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# Use of cannabidiol in the management of refractory seizures in Lafora disease: A case report of two siblings

***Deepinder Kaur Maini[1,2]; Dipti Gupta[3]; Ravindra Kumar Saran[3]; Aditi Dua[1]; Varun Rehani[1]; Rajiv Anand[1]****

*[1]Department of Neurology, Dr BL Kapur Memorial Hospital, Rajendra Place, New Delhi, India.*

*[2]Amity Institute of Neuropsychiatry and Neurosciences, Amity University, Noida, Uttar Pradesh, India.*

*[3]Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi, India.*

***Corresponding Author: Rajiv Anand**

Department of Neurology, Dr BL Kapur Memorial Hospital, Rajendra Place, New Delhi, India.

Email: anand_rajiv@hotmail.com

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## Abstract

**Background:** Lafora Disease (LD) is a rare autosomal recessive glycogen storage disorder characterized by Progressive Myoclonic Epilepsy (PME) and neurodegeneration, typically manifesting in adolescence. We aim to evaluate the potential efficacy of Cannabidiol (CBD) in managing seizures and cognitive symptoms in Lafora disease.

**Case report:** We present two cases of LD within a family of nine siblings. The eldest daughter, a 19-year-old, exhibited status epilepticus, transient blindness since the age of twelve years, aphasia, severe cognitive decline, and profound motor impairment (Barthel Index: 10/100). Her 15-year-old sister demonstrated progressive motor decline, requiring wheelchair assistance. Pathological examination under Light and electron microscopic examinations were performed on full thickness axillary skin biopsy specimens. It revealed presence of faintly eosinophilic intracytoplasmic inclusions in the eccrine sweat gland ductal epithelial cells & myoepithelial cells in the apocrine sweat glands. Genotyping was done, which confirmed diagnosis of LD. Given the refractory nature of their seizures, Cannabidiol (CBD), an FDA-approved therapy for certain epileptic syndromes, was introduced following parental consent. During follow-up assessments there was significant improvement in cognition in seizure frequency. We have also renewed UpToDate of ongoing research to reverse the pathogenesis of disease process.

**Conclusion:** These case highlights the devastating progression of LD and explores the potential role of CBD in symptom management. CBD showed subjective improvement in seizure frequency but no reversal of neurodegeneration. Further studies are needed to assess its long-term efficacy in LD treatment.

***Keywords:*** Lafora disease; Cannabidiol; Refractory seizure; Epileptic syndrome.

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## Introduction

Lafora Disease (LD) is a rare autosomal recessive glycogen storage disease first described in 1911 by Lafora and Gluck. It is an inherited disorder and is the severe form of Progressive Myoclonic Epilepsy (PME), usually with young adult onset. It is characterised by accumulation of polyglucans, called Lafora Bodies (LB), in brain, skin, muscles, and liver. The LB are localised in perikaryon and dendrites of neurons which explains the cortical hyperexcitability seen in LD [1]. Unlike in other PME inherited disorders there is no accumulation (genetic or any byproduct) in lysosomes. It is caused by loss of function mutations in EPM2 or EPM2B encoding glycogen metabolism enzymes, Laforin or Malin respectively. Its estimated prevalence worldwide is four in 100,000 people. It is frequently found in Mediterranean countries (Spain, Italy, France), Northern Africa, Middle east and South India- where the rate of consanguinity is high [2,3]. In this report we present clinical and pathological findings of two teenage siblings born from consanguineous marriage with refractory status epilepticus. Our aim was to control nonconvulsive seizure by adding newer drugs in their ongoing Anti-Seizure Medication (ASM)- CANABIDIOL in the treatment regimen.

## Patient and methods

Case report was approved by the Institutional Ethics Committee of Dr. B.L. Kapur Memorial Hospital, New Delhi. Our study identified teenage siblings of same family with LD from consanguineous marriage; parents were first degree cousins.

