

Guide to Symptomatic Treatment of  
**Neuronal Ceroid Lipofuscinosis**



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# Introduction

In the period between 2008 and 2011, Oslo University Hospital's (OUH) Department of Clinical Neurosciences for Children executed a project entitled *National knowledge base for Neuronal Ceroid Lipofuscinosis (NCL)*. In the wake of this project, the department assumed responsibility for a national medical resource centre for NCL.

There is no cure for NCL, but it is possible to treat many of the symptoms associated with the diseases. This treatment aims to alleviate symptoms and, if possible, prevent further progression and complications. Many of the symptoms can be managed with medication or supportive measures, and some forms of treatment have proven to be more effective than others.

The project, which is no longer active, provided valuable knowledge and insight, but a lot of work remains to be done in terms of collecting existing knowledge of best practices for the continuous treatment of symptoms. This includes a number of experience-based measures, all of which may contribute to improving the quality of life both for the person with NCL and his or her family.

Using the established knowledge base and the ongoing clinical follow-up of NCL patients by the Department of Clinical Neurosciences for Children, Oslo University Hospital at Rikshospitalet, the Norwegian Speilmeyer-Vogt Association (NSVF) has worked with Oslo University Hospital in the period 2013–2016 to execute a project aiming to develop a guide for symptomatic treatment that

- describes the early symptoms of the different NCL variants and offers a brief guide to the diagnostic process
- describes known symptoms for the different NCL variants, with a primary emphasis on JNCL
- describes best practices for the treatment of individual symptoms, with a primary emphasis on symptoms associated with JNCL

In recent years there have been developments in drug therapies, particularly in terms of treating epilepsy and psychological symptoms. Having knowledge of the types of medication that offer the best results can alleviate some of the problems NCL patients experience, thus contributing to a better quality of life for them and their families. In addition, the project has sought to compile a selection of non-medical interventions that have yielded good results in terms of symptomatic treatments for this patient group.

This guide is primarily aimed at medical personnel in Norway who are in, or may come into, direct contact with patients belonging to this diagnostic group, but others who are looking to learn more about the diseases may also benefit from it.

# 2

## What is Neuronal Ceroid Lipofuscinosis?

Neuronal ceroid lipofuscinoses (NCL) is a group of diseases characterized by an intracellular accumulation of fluorescent material. The diseases have been known since the early 19th century (the juvenile type was first described by Stengel in 1826 and later by Batten-Speilmeyer-Vogt), but it was not until recently that researchers were able to determine that all the diseases in this group are caused by defects in lysosomal enzymes or membrane proteins. That means these diseases are categorized as **lysosomal storage diseases**. The NCL diseases, which in English are collectively known as Batten Disease, is among the most frequently occurring hereditary neurodegenerative diseases in children, presumed to affect from 1 in 12,500 to 1 in 100,000 children (Boustany, 2013; Chabrol, Caillaud, & Minassian, 2013). In 2015, there were approx. 35 identified cases of NCL in Norway. The accumulated material is complex, and the biochemical link between the protein defect and the accumulated material is still unknown. The accumulation occurs in a wide range of tissues/organs, but tissue destruction and cell loss are primarily observed in the central nervous system.

Clinically, these diseases can be divided into three main categories: **infantile, late-infantile and juvenile neuronal ceroid lipofuscinosis** (see below). In addition, there is a congenital type, as well as several variants of the late-infantile type. There is also an adult-onset type of the disease. Common clinical symptoms include loss of vision, epilepsy and eventually dementia. Most die prematurely.

In 1995, researchers identified the first gene known to cause NCL. So far, more than a dozen genes and in excess of 430 different mutations have been identified as causing NCL (S.E. Mole & Cotman, 2015). All of the genes have been described in the NCL Mutation Base (<http://www.ucl.ac.uk/ncl>). A specific phenotype has been linked to most NCL genes associated with a complete loss of gene function, whereas “milder” mutations with residual genetic activity are associated with a later onset of the disease and a slower progression. However, identical clinical presentations can be caused by complete loss of function in several different genes, or “milder” mutations in other genes.

For example, late-infantile NCL may be caused by complete loss of gene function in the *CLN2*, *CLN5*, *CLN6*, *CLN7* or *CLN8* gene, or “mild” mutations in the *CLN1* or *CLN10* gene. All identified NCL genes so far identified lie on autosomes, and in most cases the disease is inherited in a recessive manner (S. E. Mole & Cotman, 2015).



### **Infantile Neuronal Ceroid Lipofuscinosis (INCL)**

INCL is inherited as an autosomal recessive. Most patients have a mutation in the *CLN1* gene on chromosome 1p32, which codes for palmitoyl-protein thioesterase (PPT1) (S. E. Mole & Cotman, 2015; Sara E. Mole, Williams, & Goebel, 2011; Schulz, Kohlschutter, Mink, Simonati, & Williams, 2013).

The child develops normally until approx. age 6–18 months. Psychomotor developmental delays are often observed from the end of the first year of life, and in the second year of life the child will lose acquired skills. Head growth will begin to decrease from age 6 months. Children become hypotonic and later spastic, developing contractures. Their vision deteriorates from age 1, and by age 2, most children with this diagnosis are blind. In time, the children become hyper excitable, developing myoclonus and epilepsy. The general life expectancy is 7–13 years.

MRIs of the head generally show atrophy early on in the progression. In later stages, EEGs tend to be isoelectric. Electron microscopy of isolated lymphocytes or rectal biopsies shows accumulation of granular material. INCL is diagnosed through enzyme analysis of fibroblasts and/or genetic analysis. These analyses are, inter alia, carried out at Sahlgrenska University Hospital in Gothenburg, Sweden. For more information, please see their website ([www.sahlgrenska.se/su/kliniskkemi](http://www.sahlgrenska.se/su/kliniskkemi)).

Relevant differential diagnoses include Rett syndrome (in girls) and infantile neuroaxonal dystrophy.

### **Late-Infantile Neuronal Ceroid Lipofuscinosis (Late-Infantile NCL, LINCL)**

The classical type of LINCL is inherited as an autosomal recessive, and the mutation has been mapped to the *CLN2* gene on chromosome 11p15 (S. E. Mole & Cotman, 2015; Sara E. Mole et al., 2011; Schulz et al., 2013). This mutation causes tripeptidyl-peptidase 1 (TPP1) deficiency. There are several variants of LINCL. They each have the same clinical presentation, but often have a later onset and a protracted disease progression. Electron microscopy shows similar inclusions, but the underlying enzyme defect remains unknown. The genetic mutation has been identified for several of these variants, such as the Finnish variant, which is almost exclusive to Finland. This is caused by a mutation of *CLN5* on chromosome 13q2. Others may have mutations of *CLN6*, *CLN7*, (*MFSD8*), or *CLN8*. Other variants have also been described, where the mutation is mapped to the *CLN10* or *CLN1* gene.

The onset of symptoms can generally be observed from ages 2 to 4. The children's motor skills deteriorate; they become clumsy and develop ataxia. They experience language delays and later delayed general psychomotor development. From around age 3, they develop myoclonus and epilepsy, both in the form of generalized tonic-clonic (GTC) seizures and absence seizures. Visual impairment is rarely observed as an early symptom, but all children diagnosed with LINCL go blind. The general life expectancy is 10-15 years.



MRIs of the head show non-specific infratentorial cerebellar atrophy and white matter abnormalities. EEGs often show distinct posterior spikes to “slow photic stimulation”. ERG shows loss of function early, and may even precede observed visual impairment. Visual Evoked Potentials (VEP), however, are enhanced. Electron microscopy of tissue shows curvilinear deposits. JNCL is diagnosed through enzyme analysis of fibroblasts and/or genetic analysis, carried out by, inter alia, Sahlgrenska University Hospital ([www.sahlgrenska.se/su/kliniskkemi](http://www.sahlgrenska.se/su/kliniskkemi)).

### **Juvenile Neuronal Ceroid Lipofuscinosis (JNCL, Spielmeier-Vogt)**

JNCL is a hereditary autosomal recessive disease caused by a mutation of the *CLN3* gene on chromosome 16p12.1 (S. E. Mole & Cotman, 2015; Sara E. Mole et al., 2011; Schulz et al., 2013). A 1.02 kb deletion accounts for 85 percent of all mutations in Europe. This is also the most common mutation in Norway, but other mutations have been identified. The protein this gene codes for comprises 438 amino acids and is located on the membrane. The most commonly observed mutation eliminates exon 7 and 8, and is followed by a premature stop codon. This likely results in the protein not being expressed at all. The function of this protein remains unknown, but it seems to play a role in a number of processes, including lysosomal pH regulation, autophagy, endocytosis, protein transport from the Golgi apparatus, proliferation and apoptosis (Carcel-Trullols, Kovacs, & Pearce, 2015).

There are other sub-types affecting other genes, including *CLN1*, *CLN2*, *CLN5*, *CLN7* and *CLN12* (S. E. Mole & Cotman, 2015).

The onset of symptoms is often observed at pre-school age in the form of vision impairment or behavioural changes. Central vision is affected first, but over the course of a few years, the child will become severely vision impaired or blind. Cognitive impairment can often be observed a couple of years after the onset of vision impairment, or parallel to this. Over time, many will develop sleep disorders. Epilepsy often manifests from the age of 10. Speech gradually deteriorates, and some will entirely lose the ability to communicate verbally. Parkinson-like motor impairment manifests gradually, and some become dependent on a wheelchair in their teens. Reactive depression and psychotic hallucinations may be severe and are not uncommon. The general life expectancy is 20-30 years.

Suspected JNCL is often the result of characteristic findings during an examination of the fundus ((Bozorg, Ramirez-Montealegre, Chung, & Pearce, 2009). Blood smears show distinct vacuoles in the lymphocytes of most patients. Electron microscopy of isolated lymphocytes, cells from skin biopsies or other tissue, show characteristic “fingerprint-like” intracellular inclusions. A genetic analysis confirms the diagnosis by identifying the mutation of the *CLN3* gene. Oslo University Hospital offers this type of genetic analysis.

As long as the child’s problems are limited to vision impairment only, relevant differential diagnoses include other progressive retinopathies (such as Leber’s congenital amaurosis,

Stargardt disease or retinitis pigmentosa) (Bozorg et al., 2009). If the patient has other neurological symptoms as well, white matter disorders, mitochondrial disease, peroxisomal and other lysosomal diseases should be ruled out. If the symptoms correspond to JNCL, but vacuolated lymphocytes are not observed in a blood smear, atypical mutations of the *CLN1* and *CLN2* should be considered. "Northern epilepsy" is another autosomal recessive disease that manifests around the age of 5–10. The first symptom of this disease is epilepsy, followed by dementia. Vision impairment is not always present, but some patients experience impairment of their focal vision. Autopsy findings show intracellular inclusion bodies similar to JNCL, and a mutation of the *CLN8* gene on chromosome 8p23 has been identified. This gene codes for a membrane protein whose function remains unknown. Other mutations of the same gene may cause sub-types of LINCL.

### **Adult Neuronal Ceroid Lipofuscinosis (ANCL, Kufs disease)**

ANCL is different from the other NCLs, in that lipopigment deposits are primarily observed in neurons only, and not in other parts of the nervous system, viscera or skin. Also, ANCL is not associated with retinal pigment abnormalities or vision impairment (Schulz et al., 2013). Two different clinical sub-types have been identified: phenotype A and phenotype B. The disease usually manifests around the age of 30. Mutations to the *CLN6* or *CLN1* gene may cause Kufs disease type A, whereas mutations to the *DNAJC5* or *CTSF* gene may cause Kufs disease type B. Kufs disease type A has an autosomal recessive pattern of inheritance, whereas type B has an autosomal dominant pattern of inheritance (Arsov et al., 2011; Cadieux-Dion et al., 2013).

Phenotype A presents as progressive myoclonic epilepsy, later followed by dementia, ataxia and, in later stages, pyramidal and extrapyramidal symptoms. The seizures eventually become therapy-resistant. Phenotype B is characterized by behavioural changes and dementia, associated with motor disturbances and cerebellar and/or extrapyramidal symptoms. Some also have non-progressive epilepsy.

Cerebral MRI shows non-specific cortical atrophy. Some also show cerebellar atrophy, and diffuse white matter hyperintensity in T2-weighted images has been reported. EEG abnormalities are normally non-specific and described as slow background activity and generalized spike-waves. EEG in dominant Kufs is dominated by generalized periodic discharges (GPDs). GPDs in adults presenting with myoclonus, parkinsonism, dementia or epilepsy should give rise to suspicions of ANCL.

ANCL should not be confused with protracted disease progression of NCL subtypes that normally manifest at a young age. As opposed to these types of NCL, ANCL is not accompanied by retinal degeneration and pigmentation. Other lysosomal storage diseases, including GM2 gangliosidosis, Gaucher disease, Niemann-Pick disease type C or mucopolysaccharidosis type III should be considered. Other relevant differential diagnoses include other types of progressive myoclonic epilepsy, particularly Unverricht-Lundborg disease, Lafora disease and mitochondrial diseases.

## **Congenital Neuronal Ceroid Lipofuscinosis (Congenital NCL, CNCL)**

The congenital type of NCL is caused by a mutation to the gene that codes for cathepsin D. The gene, *CTSD* or *CLN10*, is located on chromosome 11p15.5, and the disease has an autosomal recessive inheritance pattern (S. E. Mole & Cotman, 2015).

The disease manifests in utero, and affected fetuses show signs of growth retardation and a silent pattern in CTG registration. The foetus may also have seizures. Affected children experience intractable seizures from birth and central apnoea. The children normally die within days, but there have been some reports of children living up to 2 weeks (Sara E. Mole et al., 2011).

Diagnostic imaging of the brain shows generalized cerebral and cerebellar atrophy, dilated ventricles and increased amounts of CSF over the cerebral hemispheres. CNCL should be a suspected diagnosis for new-borns presenting with microcephaly and intractable seizures. There have been some reports of low-set ears and ear deformities. CNCL is diagnosed through enzyme analysis of fibroblasts and the diagnosis is confirmed by genetic analysis.

