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Current Therapies for Neuronal Ceroid Lipofuscinosis

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Abstract

The neuronal ceroid lipofuscinoses represent a group of inherited neurodegenerative and life-limiting disorders that affect children with at least 13 identified variants. These diseases share common pathological characteristics including motor problems, vision loss, seizures, and cognitive impairment. Currently, no form of the disease can be treated. This review focuses on current therapies including enzyme replacement therapies, gene therapies targeting the brain and the eye, cell therapies, and pharmacological drugs that could modulate defective molecular pathways. The first approved treatment is an intracerebroventricularly administered enzyme for neuronal ceroid lipofuscinosis type 2 disease that delays symptom progression. Efforts are underway to make similar progress for other forms of the disease.

Keywords: Neuronal Ceroid Lipofuscinosis; Enzyme replacement therapy; Stem cell therapies; Bone marrow transplantation; Haematopoietic stem cells; Gene therapy

Abbreviation: NCLs: Neuronal ceroid lipofuscinoses; ERT: Enzyme replacement therapy; TPP1: tripeptidyl-peptidase-1; CSF: Cerebrospinal fluid; BMT: Bone marrow transplantation; HSC: Haematopoietic stem cell transplantation; AAV: Adeno-associated viral

Introduction

The neuronal ceroid lipofuscinoses (NCLs), often collectively called Batten Disease, include a group of rare but fatal inherited lysosomal storage diseases. They result from monogenic mutations in 13 different genes, underlying the various known human forms of the disease [1]. This striking molecular genetic heterogeneity contrasts with the consistent morphological phenotype. In fact, the NCLs are clinically and genetically heterogenous with more than 14 distinct subtypes described with different age of onset, rate and characteristics of progression [2,3]. Nevertheless, they all share a broadly common clinical presentation characterized by seizures, dementia, progressive loss of vision, mental and motor deterioration, and eventually premature death due to a progressive and selective loss of neurons, particularly in the cerebral and cerebellar cortex and, less constantly, in the retina. Histopathologically, the NCLs are defined by the intracellular accumulation of autofluorescent lipopigments in nerve cells mainly, and to a lesser extent in all tissues throughout the body [3-6].

Each form of NCL is caused by a different gene mutation and protein deficiency, making the discovery and use of new therapies difficult [1,3,7]. In addition, lack of knowledge of the exact pathophysiology of NCLs makes it difficult to conceive a disease-modifying treatment [7,8]. In fact, the treatment of lysosomal diseases affecting the brain raises significant difficulties, with many approaches remaining experimental. Small molecule therapy, enzyme replacement therapy (ERT), stem cell and gene therapy represent promising therapeutic schemes proving positive in animal models [9,10]. Despite advances and development in experimental and clinical schemes, the NCLs remain a therapeutic challenge: currently, no curative therapy exists for the treatment of NCLs. Many of the pharmacological treatments for NCLs are palliative, focused on minimizing or controlling clinical symptoms without targeting the underlying cause [9-19]. This review provides a summary of the current state of knowledge of the therapeutic approaches explored in the treatment of this severe devastating disease.

Management strategies in NCLs

Extensive studies have been conducted in developing new therapeutic approaches in treating different forms of NCLs. However, no treatment is currently available to change the outcome of the disease. The standard of care is based on minimizing symptoms, including seizures. Additional supportive treatment includes physical and occupational therapies, speech therapy, and feeding; these measures are routinely used to help in retention of physical abilities [9-13].

Supportive treatment

The general management of the NCL disease is guided by the principle of palliative care with the purpose of improving the quality of life and the integration of the patient into his community. This is usually achieved with a multidisciplinary team including physicians, nurses, therapists (physical, occupational, and speech), dietitians, psychologists, social workers, and counselors. Goals and interventions will change along the evolution and progression of the disease, with ongoing assessments and subsequent modifications of the treatment plan [10-12].

Vision: Visual impairment is usually the first symptom of NCL, manifesting as impaired focal vision, nyctalopia, nystagmus, photophobia and color vision deficiency, eventually progressing into blindness [20]. Regular eye examination is recommended. No interventions are actually available to treat these ophthalmological manifestations. Hence, it is also important that the patient learns to train the other senses to orient himself, especially hearing which isn't affected by the disease. Introducing various learning and educational aids gives assistance with the integration of the patient in school or at home [21,22].

