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Case Report

Progressive Myoclonic Epilepsy'-like presentation of Cerebrotendinous Xanthomatosis in an Indian Family with A Novel C.646+1G>A Splice Site Mutation

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ABSTRACT

Cerebrotendinous Xanthomatosis (CTX) is a rare autosomal-recessive inborn disorder of bile acid metabolism due to mutations in the *CYP27A1* gene. It presents with a diverse range of neurological and non-neurological symptoms. We present a case of CTX with a progressive myoclonic epilepsy (PME) like phenotype and a family history of CTX. The proband had a generalized epilepsy with prominent myoclonus. He also had intellectual decline, ataxia, bipyramidal dysfunction and peripheral neuropathy. The younger sibling had a milder generalized epilepsy without myoclonus along with behavioral issues, ataxia, neuropathy, and prominent tendon xanthomas. Both the siblings had developmental cataracts. MRI Brain of both had dentate hyperintensities with cerebellar atrophy. The proband's EEG showed severe background slowing with multifocal interictal discharges. Targeted gene of analysis proband revealed a novel homozygous 5′ splice site variation in intron 3 of the CYP27A1 gene. We present a novel phenotype and genotype of CTX presenting with a syndrome of myoclonic epilepsy. This is the first PME-like presentation of CTX to the best of our knowledge. CTX may present with a PME-like clinical phenotype and should be considered as a treatable cause within the differential diagnostic evluation of syndromic epilepsies involving an atypical familial myoclonic epilepsy.

1. Introduction

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder caused by disruption of bile acid synthesis. First described in 1937 by van Bogaert, the earliest clinical manifestations commonly reported in CTX are cholestatic jaundice, intractable diarrhea, and developmental cataracts. The most common neurological manifestations in CTX are intellectual disability, neuropsychiatric symptoms, ataxia and spasticity [1]. Seizures and epilepsy have gained prominence amongst the myriad of symptoms involved in the spectrum of neurological impairments of CTX since the 1990s [2]. Seizures may be present in 18–50 percent of cases across various cohorts. A progressive myoclonic epilepsy (PME) like presentation is thus far to our knowledge unreported.

2. Clinical history

A 20-year-old male (III-16 in chart) was referred to our epilepsy clinic with suspected juvenile myoclonic epilepsy. He had history of infrequent generalized tonic-clonic seizures since the age of 12 years, which were initially well controlled on a single anti-seizure medication (ASM) (phenytoin). There was a history of jerks (since age 12), which had been increasing in frequency over the last six months. Jerks were frequent, more often upon awakening, and symmetric involving both upper extremities (proximal > distal) with an occasional negative component (see video) contributing to falls. There was no stimulus-sensitivity or any reflex component. He had a poor scholastic record with new-onset dullness and apathy. There was history of progressive imbalance for the past six months which worsened on eye closure. Past medical history revealed bilateral cataract surgery at age eight. He was born out of a consanguineous union and had an affected 18-year-old sibling (III-17) who also was a "dull" child. The sibling had history of a few bilateral tonic-clonic seizures three years ago which had been well controlled with a single ASM (phenytoin). He too

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had undergone bilateral cataract surgery at age 10. He had become very irritable and aggressive for the last few months. Both siblings had a normal birth and developmental record. They also had two other siblings (deceased) (III-10, III-15 in the chart below) who had a similar history of intellectual decline, infrequent seizures, neuropsychiatric and developmental cataracts (Chart).

The general examination revealed short stature with multiple facial injuries in both the siblings. The proband had no neurocutaneous markers. However, the younger sibling reported bilateral ankle swellings since the age 15 (see image). Cognitive evaluation revealed an IQ of 65 (proband) and 60 (sibling) respectively with impairment across all domains. Ocular examination revealed pseudophakia with normal fundi. Their neurological evaluation revealed bilateral horizontal gaze-evoked nystagmus, dysarthria, and ataxia (axial and appendicular) with bipyramidal signs and depressed ankle jerks (details in Table). Final clinical impression was that of an autosomal recessive generalized epilepsy syndrome with myoclonic and tonic-clonic seizures and a pan-cerebellar-pyramidal syndrome with neuropathy and cognitive decline. CTX was suspected because of the ankle swellings, which appeared to be due to tendon xanthomas. We considered other PME's and mitochondrial disorders in the clinical differential diagnosis.

