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Case Report
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Atypical Progressive Myoclonic Epilepsy in Adulthood: A Case Report

(*Short Title:* *Adult-onset Progressive Myoclonic Epilepsy*)

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Abstract

Rationale: Progressive myoclonic epilepsy (PME) is characterized by progressive myoclonus, cognitive impairment, ataxia, and other neurological deficits. It commonly presents in late childhood or adolescence, distinguishing it from epileptic encephalopathies that start in early childhood. This case report aims to illustrate an atypical presentation of PME in an adult patient and the importance of prompt genetic assessment when suspected.

Patient Concerns: This case involves a 48-year-old male who presented with a complex clinical picture, marked by a history of epilepsy and abnormal movements. The patient's medical journey began with a mild traumatic brain injury at the age of 12, followed by the onset of bilateral tonic-clonic seizures three months later. Initial evaluations yielded normal results, leading to a diagnosis of post-traumatic epilepsy and treatment with phenytoin. Over the years, the patient experienced sporadic seizures, escalating neurological deterioration, and the emergence of irregular myoclonic jerks. The condition progressed to continuous multifocal myoclonic jerks exacerbated by various stimuli and despite ongoing antiseizure medication, seizures persisted.

Diagnosis: Adult-onset Progressive Myoclonic Epilepsy with a complex genetic etiology.

Interventions and Outcome: Comprehensive assessments, including video-EEG monitoring with simultaneous polygraphic electromyographic (EMG) recording and genetic testing, revealed multifocal myoclonic seizures and likely pathogenic mutations in CSTB and MTFHR, along with an uncertain variant in EFHC1, respectively. The late-onset presentation and intricate genetic landscape add a layer of complexity to the diagnosis of Progressive Myoclonic Epilepsy, prompting a multifaceted treatment approach, including folinic acid supplements and pyridoxine, while avoiding specific medications.

Lessons: Incorporating video-EEG monitoring with simultaneous polygraphic EMG recording provides valuable insights when assessing a patient with myoclonic jerks. Furthermore, suspicion of progressive myoclonic epilepsy, even in adults, should prompt genetic evaluation as a component of the diagnostic work-up.

Keywords
Progressive myoclonic epilepsy; myoclonus; seizures; genetic mutations; electroencephalogram; whole exome sequencing.

List of Abbreviations
PME: Progressive Myoclonic Epilepsy
EEG: Electroencephalogram
EMG: Electromyography
CSTB: Cystatin B
MTFHR: 5,10-Methylene/tetrahydrofolate reductase
EFHC1: EF-hand domain-containing protein 1
DRPLA: Dentatorubral-pallidolusyan atrophy
BTCS: Bilateral tonic-clonic seizure
MRI: Magnetic resonance imaging
WES: Whole Exome Sequencing
ACMG: American College of Medical Genetics

Introduction

Progressive myoclonic epilepsy (PME) is characterized by progressive myoclonus, cognitive impairment, ataxia, and other neurological deficits. It commonly presents in late childhood or adolescence, distinguishing it from epileptic encephalopathies that start in early childhood. Myoclonus is typically multifocal, precipitated by various stimuli, and is particularly apparent in the face and distal extremities. PME has diverse causes, including Unverricht-Lunborg disease, myoclonic epilepsy with ragged red fibers, neuronal ceroid lipofuscinoses, dentatorubral-pallidoluysian atrophy (DRPLA), among others [1]. This case report aims to illustrate an atypical presentation of PME in an adult patient and the importance of prompt genetic assessment when suspected.

Case Presentation

A 48-year-old male with a history of epilepsy and abnormal movements presented to our clinic using a wheelchair and a helmet. No consanguinity or familial history of epilepsy was reported. Normal neurodevelopment was observed until the age of 12 when he had a mild traumatic brain injury sustained while skateboarding. No immediate seizures or loss of consciousness occurred. Three months later he presented a first bilateral tonic-clonic seizure (BTCS). Initial medical evaluations, including a brain-computer tomography scan and electroencephalogram (EEG), yielded normal results; however, the patient was discharged on phenytoin due to a possible diagnosis of post-traumatic epilepsy.

