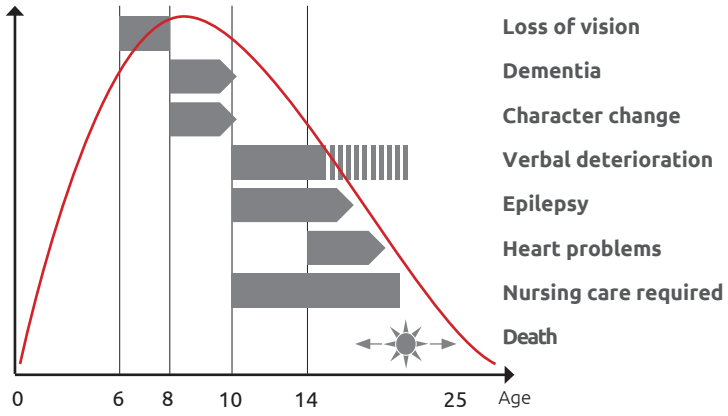
Epilepsy, developmental regression, vision loss – it could be NCL!

What is **NCL**?

Neuronal Ceroid Lipofuscinosis is a genetic lysosomal storage disorder. Genetic defects in one of the 13 CLN genes which are currently known result in lipopigments becoming locked in the lysosomes in almost all body tissues. The nerve cells in the brain's grey matter are, however, subject to the most damage. The disease is generally caused by autosomal recessive inheritance. NCL disorders are the most common group of neurodegenerative diseases among children and adolescents, with sufferers experiencing deterioration of cognitive and motor abilities, epilepsy, diffuse retinal degeneration and reduced life expectancy.



Progress of juvenile NCL (CLN3)

When could **NCL** be the cause of illness?

If the following are present i**n combination**:

- **Loss of visual acuity (unclear retinopathy)**
- **Delayed speech development**
- **Developmental regression (incl. dementia)**
- **Epilepsy**

An NCL disorder should be considered as a cause if at least two of the symptoms are present in combination. Initially sufferers' development is usually completely in line with their age, until the disease breaks out, causing their first seizures or their psycho-motoric development to stagnate.

In the case of the CLN3 form the first symptom is often a progressively worsening visual impairment at school age, caused by retinopathy.

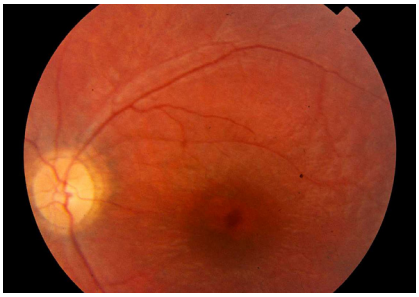
How can **NCL** be diagnosed?

Depending on the age at which NCL manifests and the sufferer's clinical picture, the cause can be narrowed down to a specific form of the disorder, using molecular-genetic criteria to obtain the diagnosis.

In the case of unclear loss of visual acuity and suspected retinopathy, a thorough examination by an ophthalmologist will be required (such as an electroretinogram or optical coherence tomography) to identify changes to the eyes which are typical for NCL.

CAVE incorrect diagnoses:

- Epilepsy with an unclear origin in combination with delayed speech development
- Retinopathia pigmentosa



Juvenile NCL fundus with so-called bull's eye maculopathy.

NCL-Stiftung
Für eine Zukunft ohne Kinderdemenz

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Suspected NCL!

How can **NCL** be diagnosed?

NEW-BORN
Epilepsy, Mikrocephaly

Enzyme test

Cathepsin D activity (in leukocytes, fibroblasts) **missing**

Dry blood spot card

CLN10

Genetic examination

TODDLER
Developmental stagnation or regression and/or epilepsy with an unclear origin

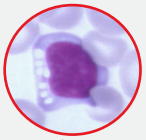
Enzyme test

PPT1 **missing**	TPP1 **missing**	both inconclusive
Dry blood spot card	Dry blood spot card	Electron microscopy*
CLN1	CLN2	CLN5, 6, 7, 8, 14

Genetic examination

SCHOOLCHILD
Loss of visual acuity and/or epilepsy

Lymphocyte test

no vacuoles	no vacuoles	**Vacuoles**
Test PPT, TTP, CtsD	both inconclusive	 Lymphocyte vacuoles in JNCL
CLN1, 2, 10	CLN5, 6, 7, 8, 12	CLN3

Genetic examination

YOUNG ADULT
Unspecific mental, motor or behavioural problems

Enzyme test

CtsD, PPT1, TPP1 activity **missing**	inconclusive
Test PPT, TTP,CtsD	Electron microscopy*
CLN1, 2, 10	CLN4, 6, 11, 13

Genetic examination

**Alternatively panel diagnosis of all genes*

What are the treatment options for **NCL**?

Palliative therapies

- Control of symptoms for epilepsy, disturbed sleep, movement disorder, behavioural problems, swallowing difficulties (PEG gastronomy), breathing/secretion problems (aspirators)
- Movement therapies – physiotherapy, speech therapy, ergotherapy, equine-assisted therapy
- Adequate provision of aids

Recommendation for palliative medication:

- Epilepsy: **Valproate** and **Lamotrigine**
- Spasticity: **Baclofen** and **Tizanidine**
- Myoclonus: **Pregabalin, Piracetam** and **Zonisamide**

Not recommended:

- **Phenytoin, Vigabatrin** and **Carbamazepine**

Causal therapies

- Development of causal therapeutic approaches is difficult as the pathomechanism of some sub-forms of NCL is not yet known
- Since July 2017, an approved intraventricular enzyme replacement therapy has been available to CLN2 patients
- Experimental therapy: gene therapy for some sub-forms of NCL (in preparation)

Advice on **NCL**-related issues

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Certified NCL online further training (2 CME) at *Medlearning.de*

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Source: Diagnostic algorithm for NCL diseases, DEM-Child
A.Schulz et al. / Biochimica et Biophysica Acta 1832 (2013) 1801-1806

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