Late infantile neuronal ceroid lipofuscinosis: A case report with review of literature

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Abstract

Neuronal ceroid lipofuscinosis (NCL) are a group of genetically mediated neurodegenerative disorders affecting children and young adults. They are characterized by global mental and motor deterioration, vision loss, and epilepsy ultimately resulting in death. Of the various types, late infantile variety is the 2nd most common form of NCL. Here the authors report a case of a 9-year-old boy who presented with progressive mental and social deterioration since the age of 2½ years. As the disease progressed, he developed progressive vision loss, gait ataxia, action myoclonus, and epilepsy. Electroencephalogram revealed generalized sharp and slow wave discharges with background slowing. Magnetic resonance imaging of the brain revealed diffuse cerebral and cerebellar atrophy markedly affecting the cerebellum along with periventricular T2 hyperintensities. Skin biopsy from axilla revealed characteristic intracytoplasmic eosinophilic inclusions and periodic acid Schiff positive bodies within the eccrine ducts suggestive of NCL.

Key Words

Ataxia, epilepsy, neuronal ceroid lipofucinosis, skin biopsy, vision loss

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Introduction

Neuronal ceroid lipofuscinosis (NCL) are a heterogenous group of progressive neurodegenerative disorders which are autosomal recessively inherited. They are characterized by the intracellular accumulation of autofluorescent lipopigments in neurons and other tissues. There are 8 different forms which result from genetic deficiency on genes Neuronal Ceroid Lipofuscinosis CLN (1) to CLN (8).[1] Depending on the age of onset, they are classified into 4 types: Infantile, late infantile, juvenile and adult forms. Late infantile NCL is the 2nd most frequent form of the eight NCL.[2] The characteristic features include mental retardation, visual impairment, progressive myoclonic epilepsy, decline in motor skills resulting in premature death.[3,4] Infantile and late infantile onset NCL have a poor prognosis with early deaths while juvenile and adult onset forms have a relatively better prognosis. Worldwide, these disorders are among the common lysosomal storage disorders, however, very few cases are reported from India.[5-7] Hence, we report this case of a 9-year-old child who had characteristic clinical features, which lead to a suspicion of NCL. Histopathology confirmed the diagnosis.

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Case Report

A 9-year-old boy born out of non-consanguineous marriage presented with complaints of difficulty in walking and seizures of 1 year duration. He had swaying on either side suggestive of gait ataxia with jerky movements involving the trunk and limbs suggestive of action myoclonus. He also developed episodes of generalized tonic clonic seizures. Seizure frequency increased and they were poorly controlled with antiepileptic drugs. Child was symptomatic for various other neurological problems, however, they were left unattended. He had normal social and language development initially with slight delay in achieving motor milestones. However, parents noticed significant deterioration in his speech, behavior, and cognition since the age of 2½ years. He became socially withdrawn. He also had progressive vision loss noticed since the age of 5 years. Later on he used to bump into objects and people while walking. Vision loss progressed so much that he could hardly do any activities without assistance, however, he could respond to sounds. There was no history of any other cranial nerve palsy or motor weakness. There was no history of birth

asphyxia, preterm delivery or any perinatal insult. Child was vaccinated. Family history was not significant.

On examination, his vitals were stable. General examination didn't reveal any abnormalities. There were no neurocutaneous markers. Child was socially withdrawn and had some stereotypic movements involving both upper limbs. Vision loss could not be objectively tested, however, he didn't fixate gaze on any objects placed in front of him and could not appreciate torch light. Fundus was suggestive of pigmentary retinopathy with peripheral intraretinal bone spicules. Vessels were attenuated with optic disc pallor. Pupils were normal in size and were reacting to light. Pendular nystagmus was present. Other cranial nerve examination was normal. Tone and power was normal in all the four limbs. Reflexes were brisk and release signs in the form of palmomental, grasp, snout, pout reflex were present. Gait was ataxic and there was action myoclonus predominantly involving the trunk and lower limbs. Detailed sensory examination could not be done, however, he winced in response to pin prick. Cardiac and respiratory system examination was normal. There was no organomegaly on abdominal system examination.