Over the years, the patient experienced sporadic BTCS with irregular medication adherence. In his early 30s, seizures intensified, accompanied by neurological deterioration, including gait and balance disturbances. Alternative antiseizure medications failed to achieve seizure freedom. Additionally, irregular myoclonic jerks emerged, evolving over the years into continuous multifocal myoclonic jerks exacerbated by various stimuli (action, touch, light, and stress). A fall caused by a BTCS resulted in traumatic brain injury, leading to an acute subdural hematoma that required urgent neurosurgical intervention. Despite ongoing treatment with antiseizure medications, including levetiracetam, topiramate, and valproate, seizures and neurological deterioration persisted.

Upon physical examination, the patient exhibited brief, involuntary muscle contractions affecting various muscle groups, particularly in the upper extremities. Assessment of muscle strength revealed no significant weakness. Coordination tests, including finger-to-nose and heel-to-shin maneuvers, highlighted moderate to severe impaired coordination and hyperreflexia was evident during deep tendon reflex testing, especially in the upper extremities. Sensory examination yielded normal results. The cognitive function was relatively preserved except for a significant speech difficulty characterized by an inability to engage in fluent conversation due to dysarthria.

Given the complexity of signs and symptoms, a comprehensive differential diagnosis was initiated. Video-electroencephalographic monitoring with polygraphic electromyographic electrodes revealed continuous cortical multifocal myoclonic jerks (Figure 1) associated with a photoparoxysmal response during intermittent photic stimulation. Brain MRI reported moderate global atrophy without focal cortical or subcortical abnormalities.

