Rare disease

Role of levetiracetam in refractory seizures due to a rare progressive myoclonic epilepsy: Lafora body disease

Mubashira Hashmi,¹ Feroza Saleem,² Muhammad Shahid Mustafa,¹ Mughis Sheerani,¹ Zeeshan Ehtesham,³ Khurram Siddiqui⁴

¹ Department of Neurology, Aga Khan University Hospital, Karachi, Pakistan

² Department of Neurology, Liaquat National Hospital, Karachi, Pakistan

³ Department of Pathology, Aga Khan University Hospital, Karachi, Pakistan

⁴ Department of Neurology, King Fahad Medical City, Riyadh, Saudi Arabia

Correspondence to Mubashira Hashmi, dr_mhashmi@hotmail.com

Summary

Lafora disease is one of the rare, most fatal progressive myoclonic epilepsies reported. We present a case of a teenager with intractable seizures and progressive mental decline, diagnosed as Lafora body disease on axillary skin biopsy. He was admitted with status epilepticus with refractory myoclonic and generalised tonic clonic seizures. Despite on maximum doses of multiple antiepileptic drugs and infusions of propofol and midazolam, his seizures were refractory to all forms of medical therapy tried. Levetiracetam (LEV), a pyrrolidine derivative, was introduced; he showed a prompt response and was weaned off successfully from infusions of anticonvulsants and mechanical ventilation within 48 h of introduction of LEV, followed by an almost seizure-free status.

BACKGROUND

Progressive myoclonic epilepsies (PME) are a group of rare, severe hereditary conditions characterised by refractory seizures, neurological deterioration, cognitive decline, an overall unfavourable course and poor prognosis.¹ Lafora disease (LD) is an autosomal recessively transmitted PME of teenagers, diagnosed by genetic testing or demonstration of periodic acid-Schiff (PAS)-positive, starch-like glucose polymers, polyglucosans (Lafora bodies) on biopsy of skin, striated muscle, liver, brain and/or bone.² Treatment of PME remains a great therapeutic challenge. Preliminary trials and case reports have shown efficacy of levetiracetam (LEV) in the treatment of various types of PME including LD due to its broad-spectrum anticonvulsant activity.^{3 4} However, as to our knowledge, there are few case reports, if any, which have shown efficacy of LEV in refractory status epilepticus due to Lafora body disease.

CASE PRESENTATION

A teenager presented to our neurology department with history of myoclonic, generalised tonic clonic and absence seizures for 5 years. His illness started with history of recurrent falls and dropping things from his hand due to myoclonic activity of limbs and trunk. On his first presentation, he had good mental status, with mildly decreased cognition, was ataxic and had myoclonic jerks of face, limbs and trunk. At that time, he was started on valproic acid and clonazepam, later on lamotrigine was added, as he was not responding to the above measures. On EEG, there were generalised polyspike and wave discharges (figure 1). MRI of the brain was normal. His axillary skin biopsy was positive for PAS-positive Lafora bodies (figure 2). He had a downhill course since then, with history of recurrent admissions due to intractable seizures and progressive mental

decline to a bed-bound status, with reduction in speech fluency. Topiramate and ketogenic diet were also tried and all anticonvulsants were gradually increased to their maximum maintenance doses. He was admitted with recurrent myoclonic and generalised tonic clonic seizures for last 24 h, he was intubated and put on mechanical ventilator and was started on simultaneous infusions of propofol and midazolam along with previous antiepileptics (AEDs), which were continued in their maximum doses. He continued to experience clinical seizures despite maximum doses of propofol and midazolam. With this continued saga of refractory status epilepticus, he was started on rapidly escalating doses of LEV, with initiation in a dose of 500 mg twice daily, which was then increased to 750 mg twice daily the next day. After 48 h of LEV, reduction in the clinical seizure activity was eminent and we were able to wean him off from mechanical ventilation and infusions of propofol and midazolam. Further titration was done at a rate of 500 mg/week up to the maximum dose of 2 g twice daily. At this dose, his seizures reduced to disappearance of generalised seizures and few myoclonic seizures. No side effects were noted. He showed sustained response to LEV, however, later on developing further complications due to bed-bound status and poor cognition. He died almost 2 years after diagnosis from aspiration pneumonia.