Epilepsy: All patients with NCL will develop epilepsy, with different age onset and different type pf seizures, including myoclonic, tonic, atonic, absence, and tonicoclonic [23,24]. Prophylactic anti-epileptic treatment is not recommended. Once the patient presents with a first episode of epileptic seizure, therapy is started [25].

Common first-line options include valproate, benzodiazepines and lamotrigine. Combination therapy including piracetam, levetiracetam, topiramate and zonisamide, may be necessary to control seizures. Carbamazepines, lamotrigine, oxcarbazepine, GABA analogues (gabapentin, vigabatrin and pregabalin), phenytoin, and fosphenytoin should be avoided, as they may exacerbate myoclonus and myoclonic seizures [26,27]. The goal of seizure management is to achieve sufficient seizure control to support function (social interactions, mobility, fall prevention), while balancing the side effects (e.g., excessive sedation). The expert consensus is that seizure freedom is not a realistic goal; rather, the aims are to minimize the impact of seizures on the child's well-being, diminish the most disabling and life-threatening seizures, and maintain quality of life. Medication regimes should be re-evaluated periodically, particularly when there is a new emerging symptom or a change in seizure pattern. For appropriate medication selection, it is important to distinguish epileptic seizures from nonepileptic events, including movement disorder (e.g., dystonia), pain, boredom, and fear [28]. Some have tried a ketogenic diet in the treatment of drug-resistant seizures in NCL2 disease and other NCLs. Adherence to the diet can be challenging, although implementation is easier when a child is tube-fed. Any child on a ketogenic diet should be closely monitored for side effects and possible complications (e.g., constipation, kidney stones, growth retardation) [29].

Motor function: Rigidity, hypokinesia, shuffling, stooped gait and poor balance are extrapyramidal symptoms that most NCLs patients develop throughout the evolution of the disease [30]. Coordination problems as well as involuntary movements are also observed. For this reason, the child and his family should be put in contact with a physical therapist as soon as the diagnosis has been confirmed. The physical therapist plays an important role in assessing the patients' skills, including moving, dressing and undressing, eating, personal hygiene, and toilet situations. The target of physical therapy is to maintain posture and range of motion, by stimulating specific motor skills and adopting measures to maintain overall function at the highest possible level, for as long as possible. Activities that involve large muscle groups are recommended. A small study from Finland showed that treatment with levodopa had a positive effect on extrapyramidal symptoms [31].

In late-stage NCL, complex movement disorders such as myoclonus, chorea, ataxia and dystonia, may be observed. A rare, but potentially life-threatening complication is status dystonicus, often triggered by infection, surgery, stress, pain and medication, especially Valproate. Treatment includes benzodiazepines and clonidine, and intrathecal Baclofen injections may be indicated. Valproate, a known risk factor of status dystonicus, should be discontinued [28].

Sleep: Sleep disorders are very common among patients with NCL [32]. Poor sleep quality can greatly impair the quality of life of affected children and their families. Moreover, poor sleep can adversely affect seizure control and exacerbate behavioral and cognitive impairments. In working to improve sleep patterns, behavioral strategies (e.g., good sleep hygiene), environmental strategies (e.g., music, massage, weighted blankets), and medications (e.g., melatonin, chloral hydrate, clonidine, pregabalin) may be helpful in treating sleep disorders [33]. Many report the positive effects of melatonin, either as "regular" melatonin, and/or in a time-release formulation [34,35]; "regular" melatonin initiates sleep, and time-release melatonin maintains sleep.

Pain: Many behavioral changes might be triggered by discomfort and pain. Body and extremity pain, stomach and head pain are mostly reported [36]. The treatment of pain in NCL patients raises many challenges among them because the communication problems and functional impairments make it difficult to determine the location of pain and its severity, as well as the distinction between pain and other forms of discomfort. Pain is believed to be central, not peripheral, making treatment more challenging [37]. However, the standard principles of pain management are applicable: Non-opioid analgesics, in combination with neuroleptics, or opioids [38]. Pain may be caused by spasms and/or rigidity. These patients may benefit from baclofen. Supportive care including positioning aids, weighted blankets, physiotherapy, and heat, endorse medical treatment [11,12,29,33].

