The Neuronal Ceroid Lipofuscinosis Disorders (for health workers)

The neuronal ceroid lipofuscinosis (NCL) disorders are a group of genetically inherited lysosomal neurodegenerative diseases characterized by the intracellular accumulation of autofluorescent lipopigment storage material that leads to progressive neurologic degeneration in all age groups. The clinical course includes progressive cognitive failure (dementia, encephalopathy), seizures which often are myoclonic, progressive visual failure, and often movement abnormalities that are often ataxic or extrapyramidal.[1]

These disorders are the most common reason for an inherited childhood neurodegenerative disease and are increasingly recognized in late-onset or adult-onset forms. Prevalence is estimated widely from 1.5 to 9 per million, and incidence, which varies among geographic ethnic regions, has been reported from 1.3 to 7 in 100,000 live births. This group of genetic disorders has an autosomal recessive inheritance, except for the rare autosomal dominant adult-onset disorder.[1,2] There is increasing recognition of a broad clinical phenotypic scope of each of these genetic forms, with reports of increased intrafamilial variability and atypical cases. It is presumed that there are important epigenetic modulators to be identified, that directly or indirectly affect clinical expression, within any one of these genetically defined disorders.

Classification of neuronal ceroid lipofuscinoses (NCLs)[3-8]

Phenotype	Age of onset	Gene	Chromosome	Protein	Ultrastructure
CLN1	Infantile, but also late-infantile, juvenile, and adult	*PPT1*	1p32	PPT1	GRODS
CLN2	Late-infantile, but also juvenile	*TPP1*	11p15	TPP1	Curvilinear profiles
CLN3	Juvenile	*CLN3*	16p12	Lysosomal transmembrane protein	Fingerprint profiles
CLN4	Adult (Parry)	*DNAJC5*	20q13.33	Cysteine string protein	Rectilinear profiles
CLN5	Late-infantile (Finnish variant)	*CLN5*	13q22	Soluble lysosomal protein	Rectilinear profiles, curvilinear profiles, fingerprint profiles
CLN6	Late-infantile, adult (Kufs type A)	*CLN6*	15q21	Transmembrane protein of ER	Rectilinear profiles, curvilinear profiles, fingerprint profiles
CLN7	Late-infantile, Turkish variant	*MFSD8*	4q28	MFSD8, lysosomal membrane protein	Fingerprint profiles
CLN8	Late-infantile, Northern	*CLN8*	8q23	Transmembrane protein of	Curvilinear profiles

	epilepsy			ER	
CLN9	Proposed, but not confirmed	*CLN9*			
CLN10	Congenital, juvenile	*CTSD*	11p15	Cathepsin D	GRODS
CLN11	Adult	*GRN*	17q21	Progranulin	Fingerprint profiles
CLN12	Juvenile	*ATP13A2*	1p36	Kufor-Rakeb syndrome	"Whorled lamellar inclusions"
CLN13	Adult (Kufs type B)	*CTSF*	11q13	Cathepsin F	Fingerprint profiles?
CLN14	Infantile	*KCTD7*	7q11	Potassium channel tetramerization domain-containing protein 7	Variable

ER: endoplasmic reticulum; GRODS: granular osmiophilic deposits.

Although the classic clinical features if all present (encephalopathy/dementia, seizures, visual loss, and/or movement disorder) point to an NCL disorder, there is a broad and important differential diagnosis that needs consideration. This may, in fact, account for the sometimes long delay in diagnosis. There are many NCL masqueraders, particularly in the early stages of the disease when only a single clinical feature is evident. [1]

Pathology

Early pathologic description of storage material in patient tissues documented an autofluorescent, waxy, dusky lipid accumulation in neuronal endosomes, reminiscent of the ageing pigment lipofuscin. By electron microscopy, these pathologic hallmarks are membrane-bound (lysosomal) inclusions, most prominently seen in neurons but recognizable in many cell types. Common sites of biopsy and inclusion identification include the skin, conjunctiva, and/or rectal tissues. Inclusions can appear as granular osmophilic deposits (GRODs), curvilinear (CL), rectilinear (RL), or as more crystalline fingerprint bodies (FP). Unique to juvenile CLN3 disease are the vacuoles seen by EM in circulating lymphocytes. These ultrastructural crystalline structures have remained an important distinguishing feature of the NCL disorders. Identification of this storage material, by biopsy and EM, strongly suggests an NCL diagnosis.