## **New Classification System**

Seeing as it has been discovered that identical clinical presentations may be caused by mutations to several different genes, and that mutations to a single gene may cause different clinical presentations, a new classification system has been proposed (Sara E. Mole et al., 2011). This system incorporates different axes, describing the clinical presentation (phenotype), biochemical expression and genetic mutation (genotype).

*The system is comprised of seven axes:*

- 1. axis: Affected gene, e.g. CLN1, CLN2, CLN3**
- 2. axis: Mutation diagnosis**
- 3. axis: Biochemical phenotype, e.g. CTSD, PPT1, TPP1**
- 4. axis: Clinical phenotype, e.g. congenital, infantile, juvenile**
- 5. axis: Ultrastructural abnormalities identified by biopsies**
- 6. axis: Level of functional impairment in accordance with the Hamburg scale or UBRDS**
- 7. axis: Other remarks**

In clinical practice, one need not provide information for all axes, but axes 1 and 4 should always be specified.

**Example 1:**

A preschool child presents with vision impairment, followed by seizures and loss of skills. Negative for vacuolized lymphocytes, mutations to the CLN1 gene.

Short form: CLN1 disease, juvenile

1. axis: CLN1
2. axis: cln1.004+cln1.009, p.[Thr75Pro]+ [Arg151X]  
(p75P/R151X heterozygote)
3. axis: PPT1 deficiency
4. axis: juvenile
5. axis: GROD (skin)
6. axis: Hamburg "JNCL" score: 5; UBDRS score: physical 47;  
seizures 12; behaviour 15
7. axis: mild asthma

**Example 2:**

Preschool child presents with vision impairment and observed vacuolized lymphocytes.

Short form: CLN3 disease, juvenile

1. axis: CLN3
2. axis: cln3.001+cln3.001, 1 kb del + 1 kb del
3. axis: not applicable
4. axis: juvenile
5. axis: FPP (skin)
6. axis: Hamburg "JNCL" score: 1; UBDRS score: physical 78; seizures 20;  
behaviour 23
7. axis: In respite home care every 4th weekend

# 3

## Diagnostics

Any child suspected of having a neurodegenerative disease should be evaluated broadly with “regular” blood panels, including LDH, metabolic screening, plasma amino acid analysis, EEG, cerebral MRI and cerebrospinal fluid analysis. Symptoms that should give rise to such suspicions include loss of skills, behavioural changes, seizures and vision impairment. The medical evaluation should begin immediately, as a potential diagnosis may also affect other family members and be a relevant consideration in terms of further pregnancies. Parents should be informed that a recessive pattern of inheritance may be present, and that any future children may also have the same disease. If the medical evaluation shows that the child does have a hereditary disease, prenatal diagnostics may be carried out in future pregnancies. Some parents may therefore choose to hold off on further pregnancies until the medical evaluation is completed.

Symptoms giving rise to suspicion of NCL in young children include treatment-refractory epilepsy, myoclonus, developmental delays (particularly speech delays), loss of acquired skills and vision impairment. Common early symptoms of JNCL or juvenile-onset CLN3 include progressive vision impairment, retinopathy and a flat electroretinogram (ERG). Later on, or parallel to these symptoms, other symptoms manifest, including behavioural problems, reduced cognitive function and epilepsy.

Symptoms that should raise suspicion of other types of NCL include any combination of vision impairment, treatment-refractory epilepsy, behavioural problems, speech delays and loss of cognitive and motor functions. It is important that ophthalmologists consider NCL as a differential diagnosis when they encounter unexpected bilateral loss of vision (Bohra, Weizer, Lee, & Lewis, 2000).

Different algorithms have been developed to aid in the investigation of those suspected of having NCL (<http://www.ucl.ac.uk/ncl/algorithms.shtml>; [http://www.dem-child.eu/index.php/wp03\\_epidemiology-natural-history.html](http://www.dem-child.eu/index.php/wp03_epidemiology-natural-history.html)).

Recently, diagnostic laboratories have developed “gene packages” for genetic analysis, including a number of neurodegenerative diseases. For example, Sahlgrenska University Hospital ([www.sahlgrenska.se/su/klinisk kemi](http://www.sahlgrenska.se/su/klinisk kemi)) offers a package that includes all NCL genes. In the future, whole genome sequencing may also become an option. These options will likely affect the diagnostic algorithms.



# 4

## Confirmed Diagnosis—What Now?

Once an NCL diagnosis has been confirmed, we recommend contacting Dr. Ingrid B. Helleland M.D, Senior Consultant with the Department of Clinical Neurosciences for Children at OUS Rikshospitalet (<mailto:ihelland@ous-hf.no>), or any other senior consultant with the same department. The department is working with the Frambu Resource Centre for Rare Diagnoses (Frambu), Statped Mid-Norway, Statped South-East and the Norwegian Spielmeier-Vogt Association (NSVF) to form a collaboration group on NCL. The group has developed some guidelines we recommend adhering to in order to support families through the initial period after a confirmed NCL diagnosis. The Department of Clinical Neurosciences for Children at Oslo University Hospital reaches out to relevant members of the collaboration group whenever necessary. In compliance with privacy laws, all information is anonymized and **will not** include names or addresses unless the family has given consent.

### **How to inform the family of the diagnosis**

The parents should be informed that they will be called in to a meeting to discuss the test results regardless of the outcome, and that information concerning test results will never be given to the parents over the phone. If the parents are called to a meeting over the phone, the person calling should not be aware of the test results. Parents are encouraged to come together or bring someone with them to the meeting. They should also be informed that neither the child who has been diagnosed nor any siblings should be present.

Parents should be informed of the diagnosis in a secure environment, in a suitable room where there is no risk of interruption. Phones and pagers should be turned off. All those present in the meeting should be sitting down. The diagnosis should be delivered by the physician who has examined the patient and who will be following up on him/her, preferably in collaboration with a senior consultant from the Department of Clinical Neurosciences for Children at Oslo University Hospital. Both parents should be informed of the diagnosis at the same time. It is important to remember that once the diagnosis has been delivered, the parents will have a limited or selective ability to pay attention. It is therefore important that the parents are offered a new meeting relatively soon, where they can ask questions and relevant information is repeated. All information provided should be written down and given to the parents. It would be preferable to have a nurse present to write a summary of the conversation. This summary should also be made available to the parents.

Preferably, the parents should be prepared for what's coming by saying you are afraid it is not good news, as this puts the body in a prepared state. When delivering the diagnosis, provide the parents with the type of medical information about the disease you believe is right for the family and not more than you feel they can handle. Having up-to-date

knowledge of the disease is important, to prevent misinterpretation of information, such as from the Internet.

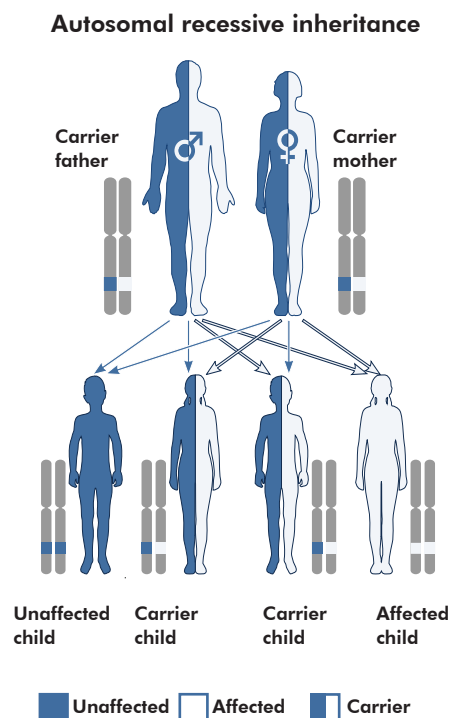
In connection with informing the family of the diagnosis, the family should also be informed of the different organizations involved in the NCL collaboration group. Statedped Mid-Norway has nation-wide special education responsibility for this diagnostic group. They should be brought in relatively quickly, as it is important to establish the best possible educational programme for the child/youth. Statedped Mid-Norway representative are prepared to visit the child and his or her family soon after they have been informed of the diagnosis. The family may also choose to have a parent representative from NSVF visit, or it is possible to communicate over the phone. Some families prefer to reach out relatively quickly, whereas others prefer to wait and see for a while. The physician following up on the child should ask for the parents' consent to contact these organizations, so that they may contact the family directly, if that is what the family prefers.

In connection with delivering the diagnosis, you should be prepared for everything from strong emotional expressions to silence and apathy from the parents. It is important to inform the parents of common psychological reactions to prevent the added burden of worrying about one's own or one's partner's reactions. It is important to reassure parents that their reactions are normal. They should be encouraged to try to maintain a regular daily rhythm in terms of mealtimes and sleep during the initial stage. Some parents may, given their background or psychological health, have need of mental health crisis services. Such services may be provided by a consulting team at the hospital, or by the crisis team at the District Psychiatric Outpatient Service (DPS). You must not leave the parents alone until some form of stability has been reestablished, and you should schedule a new meeting between the physician and the family within 1–2 weeks.

Read more about delivering diagnoses in the leaflet *En god start*, which has been developed by the Frambu Resource Centre for Rare Diagnoses ([www.frambu.no](http://www.frambu.no)).

## Genetic counselling

Once an NCL diagnosis is confirmed, the family is entitled to genetic counselling. This right is established by the Biotechnology Act. Genetic counselling is a communication process addressing human problems associated with the incidence, or risk of incidence, of a hereditary disease within a family. It is common to take blood samples of the parents. Pursuant to Section 5-7 of the Biotechnology Act, genetic testing shall not



be carried out on children under the age of 16 unless the test can detect a condition for which treatment may prevent or reduce damage to a child's health.

Genetic information and counselling is also a statutory right in connection with genetic prenatal diagnostics.

### **Follow-up during the initial stage**

Follow-up of the family shall begin immediately after delivery of the diagnosis, and must be adapted to suit the family's needs and wishes.

It is important to apply a comprehensive perspective to the support of the family during this stage, to meet their psychological, educational, medical and social needs. Statped Mid-Norway will assume an initiating and coordinating role during this stage, and will initiate a meeting with the family relatively soon. This meeting should always result in a short-term plan for further action. The family shall also be provided with names of people they can contact, and phone numbers where someone can be reached at any time, should the family need to.

The NCL collaboration group has developed a summary of the specific services each of the organizations provides during this initial stage. Each of the organizations is responsible for implementing these services, including getting local agencies involved, if necessary, providing them with necessary training in the disease and its social, educational and medical implications. The organizations must also make sure that a care team with an appointed coordinator is established, that an individual plan is developed and that the family is put in touch with the Assistive Technology Centre. It is also important to establish contact with the county's paediatric habilitation service, and to make sure that the municipality has professionals in place to help the family, such as the public health service nurse and the family's primary care physician.

It is a hard blow for parents to find out that their child has NCL. Their mind reels with thoughts and questions, and in many ways they feel like the child they knew is lost. At the same time, their child's future prospects, expectations and needs have changed dramatically. In the middle of all this, the parents must continue to parent and care for their children. If the parents want supportive counselling for themselves, the child with the diagnosis or siblings, it is important that Statped Mid-Norway, Frambu, the paediatric habilitation service, primary care physician or others help them get this in place. Agencies that can be brought in to provide supportive counselling to parents include the municipal psychiatric team, the psychologist affiliated with the health clinic, family guidance offices or other municipal first-line support services. For stronger reactions or problems, the parent's primary care physician can refer him or her to the District Psychiatric Outpatient Service (DPS). Agencies that can be brought in to provide supportive counselling to children (patient and siblings) include the public health service nurse and psychologist



affiliated with the health clinic, and the paediatric habilitation service. If the child is experiencing considerable problems, his or her primary care physician can refer the child to the Paediatric and Adolescent Psychiatric Clinic (BUP) or a psychologist in private practice.

Frambu and Statped Mid-Norway offer counselling on how to inform siblings and how siblings can cope with the feelings they may experience upon learning that their brother or sister is seriously ill and that they are different. The paediatric habilitation service can also provide counselling in this area.

“The initial stage” does not end until a functional municipal support team and a care team has been established around the family.

### **Informing the child**

Motivated by a desire to protect the child, parents will often object to the physician or other health personnel informing their child of their disease. However, children have a statutory right to insight/information (Sections 3-4 and 3-5 of the Patients’ Rights Act). For children under the age of 12, parents have unlimited competence to consent on behalf of the child, but the child has the right to make his or her opinions heard. Information is necessary for the child to be able to understand and cope with the challenges he or she is faced with as a result of the disease. Tailoring the information to the child reduces the risk of anxiety in the child, increases the chances of optimal adaptation and adjustment, and establishes a dialogue with the child. This is crucial for picking up on symptoms and changed needs.

The physician should discuss with the parents to find the best approach to providing the child with the information he or she needs, including who is in the best position to give this information to the child. It is important that the parents don’t feel alone in this, and that they get the help they need. Both Statped Mid-Norway and Frambu can assist in this process, but it is preferable to involve health care personnel who know the child. Some parents prefer to talk to their child themselves after receiving counselling from health care professionals, others prefer to have the health care professionals present for the conversation, and others still prefer to have the health care professional inform the child.

The child should be informed as soon as possible, but one must take into consideration the psychological state of the parents and their ability to handle the children’s reactions and questions afterwards. The information should be tailored to the child’s symptoms and experiences, and could initially be limited to the examinations that were performed (e.g. we looked into your eyes and took a blood sample), why (e.g. we had to find out why you aren’t seeing so well any more) and what we found (e.g. we found something wrong inside your eyes). The child should also be provided with a label they can use (e.g. a rare disease is causing this problem). The information should be updated and repeated as the

disease progresses or the child experiences additional symptoms. Information about disease progression and what they can expect later on should only be provided if the child asks specifically about these things.

Children must have answers, but the parents and health care professionals should work together to determine the type and scope of the information we provide (“you will lose your vision” vs. “you may lose your vision”). For some parents it may be beneficial to have an arrangement where “difficult questions” are written down and brought to a health care professional, so that they can buy some time before answering the child’s question. The most difficult questions involve prognoses and death. It is often a good idea to have gone over how to answer these question in advance. It can also be a good idea to give the children some information about their parents’ reactions, as these can sometimes be just as scary to the child as information about the disease (e.g. mum is crying because she wishes you did not have to have this disease”).