Child had neuroregression in the form of deterioration in speech and cognition, behavioral changes, vision loss with pigmentary retinal changes and development of new features in the form of gait ataxia, action myoclonus, and generalized tonic clonic seizures. This led to a strong suspicion of NCL: The late infantile variety. Other possibilities considered were inborn errors of metabolism like congenital defects of glycosylation, leukodystrophy and mitochondrial cytopathies. Patient was investigated accordingly.

Investigations

Complete hemogram, biochemical parameters like renal, liver, serum electrolytes, thyroid functions, plasma lactate were within normal limits. His electroencephalogram (EEG) revealed generalized 1-1.5 Hz sharp and slow wave discharges with background slowing [Figure 1]. Pseudoperiodic discharges were visualized. Visual evoked potential (VEP) study didn't show any recordable waveforms. Nerve conduction study was normal. Magnetic resonance imaging of the brain revealed age inappropriate diffuse cerebral and cerebellar atrophy. However, the cerebellar atrophy was marked and out of proportion to the cerebral atrophy [Figure 2]. T2 weighted sequence revealed diffuse white matter hyperintensity in the periventricular area and centrum semi ovale [Figure 3]. Axillary skin biopsy revealed eosinophilic rounded bodies identified in the eccrine glands located close to the basement membrane [Figure 4]. Periodic acid Schiff (PAS) staining revealed PAS positive bodies seen in eccrine glands [Figure 5]. Patient received Tab Leviteracetam 250 mg twice a day (BD) along with supportive care. His seizure frequency has reduced. Otherwise the course is progressive.

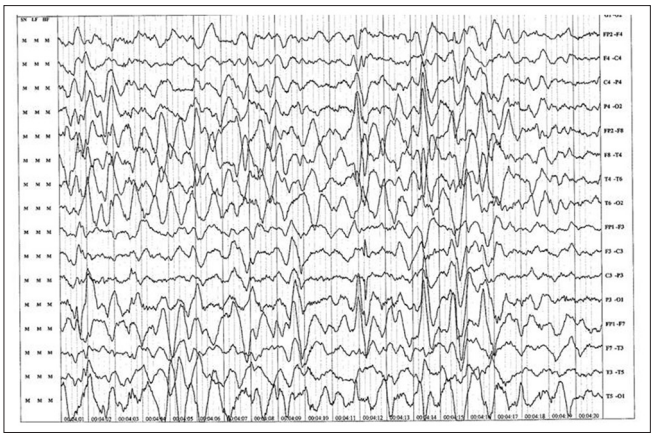

Figure 1: Electroencephalogram revealed generalized 1-1.5 Hz sharp and slow wave discharges with background slowing

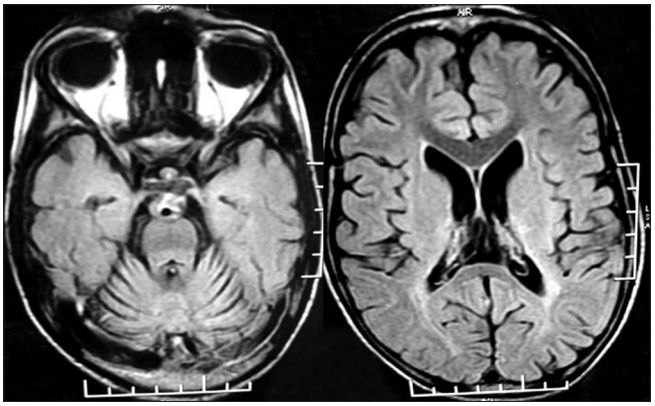

Figure 2: Magnetic resonance imaging of cranium revealed cerebellar atrophy out of proportion to the cerebral atrophy (Axial T2 Fluid attenuated inversion recovery sequence)

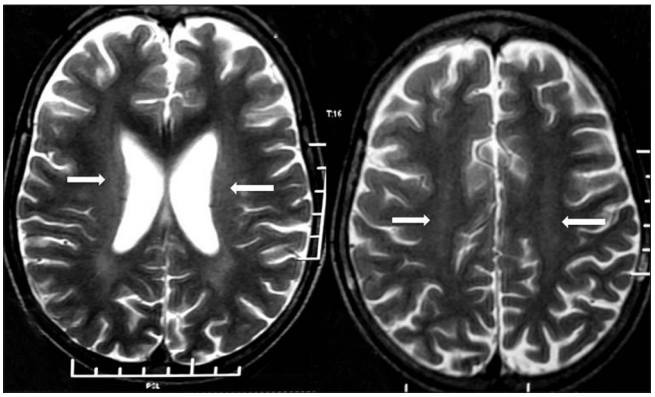

Figure 3: T2 weighted sequence revealed diffuse white matter hyperintensity in the periventricular area and centrum semi ovale

