An Unusual Case of Progressive Myoclonic Epilepsy (PME): Familial Encephalopathy with Neuroserpin Inclusion Body (FENIB)

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J Pediatr Epilepsy 2023;12:135–139.

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Abstract

Progressive myoclonic epilepsy (PME) is a spectrum with epileptic encephalopathy and myoclonus. In this case report authors describe a young patient presenting with refractory multifocal myoclonus with multiple seizure types with dyscognitive features. He was bed-bound with complete dependency on his caregivers. His electroencephalogram had an encephalopathy pattern, and his magnetic resonance imaging showed gross cortical atrophy. In this patient, the working clinical diagnosis of epileptic encephalopathy with PME phenotype had a wide differential list including neuronal ceroid lipofuscinosis, Lafora body disease, sialidosis, myoclonic epilepsy with ragged red fibers, dentatorubro-pallidoluysian atrophy, Unverricht–Lundborg, and other rare disorders such as Gaucher's disease and other genetic causes. Eventually after ruling out all common etiologies, whole-exome sequencing revealed a SERPINI1 gene mutation in exon 9 showing a pathogenic variant c1175G > A (p.Gly392Glu) which associated with PME as a part of familial encephalopathy with neuroserpin inclusion bodies.

Keywords
- myoclonic epilepsy
- neuroserpin
- encephalopathy

Introduction

Progressive myoclonic epilepsy (PME) is a spectrum with epileptic encephalopathy and myoclonus with wide range of phenotypes. Mutations in the SERPINI1 gene are known to cause familial dementia and have been associated with PME as a part of familial encephalopathy with neuroserpin inclusion bodies (FENIB). FENIB is a very rare inclusion body-related disorder with few reports in the literature.[1]

Case Presentation

A 17-year-old male born out of nonconsanguineous marriage with normal birth and developmental history presented to us with refractory seizures with dyscognitive features with gradually progressive loss of memory, praxis, attention, and executive functions from the age of 12 years. He was noncompliant with antiepileptic therapy and subsequently developed multifocal myoclonus followed by multiple episodes of generalized tonic-clonic convulsions and atypical absence seizures. Over the past 5 years, he suffered a gradually progressive multidomain cognitive decline affecting his memory and attention. Over the course of disease he became confused with difficulty in activities of daily living which were progressively deteriorating. For the past 2 years, he had become bed-bound with apathy and had become completely dependent on his caregivers. He was fully immunized and had no history of substance abuse, family history was noncontributory, except for consanguinity in his parents. On examination, our patient was drowsy but hemodynamically stable. His pupils were sluggishly reactive with normal fundoscopy, and planter response was extensor bilaterally.

received
February 6, 2023
accepted
April 20, 2023
article published online
May 26, 2023

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Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0043-1769116.
ISSN 2146-457X.

Table 1 Baseline investigations

Hb (g%)	13.2 (3–15)	FBS	89 mg/dL (75–110)	Total protein	7.66 mg/dL (6–8)	HBsAg	Nonreactive
WBC	8,200/cumm (4,000–11,000)	Urea	30 mg/dL (10–40)	Albumin	3.97 mg/dL (3.2–5)	Anti-HCV	Nonreactive
Platelet	3 lakh/cumm	Creatinine	1.10 mg/dL (0.5–1.5)	Bili(T)	1.3 mg/dL (0.1–1.0)	HIV	Nonreactive
TG	118 mg/dL (30–150)	Na+	138 mEq/L (135–145)	ALT	41 IU/L (5–35)	PT	13.4 s (13–15)
TC	163 mg/dL (< 200)	K+	4.15 mEq/L (3.5–5.0)	AST	36 IU/L (5–35)	INR	0.95
HDL	60 mg/dL (> 40)	LDL	110 mg/dL (< 100)	ALP	220 IU/L (110–310)	APTT	35.4 s (32–36)
Ft4	1.19 no/dL (0.3–2.0)	TSH	3.45 μIU/mL (0.35–6.15)			HbA1C	6.7 g% (< 6.5%)
CSF study: 4 cells/cumm, all mononuclear, protein 28 mg/dL (40–74), sugar 56 mg/dL (10–50), chloride 115 mmol/L (116–122)							

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; FBS, fasting blood sugar; Hb, hemoglobin; HbA1C, hemoglobin A1C; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; INR, international normalized ratio; K+, potassium; Na+, sodium ion; PT, prothrombin time; TC, total cholesterol; TG, triglycerides; TSH, thyroid-stimulating hormone; WBC, white blood count.
Note: ANA, ANCA, autoimmune encephalitis profile: negative.

