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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.

References

1.Williams RE. NCL incidence and prevalence: what do we know? 12th International Congress on Neuronal Ceroid Lipofuscinoses Abstract Book 2009 www.ncl2009hamburg.de/abstracts.html

2.Mole SE, Williams RE, Goebel HH. Correlations between genotype, ultrastructural morphology and clinical phenotype in the neuronal ceroid lipofuscinoses. Neurogenetics 2005;6:107-26.

3.Goebel H-H, Mole SE, Lake BD. The neuronal ceroid lipofuscinoses (Batten disease). Amsterdam ; Washington, DC Tokyo: IOS Press Ohmsha; 1999.

4.Wisniewski KE, Zhong N. Batten disease : diagnosis, treatment, and research. San Diego: Academic Press; 2001.

5.Opitz JM. Ceroid-lipofuscinoses : Batten disease and allied disorders : proceedings of the International Conference on Ceroid-Lipofuscinoses, held on Staten Island, New York, April 30 and May 1, 1987. New York: A.R. Liss; 1988.

6.Dyken PR. The neuronal ceroid lipofuscinoses. J Child Neurol 1989;4:165-74.

7.Brean A. [An account of a strange instance of disease-- Stengel-Batten-Spielmayer-Vogt disease]. Tidsskr Nor Laegeforen 2004;124:970-71.

8.Elleder M, Lake BD, Goebel HH, Rapola J, Haltia M, Carpenter S. Definition of the ultrastructural patterns found in NCL. In: H. H. Goebel SEM, B. D. Lake, ed. The neuronal ceroid lipofuscinoses (Batten disease). Amsterdam: IOS press; 1999:5-15.

9.Haltia M, Rapola J, Santavuori P. Infantile type of so-called neuronal ceroid-lipofuscinosis. Histological and electron microscopic studies. Acta Neuropathol (Berl) 1973;26:157-70.

10.de Baecque CM, Pollack MA, Suzuki K. Late infantile neuronal storage disease with curvilinear bodies. Arch Pathol Lab Med 1976;100:139-44.

11.Goebel HH, Ikeda K, Schulz F, Burck U, Kohlschutter A. Fingerprint profiles in lymphocytic vacuoles of mucopolysaccharidoses I-H, II, III-A, and III-B. Acta Neuropathol (Berl) 1981;55:247-49.

12.Martin JJ, Libert J, Ceuterick C. Ultrastructure of brain and retina in Kufs' disease (adult type-ceroid-lipofuscinosis). Clin Neuropathol 1987;6:231-35.

13.Mole S. NCL resource - NCL mutation database. 2009 http://www.ucl.ac.uk/ncl/

14.van Diggelen OP, Thobois S, Tilikete C et al. Adult neuronal ceroid lipofuscinosis with palmitoyl-protein thioesterase deficiency: first adult-onset patients of a childhood disease. Ann Neurol 2001;50:269-72.

15.Jarvela I, Autti T, Lamminranta S, Aberg L, Raininko R, Santavuori P. Clinical and magnetic resonance imaging findings in Batten disease: analysis of the major mutation (1.02-kb deletion). Ann Neurol 1997;42:799-802.

16.Persaud-Sawin DA, Mousallem T, Wang C, Zucker A, Kominami E, Boustany RM. Neuronal ceroid lipofuscinosis: a common pathway? Pediatr Res 2007;61:146-52.

17.Lyly A, von Schantz C, Salonen T et al. Glycosylation, transport, and complex formation of palmitoyl protein thioesterase 1 (PPT1)--distinct characteristics in neurons. BMC Cell Biol 2007;8:22.

18.Santavuori P, Haltia M, Rapola J, Raitta C. Infantile type of so-called neuronal ceroid-lipofuscinosis. 1. A clinical study of 15 patients. J Neurol Sci 1973;18:257-67.

19.Hofmann SL, Das AK, Lu JY, Soyombo AA. Positional candidate gene cloning of CLN1. Adv Genet 2001;45:69-92.

20.Dyke JP, Voss HU, Sondhi D et al. Assessing disease severity in late infantile neuronal ceroid lipofuscinosis using quantitative

MR diffusion-weighted imaging. AJNR Am J Neuroradiol 2007;28:1232-36.

21.Weimer JM, Benedict JW, Elshatory YM et al. Alterations in striatal dopamine catabolism precede loss of substantia nigra neurons in a mouse model of juvenile neuronal ceroid lipofuscinosis. Brain Res 2007;1162:98-112.

22.Collins J, Holder GE, Herbert H, Adams GG. Batten disease: features to facilitate early diagnosis. Br J Ophthalmol 2006;90:1119-24.

23.Lim MJ, Alexander N, Benedict JW et al. IgG entry and deposition are components of the neuroimmune response in Batten disease. Neurobiol Dis 2007;25:239-51.

24.Dyken P, Wisniewski K. Classification of the neuronal ceroid-lipofuscinoses: expansion of the atypical forms. Am J Med Genet 1995;57:150-54.

25.Mole SE. Batten's disease: eight genes and still counting? Lancet 1999;354:443-45.

26.Constantinidis J, Wisniewski KE, Wisniewski TM. The adult and a new late adult forms of neuronal ceroid lipofuscinosis. Acta Neuropathol 1992;83:461-68.

27.Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kufs' disease: a critical reappraisal. Brain 1988;111:27-62.

28.Boehme DH, Cottrell JC, Leonberg SC, Zeman W. A dominant form of neuronal ceroid-lipofuscinosis. Brain 1971;94:745-60.

29.Armstrong D, Dimmitt S, Boehme DH, Leonberg SCJ, Vogel W. Leukocyte peroxidase deficiency in a family with a dominant form of Kuf's disease. Science 1974;186:155-56.

30.Brodner RA, Noh JM, Fine EJ. A dominant form of adult neuronal ceroidlipofuscinosis (Kufs' disease) with an associated occipital astrocytoma: early diagnosis by cortical biopsy. J Neurol Neurosurg Psychiatry 1976;39:231-38.

31.Leonberg SC, Armstrong D, Boehme DH. A century of Kufs disease in an American family. In: D Armstrong, N Koppang, JA Rider, eds. Ceroid-lipofuscinosis (Batten's disease). Amsterdam: Elsevier biomedical; 1982:87-94.

32.Ferrer I, Arbizu T, Pena J, Serra JP. A golgi and ultrastructural study of a dominant form of Kufs' disease. J Neurol 1980;222:183-90.

33.Badurska B, Fidzianska A, Jedrzejowska H. A dominant form of neuronal ceroid-lipofuscinosis. An ultrastructural study of sural nerve and peripheral lymphocytes. J Neurol 1981;226:205-12.

34.Arpa J, Anciones B, Gutierrez M et al. [Our experience with Kufs disease: familial form and sporadic case]. Neurologia 1991;6:222-27.

35.Josephson SA, Schmidt RE, Millsap P, McManus DQ, Morris JC. Autosomal dominant Kufs' disease: a cause of early onset dementia. J Neurol Sci 2001;188:51-60.

36.Burneo JG, Arnold T, Palmer CA, Kuzniecky RI, Oh SJ, Faught E. Adult-onset neuronal ceroid lipofuscinosis (Kufs disease) with autosomal dominant inheritance in Alabama. Epilepsia 2003;44:841-46.

37.Ivan CS, Saint-Hilaire MH, Christensen TG, Milunsky JM. Adult-onset neuronal ceroid lipofuscinosis type B in an African-American. Mov Disord 2005;20:752-54.

38.Tyynela J, Suopanki J, Santavuori P, Baumann M, Haltia M. Variant late infantile neuronal ceroid-lipofuscinosis: pathology and biochemistry. J Neuropathol Exp Neurol 1997;56:369-75.

39.Ranta S, Savukoski M, Santavuori P, Haltia M. Studies of homogenous populations: CLN5 and CLN8. Adv Genet 2001;45:123-40.

40.Savukoski M, Klockars T, Holmberg V, Santavuori P, Lander ES, Peltonen L. CLN5, a novel gene encoding a putative transmembrane protein mutated in Finnish variant late

infantile neuronal ceroid lipofuscinosis. Nat Genet 1998;19:286-88.

41.Cannelli N, Nardocci N, Cassandrini D et al. Revelation of a novel CLN5 mutation in early juvenile neuronal ceroid lipofuscinosis. Neuropediatrics 2007;38:46-49.

42.Bessa C, Teixeira CA, Mangas M et al. Two novel CLN5 mutations in a Portuguese patient with vLINCL: insights into molecular mechanisms of CLN5 deficiency. Mol Genet Metab 2006;89:245-53.

43.Uvebrant P, Hagberg B. Neuronal ceroid lipofuscinoses in Scandinavia. Epidemiology and clinical pictures. Neuropediatrics 1997;28:6-8.

44.Pineda-Trujillo N, Cornejo W, Carrizosa J et al. A CLN5 mutation causing an atypical neuronal ceroid lipofuscinosis of juvenile onset. Neurology 2005;64:740-42.

45.Benedict JW, Getty AL, Wishart TM, Gillingwater TH, Pearce DA. Protein product of CLN6 gene responsible for variant late-onset infantile neuronal ceroid lipofuscinosis interacts with CRMP-2. J Neurosci Res 2009;87:2157-66.

46.Tammen I, Houweling PJ, Frugier T et al. A missense mutation (c.184C>T) in ovine CLN6 causes neuronal ceroid lipofuscinosis in Merino sheep whereas affected South Hampshire sheep have reduced levels of CLN6 mRNA. Biochim Biophys Acta 2006;1762:898-905.

47.Wheeler RB, Sharp JD, Mitchell WA et al. A new locus for variant late infantile neuronal ceroid lipofuscinosis-CLN7. Mol Genet Metab 1999;66:337-38.

48.Mitchell WA, Wheeler RB, Sharp JD et al. Turkish variant late infantile neuronal ceroid lipofuscinosis (CLN7) may be allelic to CLN8. Eur J Paediatr Neurol 2001;5 Suppl A:21-27.

49.Kousi M, Siintola E, Dvorakova L et al. Mutations in CLN7/MFSD8 are a common cause of variant late-infantile neuronal ceroid lipofuscinosis. Brain 2009;132:810-19.

50.Siintola E, Topcu M, Kohlschutter A et al. Two novel CLN6 mutations in variant late-infantile neuronal ceroid lipofuscinosis patients of Turkish origin. Clin Genet 2005;68:167-73.

51.Ranta S, Topcu M, Tegelberg S et al. Variant late infantile neuronal ceroid lipofuscinosis in a subset of Turkish patients is allelic to Northern epilepsy. Hum Mutat 2004;23:300-05.

52.Siintola E, Topcu M, Aula N et al. The novel neuronal ceroid lipofuscinosis gene MFSD8 encodes a putative lysosomal transporter. Am J Hum Genet 2007;81:136-46.

53.Aiello C, Terracciano A, Simonati A et al. Mutations in MFSD8/CLN7 are a frequent cause of variant-late infantile neuronal ceroid lipofuscinosis. Hum Mutat 2009;30:E530-40.

54.Aldahmesh MA, Al-Hassnan ZN, Aldosari M, Alkuraya FS. Neuronal ceroid lipofuscinosis caused by MFSD8 mutations: a common theme emerging. Neurogenetics 2009

55.Stogmann E, El Tawil S, Wagenstaller J et al. A novel mutation in the MFSD8 gene in late infantile neuronal ceroid lipofuscinosis. Neurogenetics 2009;10:73-77.

56.Schulz A, Mousallem T, Venkataramani M et al. The CLN9 protein, a regulator of dihydroceramide synthase. J Biol Chem 2006;281:2784-94.

57.Herva R, Tyynela J, Hirvasniemi A, Syrjakallio-Ylitalo M, Haltia M. Northern epilepsy: a novel form of neuronal ceroid-lipofuscinosis. Brain Pathol 2000;10:215-22.

58.Benes P, Vetvicka V, Fusek M. Cathepsin D--many functions of one aspartic protease. Crit Rev Oncol Hematol 2008;68:12-28.

59.Siintola E, Partanen S, Stromme P et al. Cathepsin D deficiency underlies congenital human neuronal ceroid-lipofuscinosis. Brain 2006;129:1438-45.

60. Fritchie K, Siintola E, Armao D et al. Novel mutation and the first prenatal screening of cathepsin D deficiency (CLN10). Acta Neuropathol 2009;117:201-08.

Chapter 2

AD-ANCL Clinical

Autosomal Dominant Adult Neuronal Ceroid Lipofuscinosis:

parkinsonism due to both striatal and nigral dysfunction

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Abstract

We describe a family with adult neuronal ceroid lipofuscinosis, with apparent autosomal dominant inheritance, observed in 6 affected individuals in three generations. Disease onset was usually in the fifth decade, but was earlier in the youngest generation. Early symptoms consisted of myoclonus in face and arms, epilepsy, auditory symptoms, cognitive decline, or depression. Parkinsonism occurred a few years after disease onset, with stooped posture, shuffling gait, bradykinesia, and mask face. Four subjects deteriorated to a state of severe handicap, with severe dementia, contractures, dysphagia, and dysarthria. Leg weakness evolved to flaccid paraparesis in 2 patients. Diagnosis was confirmed by brain biopsy in 1 patient and full autopsy in 2 patients. Abundant intraneuronal storage of autofluorescent material was found throughout the brain. Electron microscopy showed granular osmiophilic deposits and scarce fingerprint profiles. Striking loss of neurons in the substantia nigra pars compacta and reticulata was found. ^{123}I-IBZM Single photon emission computed tomography in 2 patients showed loss of postsynaptic D2 receptor binding in the striatum. We conclude that parkinsonism in ANCL is likely to be caused by both presynaptic nigral cell loss and postsynaptic striatal degeneration.

Introduction

The neuronal ceroid lipofuscinoses (NCLs, or Batten disease) form a group of progressive neurodegenerative diseases characterized by accumulation of autofluorescent pigment in neurons, with staining characteristics resembling ceroid and lipofuscin.[1] While adult forms (ANCL) are extremely rare,[2–4] infantile (INCL, Santavuori-Haltia disease), late-infantile (LINCL, Jansky-Bielschowsky disease), and juvenile forms (JNCL, Batten-Spielmeyer-Vogt disease) are the most common progressive neurodegenerative disorders in children. All childhood forms and variants are autosomal recessive disorders, clinically presenting with progressive visual loss, epilepsy, or cognitive impairment.[1] Storage material has been shown to consist of the subunit c of mitochondrial ATP-synthase.[5,6] However, in INCL, it is composed of sphingolipid activator proteins A and D (saposins).[7] Phenotypic and genotypic heterogeneity led to a classification with 13 variants,[8] in four age categories based on nine gene loci. While six genes are located, four genes are identified and more than 100 mutations are known.[9] Adult neuronal ceroid lipofuscinosis was first described by Kufs in 1925,[10] in a sibling pair with cognitive decline from ages 26 and 31 years with facial dyskinesias, gait disorder, and depressive delusions. Light microscopy showed ballooned ganglion cells with storage of yellow pigment throughout the brain. Since then, over 100 cases have been reported. While blindness occurs in childhood forms, visual symptoms are uncommon in ANCL. Although most cases are sporadic, family reports indicate both dominant (Parry disease) and recessive inheritance (Kufs' disease). We present a Dutch family with autosomal dominant adult NCL with 6 observed affected individuals in three generations.

Case reports

The family pedigree is shown in Figure 1. Regional birth archives provided data about two earlier generations, but without signs of similar disease. The mother of Patient 1, together with 2 children, died at the age of 28 years of unknown cause. A summary of patient characteristics is given in Table 1. Other family members shown in the pedigree had no abnormalities in history, neurological examination, or electroencephalogram (EEG).

Patient 1

Before presenting at age 44 years with generalized tonic clonic seizures up to five times a day, this woman had complained of dullness of hearing, dizziness, and headaches for several years. After treatment for seizures, she remained bradyphrenic and apathetic. Over the course of 1 year, she became demented, bed-ridden, and completely dependent for all daily activities. Facial expression was diminished. She was hypophonic and had myoclonic jerks. Several generalized seizures occurred each year. She became incontinent, and developed flexion contractures of the arms. Slight temporary improvement was seen after surgical release of a subdural hygroma. During this procedure, a biopsy of frontal cerebral cortex was obtained. Light microscopy showed ballooned ganglion cells with abundant autofluorescent and periodic acid–Schiff (PAS)-positive intraneuronal storage material. She died at age 51 years.

