Autosomal dominant adult neuronal ceroid lipofuscinosis

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Chapter 1

NCL Introduction

Neuronal Ceroid Lipofuscinosis

Introduction

As a group, the Neuronal ceroid lipofuscinoses (NCLs) form the most common inherited progressive childhood encephalopathies, with an incidence of between 1 and 5 per 100000 live births in different countries, while prevalence is estimated between 1 and 3 per million.[1] Accumulation of intracellular autofluorescent storage material and neurodegeneration are features of this heterogenous group of diseases, which lead to visual impairment, epilepsy, motor disorders and cognitive deterioration.

Adult presentation is very uncommon, and knowledge of adult forms is very limited compared to the childhood forms. NCLs show recessive inheritance, except for the extremely uncommon autosomal dominant adult form, of which only a few families have been reported. This dominant adult NCL form is the subject of this thesis.

The scanty literature on dominant adult NCL is reviewed below, but in this chapter we will also briefly review the knowledge of the different childhood NCLs and recessive adult NCL (Kufs' disease), as a background to further chapters on the dominant adult form.

Several excellent monographs on NCL provide more detailed information on this topic[2] [3] [4] [5].

Classification

Classically, distinction of different forms of NCL was based on age at onset[6]:

- infantile NCL (INCL , Hagberg-Santavuori disease or Haltia-Santavuori disease)
- late infantile NCL (LINCL or Jansky- Bielschowsky disease)

- juvenile NCL (JNCL , Spielmayer -Vogt or Batten-Mayou disease, which was first described by Stengel in 1826) [7]
- adult NCL (ANCL or Kufs' disease)

Later, identification of the ultrastructural morphology of the storage material added specificity to distinguish several forms:
electron microscopy shows

- granular osmiophilic deposits (GRODs) in INCL [9],
- curvilinear patterns in LINCL [10],
- fingerprint profiles in JNCL [11], and
- mixed patterns in ANCL. [12]

Thus previously, NCL's were categorized on the basis of age of onset, clinical course, and histopathology. Later the major classification system was based on genotype[2], which will also be used in this chapter. Erroneously assuming that each clinical form was caused by a single genetic defect, gene labels CLN1 - 4 were assigned even before genetic defects were known. Now, of the presumed ten variants (CLN1-CLN10), eight genes have been identified, with more than 250 different mutations[13]. It is now clear that there is not always a one to one relationship between genotype and phenotype, e.g. CLN1 can present at all ages with varying clinical presentation[14]. Furthermore, great intrafamilial heterogeneity in mental or physical handicap is seen in JNCL[15], which indicates multifactorial etiology.
While the term Batten disease is still used frequently as a label to all NCL's as a group , the use of eponyms like Hagberg-Haltia-Santavuori, Jansky-Bielschowsky, Batten-Spielmayer-Vogt-Sjögren, Kufs' and Parry disease is discouraged and largely abandoned. In this thesis they are included for historical reasons, realizing that they do not represent uniform nosological entities, which is also true for labels like INCL or LINCL. Similar to other neurodegenerative diseases, depending on the

goal and principal focus of a clinician, pathologist, geneticist or researcher, this heterogenous group of diseases could be classified on age, symptoms and signs, genes, proteins (storage protein [e.g. SCMAS or saposins] or defective enzyme, either soluble or structural), histology or ultrastructure, or involved pathophysiological pathways like apoptosis or protein degradation.
Persaud-Sawin et al indicate that the defective proteins in different NCL's may interact along a single pathway. Their view is supported by the fact that most NCL variants manifest cell death and dysregulated sphingolipid metabolism, while several CLN proteins co-immunoprecipitate, and because some CLN proteins correct disturbances caused by other CLN proteins (e.g. CLN2 protein corrects growth and apoptosis in CLN3-, CLN6-, and CLN8-deficient cell lines).[16]

We will now present a short review of all human NCL forms, using the genetic classification as an index.