A 19-year young Nigerian girl was referred to BLK Max hospital, Delhi, from Sweden due to refractory seizure, cognitive decline, bradyphrenia, inability to walk, urinary incontinence. She was the first born to the healthy consanguineous parents. She had normal developmental milestones with no significant medical history. She was attending school till 13 years of age. She began experiencing daily drop attacks, which increase in frequency each passing day. At the age of 14 years, she developed myoclonic movements of whole body which was controlled by Anti-Seizure Medication (ASM). At the age of 15 years her seizure worsened despite being compliant to the treatment and was added a second ASM From the age of 17 years she started having marked cognitive decline (slow responsiveness to verbal commands, unable to comprehend, poor attention), motor weakness (unable to walk without support with gait imbalance), and cranial nerve involvement (dysarthria, dysphagia).

On admission, the patient was bed bound, dependent completely for Activity of Daily Living (ADL). Neurological examination revealed speech and language disturbance, poor cognition, severe bradyphrenia, motor power of all four limbs was 1/5 (medical research council score), hypotonia and absent reflexes (deep tendon and superficial reflexes). The younger sibling, 15 years of age, she could comprehend and follow verbal commands, move independently for 10 m. Her symptoms started with drop attacks (atonic seizure) with vacant stare (absence seizure) at the age of 13 years. She started having visual hallucinations and slowly progressive cognitive decline. Her school performance was affected, and she was dependent for her Activities of Daily Living (ADL's).

The two siblings when came to us were on multi drug ASM's. Older one was on the maximum dosage of oral levetiracetam, lacosamide, lamotrigine, clobazam, while younger one was on levetiracetam, valproate and clobazam.

Routine blood examinations, including toxicologic and metabolic screen, were normal. Results of cerebrospinal fluid examination, including electrophoretic pattern, were within normal limits. Full thickness axillary biopsy revealed presence of faintly eosinophilic intracytoplasmic inclusions in the eccrine sweat gland ductal epithelial cells & myoepithelial cells in the apocrine sweat glands. Small fragments of fresh tissue were prepared for electron microscopy by fixation in 2% glutaraldehyde in phosphate buffer. The tissue was postfixed in 1% osmic acid, washed, dehydrated in graded alcohols, and embedded in epoxy resin. Thin sections were cut with a diamond knife, contrasted with 1% uranyl magnesium acetate-lead citrate, and examined with an electron microscope. Histological staining revealed PAS-positive, diastase-resistant, round to oval intracytoplasmic inclusions. These were diastase resistant as well