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Respiration: As the disease progresses, patients with NCL may experience short respiration and a reduced ability to cough. Some drugs may stimulate mucus production. It is recommended to sleep on the side and not on the back with frequent change of position. At this stage, the physical therapist should focus on clearing the patient's airways. Cough assist devices may be considered [39,40].

Psychiatric symptoms: Anxiety, aggression, depression, hallucinations and psychoses affect the patient's quality of life, as well as his family's. They may be related to communication problems, difficult social interaction, and cognitive impairment [41]. It is essential to assess and acknowledge the psychiatric symptoms, in order to implement treatment when indicated. There is a wide range of the psychiatric symptoms, complicated by polypharmacy considerations, making the treatment very challenging. Citalopram and Escitalopram may be effective against affective symptoms, with few side-effects. Lamotrigine has a mood stabilizing effect. Risperidone has been used to treat psychosis with good results. Experience with aripiprazole is limited, but promising, especially for organic psychoses. Clonazepam has been used with good results [42].

Nutrition: Regular assessment and monitoring of NCLs patient's nutrition is a must, since malnutrition and dehydration may aggravate the patient's general condition, and his neurological functional impairment. In fact, eating disorders can manifest as swallowing disorders, reduced appetite, nausea, gagging or frequent respiratory infections. Cardio-respiratory failure and sepsis secondary to aspiration pneumonia are common causes of death. Hence, managing secretions by proper suctioning, oral care, physiotherapy, and anticholinergic treatment, is critical [11,33]. Monitoring the patient's weight, as well as screening for vitamin deficiencies are important. Occupational physical therapy, food texture adjustments, tube feeding, and gastrostomy are all part of a nutrition plan to help maintain a certain level of function, or to assist the patient during his disease's progression [43].

Constipation is a common complication; it causes pain and exacerbate seizures and movement disorders. Preventive measures include adequate liquid intake, increasing fiber intake, stool softeners, dysmotility agents, and/or laxatives.

Cognitive impairment: Short-term memory impairment and learning difficulties may be early signs of cognitive impairment that eventually develop into dementia [44,45]. Patients with NCL have mental retardation and do not follow the standard learning curve; in addition, they show progressive dementia and lose acquired knowledge and skills. Daily physical and cognitive stimulation contribute to delay progression of the disease, as well as tailored program adjustments at school and at home [46].

Complementary therapies, such as hippotherapy, hydrotherapy, and music therapy, may be considered for anxiety, pain, and boredom, social interaction and enjoyment [45,46].

Medical treatment

The genes associated with NCL represent a unique combination of secreted, transmembrane, and cytosolic proteins, complicating the development of a specific treatment. Thirteen genes have been linked to NCLs to date (termed CLN1–CLN8 and CLN10–CLN14). A putative CLN9 has not been identified yet. Only six of these disorders are known to involve a secretable protein. The other 7 involve mutations in a transmembrane protein, a cytosolic enzyme, or a chaperone. Thus, cross-correction, which is a process referring to the alleviation of the cell's biochemical deficiency when an enzyme-deficient cell takes up the secreted protein, will not always be efficacious. In fact, only for NCLs including a soluble enzyme, cross-correction can potentially be achieved: Delivery of recombinant protein (enzyme replacement therapy, ERT), transplantation of healthy cells or cells overexpressing the affected enzyme, or gene therapy providing a healthy copy of the gene. Each method has its pros and cons [10,11,29,33].

Pharmacological approaches

Many of the pharmacological treatments for NCLs are palliative, focused on minimizing clinical symptoms [7]. Animal models and clinical observations using anti-inflammatory medication, molecular chaperones, enzyme mimics, Bcl-2 upregulators, NMDA and AMPA receptor antagonists, calcium-channel blockers, immunosuppressants, and antioxidants, have not shown clinically meaningful benefits [13,47,48]. Applying a classic drug discovery approach (from disease mechanism to target to drug) to the NCLs is challenging because little is known about which intracellular pathways are affected and if they are good candidates for drug therapy. In addition, drugs need to cross the blood–brain barrier to reach the brain. Molecular pathways common to neurodegenerative diseases (neuroinflammation, impairment of autophagy, defects in endocytic trafficking, mitochondrial alterations, or impairment in calcium homoeostasis) may be promising targets and could be entry points to cell-based phenotypic screening approaches [49,50].