Pathobiology

The pathobiologic details are still being elaborated. In the NCL disorders, there is protein deficiency, pathway blockade, and metabolic substrate accumulation, as well as downstream functional deficiencies and potentially detrimental cellular compensatory changes, which may lead to cellular pathobiology and the resultant clinical phenotypes. Active research is ongoing to elucidate the protein functions, the substrates

and interacting partners of these proteins, the mechanisms of neuronal death, and the relationships between the various NCL proteins. Affected intracellular pathways involve at least the endosomal-lysosomal autophagy degradation pathways, the synaptic trafficking and function pathways, and the neuroinflammation/immune regulation pathways.[1]

CLN1 and CLN2 diseases are caused by deficiency and metabolic block of classic soluble lysosomal hydrolases, PPT1, and TPP1, respectively. Mitochondrial abnormalities in the NCL disorders have also been described, including abnormal mitochondrial ATP synthase regulation, mitochondrial structural changes, and altered respiratory chain function, as well as decreased cellular ATP production and neuronal survival in the context of oxidative stress.[1]

CLN5 glycosylation defects have been noted and may be further evidence of the widespread and complex secondary cellular pathobiology. Current studies, focusing on the complex endosomal-lysosomal autophagy pathway, continue to highlight potential network disruptions in these disorders. Specific gene mutations may trigger distinct processes that converge on a common cellular pathway as has been shown in CLN6 and CLN3 murine models. Alternatively, there may be direct and specific interactions between these proteins as has been documented between CLN2, CLN3, and CLN5. These studies speak to the nonindependent nature of these pathways and serve to challenge or models of pathobiology and therapeutic intervention.[1]

NCL Models

Animal

Animal models, both naturally occurring and those produced by genetic technologies, have been utilized in the pathobiologic study of many NCL disorders. Canine NCL disorders have been diagnosed in at least 18 breeds and are potentially important models of human disease (www.caninegeneticdiseases.net/CL_site/basicCL.htm). Natural NCL disease has also been identified in mice: CLN6(nclf) corresponding to CLN6 human disease; a CLN8(mnd) model; and a Cathepsin F (CTSF) mutant mimicking human disease. The Ctsf-null mice have a similar progressive neurologic disorder to that seen in the human disease with difficulties of gait, progressive defects in motor coordination, as well as tremor and spasticity. At postmortem, examination showed neuronal loss and gliosis of the CNS and spinal cord, as well as autofluorescent FP inclusions in both neurons and glia.

The study of these models has been directed to the careful and comprehensive evaluation of the pathologic nature of these disorders as well as the longitudinal study of disease progression and biological consequences. More recently, the generation of iPSCs from human disease subjects and the reprogramming of these into neural progenitors have opened studies into the effects of the primary genetic mutation as well as other epigenetic factors. These models have the potential to identify therapeutic agents and serve as a foundation for human clinical trials.

All NCL genes identified in animal models to date are homologous to human NCL genes, and this has allowed a more direct correlation and fruitful study. Although the phenotypic features in these models may not be exactly parallel with those seen in human disease, the ability to study cellular biology is invaluable.

Human Models

The technologies for generating iPSCs lines from human fibroblasts and the techniques being developed that allow for reprogrammed cell-phenotypic differentiation have invaluably changed the ability to make human model systems for these disorders. A recent report of success in generating human iPSCs as models of CLN1 and CLN3 has been reported and allows for the study of the endocytic pathway. Because the genetic background of the iPSCs and differentiated cell types maintain that of the original patient, modelling and biological study will presumably reflect more accurately the complex pathobiology of these disorders. These model systems also allow for high-throughput pharmacologic screening of potential pathobiological-modifying therapeutic agents. It is the hope that as these pharmacologic agents are identified in cell culture model systems derived directly from patients and carrying the complex genetic background which is relevant to the human disease they will be quickly available for clinical trials. New protocols for tissue-specific genome engineering (CRISPR/Cas9) hold great promise for both study of human disease but also for therapy.

