Batten's Disease: A Seizure Disorder's Battle for Diagnosis

Dear Editor,

Batten's disease is a rare neurodegenerative disorder named after a British pediatrician Frederick Batten, who described the clinical entity in 1903.[1] It is considered to be a juvenile variant of neuronal ceroid lipofuscinoses (JNCL). These are a group of disorders characterized by abnormal deposition of substances like lipofuscin, ceroid, and lipopigments in the neurons of brain and other body tissues.[2] This accumulation leads to progressive atrophy of areas of brain which manifests as various neurological impairments. The early clinical features may include seizures, ataxia, and vision loss beginning between the ages of 5 and 8 years. The disease is progressive and invariably fatal leading to death in early 20s.[3] It is probably the first case report of JNCL with only seizures as presentation.

A 13-year-old girl presented to emergency with generalized tonic-clonic seizures. She had a history of multiple similar episodes for last 2 years. She was born out of a nonconsanguineous marriage, normal full-term vaginal delivery with normal perinatal period. She was vaccinated appropriately for age and her developmental milestones were normal. She was a student of class eight which is appropriate for age and was doing well in her studies. There were no similar complaints in siblings. At admission, she appeared confused with normal muscle tone and deep tendon reflexes. Withdrawal plantar reflex was present. Her pupil was mid dilated with normal response to light. On evaluation following the initial control of seizures, assessment for behavior and cognition using child behavior checklist and Wechsler Intelligence Scale for Children was found to be appropriate for age. A detailed visual examination including visual acuity, visual fields, fundus examination, and optical coherence tomography revealed no abnormality. Her metabolic profile was normal except for the raised serum lactate level of 4.6 mg/dL. Contrast-enhanced magnetic resonance imaging of brain showed edematous gyri of right parieto-temporo-occipital lobe and precentral gyrus of right frontal lobe with T2/FLAIR hyperintense signal and patchy areas of restricted diffusion. The subcortical and deep white matter beneath the edematous gyri exhibited faint hyperintense signal on T2 and FLAIR images and mild restricted diffusion on DWI images. Mass effect in form of effacement of cortical sulci, midline shift toward left side, subfalcine herniation, partial effacement of right lateral ventricle, contralateral colpocephaly, and effacement on suprasellar, quadrigeminal, interpeduncular and ambient cistern [Figure 1 a-d]. Differential diagnosis of viral encephalitis, Rasmussen's encephalitis, and mitochondrial encephalopathy was suggested. The cerebrospinal fluid (CSF) examination revealed raised lactate level (39.57 mg/dL). Rest of CSF examination was normal with negative viral studies. Muscle biopsy was done to evaluate for mitochondrial encephalopathy. Histopathological examination of muscle biopsy revealed mild variation in fiber size on Hematoxylin and Eosin (H&E) staining. Modified Gomori's trichrome staining was normal with absence of ragged red fibers. Histochemical assay for oxidative stains and succinate dehydrogenase (SDH) and nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR) [Figure 2] were normal.

Electron microscopy of muscle biopsy showed characteristic granular osmiophilic deposits (GROD) in myofibers, and fingerprint and curvilinear lysosomal inclusions [Figure 3] were also noted. With histopathological, Histochemical, and electron microscopic features, a final diagnosis of JNCL was rendered. Genetic studies could not be done due to refusal by relatives of the index patient. The patient died 2 weeks later due to complications (aspiration pneumonitis) of recurrent episodes of seizure despite being on multiple antiepileptic medications including phenytoin, valproate, and levetiracetam.