Enzyme replacement therapy (ERT)

The lysosomal enzyme tripeptidyl-peptidase-1 (TPP1) is a soluble lysosomal enzyme that plays an important role in protein catabolism. Like other soluble lysosomal enzymes, TPP1 is localized within lysosomes, discharged from cells and taken back up via cell surface receptors that recognize the mannose 6-phosphate moieties common to many lysosomal enzymes. TPP1 is synthesized as a glycosylated proenzyme that is activated by proteolytic cleavage of an N-terminal fragment after incorporation into lysosomes [51]. TPP1 proenzyme supplied exogenously to cells is taken up via cell surface mannose 6-phosphate receptors and is transported via the endosomal system to lysosomes where it is activated [52,53]. Therefore, CLN2 disease is amenable to TPP1 enzyme replacement

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therapy. Because large molecules such as TPP1 cannot cross the blood-brain barrier, delivery of the enzyme to the brain has been achieved through administration of TPP1 pro-enzyme by infusion into the cerebrospinal fluid (CSF) [54,55]. This route of TPP1 administration results in widespread distribution of the active enzyme in many structures of the brain and in reduction in the accumulation of neuronal lysosomal storage material that is characteristic of this disease [55]. Biweekly enzyme infusions delay the onset and progression of neurologic signs and brain atrophy and improve cognitive function [56].

Brineura® is an enzyme replacement therapy. Its active ingredient (cerliponase alfa) is a recombinant form of human TPP1. Intracerebroventricularly administered enzyme replacement therapy (Brineura®) in CLN2 disease is the first treatment approved by the FDA (Food and Drug Administration) and EMA (European Medicines Agency), and treatment is expected to be needed throughout the patient's life [16,57]. The deficient enzyme TPP1 is administered over 4 h as a recombinant proenzyme via a Rickham or Ommaya reservoir into the lateral cerebral ventricles at a dose of 300 mg of protein every 2 weeks into the brain of children with CLN2 disease [57]. Long-term safety and efficacy were evaluated in an open label, dose-escalation study (NCT02485899). The patients who had the highest initial baseline scores maintained these for the duration of the study, indicating that starting treatment early is likely to be most beneficial. A second study (NCT02678689) has begun to monitor the effects of beginning treatment earlier in the disease course in another group of patients. The cross-corrective approach of enzyme replacement therapy depends on delivered enzyme being recognized by receptors on the surface of cells, taken into the cell and trafficked to the lysosome, and the same enzyme replacement approach might be suitable for other types of NCLs caused by mutations in lysosomal enzymes (CLN1/palmitoyl protein thioesterase [PPT1], CLN2/TPP1, neuronal ceroid lipofuscinosis type 5 [CLN5], CLN10/CTSD, and neuronal ceroid lipofuscinosis type 13 [CLN13]/cathepsin F [CTSF]). The safety and effectiveness of Brineura® have not been established in patients less than 3 years of age. The therapy could be delivered frequently and periodically as a recombinant product, or alternatively could be produced and released continually within the body following gene therapy or cell-based therapy [13].

Stem cell therapies

Stem cell therapies, including bone marrow transplantation and stem cell transplantation, depend on the rationale that the transplanted stem cells from a healthy donor will migrate to the CNS, provide a source of functional protein/enzyme and/or differentiate into the appropriate tissue type. Stem cell therapy offers the potential to regenerate lost tissue alongside neuroprotection - a major advantage for diseases that have often progressed significantly before effective diagnosis. With established safety profiles and success in numerous animal models, stem cell therapy provides an attractive avenue in NCL treatment development [13].

Neuronal stem cells: The advantages provided by cell therapy are the possibility of a long-term engraftment as well as the delivery of a variety of therapeutic factors. On the other hand, it needs immune suppression; in addition, cells do not spread efficiently, and this is only effective for NCLs involving secreted proteins [18].

