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NEURONAL CEROID LIPOFUSCINOSES (BATTEN DISEASE)-COMPREHENSIVE REVIEW

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Abstract:
Neuronal ceroid lipofuscinoses (NCLs) constitute a heterogeneous group of rare, inherited neurodegenerative lysosomal storage disorders marked by accumulation of autofluorescent lipopigments—lipofuscin and ceroid—in neurons and various body tissues. At least 13 NCL subtypes, each associated with distinct genetic mutations, have been identified, with classification based on age of onset, clinical features, and genetic profile. NCLs most commonly affect infants and children but can present from early infancy through adulthood. Typical symptoms include progressive vision impairment leading to blindness, seizures, cognitive and motor decline, dementia, behavioral changes, and decreased life expectancy. Onset and progression differ by subtype: infantile and juvenile forms exhibit rapid neurodegeneration, while adult forms may be slower, sometimes presenting primarily with dementia or movement disorders. Diagnosis relies on a combination of clinical evaluation, neuroimaging, enzyme assays, ultrastructural studies demonstrating intra lysosomal inclusions, and definitive genetic testing for mutations in CLN genes. Early diagnosis is crucial for optimal management and genetic counseling. Currently, there is no cure for most NCL forms. Treatments are largely symptomatic, focusing on seizure control, managing neuropsychiatric symptoms, and palliative care. Recent advances include enzyme replacement therapy (ERT) for CLN2 disease and ongoing investigation into gene therapy, small molecule drugs, and stem cell therapies, although these remain experimental for most subtypes. The aim of this review is to study the causes, symptoms, pathogenesis, modern therapeutic and diagnostic strategies to enable optimal supportive interventions and to expand eligibility for disease-modifying and experimental therapies, thereby striving to slow neurological decline and improve quality of life.

Keywords:
Neuronal Ceroid Lipofuscinosis, NCL, Batten disease, lysosomal storage disorder, CLN genes, neurodegeneration, lipopigment accumulation, progressive epilepsy, vision loss, cognitive decline, genetic disorder, pediatric neurodegenerative disease, enzyme deficiency, autofluorescent storage material.

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INTRODUCTION:

Neuronal ceroid lipofuscinoses (also known as Batten disease) are a heterogeneous group of neurodegenerative lysosomal storage disorders affecting children and young and adults[1]. It constitutes a family of disastrous lysosomal storage disorders that collectively represent the most common inherited pediatric neurodegenerative disorder affecting about 1:12,500 live birth worldwide with dementia, epilepsy, retinopathy, motor disturbance, and early death[1]. Even though NCLs are still incurable, certain of their forms are now responsive to the treatments discussed here. In 2017, FDA approved a tripeptidyl peptidase enzyme replacement therapy (ERT) became the first globally approved treatment for CLN2 batten disease. Although the clinical and neuropathological features of all NCLs are similar, each form is a unique genetic entity with unique pathophysiological traits. Although all NCLs show clinical and neuropathological similarities, represents a distinct genetic entity with bizarre pathophysiological characteristics. Batten disease can result from mutation in 1 of 13 genes[2]. The present classification of NCLs is based on the mutated gene which is numbered from 1 to 13. This genetic heterogeneity results in around 14 different forms of NCLs.

Three most common forms are:

1. Infantile neuronal ceroid lipofuscinosis (INCL)
2. Late Infantile neuronal ceroid lipofuscinosis (LINCL)
3. Juvenile neuronal ceroid lipofuscinosis (JNCL)

1.INFANTILE NEURONAL CEROID LIPOFUSCINOSIS (INCL):

Infantile NCL (INCL) typically begins in infancy with rapid neurodegeneration, leading to severe motor decline, blindness, seizures, and early death[3].

2. LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS (LINCL):

Late infantile NCL (LINCL), often caused by CLN2 gene mutations, usually starts between ages 2 and 4, characterized by developmental delay, epilepsy, motor dysfunction, and vision loss, progressing to premature death[3].