Juvenile neuronal ceroid lipofuscinosis is an autosomal recessive, neurodegenerative disease characterized by progressive vision loss, seizures, and loss of cognitive and motor functions which is invariably fatal.[3] The incidence is estimated to be between 1/12,500 and 1/100,000 in European and USA populations.[4]

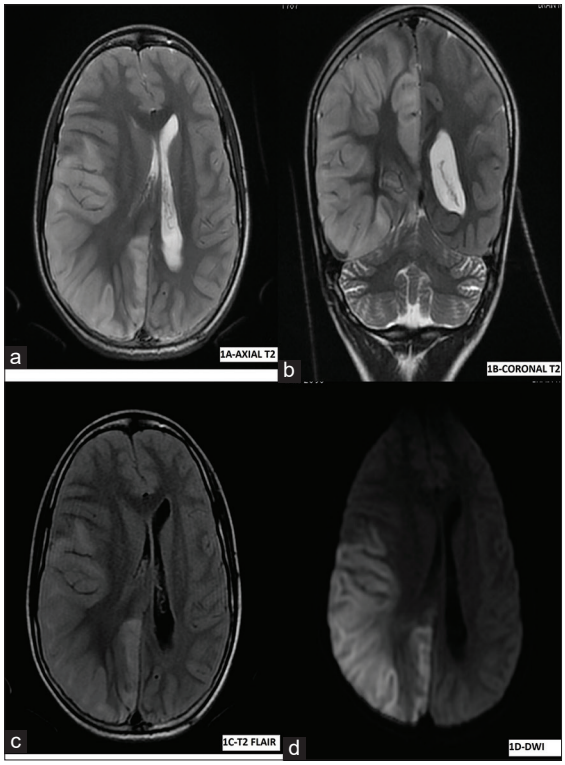

Figure 1:(a-d) CEMRI brain showed edematous gyri of right parieto-temporo-occipital lobe and precentral gyrus of right frontal lobe with T2/FLAIR hyperintense signal. The subcortical and deep white matter beneath the edematous gyri exhibited faint hyperintense signal on T2 and FLAIR images and mild restricted diffusion on DWI images

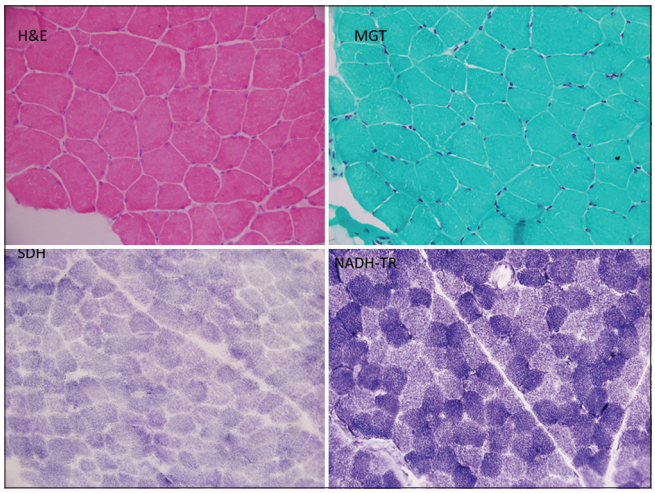

Figure 2: Photomicrographs showing mild variation in fiber size (H&E × 200); no ragged red fibers on MGT staining; Oxidative stains, SDH and NADH-TR are normal

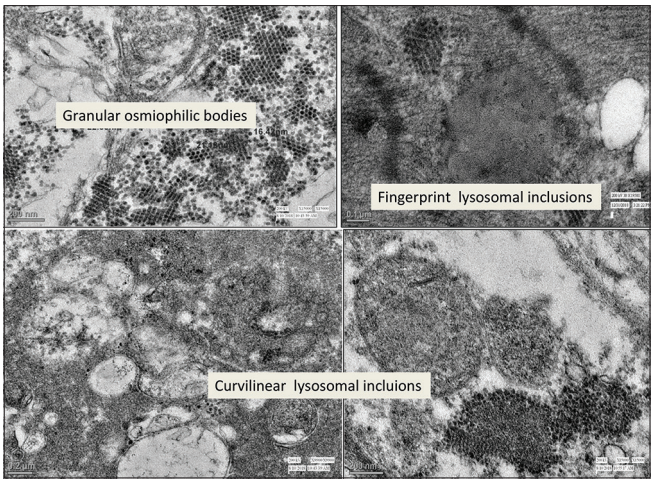

Figure 3: Electron photomicrographs showing granular osmiophilic deposits (GRODs), fingerprint (FP) and curvilinear (CV) inclusions in the myofibers