Both the information itself and the way it is provided must be tailored to the child’s age, level of maturity, cognitive abilities and understanding. However old the child is, it is important to use examples of things that happened recently (e.g. “Yesterday, when we were driving to Anne’s, you told me that a troll was sitting next to you in the seat”) and to use tools (drawing, pictures, models) to explain abstract medical concepts.

The principles for informing siblings are the same as for informing the child with the diagnosis, but the age of the sibling must be taken into account. One challenge is that healthy siblings may have questions that demand answers, but one does not necessarily want the child with the diagnosis to be aware of this information. As a guiding principle, siblings should not be put into a situation where they have to keep secrets and make sure they don’t say anything they shouldn’t. If that can’t be avoided, it is important that the healthy siblings know that the parents are responsible for shielding the child from the topic, thus minimizing any fear they have that they might accidentally say something they shouldn’t.

Frambu’s website ([www.frambu.no](http://www.frambu.no)) has more information on this issue.

# 5

## Causal Treatment of NCL

No proven causal treatment against NCL exists. However, many clinical trials have sought to combat the cause of the disease, and there are some ongoing trials showing promising results. Experimental treatments of NCL were recently summarized by Neverman et al. (Neverman, Best, Hofmann, & Hughes, 2015) and Geraets et al. (Geraets et al., 2016). NCL is an umbrella term for different genetic lysosomal storage diseases characterized by vision impairment, epilepsy, dementia and intracellular deposits of autofluorescent lipofuscin. The mutations that cause NCL can be divided into two main categories; the mutation will either cause an enzyme in the cell membrane to malfunction or it will affect soluble enzymes. Soluble lysosomal enzymes are secreted to the extracellular space, from which they can either be reabsorbed by the same cell or other cells. This process means that by rectifying the defect in some cells, other cells can absorb the enzyme and make use of it (cross-correction) (Wong, Rahim, Waddington, & Cooper, 2010). As the different NCL diseases are caused by different proteins with different functions, one cannot presume that a treatment that is effective against one type of NCL will also be effective against another (Stehr & van der Putten, 2015).

### Stem Cell Therapies

Theoretically, stem cell therapies work in one of two ways: either by the stem cells producing the missing enzyme, which can then be taken up by the enzyme-deficient cells (cross-correction), or by the stem cell differentiating and replacing the person's own (diseased) cells. There have been trials involving both hematopoietic stem cells (cells from blood or bone marrow) and neural stem cells (nerve cells). Both types have been used in animal models and clinical trials



### Hematopoietic Stem Cells

Hematopoietic stem cell transplantation has been used sought used to treat INCL, but while enzyme activity normalized in the white blood cells, activity remained low inside the brain (cerebrospinal fluid). The therapy had minimal effects on diseases progression (Lonnqvist et al., 2001). Hematopoietic stem cell transplantation has also been found to be largely ineffective against LINCL and JNCL (Lake, Steward, Oakhill, Wilson, & Perham, 1997).

### Neural Stem Cells

This method works by getting stem cells to differentiate into nerve cells (neurons or glia cells). Animal trials have shown that the therapy works primarily through "cross-correction", and that the therapy was able to delay loss of motor functions. An open

phase 1 trial on patients with INCL and LINCL proved that the method of transplanting neural stem cells directly into the brain's cavities (lateral ventricles) with subsequent immuno-suppression was safe, but so far it has not been determined whether the therapy is effective (Selden et al., 2013). Post-mortem examinations of 3 patients found donor cells in 2 of them (Selden et al., 2013).

### **ERT (Enzyme Replacement Therapy)**

Enzyme infusion has been proven effective for other lysosomal storage diseases and in vitro trials have shown that the therapy is also effective in NCL. Animal trials using, inter alia, mouse models for LINCL, have found that the onset of symptoms is delayed, and the mice are living longer when the mice were infused with a small quantity of enzymes (Sleat et al., 2008). One of several challenges associated with this method is that enzymes have a hard time penetrating the brain due to the blood-brain barrier. Therefore, it may be necessary to inject the enzyme to the cerebrospinal fluid, either directly into the lateral ventricles or by intrathecal injection (needle in the back). Other challenges include producing a "pure" enzyme, the body making antibodies against the enzyme, anaphylactic (allergic) reactions and tolerance development (the drug will, at one point, stop working). The enzyme must be injected regularly, which makes the therapy cost-prohibitive. ERT is only an option for the types of NCL where the affected enzyme is soluble (CLN1, 2, 5 and 10). Ongoing trials are looking at the efficacy of ERT in children with LINCL (ClinicalTrials.gov identifier NCT01907087), (Kohan et al., 2011).

### **Gene Therapy**

Gene therapies work in several different ways. One possibility is to harvest blood cells from the patient, correct the genetic cell defect in the laboratory by transplanting a new gene, and returning the cells to the patient. A modified virus is used as a vector to introduce the right gene into the blood cells. This is called ex vivo gene therapy. It is also possible to introduce a gene into the host cell in vivo. In vivo therapies make use of a virus with reduced virulence (a weakened virus) as a vector. This method has been tested in several animal models with varying results. Both intracranial injection and injections into the vitreous body of the eye have been tried. Central challenges include finding the right vector, and the right time to intervene. Two phase 1 clinical trials have been carried out on patients with CLN2. Both trials made use of adenoviruses as a vector. In both these trials the vector carrying the CLN2 gene was injected into 12 different locations inside the brain. One study observed a delayed progression of the disease, but the disease did progress (Worgall et al., 2008). Currently, there are two ongoing clinical trials for CLN2 (ClinicalTrials.gov identifiers NTC01161576 and NCT01414985). In addition, another trial for CLN6 was recently approved (ClinicalTrials.gov identifier NCT02725580). The main purpose of these trials is to determine whether the method is safe, and whether the patient can tolerate it. The secondary endpoint for the trials would be changes in brain atrophy and treatment efficacy.

## Therapies Involving Tiny Molecules

The idea behind this type of therapy is not to repair or replace the protein deficiency, but to enhance the patient's remaining enzyme activity. This is done in an effort to restore cell function. One benefit of this type of treatment is that it is non-invasive, and it may one day be possible to develop medication to be taken orally. This type of therapy can be divided into various sub-categories:

### Pharmacological "Chaperones"

This type of therapy is still highly experimental, but testing in cell culture models has shown promising results. The term "chaperone" can be defined as someone who accompanies and looks after another. In this context, the chaperones are small molecules stimulating enzymes with residual activity to function more normally. For example, some point mutations to NCL genes affect protein production, causing the protein to not fold properly. However, the protein may have some residual enzyme activity if it can be modified by cell machinery and transported to where it needs to go. Cell control systems often degrade the protein before it has a chance to act. Pharmacological chaperones bind themselves to the protein, preventing degradation, allowing the protein to modify and start functioning.

### Receptor Modulators

Receptor modulators are chemical compounds that bind themselves to receptors in the cell to increase, reduce or change the receptor's activity. The AMPA receptor in the central nervous system is a receptor thought to be significant for NCL. Applying a mouse model, researchers have introduced a non-competitive AMPA antagonist with good results when administered early in the progression of the disease (Kovacs & Pearce, 2008).

### Substrate Reduction Therapy (Removing NCL Deposits)

Clinical trials studied the effect of combining cysteamine bitartrate and N-acetylcysteine to treat INCL (ClinicalTrials.gov identifier NCT00028262). Unfortunately, this had no effect on the progression of the disease, even though the treatment succeeded in reducing the amount of storage material in peripheral leucocytes and parents reported less irritability and increased concentration (Levin et al., 2014).

### Immunological modulators

As with all neurodegenerative diseases, NCL is characterized by an ongoing inflammation of the central nervous system. Researchers agree that persistent inflammation involving microglia and astrocytes contribute to the progression of the disease. Serum neuronal antibodies have been observed in patients with NCL (GAD65). Immunosuppression therapy could therefore potentially affect the progression of the disease. Positive effects of treatment with mycophenolate (Cellcept®) have been observed in mouse models (Seehafer et al., 2011), and in an ongoing clinical trial in the US, patients with Juvenile CLN3 are being treated with this immunosuppressing drug (ClinicalTrials.gov identifier NCT01399047).

Treatment with prednisolone has also been shown to temporarily improve motor function, but it had no significant therapeutic effect in terms of prognoses (L. Aberg et al., 2008).

There is still a lot we don't know about the various NCL diseases. In order to collect clinical and genetic information in an effective manner, a database of information from several participating countries has been established (<http://www.dem-child.eu/index.php/wp03-epidemiology-natural-history.html>).

# 6

## Supportive Treatment—Primarily Directed at Juvenile CLN3

### Life stages

It may be useful to divide the life of a patient into stages to describe the different needs he or she has. We operate with three different stages. The first stage covers the time of diagnosis and the orientation stage, when the parents connect with the various support services. The second stage covers the childhood phase, when the child attends school, and the employment phase when the youth finishes school and moves out of his or her childhood home. The third stage is the nursing stage. During this stage, the youth will need help to manage almost everything, including personal hygiene and nutrition. The patients' needs during the different stages vary. It is important to keep in mind that there are considerable individual differences, and all measures considered must take this into account, meeting the specific needs of the individual patient.

### Vision

Visual impairment, accompanied by retinal abnormalities, is often the first symptom of JNCL. It often manifests as impaired focal vision, nyctalopia, nystagmus, photophobia and colour vision deficiency (Ouseph, Kleinman, & Wang, 2016). It is also the beginning of a more comprehensive degeneration of cerebral function. As focal vision deteriorates, parafoveal or paramacular fixation can often be observed (Brodsky, Baker, & Hamed, 1995). The child relies on his or her peripheral vision instead of central vision, e.g. by "looking at things from the side" or fixating a few degrees over or under the natural point of fixation. Fundus examinations may show pigmentation that could be confused with retinitis pigmentosa. "Bull's eye" macular dystrophy is observed in approx. 20 percent. In addition, abnormal blood vessels and optic atrophy are often observed. The entire retina is most likely affected, which can be confirmed by an electroretinograph (ERG) early on in the progression of the disease (Brodsky et al., 1995). The visual impairment progresses gradually, and by age ten, most children with JNCL are severely visually impaired or blind, but some patients retain some residual vision, inter alia in the form of light sensitivity, for a few years. One recent study in Denmark found cataracts in 5 out of 35 people with JNCL. Two of these developed acute glaucoma, and one had prophylactic cataract surgery. Regular eye examinations are recommended for JNCL patients over the age of 16 to prevent painful and potentially harmful acute glaucoma (Nielsen, Drack, & Ostergaard, 2015).

At Statped Mid-Norway, they have observed how some of the children use their vision actively to orient themselves, play, read and write up to the age of 9–10, and in some cases even longer, in spite of severely impaired visual acuity, severely reduced contrast sensitivity and major peripheral and central visual field defects (Augestad, Fosse & Diderichsen, 2008).

When central vision is lost, the child is gradually forced to use his or her peripheral vision to handle all visual tasks. However, peripheral vision is primarily used for orientation, and the child struggles to switch between orientation tasks and tasks requiring visual acuity. In addition, the child's vision gradually deteriorates. That is why it is important for the child to learn how to use his or her hands, i.e. tactile input, as a supplement to learning as much as possible about his or her surroundings. In addition, it is important for the children to also train their remaining senses, especially hearing, to help them orient themselves. When the children orient themselves, we commonly observe them getting into the habit of angling their head in specific ways. They do this to make the best use of their peripheral vision and to get their visual field to point straight ahead in the direction they are moving. Children have individual strategies for angling their head. Some vary their angles, others quickly choose a position, either by tilting the neck back or bending the neck slightly in combination with twisting it sideways.

It may seem that the child is able to navigate relatively easily and quickly in the beginning, and it is often difficult to distinguish the child with NCL from other children in a group of playing children. We need to remember, however, that focusing on distant goals, i.e. orientation, is the "easiest" hurdle for the child to overcome. It will be more difficult to master tasks requiring both visual acuity and orientation. As the child's ability to distinguish between details deteriorates, the child's frustration is likely to increase. The child may retain the ability to orient him- or herself by visual cues for a few years, particularly the ability to navigate using light perception. It is important, however, that the child develop sound learning strategies based on the use of alternative senses, such as hearing and touch, as soon as possible and as broadly as possible.

The loss of vision means that parents soon are faced with educational choices that may affect the child's learning situation, e.g. if the child is to be taught how to read Braille and whether to implement computer applications like Sarepta. It may also be important to introduce various learning and educational aids using digital tools to replace conventional text. Hearing is a key learning sense for individuals who cannot see, and this sense will not be affected by the disease. It is therefore important to reduce the noise in any learning situation. Statped will be a central partner in this regard.

## **Epilepsy**

Epilepsy manifests in most children with Juvenile CLN3 around the age of 10, but the frequency and severity of the seizures vary. Seizures often become increasingly problematic as the disease progresses.

Epileptic seizures are often divided into two main categories: generalized and focal (partial), depending on where in the brain the seizure originates. The different types of seizures are described in more detail in Appendix 1.



The most common type of seizure in Juvenile CLN3 is generalized tonic-clonic seizures (GTCS). Most youths with JNCL are able to manage their seizures relatively well on one or two types of medication, but the seizures have a tendency to worsen over time (Augustine et al., 2015).

In other types of NCL, epilepsy manifests at a younger age and is harder to manage. These patients may have several different types of seizures, and myoclonus is common. In these groups of patients, epilepsy may be resistant to treatment.

Den vanligste anfallsformen ved CLN3, juvenil type er Generaliserte Tonisk-Kloniske anfall (GTK-anfall). De fleste ungdommene med JNCL har relativt god anfallskontroll med en eller to medisiner, men anfallssituasjonen har tendens til å forverre seg over tid (Augustine et al., 2015).

In other types of NCL, epilepsy manifests at a younger age and is harder to manage. These patients may have several different types of seizures, and myoclonus is common. In these groups of patients, epilepsy may be resistant to treatment.

## Treatment

GTCS may be scary for those around the patient when it happens, and parents, teachers and others who spend a lot of time with the child/youth should prepare themselves for the first seizure by talking about epilepsy and developing a plan for how they should act when it happens. The child/youth should also develop some type of contingency plan for when the seizure happens (see Appendix 1).



