Chapter 19
Progressive Myoclonic Epilepsy

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Case Presentation

A 19-year-old, right-handed female of mixed Caucasian and Mediterranean decent presented to an epilepsy clinic with a diagnosis of "seizure disorder." At 14 years of age she experienced her first generalized tonic–clonic seizure. Subsequently, she developed multifocal myoclonus and was diagnosed with the Juvenile Myoclonic Epilepsy (JME) syndrome. However, she gradually worsened with uncontrolled frequent daily generalized myoclonus and monthly convulsions that were resistant to multiple antiseizure drugs. Over the years, her grades fell, and dedicated neuropsychological testing demonstrated a slow reduction in full scale IQ into the 60s. She developed difficulty walking with frequent falls and ultimately became wheel-chair dependent. Seizures became refractory to multiple broad-spectrum ASDs. Neurological examination revealed a young female awake and cooperative but with psychomotor slowing, visual inattention, and dysarthria. She relied on single-word answers and hand gestures. Gait revealed an unsteady ataxic gait. Her brain MRI was unrevealing, and an EEG was abnormal (Fig. 19.1).

Clinical Questions

1. Does this patient have JME?
2. Does this EEG support a particular clinical diagnosis?
3. What are myoclonic epilepsy syndromes to be considered and what are the defining characteristics for them?

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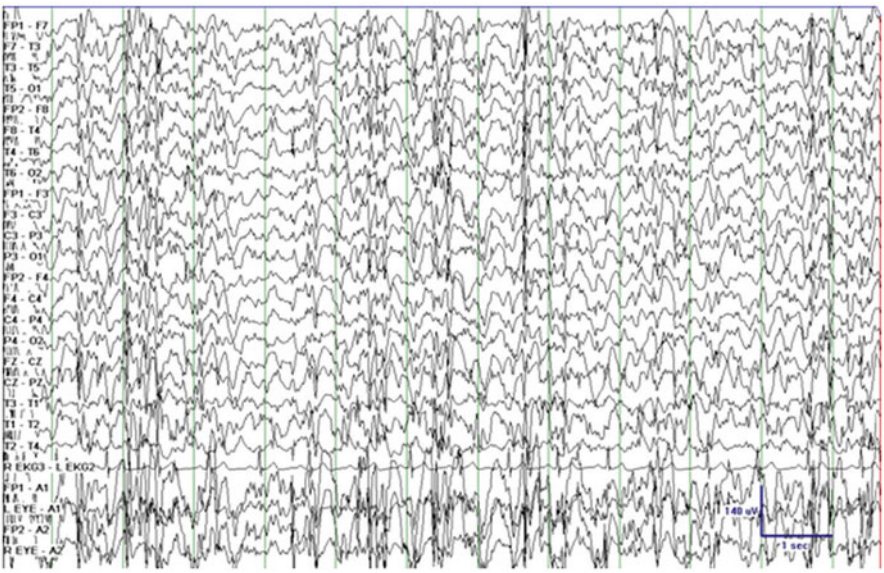

Fig. 19.1 EEG showing diffuse slowing of the background activity punctuated by nearly continuous generalized spike and polyspike discharges. Note the occipital predominant sharp waves. EEG parameters include a bipolar montage, sensitivity of 7 μV/mm, and filters of 1–70

4. What diagnostic testing should be considered?
5. What is the anticipated clinical course and prognosis with the expected diagnosis?

Diagnostic Discussion

1. JME is a common genetic generalized epilepsy that manifests in adolescence. It is characterized by repetitive irregular myoclonic jerks predominately involving the upper body. No loss of consciousness is encountered unless the patient manifests generalized (clonic)–tonic–clonic seizures. Nearly all JME patients have GTC seizures with myoclonic seizures (one-third also have absence seizures). Seizures occur with morning predominance and require long-term therapy. Interictal EEG demonstrates 3–5 Hz generalized spike- and polyspike-and-waves and photosensitivity is common. In our patient, the clinical presentation of myoclonic and convulsive seizures early on may suggest JME, but the progressive course and the abnormal EEG background activity suggests otherwise. The progressive course with worsening of mental status, gait, dysarthria, and uncontrolled seizures suggests one of the progressive myoclonus epilepsies (PME).
2. The EEG findings of the frequently intermixed generalized spike- and polyspike-and-waves would suggest generalized epilepsy. However, the diffusely

slow background activity would suggest an encephalopathic process as opposed to JME. PME has EEG changes that may precede the clinical symptoms by 6 years. Diffuse slowing and generalized IEDs occur in virtually everyone. Slowing and loss of an alpha rhythm gradually became replaced by generalized IEDs with occipital predominance in addition to focal and multifocal abnormalities. The IEDs wane during sleep unlike genetic generalized epilepsy where the IEDs become more prominent. Giant somatosensory evoked potentials and increased cortical excitation to paired pulse transcranial magnetic stimulation may be seen. The myoclonus of PME is a prominent clinical feature though, in addition, generalized, focal, and atypical absence seizures may also occur.