3.JUVENILE NEURONAL CEROID LIPOFUSCINOSIS (JNCL):

Juvenile NCL (JNCL), typically caused by CLN3 mutations, presents in childhood with gradual cognitive decline, visual impairment, seizures, and motor deterioration. Common features include progressive neurological decline and lysosomal storage pathology[3].

AIM:

The aim is to provide a clear overview of neuronal ceroid lipofuscinoses, highlighting its types, classification, symptoms, diagnosis and treatment.

OBJECTIVES:

- The objectives focus on advancing scientific understanding, clinical awareness, diagnostics, therapeutic development, and supportive care for Neuronal Ceroid Lipofuscinosis (NCL).
- To describe the genetic basis and inheritance patterns of NCL subtypes (CLN1–CLN14) and explain the cellular and molecular mechanisms underpinning NCL pathology, including lysosomal dysfunction and protein aggregation.
- Clinically, the goal is to identify key clinical features, progression patterns, and differential diagnoses, as well as to classify NCL according to age of onset and phenotype—infantile, late infantile, juvenile, and adult forms.
- Therapeutic development focuses on reviewing current treatments such as enzyme replacement and gene therapy.

SYMPTOMS:

The symptoms of neuronal ceroid lipofuscinoses (NCLs) are;

- Progressive vision loss leading to blindness is often an early and prominent symptom.
- Seizures, including epilepsy, are common and can vary in severity.
- Cognitive decline, including dementia, occurs as the disease progresses.
- Motor impairments such as ataxia (unsteady walking), loss of motor skills, and movement disorders are characteristic.
- Speech delays and loss of communication abilities develop over time.
- Behavioral and personality changes, including psychiatric symptoms like aggression, can manifest.
- Myoclonus, which involves jerking muscle movements, may be present.
- The disease is progressive and often leads to severe physical and mental decline with eventual premature death [5].

ETIOLOGY:

NCLs are a group of inherited neurodegenerative disorders caused mainly by mutations in several distinct genes affecting cellular metabolism and lysosomal function.

- These mutations disrupt normal lysosomal degradation processes, leading to accumulation of harmful lipopigments—mainly ceroid and lipofuscin—in neurons and other tissues.

- Specific gene defects vary by NCL subtype but common ones include mutations in CLN1, CLN2, CLN3, CLN6, CLN8, and others.
- For example, in CLN1 disease, a deficiency in the lysosomal enzyme palmitoyl protein thioesterase 1 (PPT1) leads to substrate build-up and cellular dysfunction.
- These mutations cause diverse yet overlapping effects on neuronal lipid metabolism, leading to characteristic symptoms such as cognitive decline, vision loss, and seizures.[6]

PATHOGENISIS:

NCLs are caused by mutations in at least 13 different CLN genes, each encoding proteins essential for normal lysosomal function.

- These mutations disrupt lysosomal degradation pathways, leading to accumulation of autofluorescent lipopigments called ceroid and lipofuscin within neurons.
- The accumulated storage material impairs neuronal function and progressively causes neuron death, especially in the central nervous system.
- Lysosomes not only degrade waste but also act as signaling hubs managing cellular metabolism, proliferation, and nutrient sensing, processes disturbed in NCL.
- Defective lysosomal acidification and impaired fusion events between endosomes, autophagosomes, and lysosomes contribute to faulty intracellular waste clearance.
- Mutations in different CLN genes affect various lysosomal enzymes or membrane proteins, with overlapping but distinct impacts on cellular pathways.
- The interaction between lysosomes, mitochondria, and the endoplasmic reticulum is disrupted, contributing to cellular homeostasis failure[7].