CLN1

Infantile neuronal ceroid lipofuscinosis (INCL)

Hagberg-Santavuori disease or Haltia-Santavuori disease

MIM 256730

The infantile form of neuronal ceroid lipofuscinosis (INCL; CLN1) is the most severe and earliest onset form of NCL, starting around 1.5 years of age. Cardinal features are early developmental deterioration, retinal blindness, microcephaly, and seizures. INCL is caused by more than 50 mutations in the CLN1 gene on chromosome 1p32. CLN1 defects may also present at later age. They cause deficiency of palmitoyl protein thioesterase 1 (PPT1), a lysosomal enzyme which removes fatty acids from fatty-acylated cysteine residues in proteins, which may also have

other functions in axons and synapses. Accumulation of granular osmiophilic deposits (GRODS) which contain saposins A and D is seen in tissues, and abundant death of neocortical neurons occurs. [17] After Santavuori's 1973 description of INCL [18], most cases were reported from Scandinavia initially, but the disease occurs worldwide.
Prospects for therapy include enzyme replacement, stem cell transplantation, gene therapy, and metabolic therapy aimed at depleting the abnormal substrate accumulation in the disease. [19]

CLN2

Late infantile neuronal ceroid lipofuscinosis (LINCL)

Jansky- Bielschowsky disease

MIM 204500

Mutations in CLN2 on chromosome 11p15 which cause loss of tripeptidyl peptidase 1 (TPP1, a lysosomal exopeptidase that sequentially removes tripeptides from the N termini of polypeptides), lead to classic late-infantile NCL (Jansky-Bielschowsky disease). More than 65 mutations are reported[13]. Electronmicroscopy of storage material shows curvilinear bodies, which are rich in subunit C of mitochondrial ATP synthase (SCMAS). LINCL usually has an onset between 1 and 5 years of age. Prevalence in the USA is around 200 children. [20] These children have progressive myoclonic seizures, ataxia, blindness and psychomotor regression that invariably results in death around age 8 to 12 years.

CLN3

Juvenile neuronal ceroid-lipofuscinosis (JNCL) or Batten/Spielmeyer-Vogt-Sjögren disease

MIM 204200

Batten disease (a name which is also confusingly used for all NCLs), or juvenile neuronal ceroid lipofuscinosis (JNCL), results from recessively inheriting mutations (48 known, most commonly a 1.02 kb deletion) in the CLN3 gene on chromosome 16p12.1, resulting in loss of battenin activity, deposition of mitochondrial ATP synthase subunit c, ultrastructural fingerprints and some curvilinear or rectilinear bodies in many cell types, and loss of CNS neurons. This disorder presents around the age of 5 years old with visual deficits, followed by seizures, cognitive impairment, motor deterioration (ataxia, myoclonus, gait problems, spasticity), hallucinations, and premature death by the third to fourth decade of life. [21] Because neurological symptoms often present years after occurrence of visual problems, JNCL should be considered in otherwise normal children presenting with visual loss with or without fundus changes like pigmentary/atrophic changes or a bull's eye maculopathy[22].

Interestingly, Cln3(-/-) mice have autoantibodies to GAD65 in their cerebrospinal fluid and elevated levels of brain bound immunoglobulin G (IgG). IgG deposition was also found within human JNCL autopsy material, and with increased age in Cln3(-/-) mice. Lim et al indicate early systemic immune dysregulation in Cln3(-/-) mice, which contributes to a progressive inflammatory cerebral response. [23]

CLN4

Autosomal recessive adult neuronal ceroid lipofuscinosis

AR-ANCL or Kufs' disease

MIM 204300

CLN4 is the gene symbol for the adult form of NCL, but no genes have been identified yet. Individual or autosomal recessive cases are referred to as Kufs' disease, while autosomal dominant adult NCL is also known as Parry disease. It is very unlikely that these 2 forms are caused by a single gene, which led some authors to suggest to use CLN5 for dominant ANCL[24], but CLN5 was soon used as the genetic label for variant LINCL. Ever since, Kufs' and Parry disease are usually lumped together under the CLN4 heading[25].

Adult NCL presents between 10 and 50 (or arguably 65[26]) years of age with epilepsy, ataxia, parkinsonism, myoclonus and cognitive decline and behavioral problems. In most cases no visual symptoms occur, and retinal pathology is usually absent.