3. Investigations and management

Routine investigations including basic metabolic panel were normal. MRI Brain revealed T2/FLAIR hyperintensities in bilateral Dentate nuclei along-with moderate cerebral and cerebellar atrophy. Video EEG in the proband revealed severe polymorphic delta-range background slowing with multifocal sharp wave interictal discharges (IED) without any generalized discharges. Sibling's EEG revealed mild intermittent theta-range background slowing without any IED's. Their nerve conduction studies revealed sensorimotor demyelinating neuropathy. Their clinical suspicion index as proposed by Mignarri et al. for CTX was 400 in the proband and 500 in siblings respectively [3]. Thus, we directly proceeded with targeted genetic analysis for CYP27A1 gene (responsible for CTX). The genetic analysis of proband revealed a homozygous 5'-splice-site variation in intron-3 of the CYP27A1-gene affecting the invariant-GT donor splice site of exon-3. This was a novel variant which had been unreported in the 1000 genomes and ExAC databases. The in-silico prediction of the variant was deemed as damaging by MutationTaster2 and the reference base was conserved across species. Thus, a final diagnosis of CTX with a developmental encephalopathy and epilepsy mimicking PME was established [4].

We switched antiseizure medication from phenytoin to valproic acid 30 mg/kg/day in view of myoclonus and ataxia. The proband was also on Clonazepam 0.5 mg/day for jerks. Both were also started on atorvastatin 20 mg/day after an ongoing, exhaustive but unsuccessful effort to procure chenodeoxycholic acid (CDCA). Presently, both cases reportedly attained seizure freedom. Behavioral issues of the younger one responded to risperidone. There was a mild improvement of the cerebellar signs, possibly due to the discontinuation of phenytoin (Fig. 1).

4. Discussion

The proband had epilepsy with prominent myoclonus, as the presentating neurological feature of CTX. The most common seizure semiology reported with CTX is convulsive . Other reported semiologies include generalized-tonic, infantile spasms, and focal impaired awareness seizures (with temporal semiology and altered awareness in the chart)[2,5–8]. . A subcortical myoclonus (resembling myoclonus-dystonia) has been reported in isolated cases of CTX. Distally predominant myoclonus (mimicking tremors) along with mild dystonia has been described in a case series where patients did not have epilepsy [9] Some of these patients also had palatal tremors and action dystonia hypothesised to be originating from the Dentato-Rubro-Olivary circuit [10] As the

