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A Case Study on Rare Disease of Neuronal Ceroid –Lipofuscinoses (NCL)

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Abstract

The Neuronal Ceroid Lipofuscinoses (NCLs) are a family of autosomal recessive neurodegenerative disorders that annually affect 1:100,000 live births worldwide. This family of diseases results from mutations in one of 14 different genes that share common clinical and pathological etiologies. Clinically, the diseases are subcategorized into infantile, late-infantile, juvenile and adult forms based on their age of onset. Though the disease phenotypes may vary in their age and order of presentation. The article depicts a case study of 7 year old male child is a known case of neuronal ceroid lipofuscinosis. At the age of 3 years he had one seizure not associated with fever, he had decline since 5 years of age and his vocabulary came down this is a late infantile type of neuronal ceroid lipofuscinoses the importance of history taking, physical assessment and medical intervention were done. Pathological hall marks of NCL include the accumulation of storage material or ceroid in the lysosome. progressive neuronal degeneration and massive glial activation. Advances have been made in genetic diagnosis and counseling for families. Current diseases management is primarily targeted at controlling the symptoms rather than curing the disease. The discussion will provide an overview of the therapeutic approaches currently being pursued in preclinical and clinical trial to treat different forms of NCL as well as provide insight to novel therapeutic approaches in the development for the NCL.

Keywords: Neuronal Ceroid; Lipofuscinoses (NCL).

Introduction

The Neuronal Ceroid Lipofuscinoses (NCLs) are a family of autosomal recessive neurodegenerative disorders that annually affect 1:100,000 live births worldwide.[1] This family of diseases results from mutations in one of 14 different genes that share common clinical and pathological etiologies. Clinically, the diseases are subcategorized into infantile, late-infantile, juvenile and adult forms based on their age of onset. Though the disease phenotypes may vary in their age and order of presentation. Pathological hall marks of NCL include the accumulation of storage material or ceroid in the lysosome.progressive neuronal degeneration and massive glial activation.[2]

Case study

A 7 year old male child is a known case of neuronal ceroid lipofuscinosis, born of term delivery. Normal vaginal delivery, Cried immediately at birth and subsequently discharged. Very active and normal for age. At 3 years of age he had one seizure not associated with fever. Semiology – In sleep sat up and vomited., had current clonic jerks lasting for a few seconds, uprolling eye balls followed by secondary generalized tonic clonic

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convulsion. Habitual seizures, once a month since then semiology- uprolling of eyeballs, clonic jerking of the left upper and lower limbs with impaired awareness. He had decline since 5 years of age. His vocabulary came down over one year such that he could only say "amma",. Then he developed gait unsteadiness since 5.5 years of age with dragging of both lower limbs and drunken gait with falls. They did not notice he had ataxia since 5.5 years of age. Started bumping into objects and started feeling around to find toys right infront of his eyes. The gait has worsened such that now he is bed bound .He cannot sit up by himself and falls down immediately. He also started having frequent myoclonic jerks. currently he has seizures once in 1.5 to 2 months, only uprolling of eyeballs lasting for 2-3 months. The child was admitted in the hospital with the complaints of seizure. Initially it was generalized clonic tonic seizure, now more over left side.

On the day of admission the vital signs were pulse rate 110/mt, respiratory rate 24/mt, and blood pressure is 110/74 mm of Hg. System wise examination reveals respiratory system : bilateral normal ventilation and breathing sound present, bilateral occasional crepitation present. CVS: S1 S2 present , CNS: No dysmorphism or neurocutaneous marker, no visual regard, fundus could not be tested, No wasting of muscles, moves upper limbs against gravity. Deep tendon reflex : bilateral exaggerated. B/L ankle clonus present. Upper limbs appear ataxic, myoclonic jerks present. Abdomen soft and nontender. On discharge the child started iv letrecilam and sodium valporate for seizure doses were increased. Now no further seizures but continous to have myoclonic seizure, refered to paediatric department. And the child is receiving the symptomatic treatment.

Discussion

Neuronal ceroid lipofusinoses is the most common class of neurodegenerative diseases in children. They are autosomal recessive disorders characterized by the storage of an autofluorescent substance within lysosome of neurons and other tissues. Individual genes mutated in six forms have been identified.

Infantile type: (Haltia-santavuori)

It begins near end of the 1st year of life with myoclonic seizures, intellectual deterioration and blindness. Optic atropy and brownish discolouration of the macula are evident , and cerebral ataxia is prominent the electro retinogram shows small amplitude or absent wave forms. Death occurs at 10 year of age.In this infantile form CLN1 gene defect is been identified. Which codes for the lysosomal enzyme palmitoyl- protein thioesterase-1 (PPT).

Late infantile type (Jansky – Bielschowsky)

Most common type of NCL. The presenting manifestation is myoclonic seizure beginning between 2 and 4 yrs of age in a previously normal child. Dementia and ataxia are combained with progressive loss of visual acuity and microcephaly. On examination retina shows marked attenuation of vessels, pheripheral block 'bone spicule' pigmentary abnormalities, optic atrophy, and asubtle brown pigment in the macular region. The ERG shows abnormality due to deposition of substance within the rod and cone area of the retina. The auto fluorescent material is deposited in the neurons, fibro blast, and secretary cells. Mutations have been identified in the CLN2 gene.