DIAGNOSIS:

1.Clinical Presentation and Initial Suspicion

The diagnostic process for NCL typically begins with observing a combination of progressive neurological symptoms. Patients, often infants or children, may show early signs such as vision problems, unexplained seizures, developmental regression, loss of motor coordination, and sudden cognitive decline. Some cases are identified in adolescence or adulthood, depending on the subtype. A detailed family history is crucial, since NCL is inherited, most often in an autosomal recessive pattern. Early clinical signs can sometimes be non-specific, making broader neurological screening necessary in the beginning.[8]

2.Genetic Testing and Molecular Confirmation

Genetic testing is the most reliable and specific diagnostic tool for confirming NCL. Modern approaches like whole exome or genome sequencing, or targeted panels for CLN genes (e.g., CLN1–CLN14), allow identification of the exact mutation responsible. Confirming the subtype molecularly is important not only for diagnosis but also for prognosis, eligibility for ongoing clinical trials, and genetic counseling for families. In families with a known mutation, prenatal testing and preimplantation genetic diagnosis are increasingly available and informative.[9]

3.Neuroimaging Techniques

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) play a supportive but valuable role in diagnosis. While imaging findings vary by disease stage and subtype, common observations include cerebral or cerebellar atrophy, changes in signal intensity in the thalamus or basal ganglia, and eventually enlarged ventricles. MRS may show altered metabolite levels such as reduced N-acetylaspartate (NAA), suggesting neuronal loss. These evaluations not only support diagnosis but also monitor disease progression over time.[10]

4.Electrophysiological Assessments

Electroencephalography (EEG) often reveals abnormal brain activity even before full clinical symptoms manifest. Characteristic findings may include slow background rhythms, loss of sleep architecture, or generalized epileptiform discharges. These help differentiate NCL from other types of epileptic encephalopathies. In parallel, ophthalmologic examinations — including fundus evaluations, electroretinograms (ERG), and visual evoked potentials (VEP) — detect early visual system involvement, a hallmark of many NCL type.[10]

5.Biochemical and Enzymatic Testing

Enzyme assays serve as useful diagnostic tools in certain NCL subtypes. For example, CLN1 and CLN2 subtypes are caused by deficiencies in PPT1 and TPP1 enzymes, respectively. Measuring these enzyme levels in blood, fibroblasts, or leukocytes can rapidly suggest the subtype and support genetic testing results. These tests are especially helpful in infants with rapidly progressing symptoms when genetic results take time.[11]

6.Tissue Biopsy and Histopathology

Although used less frequently today, ultrastructural analysis of tissue samples — such as skin, conjunctiva, or rectal biopsies — can still aid diagnosis. Under electron microscopy, these tissues exhibit storage material with distinctive appearances like fingerprint profiles, curvilinear bodies, or granular osmiophilic deposits. Such findings are

characteristic of specific NCL subtypes and historically played an essential role before molecular tools were available.[11]

7.Comprehensive Diagnostic Strategy

A modern diagnosis of NCL integrates clinical evaluation, imaging, electrophysiology, enzymatic studies, and genetic confirmation. This comprehensive approach ensures accurate identification of the disease subtype and phase, which is critical for selecting appropriate interventions and providing prognostic information. Misdiagnosis can occur due to symptom overlap with other metabolic or neurodegenerative conditions, which reinforces the need for a coordinated, multidisciplinary diagnostic process.[12]

TREATMENT:

1.Current pharmacological therapy

Any pharmacological treatment strategy for NCLs must be tightly linked to the underlying metabolic abnormality because they are hereditary metabolic illnesses. Therefore, certain pharmacological treatments will only be effective for a certain genetic variant of NCL or for groupings of illnesses that share specific metabolic pathways. There is currently only one clinically licensed medication that has been proven to be effective in treating CLN2 illness, a particular type of NCL 2.[13]

2. Alfa Cerliponase:

Cerliponase Alfa is a recombinant human proenzyme form of tripeptidyl peptidase 1 (TPP1), the enzyme deficient in CLN2 disease, a type of neuronal ceroid lipofuscinosis (NCL). Developed by BioMarin Pharmaceutical Inc. (Novato, CA, USA), it received global regulatory approval in 2017 for the treatment of CLN2 disease.