Berkovic et al. reviewed 118 cases published as Kufs' disease, but only 50 cases fulfilled their diagnostic criteria, where fingerprint profiles or granular osmiophilic deposits by electron microscopy were considered mandatory for definitive diagnosis. Sixteen had inadequate data, 21 had a storage disease but not Kufs', 10 had no neuronal storage, and 21 had atypical clinical features outside the spectrum of Kufs' disease. The 50 accepted cases were separated into two clinical phenotypes: Type A with progressive myoclonus epilepsy, often with photosensitivity, dementia and movement disorders; Type B with dementia, motor disturbances and often facial myoclonus.[27]

Autosomal dominant adult neuronal ceroid lipofuscinosis or Parry disease

MIM 162350

Autosomal dominant adult NCL (AD-ANCL) is reviewed more extensively because it is the subject of this thesis. AD-ANCL is very rare, with only 3 American and 2 Spanish families reported apart from our Dutch family. Because of the scarce literature on AD-ANCL individual data of reported family members are summarized.

Boehme et al.[28] described the first family (the 'Parry' family) with dominantly inheriting ANCL in 1971. They were living in southern New Jersey, but were from British descent. Four affected generations are reported, with details of all 6 affected members in generation IV only, but without medical information of previous generations. The pedigree indicates autosomal dominant inheritance.
These 6 family members from the Parry family are described in more detail now:

IV-2

He had an epileptic seizure preceded by seeing bright spots at the age of 39, with cognitive problems, ataxia, weakness in the left arm, nystagmus, myoclonus and dysphasia. He also had 'multicoloured scotomata'. Presence of a polyneuropathy was suggested by EMG, and later by absent tendon reflexes and wasting. EEG showed bilaterally synchronous spikes and sharp waves. He died at the age of 47. Autopsy showed cerebellar atrophy, with PAS-positive granular aggregates in neurons and astrocytes, cerebellar demyelination and loss of neurons.

IV-3

He had a first seizure at the age of 32. Cognitive deterioration with apraxia and dysgraphia, myoclonus, epilepsy and absent tendon reflexes

were seen. EEG showed bilaterally symmetrical spikes and waves. He died at the age of 42 years. Autopsy showed cerebellar and brainstem atrophy, distension of neuronal perikarya and proximal axons. Intraneuronal and glial autofluorescent PAS-positive storage material was abundant, with loss of neurons, e.g. in substantia nigra. Electronmicroscopy showed GRODs in neurons. [fig 11 and 12 in their paper shows GRODs in patient IV-3, very similar to findings in our AD-ANCL family].

IV-5

She had an epileptic seizure at age 30, shaking clumsy hands, progressive epilepsy, ataxia, severe action induced myoclonus, speech problems and mask face. EEG showed bilaterally rhythmic bursts.

IV-7

She had limited medical records, which mention clumsy hands at age 32, epilepsy, myoclonus, ataxia and delusions. EEG was abnormal. She died at the age of 39 years old.

IV-13

At 31 years of age he had an epileptic seizure, followed by myoclonus, impaired speech, ataxia, decreased tendon reflexes in the legs.

IV-15

She had non-fluent speech at 33 years of age, and myoclonus. EEG showed paroxysms of sharp waves and spikes.

Armstrong et al [29] later reported reduced leukocyte peroxidase activity in patients VI-13 and IV-15 of this Parry family.

Brodner et al.[30] describe a not previously reported single patient from the Parry family, (age and description of his mother are compatible with Boehme's case V2, which is also compatible with the pedigree as shown

by Leonberg in 1982[31]) who presented at age 24 with epileptic seizures with loss of consciousness, preceded by seeing flashing bright lights. Angiography and skull x-ray showed a calcification of the left occipital lobe, where a cystic tumor was found during craniotomy, which was identified as a low-grade astrocytoma. Irregular electron dense bodies were found in a biopsy of occipital cortex, but also in tumor cells.

An update on this Parry family has been presented in 1982 by Leonberg et al[31] , which confirms the early occurrence of seizures and myoclonus, followed by cerebellar signs, dementia, speech disorder and weakness in late stages.