Patient 2

This daughter of Patient 1 had a first attack of jerks in both arms for several seconds without losing consciousness at the age of 46 years. She had to give up her job as a cashier due to increasing slowness, memory deficit, and cognitive decline. She was admitted after she was

found unconscious at home, followed by an episode with visual hallucinations for several days. Progressive myoclonus of the arms occurred and later also facial myoclonus. She complained of painful legs which sometimes buckled. Hearing and visual acuity decreased. Since age 47 years, she had decreased facial expression, progressive bradykinesia, rigidity, stooped posture, and slow, unstable, shuffling gait with hypokinesia of the arms and start hesitation. Treatment with levodopa (L-dopa) and bromocriptine was unsuccessful. Neuropsychological tests showed severe global cognitive deterioration, with deficits in spatial orientation, eye–hand coordination, divided attention, and word retrieval. EEG showed bilaterally synchronous epileptiform complexes. Computed tomography (CT) scan of the brain showed generalized atrophy. She was admitted to a nursing home at age 53 years. She died at age 59 years of pneumonia. Autopsy was performed, showing PAS-positive intraneuronal storage material in neurons throughout the brain (Fig. 2). Electron microscopy showed extensive granular osmiophilic deposits, and sporadic fingerprint profiles. In the substantia nigra (both pars compacta and reticulata), severe cell loss was seen; only a few melanin-containing cells remained. Although uniformly affected by intraneuronal storage, the cell density of neurons seemed normal in most other areas (except cerebellar nuclei and oliva inferior).

Patient 3

In 1969, this sister of Patient 2 was referred at the age of 27 years for nervousness, vertigo, tinnitus, and deafness of the left ear. Neurological examination was normal except for bilateral perception deafness. After several depressive episodes, she developed generalized epileptic seizures at age 42 years, followed by a psychosis with hallucinations. Since age 45 years, she had progressive rigidity, shuffling gait, retropulsion, and decreased facial expression. Response to treatment

with L-dopa and bromocriptine was doubtful. She developed myoclonus of the arms, face, and tongue. Her condition progressively declined, with frequent generalized epileptic seizures, depressive episodes, and several psychotic episodes with visual hallucinations and delusions. From 1992, she was wheelchair-bound. Neuropsychological testing showed severe global cognitive impairment. CT scan and EEG were comparable with those of her sisters. She died at age 56 years of cardiac failure. Autopsy was performed with extensive intraneuronal storage ultrastructurally virtually identical to the findings in her sister. Here also, loss of melanin-containing neurons in substantia nigra was extensive. Less severe neuronal cell loss was seen in cerebellar nuclei and oliva inferior. In cerebral and cerebellar cortex and basal ganglia, only intracellular storage was seen, without cellular degeneration.

Patient 4

This patient is a brother of Patients 2 and 3. He has had myoclonic jerks of the arms since the age of 36 years. He had progressive memory impairment. In a few years he became apathetic and bradyphrenic. He had infrequent generalized tonic clonic epileptic insults, several depressive episodes, and two episodes with visual hallucinations. From age 43 years, he developed progressive parkinsonian gait, hypokinesia, stooped posture, disturbed postural reflexes, facial myoclonus, mask face, and seborrhoea. His motorsymptoms and functional disability showed day-to-day fluctuations, worsening due to stress and fatigue. He had moderate hearing difficulty. Visual acuity bilaterally decreased to 0.5. He often complained of painful legs. Strength of the leg muscles was retained, but tendon reflexes of the legs were absent. This now 55-year-old man is severely handicapped. Again, CT and magnetic resonance imaging (MRI) scans showed cerebral and cerebellar atrophy. EEGs showed bilaterally synchronous epileptiform discharges. ^{123}I-IBZM single proton emission computed tomography (SPECT) at the age of 54

years, using occipital uptake as a reference, showed decreased relative striatal uptake (right, 1.48; left, 1.37; reference, 1.89 ± 0.28; 2 S.D.), indicating loss of striatal D2 receptors (Fig. 3).

Patient 5

This now 37-year-old daughter of Patient 2 presented at age 24 years with a 5-year history of tension-type headache, migraine attacks without aura, and weight gain. Neurological examination was normal. However, EEG showed bilaterally synchronous epileptiform discharges, as were seen in other affected family members. At age 32 years, during her first pregnancy, she had myoclonus of the right arm. Since delivery, progressive myoclonus in both arms and chin occurred. Her muscles feel tight and she sometimes experiences a feeling of weakness in her legs. She has slight memory difficulties and sometimes slight dysarthria. Visual acuity is slightly decreased. Further neurological examination is normal and she is completely independent. Recently, she had a generalized tonic clonic seizure after delivery of her second child.

Patient 6

This now 35-year-old son of Patient 4 has had myoclonus of the thumb and arms from the age of 25 years. At that time, an EEG showed bilaterally synchronous epileptiform bursts, the typical pattern seen in affected family members. At age 31 years, he experienced attacks of loss of consciousness during several seconds. Two years later, he had a generalized tonic clonic seizure after heavy alcohol consumption. He had to stop working because of fatigue and a feeling of weakness in his legs. Climbing stairs became difficult. He has slightly decreased facial expression and slight hypokinesia, with continuous myoclonus of the right arm, but normal muscle strength. MRI scanning showed only moderate generalized atrophy. ^{123}I-IBZM-SPECT showed a pattern in

accordance with decreased striatal D2 receptor binding (striatal/occipital uptake: right, 1.46; left, 1.48).

Discussion

With 6 observed affected patients in three generations, our study represents the second largest reported family with ANCL. It is the first study in which more than three affected patients were seen by a single observer. The vertical inheritance pattern in this family, via both male and female lines, strongly suggests an autosomal dominant inheritance. So far, two other families with autosomal dominant inheritance have been reported [9,12,13] but there are possibly nine families.[14] Our family's phenotype resembles the Parry family, as described by Boehme and colleagues,[12] in many respects. As in our family, severe myoclonus (mainly in face and arms), cognitive decline, epileptic seizures, leg weakness, and decreased tendon reflexes in the late stage were seen in the Parry family. They also showed EEGs with bilaterally synchronous epileptiform bursts. Thus, it is very likely that these two families suffered from a single disease, possibly due to the same genetic defect. Little is mentioned in their patients about parkinsonism, but a mask face was reported in a single patient. Parkinsonism was a general feature in later stages of the disease in our family. Hypokinesia, rigidity, stooped posture, short-stepped gait, mask face and seborrhoea were prominent. While irregular trembling of hand and fingers occurred due to myoclonus, no tremor was seen. Treatment with L-dopa and bromocriptine was tried in 2 patients but had no effect. Autopsy clearly showed extensive neuronal cell loss in substantia nigra in both deceased patients. The contrasting absence of cellular degeneration in other brain areas points to a selective vulnerability of nigral cells. While the observed nigral cell loss could explain the parkinsonian features, the absent response to L-dopa and bromocriptine are suggestive of striatal dysfunction. Although IBZM SPECT was not available from the deceased patients, the clearly decreased striatal IBZM binding in Patients 4 and 6 indicates striatal D2-receptor loss. Thus, the pathophysiology of

parkinsonism in this family is probably due to both pre- and postsynaptic nigrostriatal dysfunction. Clinical presentation is heterogeneous within our family. However, as shown in Table 1, myoclonus, dementia, parkinsonism, facial dyskinesias, and psychiatric symptoms all occurred within single individuals in later stages of the disease. In 1988, Berkovic and colleagues[4] reviewed 118 reported cases published as Kufs' disease, and revealed that only 50 cases fulfilling their histological criteria for this diagnosis were present: (1) fingerprint profiles (FP) or granular osmiophilic deposits (GROD); and (2) typical light microscopy. Possible or definite Kufs' disease cases were divided into two types on prominence of clinical features: type A with seizures, myoclonus and neuropsychiatric symptoms (including dementia), sometimes with ataxia and dysarthria; and type B with dementia and motor abnormalities as the predominant features, with prominent cerebellar and extrapyramidal signs and facial dyskinesias. These two types were distinguished to serve as an aid for clinical recognition but do overlap. Although type B-like symptoms seem to occur later than type A symptoms in our family, separation of autosomal dominant ANCL in two types does not seem to be justified. As in previous reports of ANCL,[15] visual symptoms were scarce in contrast to childhood NCL, except for moderately decreased visual acuity and visual hallucinations. Auditory problems are not commonly reported in ANCL. However, tinnitus, vertigo, and hearing loss frequently occurred in this family. We assume they are part of the disease, related to the observed severe intraneuronal storage in brainstem and cerebellar nuclei. The combination of parkinsonism and facial myoclonus (possibly described as facial tics in early reports), especially with cognitive decline and bilaterally synchronous epileptiform complexes on EEG, are probably pathognomonic for ANCL. Further investigation of clinical, genetic, histological, and biochemical differences between adult types and

childhood NCLs may yield important clues to the still unknown pathophysiology of this devastating illness.

TABLE 1. *Clinical symptoms and patient characteristics*

	Patient no.					
	1	2	3	4	5	6
Age of onset (yr)	44	46	45	41	24	25
Deceased (age, yr)	51	59	56			
Symptoms						
Initial symptom	epilepsy	cognitive	epilepsy	myoclonus	myoclonus	myoclonus
Myoclonus	x	x	x	x	x	x
Facial myoclonus		x	x	x	x	
Tonic-clonic seizures	x	x	x	x	x	x
Bradykinesia	x	x	x	x		x
Rigidity	x	x	x	x		
Seborrhoe	x	x	x	x		
Hypophonia	x	x	x	x		
Dysphagia	x	x				
Incontinence	x	x		x		
Paraparesis		x	x			
Contractures	x	x	x			
Visual impairment		x	x	x	x	
Hearing difficulty	x	x	x	x		
Vertigo	x		x			
Tinnitus			x			
Headache	x			x	x	x
Personality changes	x	x	x	x		
Bradyphrenia	x	x	x	x		x
Hallucinations	x	x	x	x		
Memory disorder	x	x	x	x	x	x
Depression	x		x	x		
Aphasia	x	x				
Ataxia	x			x		x
Epileptiform EEG	x	x	x	x	x	x

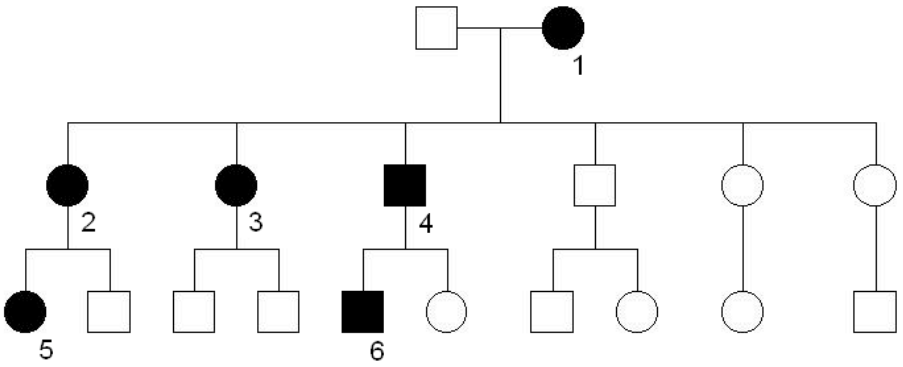

FIG. 1. Family pedigree (square, male; solid, affected).

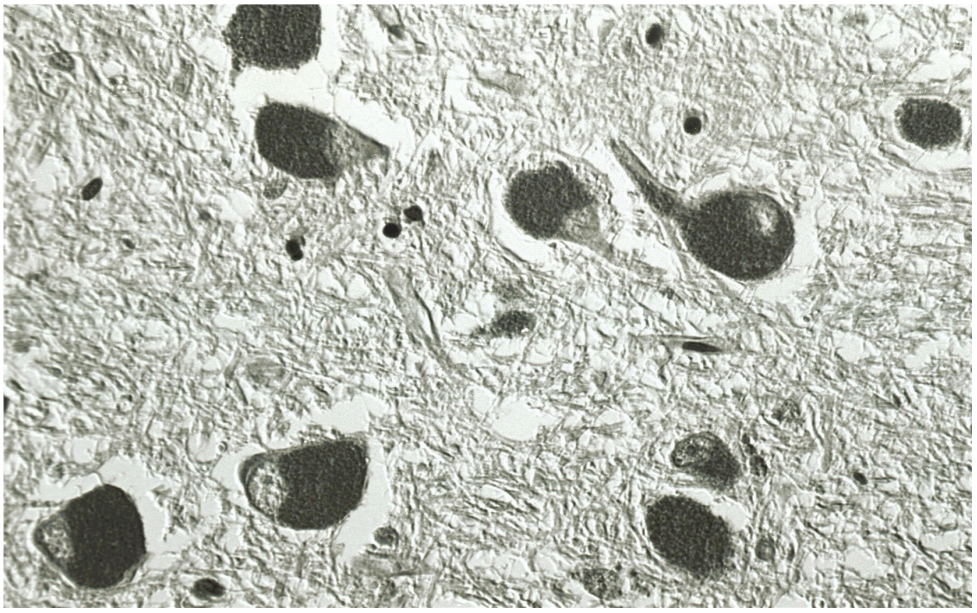

FIG. 2. Extensive intraneuronal storage is seen throughout the brain, with ballooned neurons and distended axon hillocks. Patient 2, pontine nuclei. Periodic acid–Schiff stain. Magnification, 440×.

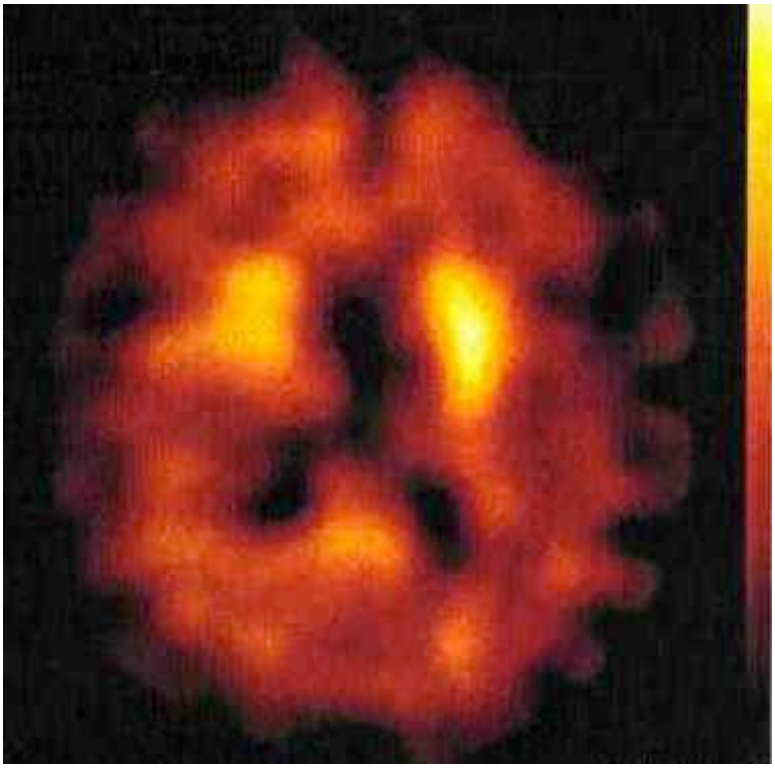

FIG. 3. 123I-IBZM SPECT of Patient 4 shows decreased striatal uptake, indicating loss of striatal D2 receptors

References

1. Goebel HH, Sharp JD. The neuronal ceroid-lipofuscinoses. Recent advances. Brain Pathol 1998;8:151–162.

2. Constantinidis J, Wisniewski KE, Wisniewski TM. The adult and a new late adult forms of neuronal ceroid lipofuscinosis. Acta Neuropathol (Berl) 1992;83:461–468.

3. Goebel HH, Braak H. Adult neuronal ceroid-lipofuscinosis. Clin Neuropathol 1989;8:109–119.

4. Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kufs' disease: a critical reappraisal. Brain 1988;111:27–62.

5. Elleder M, Sokolova J, Hrebicek M. Follow-up study of subunit c of mitochondrial ATP synthase (SCMAS) in Batten disease and in unrelated lysosomal disorders. Acta Neuropathol (Berl) 1997;93: 379–390.

6. Westlake VJ, Jolly RD, Bayliss SL, Palmer DN. Immunocyto chemical studies in the ceroid-lipofuscinoses (Batten disease) us ing antibodies to subunit c of mitochondrial ATP synthase. Am J Med Genet 1995;57:177–181.