The medication is administered intracerebroventricularly (ICV) every two weeks via a surgically implanted reservoir under the scalp. After infusion, cerliponase alfa enters neuronal cells through mannose-6-phosphate receptor-mediated endocytosis, is targeted to lysosomes, and undergoes conversion from a proenzyme to its active, proteolytic form. The active enzyme cleaves tripeptides from proteins, reducing the buildup of lysosomal storage material — a hallmark of neurodegeneration in CLN2.

Although seizures were observed during the trial, these were likely due to the underlying disease rather than the drug itself. All adverse events were clinically manageable and did not lead to discontinuation of therapy.[13]

Figure .1 Alfa cerliponase

3. Enzyme replacement therapy (ERT):

Enzyme replacement therapy (ERT) represents a promising approach for treating certain forms of Batten disease (neuronal ceroid lipofuscinoses, NCLs), which are caused by mutations in genes encoding lysosomal enzymes. These mutations lead to enzyme deficiencies that prevent proper breakdown of cellular waste, resulting in toxic accumulation and progressive neurodegeneration.

ERT involves administering recombinant versions of the missing or defective enzyme to patients to restore enzymatic activity. However, Batten disease affects the brain, so the key challenge is delivering the enzyme across the blood-brain barrier (BBB).

ERT generally requires continuous, lifelong administration, as it does not cure the disease but supplies the missing enzyme to reduce cellular damage. Although intravenous enzyme delivery works well for systemic tissues, it is ineffective for neurological symptoms without direct CNS delivery methods such as intrathecal or intracerebroventricular infusion.[14]

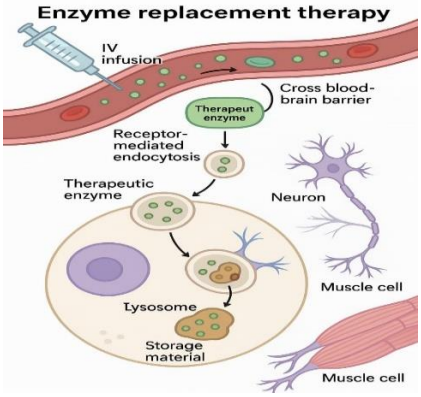

Figure .2 Enzyme replacement therapy

4.GENE THERAPY:

Gene therapy for lysosomal storage disorders works by delivering a functional copy of the faulty gene into affected cells, enabling them to produce the missing enzyme. This is usually achieved using viral vectors, particularly modified viruses like adeno-associated viruses (AAV), lentiviruses, or adenoviruses. In these recombinant vectors, disease-causing viral genes are removed and replaced with

the therapeutic gene, ensuring the virus can no longer replicate or cause illness.

A key principle behind this approach is cross-correction: even if only a small percentage of cells are corrected, they can overproduce the enzyme, release it, and allow nearby cells to take it up, amplifying the therapeutic effect. Unlike traditional enzyme replacement therapy, which is temporary, gene therapy can provide a continuous, long-term enzyme source from within the patient's own cells.[15]

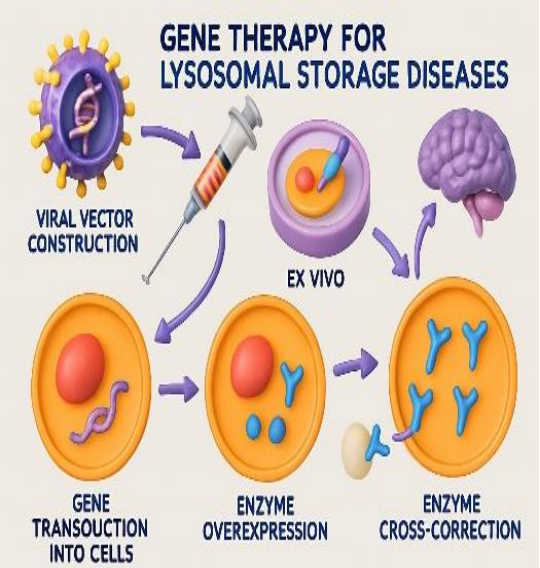

Figure .3 Gene therapy

5.STEM CELL THERAPY:

Stem cell therapy is being explored as a potential treatment for JNCL, aiming to supply the missing enzyme, support cell health, reduce inflammation, and possibly replace damaged neurons. Unlike fully developed cells, stem cells can self-renew and divide multiple times, offering the possibility of longer-lasting effects.