Clinical Trials[1]

Therapeutic approaches to the NCL disorders have included enzyme replacement, gene and stem cell delivery, and pharmacologic therapies. An initial trial using stem cells able to produce TPP1 and PPT1 was used in direct CNS parenchymal injection in a small number of CLN2 patients. No subsequent stem cell therapeutic approach has been again reported.

After successful rodent and nonhuman primate studies showing long-term TPP1-expression and reduced brain pathology in a mouse model of CLN2 disease, an AAV2-mediated CLN2 gene transfer by direct intracranial injection was developed for humans. This protocol showed a slowing of disease progression using a modified Hamburg scale. In the CLN1/CLN2 disease, using a gene therapy approach with a second-generation adenovirus vector (AAVrh.10hCLN2;), a dose of 1.8×10(12) GC of AAVrh.10hCLN2 was administered to the CNS of 8 African green monkeys. The vector-treated monkeys did not differ from controls in any safety parameter except for mild to moderate white matter oedema and inflammation localized to the administration sites of the vector. There were no clinical sequelae to these localized findings. TPP-I activity was >2 SD over the background in 31.7±8.1% of the brain at 90 days. These findings establish the dose and safety profile for human clinical studies for the treatment of LINCL with AAVrh.10hCLN2.[9] Some researchers have suggested that combination therapies may be more successful.

Pharmacologic trials have included diet manipulation in CLN3 disease using human patient-cultured lymphoblasts without clear success. Dietary polyunsaturated fatty acid supplementation in utero and throughout life did not alter the clinical or pathologic course of disease in CLN8(mnd) mice. Dietary

administration of carnitine has slowed disease progression in murine and canine models, raising the possibility of use in human disease. More recently, cystagon and N-acetylcysteine have been studied together in human CLN1 disease patients with the report of delay in degeneration to an isoelectric EEG, depletion of granular storage material, and subjective clinical benefit. In human CLN2 nonsense mutation-associated fibroblasts, gentamicin promotion of read-through has been reported with variable success. The role of nonsense-mediated decay (NMD) in the NCL disorders suggests inhibition of NMD as a potential therapy. The development of a mouse model for CLN1 disease with a novel stop mutation may serve to further explore the therapeutic potential of read-through drugs to increase PPT1 enzyme production and activity. Researchers at the University of Rochester have an ongoing trial using mycophenolate (CellCept) in CLN3 disease, founded on the preclinical work identifying immunologic markers in the CNS and the experimental suggestion that inflammation may play a role in at least some component of the human pathologic process underlying juvenile Batten disease. Partial correction of brain lysosomal storage in a mouse model of CLN3 using AAVrh.10hCLN3 holds promise for future human trials.[1]

Diagnosis

For the child presenting with developmental regression or concern for neurodegenerative disease, efficiently achieving an accurate, early diagnosis, if possible, is important for guiding treatment decision-making, anticipatory guidance, family planning, bringing to a close the diagnostic odyssey, connecting to disease-specific support groups, and determining eligibility for clinical trials.[2]

Several clusters of signs and symptoms suggest an NCL diagnosis; Developmental regression affecting infants and children, Refractory epilepsy plus neurologic symptoms at any age, Vision loss (especially retinopathy) plus neurologic symptoms at any age, Progressive ataxia with cerebellar atrophy at any age.

It is important to include CLN2 disease in the growing list of treatable neurologic disorders of childhood, making ascertainment of an NCL diagnosis, when present, critically important.