The second AD-ANCL family was reported in Spain by Ferrer et al.[32], who describe cerebral biopsy findings in a single patient, from a family with 6 affected individuals. Their pedigree is shown in the paper, and some details of other family members were reported: disease onset was between 33 and 37 years of age; cognitive deterioration, facial dyskinesias and epilepsy occurred. In the single patient who was described in more detail, PAS-positive storage material was seen in pyramidal neurons. Ultrastructure showed GRODs. An EEG was normal.

Badurska[33] found cytoplasmic inclusions in lymphocytes of a father of 2 children with late-infantile neuronal ceroid-lipofuscinosis (LINCL), who had had epilepsy since the age of 32. This interesting report is insufficient for a diagnosis of AD-ANCL.

Arpa[34] presented a single case from a family with dominant ANCL at the 1978 meeting of the Spanish Neurological Society, and later in a Spanish

report in 1991. Onset in this family was between age 31 and 48. Epilepsy, dementia, myoclonus, ataxia, dysarthria and pyramidal signs were seen. Ultrastructure showed GRODs in cortical neurons.

Josephson et al.[35] report a large ANCL family of English ancestry, with 10 affected persons in 5 generations, with autosomal dominant inheritance. The index patient presented at St Louis, USA, where one other family member was evaluated repeatedly, and 2 others only once. Histology was available from 3 patients, showing cortical atrophy, PAS positive storage material in neurons in many brain regions, while ultrastructure showed GRODs. These were also seen in sweat glands. Age of onset was between 32 and 40. Seven patients died at an age between 41 and 58. Seizures, dementia and movement disorders were common, but no retinal pathology was seen.
Some patients were reported in more detail:
V-3 had an abnormal EEG before occurrence of cognitive decline, dyskinesias, dystonia, and hip girdle muscle weakness.
IV-1 had jerks dementia, mask face and seizures.
IV-2 had seizures, memory loss, aphasia, mask face and myoclonus.
V-4 had jerks, chorea, dementia, myoclonus, seizures, hallucinations, and paroxysmal EEG activity
V-5 presented with seizures, while an EEG showed spikes. Myoclonus and memory decline were reported.
VI-6 presented with a seizure, with epileptiform EEG. Myoclonus and cognitive deterioration were seen.
VI-7 presented with a seizure, EEG showed spikes. He showed cognitive decline.

Burneo[36] et al. report an adult NCL family with autosomal dominant inheritance from Alabama, with 9 affected individuals in 4 affected generations, while 3 other family members had a history of seizures. The initial symptom was often a tonic clonic seizure between ages 27 and 29.
Patient B1 had a history of seizures.
C1, C2 and D1 had seizures, dementia and myoclonus.
E1 had seizures, dementia, myoclonus and parkinsonism.
E3, 4 ,5 and 6 all had seizures, dementia, myoclonus and parkinsonism.
F1 & F2 had seizures.
F4 Onset age was 30. He had dysarthria, tremor, myoclonus, ataxia, seizures and dementia. EEG showed generalized spike and slow wave discharges.
In patient E3, ultrastructure of PAS positive storage material in neurons showed GRODs, which were also found in the skin.

Ivan[37] et al. describe an African American woman with supposed dominant adult NCL. She, and her father had behavioral abnormalities, dementia and extrapyramidal signs, but no epilepsy. Fathers' brother and her paternal grandfather also had behavioral changes and memory loss. Unlike the typical GRODs in other known dominant ANCL families, fingerprint profiles were the main findings on electron microscopy. However, ultrastructure was limited to skin biopsy only, which is insufficient for a conclusive diagnosis.

CLN5

vLINCL(Fin), Finnish late infantile variant NCL

MIM 256731

CLN5 is localized to chromosome 13q22, with 18 known mutations. Subunit c of the mitochondrial ATP synthase is the major protein in brain storage cytosomes, which also contain minor amounts of sphingolipid activator proteins (SAPs) A and D[38]. Electronmicroscopy shows fingerprints, curvilinear profiles, but also rectilinear complexes[39]. It usually presents at 3-7 years of age with motor clumsiness, followed by progressive visual failure, mental decline and later by myoclonus and seizures[40]. A more aggressively developing cognitive impairment has been described in a single family. [41] Occurrence outside Scandinavia is uncommon[42, 43].