7. Tyynela J, Suopanki J, Baumann M, Haltia M. Sphingolipid activator proteins (SAPs) in neuronal ceroid lipofuscinoses (NCL). Neuropediatrics 1997;28:49–52.

8. Mole SE. Batten's disease: eight genes and still counting? Lancet 1999;354:443–445.

9. Neuronal Ceroid Lipofuscinoses (NCL) Mutations website. http://www.ucl.ac.uk/ncl.

10. Kufs H. Über eine Spätform der amaurotischen idiotie und ihre heredofamiliären Grundlagen. Zeitschr f d ges Neurol u Psychiatrie 1925;95:169–188.

11. Martin JJ, Ceuterick C. Adult neuronal ceroid-lipofuscinosis—personal observations. Acta Neurol Belg 1997;97:85–92.

12. Boehme DH, Cottrell JC, Leonberg SC, Zeman W. A dominant form of neuronal ceroid-lipofuscinosis. Brain 1971;94:745–760.

13. Leonberg SC, Armstrong D, Boehme D. A century of Kufs' dis ease in an American family. In: Armstrong D, Koppang N, Rider JA, editors. Ceroid-lipofuscinosis (Batten's disease). Amsterdam: Elsevier Biomedical Press; 1982. p 87–93.

14. Dyken P, Wisniewski K. Classification of the neuronal ceroid lipofuscinoses: expansion of the atypical forms. Am J Med Genet 1995;57:150–154.

15. Martin JJ, Gottlob I, Goebel HH, Mole SE. CLN4: adult NCL. In: Goebel HH, Mole SE, Lake BD, editors. The neuronal ceroid lipofuscinoses (Batten disease). Amsterdam: IOS Press; 1999. p 77–90.

Chapter 3

AD-ANCL Pathology

Autosomal dominant adult neuronal ceroid-lipofuscinosis:

a novel form of NCL with granular osmiophilic deposits without palmitoyl-protein thioesterase 1 deficiency

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Abstract

We describe the neuropathological and biochemical autopsy findings in three patients with autosomal dominant adult neuronal ceroid lipofuscinosis (ANCL, Parry type; MIM 162350), from a family with six affected individuals in three generations. Throughout the brain of these patients, there was abundant intraneuronal lysosomal storage of autofluorescent lipopigment granules. Striking loss of neurons in the substantia nigra was found. In contrast, little neuronal cell loss occurred in other cerebral areas, despite massive neuronal inclusions. Visceral storage was present in gut, liver, cardiomyocytes, skeletal muscle, and in the skin eccrine glands. The storage material showed highly variable immunoreactivity with antiserum against subunit c of mitochondrial ATP synthase, but uniform strong immunoreactivity for saposin D (sphingolipid activating protein D). Protein electrophoresis of isolated storage material revealed a major protein band of about 14 kDa, recognized in Western blotting by saposin D antiserum (but not subunit c of mitochondrial ATPase (SCMAS) antiserum).
Electron microscopy showed ample intraneuronal granular osmiophilic deposits (GRODs), as occurs in CLN1 and congenital ovine NCL. These forms of NCL are caused by the deficiencies of palmitoyl protein thioesterase 1 and cathepsin D, respectively. However, activities of these enzymes were within normal range in our patients. Thus we propose that a gene distinct from the cathepsin D and CLN1-CLN8 genes is responsible for this autosomal dominant form of ANCL.

Introduction

The neuronal ceroid lipofuscinoses (NCLs or Batten disease) represent a group of progressive neurodegenerative diseases with intraneuronal storage of autofluorescent lipopigment. NCLs have originally been classified in four major categories according to the age of onset: infantile , late-infantile , juvenile and adult forms [10]. A new classification based on phenotypic and genotypic heterogeneity distinguishes 13 variants. Six genes have been cloned (CLN 1,2,3,5,6,8), and mutations in these genes have been identified. Two further genes (CLN4 and 7) have been postulated by exclusion of other genes [11;17]. Inheritance of childhood forms of NCL is autosomal recessive. The NCLs are the most common progressive neurodegenerative disorders in children, with visual loss, epilepsy and cognitive impairment. In adults, the common form of NCL is known as Kufs' disease, which also has autosomal recessive inheritance. In addition, a very rare form of adult NCL with autosomal dominant inheritance (Parry disease; MIM 162350) has been described [16]. Genes associated with adult forms of NCL have not yet been characterized.

In all NCLs, loss of neurons and abundant intraneuronal autofluorescent lysosomal inclusions are seen. Ultrastructural patterns in NCL can be multiform [6]: in CLN3, CLN5 and CLN6 a mix of fingerprint profiles, rectilinear complexes and curvilinear profiles can be found in neurons. In CLN2 curvilinear profiles dominate, while CLN1 (caused by mutations in the palmitoyl protein thioesterase 1 or CLN1 gene) is characterized by granular osmiophilic deposits (GRODs) [19]. In addition to CLN1, GRODs are found in congenital ovine NCL, caused by mutations in the cathepsin D gene[22], as well as in rare undefined types of NCL [3]. In CLN1 and congenital ovine NCL, GRODs are associated with storage of sphingolipid

activator proteins (SAPs, also called saposins) A and D. In most other NCLs the storage material largely consists of the subunit c of mitochondrial ATP-synthase (SCMAS) [7].

Recently, we described the clinical characteristics of a Dutch family with autosomal dominant adult NCL[18]. Here we report on the morphological, histochemical, and biochemical findings in autopsies of two sisters and a brother from this family.

Materials and methods

Patients

Patient 1

From the age of 44 this woman had progressive dementia, epilepsy, myoclonus and parkinsonism. A biopsy of frontal lobe cortex was taken in 1962.

Patient 2 (a daughter of patient 1)

From the age of 46 she had myoclonus, cognitive decline, parkinsonism and epilepsy. She died at the age of 59 years.

Patient 3 (also a daughter of patient 1)

This patient suffered from epilepsy, myoclonus, parkinsonism, depressions and progressive dementia from the age of 42 years, and died at the age of 56.

Patient 4 (a son of patient 1)

This man had myoclonus from the age of 36 years, followed by cognitive decline, parkinsonism and epilepsy. He died at the age of 56.

Patient 5 (a daughter of patient 2)

This patient had myoclonus and cognitive problems since a pregnancy at the age of 32. Several years before, bilaterally synchronous epileptiform discharges on electroencephalography (EEG) were seen.

Patient 6 (a son of patient 4)

This man had myoclonus of the arms from the age of 25, epilepsy, parkinsonism and EEG features comparable to those of his niece (patient 5).

Tissue material

Tissue material was available from three autopsies (patients 2, 3 and 4). Additional samples, including a brain biopsy sample (patient 1), a rectal biopsy samples (patient 3 and 4) and blood samples (patients 5 and 6) were obtained. All patients were clinically affected.

Tissue from cerebral cortex (frontal, cingulate, temporal), hippocampus, striatum and globus pallidus, thalamus, hypothalamus, pituitary gland, mesencephalon, pons, medulla oblongata, cerebellum and spinal cord was systematically investigated.

Histochemistry and immunohistochemistry

Brain and spinal cord were fixed in formalin for 6 weeks. Paraffin sections were stained for hematoxylin eosin (HE), Klüver-Barrera, periodic acid Schiff (PAS), Nissl, Gomori trichrome, Bodian, Congo red,

Sudan Black B, permanganate-aldehyde fuchsin sequence, and a modified Spielmayer technique as in previous reports [5].
Paraffin slides were also stained by monoclonal antibodies against glial fibrillary acidic protein (GFAP; BioGenex, San Ramon, USA), CD57 (Leu-7, natural killer cells; Neomarkers, Fremont, USA), CD15 (Leu-M1; Becton Dickinson), CD68 (macrophages, Dako, Glostrup, Denmark), tau protein (microtubules; Sigma, St. Louis, USA), HLA-DR-DP-DQ (Dako), ubiquitin (Dako), synaptophysin (BioGenex), neural cell adhesion molecule (Zymed, San Francisco,USA), human neurofilament protein (Dako), neuron specific enolase (BioGenex), smooth muscle actin (BioGenex), human β-amyloid (Dako), Alzheimer precursor protein A4 (Boehringer Mannheim Biochemica) and polyclonal antibodies against desmin (BioGenex). Cathepsin D (Dako, Copenhagen, Denmark) and subunit c of mitochondrial ATP synthase (SCMAS; a generous gift of prof. Eiko Kominami, Jutendo University, Tokyo, Japan) and sphingolipid activator protein D (SAP D, a generous gift of prof. Konrad Sandhoff, University of Bonn, Germany) were detected by polyclonal antibodies as described [5]. LSAB+ detection kit (DAKO) or Vectastain ABC detection kit (Vector Laboratories) were used for immunodetection. Electron microscopy was performed on cerebral cortex, pons, cerebellum, spinal cord, muscle, peripheral nerve and skin, as well as isolated storage material. Standard methods consisted of fixation in glutaraldehyde, post-fixation in osmium tetroxide, embedding in araldite and contrasting with uranyl acetate and lead citrate. A Philips CM10 electron microscope was used.

Enzyme activity assay

Assays of enzyme activity in leukocytes were carried out as described recently, for palmitoyl protein thioesterase (PPT1)[24], tripeptidyl peptidase 1 (TPP1) [28] and cathepsin D[20].

Isolation of the storage material, electrophoresis and Western blotting

Frozen autopsy samples from the frontal, occipital and parietal cortices of patients 2,3 and 4 were pooled and storage material was isolated using CsCl centrifugations as described before[22]. The purity of the isolated storage cytosomes was confirmed by EM, and the protein content of the samples was measured according to Markwell et al.[15]. The storage material was analyzed by 17% SDS-polyacrylamide gels[13] and by Western blotting using antiserum against SAP D, kindly provided by prof. Konrad Sandhoff (University of Bonn, Germany), and against the mitochondrial ATP synthase subunit c, kindly provided by dr. David Palmer (Lincoln University, New Zealand).

Results

Clinical data

Myoclonus in face and arms, epilepsy, parkinsonism, dementia and personality changes were the cardinal clinical features in this family. Moderate visual symptoms and hearing loss occurred. Disease onset varied from 24 to 46 years of age.
For detailed description of clinical characteristics see Nijssen PCG et al. [18].

Macroscopy

The brain of patient 2 weighed 896 g, with severe global cerebral and cerebellar atrophy. The brain had a rubber-like consistency, and the substantia nigra was markedly depigmented. The brain of patient 3 weighed 1012 g, with moderate frontal and cerebellar atrophy. The brain of patient 4 weighed 1144 g, with moderate global atrophy. Heart, intestines, liver, pancreas, kidneys and spine of all 3 patients were normal. Both women had normal female organs.

Light microscopy

Abundant storage of autofluorescent PAS-positive grains was seen in neurons throughout the central nervous system (fig 1A), but not in hypophysis, choroid plexus or dura mater. In some neurons individual grains of ceroid lipofuscin storage material were found; in other neurons more dense aggregates were seen. The nucleus was displaced by the lipopigment to the periphery, and ballooning of the perikaryon was seen. Some neurons, especially Purkinje cells, had a short, funnel-like broadening of proximal cell processes of axons, but probably also of dendrites. Neuronal density in cerebral cortex and basal ganglia was

slightly decreased, but the cytoarchitecture was normal (Prof. H. Braak, Frankfurt, Germany). Neuronal depletion was severe in substantia nigra (fig 1B) (which was depigmented in patient 3) and inferior olive, and moderate in cerebellar nuclei. Slight loss of Purkinje cells was seen in patient 2. The storage granules uniformly stained with permanganate-aldehyde fuchsin sequence, and with Sudan Black B. There was no staining of the storage granules with the modified Spielmayer technique, except for occasional rudimentary deposits. No perikaryal spheroids of any type [5,8] were recorded.

Immunohistochemistry

Increased GFAP and CD15 immunoreactivity was found in white matter, due to astrocytosis. HLA-DR-DP-DQ immunoreactivity was increased in striatum and globus pallidus, thalamus, N. ruber, arcuate nuclei, inferior olive and vestibular nuclei, suggesting increased activity of microglia cells. Neurons in cerebellar nuclei and sporadic substantia nigra neurons were labeled by tau antibodies. Diffuse ubiquitin reactivity in white matter, and sporadic ubiquitin labeling of neurons in substantia nigra and the arcuate nuclei was found. In Purkinje cells, the thickening of dendrites had neurofilament immunoreactivity. All neurons throughout the cerebrum stained strongly with SAP D antiserum (Fig 2 A-B), and also the astroglial cells showed positive signal. Further, the spinal cord was filled with SAP D-positive structures, which were, however, irregular in shape and thus represented either disrupted large neurons or, potentially, axonal enlargements filled with storage material. Most neurons displayed no staining for SCMAS, but some were strong or moderately stained.(Fig 2 C-D). Other markers were normal.
Visceral (non-neuronal) autofluorescent permanganate aldehyde fuchsin positive storage material was found in cardiocytes, skeletal muscle, liver (hepatocytes and occasional Kupffer cells), smooth muscle of gut,

peripheral nervous system of gut and in skin eccrine glands. Here, histochemical properties were similar to those in neurons.

Electron microscopy

Abundant compact granular osmiophilic deposits (GRODs) were found in neurons throughout the CNS (Fig. 3A). Their size varied from 0.5 to 2.5 µm ø. Membrane-bound vacuoles were found in neurons, with polylobulated subunits, filled with GRODs and fat droplets (0.7 µm ø) (fig. 3B and C). In spinal cord neurons the prevailing ultrastructure was GRODs, but also membrane covered 'zebra body' inclusions of 1 µm ø, containing parallel lamellar profiles, were observed. In glia cells, inclusions up to 4 µm ø were seen filled with numerous dense osmiophilic granules. Sporadic cell processes in cerebral cortex showed membrane-covered groupwise inclusions of fingerprint aggregates (fig. 3D), sometimes associated with lipid droplets of <0.5 µm ø. No curvilinear or rectilinear complexes were found.

In muscle, subsarcolemmal lipofuscin grains were found, composed of numerous lipid droplets (size up to 2 µm ø), and GRODs. However, few fingerprints were seen in smooth muscle cells of perimysial capillaries and in eccrine sweat glands in the skin, where many GRODs were seen with lipid droplets.

In a rectal biopsy of patient 3 at the age of 45, lipofuscin like inclusions were found in ganglion cells. Further, in a rectal biopsy from patient 4, some intraneuronal inclusions were seen in nerve cell processes in the tunica muscularis.

Analysis of storage material

Storage cytosomes isolated from the pooled autopsy brain tissue of patients 2, 3 and 4 were brown in color and weakly autofluorescent, similar to storage material isolated from other forms of NCLs. Protein electrophoresis revealed a major protein band of about 14 kDa in molecular weight (Fig 4A). In addition, a double band of approximately 40 kDa in molecular weight was detected, while no small molecular weight proteins were seen. In Western blotting the 14 kDa band was recognized by sphingolipid activator protein D antiserum (Fig 4B), while SCMAS was not detected.

Enzyme activities

The activities of PPT1, TPP1, and cathepsin D, (the deficiencies of which are associated with CLN1, CLN2, and congenital ovine NCL respectively), were determined in patients 5 and 6. All activities measured from leukocytes of patients 5 and 6 were normal. PPT1 activities of patients 5 and 6 were 59 nmol/h/mg and 34 nmol/h/mg (reference: 24-100 nmol/h/mg), TPP1 activities were 290 nmol/h/mg and 216 nmol/h/mg (reference: 120-310 nmol/h/mg). Cathepsin D activity in fibroblasts of patient 5 was 3350 pmol/h/mg (reference: 2750-4850 pmol/h/mg).

Discussion

The neuropathological, electron microscopical and biochemical findings in our family unequivocally point to a diagnosis of adult neuronal ceroid lipofuscinosis. The pedigree of this family (fig. 5) indicates an autosomal dominant inheritance pattern. Dominant adult NCL has until recently been described in only two other families[2, 9, 14], and suspected in a few additional isolated cases and small families [1;4]. There was a striking clinical similarity between our family and the Parry family, as discussed before [18]. Recently, a new family with autosomal dominant adult NCL was reported by Josephson et al. [12]. Comparison of the Parry and Josephson families with our family strongly suggests that these patients suffer from a single disease: the light microscopical and ultrastructural findings are virtually identical, and clinical presentation is very similar.

