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Review

Experimental therapies in the neuronal ceroid lipofuscinoses☆

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ABSTRACT

The neuronal ceroid lipofuscinoses represent a group of severe childhood lysosomal storage diseases. With at least 13 identified variants they are the most common cause of inherited neurodegeneration in children. These diseases share common pathological characteristics including motor problems, vision loss, seizures, and cognitive decline, culminating in premature death. Currently, no form of the disease can be treated or cured, with only palliative care to minimise discomfort. This review focuses on current and potentially ground-breaking clinical trials, including small molecule, enzyme replacement, stem cell, and gene therapies, in the development of effective treatments for the various NCL subtypes. This article is part of a Special Issue entitled: "Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease)".

1. Overview of the NCLs and the need for treatment

The neuronal ceroid lipofuscinoses (NCLs, Batten disease) are a group of severe primarily autosomal recessive and incurable childhood lysosomal storage disorders (LSDs). They have a combined incidence of 1 in 12,500 live births, affecting males and females with equal frequency [26,74]. There are at least 13 distinct forms of NCL caused by mutations in different genes (Table 1) [27]. The NCLs are among the most common neurodegenerative disorders of childhood; characterised by severe cortical atrophy, visual impairment, seizures, personality and behavioural changes, dementia, and regression in communication and motor skills, culminating in premature death [46].

In young children, NCL results from mutations in genes CLN1 through CLN14, excluding adult onset CLN4, 11 and 13 (NCL mutation database; http://www.ucl.ac.uk/ncl/). Although all childhood forms of the disease share common features, there is also substantial clinical variation based on the affected gene and specific mutations. For example, CLN2 mutations cause typical progressive myoclonus epilepsy, whereas CLN3 mutations produce cognitive and motor decline over most of the disease course with mild myoclonus and epilepsy at later stages [73]. Historically, each mutation in an NCL associated gene was believed to cause the same NCL disease variant, i.e., CLN1 mutations caused infantile NCL, CLN2 mutations; late infantile NCL and so on. However, with advances in genetic screening technology, it has become clear that mutations in an NCL-associated gene may lead to numerous overt NCL disease subtypes. This is especially well characterised in the CLN1 gene, where mutations have been identified in cases of infantile, late infantile, juvenile, and adult NCL [43] with age of onset correlating with level of residual enzyme activity.

Lysosomal diseases affecting the brain present significant difficulties for treatment. Historically trialled techniques, such as peripherally-administered enzyme replacement therapy (ERT), have shown limited success for treating CNS disease. Other strategies, such as chaperone therapy, gene therapy, CNS-administered ERT and cell mediated therapy show promise in their ability to impact upon the CNS (Fig. 1). However these approaches remain largely experimental.

This schematic outlines the experimental therapeutic strategies presented in this review, highlighting the major routes of administration, either direct brain or ventricle injection (grey) or intravenous/intramuscular or oral (blue). Small molecule therapies are administered intravenously, intramuscularly, or orally. The potential for development of orally available formulations makes these therapies non-invasive. Enzyme replacement therapies involve intracerebroventricular administration. Stem cell therapies and gene therapies differ in terms of administration route depending on the type of stem cell or viral vector used. Bone marrow transplants and AAV vectors can be administered systemically, whilst neural progenitor cells and lentiviral vectors are administered directly to the brain or ventricles. AAV therapies are often administered into the CNS.

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t1.1 **Table 1**
t1.2 Summary of the NCL diseases.