While all patients with NCL will develop epilepsy, we do not recommend starting the child on anti-epileptic drugs as a means of prophylaxis, i.e. before the child has had a seizure. However, families should have access to anticonvulsants (**midazolam or diazepam**), even before the first seizure. When epilepsy has been diagnosed, all families and others who are in regular contact with the child/youth should have access to this. Midazolan (Buccolam®) given on the inside of the cheek is the one easiest to administer. The drug is fast-acting and short-lived. If the drug is prescribed to individuals over the age of 18, prescription reimbursement is by application only. Diazepam (Stesolid®) administered rectally is another option.

When the child/youth has had an epileptic seizure, he or she should be put on anti-epileptic drugs, and **lamotrigine (Lamictal®)** or **valproate (Orfiril Long®)** are the most commonly used for Juvenile CLN3 (Augustine et al., 2015). In addition to its anti-epileptic effect, lamotrigine also has a mood stabilizing effect, which may be beneficial for many NCL patients. Dosing is equivalent to other types of epilepsy. Read more about medication on Oslo University Hospital's website: ([Oslo-universitetssykehus.no](http://Oslo-universitetssykehus.no); search for anti-epileptic drugs).

It is important to monitor ammonia levels in patients with NCL on valproate (Larsen & Ostergaard, 2014). Valproate binds to carnitine and is excreted through urine. Low carnitine levels could lead to hyperammonemia, so carnitine supplements may be a good idea.

Sometimes one type of medication is not enough; sometimes we have to combine two or more. Other relevant drugs include **levetiracetam (Keppra®)** and **topiramate (Topimax®)**. One must take into account, however, that many NCL patients often use several types of medication, even for other problems, and one should take care to avoid polypharmacy insofar it is possible.

In other types of NCL, where myoclonic seizures are the primary type of seizure, valproate (Orfiril Long®) will be the primary choice, supplemented by klonazepam (Rivotril®) if necessary. Other effective drugs in progressive myoclonic epilepsy include high-dosage piracetam (Nootropil®) and levetiracetam (Keppra®). Topiramate (Topimax®) and zonisamide (Zonegram®) may be added. Phenytoin (Epinat®) and fosphenytoin (Pro-Epanutin®) should generally be avoided, as they may exacerbate neurological symptoms. In addition, sodium channel blockers (carbamazepine (Tegretol®, Trimonil®), lamotrigine (Lamictal®), oxcarbazepine (Trileptal®) and phenytoin (Epiat®)) and GABA analogues, including gabapentin (Neurontin®), vigabatrin (Sabrilex®) and pregabalin (Lyrica®) should also be avoided, as they may exacerbate myoclonus and myoclonic seizures (Kalviainen, 2015). Some have tried a ketogenic diet, others vagus nerve stimulation, but these cannot be said to be established or proven forms of treatment. In some cases, myoclonus may develop into status myoclonicus. If this happens, shield the patient from light and sound, and administer acute treatment with benzodiazepines, valproate and/or levetiracetam intravenously (Kalviainen, 2015).

While most patients with Juvenile CLN3 manage their seizures well on one or two anti-epileptic drugs, the epilepsy may, in some cases, be resistant to treatment. These patients may be referred to the National Centre for Epilepsy (SSE) at Oslo University Hospital.

## **Motor Function**

The type of follow-up a child/youth with NCL needs, will be dependent on the life stage he or she is in. We recommend that physical and occupational therapists work together to optimize the situation for both the patient and those around him or her.

In addition to visual impairment affecting motor function, the child/youth will also gradually develop fine and gross motor function impairment. By age 12–14, approx. 50 percent of patients have already developed extrapyramidal symptoms, including rigidity, hypokinesia, a shuffling, stooped gait and poor balance (Jarvela et al., 1997). Coordination problems and involuntary movements are also observed.

The child and his or her family should be put in contact with a physical therapist as soon as the diagnosis has been confirmed. The physical therapist will identify and assess the child's/youth's skills and motor function, and monitor the situation for any changes. Areas of assessment include everyday skills, including moving, dressing and undressing, personal hygiene and toilet situations and meals. An assessment should be made of the patient's gait, balance, muscle strength, active and passive range of motion in arms, legs, neck and back, and degree of tonus, dystonia and resting tremor. Measures shall be planned and implemented on the basis of this assessment. The physical therapist should encourage the patient to participate in a wide range of activities, just like other children and youths. Assistants and teachers at school will have to be trained, and the patient should be assigned an activity or sports contact who can accompany him or her to various activities in his or her free time. We recommend that every effort be made to generate an interest in physical activity early on, preferably in the form of play and general activity, but also organized sports. The children should learn different skills as early as possible, and it should be possible to change the nature of these skills in line with the patient's motor function. We recommend activities that involve large muscle groups and that are not too technical. The idea behind this principle is that the child should be able to continue doing the same activity over an extended period of time, thereby experiencing having a shared interest with others for as long as possible. Children and youths with JNCL should be physically active both at school and at home. Exercise should be general at first, and the patient should exercise at least once a day. In addition to this, we recommend walking as much as possible. Participating in play activities at school, climbing trees, swimming, riding, hiking and walking around the neighbourhood are all examples of good activities.

In addition to general activities, the patient may need more systematic training and stimulation, e.g. in physical education classes and other types of situations. The goal is to stimulate specific motor skills in the child/youth. This applies to their entire lives—while they live at home with their parents, at school, in their free time, when they move out. It is essential that we try to automate as many movements as possible early on, while the child/youth is susceptible to it, because both motor and cognitive function deteriorates over time.

As the child gets older, targeted cardiovascular exercise and strengthening of large muscle groups is beneficial. At this stage, problems related to motor control really begin to manifest. Rigidity, or increased reflex activity, works against the child's movements. As a result, range of motion is reduced and balance and coordination deteriorates. The most important goal at this stage is to optimize measures designed to help the child/youth maintain overall function at the highest level possible for as long as possible. In this context, physical activity and sports are two central factors, and it is essential that the youth be seen by a physical therapist.

In order to optimize the effect of the training exercises, it is crucial to ensure good communication. This is best achieved working one on one, as concentration and memory will become more fleeting as the patient enters stage 2.

When the youth is no longer able to move freely, it is important that the patient maintains good posture while seated and has a well-adjusted chair. Good posture is important to prevent misalignment and contracture, and it is essential for good upper body stability, head control and willed and conscious control over arm and hand movements. Physical activity is important to prevent complications, and we recommend trying to maintain the ability to walk for as long as possible. The best way to do this is to have two people supporting the patient, with the use of mobility aids, if necessary. Most patients will not be able to use such mobility aids on their own. They are at risk of falls, so it is important to develop good procedures for transfers from the bed to the chair and in toilet situations. Many patients benefit from using various types of lifts at this stage of the disease. The patient needs to change positions often, and should do physical and mobility training every day. Moving all the joints of the body increases well-being, and it can help reduce misalignments. Having ones chest indirectly stretched may help the patient breathe more deeply. Pulmonary rehabilitation may become necessary to prevent stagnation and accumulation of mucous and pulmonary infection.

In order to be able to plan and facilitate for physical activity, both general and specific, knowledge is essential, both about the diagnosis and about the level of function the patient has. The level of function will determine what to prioritize in the here and now, and which possibilities and limitations the patient has.

Recommendations for assessments are listed in “NCL and physical activity” (Rita E. Hinsverk Jeremiassen, 2016). The book also includes recommended exercises and activities.

Available data indicate that varied and frequent physical activity positively affects the child’s/youth’s ability to cope with his or her disease, and we should actively encourage physical activity, even beyond what would be normal for children of the same age.

A small study from Finland shows that treatment with levodopa had a positive effect on extrapyramidal symptoms (L. E. Aberg, Rinne, Rajantie, & Santavuori, 2001).

In late-stage LINCL, we often see complex movement disorders, such as myoclonus, chorea, ataxia and dystonia. A rare, but potentially life-threatening complication is status dystonicus. Infections, surgery, stress, pain and medication may trigger this state. Treatments include various medications, including benzodiazepines and clonidine, and intervention with baclofen via intrathecal injection may be an option. Valproate is a known risk factor, and by discontinuing use of this medication, the situation may soon resolve (Johannsen, Nickel, Schulz, & Denecke, 2016).

## **Sleep**

Sleep disorders are very common among children and youths with JNCL (Kirveskari et al., 2000). They sleep less and have a sleep pattern that deviates from that of healthy peers.

They have problems calming down at night, wake up often, have frequent nightmares and have less REM sleep. The sleep disorders may be caused by neurodegeneration and disturbed neurotransmission, epilepsy or psychological factors. Another possible explanation for a disturbed circadian rhythm may be a reduced response to retinal light stimulation, but studies have not found any evidence of this (Heikkila et al., 1995). Even in individuals with retinal degeneration and loss of vision, light stimulation seems to affect the hypothalamus, thus being able to regulate our circadian rhythm.

However, as the patient's motor skills deteriorate, so do his or her level of activity. Reduced needs to rest may affect how much sleep we need, which can easily develop into displacement of the sleep-wake cycle. A lack of stimulation/activation in the patient's everyday life may lead to the patient taking short naps during the day, which may also affect sleep patterns at night.

In working to improve sleep patterns, good sleep hygiene is important; implement a regular bedtime, and eliminate "sources of entertainment", such as access to music and audio books after bedtime. Furthermore, all efforts should be made to optimize treatment of the patient's epilepsy and any psychological issues. Many report positive effects from taking melatonin, either as "regular" melatonin or in the form of a time release formulation, even though studies have not been able to prove its efficacy (Hatonen et al., 1999; Heikkila et al., 1995). Some also use a combination of the two. The idea is that the "regular" melatonin will aid in the process of falling asleep, whereas the time release formulation will help the patient stay asleep. "Regular" melatonin is not on the market in Norway, but is available through so-called compassionate use for named patients. Circadin® is a registered time release drug that may also be used for younger children and adults, even though it is only approved for individuals over the age of 55. Taking benzodiazepine at night may be an option, both as a supplement to other epilepsy treatments and as a means to improve sleep quality. Many report positive effects from taking nitrazepam (Apodorm®, Mogadon®) in particular, but diazepam (Stesolid®, Valium®, Vival®) also seems to be a valid option.

Part of the sleep pattern for many youths in this group is frequent awakenings, often combined with episodes of hallucinations and anxiety. The best medicine under such circumstances may be security, adaptations for optimum sleep comfort and the presence of a caregiver.

## **Physical Symptoms**

### **Pain**

It is important to keep in mind that behavioural changes may be brought on by pain and discomfort, and should initiate medical assessment. Pain may be caused by "regular" conditions, including tooth aches, obstipation or gastro-oesophageal reflux, and it is important to identify these underlying problems and take action to reduce or eliminate them.

The website of the National Institute on Intellectual Disability and Community ([naku.no](http://naku.no)) offers information about pain and intellectual disability and measuring pain in individuals with severe communication problems. Among other things, they refer to assessment tools developed and tested in Denmark. Even though these assessment tools have been developed for other diagnostic groups, it may be well worth looking into whether these tools can be of use for patients with NCL.

Body and extremity pain, including joint pain, is not uncommon in patients with NCL. Stomach pain and head aches are also frequently reported (Breau & Camfield, 2011; Santavuori et al., 1993). In patients with advanced communication problems and functional impairment, it may be difficult to ascertain where the pain is and how severe it is. Children and youths with NCL may very well have been undertreated for pain.

Also, researchers have not been able to determine why the children/youths are in so much pain. A recently published study indicates that the pain children and youths with NCL experience is central and not peripheral (Barney, Hoch, Byiers, Dimian, & Symons, 2015). That makes treating the pain challenging, but one study showed that fentanyl patches worked well for children with INCL (Mannerkoski, Heiskala, Santavuori, & Pouttu, 2001).

In general, however, standard principles of pain management are recommended: non-opioid analgesics, if necessary in combination with a neuroleptic, such as amitriptyline (Sartex®). If this is insufficient, fentanyl patches may be an option. Sometimes pain is caused by spasms and/or rigidity of the extremities related to “parkinsonism”, and if so, one should consider whether treatment for these symptoms is necessary. For patients where spasms are a major concern, treatment with baclofen (Baklofen®) should be tried.

However, we must not forget that non-drug treatment and care is important, too. Calmness, comfort and diversion can be quite effective, either alone or in combination with medication.

### **Respiration**

As the disease progresses, patients with NCL may experience reduced respiration and a reduced ability to cough. Some drugs also stimulate mucus production. If phlegm is a major concern, inhalation of saline solution may help move the mucus. Also, we recommend that the patient lie on his or her side, and not on his or her back. It's important to change positions often. At this stage, the physical therapist should focus on clearing the patient's airways of mucus, and assistive aids, such as a cough assist machine, should be considered.

### **Dental Health**

Dental health is often overlooked in individuals with functional impairments. Chronically ill individuals are more at risk of developing dental problems. They may have reduced saliva production due to their illness or the medication they are taking, and this reduced saliva secretion increases the risk of tooth decay and may make the mucous membranes

more sensitive. Reduced fluid intake may also cause dryness of the mucous membranes in the oral cavity. Medications sometimes affect dental health. Sugary drugs increase the risk of cavities. Other drugs, such as phenytoin for epilepsy, may cause problems with the gums. Maintaining good oral hygiene can also be challenging, both due to physical circumstances, and due to a lack of understanding on the part of the individual. Dental examinations can also pose a challenge, due to circumstances like a reduced ability to open the mouth and swallow; reduced sensation and weak musculature are not uncommon.

While maintaining good oral hygiene can sometimes pose a problem, it is important for the individual patient that this is followed up. We recommend semiannual check-ups insofar this is possible.

All costs associated with dental care for children under the age of 18 are covered by the public dental service. Individuals with rare medical conditions receive subsidized dental care, and the Directorate of Health is responsible for updating the list of diagnoses covered under this scheme. NCL is included on the so-called A-list, which means that patients are entitled to coverage for all necessary dental examinations and treatments. The Norwegian Health Economics Administration (HELFO) has published a brochure explaining who is eligible for free dental in accordance with the standard rates. TAKO, a resource centre for dental health and rare disorders, offer advice and counselling on dental care for patients with NCL, as well as reimbursements for dental health expenses.