Three related patients from Colombia with a JNCL with fingerprint profiles, had a novel missense mutation in CLN5. CLN5 mutation may cause atypical late-onset neuronal ceroid lipofuscinosis, in addition to the late infantile form described in Finland.[44]

CLN6

variant Late Infantile/early juvenile NCL, 'Indian vLINCL'

MIM 601780

The CLN6 gene on chromosome 15q23 is coding for an endoplasmatic reticulum resident transmembrane protein, which interacts with collapsin response mediator protein-2 (CRMP-2) that controls axon growth[45]. Defects are responsible for relatively rare NCL cases (some 80 reported families) that resemble LINCL clinically, presenting between 1 and 8

years of age with motor delay, dysarthria, ataxia and seizures. Visual failure can be the first symptom, but is sometimes absent. Electronmicroscopy shows not the expected curvilinear profiles, but fingerprint and rectilinear profiles. Initially found in India and in Czechs with a Roman Gypsy background, now more than 40 mutations were reported from nearly all continents. This gene is also responsible for NCL in Merino sheep and South Hampshire sheep[46].

MFSD8/CLN7

variant late infantile NCL

MIM 610951

CLN7 was initially used as a gene symbol for a presumed single gene behind a clinical variant LINCL form in Turkish patients[47, 48], but the now known CLN7 mutations are not restricted to the Turkish population[49]. Furthermore, some Turkish LINCL cases are related to CLN6[50] or CLN8 mutations[51], thus 'Turkish vLINCL' is genetically heterogenous, caused by CLN 6, 7 and 8.
With the identification of the MFSD8/CLN7 gene, in Turkish and Indian families[52], it does explain a part of Turkish vLINCL, but is also seen in Italy[53], Saudi Arabia[54], and in an Egyptian family with clinical findings similar to LINCL , but without overt visual loss[55].

CLN8

Northern epilepsy

MIM 600143

Mutations in the CLN8 gene cause Northern epilepsy (progressive epilepsy with mental retardation [EPMR], OMIM 600143) and a subset of Turkish variant late infantile NCL[51]. CLN8 is one of the TRAM-Lag1-CLN8 proteins containing a Lag1 motif, which is involved in (dihydro)ceramide synthesis.[56] Northern epilepsy is an autosomal recessive syndrome with tonic-clonic seizures, and onset at 5 to 10 years of age. While epilepsy decreases after puberty, mental retardation begins 2-5 years after the onset of seizures and continues through adulthood. The patients may reach 50 or 60 years of age. Curvilinear profiles and some granular components are seen ultrastructurally, containing subunit c of mitochondrial ATP synthase[57].

CLN9

MIM 609055

This is a putative gene, postulated to explain two Serbian sisters and two German brothers with a clinical history characteristic for juvenile NCL, but with curvilinear inclusions, fingerprint profiles, and granular osmiophilic deposits in neurons, lymphocytes, and conjunctival cells. Enzyme screening and sequencing of the coding regions of other NCL genes was negative. CLN9 is mainly studied in fibroblasts, which have a distinctive phenotype of rapid growth and increased apoptosis and diminished levels of ceramide, dihydroceramide, and sphingomyelin. CLN9 protein may be a regulator of dihydroceramide synthase. [56]

CLN10

congenital NCL, cathepsin D (CTSD) deficiency

MIM 610127

Only a few patients with this rare disorder have been reported, all with similar clinical and neuropathological findings. Cathepsin D is a lysosomal aspartic protease involved in protein degradation, but it may also regulate apoptosis[58]. The cathepsin D gene causes congenital NCL in sheep. In a patient of Pakistani origin, a nucleotide duplication, c.764dupA was found in the cathepsin D gene in homozygous form in the patient, and in heterozygous form in his father. It creates a premature stop codon, predicting a truncation of the protein. Cathepsin D deficiency mutations may underlie all cases of congenital NCL. Cathepsin D deficiency should be considered as a possible diagnosis in microcephalic neonates, who present with seizures at or before birth.[59] In a prematurely born infant with microcephaly and hypertonia, a mutation in the cathepsin D gene was found[60]. He died after 2 days. Storage material composed of GRODs with saposin D was found in neurons and astrocytes.

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