JNCL is caused by mutations of *CLN3*, a gene that is located on short arm of chromosome 16 (16p12.1) and encodes a hydrophobic transmembrane protein, which localizes to membrane lipid in cell membranes, endosomes, and lysosomes.[5] Broadly, NCL diseases have been classified based on the age of disease onset, i.e., infantile, late-infantile, juvenile, and adult form. However, recently they have been reclassified on the basis of newer molecular findings.[6] Functional vision loss occurs as first symptom in more than 80% of patients and is most clearly linked to JNCL. It typically manifests between 4 and 7 years of age. Fundus examination classically reveals bull's eye maculopathy; however, granularity in retinal pigment epithelium, optic atrophy, and pigment accumulation may also be seen. The retinal degeneration is very rapid leading to blindness in 1–2 years.[1] Cognitive impairment is also common clinical feature and usually appears approximately 2 years after onset of visual impairment. Nearly half of the patients of the develop which generalized tonic–clonic seizure alone and in one-third of them, it occurs along with partial seizures.

Patients with JNCL commonly do not have motor symptoms at diagnosis; however, these symptoms develop soon after with increasing severity and frequency, eventually leading to a bedridden state. Death usually occurs in third decade. Any child with visual loss, seizures, and/or cognitive impairment should be evaluated for JNCL. A detailed fundus examination for characteristic changes should be looked for along with gene testing. Histopathological examination of various tissues including muscle shows characteristic changes on electron microscopy which can help in making the diagnosis.[7,8]

Our patient did not have typical presentation of JNCL as her detailed visual evaluation and cognitive and behavioral assessments were normal. She did not have any other neurological deficits and the only presentation was seizure episodes. Diagnosis of JNCL becomes extremely difficult in the absence of typical clinical features; however, in the absence of any other definitive cause of seizures, JNCL should be kept as a rare differential diagnosis and should be evaluated accordingly. We were able to reach the diagnosis with the help of histopathological, histochemical, and electron microscopic features that were clearly suggestive of JNCL.

Although enzyme replacement therapy is available for the treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN), there is no definitive therapy available for JNCL and management remains symptomatic and supportive.[9] The parents of the patient should be informed and counselled in advance as the disease is invariably fatal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Spalton D, Taylor DS, Saunders MD. Juvenile Batten's disease: An ophthalmological assessment of 26 patients. Br J Ophthalmol

1980;64:726-32.
2. Ekazi J, Kominami E. Symposium: The neuronal ceroid-lipofuscinoses (NCL)—a group of lysosomal storage diseases come of age. The intracellular location and function of proteins of neuronal ceroid lipofuscinoses. Brain Pathol 2004;14:77-85.
3. Goebel H, Wisniewski K. Symposium: The neuronal ceroid-lipofuscinoses (NCL)—a group of lysosomal storage diseases come of age. Current state of clinical and morphological features in human NCL. Brain Pathol 2004;14:61-9.
4. Uvebrant P, Hagberg B. Neuronal ceroid lipofuscinoses in scandinavia. Epidemiology and clinical pictures. Neuropediatrics 1997;28:6-8.
5. The International Batten Disease Consortium. Isolation of a novel gene underlying batten disease, CLN3. Cell 1995;82:949-57.
6. Mink JW, Augustine EF, Adams HR, Marshall FJ, Kwon JM. Classification and natural history of the neuronal ceroid lipofuscinoses. J Child Neurol 2013;28:1101-5.
7. Sinha S, Satishchandra P, Santosh V, Gayatri N, Shankar SK. Neuronal ceroid lipofuscinosis: A clinicopathological study. Seizure 2004;13:235-40.
8. Mantel I, Brantley MA Jr, Bellmann C, Robson AG, Holder GE, Taylor A, *et al*. Juvenile neuronal ceroid lipofuscinosis (Batten disease) CLN3 mutation (Chrom 16p11.2) with different phenotypes in a sibling pair and low intensity *in vivo* autofluorescence. Klin Monbl Augenheilkd 2004;221:427-30.
9. Kohlschütter A, Schulz A, Bartsch U, Storch S. Current and emerging treatment strategies for neuronal ceroid lipofuscinoses. CNS Drugs 2019;33:315-25.

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