### **Nutrition and Eating**

Eating disorders may manifest as problems with eating and swallowing, or as a lack of appetite, nausea, gagging and visible discomfort in connection with meals. Eating disorders may be caused by the disease affecting the central nervous system and therefore also coordination and the nerve supply to muscles in the mouth, tongue and throat, or the disease may affect the gastrointestinal system, causing nausea and obstipation. Some types of medications affect appetite and others cause nausea. Undernutrition and dehydration may exacerbate the patient's general condition and neurological functional impairment. **It is therefore very important to monitor and regularly and carefully assess the patient's nutritional situation.**

Chewing and swallowing require good control and accurate coordination of many muscle groups in the face and neck. In addition to requiring activation of voluntary musculature, swallowing also requires activation of smooth musculature, and this is dependent on active reflexes. Reduced neuromuscular control may cause problems with swallowing and aspiration. Normally, a person who accidentally inhales food will cough when food enters the oesophagus, but if the person has weak reflexes he or she will not necessarily cough. The result is "silent aspiration". Frequent respiratory infection may be a sign that the patient is aspirating food.

Some may develop problems swallowing before they develop problems processing the food with their mouth, but in others we observe a general impairment in both the ability to process the food with their mouth and the ability to swallow.

It is important to monitor the patient's weight over time, and it is a good idea to take blood samples to screen for iron and vitamin deficiencies. *Changes in eating patterns* compared to previous patterns may be a sign of impaired oral motor function and a reduced ability to swallow. Examples of changing patterns could be that the patient no longer eats raw fruits and vegetables, that he or she prefers yoghurt or cereals with milk over bread and crispbread, or that the patient reduces his or her intake of fluids, such as water, juice, etc., or all liquid food. The patient may begin to prefer dinners with minced meat, other minced products or fish over cuts of meat, or the patient may suddenly prefer foods with strong or spicy flavours. The latter may be a sign of sensory impairment, which would mean the patient can no longer taste the food as well as before. Changes in eating patterns often happen gradually, even without the patient or those closest to him or her noticing.

Many parents of youths with NCL report that meals often take a very long time. This may be because the youth have so much they want to say during the meal that they do not have time to eat, or they may struggle to eat food with a consistency or texture they can no longer handle.

If symptoms of aspiration occur in combination with meals, such as coughing, hawking, regurgitation or a hoarse voice, especially in combination with frequent respiratory infection, the patient may need to go through a videofluoroscopic swallow study (an X-ray examination of the swallowing process). Thin liquids are the most difficult thing to swallow, and problems with drinking are often reported first.

When eating becomes a problem, it is important to adapt the physical setting of the meal and to help the patient eat. The occupational or physical therapist can be of assistance in this context. If the child/youth struggles with advanced consistencies and textures, they should be offered food with a consistency they can handle, while preserving the patient's joy for food and food preferences. As for thin liquids, it may be an option to add a thickener, if the patient is having problems swallowing. Frambu's website ([www.frambu.no](http://www.frambu.no)) offers advice on nutrition for patients with eating disorders under the tab called "Nutritional problems in progressing central nervous system diseases". In some cases nutritional drinks may be a good option.

If texture adjustments are no longer sufficient to ensure good nutritional value in the patient's diet, or if the meals take too long to complete, gastrostomy may be a good option. For most patients, the nutrition they get through their gastrostomy is a supplement to what they eat. Some use the gastrostomy to ensure their fluid intake is high enough, others just need it for medication. There are many different commercially available feeding tube solutions on the market, with minor differences between them. These are available under the prescription reimbursement scheme. Regular food that has been mashed and



mixed with fluid may be administered through the feeding tube. When a patient has been fitted with a gastrostomy, he or she should be followed up by a clinical nutritionist in terms of food quantities. When the disease has progressed to the point where a feeding tube is necessary, the activity level is normally also considerably reduced. Standard tables for nutritional requirements therefore do not apply. Becoming overnourished is just as bad as being undernourished.

Individuals whose musculature is weakened are at risk of developing gastroesophageal reflux (GOR). In some cases, the stomach content may come all the way up into the mouth, from which it can be aspirated to the lungs, with chemical pneumonia as the result. On suspicion of GOR, 24-hour pH monitoring should be carried out, and if the diagnosis is confirmed, relevant treatment should be implemented, such as putting the patient on proton-pump inhibitors.

In progressive diseases, the gastric emptying process may be delayed, i.e. it takes longer for food to pass from the stomach to the duodenum. As a consequence, it may take longer to feel hunger again, and fullness sets in quickly after the next meal. Many also experience nausea. Under such circumstances it may be a good idea to change the composition of tube nutrition. Some reports indicate that a small dose of erythromycin (3 mg/kg x 4) may positively affect gastric emptying.

Whether or not to introduce tube feeding of a child or youth with advanced neurodegenerative disease will always be a question of ethics. On the one hand, good nutrition is essential in protecting and maintaining the level of function the patient has, but on the other tube feeding may just prolong the process of dying. This ethical dilemma is discussed quite well in an article by Kohlschutter et al. (Kohlschutter et al., 2015). The primary consideration must always be the best interest of the patient in each individual case. If a patient with NCL “just” has problems swallowing, but is otherwise doing well, the decision is not difficult. If, on the other hand, the patient is suffering with severe motor and cognitive impairment, tube feeding may not necessarily improve the patient’s quality of life. However, quality of life is not easily determined and these decisions must be considered carefully, in consultation with the patient’s family and others close to him or her in each individual case.

### **Elimination (Bowel Movements and Urination)**

Obstipation is a common problem, but it is often overlooked. Obstipation may be caused both by immobility and by impairments of the autonomous nervous system. Sometimes diarrhoea may be a symptom of obstipation (obstipation diarrhoea). Treatment for obstipation in NCL patients will be the same as for other patients. It is important to eat regular meals, get enough rest and physical activity and to ensure regular visits to the toilet. If at all possible, the patient should be encouraged to move his or her bowels in the morning after breakfast, as this is the time of day when reflexes are the strongest.

Proper hydration is important (avoid tea and sweet milk) to prevent obstipation. If the patient suffers from chronic obstipation, soluble fiber products, such as psyllium husks, have been proven to be effective. If necessary, supplement this with an additional cereal product, such as wheat bran, flaxseed, psyllium husks, lactulose, etc. Adjust dosages to suit the needs of the individual. Sometimes polyethylene glycol may be necessary (e.g. Laxabon®, Movicol®).

Urination may also become a problem in time. It may be difficult to empty the bladder completely, which may give rise to urinary tract infections.

As the disease progresses, the youth will eventually lose control of urination and bowel movements, and he/she will become incontinent. Initially, regular toilet times will be important, and after a while diapers will be required. These are available under the prescription reimbursement scheme.

### Cardiovascular Problems

Heart problems are not uncommon in patients with advanced-stage progressive diseases, but very little systematic research has been carried out in this area. One Danish study looked at 29 JNCL patients ranging in age from 7 to 33. The study followed the surviving patients for 7.5 years. 24-hour ECGs were repeated after 3 years (Ostergaard, Rasmussen & Molgaard, 2011). T-wave inversions were observed for a third of the patients at the initial examination, and the youngest patient for whom such inversions were observed was 14 years old. The study also found a connection between the presence of repolarization abnormalities in the ventricle at the initial examination and risk of death during the period of observation. As the patient grew older, the heart rate, expressed as beats per minute, decreased, and heart rate variability (HRV), as indicated by the vagal index, also decreased. This may indicate that the disease affects the heart in two ways as the patient grows older: by reduced cardiac parasympathetic activity and by negatively affecting the sinoatrial node. The connection between bradycardia and arrhythmia and the incidence of sinoatrial arrest and atrial fibrillation with increasing age indicates an age-dependent reduction in sinoatrial node activity. From approx. age 20, researchers found increased incidence of ventricular hypertrophy. The authors recommend annual ECGs from age 18, and if pathology is observed, including bradycardia, they recommend 24-hour ambulatory ECGs every six months.



At Oslo University Hospital, we examined 13 patients aged 13–35 with ECG and echocardiography. Ten patients were re-examined after 19 months and  $\pm 2$  months. In the initial examination, two patients were found to have slightly reduced left ventricular function, and four were found to have moderate left ventricular hypertrophy. One patient had AV-block grade 1, one had right bundle branch block, and one presented with T-wave

inversions in the ECG. In the follow-up examination, two patients had developed T-wave inversion, but no additional patients had developed hypertrophy or significantly reduced left ventricular function (Helge Skulstad, Oslo University Hospital).

A German study included reports of three patients who had had pacemakers installed due to severe sinoatrial bradycardia and one patient who had asystole (Khosrawi, Kohlschutter, Mir & Schulz, 2009). These patients had had very good results in terms of alertness and general well-being. There have also been reports of a 32-year-old patient in Greece who has benefitted from being implanted with a pacemaker (Dilaveris et al., 2014).

Whether end-stage NCL patients should be considered for this type of treatment, however, remains an ethical dilemma, and a thorough and comprehensive assessment should be carried out before any such decisions are made.

Many patients with advanced neurodegenerative disease struggle with poor temperature regulation and cold extremities. This is likely caused, in part, by the centres of temperature and blood pressure regulation in the brain being affected by the disease, but also, in part, by immobility. That is why it is very important to mobilize the patient. There are a number of assistive aids available to help stimulate circulation in cold hands and feet, and the occupational therapist will be able to give more specific advice.

## **Emotions and Behaviour**

As their vision deteriorates, many children and youths with Juvenile CLN2 tend to talk more. Continuous blabbering may pose a challenge for the environment, not least because the children tend to talk about themselves and the things that interest them, and they are not very good at listening to others. Many also develop considerable rigidity in terms of switching activities, e.g. discontinuing a play activity to begin a meal. Unexpected changes may also pose a major hurdle for them. Some children develop rituals they must follow daily, e.g. the order in which they put on their clothes, what needs to happen before, during and after meals, etc. Compulsive thinking is also not uncommon. Many develop anxiety and worry about all sorts of things. This may, in part, be related to visual hallucinations and psychoses. Some may also become very angry at times, at both themselves and others.

Both parents and the youths themselves report that the youths often feel sad. This is perhaps most common in early adolescence, as the developmental gap between the person with Juvenile CLN3 and his or her classmates begins to widen. It no longer feels natural to invite the person with the disease along for activities, and the patients themselves begin to notice that they cannot keep up with or understand what their friends are doing or saying. Adolescent patients may experience a profound sense of loneliness (Adams et al., 2010).

For the child/youth, predictability and good planning are essential. It is also important that adjustments be made so that the child/youth can participate in activities with peers. Municipal services, such as personal support contacts or user-directed personal assistance (BPA), could be beneficial. Many parents also choose to “buy” friends for shorter or longer periods of time. When the children start lower secondary school, former classmates may serve as social contacts and accompany the youth to activities.

### **Cognitive Impairment**

Sooner or later, children and youths with NCL will develop some type of dementia. Both the onset and progression of dementia vary considerably between individual patients. However, dementia manifests when the child/youth is still in school and while growth, learning and development in other areas continue. Eventually, dementia will considerably limit the patient’s ability to learn new things (von Tetzchner, Fosse, & Elmerskog, 2013). In addition to vision impairment, short-term memory impairment and difficulty repeating what they have been told are early symptoms. Lamminranta et al. (Lamminranta et al., 2001) found that over the course of 5 years—from age 6 to age 10—the average IQ score dropped from 88 to 72 (Wechsler Intelligence Scale for Children, WISC), but with considerable individual variation. In part, this drop can be attributed to the lack of new learning, whereas parts of it also reflect the loss of acquired knowledge. Cognitive function in blind people is primarily based on a verbal assessment, which is particularly problematic in this group. While hearing is less affected than other sensory organs, children with NCL may have problems understanding what they are being told. Long-term memory may, however, be intact, and children can relive past experiences from before they lost their vision.

Whether the lack of cognitive development should be characterized as a type of mental retardation or progressive dementia is not clear. The child has both a form of mental retardation, in that it does not follow the standard learning curve, and a type of progressive dementia, in that it is losing acquired knowledge and skills (von Tetzchner et al., 2013). Parallel to, and likely also related to, the progressive dementia, some patients may also experience psychological problems, such as anxiety and delusions (Backman et al., 2005).

Experience indicates that daily physical and cognitive stimulation contributes to delaying the progression of the disease. Consequently, adjustments should be made to implement a tailored programme that ensures this at school, at his/her place of work and at home. For example, various types of games can help make learning a more joyful experience.

## Communication/Language

Language and communication are at the heart of all types of social experiences. They are the vehicle by which we share knowledge, experiences and emotions. Communication is a fundamental condition for life, development and social interaction for all humans, including children and youths with NCL. An inability to express oneself and to understand what others are saying can lead to misunderstandings, an inability to cope and frustration (von Tetzchner et al., 2013), (Tetzchner, 2003).

Children and youths with NCL may experience communication impairment early on. Initially, the disease affects their ability to take in visual communication. As their motor function and memory deteriorate, many children with NCL will also struggle to express themselves verbally and be understood by others. The ability to remember words deteriorates, many children begin to stutter, and their speech becomes mumbly, choppy and incomprehensible, even for those closest to them. For some NCL patients, Augmentative and Alternative Communication (AAC) will be a good alternative. AAC encompasses a range of modes of communication that complement and/or replace conventional speech. For individuals with NCL, where the progression of the disease entails a loss of function, it is, however, extremely important that a thorough assessment be made into which mode of communication may be appropriate for them. This must be done to ensure that the person does not start something he or she at some point will be unable to do due to functional impairment. The municipal habilitation service, in collaboration with the Assistive Technology Centre, can assist the patient in trying different types of communicational aids. Speech therapist services are important for maintaining oral-motor skills, as these help the patient maintain speech for as long as possible, but also strengthens respiration and reinforces chewing and swallowing skills.

In order for the person with NCL to experience good communication, it is essential that his or her communication partner has acquired the skills and strategies required to become a good communication partner. Good communication partners are patient, motivated, interested and comfortable with various modes of communication. Communicating with someone who cannot speak, or whose language skills are impaired, requires that you know the person well and that you take your time. Someone who knows the person with NCL well, will know what he/she cares about and will also learn to interpret his/her body language. It is very important that family members and others close to the patient help him or her retain the experiences, memories and stories from his or her younger days.