Some children with NCL are first diagnosed with autism spectrum disorder, and some children with an NCLdiagnosis have hand stereotypies reminiscent of Rett syndrome or FOXG1 disorders.[2]

When infants or children present with global developmental delay or developmental regression, early brain imaging is suggested, especially in the setting of seizures, abnormal neurologic examination findings, and/or macrocephaly or microcephaly. Brain magnetic resonance imaging(MRI) is likely to have a greater diagnostic yield. While imaging alone is nonspecific and is insufficient for establishing an NCL diagnosis, it may provide important clues that suggest a neurodegenerative condition is present, especially when cerebral and cerebellar atrophy are observed, which has been reported in most NCLs. Of note, while diffuse cerebellar atrophy is an eventual universal finding in infantile-onset CLN1 disease, conventional brain MRI may be normal in children with CLN3 disease younger than age 10 years; cerebral atrophy becomes evident in adolescence followed by cerebellar atrophy. Thalamic T2 hypointensity has been reported in several

NCLs including CLN1, CLN2, CLN3, CLN5, and CLN7; this finding may also be observed in other neuronal lysosomal storage diseases

The NCLs are primarily considered grey matter disorders, but white matter abnormalities have been described in CLN2 and CLN3.[2]

Enzyme testing, once a first-line diagnostic test for CLN1 and CLN2 disease, increasingly represents a secondary line of diagnostic or confirmatory testing. Similarly, tissue biopsy with electron microscopic analysis was once considered first-line in the diagnostic approach for all NCLs, but it, too, now represents a means of confirming or excluding an NCL diagnosis when genetic testing results are uncertain or inconclusive. Tissue sampling from the skin is the most common; conjunctiva and rectal tissues constitute additional sources.[10]

The diagnostic approach has changed through the years and will continue to evolve as panels and whole exome/whole genome technologies and bioinformatics improve. As a general approach, when a patient presents with refractory epilepsy and/or signs/symptoms concerning for an NCL disorder, performing an epilepsy panel that has several NCL genes included, is a good strategy. Whole exome sequencing (WES) plays an increasingly prominent role in NCL patient identification, particularly in atypical cases. [1]

CLN1 (PPT1; OMIM #256730)

The CLN1 gene codes for palmitoyl-protein thioesterase-1 (PPT1), a soluble lysosomal protein; pathogenic variants in CLN1 are generally associated with classic infantile NCL.The typical presentation is of an infantile-onset disorder presenting at around 10 to 18 months of age and characterized by profound neurodevelopmental regression with motoric deterioration, seizures, and visual failure. The course of the disease is rapidly progressive and leads to an early vegetative state with prominent spasticity. The children usually die within the first 10 years of life.[1,2]

Some pathogenic variants in CLN1 can cause later onset disease with more extended disease courses. All forms of childhood-onset CLN1 disease progress to premature death, though typically, the later the symptom onset, the more protracted the course. Late infantile CLN1 disease begins between two and four years of age. There is visual and cognitive decline followed by the development of ataxia and myoclonus. Juvenile CLN1 disease, also referred to as "juvenile NCL with granular osmiophilic deposits," typically presents between the ages of 5 and 10 years, with cognitive decline followed by epilepsy, motor decline, and vision loss.

Clinical Trials

A phase I study of the safety and preliminary effectiveness of implanting human CNS stem cells in patients with PPT1 deficiency was completed. These stem cells had been shown to produce the PPT1 and TPP1 enzymes. In mice missing the PPT1 enzyme, human CNS stem cells had been shown in the brain to increase

the amount of this enzyme, reduce the amount of abnormal storage material, and prevent the death of some neurons. The study failed to show efficacy in human trials. ClinicalTrials.gov identifier: NCT00337636

• Oral cysteamine bitartrate and N-acetylcysteine use in patients with infantile NCL was correlated with complete depletion of the stored GRODS. Patients and physicians reported less irritability and improved alertness in 7/9 patients. No treatment-related adverse events occurred apart from mild gastrointestinal discomfort in two patients, which disappeared when liquid cysteamine bitartrate was used in capsule form. However, none of the children acquired new developmental skills and their retinal function decreased progressively. The average time to isoelectric EEG was longer than reported previously (36 versus 52 months). ClinicalTrials.gov identifier: NCT00028262

CLN2 (TPP1; OMIM #204500)

The CLN2 gene codes for tripeptidyl peptidase-1 (TPP1), a soluble lysosomal protein, and is associated with the classic late infantile-onset form of NCL. CLN2 disease, in its classic form, has an onset between 2 and 4 years of age with epilepsy being the initial symptom in most cases. Seizures can be generalized tonic-clonic, focal, absence, and/or myoclonic (most prominent in the face). Thereafter, there is a decline in motor skills, often with ataxia and deterioration of speech and language. Sometimes slowing of developmental milestones is evident before the onset of seizures.