Fig. 1 Magnetic resonance imaging (MRI) brain T1- (**A**) and T2- (**B**) weighted imaging showing gross cortical atrophy.

Multifocal fragmented myoclonus was noted with stereotypy. He had coarse crepitation in the right lower chest suggesting aspiration pneumonitis.

His initial presentation and detailed analysis from history revealed a progressive case of epilepsy with encephalopathy and myoclonus suggesting a possible PME syndrome with epileptic encephalopathy.

Routine laboratory investigations were noncontributory (►**Table 1**) though chest imaging had a right lower lobe consolidation. Magnetic resonance imaging brain showed cortical atrophy with relative sparing of cerebellum (►**Fig. 1**). Progressive brain parenchymal atrophy was noted while reviewing his previous brain imaging, confirming the progressive parenchymal degeneration.

Cerebrospinal fluid analysis and an extensive autoimmune encephalitis panel (anti-AMPA, GABA, CASPR2, LGI1, NMDR) were noncontributory. Awake electroencephalogram showed generalized slowing with theta rhythm, a mild encephalopathy pattern (►**Fig. 2**).[2] Possibilities of a genetic epilepsy had to be ruled out with an abnormally atrophied brain parenchyma. Axillary skin fold biopsy did not show any inclusion bodies. At last, genetic whole-exome sequencing revealed a rare mutation in SERPINI1 gene which is associated with PME as a part of FENIB (►**Table 2**). The patient was managed with intravenous antibiotics, and antiepileptic drugs were added in the form of sodium valproate (at 25 mg/kg body weight [BW]), levetiracetam (at 40 mg/kg BW), and clobazam (0.5 mg/kg BW) and, on this regimen,