In the Parry and Josephson families, the EM pattern was dominated by GRODs, and no fingerprints or curvilinear profiles were found. Although some scarce fingerprints were seen in our family (especially in glial cells), ultrastructure of tissue of our patients was also dominated by intraneuronal and glial GRODs. As in the Parry family [2], severe loss of neurons was seen in the substantia nigra, which correlates with the occurrence of parkinsonism in our patients. However, previously reported SPECT studies also indicated striatal D2 receptor loss [18]. Thus, parkinsonism in our family can be attributed to both nigral and striatal degeneration. Neuronal cell loss was strikingly absent in certain areas, like pontine nuclei, despite abundant intraneuronal inclusions. The role of intraneuronal inclusions in the pathophysiology of neurodegenerative diseases has recently been the subject of discussion [26;27]. The relation between neuronal storage and cell loss is unclear in our patients. Regional differences may indicate independence of

neuronal degeneration and the storage process, but it is possible that cell death has occurred as a consequence of inclusion storage. SCMAS is stored uniformly only in CLN2, where it has been suggested to be the substrate of the deficient TPP1 [7]. In CLN 3, 5 and 6 SCMAS storage is generalized, missing only in certain visceral storage sites [7]. In typical CLN1, histochemical SCMAS reactivity is almost absent, found only in some restricted neurons [7]. In all forms of NCLs, the storage material is strongly immunoreactive for SAPs, although SAP A and D are the major storage proteins only in CLN1, congenital ovine NCL and in Schnauzer NCL [21, 22, 23]. In our family, the participation of SCMAS in the storage process was also limited, and restricted to a subpopulation of neurons, while storage of SAPs appeared to be relatively uniform throughout the brain. Thus, immunohistochemically this family represented either a SAP storage disease or a mixture of SAP and SCMAS storage. Accumulation of SAP D was also confirmed by Western blotting from isolated storage cytosomes, which, however, did not contain SCMAS.

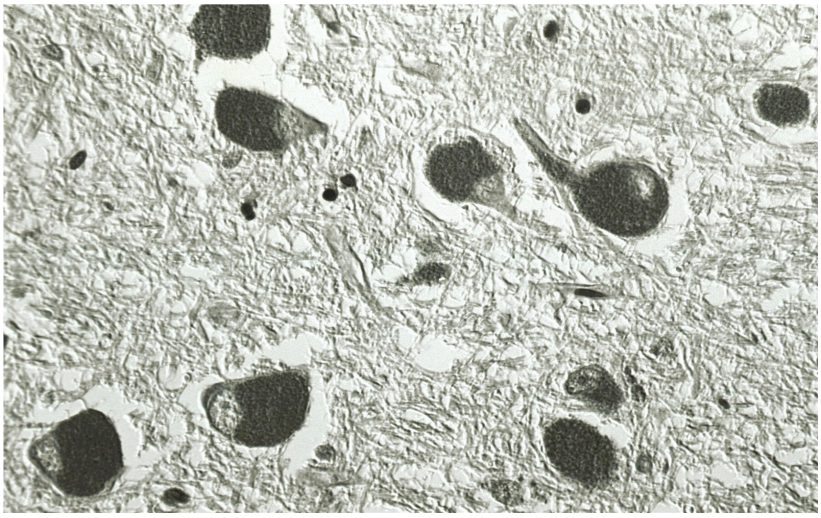
Based on the ultrastructural, immunohistochemical and storage cytosome analyses, the disease of the present family resembles CLN1 and congenital ovine NCL, which are caused by deficiencies of PPT1 and cathepsin D, respectively. Recently, an adult variant of PPT1 deficiency, characterized by GRODs and recessive inheritance, was described in a French family[25]. In the present family, however, the activities of PPT1 and cathepsin D, were normal, excluding them as the cause of the disease. In addition, CLN2 has been excluded as the etiological factor by normal TPP1 enzyme activity. Other NCLs, such as CLN 3, 5, 6, 8 and Kufs' disease have been indirectly excluded by the different clinical presentation, ultrastructure, immunohistochemical and biochemical findings, as well as by the dominant inheritance. In addition to the above-discussed forms of NCL, GRODs have been reported in two

genetically undefined NCLs: the congenital human NCL and adult Schnauzer NCL. The immunohistochemical characteristics of the congenital human (Tyynelä, unpublished data) and the adult Schnauzer NCL resemble those described here [23].

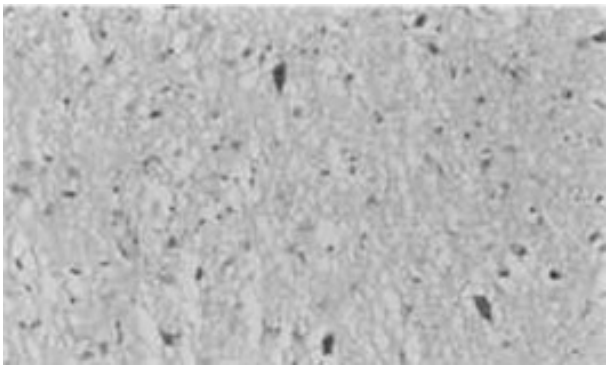
Therefore, it is likely that the gene underlying the presented form of autosomal dominant adult NCL is different from the identified NCL genes as well as from the (undiscovered) Kufs gene. Further genetic and biochemical studies will be needed to define this novel genetic locus.

Figures

Fig 1 Light microscopy of paraffin embedded tissue sections from patients with adult NCL.



1A Periodic-acid Schiff (PAS) staining of pontine nuclei, showing intraneuronal storage of PAS-positive material, with ballooning of axon hillocks.



1B In substantia nigra, severe loss of neurons was seen. (Bodian stain).

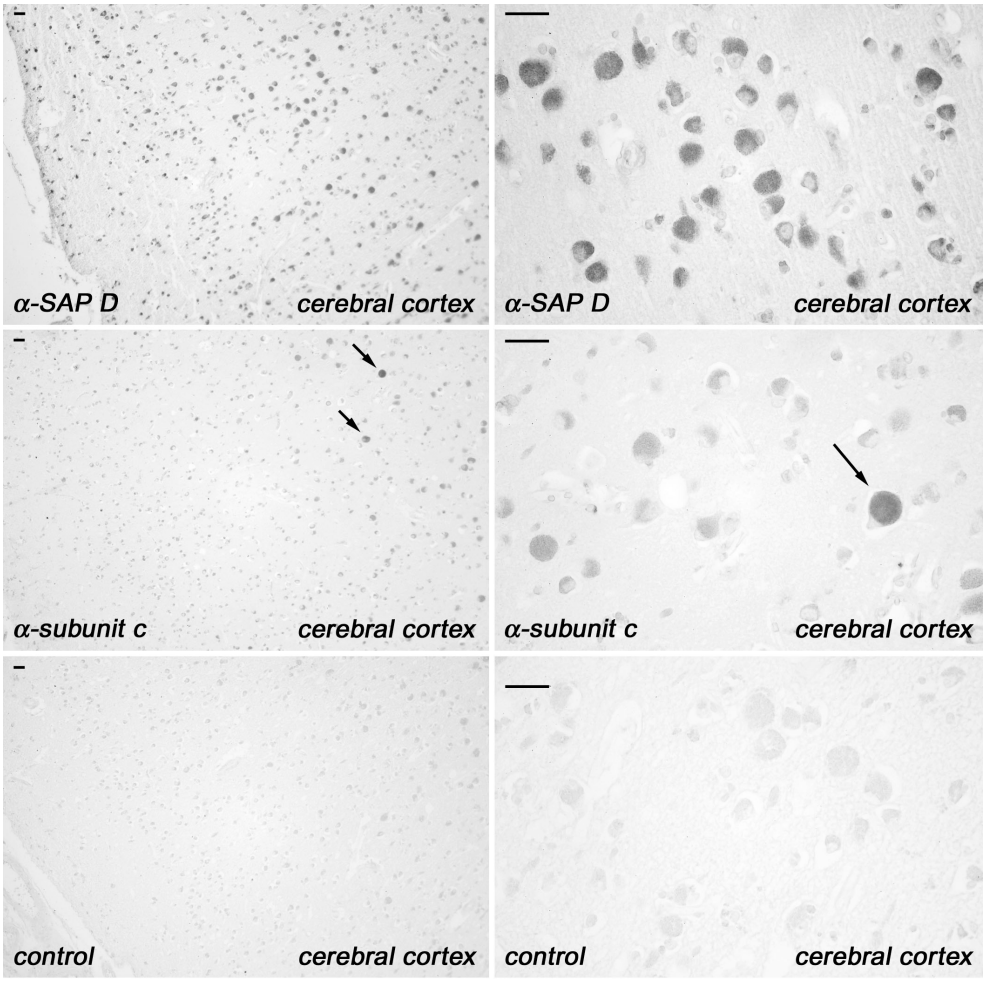


Fig 2 Immunohistochemical staining of paraffin embedded tissue sections from patients with ANCL. Bars, 20 μmeter.

A (top left) Sphingolipid activator protein D (SAP D) antiserum strongly stained the neurons throughout the cerebral cortex. Also the glial cells close to the surface of the cortex show positive staining for SAP D.

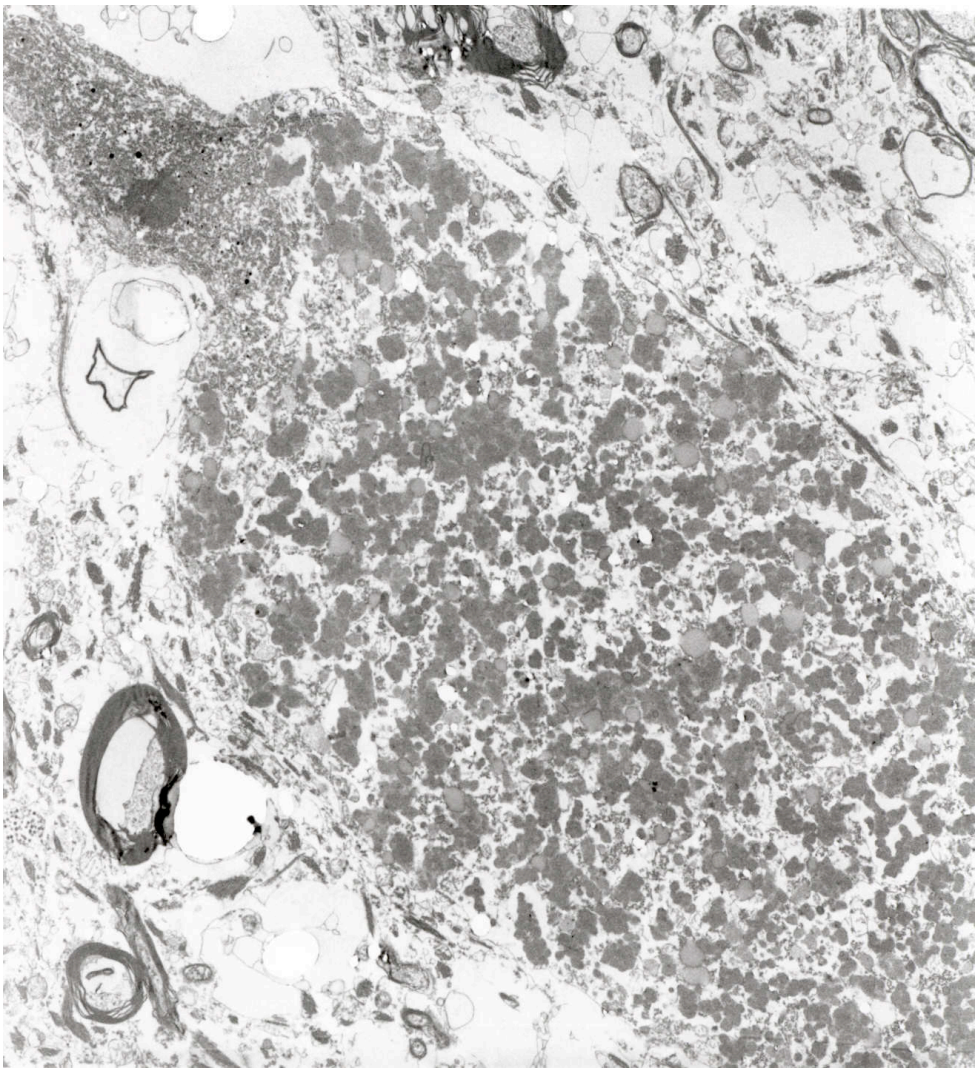
B (top right) At higher magnification, the neurons showed pronounced accumulation of SAP D-positive storage material.

C (middle left)In contrast, antiserum against subunit c of the mitochondrial ATP synthase (SCMAS) stained selected neurons in the cerebral cortex (arrows).

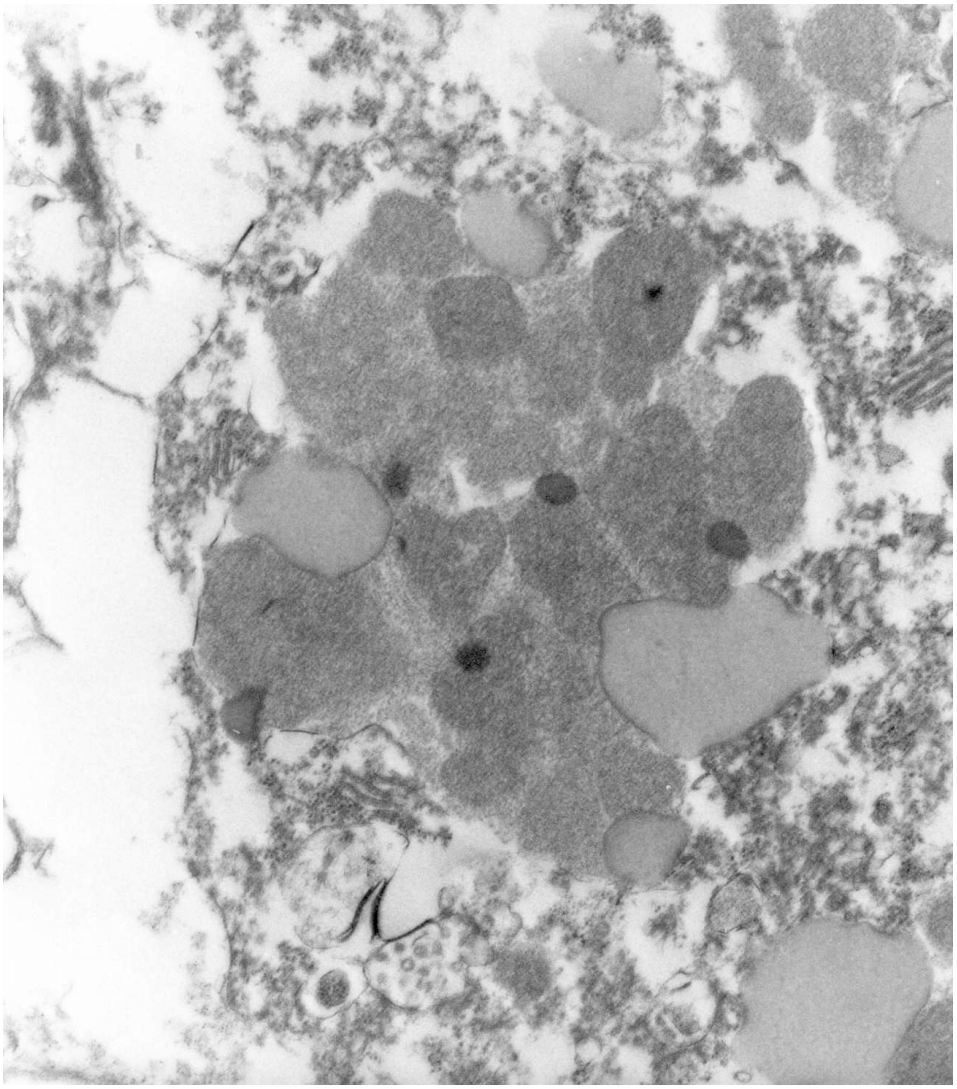
D (middle right) At higher magnification, one neuron in the deeper cortical layers shows strong positive staining for SCMAS whereas the neighbouring neurons are negative or mildly stained.

E (bottom left) and F (bottom right) In control experiments (where primary antiserum was omitted or replaced by pre-immune serum) there was no staining.