CLN2 should be suspected in a previously healthy child who shows arrest of psychomotor development or onset of unexplained seizure disorder around the age of 3 years. TPP1 enzyme testing is the most definitive test. Enzyme activity less than 5% of normal is diagnostic for CLN2. Molecular testing is useful to confirm the diagnosis and for genetic counselling.

Clinical Trials

A study evaluating the direct CNS implantation of human stem cells expressing TPP1 has been completed. The study failed to show efficacy.121 ClinicalTrials.gov identifier: NCT00337636

CLN3 (CLN3; OMIM #204200)

The juvenile form of NCL (JNCL), the most common form of this group of neurodegenerative disorders, is associated with mutations in the CLN3 gene. The first sign of the disease is decreased central vision caused by progressive retinal degeneration (retinitis pigmentosa) usually observed between 4 and 6 years of age. There is slow cognitive regression that occurs during the initial years of this disorder. A subset of affected children may manifest difficult behaviour between the ages of 7 and 9 years. There also can be a variety of behavioural symptoms including anxiety, aggressive behaviour, depression, and visual hallucinations. By at least 10 years of age, cognitive decline is noted. Epilepsy can start as early as 12 years of age, but usually, seizures do not occur until 14 years of age. Cogwheel rigidity is also present in the limbs, and patients walk

with a stooped, shuffling gait reminiscent of patients with Parkinson's disease. An intention tremor of variable severity is often observed.

Clinical Trials

• Mycophenolate mofetil for Treatment of Juvenile Neuronal Ceroid Lipofuscinosis (JUMP) trial. The study aims to assess the safety and tolerability of short-term (8 weeks) administration of mycophenolate mofetil in ambulatory children with CLN3. The secondary objective is to gather preliminary evidence of the short-term (8-week) effect of mycophenolate mofetil on clinically relevant features of CLN3. ClinicalTrials.gov identifier NCT01399047. Mycophenolate was well tolerated. There were no definite effects on measured autoimmunity or clinical outcomes in the setting of short-term administration. A study of long-term exposure is needed to test the impact of mycophenolate on key clinical features and CLN3 disease trajectory.[11]

• Umbilical Cord Blood (UCB) Transplant of Inherited Metabolic Diseases With Administration of Intrathecal UCB Derived Oligodendrocyte-Like Cells. The study aims to determine the safety and feasibility of intrathecal administration of DUOC-01 as an adjunctive therapy in patients with inborn errors of metabolism who have evidence of early demyelinating disease in the central nervous system (CNS) and who are undergoing standard treatment with unrelated umbilical cord blood transplantation. ClinicalTrials.gov identifier NCT02254863

CLN4 (DNAJC5; Autosomal Dominant Kufs; OMIM #162350)

DNAJC5 encodes cysteine-string protein alpha (CSFα) and has been recently identified to cause adult-onset NCL disorder in five kindreds. These familial cases were previously well-described with autosomal dominant inheritance.

Symptoms usually start during the fourth decade with myoclonic seizures, dementia, and movement abnormalities. Brain pathology documented autofluorescent storage material and GRODS by electron microscopy. Normal ophthalmologic examination was noted up to 34 years of age. Other family members were variably affected by a progressive seizure disorder, ataxic gait, and/or progressive dementia, typically starting in the 20s to 30s.