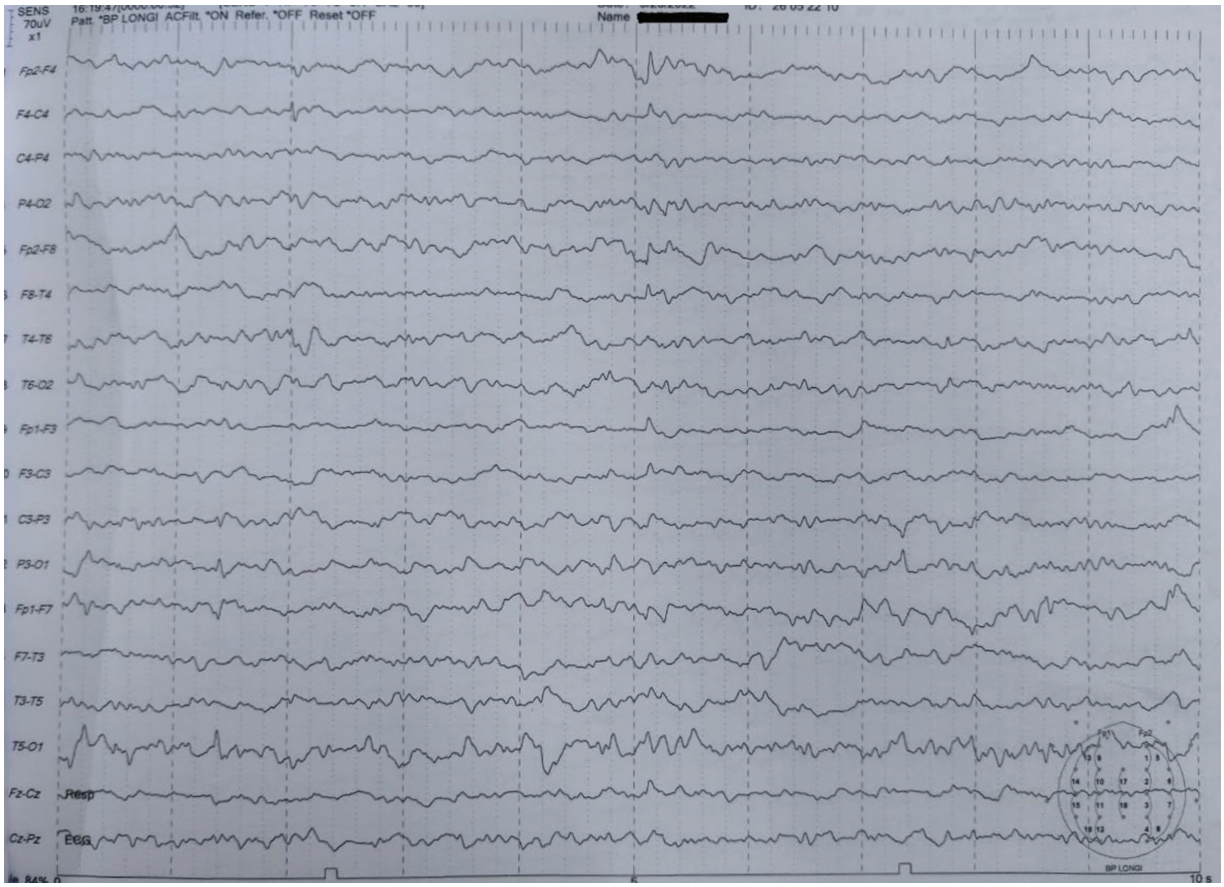

Fig. 2 Electroencephalogram (EEG) in awake state with double banana montage in bipolar tracing showing generalized slowing with theta activity suggesting encephalopathy pattern.

his seizures were controlled. He had grade 2 bedsores which were managed conservatively with proper dressing, local antibiotics, and positioning. Unfortunately the patient succumbed to sepsis 2 months later. His family members were offered Sanger's sequencing deoxyribonucleic acid testing in view of history of consanguinity (►**Fig. 3**), but this was not feasible for them. An autopsy was requested but his caregivers did not give consent for this.

Discussion

This young male with PME presentation was worked using the wide range of differential diagnosis for this condition. One diagnosis considered was neuronal ceroid lipofuscinosis (NCL), which typically has onset from infancy to childhood with myoclonus, progressive seizure, ataxia, and pyramidal and extrapyramidal symptoms with cerebral atrophy on

Table 2 Features of FENIB and presentation in our case

Category	Details
Causative gene SERPINI1	Pathogenic variant c1175G > A (p.Gly392Glu) in exon 9 of SERPINI1 gene
Inheritance	Autosomal dominant
Typical features	- Seizures[a] - Progressive myoclonic epilepsy[a] - Dementia[a] - Extrapyramidal signs - Cerebral atrophy[a] - Diplopia - Nystagmus - Gliosis - Neuronal loss - Mild distal sensory impairment - Variable age at onset, ranges from third to fifth decade of life

Abbreviation: FENIB, familial encephalopathy with neuroserpin inclusion bodies.
[a]Present in our case