Juvenile type (Spielineyer-vogt)

Is characterized by progressive visual loss and intellectual impairment beginning between 5 and 10 yrs of age. The funduscopic changes are similar to those for the late infantile type. The ERG also abnormal as early, myoclonic seizures are not prominent as infantile type. Dystonic posturing is marked in the late stages. Mutation in CLN2 and CLN3 genes have been identified in juvenile forms.[3]

Current medical management for NCLs

The NCLs present different diseases caused by mutations in as many as 14 different genes. NCLs have some common features but they present with different clinical features i.e. onset of cell biology and biochemistry, gene mutation and rate and characteristics of progression. This hetrogeneity make the discovery and use of new therapies difficult.[4] There are ongoing studies with anti inflammatories that have provided some evidence of improved visual outcome in NCLs. Many treatment for epilepsy but very few of these have been tested. Myoclonus is treatable but difficult. Supportive treatment for NCL is also available. Physical therapy, occupational therapy, speech therapy, feeding gastrostomy, suction and airway management and caregiver support and respite.[5]

Newer therapies in pipe line treatment of NCLs

Newer therapies may halt or slow the progression of the disease unlikely to completely reverse the disease . In NCL these have been lamotrigine for epilepsy, transdermal fentanyl for pain, melatonin for sleep circadian rhythm disturbance, and haemopoitic stemcell transplant umbilical cord blood and bone marrow transplant for disease modification. These treatment with a limited number of participants, are difficult to interpret, which significantly increases the variability between the subjects.[6] There have been number of LINCL disease modification studies such as bone marrow transplantation and antioxidants (selenium, vit E).

Gene therapy

Recently European union approved its first gene therapy for the treatment of lipoprotein lipase deficiency, NCLs are predominantly neuro generative diseases thus harder to treat. Delivery to the primary diseased tissue is critical. In the case of NCLs this means delivery of virus into central nervous system. There are a number of different viral vectors that are currently utilized for gene therapy including as adeno associated virus (AAV) and lentivirus (LV). A particular vector is selected based on several factors including (Pay load) the region they need to be delivered to and types of cell to be expressed. In addition , these vectors and their associated sero types can be modified to gain additional desired properties.

Enzyme replacement therapy

In addition to gene therapy, enzyme replacement therapy is also being heavily pursued as a therapeutic approach for the treatment of LSDs. In recent technical brief, it was noted that nine ERTs are available for the treatment of a limited number of LSDs within the united states. Numerous preclinical studies have been conducted using ERT to treat different forms of NCL.[7] ERT seem promising specifically in INCL and LINCL as these forms of NCL are caused by enzyme deficiencies.

Stem cell therapy

Various different types of stem cells are providing increased utility in the treatment of neurological disorders. There are number of technical considerations that must be taken which type of stem cells to test for use in treatment. The most promising of these studies has suggested that Hematopoietic stem cell , specifically bone marrow treatment, offered in combination gene therapy in Ppt -/- mice significantly improved outcomes even when Hematopoietic stem cell therapy alone provided limited or no benefit.

RNA modulation

RNA modulation therapies are a relatively new therapeutic approach for lysosomal storage diseases , especially the NCLs. There are a number of different RNA modulation therapies (i.e. antisense oligonucleotides, nonsense suppression compounds, nonsense mediated decay inhibitors) that have been used effectively in preclinical and clinical trials for a number of different diseases. These therapies use different stratergies to reach end goal that of producing a partially or fully functional protein from the targeted mRNA transcript.[8]

Anti -inflammatories

Normal inflammation response has long been suspected as an integral part of the pathobiology of a number of neurogenerative diseases including lysosomal storage disorders. It appears that neuroinflammation in LSDs can encompass numerous components such as, alteration in inflammatory associated gene expression, adjustments in cytokine levels, microglia activation, lymphocyte infiltration and production of auto bodies.

Based on the fact that inflammation is involved in NCL disease progression, the use of anti inflammatories as a therapeutic approach has been addressed. Mycophenolate moeftil, an immuno suppressant, when used in cln3 -/- mice appeared to protect against neuro inflammation , deposition of immunoglobulin G in the brain , and neuronal cell death and these findings contributed to an ongoing JNCL clinical trail. (NCT 01399047; clinical trails.gov).[9]

Lysosome modulators

Sardiello et. al. have previously reported that a transcription factor, can modulate the lysosome by altering the expression of a number of lysosomal genes. Studies have identified a number of transcription factor activator ; one of which

reduces storage accumulation in LINCL patient fibroblast. TFEB transcription factor targeting of CLN genes and the recently identified activators of TFEB, lysosome modulation via TFEB appears to be a viable therapeutic approach for NCLs.

Natural treatments (Antioxidents, selenium, vit E, curcumin)

Anti oxidents, vit E, and Resveratol, endoplasmic reticulum modifiers and Nt BuHA, Particularly Resvetrol has shown beneficial effects when used to treat both INCL and JNCL cell lines in addition to Clni knock mice.haemopathic treatments have demonstrated promising results. In addition to lysosomal modulators, this therapeutic approach may function well as a combinational therapy.[10]

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Conclusion

Based on the numerous therapeutic approaches discussed here and their potential as treatments of NCLs, these factors have to be strongly considered due to the limited number of patients and the ultimate goal of identifying curative therapeutics. Updates on translational research for management of INCL / LINCL, The field of translational research is moving at an accelerated pace and as scientists clinical and regulatory officials must work collectively to streamline efforts that effectively and efficiently allow new drugs and treatment strategies to move from the basic laboratory to the patient as quickly as possible.

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