of the disease. The clinical examination should also include an evaluation of walking, coordination, handwriting, school performance, and emotional states. An examination of the myoclonus should entail an evaluation of the myoclonus at rest, with action, and in response to stimuli including light, noise, and/or stress (Lehesjoki and Kälviäinen 2007; Kälviäinen *et al.* 2008).

An EEG should be obtained prior to therapeutic intervention. Abnormalities in the EEG (spike–wave discharges,

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photosensitivity, polyspike discharges during rapid eye movement [REM] sleep, background slowing) are more pronounced at initial diagnosis, when disease onset may be accompanied by generalized tonic–clonic seizures (Koskiniemi *et al.* 1974b; Franceschetti *et al.* 1993). Any physiological sleep patterns that are initially observed disappear in about one-half of the patients after 16 years of having the disease. Some patients also present with focal epileptiform discharges, primarily in the occipital region. In general, EEG abnormalities diminish as the disease stabilizes (Ferlazzo *et al.* 2007; Kälviäinen *et al.* 2008). Navigated transcranial magnetic stimulation (TMS) has also revealed significant neurophysiological changes in cortical excitability in which the motor thresholds are elevated and the silent periods are prolonged in EPM1 patients (Danner *et al.* 2009).

Clinical diagnosis can be complemented with genetic testing. Classical EPM1 is an autosomal recessive disorder associated with mutations in the *CSTB* gene (Lalioti *et al.* 1997; Pennacchio *et al.* 1998; Joensuu *et al.* 2008). The majority of EPM1 patients harbor an unstable dodecamer repeat expansion (5′-CCC-CGC-CCC-GCG-3′) in at least one allele in the *CSTB* promoter region (Lalioti *et al.* 1997; Joensuu *et al.* 2008). While normal alleles typically contain two or three dodecamer repeats, disease-causing expansions contain at least 30 such repeats. Heterozygosity for the dodecamer repeat expansion can be accompanied by a number of additional mutations in the coding region of *CSTB* (Lehesjoki and Kälviäinen, 2007; Joensuu *et al.* 2008). The dodecamer repeat expansion mutation accounts for approximately 90% of EPM1 cases worldwide (Lalioti *et al.* 1997; Lehesjoki and Kälviäinen 2007; Joensuu *et al.* 2008).

Patients presenting with symptoms closely resembling EPM1 but who do not harbor mutations in *CSTB* should be evaluated for additional progressive myoclonic epilepsies (PMEs) that closely resemble EPM1 including the recently described EPM1B. The latter is a variant of EPM1 that arises due to a missense nucleotide mutation in the *PRICKLE1* gene (Bassuk *et al.* 2008). Patients with EPM1B present with symptoms at a slightly younger age than EPM1 patients, and in addition to the classic progressive myoclonus and ataxia observed in EPM1 patients, EPM1B patients may present with an impaired upgaze (Bassuk *et al.* 2008). Another PME syndrome that may be considered in differential diagnosis is action myoclonus–renal failure syndrome (AMRF), which arises from mutations in the gene encoding SCARB2/Limp2 (Berkovic *et al.* 2008). Patients with AMRF present typically at 15–25 years of age with either neurological symptoms including tremor, action myoclonus, seizures, and ataxia, or with proteinuria that progresses to renal failure (Berkovic *et al.* 2008). The PMEs as a whole share many key features that make it difficult to distinguish between distinct PMEs. Thus, completing the differential diagnosis among PMEs is critical as the principles of disease management differ greatly depending on the final diagnosis (Table 16.1).

