CASE REPORT

Neuronal ceroid lipofuscinosis: A case report

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ABSTRACT

Neuronal ceroid lipofuscinoses (NCL) represent severe neurodegenerative conditions which is one of the lysosomal storage disorders. There are four main clinical forms of NCL among which late infantile variety is the second most common condition. Here, we discuss a case concerning a boy aged 5 years and 4 months who exhibited a continuous decline in cognitive and motor functions starting from the age of 4. As the disorder advanced, he experienced gradual deterioration of his eyesight, unsteady walking and myoclonic seizures. An electroencephalogram performed on the child demonstrated widespread instances of sharp and slow wave discharges alongside a slowed background activity. Magnetic resonance imaging revealed extensive cerebral and noticeable cerebellar degeneration. A skin biopsy extracted from the armpit area displayed distinctive eosinophilic inclusions within the cells and structures in the eccrine ducts which stained positively for periodic acid-Schiff. These findings indicated a possibility of neuronal ceroid lipofuscinoses.

Keywords: neuronal ceroid lipofuscinosis, skin biopsy, lysosomal storage disease

INTRODUCTION

Neuronal ceroid lipofuscinoses (NCLs) constitute a cluster of the most prevalent hereditary and childhood neurodegenerative conditions. The worldwide incidence is 1:100000.[1] These conditions are identified by the buildup of self-fluorescent lipopigments within neurons and other body tissues.[2,3] Clinically, NCL is classified according to the age of onset into infantile, late infantile, juvenile and adult form.[3] The distinctive symptoms that serve as diagnostic indicators for NCLs encompass diminished vision alongside cognitive and motor decline. These symptoms are frequently accompanied by ataxia, myoclonus, and epilepsy, ultimately leading to premature demise.

Typically, the classic late-infantile NCL disease emerges around the age of three. Early in the progression, myoclonus and ataxia are commonly observed, succeeded by gradual declines in cognitive and motor functions. Retinopathy may not be prominently evident in the early stages and can be overlooked as the disease advances toward a more severe neurological impairment. Manifestations like spasticity, truncal hypotonia, loss of head control, persistent myoclonus, frequent seizures, and an extended state of reduced responsiveness characterize the disease until death occurs in early adolescence. Diagnosis is affirmed through histopathological examination, enzymatic assays, and genetic testing. There are no specific treatment options for any of NCLs. Treatment is mainly supportive and symptomatic. Infantile and late infantile onset NCL has a poor prognosis than that of juvenile and adult onset forms. Death occurs often due to aspiration pneumonia and seizure-related complications.[4] To our knowledge, no case of NCL has been reported from Bangladesh. Hence, we report this case of a male child who had characteristic clinical features which lead to a suspicion of NCL.

CASE DESCRIPTION

A 5 years and 4 months old fully immunized boy is the second child of consanguineous parents, presented with difficulty in walking since four years of age and repeated episodes of seizures for the last one year. Seizure was myoclonic and generalized tonic-clonic in nature which occurred in both sleep and awake state. He had normal social and language development initially with a slight

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LEARNING POINTS

1. Diagnostic clinical hallmark of NCL are myoclonic epilepsy, ataxia, visual impairment and cognitive regression.
2. NCL can be diagnosed by detecting characteristic intracytoplasmic eosinophilic inclusions and periodic acid schiff positive bodies within the eccrine ducts by skin punched biopsy from axilla.

delay in motor milestones. Moreover, the parents observed considerable decline in speech, behavior, and cognitive functions along with disturbance in motor abilities. At the time of admission, he did not have neck control, only cooing was present and could not interact with family members. He had no history of perinatal insult. His elder brother had the same type of illness and died at 8 years of age.

CASE MANAGEMENT

On examination, patient was conscious, vitally stable but not interested to the surroundings. He had microcephaly and skin findings were normal. Neurological examination showed: decreased tone and power in all limbs, reflexes were normal and gait could not be elicited. Cranial nerves were intact. Cerebellar function showed ataxia, intention tremor and nystagmus. Cardiac and respiratory system examination were normal. There was no abdominal organomegaly. These clinical findings led to a strong suspicion of NCL: the late infantile variety. Other possibilities were leukodystrophy and mitochondrial cytopathies. Labortory investigations-, e.g., complete hemogram, as well as biochemical measures such as renal, hepatic, serum electrolytes, thyroid functions, and plasma lactate, were normal. Patients electroencephalogram (EEG) exhibited generalized sharp and slow wave discharges at 1–1.5 Hz with background slowing **(FIGURE 1)**. Eye examination revealed pale optic disc. Brain magnetic resonance imaging unveiled widespread atrophy affecting both cerebral and cerebellar regions **(FIGURE 2)**. Axillary skin punched biopsy from armpit revealed distinctive intracellular inclusion bodies that stained positively with periodic acid-Schiff within the eccrine ducts, indicative of NCL **(FIGURE 2)**. He was treated by sodium valproate, levetiracetam, clobazam, and topiramate along with other supportive care. However, the frequency of seizures did not diminish and the disease progression continued. Currently, patient is on regular follow-up.