CLN5 (CLN5; OMIM #256731)

CLN5 disease can present as a variant late-infantile NCL. The usual age of onset is between 3 and 7 years, but juvenile-onset and adult-onset cases have been reported. Patients usually present with slight motor clumsiness and hypotonia followed by learning problems. Visual failure and blindness may also be early signs and by the age of 7 to 9 years, there is significant optic atrophy. Seizures usually appear at about age 9. Myoclonus is frequently observed and can appear earlier and independent of generalized or focal seizures. Behavioural problems seem to be infrequent. Ataxia and athetosis can occur later. Children lose the ability to ambulate by about 10 years of age, and death occurs between the ages of 14 and 32 years. Brain MRI is

almost always abnormal at the time of diagnosis and shows severe cerebellar atrophy. Thalamic nuclei may appear hypointense on T2-weighted images. The EEG shows posterior spikes to low-frequency photic stimulation. Giant VEP and SEPs are often seen.

CLN6 (CLN6; OMIM #601780)

CLN6 disease presents as other late-infantile variant forms of NCL. The clinical features are similar to the classic late-infantile form of NCL. However, a significant proportion of patients have a slightly later onset and a more protracted course with seizures, ataxia, and myoclonus as the leading symptoms. The age of clinical onset of the disease is broad with a usual range between 2 to 5 years of age. Initial clinical features include motor delay and cerebellar findings of dysarthria and ataxia. Seizures (including myoclonic jerks) start in more than 50% of patients before 5 years of age. The visual failure occurred early in 50% of patients. This disease is rapidly progressive to a vegetative state. Just as in CLN2, the EEG may show high-amplitude posterior discharges in response to photic stimulation. Brain MRI shows progressive generalized cerebral and cerebellar atrophy. There may be an increased T2-weighted signal in the periventricular white matter and decreased intensities in the thalami and putamen.

CLN7 (MFSD8; OMIM #610951)

This disorder was initially called the Turkish variant of late-infantile NCL as it was described in this ethnic group. It is now recognized to be pan-ethnic. This disease is hard to distinguish from other late infantile NCL forms (CLN2, CLN5, CLN6, or CLN8). Its onset is usually between 2 to 7 years of age. Initial symptoms are typically aggressive behaviour and severe epilepsy in association with developmental regression. The clinical course is rapidly progressive with the appearance of myoclonus/clonic and nocturnal epilepsy, ataxia, dementia, and blindness. Some cases have presented with the onset of visual failure and ataxia. Rett-like onset and a clinical picture that includes midline stereotypic hand movements have been described. Death usually occurs in late childhood, but some patients survive until the second and third decades. Compared with classical CLN2 disease, CLN7 disease shows a somewhat later onset and a more severe seizure phenotype.

CLN8 (CLN8; OMIM #600143)

CLN8 disease was first recognized in the Finnish population in a childhood epilepsy syndrome or progressive epilepsy with mental retardation (EPMR), when neuropathologic studies identified cytoplasmic autofluorescent storage typical of a NCL-like disorder. Initial symptoms are short, frequent, and drug-resistant generalized tonic-clonic seizures as well as focal seizures, with onset between 5 and 10 years of age, and cognitive decline. Cognitive decline starts 2 to 5 years after the onset of seizures. After 30 years of age, the patients have difficulties with equilibrium and they walk slowly using broad-based small steps. The speech becomes dysphasic in some patients. During childhood and puberty almost half of the patients also suffer from behavioural problems such as irritability, restlessness, disobedience, and inattentiveness. Age at death varies from 17 years to late middle age, yet some survive into the fifth decade.

CLN8 disease can present as a typical late-infantile variant NCL, showing an earlier onset and more rapidly progressive disease course than EPMR.237 Symptoms usually start around 2 to 7 years of age with developmental delay (motor and language) and then onset of myoclonic seizures and ataxia. There is rapid disease progression after the onset of disease, and by the age of 8 to 10 years, there is severe disability and worsening epilepsy. Focal and generalized seizures, as well as absence seizures, may evolve, and seizures can become very difficult to control. There are frequently behavioral problems. Spasticity, tremors, and extrapyramidal movement abnormalities are common. By 10 years of age, most of the children are wheelchair-bound.

The EEG shows a slowed background with multifocal epileptic bursts and abundant rhythmic delta activity. There can be significant loss of sleep organization. Cerebellar and brainstem atrophy is manifested in young adulthood. ERG demonstrates attenuated amplitudes and then loss of signal.