Neural stem cells are a logical choice given JNCL's neurodegenerative nature. In a Ppt1 −/− mouse model, human neural stem cells improved motor function, reduced storage material buildup, migrated within brain tissue, and survived for at least four months. However, the model's short lifespan limited long-term evaluation, and the cells did not fully cure the disease. Researchers suggest that modifying these cells to overexpress the deficient enzyme (palmitoyl-protein thioesterase 1) might improve results.

Hematopoietic stem cells, typically derived from bone marrow or cord blood, have also been used for lysosomal storage disorders. These donor cells produce the missing enzyme and can reduce inflammation, which is an early feature of JNCL. Despite this, bone marrow transplantation has not shown significant success in affected children.[16]

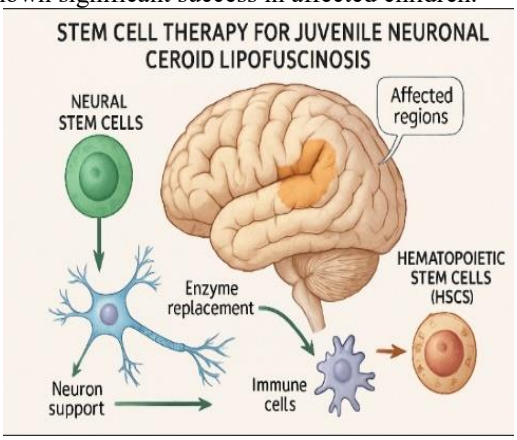

Figure .4 Stem cell therapy for juvenile

Advances in Therapy Development for Batten Disease:

Research into Batten disease has advanced significantly, thanks to accurate animal models that replicate key human disease features. These models have accelerated the study of disease mechanisms and enabled faster testing of potential treatments, even for rare patient-specificmutations. Collaborative efforts between laboratories, clinicians, and researchers have improved patient monitoring tools and pushed several therapies, including cerliponase alfa, into preclinical and clinical stages.[17]

Neuroprotection

In CLN8 mutant mice, intravitreal transplantation of neural or embryonic stem cells reduced storage bodies and increased photoreceptor survival.
Overexpression of ciliary neurotrophic factor in transplanted cells further protected photoreceptors, suggesting neuroprotective factors may slow degeneration in NCLs caused by defective transmembrane proteins.

Immunomodulation

Studies in Ppt1 and Cln3 knockout mice identified CD8+ T cells and sialoadhesin-expressing microglia as contributors to retinal damage.

Blocking these immune pathways — through genetic deletion or drugs like fingolimod, teriflunomide, curcumin, and DHA — reduced inflammation, protected retinal ganglion cells, and partially restored function.

CONCLUSION:

Neuronal Ceroid Lipofuscinosis represents a group of rare, inherited neurodegenerative disorders characterized by the progressive accumulation of autofluorescent lipopigments within neurons and other cell types. These conditions typically manifest with a combination of visual impairment, cognitive

decline, seizures, motor dysfunction, and premature death. Despite differences in genetic subtypes and age of onset, NCLs share a common underlying mechanism involving lysosomal dysfunction and abnormal storage material deposition. Although no curative therapy currently exists, advances in genetic testing, neuroimaging, and molecular research have improved early diagnosis, enabling timely supportive care and, in some cases, access to emerging experimental treatments such as gene therapy and enzyme replacement. Continued research is essential to further understand disease mechanisms, develop effective interventions, and improve quality of life for affected individuals and their families

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