Discussion

NCL are a mixed group of genetically mediated lysosomal storage disorders occurring due to various enzymatic defects which lead to progressive neurodegeneration. All are autosomal recessive except adult onset NCL which is both autosomal recessive and dominant.[5] Disease occur worldwide with varying incidences, however, they are more prevalent in Scandinavian and populations of European descent. It is rarely reported from Asian countries.[8] There are two major case series reported from India.[5,6] Kamate reported 16 cases of which 11 were late infantile onset. Sinha *et al*., reported 12 cases of which 8 were juvenile onset. Gulati reported a case of juvenile NCL from India.[7] Our case belonged to the late infantile onset group.

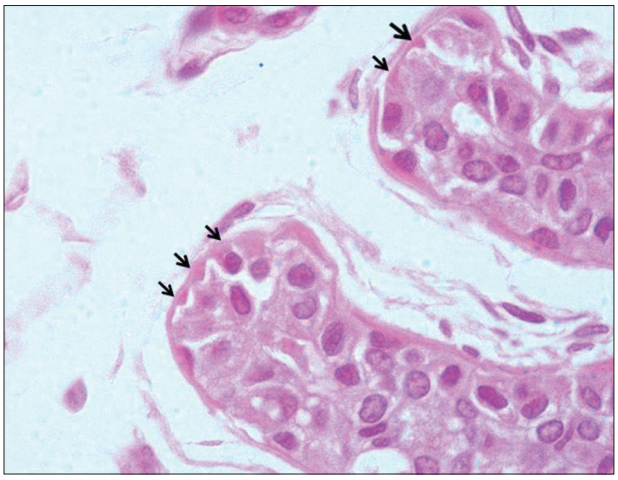

Figure 4: H and E, ×400. Section showed two eccrine ducts. Numerous eosinophilic inclusions are seen within the epithelial cell cytoplasm (arrows)

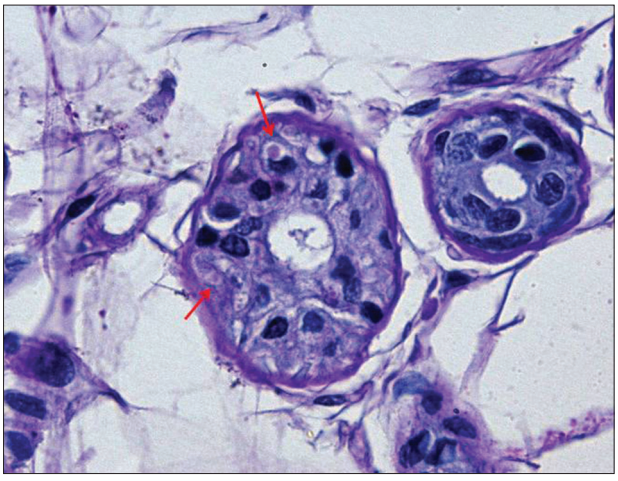

Figure 5: Periodic acid Schiff with diastase ×400. Section demonstrated two eccrine ducts in cross section. Arrows revealed rounded intracytoplasmic inclusions within the epithelial cells

Late infantile NCL first described by Jansky in 1908 and later defined by Beilchowsky as the 2nd variant of NCL in 1913[9] is caused by mutations in the Neuronal Ceroid Lipofuscinosis CLN2 gene located on chromosome 11q15 encoding the lysosomal enzyme tripeptidyl peptidase 1.[2] Accumulation of S adenosyl methionine in lysosomes due to defect in transportation and degradation of the mitochondrial subunit C results in apoptosis of the neuronal and photoreceptor cells. Although, the usual age of presentation is 2-4 years, there is often slight clumsiness and slowness in the acquisition of speech.[10] Our case presented at the age of 2½ years. Initial features are seizures and mental deterioration. The seizures can be of partial, complex partial or generalized tonic clonic type. Progressive developmental regression occurs since the onset of disease. Other features like myoclonus, ataxia and vision loss develop later in the course with optic atrophy being detectable within 2½ years of vision loss. By the age of 10 years, the affected children are usually unable to walk and sit unsupported and become blind. Death occurs in mid-childhood.[2] Our case initially had developmental regression followed by vision loss, myoclonus, and gait ataxia. Seizures occurred later in the course and they were of generalized tonic clonic type.