CLN10 (CTSD; OMIM #610127)

CLN10 disease seems, at this point, to be a rare disease. It has been primarily recognized as a congenital form of NCL, although severe late-infantile cases have been described. Clinically, these patients present at birth with microcephaly, respiratory failure, rigidity, and status epilepticus. Death occurs within hours to weeks after birth. Enzymatic testing of CTSD usually shows significantly reduced activity in leukocytes or fibroblasts. Definitive Diagnosis: CTSD enzyme analysis with identification of confirmatory CTSD pathologic mutations.

CLN11 (GRN; OMIM #614706)

Report of two siblings with an autosomal recessive late-onset neurodegenerative phenotype, lysosomal NCL-like inclusions, and homozygous progranulin (GRN) mutations established CLN11 as a variant phenotype-genotype from the loss-of-function heterozygous GRN mutations seen in autosomal dominant frontotemporal lobar dementia (FLTD) with TAR DNA-binding protein (TDP)-43 inclusions (FTLD-TDP/GRN; OMIM #607485). The identification of NCL cases with GRN homozygous mutations suggests a link between a rare lysosomal disorder and a common late-onset neurodegenerative disease.

The clinical and neurophysiologic features of the CLN11 disorder include onset in third decade of a retinal dystrophy with optic atrophy, seizures, myoclonus and ataxia. Retinal examination showed pigment epithelial dystrophy, vessel attenuation, and optic neuropathy. OCT showed retinal thinning and disruption of retinal pigment epithelium. Brain MRI shows cerebellar atrophy.

CLN 12 (ATP13A2; Autosomal Recessive Kufs Disease; OMIM#610513)

ATP13A2 mutations were first associated in the very rare autosomal recessive juvenile parkinsonism with dementia phenotype (Kufor-Rakeb syndrome, PARK9, KRS, OMIM #606693) in 2006. CLN12 disease is better known as Kufor-Rakeb syndrome (or PARK9). CNS pathologic study showed whorled lamellar inclusions typical of NCL in brain tissue, and there was lipopigment deposition in the retina. Other affected

family members showed spinocerebellar ataxia, bulbar signs, extrapyramidal and pyramidal abnormalities, as well as dementia. Further pathologic study of KRS patients is needed to confirm that KRS and CLN12 are allelic. Age at onset is in early adolescence; symptoms progress rapidly. Kufor-Rakeb syndrome is caused by loss-of-function pathogenic variants in a predominantly neuronal P-type ATPase gene, ATP13A2.

CLN13 (CTSF, OMIM#615362)

This is, as of yet, a rare identified cause of adult-onset NCL. Clinical features were different with cerebellar syndrome characterized by tremor, ataxia, and dysarthria, depression and cognitive decline. Seizures were noted.

CLN14 (KCTD7; OMIM #611725)

More than 10 patients have been described to date. Mutations in the KCTD7 gene are associated with an infantile form of NCL and an infantile progressive myoclonus epilepsy. Normal development was until 18 months of age, followed by motor and speech regression.

In the infantile progressive myoclonus epilepsy presentation, the disease onset was under 5 years of age (range 10 months to 3 years), presenting with seizures and/or progressive mental and motor impairment with progressive psychomotor regression to severe mental and motor handicap within 2 years (range 1 to 22 months) after onset of seizures. Seizures were myoclonic, atonic, atypical absence, or/and tonic-clonic seizures.

Management and Treatment of NCL Disorders

The management is mainly symptomatic for the range of clinical problems, including seizures, sleep-related problems, malnutrition, gastroesophageal reflux, pneumonia, sialorrhea, hyperactivity, behaviour problems, psychosis, anxiety, spasticity, parkinsonian symptoms, and dystonia.

Seizures. Seizures are one of the hallmark manifestations and can cause the most anxiety in the family. There is no single anticonvulsant medication that will work for all NCL disorders. An anticonvulsant medication should be selected in discussion with the family and based on the stage of the disease, age of the affected individual, and quality of life assessment. A goal of complete control of seizures may be unrealistic in this disorder. A balance between the number of seizures and sedation (which is one of the most common side effects of anticonvulsant medications) should be discussed with the family and patient (if able to communicate).