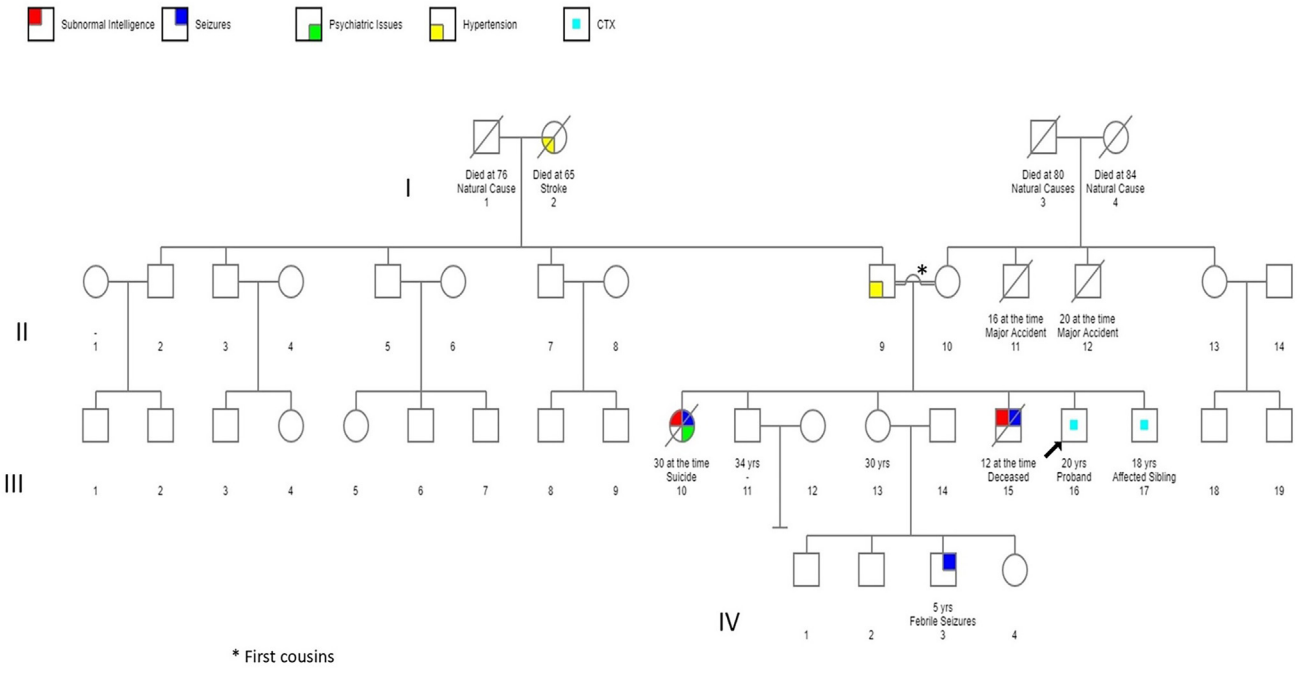

Chart 1. Three generation pedigree chart; proband: III-16 (see arrow), Sibling: III-17, potentially affected deceased siblings: III-10, III-15.

Table 1
Summary of publications on CTX where epilepsy was a reported symptom.

Study	No.of CTX Patients	No. of patients with Epilepsy	No. of patients with Epilepsy as initial neurological symptom	Semiology	EEG Findings
Arlazoroff et al. (1992) [15]	Case Report	1	1	Bilateral tonic-clonic	HV T-D BG-Slowing, Paroxysmal discharges.
Matsumoro et al. (1990)	Case Report	1	1	Bilateral tonic-clonic	HV T BG-Slowing
Dotti et al. (1991) [16]	10	5 (1F.S.)	N/A	N/A	Diffuse Slowing, No focal discharges.^
Verrips et al. (2000) [17]	54	14	N/A	N/A	Diffuse Slowing, Paroxysmal discharges.
Su et al. (2010) [18]	8	1	N/A	N/A	N/A
Pilo-de-la-Fuente et al. (2011) [19]	25	8	4	N/A	BG Slowing, Paroxysmal discharges, GSW, Disorg. BG
Koyama et al. (2012) [20]	Case Report	1	1	Altered conscousness	HV TD BG-Slowing, No IED
Kauffmann et al. (2012) [21]	Case Report	1	1	Focal, Temporal	Disorg. BG, Right Temporal Slowing
Pedroso et al. (2012) [22]	Case Report	1	1	Bilateral Tonic-Clonic	No IED, no details on BG changes
Mignarri et al. (2014) [23]	55	18	N/A	N/A	N/A
Larson et al. (2016) [24]	Case Report	1	1	Infantile Spasms	HA, Electrodecrement
Del mar Amador et al. (2018) [25]	12	2	N/A	N/A	N/A
Sekijima et al. (2018) [26]	40	4	3	N/A	BG Slowing in 13, IED in 2 cases^
Stelten et al. (2019) [27]	56	4	4*	N/A	N/A
Lee et al. (2019) [28]	9	1	N/A	N/A	Generalized Slowing^
Tao et al. (2019) [29]	25	1	N/A	Bilateral Tonic-Clonic	N/A

Abbreviations: F.S. – Febrile Seizures, N/A – Details unavailable, HV – High Voltage, TD – Theta Delta, BG – Background, disch. – discharges, IED – Interictal Discharges, Disorg. – Disorganized, HA – Hypsarrhythmia.
*One Patient had Parechovirus encephalitis.