t1.3 Disease form t1.4	Clinical phenotype	Presenting symptom	Gene/locus	Protein name	Cellular localisation
t1.5 CLN1	Infantile classic, late infantile, juvenile, adult	Cognitive and motor decline, vision loss	*CLN1, 1p34.2*	PPT1	Lysosomal lumen
t1.6 CLN2	Late infantile classic, juvenile	Seizures and ataxia	*CLN2, 11p15.4*	TTP1	Lysosomal lumen
t1.7 CLN3	Juvenile classic	Visual failure	*CLN3, 16p11.2*	CLN3	Lysosomal membrane
t1.8 CLN4	Adult autosomal dominant	Myoclonic epilepsy	*CLN4, 20q13.33*	DNAJC5	Synaptic vesicles
t1.9 CLN5	Late infantile variant, juvenile, adult	Motor clumsiness	*CLN5, 13q22.3*	Unknown	Lysosomal lumen
t1.10 CLN6	Late infantile variant, adult (Kufs type A)	Motor problems and seizures	*CLN6, 15q23*	Unknown	ER membrane
t1.11 CLN7	Late infantile variant, juvenile, adult	Cognitive and motor decline	*CLN7, 4q28*	MFSD8	Lysosomal membrane
t1.12 CLN8	Late infantile variant, progressive epilepsy with mental retardation	Epileptic seizures	*CLN8, 8p23.3*	Unknown	ER–Golgi membrane
t1.13 CLN10	Congenital classic, late infantile, adult	Seizures	*CLN10/CTSD, 11p15.5*	Cathepsin D	Lysosomal lumen
t1.14 CLN11	Adult	Visual failure and seizures	*CLN11, 17q21.31*	Progranulin (GRN)	Secretory pathway
t1.15 CLN12	Juvenile, Kufor-Raheb syndrome	Learning difficulties	*CLN1/ATP13A2, 1p36.13*	ATPase Type 13A2	Lysosomal membrane
t1.16 CLN13	Adult Kufs type	Dementia and motor disturbances	*CLN13/CTSF, 11q13.2*	Cathepsin F	Lysosomal lumen
t1.17 CLN14	Infantile, progressive myoclonus epilepsy 3	Seizures	*CLN14/KCTD7, 7q11.21*	Potassium channel tetramerist-ion domain-containing protein 7 (KCTD7)	Intracytoplasmic

t1.18 Adapted from www.ucl.ac.uk/ncl.

Currently, no specific clinically available therapies exist for the treatment of NCL. Patient care is focused on minimising symptoms, including seizures, behavioural problems, and depression. Physical and occupational therapies are routinely used to aid in the retention of physical abilities [80]. Some experimental treatments result in mild improvements but none have been able to halt disease progression or significantly improve quality or duration of life.

Therapies relying on the correction or replacement of the faulty protein require expression of the corrected protein to be sustained within the brain, without any associated toxicity, for long-term treatment. These prerequisites represent a formidable challenge for therapy design. However, LSD therapy generally requires an achievable 5–15% restoration of normal enzyme activity to restore normal function [18,48, 79].

This review focuses on recent developments in the search for effective NCL treatments. The studies outlined in this review do not provide a comprehensive list of all current investigative therapies but rather highlight promising examples in each major category of clinical investigation.

2. The importance of animal models in therapeutic development

2.1. Small animal models

Mice have been the primary model organism for investigating NCL pathogenesis. Currently, there are ten mouse models, either genetically developed (CLN1/PPT1 (two models), CLN2/TPP1, CLN3 (three models), CLN5, and CLN10/CTSD), or spontaneous naturally-occurring models (CLN6/nclf and CLN8/mnd) thus representing each of the major forms of human NCL as well as a number of variant forms [15]. Each model exhibits key pathological features of their human counterparts, including autofluorescent cellular storage and progressive neurodegeneration [15]. Murine studies have focused on behavioural, pathological, cellular, and molecular abnormalities, as well as the development and

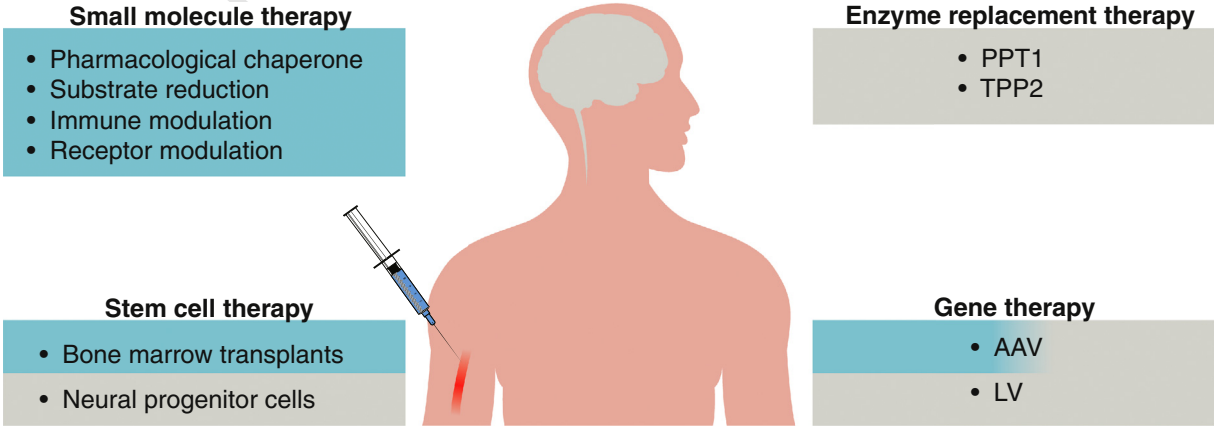

Fig. 1. Experimental therapies target sites for administration.

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