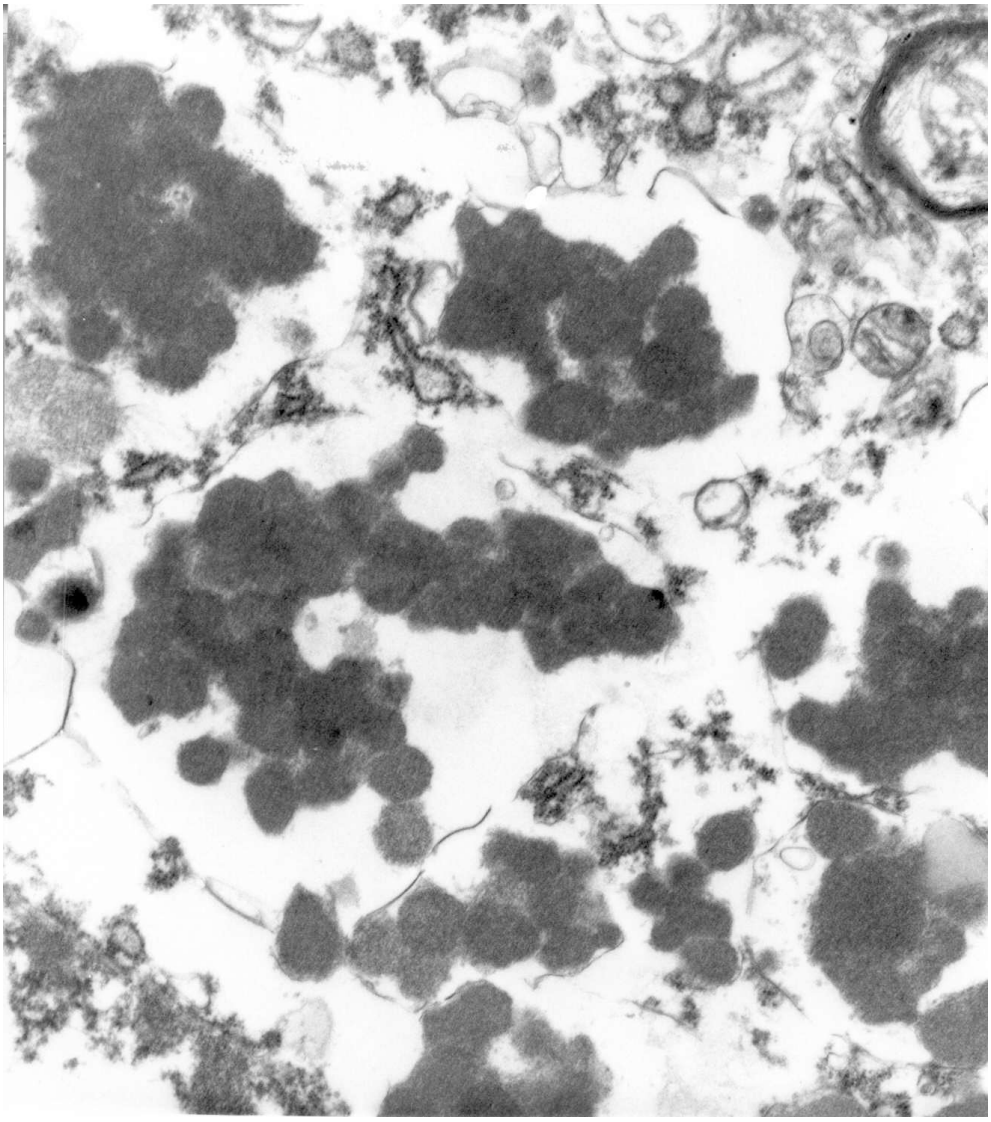
Fig. 3 Electron micrographs of autopsy brain material from patients with adult NCL.



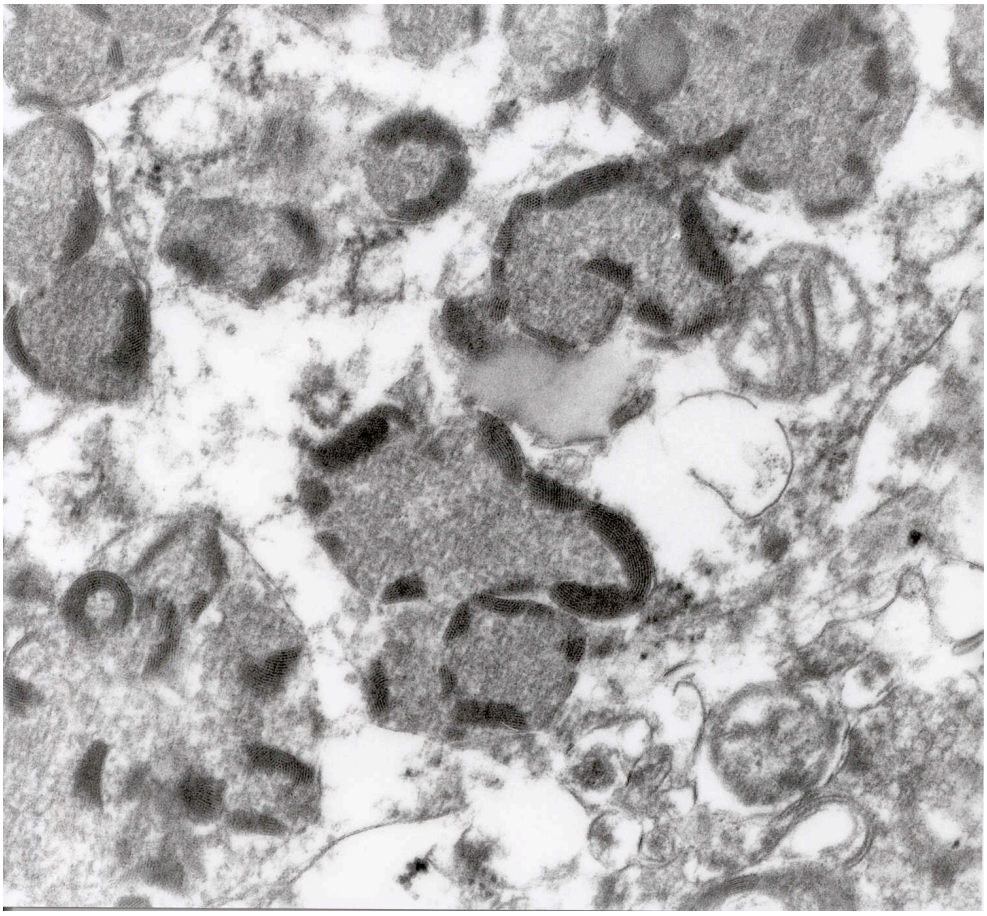
3A Patient 3, cerebral cortex. Electron micrograph of a ballooned neuronal perikaryon showing massive storage of electron dense granular inclusions with lipid droplets. Magnification x 6075.



3B Patient 2. Neuronal storage in a cerebellar Purkinje cell: polylobulated inclusion revealing numerous globular GROD and lipid droplets. Magnification x 40500



3C Patient 2. Neuronal storage in cerebral cortex: polyglobular subunits filled with GROD in clear vacuoles. Magnification x 31500.



3D Patient 2. Electronmicrograph of a neuronal process containing abundant membrane-bounded granular storage, electrondense fingerprints and lipid droplets. Magnification x 78750

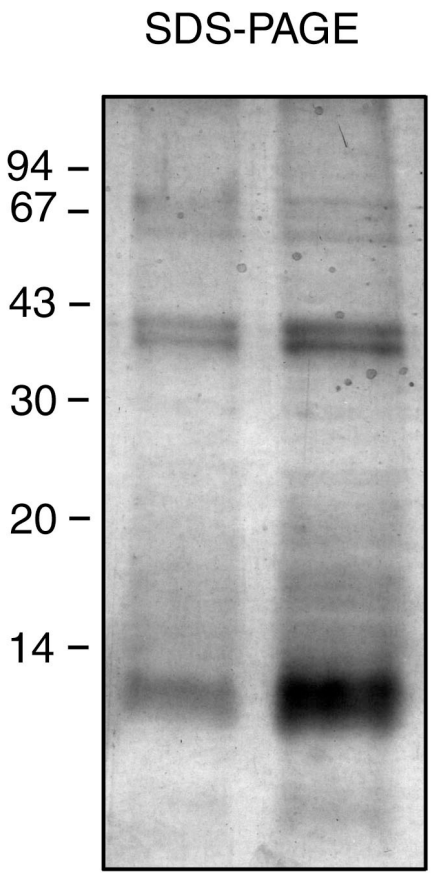


Fig 4A 17% SDS-PAGE of brain storage material isolated from patients with adult NCL .

The isolated storage material (10 [left] and 20 µg [right] of protein per lane) showed a major protein band of 12-14 kDa in molecular weight in silver stain. Molecular weight markers are shown on the left.

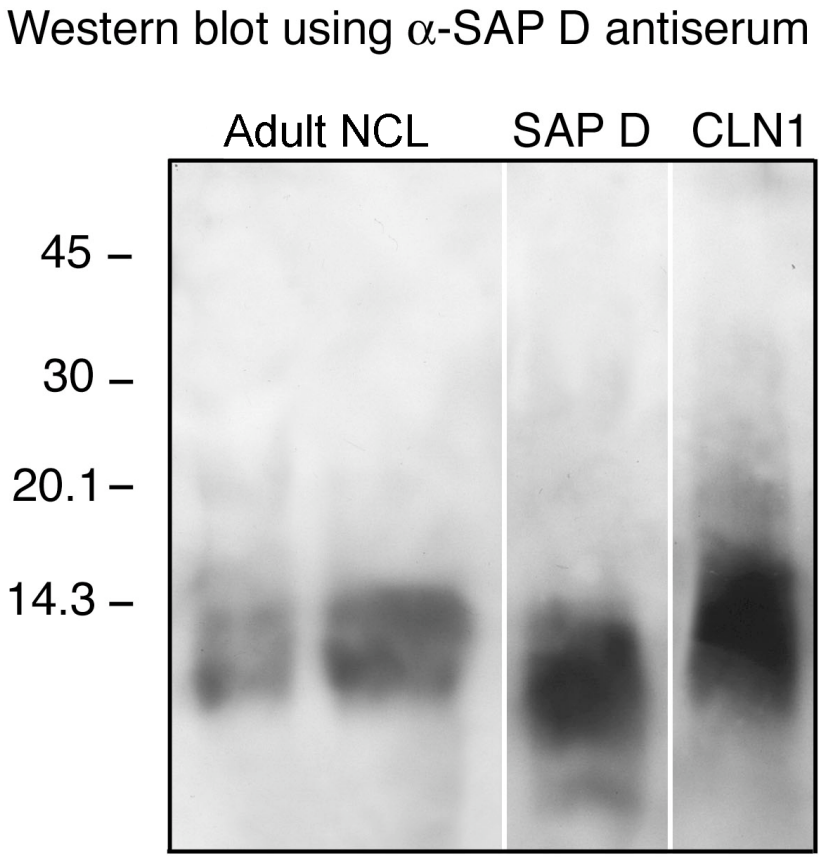


Fig 4B Western blotting of isolated brain storage material using anti-SAP D antiserum.

The major 12-14 kDa protein band of isolated storage material reacts strongly with SAP D antiserum (lanes 'adult NCL', 10 [left] and 20 µg [right]). Purified SAP D (lane SAP D) and CLN1 storage material (lane CLN1) are shown as controls.

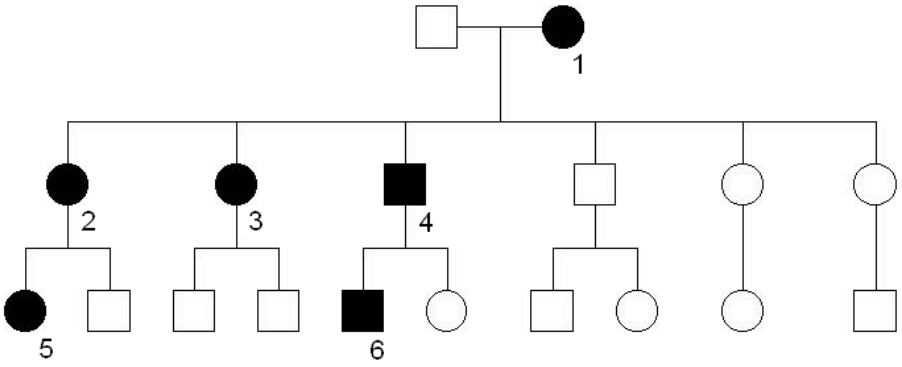


Fig 5 Family pedigree, indicating autosomal dominant inheritance. (Black symbols = affected).

References

1. Arpa Gutierrez J, Gutierrez Molina M, Barreiro Tella P, Fernandez Balaños R, Morales Bastos MC, Amcosta Varo J, Sebastian de la Cruz F, Diaz Tejedor E (1978) El tipo dominante de ceroide lipofuscinosis del adulto. Soc Español Neurol XXX Ann Meet Proc.

2. Boehme DH, Cottrell JC, Leonberg SC, Zeman W (1971) A dominant form of neuronal ceroid-lipofuscinosis. Brain 94: 745-760.

3. Das AK, Becerra CH, Yi W, Lu JY, Siakotos AN, Wisniewski KE, Hofmann SL (1998) Molecular genetics of palmitoyl-protein thioesterase deficiency in the U.S. J Clin Invest 102: 361-370.

4. Dyken P, Wisniewski K (1995) Classification of the neuronal ceroid-lipofuscinoses: expansion of the atypical forms. Am J Med Genet 57: 150-154.

5. Elleder M (1978) A histochemical and ultrastructural study of stored material in neuronal ceroid lipofuscinosis. Virchows Arch B Cell Pathol 28: 167-178.

6. Elleder M, Lake BD, Goebel HH, Rapola J, Haltia M, Carpenter S (1999) Definitions of the ultrastructural patterns found in NCL. In: The neuronal ceroid lipofuscinoses (Batten disease). Goebel HH, Mole SE, Lake BD (eds.), pp. 5-7, IOS press, Amsterdam.

7. Elleder M, Sokolova J, Hrebicek M (1997) Follow-up study of subunit c of mitochondrial ATP synthase (SCMAS) in Batten disease and in unrelated lysosomal disorders. Acta Neuropathol (Berl) 93: 379-390.

8. Elleder M, Tyynela J (1998) Incidence of neuronal perikaryal spheroids in neuronal ceroid lipofuscinoses (Batten disease). Clin Neuropathol 17: 184-189.

9. Ferrer I, Arbizu T, Pena J, Serra JP (1980) A Golgi and ultrastructural study of a dominant form of Kufs' disease. J Neurol 222: 183-190.

10. Goebel HH (1995) The neuronal ceroid-lipofuscinoses. J Child Neurol 10: 424-437.

11. http://www.ucl.ac.uk/ncl.

12. Josephson SA, Schmidt RE, Millsap P, McManus DQ, Morris JC (2001) Autosomal dominant Kufs' disease: a cause of early onset dementia. J Neurol Sci 188: 51-60.

13. Laemmli UK (1970) Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature 227: 680-685.

14. Leonberg SC, Armstrong D, Boehme D (1982) A century of Kufs' disease in an American family. In: Ceroid-lipofuscinosis (Batten's disease), Armstrong D, Koppang N, Rider JA (eds). pp. 87-93, Elsevier biomedical press, Amsterdam.

15. Markwell MA, Haas SM, Bieber LL, Tolbert NE (1978) A modification of the Lowry procedure to simplify protein determination in membrane and lipoprotein samples. Anal Biochem 87: 206-210.

16. Martin JJ, Gottlob I, Goebel HH, Mole SE (1999) CLN4: Adult NCL. In: The neuronal ceroid lipofuscinoses (Batten disease). Goebel HH, Mole SE, Lake BD (eds.), pp. 77-90, IOS press, Amsterdam.

17. Mole SE (1999) Batten's disease: eight genes and still counting? Lancet 354: 443-445.

18. Nijssen PCG, Brusse E, Leyten ACM, Martin JJ, Teepen JLJM, Roos RAC (2002) Autosomal dominant adult neuronal ceroid lipofuscinosis: Parkinsonism due to both striatal and nigral dysfunction. Mov Disord 17: 482-487

19. Santavuori P, Gottlob I, Haltia M, Rapola J, Lake BD, Tyynelä J, Peltonen L (1999) CLN1: Infantile and other types of NCL with GROD. In: The neuronal ceroid lipofuscinoses (Batten disease). Goebel HH, Mole SE, Lake BD (eds.), pp. 16-36, IOS press, Amsterdam.