Bone marrow transplantation: The first use of bone marrow transplantation (BMT) to treat NCL was performed in a canine model with successful reconstitution of the hematopoietic system without alteration of the disease progression [58]. A similar therapy was also evaluated in the South Hampshire sheep model, without changing the course of the disease. BMT did not significantly alter the disease course, probably because of the absence of cross-correction for some forms of the disease and slow engraftment into the CNS and low levels of enzyme expression by donor cells for others. Therefore, BMT is not considered beneficial to patients59. Positive therapeutic effects on motor performance and longevity are significant when gene therapy is combined with BMT [59].

Haematopoietic stem cells: Haematopoietic stem cell transplantation (HSC) is recommended for selected patients with lysosomal storage diseases that affect the brain and are caused by deficiencies in soluble lysosomal enzymes [60]. However, this approach showed limited or no success. Haematopoietic stem cell transplantation was performed to normalize PPT1 activity in NCLs patients. This was based on the hypothesis that donor derived HSCs are precursors to microglial cells in the CNS, thereby allowing HSCs to act as a carrier of the correct enzyme for CNS delivery. PPT1 activity was normalized in circulating peripheral leukocytes, but the activity of PPT1 in the cerebrospinal fluid remained low in all patients, except one who showed relatively normal levels five years post transplantation [61].

Gene therapy: A promising treatment option for all forms of NCLs is viral-mediated gene therapy in which a cDNA encoding wildtype protein (e.g., CLN2) is packaged into lentiviral or adeno-associated viral (AAV) particles. These are then injected into the CNS of patients in the hope that the corrected version will be expressed in the transduced cells, thereby restoring protein function. Viral mediated gene therapy relies on a small population of cells receiving the normal copy of the gene, then over-expressing the gene product and secreting the protein for uptake by neighboring cells: a process known as cross-correction [62]. Gene therapy studies using viral vectors to introduce a healthy NCL gene into animal models for NCLs have mainly focused on targeting the brain for diseases caused by lysosomal enzyme deficiencies, which provide the advantage of cross-correction [63].

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Initial forays into gene therapy provide only marginal improvements, either due to low transduction or poor spread. Newer gene therapy vectors, in contrast, show much promise, not only for soluble proteins but for transmembrane proteins as well. The relative success of gene therapy versus cell therapies is due to its ability to drive high levels of enzyme expression as well as using more distributed delivery methods: intracerebroventricular injection and intravenous delivery. The gene therapy offers the advantages of long-term expression, the possibility of providing wide-spread transduction including the eye and the brain. But it is likely to need immune suppression at the time of treatment and neutralizing antibodies may be problematic in elderly patients [57,64]. For NCLs deficient in membrane-bound proteins, it will be more difficult to develop a gene therapy, as a significantly higher proportion of cells must be transduced. Current pre-clinical and clinical trials of gene therapy in NCLs use adeno-associated viral or lentiviral derived vectors for gene delivery [63].

Cell-based therapy: The goal of cell-based therapy lies in its ability to replace cells lost in advanced disease. However, this seems unlikely to happen because the therapy is not capable of replacing enough cells in the brain [65]. The aim of stem cell trials for the NCLs is to preserve remaining function by providing cells that secrete a missing lysosomal enzyme [65].

These cell factories will either need to be located where the enzyme is needed (in the brain or eye) or the secreted enzyme will need to be transported in the blood and taken up by distant tissues and will need to cross the blood–brain barrier to reach the brain. Ideally, such cells would be derived from an individual patient, manipulated to produce the required product by an introduced vector or by correcting the cell's own genome, and then being reintroduced. A phase 1 trial established the safety of neuroprogenitor cell implantation in six patients with advanced CLN1 or CLN2 disease. There was no clinical benefit to this trial, perhaps because donor engraftment was low, and migration limited [67]. There is an ongoing phase 1 trial (NCT01586455) testing whether transplantation of human placental-derived stem cells benefits patients with a range of diseases including NCLs.

Conclusion

In conclusion, a multidisciplinary approach to management is essential for optimal care and quality of life of NCL patients and families. Effective strategies currently exist to manage many of the symptoms of NCL disease. Numerous therapeutic strategies are currently explored as treatment options for NCLs. Cerliponase alfa is presently the only one clinically approved drug that has been shown to effectively attenuate the progression of a specific form of neuronal ceroid lipofuscinosis, CLN2 disease. Future works should aim to develop therapies that effectively attenuate neurodegeneration in the brain in addition to retinal degeneration.

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