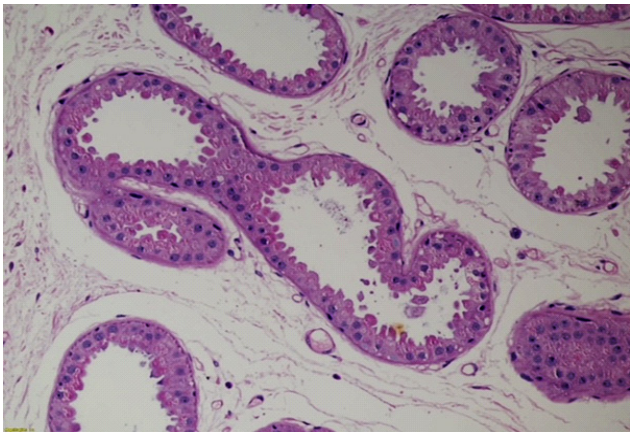

**Figure 1:** Lafora bodies (Polyglucosan bodies) in Apocrine glands (H&E).

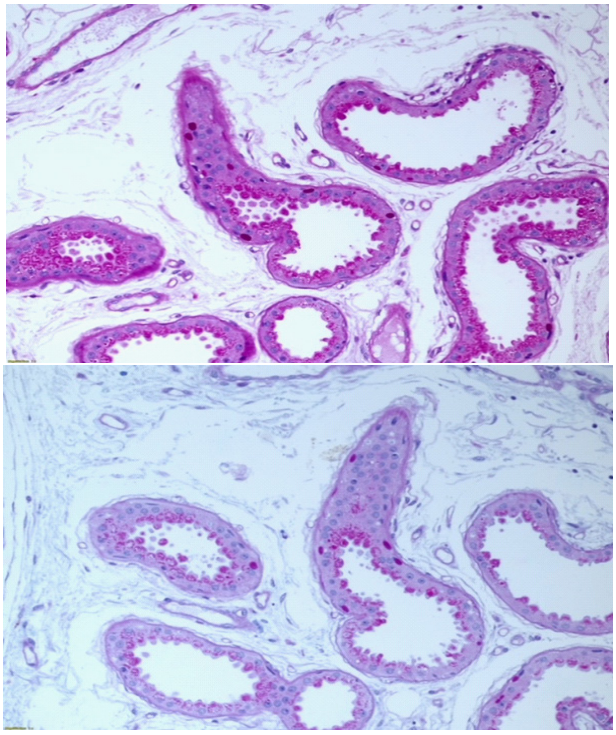

**Figure 2:** PAS & PASD-Stained formalin fixed skin biopsy. Apocrine glands containing Lafora bodies.

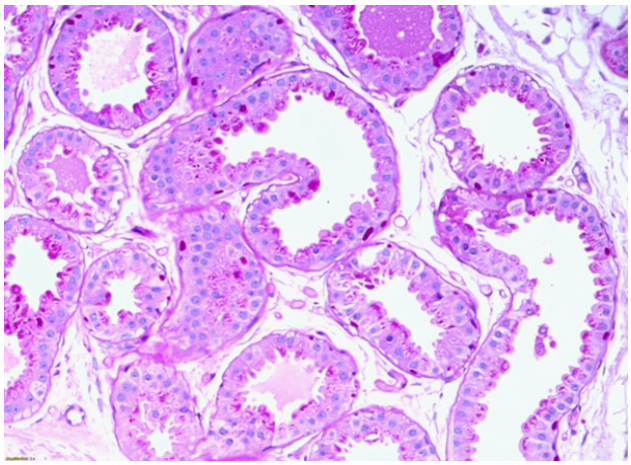

**Figure 3:** PAS formalin fixed skin biopsy. Apocrine glands containing Lafora bodies.

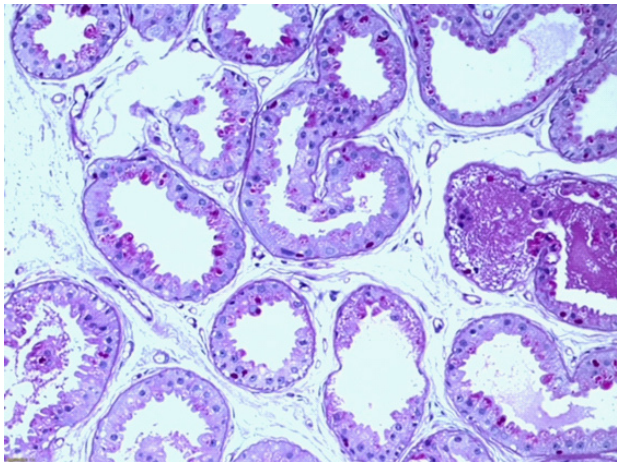

**Figure 4:** PAS AB Stain.

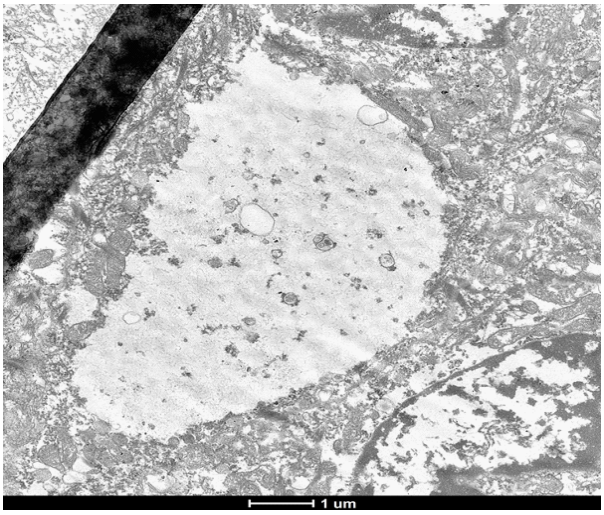


**Figure 5:** First sibling.

(PAS-D resistant), confirming their non glycogenic nature. The epidermis and dermis were essentially unremarkable. Electron microscopy showed granular intracytoplasmic electron-lucent structures corresponding with these inclusions. Identification of LD in full thickness skin biopsy supports the clinical diagnosis, particularly when combined with genetic testing (Figures 1-6).

Electron micrograph showing a round inclusion body without a limiting membrane within a secretory cell of an apocrine sweat gland. Note the the granular material forming the Lafora body.

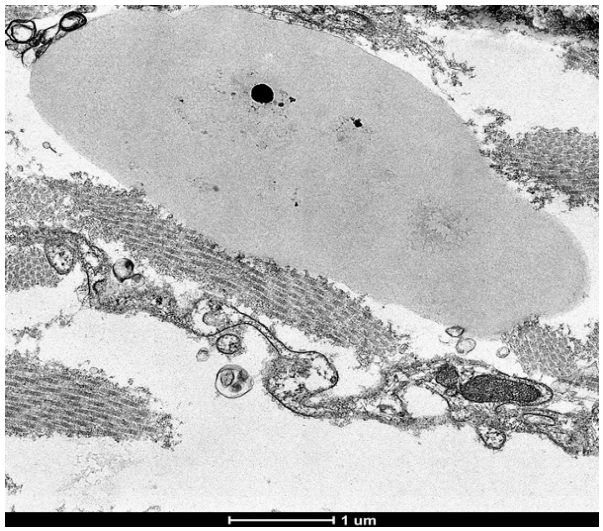


**Figure 6:** Second sibling.

Electron micrograph showing a round inclusion body without a limiting membrane within a secretory cell of an apocrine sweat gland

## Discussion

LD typically manifests during adolescence (8-19 years), presenting with progressive cognitive decline, headaches, academic difficulties, seizures, visual hallucinations, drop attacks, and muscle wasting. Seizure types may include absence seizures, atonic seizures, action- or stimulus-sensitive myoclonus, and generalized tonic-clonic seizures. Several classical features have been described: EEGs often reveal characteristic 3 Hz spike-and-wave discharges; visual evoked potentials may show increased amplitudes; and neuroimaging is often normal [3].