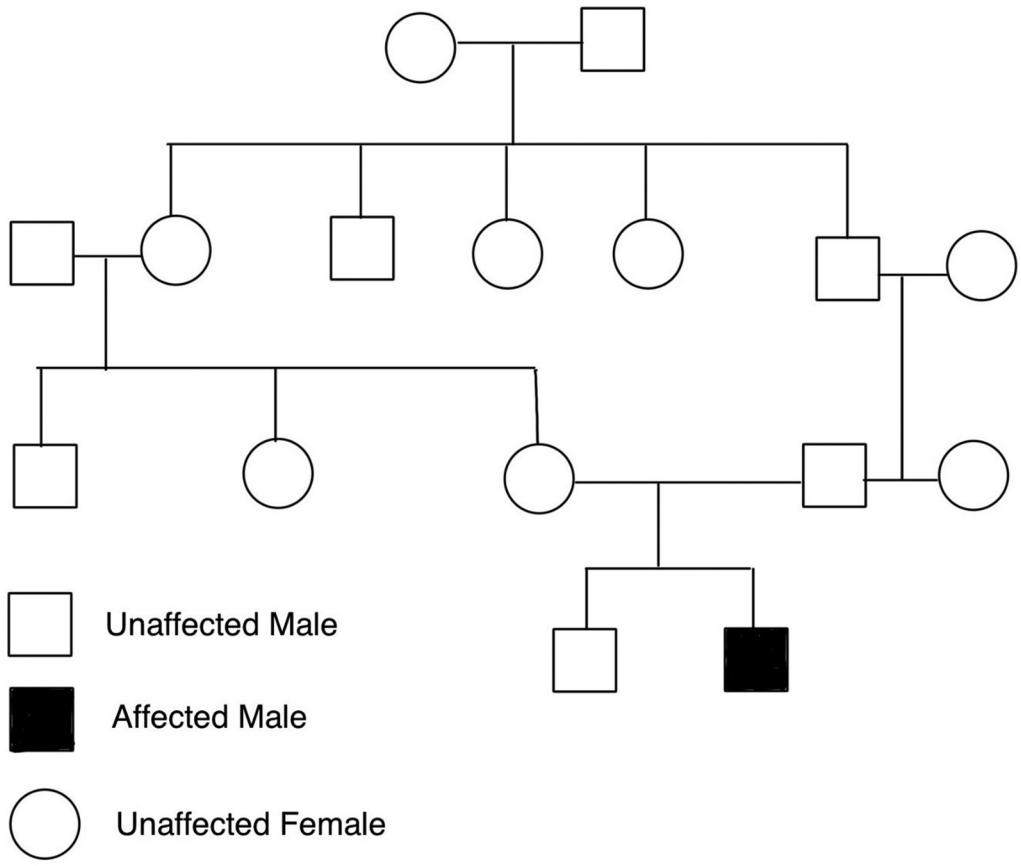

Fig. 3 Pedigree chart of the patient's family with consanguinity.

neuroimaging studies. Classically, skin biopsy shows ultrastructural (electron microscopy) pathology of NCL. Lafora body disease was another diagnosis to consider with generalized tonic-clonic seizures (GTCS), occipital seizures, and rapid cognitive decline with a genetic mutation at EMP2A or EMP2B. Myoclonic epilepsy with ragged red fibers (MERRF) is a mitochondrial disease characterized by seizures, deafness, myopathy, and optic atrophy. Unverricht-Lundborg disease, another entity with PME phenotype, is a slowly progressive genetic disease with EPM1 mutations, characterized by ataxia, cognitive decline, and GTCS. A few other rare possibilities include juvenile Huntington disease (HD) and dentatorubro-pallidoluysian atrophy (DRPLA) both being associated with choreoathetotic movements. Additionally, sialidosis type 1 and Gaucher disease are also associated with myoclonic epilepsy.[3]

Absence of organomegaly (associated with Gaucher disease), no ataxia or cherry red spot on fundoscopy (seen in MERRF, sialidosis), no pyramidal or extrapyramidal signs (seen in NCL), no choreoathetosis (seen in DRPLA, juvenile HD), and no inclusions in axillary skin biopsy (found in Lafora body disease) negated the abovementioned possibilities.[4]

Genetic whole-exome sequencing revealed a SERPINI1 gene mutation in exon 9, a pathogenic variant c1175G > A (p.Gly392Glu) which associated with PME as a part of FENIB [OMIM #604218]. The neuroserpin-associated FENIB is a well-known entity leading to dementia but a PME-like presentation is very rare.[5]

Neuroserpin is a serine protease inhibitor which is widely present in the central nervous system where it acts as an inhibitor of tissue type plasminogen activator. Normally, the neuroserpin protein acts to regulate neuronal plasticity and is neuroprotective against ischemic brain injury.[4] Six mutations of neuroserpin have been reported previously in literature (Ser49Pro (*Syracuse*) Ser52Arg (*Portland*), His338Arg, Gly392-Glu, Gly392Arg, and Leu47Pro); among them 3 mutations are associated with PME. In our case, the pathogenic variant c1175G > A (p.Gly392Glu) mutation in exon 9 is one of the very few cases reported worldwide and the first one from the Indian subcontinent.[6–10] In a transgenic mouse model this p. Gly392Glu mutation showed aggregation of neuroserpin in the endoplasmic reticulum and lysosomes of neurons creating neuroserpin inclusion bodies, also known as Collin bodies (periodic acid-Schiff positive, diastase resistant, and stains darkly with Heidenhain-Woelcke method).[11]

In conclusion, we describe here a very rare case of PME associated with neuroserpin inclusion bodies and a G392E mutation in the SERPINI1 gene. This mutation appears to be a de novo mutation as no other family members have been found to be diagnosed with similar neurological disorder. This case gives professionals insight into FENIB as a rare cause of PME, expanding the differential diagnosis of PME.

Patient Consent

A full and detailed consent from the guardian has been taken. The patient's identity has been adequately anonymized. If

anything related to the patient's identity is shown, adequate consent has been taken from the guardian.

Note

The authors hereby certify that the work shown here is genuine, original, and not submitted anywhere, either in part or full.

Conflict of Interest

None declared.

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