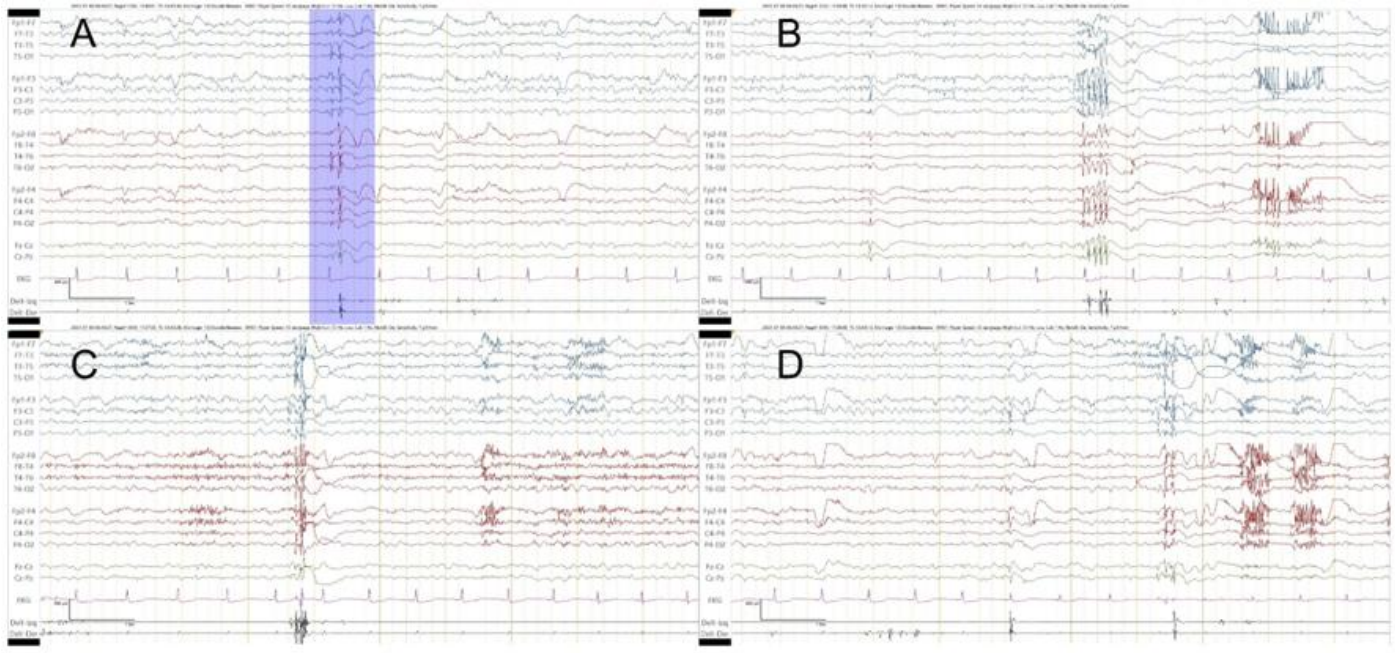

Figure 1: Four independent and nonconsecutive epochs (10 seconds each) showing generalized epileptiform discharges time-locked to myoclonic jerks (the last two channels represent polygraphic recording from both deltoids). Recording parameters: Sensitivity 7µV/mm; Filters 0.5-70 Hz; Montage: Double banana plus polygraphic electromyographic channels: Notch: On.

Suspecting progressive myoclonic epilepsy (PME) due to the progressive and diffuse onset, genetic testing was pursued. Whole exome sequencing (WES), including mitochondrial DNA, was conducted, revealing likely pathogenic mutations in CSTB and MTFHR, along with a variant of unknown significance in EFHC1 (Table 1).

Table 1: Whole Exome Sequencing results considering gene, pathogenicity, disease and mode of inheritance. OMIM: Online Mendelian Inheritance in Man.

Gene	Variants Coordinates	Zygosity	Pathogenicity	OMIM Disease /Heredity model
CSTB	Chr21:45194571 NM_000100.3:c.136C>T(p.Gl n46*)	Heterozygous	Likely Pathogenic	-Progressive Myoclonic Epilepsy 1A(OMIM:254800)/AR
MTHFR	Chr1:11796321 NM_005957.5: c.665C>T(p.Ala222Val)	Homozygous	Likely Pathogenic	-Homocystinuria due to deficiency of n(5,10)-methylenetetrahydrofolate reductase activity (OMIM: 236250)/AR
EFHC1	Chr6:52343926 NM_018100.3: c.1370G>T(p.Arg457Leu)	Heterozygous	Uncertain Significance	-Epilepsy, juvenile absence, susceptibility to, (OMIM:607631)/AD -Myoclonic epilepsy, juvenile, susceptibility to, (OMIM:254770)/AD

Discussion

Myoclonus, defined as involuntary, brief (10–50 ms duration) non-rhythmic movement, can manifest as a component of a seizure or occur separately, as seen in progressive progressive myoclonus ataxia. In the context of PMEs, stimulus- and action-induced myoclonus plays a central role [2]. The etiology of myoclonus varies from benign to life-threatening, necessitating a stepwise diagnostic approach. PMEs typically emerge in childhood or adolescence, exhibiting diverse progression rates, from slow development to a fatal outcome within a few years [1]. Epidemiological studies indicate an estimated annual incidence of about 1.3 cases per 100,000 persons/year, accounting for up to 1% of epileptic syndromes in children and adolescents globally [3].

In our case, myoclonus onset occurred in the patient's 30s, almost two decades after the initial epileptic seizure. While PMEs are rare, this presentation is even more uncommon. The possibility of overlooked sporadic myoclonus over the years raises uncertainty about its exact onset. Additionally, the patient's preserved cognitive function and adult-onset neurological deterioration over ten years leading to wheelchair dependence deviate from typical patterns.