LB are not exclusive to LD. Similar inclusions can be found in other conditions, including normal aging, glycogen storage disorder type IV (Andersen disease), arylsulfatase A pseudodeficiency, Amyotrophic Lateral Sclerosis (ALS), and other motor neuron diseases [3,4].

Skin biopsy, especially from axillary sites rich in sweat glands, remains a minimally invasive and effective method for detecting LB. Electron microscopy reveals that LBs consist of insoluble polyglucosan aggregates, indicating a high glucose polymer content [5,6].

Recent studies have also confirmed that LBs are not mere byproducts but play a causative role in neurodegeneration. Consequently, therapies now aim to inhibit glycogen synthesis and enhance clearance mechanisms in neurons and astrocytes. Currently, treatment is symptomatic, primarily relying on antiepileptic drugs, which often fail to prevent disease progression. However, several experimental interventions are showing promise. For instance, metformin, an AMPK activator, has demonstrated efficacy in preclinical models by reducing LB accumulation and promoting neuronal survival, likely via enhanced autophagy and suppression of glycogen synthesis [7].

The identification of LB as pathogenic agents has shifted therapeutic focus toward glycogen metabolism. Strategies under investigation include downregulation of Glycogen Synthase (GYS1), modulation of laforin or malin activity, and enhancement of autophagy to promote LB clearance. Animal studies show that even partial inhibition of glycogen synthesis can substantially reduce LB formation and improve neurological outcomes. In addition, gene therapies such as CRISPR-Cas9 editing

and antisense oligonucleotides are being explored to correct or compensate for the underlying genetic mutations [8,9].

