BANGLADESH J CHILD HEALTH 2023; VOL 47 (2) : 113-116

# Late Infantile Neuronal Ceroid Lipofuscinosis: Two Case Reports

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**Abstract:**

*Neuronal ceroid lipofuscinoses (NCLs) are a group of lysosomal storage disorders characterized by progressive, neurodegenerative course. NCLs are classified into four subtypes according to age of onset. Among them, late infantile variety is the second most common condition. Patients typically manifest with seizures, cognitive, motor deterioration and vision loss. Here, we reports two cases of NCLs, because of rarity of this disease in such a young age. As the disease advanced, patients experienced repeated episodes of seizures, ataxia, gradual deterioration of vision and loss of ambulation and speech. The electroencephalogram showed focal epileptiform discharges over left central and parietal region. Magnetic resonance imaging of Brain revealed extensive cerebral and cerebellar atrophy. A skin biopsy extracted from the armpit area displayed periodic acid-schiff (PAS) stained eosinophilic intracytoplasmic inclusions (curvilinear like). These findings are compatible with neuronal ceroid lipofuscinoses. Genetic testing for NCL is the gold standard investigation but patient can also be diagnosed by clinical correlation and positive histopathology findings in low income countries.*

***Keywords****: Neuronal ceroid lipofuscinosis, skin biopsy, neurodegenerative condition.*

*DOI: https://doi.org/10.3329/bjch.v47i2. 77662*

## Introduction:

Neuronal ceroid lipofuscinoses (NCLs) are rare neurodegenerative diseases due to defective lysosomal storage causing intracellular accumulation of ceroid and lipofuscin. This condition is characterized by myoclonus, ataxia, frequent seizures, progressive vision loss, gradual declines in cognition and motor functions and early death. NCL is classified into 14 subtypes according to genetic mutations. Clinically, NCL is also classified according to the age of onset into infantile, late infantile, juvenile and adult form.[1] Late-infantile NCL (LINCL) emerges in two to three years of age. *CLN2* gene mutation occurs in LINCL and causes tripeptidyl peptidase (TPP) enzyme deficiency. The prominent diagnostic clues for CLN2 NCL (genetic subtypes) includes reduced visual acuity with severe neurological impairment. Patients present clinically with spasticity, truncal hypotonia, persistent myoclonus, frequent seizures, poor response to drugs, loss of ambulation and speech. Ophthalmological findings are optic atrophy and pigmentary retinopathy.[2] Diagnosis is confirmed by histopathological examination, enzymatic assays and genetic testing. Treatment is mainly supportive and symptomatic. Infantile and late infantile onset NCL has a poor prognosis. Death occurs often due to sepsis, aspiration pneumonia and seizure-related complications.[3] Here we report two cases of NCLs who were diagnosed as late infantile form of NCL on the basis of phenotype and skin biopsy.

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## Case description

### Case-1

A 6 years fully immunized boy ,fifth issue( 2nd alive issue)of consanguineous parents, presented with loss of previously acquired skills, repeated attacks of seizures, ataxia and abnormal posturing since 3 years of age. Then he developed difficulty in walking, subsequently stopped walking, sitting and stopped

talking. He lost his interest to surroundings. Seizure was focal tonic to secondary generalization, tonic clonic and myoclonic in nature which occurred in both sleep and awake state. Moreover, the parents observed considerable decline in speech, behavior and cognitive functions along with motor regression. At the time of admission, he was having repeated seizures, did not have neck control, only cooing was present and could not interact with family members. He was delivered by NVD at home and he had history of perinatal insult. His siblings (all 3 females) had same type of illness and died between 6-7 years of age.

On examination, the patient was conscious, vitally stable but not interested to the surroundings. Microcephaly was present. Neurological examination showed: decreased tone and power in all limbs, reflexes were normal and gait could not be evaluated. Cranial nerves were intact. Cerebellar function showed ataxia, intention tremor and nystagmus. Cardiac and respiratory system examination were normal. There was no organomegaly. Laboratory investigations e.g., complete hemogram , as well as biochemical measures such as renal, hepatic, serum electrolytes, thyroid functions and plasma lactate were normal. Brain magnetic resonance imaging unveiled widespread atrophy affecting both cerebral and cerebellar regions (Figure 1).

Patients electroencephalogram (EEG) showed focal epileptiform discharges over left central and parietal region. (Figure 2). Eye examination revealed pale optic disc. 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 3). He was treated with sodium valproate, levetiracetam ,phenobarbitone, trihexy phenydyl along with other supportive care. Currently, the patient is on regular follow-up and bedridden.