20. Sohar I, Sleat DE, Jadot M, Lobel P (1999) Biochemical characterization of a lysosomal protease deficient in classical

late infantile neuronal ceroid lipofuscinosis (LINCL) and development of an enzyme-based assay for diagnosis and exclusion of LINCL in human specimens and animal models. J Neurochem 73: 700-711.

21. Tyynelä J, Palmer DN, Baumann M, Haltia M (1993) Storage of saposins A and D in infantile neuronal ceroid-lipofuscinosis. FEBS Lett 330: 8-12.

22. Tyynelä J, Sohar I, Sleat DE, Gin RM, Donnelly RJ, Baumann M, Haltia M, Lobel P (2000) A mutation in cathepsin D gene causes a congenital lysosomal storage disease with profound neurodegeneration. EMBO J, 19: 2786-2792.

23. Palmer DN, Tyynela J, van Mil HC, Westlake VJ, Jolly RD (1997) Accumulation of sphingolipid activator proteins (SAPs) A and D in granular osmiophilic deposits in miniature Schnauzer dogs with ceroid-lipofuscinosis. J Inherit Metab Dis 20:74-84

24. van Diggelen OP, Keulemans JL, Winchester B, Hofman IL, Vanhanen SL, Santavuori P, Voznyi YV (1999) A rapid fluorogenic palmitoyl-protein thioesterase assay: pre- and postnatal diagnosis of INCL. Mol Genet Metab 66: 240-244.

25. van Diggelen OP, Thobois S, Tilikete C, Zabot MT, Keulemans JL, van Bunderen PA, Taschner PE, Losekoot M, Voznyi YV (2001) Adult neuronal ceroid lipofuscinosis with palmitoyl-protein thioesterase deficiency: first adult-onset patients of a childhood disease. Ann Neurol 50: 269-272.

26. Wolozin B, Behl C (2000) Mechanisms of neurodegenerative disorders: part 1: protein aggregates. Arch Neurol 57: 793-796.

27. Wolozin B, Behl C (2000) Mechanisms of neurodegenerative disorders: part 2: control of cell death. Arch Neurol 57: 801-804.

28. Young EP, Winchester BG, Peter LW, Wheeler RB, Lake BD (2000) Exclusion of late infantile neuronal ceroid lipofuscinosis (LINCL) in a fetus by assay of tripeptidyl peptidase I in chorionic villi. Prenat Diagn 20: 337-339.

Chapter 4

AD-ANCL Genetics

Genetic analysis of a family with autosomal dominant neuronal ceroid lipofuscinosis

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Not to be submitted, this chapter is exclusively published in this thesis

Abstract

Objective: to identify the genetic defect in a family with autosomal dominant adult neuronal ceroid lipofuscinosis.
Methods: We applied genome wide STR-based linkage analysis to a Dutch multigenerational family with autosomal dominant ANCL, and performed subsequent fine-mapping of candidate loci.
Results: Under an autosomal dominant model 8 loci were suggestive for linkage with a LOD-score > 1. Three of these loci were most promising: two subsequent markers gave a LOD-score above 1 (on chr. 2 and chr. 21) ; multipoint LOD-score calculations achieved a maximum score of 1.96 on chr. 12. These 3 loci were further analyzed by genotyping with additional STR markers in the region. In the 3 loci a disease haplotype appeared to segregate with the disease. Markers in the proximity of the known NCL loci (1p32, 11p15, 16p12.1, 13q21, 15q21-33, 8p23, 11p15.5) were checked, but none passed a LOD-score value of 1.
Conclusion: linkage analysis in this small family with autosomal dominant ANCL identified 3 genetic loci which segregate with the disease, but further studies are needed.

Introduction

Although the gene symbol CLN4 has been assigned to adult NCL, no genetic defects are known in adult forms as yet. Unlike childhood NCL forms which are inherited in an autosomal recessive mode [1-3], the genetic defects in adult NCL are most likely heterogeneous: adult NCL occurs sporadic or familial with recessive inheritance (Kufs' disease), but also with an autosomal dominant mode of inheritance in some families, called Parry disease [4 5 6 7 8 9].
Our Dutch dominant ANCL family has been the subject of previous reports, concerning clinical [8], pathological [10], neurophysiological [11], auditory (chapter 6) and visual aspects (chapter 7).
Here we report on genome-wide linkage analysis of this family.

Methods and patients

We analysed a multigenerational family with autosomal dominant ANCL, with 6 known affected individuals in 3 generations. Blood samples for DNA extraction were obtained from 22 individuals including 5 patients, 13 healthy at risk individuals and 4 spouses. The family pedigree is shown in fig.1 . Genome-wide linkage analysis was performed, using 400 STR markers, with an average distance of 8 cM, and with subsequent fine-mapping of candidate loci.

Family characteristics:

Patient 1

This woman with generalized tonic clonic seizures from the age of 44 years, had progressive cognitive decline, myoclonus and parkinsonism. She died at the age of 51.

Patient 2

This woman is a daughter of patient 1. She had myoclonus of arms and face from the age of 46 years, followed by progressive dementia, parkinsonism, generalized tonic clonic seizures and psychotic episodes. She died at the age of 59 years.

Patient 3

This sister of patient 2 had several depressive episodes, and developed generalized epileptic seizures at the age of 42 years, followed by psychotic episodes, parkinsonism, myoclonus and progressive dementia. She died at the age of 56 years.

Patient 4

This brother of patients 2 and 3 had myoclonic jerks of the arms since the age of 36 years. He had progressive memory impairment, depressive episodes, parkinsonism, facial dyskinesias and generalized tonic clonic epileptic insults. He died at the age of 56 years.

Patient 5

This daughter of patient 2 had tension-type headache and migraine attacks without aura from the age of 19 years. Since the age of 32, she has had progressive myoclonus and slight memory difficulties, and epilepsy.

Patient 6

This son of patient 4 has had myoclonus of the thumb and arms from the age of 25, and frequent tonic clonic seizures since age 31. He has severely decreased visual acuity, and moderate parkinsonism.

Genome-wide linkage analysis

A genome-wide scan was performed by use of multiplex mapping panel of 400 autosomal STR markers with an average inter-marker distance of 8 cM.
Genomic DNA was PCR amplified in 26 multiplex reactions using fluorescently labeled primers. PCR products were resolved on an ABI3730 automated sequencer (Applied Biosystems). Genotypes were assigned using in-house developed genotyping software.
Two-point and multi-point LOD-scores were calculated using MLINK and LINKMAP from the LINKAGE software package version 5.2 (Lathrop et al. 1985). We assumed an autosomal dominant inheritance model with reduced age-dependent penetrance for the trait locus. The estimated population frequency of the disease gene was set at 0.00001. Nine liability classes for disease penetrance were used, based on the cumulative risk curve calculated from the mean onset age for ANCL in the family, with a maximal disease penetrance of 100% when ≥ 60 years. Phenocopy rates were also age-dependent.

Results

Genome-wide STR-based linkage analysis

In an 8 cM density genome-wide scan, we calculated 2-point LOD-scores ≥ 1 for 10 STR markers in 8 distinct chromosomal regions (table 1). On chromosomes 2 and 21 two subsequent markers achieved a 2-point LOD-score above ≥ 1. A maximum 2-point LOD-score of 1.647 was reached at the chromosome 21. Multipoint linkage analysis of the 8 loci resulted in a maximum score of 1.731, for the chromosome 12 locus. Markers in the proximity of the known NCL loci (1p32, 11p15, 16p12.1, 13q21, 15q21-33, 8p23, 11p15.5) were

checked but none passed a LOD-score value of 1. Three loci were prioritized for further examination. The loci on chromosomes 2 and 21 were selected because two subsequent markers showed suggestive linkage, and the chromosome 12 locus was selected because of the maximum multipoint LOD-score. Additional STR markers were selected for genotyping to achieve a marker density of about 1 STR/1 cM/locus.

Fine mapping of candidate loci and sequencing of positional candidate genes

Chromosome 12

For the markers included in the genome-wide scan a maximum multipoint LOD-score of 1.731 was obtained on chromosome 12 at D12S1056 . Twenty-two additional STR markers in the region covering 25 MB were used for genotyping in our family. LOD score calculations achieved a new maximum of 1.962 for 4 markers in the region (Table 2). Segregation analysis defined a risk-haplotype that appeared to segregate with the disease in the family. All patients were carrier of the risk-haplotype and meiotic recombination events in one patient deliniated the candidate region to a 13.11Mb region flanked by markers D12S1655 and GATA194G07. However, the entire risk-haplotype was also observed in one at risk individual. A small part of the risk haplotype at the telomeric end was also present in an individual who has just a 1% probably to still become ill, while meiotic recombination finemaps a priority region from D12S1655 till D12S375.

The potential candidate region on chromosome 12q14-21 contains 95 known genes. Of these, 3 positional candidate genes, FAM19A2 (coding for a gene product which is postulated to function as a brain-

specific chemokine), GNS (glucosamine (N-acetyl)-6-sulfatase) , LYZ (lysozyme), were subjected to mutation analysis but did not reveal any mutations that could explain the disease in this family.

Chromosome 2

Two of the 27 markers tested on chromosome 2 gave a 2-point LOD-score above 1. At two subsequent markers, D2S1360 and D2S144, a LOD-score of 1.332 was calculated. Multi-point LOD-score analyses at this locus achieved a maximum score of 1.333. Following the genome-scan results, 8 additional STR markers were typed for segregation analyses. A minimal risk haplotype of 14.6 Mb was defined in a patient by two meiotic recombinants. The risk haplotype was present in all patients but also in two at risk sibs and one more relative.

Chromosome 21
In the genome-wide scan the highest 2-point LOD score of 1.647 was achieved at marker D21S1893. The adjacent marker D21S1440 also reached a LOD-score above 1.
Four additional STR markers were genotyped in this region yielding a risk-haplotype from D21S11920 till the telomeric end. In addition to the patients parts or the entire risk haplotype was also present in 3 at risk individuals.

Discussion

To our knowledge, this is the first report on genetic analysis of a family with adult NCL, with a pedigree which suggests autosomal dominant inheritance. Although this study was unable to identify a

single genetic defect, three haplotypes were identified which segregate with the disease. However, conclusions are hampered by segregation with some unaffected family members. The study is limited by the small number of affected family members, and also by lack of predictive information in unaffected individuals. Although we showed that an abnormal electroencephalogram in an asymptomatic family member could be predictive of disease [11] , it was not applied in this study because of ethical reasons.

Because of small family size, relatively low LOD scores were expected and obtained from the initial genome-wide STR-based linkage analysis. We used an approach where (from the 8 loci suggestive for linkage with a LOD-score > 1, in an autosomal dominant model) only 3 loci were selected for detailed analysis by genotyping additional STR markers in the region: the locus with the highest multipoint LOD score of 1.73 on chr. 12, and two other loci (on chr. 2 and chr. 21, where two subsequent markers gave a LOD-score above 1). The current findings are therefore insufficient to exclude genetic loci apart from our 3 investigated loci.

It is unlikely that known genetic loci for NCL contribute to the etiology of our family, since markers in the proximity of the known NCL loci (1p32, 11p15, 16p12.1, 13q21, 15q21-33, 8p23, 11p15.5) were checked, while none passed a LOD-score value of 1. Furthermore, PPT activity was normal in patients of our family [10], which excludes CLN1. GRODs are present in our patients, but are uncommon in NCL forms other than CLN1.
Besides , our pathological and clinical findings were very similar to other reported AD-ANCL families, which suggests a nosological entity. AD-ANCL is also distinct from other ANCL forms because of its dominant inheritance. It is intriguing that all other NCL forms show

an autosomal recessive mode of inheritance. Dominant occurrence at young age of a devastating disease like NCL would most likely have a very negative effect on the chance of reproductive offspring.

While 8 genes are identified in childhood NCL[3], knowledge on the genetic basis of adult NCL is very limited. Our study did not identify a single gene. However, our limited findings may contribute because genetic knowledge on ANCL is so far completely lacking.
Some individual cases with adult presentation of one of the childhood NCL forms have been reported. For example, two sisters with neuronal ceroid lipofuscinosis presenting in the fourth decade had a profound deficiency of PPT related to the CLN1 gene mutation R151X and a novel missense mutation G108R[12]. Another ANCL patient was reported, who also was a compound heterozygote with mutation R151X, but here the other mutation was a novel mutation, p.Cys45Tyr, which probably disrupts one of two hydrogen bonds with Asp79,6 causing a less severe structural defect. Enzyme activity of PPT1 was diminished but not abolished[13]. PPT activity was normal in patients of our family [10].
Sleat et al identified CLN5 as a cause in an ANCL patient, using an innovative proteomic approach, using the presumption that lysosomal storage diseases arise from mutations in genes encoding lysosomal proteins that contain mannose 6-phosphate, a carbohydrate modification that acts as a signal for intracellular targeting to the lysosome. Purification and quantification of mannose 6-phosphorylated proteins by affinity chromatography in 23 patients with confirmed or possible lysosomal disease, identified or validated the genetic basis for disease in 8 cases[14]. In one ANCL patient [CABM-BR19], this method indicated loss of CLN5, which confirmed previously identified but unreported missense changes (377G>A (Cys126Tyr) and 1121A>G (Tyr374Cys)).

This group also found an unusual cause in a patient suspected of ANCL (HSB#4165), where this chromatographic method indicated absence of SGSH, which is a lysosomal enzyme that is defective in MPSIIIA, a disorder unrelated to the NCLs. Sequence analysis indicated compound heterozygosity for two missense mutations, Glu355Lys and Ser298Pro in SGSH, both of which are documented pathogenic alleles in MPSIIIA. While clinical details and ultrastructure were not reported in this case, it is unclear whether this case fulfills diagnostic criteria for ANCL, which has often led to misdiagnosis [15].

This proteomic approach directed towards study of lysosomal enzymes could also be useful in future studies of AD-ANCL. A different approach for further research could be genetic linkage study of multiple families with presumed identical autosomal dominant disease, with similar clinical presentation and ultrastructure. This is now the focus of the Rare NCL Gene Consortium (RNGC), which was set up in 2006 to facilitate identification of all NCL genes [16].

Figures

STR Marker	Chr.	Mb	cM	theta = 0
D1S2682	1	246.196	288.29	1.143
D2S1360	2	17.355	38.33	1.332
D2S144	2	25.354	45.30	1.332
D7S637	7	154.034	173.03	1.009
GATA114H09	10	106.636	127.11	1.332
D12S1056	12	58.832	75.17	1.165
D15S652	15	90.318	90.02	1.181
ATA67B07	16	1.942	6.08	1.472
D21S1440	21	38.063	36.77	1.109
D21S1893	21	40.278	43.67	1.647

Table 1 : 8cM density genome-wide scan, showing 2-point LOD-scores ≥ 1 for 10 STR markers in 8 distinct chromosomal regions

STR Marker	Mb	0	0.01	0.05
D12S297	50.899	-0.472	-0.157	0.248
D12S398	51.483	-0.472	-0.157	0.248
D12S1586	52.433	1.165	1.139	1.035
D12S104	57.188	-0.013	-0.013	-0.013
D12S1056	58.832	1.165	1.139	1.035
D12S1662	59.131	-1.658	-1.254	-0.733
D12S83	59.176	-1.883	-1.539	-1.003
D12S1655	59.222	-1.641	-1.308	-0.819
D12S1726	60.746	1.926	1.889	1.739
GATA71A08	61.11	1.165	1.139	1.035
D12S1022	61.941	0.511	0.499	0.449
D12S1610	63.291	1.963	1.926	1.775
D12S1649	63.874	1.963	1.926	1.775
D12S1686	63.951	1.963	1.926	1.775
D12S2202	64.059	0.457	0.446	0.403
D12S75	64.784	1.963	1.926	1.775
D12S375	67.231	-0.124	0.297	0.703
GATA134C11	69.409	0.457	0.446	0.401
GATA194G07	72.329	-2.321	-1.775	-0.93
D12S375	73.500	0.456	0.445	0.402
D12S1660	74.749	-4.144	-1.875	-0.724
D12S326	76.498	-4.14	-1.866	-0.722

Table 2: genotyping on chromosome 12 using 22 additional STR markers, covering 25 MB, where LOD score calculations achieved a new maximum of 1.963 for 4 markers in the region.