Diagnostic challenges in such cases demand a comprehensive approach, considering the wide differential diagnosis. Limited resources in developing countries necessitate cautious utilization. Given the strong suspicion of PME, we opted first for video-EEG monitoring with EMG polygraphic channels to confirm the cortical origin of myoclonus. The EEG in PMEs has been reported to show an abnormal background activity with superimposed generalized epileptiform discharges sometimes locked to myoclonic jerks [4]. In some cases, additional post-processing analysis is necessary to bring this out (i.e., a back-averaging technique) [5]. In our case, the EEG revealed abnormal background activity with frequent generalized polyspike and wave time-locked to myoclonic jerk (Figure 1). Photoparoxysmal response with a wide photosensitivity range (2-30Hz) was also noted (Figure 2).

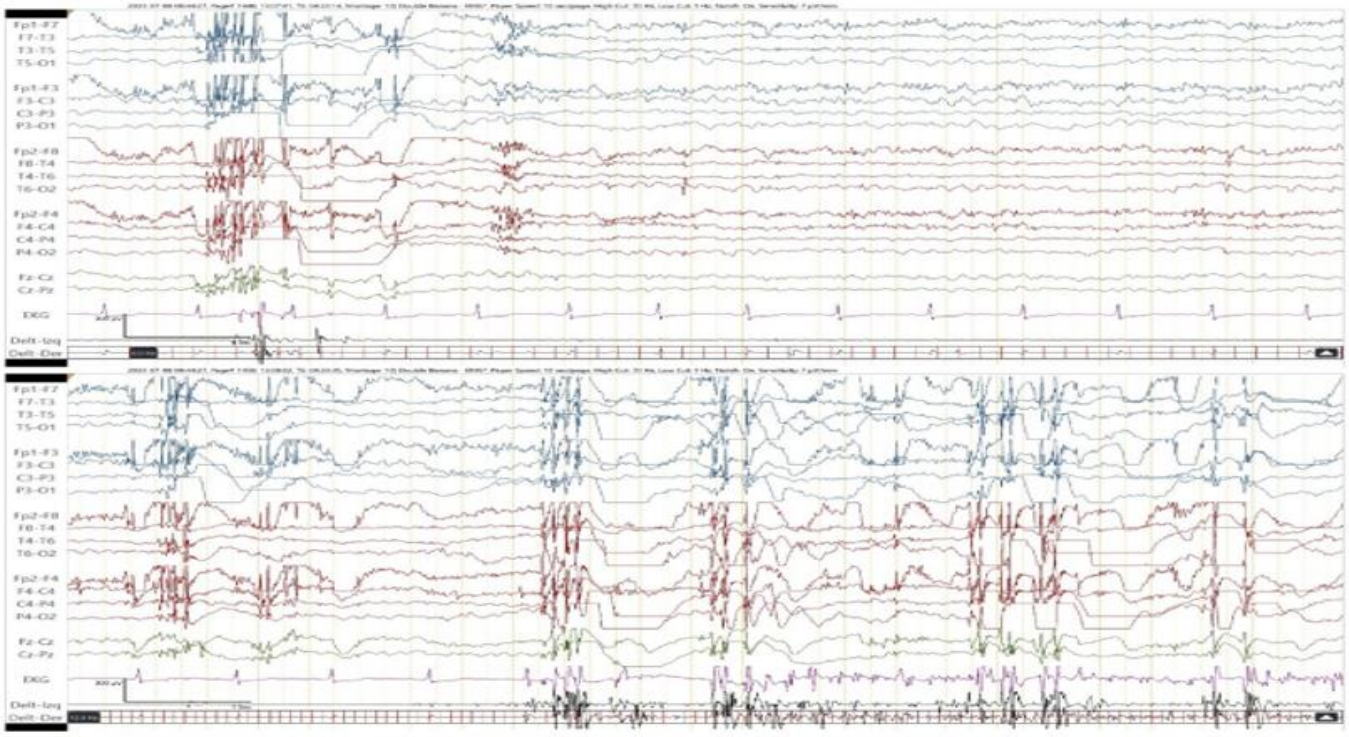

Figure 2: Two epochs (10 seconds each) showing generalized epileptiform discharges time-locked to myoclonic jerks (the last two channels represent polygraphic recording from both deltoids) in response to Intermittent Photic Stimulation (above: 6Hz and below: 12Hz) consistent with photoparoxysmal response. Recording parameters: Sensitivity 7µV/mm; Filters 0.5-70 Hz; Montage: Double banana plus polygraphic electromyographic channels: Notch: On.