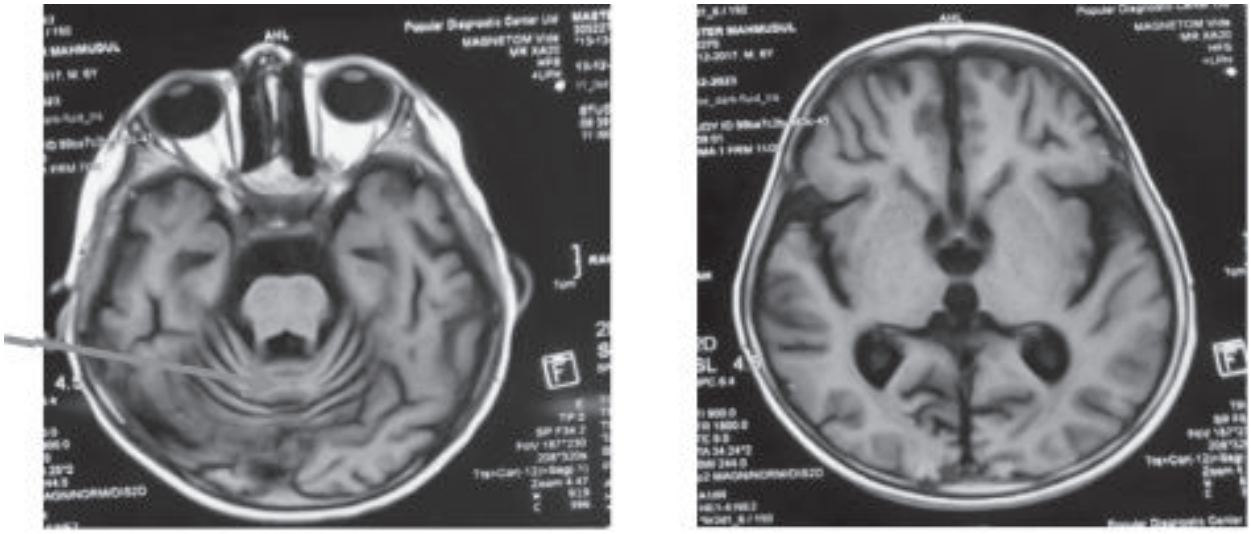

**Fig.-1:** *MRI of Brain showing cerebellar atrophy*

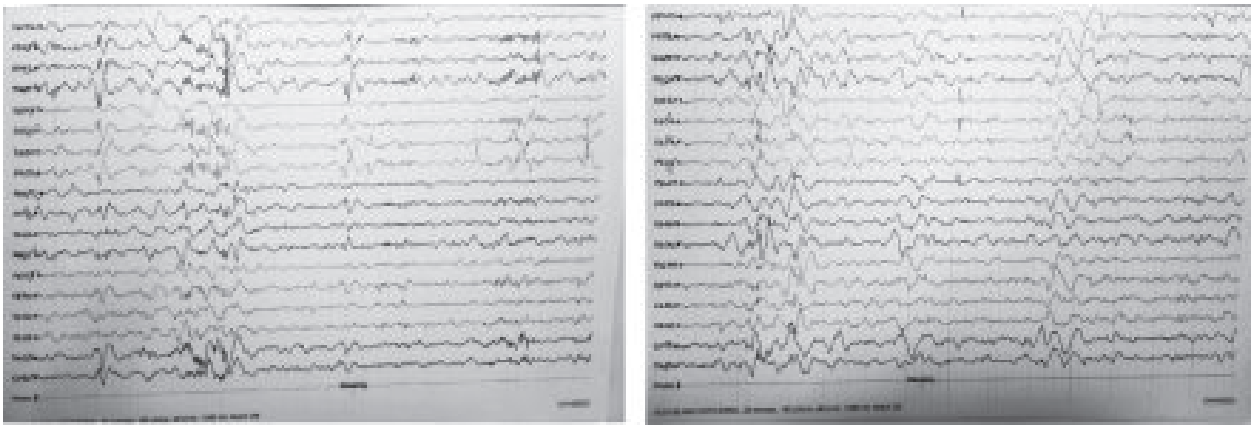

**Fig.-2:** *EEG showing focal epileptiform discharges over left central and parietal region*

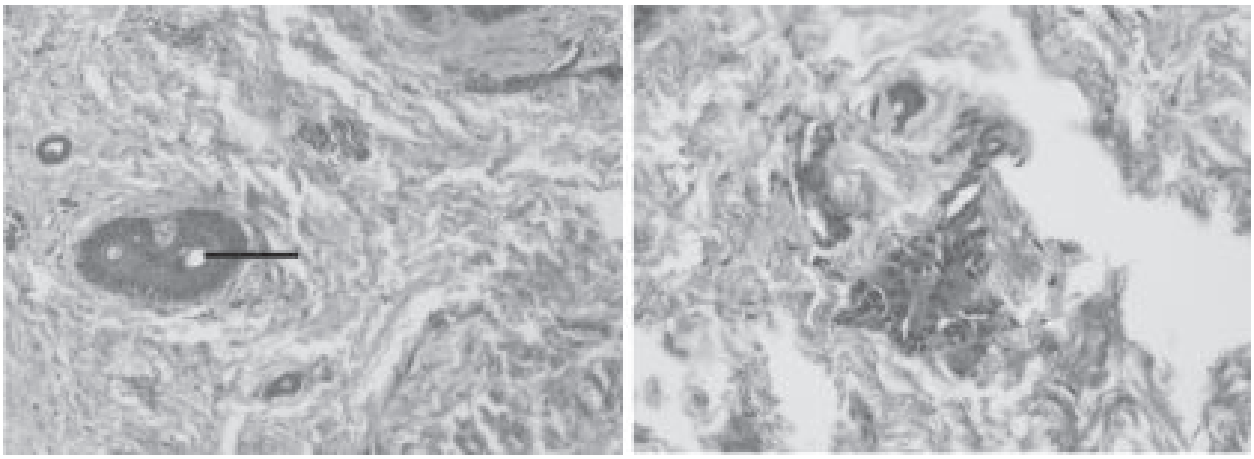

**Fig.-3:** *Skin biopsy shows eosinophilic intracytoplasmic inclusions in eccrine gland epithelium*

**Case-2**

A 5.5, years old immunized boy, 2nd issue of nonconsanguineous parents, got admitted into the department of Pediatric Neurology, BSMMU with the complaints of repeated episodes of tonic clonic seizures for 2.5 yrs. Seizure was myoclonic and generalized tonic clonic in nature occurred several times per day, both in sleep and awake with post-ictal drowsiness. Following seizure he gradually lost his previously acquired skill for 1.5 year. Now he is bed-ridden, can sit only and cannot interact with family members. For last 6 months, he developed visual and speech impairment. He had no history of fever, unconsciousness, respiratory difficulties, measles, behavioral problems or swallowing abnormality. He had uneventful birth history & achieved his developmental milestone in age appropriate manner prior to this illness. He was treated with several antiepileptic drugs without significant improvement. On examination: The child was conscious but not interested to surroundings, vitally stable, anthropometrically well thriving, skin survey revealed normal finding. Pupil-reacting to light but bilateral pale optic disc present on fundoscopy. Developmental assessment & neurological examination revealed cognition impaired, speech-vocalization present, memory impaired, not oriented. Cranial nerves were intact except 2nd cranial nerve. Motor system examination revealed, hypotonia, power 3/5, DTR normal in all 4 limbs, planter bilaterally extensor and gait could not be elicited; sensory intact, cerebellar functions impaired, truncal ataxia and titubation present .EEG showed focal epileptiform discharges over frontal and parietal region. MRI of brain showed cerebral and cerebellar atrophy. Skin biopsy revealed eosinophilic intracytoplasmic inclusions that stained positively with periodic acid-Schiff suggestive of NCL. He was treated with sodium valproate, levetiracetam along with other supportive care. Currently, the patient is on regular follow-up .

**Discussion:**

NCLs are a group of genetically inherited lysosomal storage disorders, arising from various enzymatic deficiencies that result in progressive neuro-degeneration. These disorders are rarely reported in Asian countries and common in Scandinavian countries.[2]

Clinically similar NCL disease arising from mutations in more than one gene eg.-loss-of-function mutations in CLN5, CLN6, CLN7, or CLN8. [4] Late infantile NCL can be caused by several gene mutations that are transmitted by autosomal recessive inheritance. These include CLN2, CLN6 and CLN7 genes.