In order to give family members and other communication partners the best possible starting point for good communication, it would be a good idea to develop support material (Ursin & Slåtta, 2010). The brochure "Support material for good practices" includes examples of how this type of material can be designed. Download the brochure free from Statped's website ([www.statped.no](http://www.statped.no)). Knowledge of the individual and his or her personality, preferences and life story is essential for building relationships between people. Everyone has a story and a personality we have to accommodate. Personal presentations about the individual can be very helpful to those who are unable to tell their

own story (Ursin & Slåtta, 2010). Without them, their diagnosis tends to take centre stage instead of their personality. One way to do this is to make a basic presentation, e.g. “The Book about Me”. The book should say a little bit about who they are, what they like to talk about, their background and who the most important people in their life are. The book can be supplemented by pictures, videos, albums, etc. NSVF is available to provide advice on good ways to build a book like that. Youths and young adults with NCL and impaired speech will benefit greatly from different types of “communication presentations”. The goal is that the knowledge of good practices is shared between those who communicate with the youth/young adult. We refer to Ursin & Slåtta, 2010, where they provide detailed instructions for how to go about doing this. NSVF can assist, offering advice and specific examples.

Sign language has not been widely used for children and youths with NCL. This area has become increasingly popular in recent years, however, and the method is currently being used with a growing number of children/youths under the direction of Statped Mid-Norway. The idea is to give them a set of simple hand signs they can continue to use when they lose their ability to speak.

There are a wide range of assistive aids available to support communication, including RollTalk, etc. The Assistive Technology Centre can assist in trying these aids in collaboration with an occupational therapist.

## **Learning**

The ability to learn new things is always there, even in children and youths with NCL. However, teaching activities require more planning and closer follow-up than usual. The gradual cognitive impairment of children with NCL means that the learning curve is different than for healthy children. For most of us, learning is a cumulative process, wherein we build new knowledge on past competence. For children with NCL, we have to take into account the loss of acquired skills over time (von Tetzchner et al., 2013).

Reduced cognitive function requires a unique approach to learning, individually adapted learning methods and special knowledge from the ones who are teaching the target group. All children and youths with NCL develop differently. Key factors for successful teaching strategies include continuity and experiences with the individual student, more so than knowledge of a standardized disease progression. The book entitled “Learning for Life”, edited by Bengt Elmerskog and Per Fosse (Elmerskog & Fosse, 2012), presents central approaches and methods in more detail.

“The here and now” is a key principle for all of life’s areas in the interaction with people who have NCL, even in learning situations.

*Key elements in teaching activities include:*

- Security and predictability
- Physical, cognitive and social stimulation
- Make adjustments to ensure that the student can experience a sense of accomplishment in all contexts, and make sure that he or she gets assistance tailored to his or her needs
- Retain knowledge by constant repetition
- The development and maintenance of good relationships and a healthy environment promotes happiness and well-being and makes it easier to learn
- It is important to stay one step ahead: make a plan for how to handle problems you know will come

The learning activity itself, from beginning to end, and the involvement it generates, is equally important to the final product. For more information, please cf. "Learning for Life" (Elmerskog & Fosse, 2012).

Learning is not limited to formal instruction; it happens in all of life's facets. Just like the transfer of formal knowledge (reading, writing, arithmetic, ICT) is important, so, too, is making adjustments so that the child/youth, as soon as possible, and as a continuous process, acquires competence/skills in other areas. Acquired skills contribute to a higher quality of life, even in the more advanced stages of the disease.

### **Psychiatric Symptoms**

It is not uncommon for children and youths with JNCL to experience psychiatric symptoms. These symptoms include anxiety, aggression, depression, hallucinations and psychoses. These symptoms have a detrimental effect on quality of life, not just for the person with Juvenile CLN3, but also for his or her family. The symptoms are largely attributable to the progression of the disease, but they may also be a natural reaction to the loss of vision and cognitive impairment.

A Finnish study (Backman, Santavuori, Aberg, & Aronen, 2005) found that the most common symptoms were problems related to social interaction, concentration problems and aggression. Aggression manifests as a low threshold for frustration, rapid mood swings and continuous talking. Concentration problems and a low threshold for frustration are likely attributable to cognitive impairment, whereas somatic problems, such as headaches and stomach pain, can be expressions of anxiety and/or depression.

Previous studies have shown that a large number of JNCL patients are depressed (Santavuori et al., 1993). In time, many struggle with interaction and communication with their peers. They may be cast out and bullied for their behaviour, and many of these

children/youths will, in a school setting, be perceived as children with behavioural issues. Loneliness and isolation can have a negative effect on quality of life.

In order to help individuals with JNCL, it is important to assess and acknowledge the psychiatric symptoms, and to implement treatment where indicated. It may be relevant to evaluate all newly-diagnosed patients using standardized tools and to follow up on these evaluations regularly.

Treating the patient's symptoms can be challenging, both due to the considerable range of symptoms, and due to polypharmacy considerations (many patients are also taking anti-epileptic and anti-parkinson medication). It is therefore important to evaluate the patient's symptoms carefully to find the optimal treatment given his or her individual symptoms.

A study from Finland (Backman, Aberg, Aronen, & Santavuori, 2001) showed that citalopram (Citalopram®, Cipramil®) is effective against affective symptoms with few side-effects. Escitalopram (Cipralext®) has also been proven effective. Lamotrigine, which is used to treat epilepsy, also has a mood stabilizing effect. In our experience, sertraline hydrochloride (Zoloft®) is effective against depression.

Risperidone (Risperdal®, Rispolept®) has been used to treat psychosis with good results. Experiences with aripiprazole (Abilify®) are limited but good. It has been said to be effective against organic psychoses. The most common side-effects include fatigue during the initial phase, weight gain and extrapyramidal symptoms. Klonazepam (Rivotril®), which is registered as an anti-epileptic drug, may, in some cases, also be effective.

Increased epileptic activity and psychiatric symptoms seem to be related. In order to prevent the development of psychosis, it is essential to manage the epileptic symptoms well. Likewise, it is important to treat a potential psychosis to prevent the extra stress these psychotic symptoms entail, as these also increase the patient's epileptic activity.



# 7

## Follow-Up on Individuals with NCL

Once the diagnosis of NCL has been confirmed, the child and his or her family should be put on a regular follow-up schedule, in addition to the special education follow-up provided by Statped Mid-Norway. It is standard practice to refer the patients to the paediatric habilitation service. This service can offer the families an interdisciplinary programme for medical follow-up and diagnostics related to the child's psychological and somatic health, communication and motor function, as well as assistance from a social worker. While the need for the services the habilitation service offers is not as dire at the onset of NCL as it can be for other progressive diseases, we recommend that you contact the paediatric habilitation service in your county. The scope of contact with the habilitation service varies from family to family, but many can likely benefit from working with a social worker and/or physical therapist right from the start. Over time, as the child develops problems in several areas, and the family may need more specialized medical and other follow-up, e.g. in connection with implementing assistive aids, the paediatric habilitation service is there to provide help and support to the family.

We recommend that the patient's transition from the paediatric habilitation service to the adult habilitation service is planned in due time when the youth with NCL is between 16 and 18 years old. We also recommend that you contact the Department of Neurology at your local hospital when the youth turns 18. Some patients have to undergo emergency hospitalization as a result of status epilepticus, and in those cases it is a major advantage that the patient has connected with the department beforehand.

As for medical follow-up, we recommend annual check-ups with a clinical examination of weight and height (monitor weight loss/overweight), and an assessment of how the disease is progressing. Several tools have been developed to aid in this process. In the United States it is common to use the Neuronal Ceroid Lipofuscinosis (NCL) Study Group Unified Batten Disease Rating Scale (UBDRS, Appendix 2), whereas Europe has favoured the Hamburg Rating Scales (cf. Appendix 3).

*At Oslo University Hospital, we apply the following annual follow-up regimen:*

### **\*\*UBDRS form**

Supplemented with questions concerning:  
Natural functions (sleep, nutrition, bowel movements, urination)  
Circulation  
School/work  
Living with parents/in respite home/in own home/institutionalized

**\*Clinical examination**

Weight/height  
Ordinary organ status  
According to form (see above)

**\*Laboratory testing**

*Blood tests*

Haematology (Hb, white, thrombocytes, diff.count)  
Transaminases (ASAT, ALAT, GT)  
Creatinine  
Standard blood panel with electrolytes (Na, K, Ca)  
Iron status (s-iron, ferritin, transferrin, transferrin saturation, transferrin receptor)  
If necessary Vitamin A, D  
If necessary, serum drug concentrations  
Ammonia (valproate)  
Carnitin (valproate)

*EEG*

**\*Physical therapist**

Functional evaluation  
Recommendations for further follow-up

We also recommend compliance with Østergaards recommendations based on the Danish study (Østergaard et al., 2011), for an annual ECG from the age of 18 and a 24-hour ambulatory **ECG** if pathology is observed. According to another Danish report (Nielsen et al., 2015), youths over the age of 16 should receive regular eye exams for possible cataracts.

In order to collect as much knowledge about the NCL diseases as possible, we would prefer for a copy of all notes to be forwarded to *The Department of Clinical Neurosciences for Children*, Oslo University Hospital, Rikshospitalet.

## **Support programmes**

Children, youths, and adults with functional impairment and their families need a wide range of services, provided by a wide range of agencies and authorities. Families of children with NCL are no exception. In that NCL is a progressive disease, where the need for services increases in step with the progression of the disease, it is a great advantage for the family to get as many support programmes in place as early as possible.

Many parents spend an inordinate amount of time and effort on navigating a confusing jungle of laws and services. For many, it may also be emotionally difficult to ask for support, both because their situation is already quite difficult, but also because most of them have never done anything like it before. Many therefore ask for help in writing the applications.

Social workers in the specialist health service are experts on the different support programmes and the experience needed to write a good application. Both hospital social workers and social workers affiliated with the habilitation service are available to assist families in claiming various benefits and services. Through NSVG, families can learn more about how other families did on their applications. The parents (or the person with functional impairment) determine whether they want to submit the application and ultimately sign the application and submit it. In addition, it often speaks in the applicant's favour that a professional who knows the child/youth and the family has provided a statement. It is important to make sure that the medical certificate includes a detailed description of the diagnoses and what the consequences are.

From NAV, the most relevant benefits early on in the progression of the disease will be attendance benefit/higher rate attendance benefit, basic benefit and attendance allowance. In addition, NAV has Assistive Technology Centres in each county, where you can borrow assistive aids for play activities, exercises and stimulation, coping with daily life and for use in kindergartens and schools. The municipal occupational therapist can help the family find the most useful aids. Statped Mid-Norway has unique expertise on visual aids and other relevant learning tools, and these are particularly relevant for individuals with NCL. It is also possible to apply for a user account for NAV's Assistive Technology Centre, to place orders directly. NAV accepts applications for disability benefit from individuals aged 18 and older. Individuals with JNCL qualify for permanent disability benefit and from the age of 20, they qualify for payments under the Young Disabled scheme, which yields higher disability payments.

The most relevant municipal support programmes while the child lives at home with his or her parents include respite homes, personal support contact, user-directed personal assistance (BPA), care benefits, companion passes and «TT Kort» ( transport concession

card ). All disabled pupils, including pupils with NCL, are entitled to transportation to school, regardless of the distance between the home and the school. Pupils are also entitled to travel with a companion, if necessary, and to supervision. This also applies to transportation to and from the day care programme for school-aged children (SFO). Disabled children are entitled to a place in SFO until the end of their seventh school year.

Many families are forced to move or to renovate their home as a result of their child's functional impairment. The municipal occupational therapist can help the family in this regard. The Norwegian State Housing Bank offers various loan and housing grants for households including persons with functional impairment. Read more at [www.husbanken.no](http://www.husbanken.no).

As long as the child/youth lives at home with his or her parents, all information and counselling concerning financial benefits and services will be addressed to the child's parents. When they move out, however, they must stake their own claims and submit their own applications. If the youth is unable to do this by him- or herself, the parents or others may act as guardians. In order to be appointed guardian, the parents must contact the County Governor, who is the local guardian authority. There are many considerations to keep in mind in connection with guardianships. Read more about this at [www.vergemål.no](http://www.vergemål.no).

When the child with NCL turns 18, the parents no longer have any legal responsibility for him or her. At the same time, or when the person moves away from home, most financial support programmes for the parents cease to apply. Regardless of whether a child lives in foster care or by him- or herself, the municipality is responsible for making sure those over the age of 18 have their care needs met.

### **Personal/Individual Plan (IP)**

All children/youths with NCL are entitled to a personal plan (IP). This plan is a key tool in the coordination of public services and a good starting point for going after the necessary administrative decisions from the municipality. An IP shall be comprehensive and must describe the person's need for different services and how these needs can best be met. The plan shall also be future-oriented and establish long-term goals for the individual with NCL. In preparing an IP, the municipality will normally appoint a coordinator, who will be tasked with forming a care around the individual team, involving personnel from and external to the municipality it is natural to collaborate with to reach the goals established for the plan. As a minimum, the school and Statped Mid-Norway must be included in this work. NSVF can also advise on the design of IPs for individuals with NCL.



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## Individual Subject Curriculum (IOP)

Pupils who do not sufficiently benefit from regular instruction in school, are entitled to special needs education. Pupils with NCL will be entitled to training in vision-compensating subjects, and, if relevant, training in the use of Augmentative and Alternative Communication (AAC). These types of decisions are made by the municipality/county (often delegated to the headmaster) on the basis of an expert assessment prepared by the municipality's educational and psychological counselling service (PPT) or the county's follow-up service (PPO). PPT/PPO should involve Statped Mid-Norway as a central part of this effort. Youths with JNCL may, subject to certain criteria, be granted the right to upper secondary education for up to 2 additional years.

The school is obligated to prepare an IOP for all pupils for whom a decision concerning special needs education has been met. The IOP must describe the pupil's educational objectives, and these should, insofar it is possible, support the objectives specified in the personal plan (IP). An IOP must also specify the content of the education and how the education shall be organized. Statped Mid-Norway, who is responsible for assisting municipal and county agencies in their educational work with pupils who have NCL, can advise on how to prepare the IOP.