Although PMEs typically onset in childhood or adolescence, a well-established late-onset phenotype exists. Our patient's phenotype aligns with the late-onset PME subgroup characterized by cortical myoclonus and minimal or no cognitive impairment, as per Courage et al.'s [6] classification. These authors used whole-exome sequencing (WES) and found 19 involved genes in previously unsolved PME-affected individuals.

In our patient, the heterozygous detection of the mutation in Cystatin B (CSTB) NM_000100.3:c.136C>T (p.Gln46*) is classified as Likely Pathogenic according to American College of Medical Genetics (ACMG) Standards and Guidelines, with strong evidence of loss of function. However, this result suggests that the patient is a carrier, and it does not fully explain the clinical course of the case. Special attention is warranted due to the possibility of a compound heterozygous mutation involving the classic CSTB gene promoter expansion along with a different mutation in the same gene. However, it is crucial to note that the number of repeats on the other allele of CSTB should be investigated, as this technique identifies point mutations, whereas 90% of the mutations are triplet repeats, which may not be fully identified by this method [7].

5,10-Methylene-tetrahydrofolate reductase (MTHFR) deficiency is a rare autosomal recessive metabolic disorder affecting folate metabolism, leading to homocysteine remethylation issues [8]. In this case, the homozygous mutation

in the MTHFR thermolabile variant is a recognized cause of homocystinuria and variable phenotypes of methylation defects [9]. It is also in the same metabolic route as CSBT, suggesting a potential interaction explaining the clinical course in this case.

Beyond these likely-pathogenic mutations, the EF-hand domain (c-terminal)-containing protein 1 (EFHC1) gene, associated with Autosomal Dominant Juvenile Myoclonic Epilepsy, revealed a Variant of Uncertain Significance not reported in the literature. Myoclonin 1/EFHC1, a microtubule-associated protein involved in cell division regulation, undergoes conformational changes after ion binding (Ca, Mg) with 44% similarity to the Ca^{2+}-regulator calmodulin [10]. According to ACMG Standards and Guidelines, it is classified as Uncertain Significance (PP3), with multiple lines of computational evidence supporting a deleterious effect on the gene or gene product.

Given the evidence, the patient is being treated for PME but also with a focus on all detected genetic changes. This includes folinic acid supplements, therapeutic doses of pyridoxine, while avoiding sodium and calcium channel blockers.

Conclusion

This case presents a unique and atypical manifestation of Progressive Myoclonic Epilepsy (PME) in an adult patient, challenging traditional expectations of the disorder's onset and progression. The late onset of myoclonus in the patient's 30s, coupled with a complex clinical course involving sporadic seizures, neurological deterioration, and continuous multifocal myoclonic jerks, underscores the diagnostic complexities associated with PME. The genetic analysis revealed likely pathogenic mutations in CSTB, MTHFR, alongside a variant of unknown significance in EFHC1, suggesting a complex genetic landscape probably contributing to the patient's clinical presentation.

Author Contributions:

FAM: Conceptualization, Data curation, Writing- Original draft preparation. NELO: Data curation, Writing- Original draft preparation. JCBL and FVVV: Resources, Writing- Reviewing and Editing, Resources, PMT and MAAV: Writing- Reviewing and Editing. AGA: Supervision, Writing- Reviewing and Editing. Visualization and Project Administration. All authors discussed the results and commented on the manuscript.

Conflict of Interest:

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Informed Consent:

Our institution does not require ethical approval for reporting individual de-identified cases. Complete written informed consent was obtained from the patient´s relatives for the publication of this study and accompanying images.

Data Access:

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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