Late infantile NCL was first reported in 1908 caused by mutations in the CLN2 gene located on chromosome 11q15.[5] This gene encodes the lysosomal enzyme tripeptidyl peptidase 1 (TPP1). Despite genetic diversity, NCLs share common clinical and histopathological traits. Clinical manifestations often include retinopathy, motor and cognitive deterioration, epilepsy, dementia, and ultimately, premature death. Then progressive myoclonus, ataxia and vision loss appears later as disease progression occurs. Our patient had seizure, neuroregression, ataxia, visual impairment etc which matches with the previous reported cases.

Diagnosis confirmation hinges on histopathology, enzymatic assays and genetic testing.

Ophthalmological assessment plays a vital role in diagnosing NCL. In our index case, 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, conjunctiva and skeletal muscles. This approach is easier and cost effective.

The prognosis of late infantile onset NCL is poor, followed by early mortality. No specific treatment are available for any form of NCLs. Dysphagia and difficulty with management of oral secretions leads to recurrent aspiration pneumonia. Pneumonia, sepsis and seizure related complications are the usual causes of death for NCLs patient.[5]

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 case, frequency of seizures decreased with the administration of Levetiracetam. Management was based on symptomatic care and supportive and palliative strategies, but the approval of the enzyme replacement therapy cerliponase alfa in the USA and Europe in 2017 created different treatment opportunities for NCL patients.[6]

**Conclusion:**

NCLs are a group of neurodegenerative conditions that worsen over time. Late infantile NCL is the second most common NCL. Progressive neurodegeneration with myoclonic epilepsy, ataxia, visual loss, motor and cognitive regression are important diagnostic clues for NCL in children . We are reporting two cases with seizure, neuroregression , visual impairment, positive family history with characteristic skin biopsy change.

**Learning Points**

1. The diagnostic clinical hallmarks of NCL are myoclonic epilepsy, ataxia, visual impairment, cognitive regression and positive family history.
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.
3. Typical clinical, ophthalmoscopic, EEG and neuroimaging findings can provide significant insights for diagnosis of this rare disease and helps in genetic counselling.

**Acknowledgements:**

We would like to acknowledge and thank to the Department of Dermatology and Pathology of BSMMU for their assistance.

**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 but informed consent was taken from the parents of the patient.

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