DISCUSSION

NCLs constitute a diverse group of genetically inherited lysosomal storage disorders, arising from various enzymatic deficiencies that result in progressive neurodegeneration. Primarily, they are inherited as autosomal recessive disorders. These disorders are observed globally but exhibit varying incidences, being rarely reported in Asian countries. Late infantile NCL, initially described by Jansky in 1908 and later characterized as the second variant of NCL by Beilchowsky in 1913,[5] arises from mutations in the CLN2 gene located on chromosome 11q15. This gene encodes the lysosomal enzyme tripeptidyl peptidase 1 (TPP1).

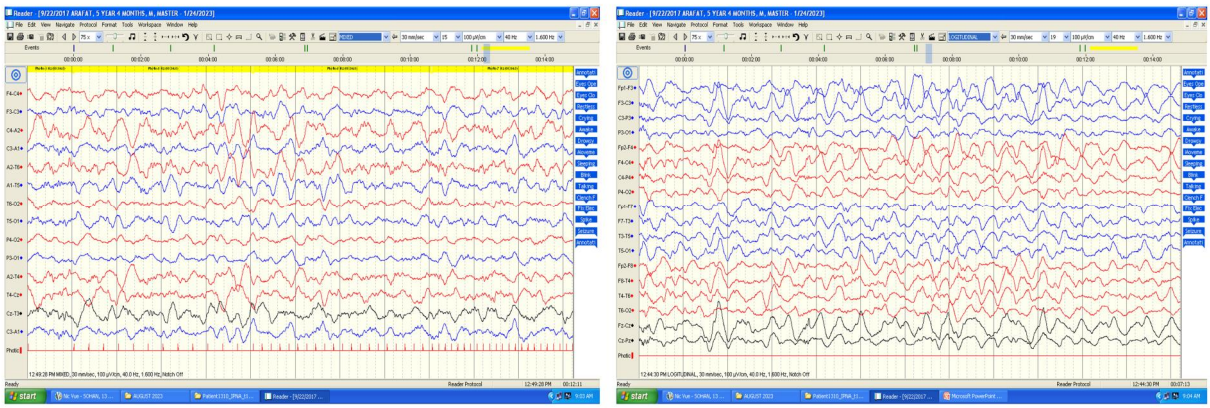

FIGURE 1 The electroencephalogram displayed widespread sharp and slow wave discharges at a frequency of 1-1.5 Hz