DISCUSSION

LD was first described by Lafora and Glueck in 1911.² Clinical findings often begin at the end of first decade or at the beginning of the second decade; however, onset as late as mid-20s has been reported in four siblings.⁵ LD is caused by mutation either in gene EPM2A or EPM2B. EPM2A encodes for laforin, a dual-specificity tyrosine phosphatase protein, localised at plasma membrane and endoplasmic

Figure 1 EEG showing generalized polyspike and slow wave discharges.

Figure 2 (A,B) Axillary skin biopsy demonstrating Lafora bodies (arrows) positive for periodic acid-Schiff.

reticulum. EPM2B encodes for malin, a putative E3 ubiquitin ligase with a possible role in the ubiquitination pathway. Furthermore, the existence of a third LD locus has also been suggested. It is more frequently seen in India, Pakistan, Middle East and other countries in which consanguineous marriages often occur.⁶ Although the patient described had no affected siblings, his parents were not related to each other.

Illness begins with epileptic seizures; generalised tonic clonic, diffuse myoclonus and occipital seizures characterised by photoconvulsive reactions, and visual hallucinations and scotoma might also be seen. Visual ictal phenomena appear in half of the cases and are relatively specific clinical clues to the diagnosis of the disease;^{2 5 6} however, this feature was not seen in our case. Progressive neurological deterioration such as ataxia, dementia, psychosis, dysarthria, amaurosis, mutism, muscle weakness and respiratory failure are associated with seizures, resulting in death within a decade of disease onset.

Diagnosis is confirmed by demonstration of typical PAS-positive spherical inclusion bodies in the brain, spinal cord, skin, liver and skeletal muscle on biopsy or by genetic testing. Axillary skin biopsy is preferred because it is less invasive and gives lower false-negative results.^{2 6–8}

Treatment of seizures in LD has been a therapeutic challenge. Multiple AED drugs including Na valproate, clonazepam, lamotrigine, topiramate and zonisamide have been tried with variable response.⁹ Piracetam, also a piperidine derivative, though one of the most effective agents for myoclonus, usually requires administration of

high doses with no stable and long-term effect in patients with LD.^{4 9}

LEV is chemically similar to piracetam, but has different pharmacological profile, therefore was found effective in controlling seizures, which were refractory to piracetam. Its exact mechanism of action is unknown, possibly including effects on zinc mediation of γ -aminobutyric acid responses, blockade of N-type calcium channels and activation of potassium channels.⁴ Its broad-spectrum activity and favourable pharmacokinetics have been reported to be successful in the treatment of refractory seizures and status epilepticus due to various epilepsy syndromes other than LD.^{10–12} Effective doses range from 500 to 6000 mg. It has a rapid onset of action, reducing seizure frequency in 12–96 h, even in intubated patients on nasogastric tube, without interacting with other anticonvulsants and any significant side effects.^{11 12} Reported patient also showed a rapid response to LEV, and no side effects were noted even on rapid titration. Preliminary studies including open-label trials and multiple case reports have shown efficacy of LEV in controlling myoclonus and thus improving quality of life in patients with PME, mainly Unverricht–Lundborg and myoclonus epilepsy with ragged red fibres, with few case reports of LD.^{3 4}

However, there are few case reports, if any, of status epilepticus due to Lafora body disease, in which LEV was used. Although individual case reports do not prove efficacy beyond doubt, it is important to report individual cases, as patients with various types of PME are rare, making larger randomised trials unfeasible.

Learning points

- ▶ In patients with refractory myoclonic seizures and cognitive decline, consider PME as possible diagnosis.
- ▶ Axillary skin biopsy is valuable in the diagnosis of LD, as it is less invasive, has lower false-negative results and especially useful in regions where genetic testing is not available.
- ▶ LEV has a significant antimyoclonic activity and one of the few AEDs that is useful in refractory myoclonic seizures and status epilepticus even in oral form.

Competing interests None.

Patient consent Not obtained.

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