Principles of management

The primary therapeutic approaches for EPM1 patients include rehabilitation and symptomatic pharmacologic management. Pharmacologic intervention includes: valproic acid (the first drug of choice) (Norio and Koskiniemi 1979; Iivanainen and Himberg 1982; Somerville and Olanow 1982; Shahwan *et al.*, 2005), clonazepam (the only drug approved by the US Food and Drug Administration for the treatment of myoclonic seizures) (Iivanainen and Himberg 1982; Shahwan *et al.* 2005), high doses of piracetam (for myoclonus) (Remy and Genton 1991; Koskiniemi *et al.* 1998), levetiracetam (for myoclonus and generalized seizures) (Genton and Gelisse 2000; Frucht *et al.* 2001; Crest *et al.* 2004; Magaudda *et al.* 2004), and topiramate and zonisamide (as supplements) (Henry *et al.* 1988; Aykutlu *et al.* 2005). Myoclonus is resistant to known therapies, and during time periods when stimulus-activated myoclonus is particularly sensitive, loud noises and bright lights should be avoided and the patient should remain in a quiet, peaceful space. In practice, patients require lifelong clinical follow-up and psychosocial support. However, provided with the appropriate social infrastructure, mental balance can be maintained and depression can be prevented (Lehesjoki and Kälviäinen 2007; Kälviäinen *et al.* 2008).

Several case reports suggest that treatment of EPM1 patients with the antioxidant *N*-acetylcysteine (NAC) alleviates key features of the disorder including dysarthria, ataxia, and seizures (Edwards *et al.* 2002). Although the role of oxidative stress in EPM1-linked neuronal degeneration is not completely understood, a specific decrease in cerebellar defenses against oxidative stress and a concomitant increase in lipid peroxidation occurs in the mouse model for EPM1 (Lehtinen *et al.* 2009).

Phenytoin and fosphenytoin should be avoided as these medications trigger detrimental neurological side effects, specifically exacerbating cerebellar degeneration (Eldridge *et al.* 1983). In addition, other sodium channel blockers (carbamazepine, oxcarbazepine), GABAergic drugs (tiagabine, vigabatrin), gabapentin, and pregabalin should be excluded as they may negatively contribute to myoclonus and myoclonic seizures (Medina *et al.* 2005).

In emergencies, intravenous benzodiazepines (diazepam, lorazepam, clonazepam, and midazolam), valproate, and levetiracetam may be administered (Kälviäinen *et al.* 2008). Phenytoin should be used only if the patient is experiencing a distinct localization-related status epilepticus, such as that due to head trauma (Kälviäinen *et al.* 2008).

Ultimately, some EPM1 patients suffer from drug-resistant forms of progressive myoclonus. Myoclonic seizures can also be easily misdiagnosed as tonic–clonic seizures or even pseudoepileptic seizures, especially as the majority of the myoclonic movements are not time-locked to EEG discharges (Kälviäinen *et al.* 2008). Thus, extreme care should be taken when choosing the correct therapeutic intervention.

Table 16.1 Differential characteristics of progressive myoclonic epilepsies

Disease	EPM1 (Unverricht–Lundborg disease)	EPM1B	Lafora disease	Mitochondrial encephalopathy with ragged red fibers (MERRF)	Neuronal ceroid lipofuscinosis (NCL)	Sialidoses
Inheritance[a]	AR	AR	AR	Maternal	AR/AD[b]	AR
Gene	*CSTB*	*PRICKLE1*	*EPM2A, NHLRC1*	*MTTK*	*TPP1, CLN3, CLN5, CLN6*	*NEU1*
Age of onset (years)	6–16	5–10	12–17	Variable	Variable	Variable
Prominent seizures[c]	Myoclonus	Myoclonus	Myoclonus, occipital seizures	Myoclonus	Variable	Myoclonus
Cerebellar signs	Mild and late	Unknown	Early	Variable	Variable	Gradual
Dementia/ Cognitive decline	Mild and late or absent	Mild or absent	Early, relentless	Variable	Rapidly progressive	Absent in Type I; learning difficulty in Type II
Fundi	Normal	Unknown	Normal	With or without optic atrophy or retinopathy	Macular degeneration and visual failure, except Kuf disease	Cherry-red spot
Dysmorphism	No	No	No	Variable	No	Type II
Evolution/ prognosis	Typically mild/ chronic, occasionally severe	Typically mild/ chronic, occasionally severe	Very severe, death within 2–10 yrs	Variable from very mild to very severe	Severe	Variable, usually severe; late onset usually less severe

Notes:
[a]AR, autosomal recessive; AD, autosomal dominant.
[b]Only Kuf (adult NCL) can be inherited in either an autosomal recessive or autosomal dominant manner.
[c]Prominent features.
Source: Modified and updated from Kälviäinen *et al.* (2008).

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