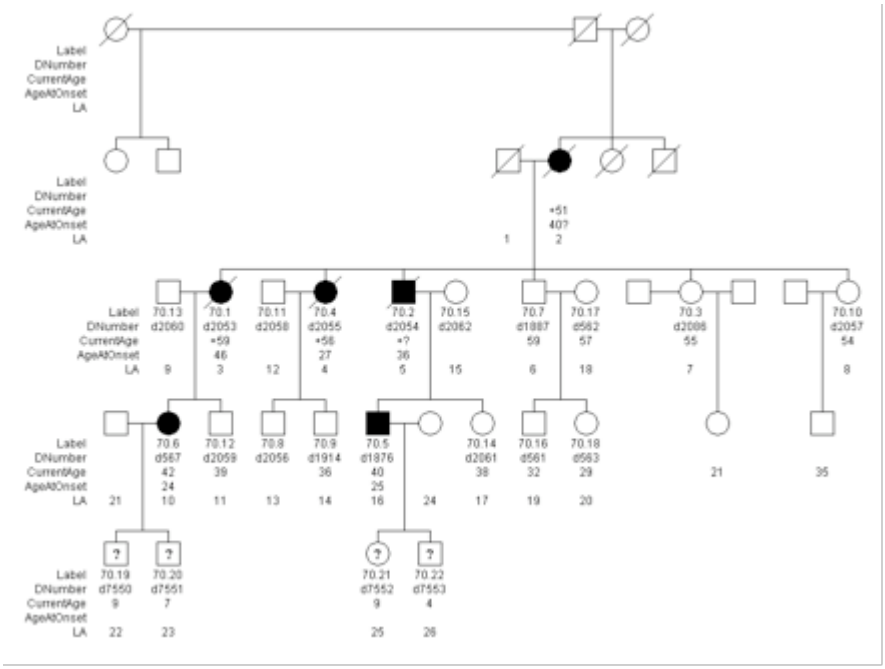

Fig. 1 pedigree

References

1.Jalanko A, Braulke T. Neuronal ceroid lipofuscinoses. Biochim Biophys Acta 2009;1793:697-709.

2.Mole SE. Neuronal ceroid lipofuscinoses (NCL). Eur J Paediatr Neurol 2006;10:255-57.

3.Mole S. NCL resource - NCL mutation database. 2009

4.Boehme DH, Cottrell JC, Leonberg SC, Zeman W. A dominant form of neuronal ceroid-lipofuscinosis. Brain 1971;94:745-60.

5.Ferrer I, Arbizu T, Pena J, Serra JP. A golgi and ultrastructural study of a dominant form of Kufs' disease. J Neurol 1980;222:183-90.

6.Arpa J, Anciones B, Gutierrez M et al. [Our experience with Kufs disease: familial form and sporadic case]. Neurologia 1991;6:222-27.

7.Josephson SA, Schmidt RE, Millsap P, McManus DQ, Morris JC. Autosomal dominant Kufs' disease: a cause of early onset dementia. J Neurol Sci 2001;188:51-60.

8.Nijssen PC, Brusse E, Leyten AC, Martin JJ, Teepen JL, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: parkinsonism due to both striatal and nigral dysfunction. Mov Disord 2002;17:482-87.

9.Burneo JG, Arnold T, Palmer CA, Kuzniecky RI, Oh SJ, Faught E. Adult-onset neuronal ceroid lipofuscinosis (Kufs disease) with autosomal dominant inheritance in Alabama. Epilepsia 2003;44:841-46.

10.Nijssen PC, Ceuterick C, van Diggelen OP et al. Autosomal dominant adult neuronal ceroid lipofuscinosis: a novel form of NCL with granular osmiophilic deposits without palmitoyl protein thioesterase 1 deficiency. Brain Pathol 2003;13:574-81.

11.Nijssen PCG, Brekelmans GJF, Roos RAC. Electroencephalography in autosomal dominant adult neuronal ceroid lipofuscinosis. Clin Neurophysiol 2009

12.van Diggelen OP, Thobois S, Tilikete C et al. Adult neuronal ceroid lipofuscinosis with palmitoyl-protein thioesterase deficiency: first adult-onset patients of a childhood disease. Ann Neurol 2001;50:269-72.

13.Ramadan H, Al-Din AS, Ismail A et al. Adult neuronal ceroid lipofuscinosis caused by deficiency in palmitoyl protein thioesterase 1. Neurology 2007;68:387-88.

14.Sleat DE, Ding L, Wang S et al. Mass spectrometry-based protein profiling to determine the cause of lysosomal storage diseases of unknown etiology. Mol Cell Proteomics 2009

15.Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kufs' disease: a critical reappraisal. Brain 1988;111:27-62.

16.Rare NCL Gene Consortium http://www.ucl.ac.uk/ncl/RNGC.shtml

Chapter 5

AD-ANCL neurophysiology

Chapter 5

Electroencephalography in autosomal dominant adult neuronal ceroid lipofuscinosis

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Abstract

Objective: To describe the findings in 59 EEGs from six patients from three generations in a family with autosomal dominant adult neuronal ceroid lipofuscinosis (Parry disease), autopsy proven, with a follow up of 9–21 years.
Methods: Descriptive, visual EEG analysis.
Results: In these patients with epilepsy, myoclonus, dementia and Parkinsonism, EEGs were all severely abnormal, with generalized or bilateral independent periodic epileptiform discharges the most common pattern. In a few EEGs periodic discharges were seen. No alpha rhythm was present. No paroxysmal response to photic stimulation was seen. Intraindividual EEG changes in the course of the disease were modest, despite severe clinical disease progression. No cortical component linked to myoclonus could be found with a backaveraging technique.
Conclusion:EEG in autosomal dominant neuronal ceroid lipofuscinosis is dominated by generalised periodic epileptiform discharges (GPEDs, or GPD+).
Significance: GPD/GPEDs in adults with myoclonus, Parkinsonism, dementia or epilepsy should raise the possibility of adult neuronal ceroid lipofuscinosis, especially with familial occurrence.

Introduction

Electroencephalography (EEG) is very helpful in the diagnosis of epilepsy, sleep disorders, herpes encephalitis, Creutzfeldt–Jakob disease (CJD) and subacute sclerosing panencephalitis (SSPE), where patterns can be very specific. Kurlemann and Schuierer (1994) emphasized the occurrence of several other specific EEG patterns in neurological disorders of childhood, including positive spikes during low frequency photostimulation for late infantile neuronal ceroid lipofuscinosis(LINCL).

Neuronal ceroid lipofuscinosis(NCL, Batten disease)is a group of genetic disorders with intraneuronal lysosomal storage of autofluorescent lipopigment, leading to blindness, myoclonus, epilepsy, cognitive and motor dysfunction. Classically they were categorized according to age of onset: infantile(INCL), late infantile(LINCL), juvenile(JNCL) and adult (ANCL). Now 8 forms are distinguished (CLN1–8), while five genes have been isolated and characterized (CLN1, 2, 3, 5&8)(Mole, 1999, 2004). EEG has been shown to provide several more or less specific patterns in the different childhood neuronal ceroid lipofuscinosis (NCL) forms. Absence of sleep spindles occurs in Infantile NCL (INCL), even while ERG and VEP are still normal (Santavuori et al., 1992). Vanhanen et al. (1997) indicated that although the EEG may be normal at the preclinical stage, electroencephalography is the first electrodiagnostic examination to reveal abnormalities in INCL, showing an attenuated reaction to passive eye opening and closing, followed by disturbances in background activity, diminution in amplitude and disappearance of sleep spindles. In later stages, slowing or attenuation of EEG to inactivity is seen. All neurophysiologic reactions are abolished by the age of 4 years. No photic response occurs in INCL (Vanhanen et al., 1997;Santavuori et al., 1992).

In late infantile NCL the electroencephalogram may show high amplitude, irregular delta–theta activity and spike-or polyspike-wave discharges (without localized preponderance) and grossly enlarged responses to single light flashes. Spikes in response to intermittent low frequency(<3Hz) photostimulation appear by the age of 7–8 years and disappear after 11 years of age. Increased slowing and decreased amplitude is seen in the course of the disease (Binelli et al., 2000). In variant LINCL, electrophysiological abnormalities on EEG, ERG and VEP are similar as described in the classical LINCL (Wisniewski et al., 1993). In juvenile NCL (JNCL) Lagenstein et al. reported 2.5–3.5 Hz slow-spike-waves, meeting the criteria of the Lennox syndrome (Lagenstein et al., 1978). Runs of slow spikes and waves are often seen, (Sainio, 1997; Williams et al., 1999) but EEG findings are less specific than in most other NCLs. Adult NCL is rare, with onset around the age of 30, leading to myoclonus, epilepsy, Parkinsonism, dementia or ataxia. Visual symptoms are uncommon, unlike in childhood forms. Knowledge of adult NCL forms develops slowly, compared to the major advances in childhood NCL in the last 15 years. Most adult NCL reports indicate autosomal recessive inheritance, known as Kufs' disease. Berkovic et al. (1988) reviewed 118 cases of autosomal recessive ANCL. They concluded that in this recessive form of the disease, EEG is less specific, showing diffuse slowing, or generalized spike-wave discharges (in a so-called type A phenotype). As in LINCL, an intense photoparoxysmal response may occur, especially to low-frequent flashes of 1–2Hz (Vadlamudi et al., 2003).

Here we report on EEG findings in a family with the extremely rare autosomal dominant form of adult neuronal ceroid lipofuscinosis, called Parry disease. Detailed clinical and autopsy findings of this family have been reported (Nijssen et al., 2002, 2003).

Methods

This observational study describes visual EEG analysis of 59 EEG recordings in six patients, in three generations of a family with autosomal dominant adult neuronal ceroid lipofuscinosis. The diagnosis was confirmed with electronmicroscopy in two autopsies, where massive intraneuronal storage was seen throughout the brain, mainly consisting of granular osmiophilic deposits (GRODs)(Nijssen et al., 2003). Twenty-four EEGs were digitally recorded, 35 on paper, from Ag/AgCl surface electrodes, using the international 10–20 system, with a timebase of 30mm/s, RC=1.2s, gain 70 μV/cm. All EEGs were recorded while awake, with eyes open and closed.

Results

Patient 1

This woman with generalized tonic clonic seizures from the age of 44 years, had progressive cognitive decline, myoclonus and Parkinsonism, leading to death at the age of 51. Her medical records report a severely disturbed EEG at the age of 45 years, with frequent intermittent epileptiform bursts; the recording could not be retrieved.

Patient 2

This woman is a daughter of patient 1. She had myoclonus of arms and face from the age of 46 years, followed by progressive dementia, Parkinsonism, generalized tonic clonic seizures and psychotic episodes. She died at the age of 59 years. Thirteen EEGs were recorded, from the age of 45 until 54. The first EEG showed normal backgroundactivity, with frequent generalized bursts of slow waves mixed with spikes. While burst activity remained similar, spike activity increased in the course of

the disease: in the last years runs of spikes dominated, eventually with very long trains of bilaterally synchronous spikes.

Patient 3

This sister of patient 2 had several depressive episodes, and developed generalized epileptic seizures at the age of 42 years, followed by psychotic episodes, Parkinsonism, myoclonus and progressive dementia. She died at the age of 56 years. Five EEGs were recorded, from the age of 45 until 52. Compared to her sister, these EEGs had almost twice as many bursts, of shorter duration. Spikes were less frequent, and except for some duplets in complexes, isolated polyspikes were not seen. Her last EEG showed continuous bilaterally synchronous delta activity of around 1 Hz, amplitude 10 μV.

Patient 4

This brother of patients 2 and 3 had myoclonic jerks of the arms since the age of 36 years. Progressive memory impairment, depressive episodes and visual hallucinations, Parkinsonism and generalized tonic clonic epileptic insults led to severe disability, he died at the age of 56 years old. Ten EEGs were recorded, from the age of 40 until 55. As in his sisters, the EEGs showed bilaterally synchronous epileptiform discharges, of intermediate frequency and duration compared to his sisters'. Here also, the number of isolated spikes increased during the years. One postictal tracing showed continuous bilaterally synchronous highvoltaged (300μV) 1.5–2 Hz delta activity. A week later –after treatment with phenytoin– the EEG was as before. During a period with overt myoclonus, an EEG was recorded with backaveraging, using the myoclonus as a trigger. No cortical analogue could be traced however.

Patient 5

This daughter of patient 2 had tension-type headache and migraine attacks without aura from the age of 19 years. Neurological examination at the age of 24 years was normal. During her first pregnancy, at the age of 32, she developed myoclonus of the right arm. Since delivery, progressive myoclonus in both arms and chin occurred. She has slight memory difficulties and dysarthria. She had a generalized tonic clonic seizure after delivery of her second child. Ten EEGs were recorded, from the age of 24 until 45. Despite lack of symptoms and signs at the age of 24, by then an EEG showed bilaterally synchronous epileptiform discharges, morphologically similar to those in affected family members, but with very few spikes, and no polyspikes. The number of spikes fluctuated in the course of the disease; no isolated spikes were seen (Fig. 1).

Patient 6

In the son of patient 4, 21 EEGs were recorded, from the age of 25 until 43. He has had myoclonus of the thumb and arms from the age of 25. At that time, an EEG showed bilaterally synchronous epileptiform bursts. At the age of 31 he experienced attacks with loss of consciousness for several seconds. Two years later he had a generalized tonic clonic seizure after heavy alcohol consumption, followed by frequent generalized seizures. His EEGs show relatively short bursts, with a few low voltaged spikes interspersed in the high voltaged complexes, but no isolated spikes(Figs. 2 and 3).

Features common to all EEG recordings

The epileptiform bursts were often bilaterally synchronous, with GPEDs (generalized periodic epileptiform discharges, now called GPD), sometimes also more bilaterally independent. Although burst length was variable, they were often of similar morphology, but never identical.

Also, the length of interburst intervals was never predictable, but patients with longer discharges often also had longer intervals. No response to photostimulation was seen in any EEG with either single flash, low or high frequency stimulation. No alpha rhythm was seen in any of the tracings, although a response to eye opening and closing was sometimes clear (altered burst frequency, or runs of highvoltaged delta). The background activity in intervals between bursts consisted of an irregular mix of beta and alpha activity with some theta.

Discussion

Autosomal dominant adult NCL ('Parry disease') is an extremely rare disorder: only a few families have been reported (Boehme et al., 1971, 1980; Josephson et al., 2001; Nijssen et al., 2002, 2003; Brodner et al., 1976; Ferrer et al., 1980; Arpa et al., 1991). EEG findings in our family are very similar to those reported in the Parry family as described by Boehme et al. (1971): in their patient IV/2'... an EEG was grossly abnormal, showing long runs of slow waves in the 0–4 and 4–7 cps range, preceded by spikes and sharp waves. ...bilaterally diffuse and synchronous...'. In patient IV/3 'several EEGs revealed an atypical spike and wave pattern which was bilaterally symmetrical and superimposed on a slow background rhythm with a predominance of 3–5 cps'. In patient IV/5 'the waking EEG showed a dominant activity of 10–11 cps, interspersed with general slowing. When drowsy, frequent bursts of bilateral rhythmic slowing with 2–3 cps appeared. Simultaneously paroxysms of high voltaged spikes developed with atypical spike-slow wave complexes, usually seen in both hemispheres synchronously'. In patient IV/15 'an EEG showed frequent generalized paroxysms of highvoltaged rhythmic slowing, sharp waves, and occasional spikes, suggestive of a ''burst-suppression pattern'' '. Besides, the electronmicroscopical and clinical findings in their family are also very

similar. These findings strongly suggest that their and our family suffer from a single disease. The evidently pathological EEG findings in patient 5 at the age of 24 years old, while she was clinically asymptomatic (except for migraine with aura, which is most likely unrelated to the NCL), suggests that the EEG could be used as a screening tool in asymptomatic patients. If the EEG shows abnormalities similar to those described above, in an asymptomatic member of a family with autosomal dominant NCL,this probably indicates that this person is affected, and will develop symptoms later on. The negative predictive value or sensitivity of the EEG cannot be determined from this observation. In the single case of a family with autosomal dominant adult NCL described by Ferrer et al. (1980), the EEG was normal. In a single case reported by Brodner et al. (1976) the EEG was normal in an individual with biopsy–proven NCL from a family with autosomal dominant NCL described previously by Boehme et al. (1971). The diagnosis was made during surgery for an astrocytoma at the age of 24, while disease onset in other affected familymembers was usually at the age of 31. Similarly, normal EEGs have been reported in patients with autosomal recessive Kufs disease. The sensitivity of the EEG as a screening test for adult NCL in asymptomatic individuals may thus be limited. Although a few EEGs in our family showed episodes with periodic discharges, the common epileptiform burst pattern showed large variation of the intervals between the complexes. The term ’pseudoperiodic’, as suggested by Markand and Daly(1971) may be more indicative, but is not sharply defined. In many of our EEGs, spikes and polyspikes occurred in slowwave complexes with long intervals (max 25s) resembling GPEDs (generalised periodic epileptiform discharges), or according to more recent nomenclature GPD’s (generalised periodic discharges) plus (Hirsch et al., 2005).
Veneselli et al. (2001) reported on findings in 60 electroencephalograms in a group of 30 Italian childhood NCL cases. They observed 4 INCL, 18

LINCL (and variants) and 8 JNCL patients, with electronmicroscopic conformation of the diagnosis in all cases. In 3 of 4 INCL cases a 'vanishing' (low voltage) EEG pattern was seen, a single INCL case had slowed background activity and atypical spikes and waves. In EEGs from 18 LINCL patients they distinguished three different patterns:(A) slowed background activity and pseudoperiodic, atypical highvoltage slow spikes and waves, mostly in the posterior regions (15 of 18); (B) subcontinuous/continuous slow spike and wave activity(2 of 18);(C) multifocal epileptiform abnormalities (single case). In 8 JNCL patients, they found normal background activity with runs of slow spikes and waves in 5; and slightly slowed background with frequent abnormalities resembling a pattern of generalized epilepsy. Vanishing EEG, as seen in the final stage of INCL was not seen in our family. However, no EEGs were obtained in the final 4 years of life of patients 2 and 3, which might have shown decreasing amplitude. However, no amplitude reduction occurred during the many years of follow up in our patients. Similar to the series of variant LINCL patients described by Veneselli, we found no correlation between the EEG characteristics and the stage of the disease, except for an increasing number of spikes with increasing age in patient 2.