Ophthalmological evaluation gives important clues to the diagnosis of NCL. Opthalmoscopic findings can occur even before onset of vision loss. Early changes include defective macular light reflex and optic disc pallor followed by attenuation of vessels, pigmentary retinal changes, degeneration of macula and optic atrophy. Similar findings were observed in this case. Electroretinogram (ERG) is abnormal in the early stages. VEP is often abnormal characterized by gross enlargement of initial components. In our case, the child was completely blind and had no recordable waveforms on VEP study. Characteristic EEG finding include diffuse background slowing with occipital spikes more prominent during sleep.

Photic stimulation below 4 Hz (low frequency photic stimulation) can typically elicit a high amplitude polyspike and wave discharges in the occipital areas, which has a great utility in diagnosing disorders of childhood progressive myoclonic epilepsy. This typical EEG response on low frequency photic stimulation along with giant VEP and early diminution or extinction of the ERG forms a characteristic triad for the diagnosis of NCL.[11] Somatosensory evoked potential (SEP) study, an electrophysiological tool for assessment of the sensory pathway also adds to the diagnostic utility of NCL. These are often normal in the early stages. As the disease progresses, characteristic features appear which are abolished in the terminal stages of the disease. The characteristic feature include biphasic, nearly monophasic, very high voltage complexes (cortical components of SEP).[12] Although, it is of diagnostic importance for NCL, SEP abnormalities are found less consistently than an enlarged VEP. A study by Veneselli *et al*., observed that occurrence of pseudoperiodic discharges on EEG can be useful in early diagnosis of late infantile NCL.[13] In this case, EEG showed generalized sharp and slow wave discharges on a slow background with pseudoperiodic discharges. Neuroimaging reveals diffuse cerebral and cerebellar atrophy, atrophy being most obvious in the infrantentorial region as cerebellum is involved out of proportion to that of cerebrum. T2 weighted hyperintensities involving periventricular white matter mimicking leucokystrophy can occur.[14] Magnetic resonance spectroscopy reveals a reduced N-Acetyl Aspartate NAA/creatine ratio as a result of neuronal loss. Our case had similar neuroimaging features.

Confirmation of diagnosis is on the basis of histopathology, enzymatic assay and genetic testing.[2] Biopsy can be obtained from rectum, skeletal muscle, skin and conjunctiva.[15] Four distinct types of membrane-bound osmiophilic profiles are classic lipofuscin, fingerprint profiles which predominate in chronic juvenile form, curvilinear inclusion bodies (curved stacks of lamellae with alternating dark and pale lines) in infantile forms and pure granular profiles which predominate in some infantile and adult type.[16] Although, biochemical and molecular genetic studies allow for definitive diagnosis, they are laborious and may not be feasible in countries with low prevalence of NCL. Thus, histopathological and ultrastructural study of biopsy material can be of utmost importance for diagnosis of NCL.[17] Skin biopsy is easier, safe and a non-invasive test by neurological standards.[18] The characteristic features are eosinophilic intra-cytoplasmic

inclusions within the eccrine glands. Staining with periodic acid-Schiff stain highlights these inclusions. Enzymatic assay and genetic testing wasn't feasible in our case and the diagnosis was confirmed on the basis of skin biopsy which showed characteristic features of NCL.

There is no definitive treatment. Bone marrow transplant, stem cell transplant and gene therapy have been tried but none have shown any long term benefit. Flupirtine has been suggested to possibly slow down the progress of NCL, particularly in the juvenile and late infantile forms.[19] Seizures are usually difficult to control. Polytherapy is usually required and newer antiepileptic agents may help in control of intractable seizures. In our case, seizure frequency got reduced with Leviteracetam.

To conclude, NCL are a group of progressive neurodegenerative disorders rarely reported from Asian countries, which could be due to lack of awareness and underreporting of this disease. Typical clinical, ophthalmoscopic, EEG, and neuroimaging features can be suggestive of this rare disease preventing misdiagnosis, thus helping in genetic counseling. Axillary skin biopsy is of immense utility for diagnostic confirmation.

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