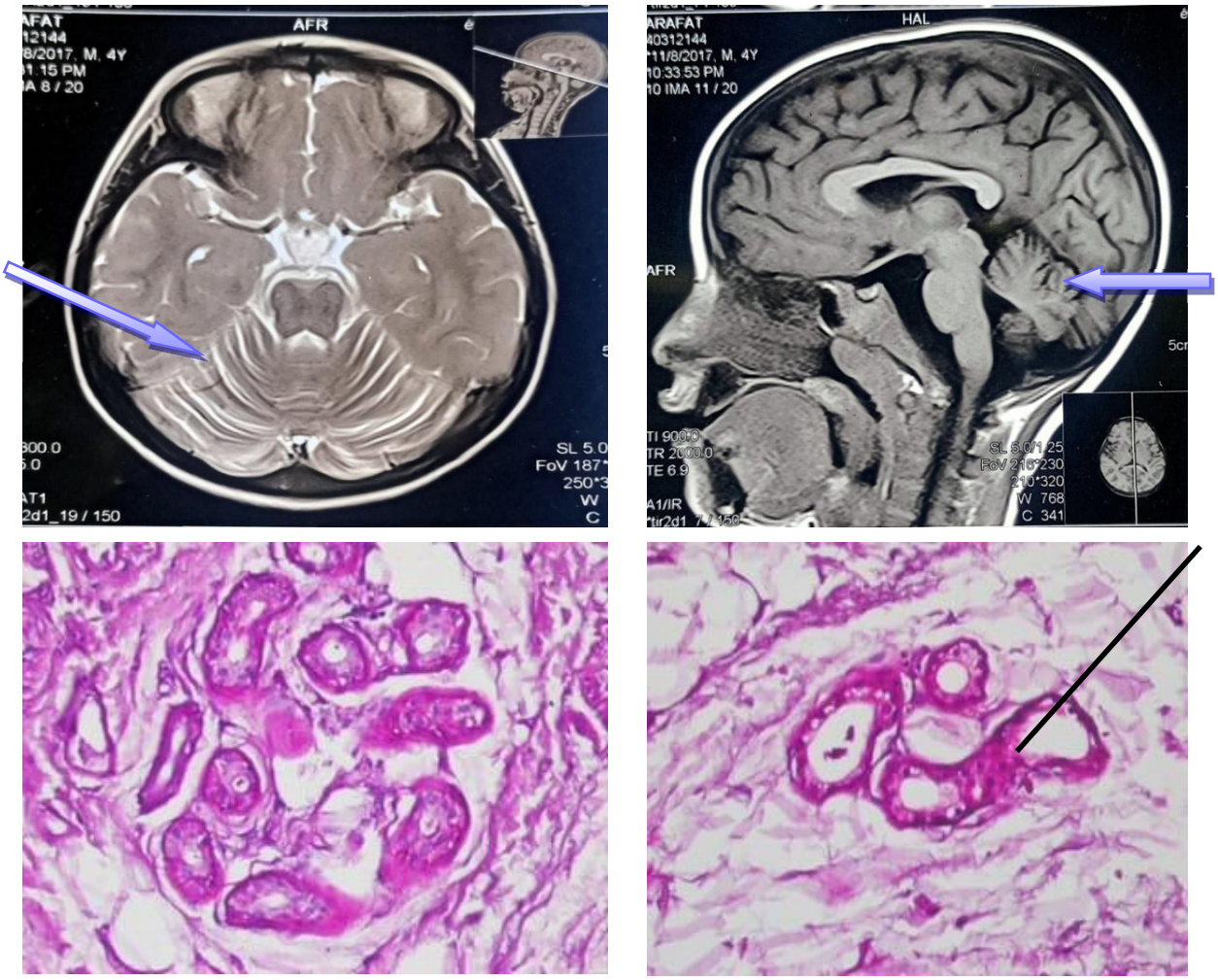

FIGURE 2 Magnetic resonance imaging of brain revealed cerebellar atrophy (Arrow) out of proportion to the cerebral atrophy (Axial T2 and Sagittal T1 sequence); Section demonstrated two eccrine ducts in cross section. The eccrine gland epithelium shows eosinophilic intracytoplasmic inclusions. Periodic acid Schiff (PAS) also highlighted these inclusions (Arrow)

Despite genetic diversity, NCLs share common clinical and histopathological traits. Universal features encompass neurodegeneration in the cerebral and cerebellar cortices, coupled with the accumulation of autofluorescent ceroid lipopigments in neural and peripheral tissues, as observed in our case. Clinical manifestations often include retinopathy, sleep disturbances, motor abnormalities, epilepsy, dementia, and ultimately, premature demise. Additional symptoms such as myoclonus, ataxia, and vision loss typically emerge later in the disease's progression. Diagnosis confirmation hinges on histopathology, enzymatic assays, and genetic testing.

In the case of rapid visual loss in children aged between 4 and 7 years, testing for CLN3 disease is advisable. Ophthalmological assessment plays a vital role in diagnosing NCL and provides valuable diagnostic hints.

Typical clinical, ophthalmoscopic, EEG, and neuroimaging features can provide clues to this rare disease, assisting in the prevention of misdiagnosis and offering significant insights for genetic counselling. In this specific scenario, enzymatic assays and genetic testing were not possible, rather axillary skin biopsy was done for confirming the diagnosis. The storage material could be identified in easily accessible non-neural tissues (like skin, blood lymphocytes, and skeletal muscle) that prompted a significant shift from central nervous system to peripheral biopsies. This approach is safer.[6] In cases of late infantile onset NCL, the prognosis is unfavorable, marked by a progressive disease trajectory and early mortality.

No specific treatment approaches are available for any form of NCLs. The primary approach involves providing symptomatic and supportive care to mitigate the effects of seizures, dysphagia, and aspiration pneumonia.[7] While attempts have been made with interventions like bone marrow transplant, stem cell transplant and gene therapy, none have exhibited sustained positive outcomes. Managing seizures often proves to be challenging, necessitating the use of multiple medications, and newer antiepileptic drugs might offer assistance in managing hard-to-control seizures. In our instance, the frequency of seizures decreased with the administration of levetiracetam.

NCLs are a class of neurodegenerative conditions that worsen over time. High index of suspicions with progressive neurodegeneration with myoclonic epilepsy, visual loss and ataxia are crucial for the diagnosis of NCL. Genetic testing for NCL is the key investigation but it can also be diagnosed by histopathology in low resource countries.

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Author Contributions

Conception and design: GKK. Acquisition, analysis, and interpretation of data: SA, BP, SN, MA. Manuscript drafting and revising it critically: GKK, SA, MA. Approval of the final version of the manuscript: GKK, SN. Guarantor accuracy and integrity of the work: GKK.

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Conflict of Interest

The authors have no conflict of interest to declare.

Ethical Approval

The study does not have any ethical approval from any review board butinformed consent was taken from the parents of the patient.

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