## Transitions

Transitions between kindergarten and school, between different schools and types of schools, between the school and the patient's place of employment/community service, and between his or her parents' home and his or her own home are central and challenging periods for children and youths with functional impairment. These transitions often generate a lot of uncertainty for the child/youth and his or her parents, who lose their familiar network of contacts and case workers. By planning the transition in good time, preferably several years in advance, a lot of confusion and uncertainty can be avoided. A sound, up-to-date and future-oriented IP with clearly defined objectives will serve as a central tool in this planning. The resources of the care team should be used actively, and action plans for competence and knowledge transfers between old and new personnel must be established. Statped Mid-Norway has the required expertise and experience needed to execute transitions for children/youths with NCL, and they can assist the family in this matter.

## Housing

When time has come for the youth to move out of his or her parents' home, planning should preferably begin years in advance of the move. When the youth turns 18 years, the legal responsibility of his or her parents ceases to apply. The health and care service shall contribute to finding housing for individuals who are unable to protect their own interest in the housing market. This provision does not guarantee the person's right to housing, but it obligates the municipality to contribute insofar as the need exists. There are several

different types of housing, and the housing market varies from municipality to municipality. Combined with the right to user-directed personal assistance and the use of extended work shifts in one form or another, it is possible to limit the number of service providers. Feel free to contact NSVF to hear about the experiences of other parents.

For many with NCL it would be natural to move out of their parents' home after graduating from upper secondary school. The younger and more able-bodied the person with NCL is, the easier it is to learn new routines and get to know new people. If the move is postponed until the parents are exhausted and cannot go on, the move will not always be made on the terms of the youth, and emergency housing solutions may be necessary. In our experience, a scheduled and well-planned move is more likely to succeed than an emergency move.

### **The Family Perspective**

Family life changes dramatically when a child is diagnosed with NCL. Practicalities may change, and so may the parents' reactions and way of being, and the interactions in the family.

Being the parents of a child with NCL entails other and more demanding care and parenting responsibilities than the ones other parents have. For many parents, it takes a mental toll to see your child lag behind his or her peers and having to handle the child's frustrations over losing acquired skills and being different. Some go through so-called anticipatory grief, which is the grief you feel when you know someone is going to die, which is the case with an NCL diagnosis. Grief is a normal reaction to loss, but it may have major consequences, including emotional pain, concentration problems, memory problems and sleep disorders. Individuals who live in a perpetually stressful situation may also develop symptoms of post-traumatic stress disorder (PTSD).

Most parents who have children with NCL find that they are forced to assume the role of administrator, and many consider this to be one of the greatest stress factors related to having a child with functional impairment. Many also fight a never-ending battle with the municipality, NAV and health care services to get the help and follow-up they are entitled to and need. Communicating with other parents who have gone through the same things is a boon to many; parents find help and support in the community of parents.

Parents of children with NCL can easily find themselves in situations where their relationship with their child swallows all their attention at the expense of their relationship as a couple and their need to be present for the child's siblings. Respite care, personal support contacts and BPA are key tools, providing the parents with a better opportunity to work on their relationship as a couple, follow up on the child's siblings and have a social life outside of the family.

Siblings often find the lack of attention from their parents to be the most stressful and unfair (Trachtenberg & Batshaw, 1997). At the same time, siblings can see that their parents are struggling, and they try to protect them. It can be hard for parents to see and recognize when the siblings need support and comfort.

Experiences from working with other diagnostic groups indicate that siblings may find it hard to address the things they experience as hard, unfair and sometimes embarrassing. Being different as a family can sometimes be problematic. All of the “forbidden” feelings—shame, annoyance, anger and jealousy—must be allowed, and parents must make sure to tell their children this. Some siblings may need to talk to an adult who is not their parent about their experiences. Potential listeners include the social worker at school, the PPT, the school nurse, the habilitation service or BUP. (Lerdal & Sørensen, 2008). Every year, Frambu organizes a seminar for siblings of children/youths with rare diagnoses ([www.frambu.no](http://www.frambu.no)).

Other major events, such as illness, the death of a loved one or divorce could put an additional strain on families that are already under pressure. Children/youths with impaired cognitive function may struggle to understand that one of their parents is gone, or will have a hard time adjusting to moving between the parents. In these situations the families, family counselling office and other local support agencies working with the child may have to work together.

## **End-stage**

When a person with NCL dies, their death is often the result of infection or status epilepticus. Frambu has developed a leaflet called “The final part of life”, which addresses the final stage of progressive diseases.

After the death of the person with NCL, the family may need help to process their grief and to solve practical and financial problems. Many parents, however, report that former collaborative partners in the support services suddenly become unavailable, because the service was attached to the person with the diagnosis, and not to the family. Similarly, practical and eventually also financial support programmes cease to apply after the death of the person with the diagnosis, which may make the family’s situation even harder in a transitional phase.

Families solve problems and challenges differently, and their needs for help and support after the death of the person with NCL also vary. It is important that the service providers consider the needs of the family, listen to the parents and give them time, while remaining flexible about the termination of various support programmes and assistive aids. Read more about grief reactions and various challenges associated with the loss of a child to progressive disease on Frambu’s webpage concerning Grief in connection with early, but expected death (<http://www.frambu.no/hovedmeny/tema/sorg-ettertidlig-men-ventet-dod/stotte-fra-nettverket-rundt>).

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# Appendix 1

## **XX's background information**

From time to time, XX may have an epileptic seizure, and the frequency with which the seizures occur may vary. For those who have not had experience of such episodes, the seizures may seem very dramatic. This is a brief introduction to epilepsy, the different types of epileptic seizures, and what to do in the event of an epileptic attack.

### **What is epilepsy?**

Epilepsy is not a disease. Rather, it is symptomatic of a number of conditions that commonly lead to a paroxysmal brain dysfunction. The cause of epilepsy varies from person to person, and can be due to almost any type of illness or injury to the brain. However, in more than half of the cases it is not possible to detect any definite cause. An epileptic seizure is the expression of a transitory brain dysfunction, due to a sudden and uncontrolled disruption of cortical electrical activity. In principle, anyone can have an epileptic seizure, particularly if they are under stress or have certain types of diseases. People with epilepsy have a lower seizure threshold than others and therefore have a tendency to have repeated attacks. The various types of seizures are described below.

### **The different types of seizures**

Epileptic seizures are broadly divided into two main groups – generalized seizures and partial seizures – depending on whereabouts within the brain the seizure starts. A generalized seizure is one that starts within whole brain, whereas a partial seizure is one that starts in a particular area of the brain.

#### **Generalized seizures**

##### *Absence seizures*

These are short episodes of loss of consciousness when the person suddenly stops what they are doing and does not respond when spoken to. Such absences only last a few seconds and can occur many times a day. Absence seizures are most often observed in children.

##### *Generalized tonic-clonic seizures (GTC)*

The persons lose consciousness, fall, and their body stiffens, and thereafter they may have cramps in their arms and legs. During the seizure, their breathing will stop, they may foam at the mouth, and occasionally they may involuntarily release urine and faeces.

##### *Myoclonic seizures*

There are short-lasting jerks of just a few seconds, most often in the arms and shoulders. The person is conscious during the seizure.

##### *Atonic seizures*

The persons suddenly lose strength in their body and falls.

## **Partial seizures**

### *Simple partial seizures (SPS)*

These types of seizures vary greatly, depending on the area of the brain in which they originate. For example, the seizure may be manifest as jerking movements in one hand, the persons may have a strange feeling in their legs, experience strange tastes and smells, or they may have abdominal discomfort or pain. Some persons have psychological symptoms, such as anxiety or fear. Usually, the person is conscious throughout the attack.

### *Complex partial seizures (CPA)*

These attacks, too, can vary greatly. However, a person experiencing a CPA attack will have a reduced level of awareness and will appear absent. Often, they will stop talking, they may pick at their clothing, make chewing movements, lick their lips, swallow, and repeat whatever they doing over and over again. Some may get up and walk about rather aimlessly.

### **Partial seizures with secondary generalization**

Both simple and complex partial seizures may develop into generalized seizures, usually GTC attacks.

## **Status epilepticus**

On rare occasions, an epileptic seizure may not stop or one attack will follow straight after another. This condition is called status epilepticus. *It is a serious condition and requires immediate hospitalization (see next page).*

## **First Aid for seizures:**

- Stay calm. A seizure will not be painful and most seizures will end within 2–3 minutes. Keep a note of the time.
- Ensure that the persons are as comfortable as possible and protect their head from injury.
- Do not put anything between their teeth, as this could damage them. Do not give the person anything to drink during the seizure.
- Do not attempt to stop the spasms or try to 'revive' the person. Leave them undisturbed until the seizure has stopped. When the spasms have subsided, it is important to ensure the person's airway is clear.
- When the seizure is over, the person will be tired. It is important to establish contact before allowing them to sleep.
- Telephone the person's parents (see next page for telephone numbers)
- For long-lasting seizures (i.e. more than 3–5 minutes), the person should be given medication by mouth to stop the seizure (see below).
- Medical attention or hospitalization is only required if the person is injured, if their seizure is prolonged, or if they have repeated attacks without becoming fully conscious between them.

**If the seizure lasts longer than 3–5 minutes:**

- Administer the prescribed medication. This can be found .....
- Wait 10 minutes. If the attack still has not stopped, try to give the medicine again
- Ring 113 for an ambulance.
- If there is more than one seizure after another without the person gaining consciousness between them, ring 113 for an ambulance.

**Status epilepticus**

On rare occasions, an epileptic seizure may not stop or one attack will follow straight after another. This condition is called status epilepticus. *It is a serious condition and requires immediate hospitalization.*

See Norsk Epilepsiforbund's web page, [www.epilepsi.no](http://www.epilepsi.no) for more information.

## **Information on XX, ID No. xxxx xxxxx, in connection with hospitalization**

XX suffers from Juvenile Neuronal Ceroid Lipofuscinosis (Spielmeier-Vogt disease), a progressive disorder that primarily attacks the nervous system. He/She is blind and has epileptic seizures (GTC) at irregular intervals.

XX currently takes the following medications to prevent seizures:

Medication 1:	xxx mg morning and evening
Medication 2:	xxx mg morning and evening
Medication 3:	xxx mg morning and evening

He/She does not take any other medications, but if necessary Buccolam® mouthwash (Midazolam, one 10 mg syringe), can be given inside the cheek to stop the seizure.

XX is a patient at ....., where XX's condition and disease is known.

.....: Tel. (0000) 0000 0000 Contact person: .....
---

NCurrently, XX has no known allergies or any other disorders or disease symptoms.

*XX is not aware of his/her diagnosis or the expected development of the condition.  
He/She is aware that he/she is blind and has epilepsy.*

XX's parents should be informed, if for any reason they are not present when XX is admitted to hospital:

Mother:	First name, Surname, Tel. (0000) 0000 0000
Father:	First name, Surname, Tel. (0000) 0000 0000

XX's address is: .....



**NEURONAL CEROID LIPOFUSCINOSIS (NCL) STUDY GROUP  
UNIFIED BATTEN DISEASE RATING SCALE**

All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.

SUBJECT NO.    INITIALS (First, Middle, Last)    SITE NO.

DATE INFO OBTAINED (mm/dd/yyyy)

**I. PHYSICAL ASSESSMENT**

1. SPEECH CLARITY 1.

- 0 = normal
- 1 = unclear, no need to repeat
- 2 = must repeat to be understood
- 3 = mostly incomprehensible
- 4 = anarthria

1A. ABNORMAL REPETITIVE SPEECH SOUNDS 1A.

- 0 = none
- 1 = sometimes
- 2 = most of the time
- 3 = constant
- 4 = anarthric

2. TONGUE PROTRUSION 2.

- 0 = maintains full protrusion for 10 seconds
- 1 = maintains full protrusion for more than 5 seconds
- 2 = maintains full protrusion for less than 5 seconds
- 3 = cannot fully protrude tongue
- 4 = cannot protrude tongue beyond lips

3. VISUAL ACUITY 3.

- 0 = normal
- 1 = mildly impaired
- 2 = finger counting only
- 3 = light/dark perception
- 4 = blind

4. PASSIVE MOTION-ARMS Right  4a. Left  4b.

- 0 = normal tone/full range
- 1 = mildly increased tone/full range
- 2 = moderately increased tone/full range
- 3 = markedly increased tone/incomplete range
- 4 = minimal or no passive range of motion

5. PASSIVE MOTION-LEGS Right  5a. Left  5b.

- 0 = normal tone/full range
- 1 = mildly increased tone/full range
- 2 = moderately increased tone/full range
- 3 = markedly increased tone/incomplete range
- 4 = minimal or no passive range of motion

6. PASSIVE MOTION-NECK 6.

- 0 = normal tone/full range
- 1 = mildly increased tone/full range
- 2 = moderately increased tone/full range
- 3 = markedly increased tone/incomplete range
- 4 = minimal or no passive range of motion

7. POWER-ARMS Right  7a. Left  7b.

- 0 = full power
- 1 = pronator drift/mild weakness
- 2 = moderate weakness/able to actively resist
- 3 = severe weakness/able to overcome gravity
- 4 = paralysis/unable to overcome gravity



**All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.**

8. POWER-LEGS 8a. <sup>Right</sup> 8b. <sup>Left</sup>

- 0 = full power
- 1 = mild weakness
- 2 = moderate weakness/able to actively resist
- 3 = severe weakness/able to overcome gravity
- 4 = paralysis/unable to overcome gravity

9. HAND TAPS (table or thigh) 9a. <sup>Right</sup> 9b. <sup>Left</sup>

- 0 = normal for age
- 1 = mild slowing and or reduction in amplitude
- 2 = moderately impaired; definite and early fatiguing; may have occasional arrests in movement
- 3 = severely impaired; frequent hesitation in initiating movements or arrests in ongoing movements
- 4 = cannot perform the task

10. MAXIMAL DYSTONIA (UPPER EXTREMITIES) 10a. <sup>Right</sup> 10b. <sup>Left</sup>

- 0 = absent
- 1 = slight/intermittent
- 2 = mild/persistent or moderate/intermittent
- 3 = moderate/persistent or marked/intermittent
- 4 = marked/prolonged