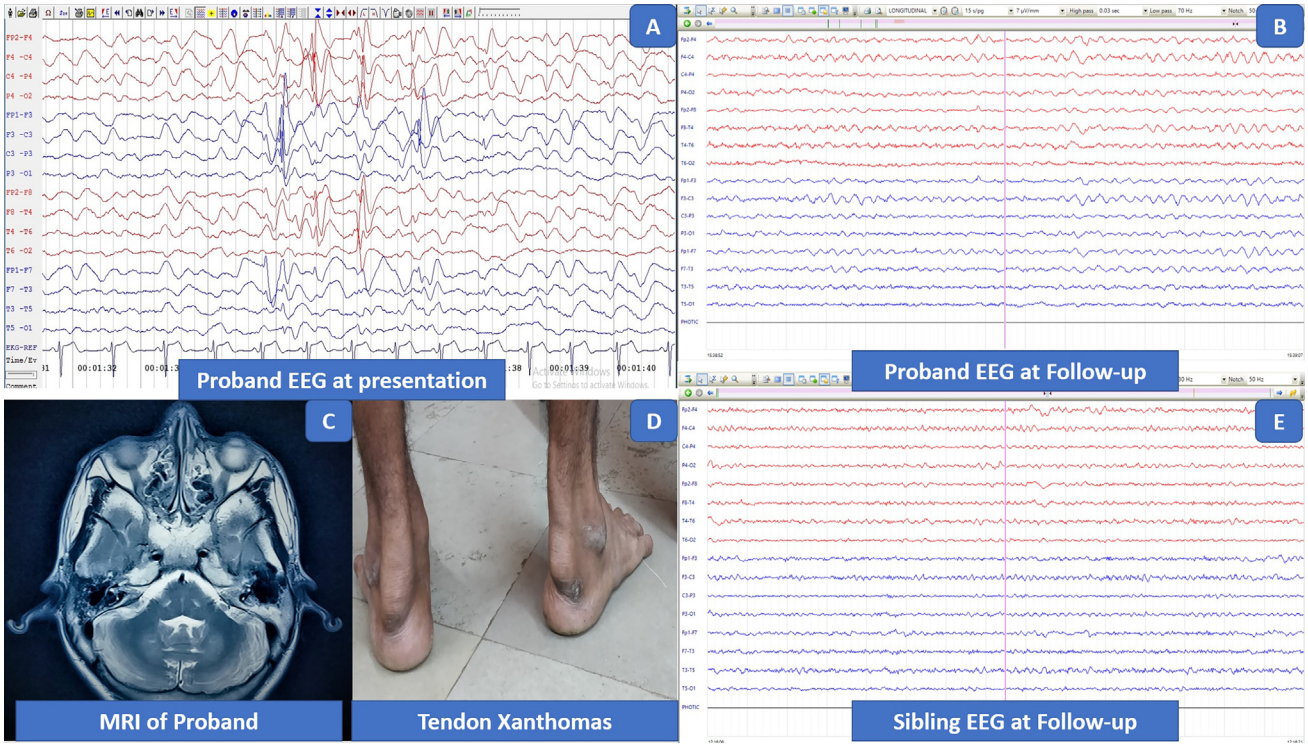

Fig. 1. (A) EEG of Proband at baseline – Severe High Voltage Delta range background slowing with multifocal epileptiform interictal discharges (IED); (B) Follow-up EEG of proband – Complete disappearance of IED's and significant improvement in background; (C) T2W Axial MRI Brain of Proband revealing bilateral dentate hyperintensities; (D) Tendon Xanthomas of the sibling; (E) Follow-up EEG of the sibling – Mild, intermittent polymorphic theta range background slowing.

ictus and myoclonus were not recorded during video-EEG, we cannot comment on the exact electrographic origin of the myoclonus. Interestingly, there were frequent multifocal IED's in the proband's interictal recording, an electroclinical profile that has also been reported in the PME's [11]. The background EEG in CTX seems to be abnormal and out of proportion to the intensity of the epilepsy. In fact, EEG abnormalities have also been described in CTX-patients without epilepsy [12]. Unfortunately, there is a lack of literature on the profile of seizure semiology and their EEG correlates in cohorts of CTX (see table). The cause of seizures in CTX is hypothesized to

be due to circulating high levels of bile alcohols as a result of accumulation of cholestenol, causing damage to the blood-brain-barrier [5,13]. Additionally, the sterols might cause overexpression of *ABCC2*-gene, which has been implicated in epilepsy treatment failure processes [14,14]. This could explain why CDCA therapy causes reduction in seizures as well. The younger sibling had very prominent Achilles tendon xanthomas, and even though tendon xanthomas are pathognomonic for CTX, its absence does exclude the diagnosis. In such cases, a high clinical suspicion could help in establishing an early diagnosis. Though our case had a novel pathogenic splice-site mutation, a single case report would be insufficient to establish causality with the novel presentation of a PME-like epilepsy.

5. Conclusion

We report the first PME-like presentation of CTX to the best of our knowledge. CTX should be suspected in all hereditary syndromic generalized epilepsies and familial myoclonic epilepsies even in the absence of classical neurocutaneous markers. This must be given due consideration when ordering epilepsy genetics as a timely diagnosis of CTX can prevent some of the irreversible neurological impairments.

Author roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

KMD: 1A,1B,1C. 3A,3B.
PK: 1B,1C. 3B.
PSR: 1B. 3B.
SHR: 1A,1B. 3B.
NJ: 1A,1C. 3B.
SA: 1B. 3B.
RA: 1B. 3B.

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Ethical compliance statement

The authors confirm that the approval of an institutional review board was not required for this work. We also confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Images and clinical reports of the patients have been shared after taking appropriate informed consents of their guardians.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2020.100401.

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