Abstract:
Neuronal ceroid lipofuscinosis (NCL) is a group of lysosomal neuro degenerative disorder inherited by autosomal recessive inheritance. This is characterized by accumulation of lipofuscin and ceroid pigment in neuronal and non-neuronal cells. The incidence of NCL in Europe and North America is 1 in 12500(1). They usually manifest during childhood and young adolescents in the form of progressive loss of vision, dementia, myoclonic seizures with myclonic jerks and cerebral and cerebellar atrophy (2). They are genetically classified into 8 types, NCL1 to NCL8. Their pathophysiology is poorly understood and involves a combination of storage process and progressive loss of nerve cells. They are caused by defect in lysosomal enzymes namely palmitoyl protein thioesterase in CLN1 and tripeptidyl peptidase in CLN2. In some others, there is membrane proteins of unknown function are deficient. They are generally incurable and lead to early death (3).

Keyword: NCL, blindness, dementia, myoclonic seizure, cerebellar atrophy.

A CASE OF JUVENILE NEURONAL CEROID LIPOFUSCINOSIS

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Introduction
Neuronal ceroid lipofuscinosis (NCL) is a group of progressive neuro degenerative disorder characterised by visual loss, seizures, dementia, and cerebral and cerebellar atrophy. The incidence of NCL in Europe and North America is 1 in 12500. They usually manifest during childhood and early adolescents. We report here a case of juvenile NCL in an 18 old male. Depending upon the age on onset and presence of the clinical symptoms they can be classified into 4 types. Infantile (INCL)- Santavuri-Haltia, Hagberg disease, Late Infantile (LINCL)-Jansky-Bielschowsky disease, Juvenile (JNCL)-Batten’s disease and Adult onset NCL-Kuff’s disease (4). Jansky first described this form in 1908. The first clinical description was described by Bielschowsky in 1913. Juvenile NCL is the most commonest form with 43.2% followed by Late Infantile NCL- 40.6%, Adult form- 9.2% and Infantile form- 7% (5). They are generally incurable.
CASE REPORT

We report an 18 year old male who presented with intermittent generalised tonic clonic convulsions of 4 years duration, refractory in nature associated with myoclonic jerks, blindness, ataxia, slurring of speech, tremors and bipyramidal signs. His perinatal history was uneventful but developmental motor milestones were delayed.

Fundus showing optic atrophy, degeneration of macula and narrowing of retinal vessels.

Loss of eye contact was first noticed at the age of 3 years. Ophthalmic examination revealed blindness due to optic atrophy and retinitis pigmentosa. His younger sister also had blindness due to optic atrophy from the age of 10 years. He developed progressive mental deterioration from the age of 8 years. At the age of 12 he was totally blind. He developed generalized tonic clonic with myoclonic jerks which was refractory in nature at the age of 14 years. He developed slurring of speech, ataxia, tremors and bipyramidal signs at the age of 16 years (4). His complete hemogram, liver and renal function tests were normal, serum amino acid chromatography, urine organic acid analysis were normal. EEG shows abnormal seizure activity at 2 to 4 Hz in the form of large amplitude spikes with slow wave complex in the occipital region. MRI reveals severe spino cerebellar degeneration, hypoplasia of cerebral and cerebellar hemisphere with prominent ventricles and deep cerebral sulci. Biopsy from the skin did not reveal any inclusion bodies on PAS staining.

CT brain showing cerebral, cerebellar atrophy and deep sulci

Discussion

The various forms of Neuronal ceroid lipofuscinosis (NCL) are differentiated by the age on onset, clinical presentation, ultra structural morphology and genetic analysis. They are characterised by progressive visual loss, mental deterioration, seizures including myoclonic jerks with cerebellar symptoms. The pathological mechanism underlying enzymatic defects and lysosomal accumulation results in severe neuronal loss in the cerebral and cerebellar cortices and retina is unclear. There is accumulation of mitochondrial ATP synthase protein in all forms except in NCL1 where there is accumulation of sphingolipid protein A and D. In Juvenile NCL, there is a defect in the CLN3 gene on chromosome 16p12 leads to deficiency of membrane protein containing 438 amino acids. The function of this protein is unknown. The age of onset usually ranges from 2 to 5 years. There is progressive deterioration of visual loss within 3 years. Ophthalmic examination reveals early
optic atrophy, attenuation of vessels, and degeneration of macula due to accumulation of storage material in the retina and retinitis pigmentosa. Retinal atrophy has been found in all form of NCLs except Adult NCL and NCL8. Pathological examination shows neuronal loss in cerebral and cerebellar cortices (granular and purkinje cells) and curvilinear storage particles and osmophilic granules are visible in the remaining neurons. They can also be demonstrated by electron microscopy of skin, conjunctiva or rectal mucosal biopsies.

Juvenile NCL shows vacuolated lymphocytes on peripheral smears in 10 to 30% cases. There is varying degrees of gliosis with evidence of myelin loss. The granular deposits in neurons stained by PAS, Sudan black and luxol fast blue show strong auto fluorescence. In the differential diagnosis one must consider infantile GM1 gangliosidosis, idiopathic epilepsy, and other forms of NCL. Infantile and Late infantile forms usually present with seizures at the age of 2-4 years. Adult forms are usually characterised by seizures and behavioural changes above 30 years. Life expectancy varies from late teens to 30 yrs in Juvenile form, 8-11 yrs in Infantile form, 6-30yrs in Late Infantile form and more than 30 yrs in Adult forms. Currently there is no effective treatment available for NCL. Though bone marrow transplantation improves seizure control to some extent, there is progressive deterioration of clinical symptoms. Seizures are treated with sodium valproate and lamotrigine. Phenytion and carbamazepine worsens seizure activity. Low dose risperidone given for hallucination triggered a malignant neuroleptic syndrome due to loss of dopaminergic neurons. A newer therapeutic option under study includes gene therapy. Genetic counselling and antenatal diagnosis can be done to identify the molecular genetic defect. Increased awareness of this rare disorder would prevent its diagnostic delay. Any previously normal child who presents with intractable epilepsy refractory in nature, visual loss, and mental deterioration should be screened for this rare disorder.

CT brain showing dilated ventricle, deep sulci and cerebral atrophy
EEG shows abnormal seizure activity at 2 to 4 Hz in the form of large amplitude spikes and slow waves in the occipital region. Neuro imaging studies are characterized by progressive cerebral and cerebellar atrophic changes. The neurons of hippocampus were relatively spared in all forms of NCL despite progressive seizures. Electron microscopic findings show characteristic inclusion bodies, curvilinear inclusion bodies in Infantile NCL, fingerprint cytosomes in Juvenile NCL, granular cytosomes in Adult NCL. The specificity of various intralysosomal inclusion bodies has been the subject of much discussion particularly the justification of using them as markers for the diagnosis of NCL. Insipid of not being able to demonstrate inclusion bodies in skin biopsy on PAS staining, a diagnosis of Juvenile NCL was made on the basis of characteristic clinical presentation. Hence skin biopsy though confirmatory, is not mandatory for the diagnosis of NCL.
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