Gene therapy using Adeno-Associated Virus (AAV)-mediated delivery of EPM2A or EPM2B has also shown encouraging results in animal models. These strategies restore enzymatic function, decrease LB burden, and delay symptom onset. Suppressing glycogen synthase pharmacologically is another promising direction, aimed at halting the upstream formation of aberrant glycogen. Parallel approaches using AAV vectors, particularly neurotropic serotypes such as AAV9, have demonstrated sustained expression of therapeutic genes, reduction of LB pathology, and slowed neurodegeneration. With favourable safety profiles and low immunogenicity, these vectors represent a viable long-term treatment platform [10,11].

Moreover, research is underway to develop enzymes that actively degrade existing Lafora bodies. One such enzyme-based therapy is VAL-0417, an investigational fusion protein combining human pancreatic α-amylase with a cell-penetrating peptide. This construct enables cellular entry and enzymatic degradation of LB. In preclinical studies, VAL-0417 has led to significant clearance of LB from neural tissues, reduced neuroinflammation, and decreased seizure frequency—indicating potential disease-modifying effects [12,13].

These experimental therapies reflect a significant shift from symptomatic control to disease-modifying strategies targeting the molecular basis of LD. Ongoing preclinical investigations and upcoming clinical trials will be critical in validating these therapies and determining their place in clinical practice [14].

In this case report, we explored the use of Cannabidiol (CBD)—a compound derived from cannabis and the third most widely used recreational drug globally, with increasing medicinal applications. Medicinal cannabis includes formulations with CBD alone or in combination with Tetrahydrocannabinol (THC) and other cannabinoids. Unlike THC, CBD has well-documented antiseizure properties and lacks psychoactive effects [15].

CBD and THC both interact with cannabinoid receptors CB1 and CB2. CB1 receptors, prevalent in the brain and nervous system, regulate neuronal excitability. CB2 receptors, found mainly on immune cells, become upregulated in pathological conditions. Synthetic cannabinoids that mimic THC bind CB1 receptors strongly, contributing to their psychoactive effects [16].

Although the precise antiseizure mechanism of CBD is not fully understood, proposed pathways include modulation of intracellular calcium via GPR55 and TRPV1 receptors, as well as adenosine-mediated signalling that reduces neuronal excitability. Additionally, CBD acts as a positive allosteric modulator of GABA-A receptors, enhancing inhibitory neurotransmission—a mechanism especially relevant in epilepsy syndromes like Dravet syndrome, where impaired GABAergic tone plays a key role [17].

CBD has garnered significant attention as an adjunctive therapy for drug-resistant epilepsies, such as Dravet and Lennox-Gastaut syndromes. Its potential role in LD, as demonstrated in this report, highlights its promise for symptomatic management. While CBD does not directly target the aberrant glycogen metabolism that underlies LD, its antiseizure, neuroprotective, and anti-inflammatory properties may offer substantial symptomatic relief [16,17].

This report adds to the growing body of evidence suggesting a supportive role for CBD in managing refractory seizures associated with progressive myoclonic epilepsies. Nonetheless, further studies, particularly controlled clinical trials are essential to establish long-term efficacy, optimal dosing regimens, and any potential disease-modifying effects.

## Conclusion

This case report highlights the progressive and debilitating nature of Lafora disease in two siblings and explores the potential role of cannabidiol in symptom management. While CBD demonstrated promise in seizure control, further studies are needed to establish its role in altering disease progression. Early genetic diagnosis, symptomatic management, and emerging therapeutics like CBD could improve quality of life for LD patients.

## Declarations

**Consent for publication:** yes.

**Availability of supporting data:** Yes, data is available on request.

**Competing interest:** Nil.

**Funding:** Nil.

**Conflict of interest:** There is no conflict of interest from any of the authors.

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