11. NORMAL SPONTANEOUS MOVEMENTS 11.

- 0 = normal
- 1 = minimally reduced (could be normal)
- 2 = mildly diminished
- 3 = moderately diminished
- 4 = markedly diminished, or absent

12. GAIT 12.

- 0 = normal gait
- 1 = small steps and/or slow
- 2 = walks with difficulty
- 3 = requires assistance

4 = cannot walk

13. RETROPULSION PULL TEST 13.

- 0 = normal
- 1 = recovers spontaneously, may take a step back
- 2 = would fall if not caught
- 3 = tends to fall spontaneously
- 4 = cannot stand

14. HEEL STOMPING 14a. <sup>Right</sup> 14b. <sup>Left</sup>

- 0 = normal
- 1 = mild slowing or reduced amplitude
- 2 = definite and early fatiguing or occasional arrests in movement
- 3 = frequent hesitation in initiating movement or arrests in ongoing movement
- 4 = cannot perform task

15. MOTOR TICS OR STEREOTYPIES 15.

- 0 = absent
- 1 = rare
- 2 = mild/common or moderate/intermittent
- 3 = moderate/common
- 4 = marked/prolonged

16. MYOCLONUS 16.

- 0 = absent
- 1 = rare
- 2 = mild/common or moderate/intermittent
- 3 = moderate/common
- 4 = marked/prolonged

17. REST TREMOR 17.

- 0 = absent
- 1 = mild amplitude and infrequently present
- 2 = mild amplitude and usually present
- 3 = moderate amplitude and usually present
- 4 = marked amplitude and usually present





**All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.**

18. TREMOR WITH MAINTAINED POSTURE OR ACTION 18.

- 0 = absent
- 1 = mild amplitude with action
- 2 = moderate amplitude with action
- 3 = moderate amplitude with action or sustention
- 4 = marked amplitude with action or sustention

19. DYSMETRIA (Finger-to-Nose) 19.

- 0 = normal
- 1 = mild irregularity
- 2 = moderate irregularity
- 3 = marked irregularity
- 4 = unable to hit target

20. APPENDICULAR CHOREA 20.

- 0 = absent
- 1 = slight/intermittent
- 2 = mild/common or moderate intermittent
- 3 = moderate/common
- 4 = marked prolonged

21. WEIGHT(lbs.) 21.    .

22. MOTOR EXAMINER 22.

**II. SEIZURE ASSESSMENT**

23. GENERALIZED TONIC/CLONIC SEIZURES: AVERAGE FREQUENCY 23.

- 0 = none
- 1 = fewer than one per 6 months
- 2 = between one per 3 months and one per 6 months
- 3 = between one per month and one per 3 months
- 4 = between one per week and one per month
- 5 = between one per day and one per week
- 6 = more than one per day

24. GENERALIZED TONIC/CLONIC SEIZURES: POST-ICTAL PERIOD 24.

- 0 = none/not-applicable
- 1 = less than 1 minute
- 2 = between 1 and 10 minutes
- 3 = between 10 minutes and 1 hour
- 4 = between 1 hour and 3 hours
- 5 = more than 3 hours

25. ATONIC SEIZURES: AVERAGE FREQUENCY 25.

- 0 = none
- 1 = fewer than one per 6 months
- 2 = between one per 3 months and one per 6 months
- 3 = between one per month and one per 3 months
- 4 = between one per week and one per month
- 5 = between one per day and one per week
- 6 = more than one per day

26. MYOCLONIC SEIZURES: AVERAGE FREQUENCY 26.

- 0 = none
- 1 = fewer than one per 6 months
- 2 = between one per 3 months and one per 6 months
- 3 = between one per month and one per 3 months
- 4 = between one per week and one per month
- 5 = between one per day and one per week
- 6 = more than one per day

27. COMPLEX PARTIAL SEIZURES WITHOUT GENERALIZATION AND/OR ABSENCE: AVERAGE FREQUENCY 27.

- 0 = none
- 1 = fewer than one per 6 months
- 2 = between one per 3 months and one per 6 months
- 3 = between one per month and one per 3 months
- 4 = between one per week and one per month
- 5 = between one per day and one per week
- 6 = more than one per day



**All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.**

28. COMPLEX PARTIAL SEIZURES WITHOUT GENERALIZATION: POST-ICTAL PERIOD 28.

- 0 = none/not-applicable
- 1 = less than 1 minute
- 2 = between 1 and 10 minutes
- 3 = between 10 minutes and 1 hour
- 4 = between 1 hour and 3 hours
- 5 = more than 3 hours

29. SIMPLE PARTIAL SEIZURES: AVERAGE FREQUENCY 29.

- 0 = none
- 1 = fewer than one per 6 months
- 2 = between one per 3 months and one per 6 months
- 3 = between one per month and one per 3 months
- 4 = between one per week and one per month
- 5 = between one per day and one per week
- 6 = more than one per day

30. SIMPLE PARTIAL SEIZURES: AVERAGE DURATION OF EVENT 30.

- 0 = none/not-applicable
- 1 = less than 1 minute
- 2 = between 1 and 10 minutes
- 3 = between 10 minutes and 1 hour
- 4 = between 1 hour and 3 hours
- 5 = more than 3 hours

31. FREQUENCY OF INJURY RELATED TO SEIZURES 31.

- 0 = never
- 1 = sometimes
- 2 = usually
- 3 = always

32. MAXIMAL LEVEL of CARE FOR SEIZURE COMPLICATIONS (due to any seizure type/past 6 months) 32.

- 0 = none/no care required
- 1 = first aid at home
- 2 = paramedic called

3 = emergency department visit

33. HOSPITALIZATION REQUIRED FOR TREATMENT OF SEIZURES (due to any seizure type/past 6 months) 33.

- 0 = none/not applicable
- 1 = once
- 2 = more than once

34. ANTICONVULSANT ADJUSTMENT REQUIRED TO CONTROL SEIZURES IN PAST MONTH (1 = Yes, 2 = No) 34.

35. SEIZURE ASSESSOR 35.

**III. BEHAVIORAL ASSESSMENT (past month)**

36. SAD MOOD  
36a. Frequency  36b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

37. APATHY  
37a. Frequency  37b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

38. ANXIETY  
38a. Frequency  38b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |



**All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.**

**39. AGGRESSION TOWARD OTHERS**

39a. Frequency  39b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

**40. AGGRESSION TOWARD SELF**

40a. Frequency  40b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

**41. STEREOTYPED/REPETITIVE BEHAVIOR**

41a. Frequency  41b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

**42. COMPULSIONS**

42a. Frequency  42b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

**43. AUDITORY HALLUCINATIONS**

43a. Frequency  43b. Severity

- |                   |              |
|-------------------|--------------|
| 0 = never         | 0 = none     |
| 1 = sometimes     | 1 = mild     |
| 2 = frequent      | 2 = moderate |
| 3 = almost always | 3 = severe   |

**44. OBSESSIONS**

44a. Frequency  44b. Severity

- |               |          |
|---------------|----------|
| 0 = never     | 0 = none |
| 1 = sometimes | 1 = mild |

2 = frequent                      2 = moderate  
3 = almost always              3 = severe

45. MEDICATION REQUIRED FOR BEHAVIOR 45.

(1 = Yes, 2 = No)

46. BEHAVIORAL ASSESSOR 46.

CONTINUE ON NEXT PAGE



All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.

**IV. CAPABILITY ASSESSMENT ASSUMING NORMAL VISION** (answer as if child's vision were normal)

47. SCHOOL 47.

- 0 = unable to attend special needs classroom
- 1 = requires special needs classroom
- 2 = marginal ability in mainstream classroom
- 3 = normal ability in mainstream classroom

48. CHORES 48.

- 0 = unable to do even simple chores
- 1 = able to do simple chores with help
- 2 = able to do simple chores independently
- 3 = able to do all age appropriate chores independently

49. PLAY 49.

- 0 = unable to play even simple games
- 1 = able to play simple games with help
- 2 = able to play simple games independently
- 3 = able to play age appropriate games independently

50. ADL 50.

- 0 = total care
- 1 = gross tasks only
- 2 = minimal impairment
- 3 = normal

51. CARE LEVEL 51.

- 0 = full time skilled nursing
- 1 = chronic care at home
- 2 = home

**V. CAPABILITY ASSESSMENT GIVEN ACTUAL VISION**

52. SCHOOL 52.

- 0 = unable to attend special needs classroom
- 1 = requires special needs classroom
- 2 = marginal ability in mainstream classroom
- 3 = normal ability in mainstream classroom

53. CHORES 53.

- 0 = unable to do even simple chores
- 1 = able to do simple chores with help
- 2 = able to do simple chores independently
- 3 = able to do all age appropriate chores independently

54. PLAY 54.

- 0 = unable to play even simple games
- 1 = able to play simple games with help
- 2 = able to play simple games independently
- 3 = able to play age appropriate games independently

55. ADL 55.

- 0 = total care
- 1 = gross tasks only
- 2 = minimal impairment
- 3 = normal

56. CARE LEVEL 56.

- 0 = full time skilled nursing
- 1 = chronic care at home
- 2 = home

57. CAPABILITY ASSESSOR 57.



**All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.**

**VI. NCL HISTORY (TO BE COMPLETED BY FIRST RATER)**

**Instructions:** For each symptom, ask if child has experienced the symptom and if so, obtain approximate age of onset in years and months (e.g., age 4 1 / 2 should be coded as 04 for years and 06 for months). For each symptom reported as experienced, the rater should rank in order of onset beginning with 1. If child has not experienced symptom, code as N for not applicable.

Symptom	Experienced Symptom 0 = No, 1 = Yes	Onset Age		Rater Ranking Order of Onset (1 = first, 8 = last)
		Years	Months	
58a. Loss of vision	58a. <input type="checkbox"/>	58a1. <input type="text"/> <input type="text"/>	58a2. <input type="text"/> <input type="text"/>	58a3. <input type="checkbox"/>
58b. Motor difficulties	58b. <input type="checkbox"/>	58b1. <input type="text"/> <input type="text"/>	58b2. <input type="text"/> <input type="text"/>	58b3. <input type="checkbox"/>
58c. Cognitive difficulties	58c. <input type="checkbox"/>	58c1. <input type="text"/> <input type="text"/>	58c2. <input type="text"/> <input type="text"/>	58c3. <input type="checkbox"/>
58d. Behavioral difficulties	58d. <input type="checkbox"/>	58d1. <input type="text"/> <input type="text"/>	58d2. <input type="text"/> <input type="text"/>	58d3. <input type="checkbox"/>
58e. Seizures	58e. <input type="checkbox"/>	58e1. <input type="text"/> <input type="text"/>	58e2. <input type="text"/> <input type="text"/>	58e3. <input type="checkbox"/>
58f. Weight loss/feeding difficulties	58f. <input type="checkbox"/>	58f1. <input type="text"/> <input type="text"/>	58f2. <input type="text"/> <input type="text"/>	58f3. <input type="checkbox"/>
58g. Sleep disturbance	58g. <input type="checkbox"/>	58g1. <input type="text"/> <input type="text"/>	58g2. <input type="text"/> <input type="text"/>	58g3. <input type="checkbox"/>
58h. Other (Specify) _____ _____ _____	58h. <input type="checkbox"/>	58h1. <input type="text"/> <input type="text"/>	58h2. <input type="text"/> <input type="text"/>	58h3. <input type="checkbox"/>

**59. COMMENTS** \_\_\_\_\_

**60. NCL HISTORY RATER**

60.

**VII. CLINICAL SUMMARY**

**61. ASSESSOR'S GLOBAL IMPRESSION OF CHANGE  
SINCE LAST ASSESSMENT**

61.

- 1 = much better
- 2 = somewhat better
- 3 = about the same
- 4 = somewhat worse
- 5 = much worse
- N = not applicable (never seen before)

SUBJECT NUMBER

INITIALS (First, Middle, Last)



---

**All items must be completed. Use U if information is Unavailable. Use N if Information is Not Applicable.**

---

**62. CLINICAL GLOBAL IMPRESSION – SEVERITY OF SEIZURES**

62.

- 1 = none
- 2 = minimal
- 3 = mild
- 4 = moderate
- 5 = severe

**63. CLINICAL GLOBAL IMPRESSION – COGNITIVE FUNCTION**

63.

- 1 = no impairment
- 2 = minimally impaired
- 3 = mildly impaired
- 4 = moderately impaired
- 5 = severely impaired

**64. CLINICAL GLOBAL IMPRESSION – BEHAVIOR**

64.

- 1 = no impairment
- 2 = minimally impaired
- 3 = mildly impaired
- 4 = moderately impaired
- 5 = severely impaired

**65. CLINICAL GLOBAL IMPRESSION – MOOD**

65.

- 1 = no impairment
- 2 = minimal distress
- 3 = mild distress
- 4 = moderate distress
- 5 = severe distress

**66. CLINICAL GLOBAL IMPRESSION – MOTOR**

66.

- 1 = no impairment
- 2 = minimally impaired
- 3 = mildly impaired
- 4 = moderately impaired
- 5 = severely impaired

**67. CLINICAL GLOBAL IMPRESSION – OVERALL**

67.

- 1 = no impairment
- 2 = minimally impaired
- 3 = mildly impaired
- 4 = moderately impaired
- 5 = severely impaired

**68. CLINICAL SUMMARY RATER**

68.

## Appendix 3

### **Hamburg Rating Scale for JNCL**

<b>Problem</b>	<b>Function</b>	<b>Score</b>
<b>Vision</b>	Normal	3
	Poor, but good orientation	2
	Poor, orientation difficult	1
	Blind	0
<b>Intellect</b>	Normal	3
	Abstract thinking difficult	2
	Clear signs of dementia	1
	Total loss	0
<b>Speech</b>	Normal	3
	Minor difficulties	2
	Difficult to understand	1
	No verbal contact	0
<b>Motor skills</b>	Normal	3
	Slightly handicapped	2
	Mainly uses a wheelchair; some mobility preserved	1
	Immobile; bedridden	0
<b>Epilepsy – (only GTC)</b>	No seizure	3
	1–2 per year	2
	< 1 per month, < 12 per year	1
	> 12 per year	0







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