Benzodiazepines may be of benefit for seizures, anxiety, spasticity, and sleep difficulties. Trihexyphenidyl has been used to improve dystonia and sialorrhea. Antidepressants and antipsychotic agents are sometimes indicated for those with severe mood problems/aggression.

Unfortunately, most of the patients become bedridden, and because of swallowing dysfunction and aspiration, pneumonia is a risk. Patients with swallowing problems may benefit from the placement of a gastric feeding tube.

Disease-modifying therapy for CLN2[12-15]

For patients with symptomatic CLN2 disease who are aged 3 years and older, we recommend treatment with recombinant human cerliponase alfa. This drug is a proenzyme form of human TPP1, which is deficient in patients with CLN2 disease. It is administered into the cerebrospinal fluid via the lateral ventricles. It represents the first disease-modifying therapy for any NCL.

Indication

Recombinant human cerliponase alfa was approved to slow the loss of ambulation in children aged 3 years and older with symptomatic CLN2 disease.

Efficacy

The efficacy of recombinant human cerliponase alfa was established in an open-label study of 23 children ages 3 to 16 years with CLN2 disease who were treated with intraventricular infusion ofcerliponase alfa for at least 96 weeks and a historical control group of 42 patients with CLN2 disease. The outcome was measured using the motor and language domains of the Hamburg CLN2 Clinical Rating Scale, where 0 represents no function and 3 represents a normal function in each of the two domains, and aggregate scores range from 0 to 6.

Compared with historical controls, treated patients were less likely to decline in motor and language function, as measured by the median time until a two-point decline in the combined motor-language score, a lower risk of an unreversed two-point decline in the combined motor-language score (hazard ratio 0.08; 95% CI 0.02-0.23), and a lower unadjusted mean rate of decline per 48-week period in the combined motor-language score (-0.27 for treated patients, compared with -2.12 for controls)

Dosing

Pretreatment with antihistamines with or without antipyretics or glucocorticoids is given 30 to 60 minutes prior to the start of the infusion. Cerliponase alfa 300 mg (10 mL) is given once every other week (followed by intraventricular electrolytes 2 mL, included in the administration kit) and infused at a rate of 2.5 mL per hour via a surgically implanted intracranial ventricular reservoir and infusion device. The first dose may be given five to seven days after device implantation. Treatment should be managed by clinicians with expertise in intraventricular administration. Since there is a risk of anaphylaxis, the drug should be given in a setting with appropriate facilities and medical support.

Adverse effects

The most common adverse clinical effects of cerliponase alfa are pyrexia, electrocardiogram (ECG) abnormalities, vomiting, seizures, hypersensitivity, hematoma, headache, irritability, device-related infection, bradycardia, jittery feeling, hypotension

Genetic Counseling

The NCL disorders are autosomal recessive except for one form of adult disease (CLN4) that is autosomal dominant. Once a mutation has been identified in a patient, obtaining parental samples to confirm carrier status is recommended. This will allow family planning for the family as well as discussion with related family members of the risk of inheritance. When the sibling is underage, a discussion with the parents, taking into account current guidelines of national/international genetic associations, is of importance before the presymptomatic genetic testing of a minor child. This is particularly controversial and more challenging when the proband has a later onset presentation and there is a younger sibling. There are genetic guidelines that one should take into account along with the wishes of the family.

Resources

NCL Mutation and Patient Database: https://www.ucl.ac.uk/ncl-disease/ncl-resource-gateway-batten-disease

Gene Reviews: http://www.ncbi.nlm.nih.gov/books/NBK1428/

NCL Resource - A Gateway for Batten Disease: www.ucl.ac.uk/ncl

Clinical Trials: https://clinicaltrials.gov/,

Clinical Trials For the NCL

https://clinicaltrials.gov/ct2/results?cond=Neuronal+Ceroid+Lipofuscinosis&term=&cntry=&state=&city=&dist=

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The section has been written mainly using *Swaiman's Pediatric Neurology*