3. The progressive myoclonus epilepsies (PME) are a rare group of disorders (Table 19.1). Unverricht–Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF), the adult form of neuronal ceroid lipofuscinosis (Kufs), and sialidosis are the principal PMEs. Our patient presented in early adolescence and at first mimicked JME. The progressive cognitive decline, worsening myoclonus, dysarthria, and gait disorder led to a clinical diagnosis of Lafora Disease (LD). LD presents in early adolescence and may initially mimic IGE though progressively worsening myoclonus after an initial GTC signals a different course. Slow cognitive decline, visual impairment, visual hallucinations, and occipital seizures become evident. Progressive myoclonus, refractory epilepsy, dementia, ataxia, and speech dysfunction occurs. Total care is evident prior to a fatal demise which occurs within 10 years after onset.
4. MRI brain may identify atrophy in the more aggressive PMEs. Basal ganglia signal changes may be seen in MERRF but were absent in our patient. In our patient, EEG demonstrated a diffusely slow background with frequent GSW and PSW coupled with myoclonic jerks. SSEPs were performed without high amplitudes of the N19 waveform to median nerve stimulation. Genetic testing is helpful to establish the diagnosis. In our patient, EPM1 and EPM2 were normal. A point mutation on tRNALys gene was not recovered. An axillary skin biopsy was without Lafora bodies but did demonstrated intracytoplasmic “fingerprint” inclusions and lipofuscin pigment stored in the lysosomes characteristic of adult NCL (Kuf’s disease).
5. The prognosis for patients with PME is oftentimes poor. Treatment is usually supportive. ASDs chosen should have broad spectrum utility due to the possibility of narrow spectrum ASDs aggravating seizures. Valproate is useful, though needs to be avoided in MERRF. Lamotrigine may worsen myoclonus in some. Neurostimulation may have a role for some. Unverricht–Lundborg disease has the most favorable prognosis. The epilepsy is usually less refractory to ASDs though phenytoin is contraindicated. Patients may become wheelchair bound, though the cognitive decline may be mild and the course tends to stabilize over time. Our patient with Kuf’s requires complete care and has already become wheelchair bound. Her rapid deterioration reflects a poor prognosis. Most patients with PME, including adult NCL and Lafora disease, have limited lifespans with the course culminating in death within a decade. Genetic markers are helpful, though biopsy may still be required for confirmation.

Table 19.1 Comparison of the progressive myoclonus epilepsies

	Onset (years)	Clinical features	EEG	Pathology	Outcome
Unverricht–Lundborg	6–18	Myoclonus, GTC seizures, ataxia, dysarthria, tremor. Become wheelchair dependent. Mental decline late	Similar to GGE at onset with worsening background activity over time with GSW and PSW	Recessive mutation in cystatin B a protease inhibitor (EPM1) on chromosome 21	Long-term survival
Lafora	6–19	Rapidly progressive myoclonus, epilepsy, blindness, and mental decline. Occipital seizures, absence, GTC	Normal at the beginning, declining over time. Background slowing with GSW, PSW and occipital IEDs	Autosomal recessive polyglucosan stored in sweat glands on biopsy. EPM2A and EPM2B on chromosome 6	Death usually within 10 years of onset, often from status
MERRF-MELAS	Childhood to adolescence	Abrupt or slow onset of generalized myoclonus, epilepsy, and ataxia. ± Spasticity, deafness, ocular defects. Lactic acid and stroke-like episodes in MELAS	EEG background activity slows with progression. GSW and focal IEDs. Photosensitive and photomyoclonic	Point mutations of tRNALys gene (most maternal inheritance). Atrophy and signal changes evident in basal ganglia on MRI brain antemortem	Variable course
Adult NCL	Adolescence early adulthood	Dementia ataxia and later myoclonus and seizures. Normal vision in contrast to other forms of NCL	Background activity is slow with GSW. Photosensitivity at 1–3 Hz. Enlarged SSEPs	Autosomal recessive lipopigment storage in the lysosomes. Fingerprint inclusion on axillary skin biopsy	Death usually within 10 years
Sialidoses	Adolescence early adulthood	Action and intention tremor and GTC seizures. Cognitive decline. No real visual deficit	Few IEDs and low amplitude fast background activity. Myoclonus with 10–20 Hz central activity. Large SSEPs and reduced VEPs	Autosomal recessive deficiency of neuraminidase A. Sialidated oligosaccharides in urine. Vacuolated Kupffer cells on histology	Variable course

GTC generalized tonic–clonic, *GGE* genetic generalized epilepsy, *SSEPs* somatosensory evoked potentials, *IEDs* interictal epileptiform discharges, *VEPs* visual evoked potentials

Clinical Pearls

1. PME is a rare epilepsy syndrome caused by a heterogeneous group of disorders. PME may mimic JME at the onset of the clinical course due to the presence of myoclonus and convulsions but is soon defined after the onset by progressive neurological deterioration.
2. Diffuse slowing of the background with GSW and PSW occurs with time and suggests one of the encephalopathic generalized epilepsies with myoclonus. Neurophysiological studies may additionally demonstrate enlarged evoked potentials in some reflecting the cortical hyperexcitability that are encountered in PME.
3. The PMEs are a rare group of patients with progressive neurological deterioration with seizures comprising <1 % of the epilepsies. Unverricht–Lundborg disease, Lafora disease, MERRF, NCL, and sialidosis are the primary types of PME seen that are represented by this group of conditions.
4. Genetic testing and enzyme identification is usually helpful in establishing the diagnosis in the appropriate clinical context of PME. By identifying the precise molecular defect in individual disease states, an etiological diagnosis is possible. Axillary skin biopsy may be useful in confirming Lafora bodies and inclusions seen in adult NCL. Muscle biopsy may be confirmatory in MERRF.
5. The prognosis is usually unfavorable with disability and wheelchair-bound states when survival occurs. Seizures often become resistant to ASDs. Some courses are slower than others though usually neurological deterioration to a premature death is the rule. No disease modifying treatments are available at this time and treatment is with broad spectrum ASDs and is otherwise supportive.

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