The consistent findings in this family with autosomal dominant adult NCL indicate that GPEDs in adults with myoclonus, Parkinsonism, dementia or epilepsy should raise suspicion of adult neuronal ceroid lipofuscinosis, especially with familial occurrence.

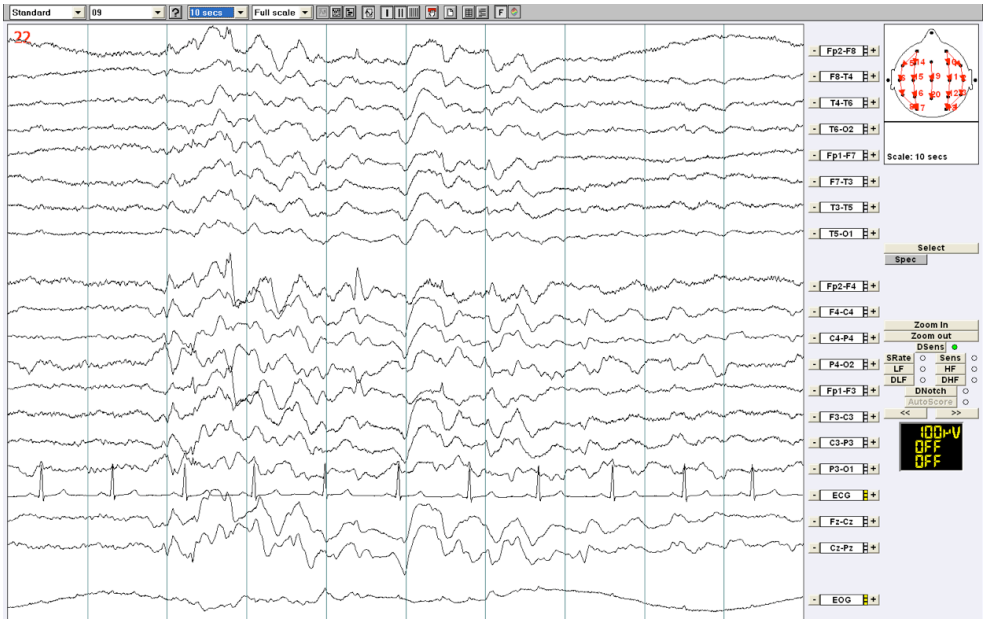

Fig. 1. Electroencephalogram of patient 5 at the age of 38 shows highvoltaged generalised epileptiform discharges of slow waves mixed with sharp waves.

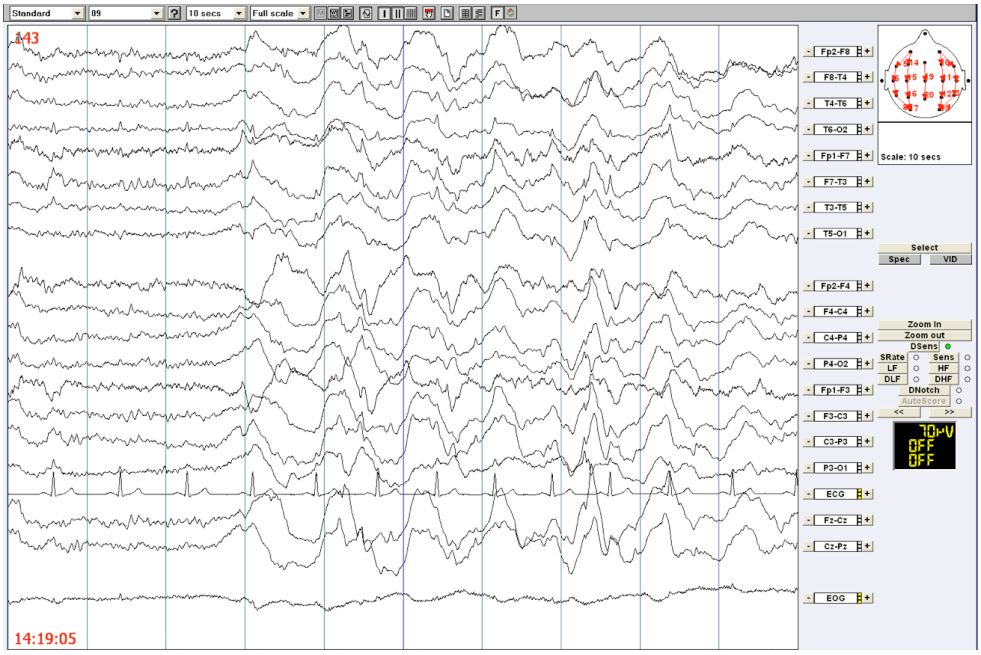

Fig. 2. EEG of patient 6 at the age of 39 shows long bursts of generalized high amplitude slow waves mixed with spikes and sharp activity.

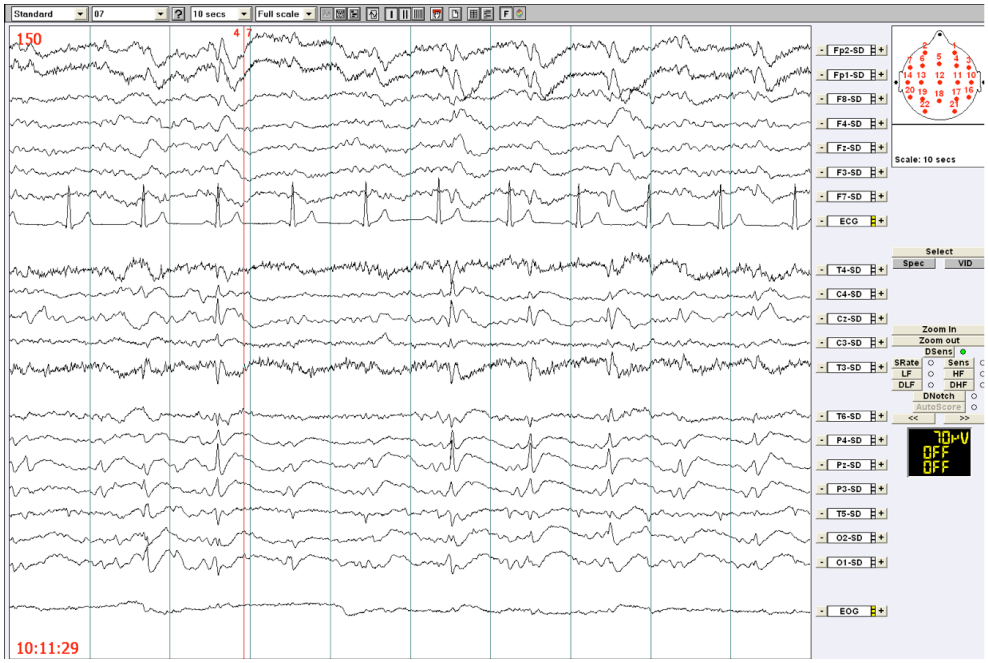

Fig. 3. EEG of patient 6 at the age of 41 shows bilaterally synchronous periodic short complexes with spikes/sharpwaves and slow waves at regular intervals.

References

Arpa J, Anciones B, Gutierrez M, Morales C, Barreiro P, Caminero A, et al. Our experience with Kufs disease: familial form and sporadic case. Neurologia 1991;6(6):222–7.

Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kufs' disease: a critical reappraisal. Brain 1988;111(Pt. 1): 27–62.

Binelli S, Canafoglia L, Panzica F, Pozzi A, Franceschetti S. Electroencephalographic features in a series of patients with neuronal ceroid lipofuscinoses. Neurol Sci 2000;21(3Suppl.):S83–7.

Boehme DH, Cottrell JC, Leonberg SC, Zeman W. A dominant form of neuronal ceroid-lipofuscinosis. Brain 1971;94(4): 745–60.

Boehme DH, Leonberg SC, Varagiannis E, Marks N. On the neurochemistry of an adult form of ceroid lipofuscinosis (Kuf's disease). Prog Clin Biol Res 1980;39:305–14.

Brodner RA,Noh JM, Fine EJ. Adominant form of adult neuronal ceroid lipofuscinosis (Kufs' disease) with an associated occipital astrocytoma: earlydiagnosis by cortical biopsy. J Neurol Neurosurg Psychiatry 1976;39(3):231–8.

Ferrer I, Arbizu T, Pena J, Serra JP. A Golgi and ultrastructural study of a dominant form of Kufs' disease. J Neurol 1980;222(3):183–90.

Hirsch LJ, Brenner RP, Drislane FW, So E, Kaplan PW, Jordan KG, et al. The ACNS subcommittee on research terminology for continuous EEG monitoring: proposed standardized terminology for rhythmic and periodic EEG patterns encountered in critically ill patients. J Clin Neurophysiol 2005;22:128–35.

Josephson SA, Schmidt RE, Millsap P, McManus DQ, Morris JC. Autosomal dominant Kufs' disease: a cause of early onset dementia. J Neurol Sci 2001;188(1–2):51–60.

Kurlemann G, Schuierer G. EEG in diagnosis of other disease pictures than epilepsy. Klin Padiatr 1994;206(2):100–7.

Lagenstein I, Sternowsky HJ, Koepp P, Leiber U. Myoclonic-astatic seizures(Lennox syndrome) in the course of juvenile neuronal ceroid-lipofuscinosis [Batten- Spielmeyer-Vogt M, Trans.]. Klin Padiatr 1978;190(5):507–11.

Markand ON, Daly DD. Pseudoperiodic lateralized paroxysmal discharges in electroencephalogram. Neurology 1971;21(10):975–81.

Mole SE. Batten's disease: eight genes and still counting? Lancet 1999;354(9177):443–5.

Mole SE. The genetic spectrum of human neuronal ceroid-lipofuscinoses. Brain Pathol 2004;14(1):70–6.

Nijssen PC, Brusse E, Leyten AC, Martin JJ, Teepen JL, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: Parkinsonism due to both striatal and nigral dysfunction. Mov Disord 2002;17(3):482–7.

Nijssen PC, Ceuterick C, van Diggelen OP, Elleder M, Martin JJ, Teepen JL, et al. Autosomal dominant adult neuronal ceroid lipofuscinosis: a novel form of NCL with granular osmiophilic deposits without palmitoyl protein thioesterase1 deficiency. Brain Pathol 2003;13(4):574–81.

Sainio K. Neurophysiological findings in neuronal ceroid lipofuscinoses. Neuropediatrics 1997;28(1):70.

Santavuori P, Raininko R, Vanhanen SL, Launes J, Sainio K. MRI of the brain, EEG sleep spindles and SPECT in the early diagnosis of infantile neuronal ceroid lipofuscinosis. Dev Med Child Neurol 1992;34(1):61–5.

Vadlamudi L, Westmoreland BF, Klass DW, Parisi JE. Electroencephalographic findings in Kufs disease. Clin Neurophysiol 2003;114(9):1738–43.

Vanhanen SL, Sainio K, Lappi M, Santavuori P. EEG and evoked potentials in infantile neuronal ceroid-lipofuscinosis. Dev Med Child Neurol 1997;39(7):456–63.

Veneselli E, Biancheri R, Buoni S, Fois A. Clinical and EEG findings in 18 cases of late infantile neuronal ceroid lipofuscinosis. Brain Dev 2001;23(5):306–11.

Williams RE, Boyd S,Lake BD. Ultrastructural and electrophysiological correlation of the genotypes of NCL. Mol Genet Metab 1999;66(4):398–400.

Wisniewski KE, Kida E, Connell F, Elleder M, Eviatar L, Konkol RJ. New subform of the late infantile form of neuronal ceroid lipofuscinosis. Neuropediatrics 1993;24(3):155–63.

Chapter 6

AD-ANCL auditory

Hearing impairment and abnormal Auditory Brainstem Responses in autosomal dominant adult neuronal ceroid lipofuscinosis

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submitted

Abstract

Objective: to investigate the occurrence of auditory dysfunction in a family with autosomal dominant adult neuronal ceroid lipofuscinosis (ANCL).
Methods: descriptive
Results: Hearing impairment was common in our autosomal dominant ANCL family, which has 6 affected family members in three generations. In all 5 affected siblings who had Auditory Brainstem Responses, waves I to V were delayed, with progressive abnormalities in later disease stages.
Conclusion: occurrence of progressive auditory dysfunction is very common in autosomal dominant ANCL, which has not been reported in other NCL forms.

Objective

Neuronal ceroid lipofuscinosis is a group of inherited lysosomal storage diseases with neurodegeneration characterized by storage of intraneuronal lipofuscin-like material[1]. Most forms have an autosomal recessive mode of inheritance[2] and present at childhood with prominent visual loss, epilepsy, cognitive decline and movement disorders[3]. We study a family with a very rare form of neuronal ceroid lipofuscinosis ('Parry disease') which presents at adult age, and has an autosomal dominant inheritance pattern[4, 5]. Auditory symptoms are not a common feature of childhood NCL. We studied the occurrence of auditory dysfunction in autosomal dominant adult NCL (ANCL).

Patients

Clinical records and clinical neurophysiological records of 6 affected members of a reported family with autosomal dominant ANCL (fig 1: family pedigree) which was proved by autopsies[5], were retrospectively reviewed for auditory symptoms and brainstem auditory evoked potential recordings. A short description of clinical symptoms and signs is given for each patient.

Patient 1

She had tonic clonic seizures from the age of 44 years, progressive dementia, myoclonus and parkinsonism. She complained of slowly progressive hearing impairment since the start of other symptoms at age of 44. She died at the age of 51.

Patient 2

This daughter of patient 1 had myoclonus of arms and face from the age of 46 years, followed by progressive dementia, parkinsonism, generalized tonic clonic seizures and psychotic episodes. She reported

progressive hearing impairment at the age of 46. By then, moderate to severe hearing difficulty was reported by a psychologist in a neuropsychological test report. Auditory Brainstem Responses (ABR) recorded at age 47 showed a severely disturbed pattern of hardly distinguishable responses. A year later only a wave V was discernible in the right ABR, while at the left all waves (including wave I) were severely delayed. The last ABR at age 51 showed only a severely delayed wave V (latency 5 SD at the right, 2.5 SD at the left). She died at the age of 59 years.

Patient 3

This sister of patient 2 had depressive episodes, and developed generalized epileptic seizures at the age of 42 years, followed by psychosis, parkinsonism, myoclonus and progressive dementia. She died at the age of 56. She had hearing difficulty of the left ear from the age of 24, and both vertigo and tinnitus from age 27. She had severe bilateral perception deafness requiring hearing aids on both sides from the age of 40.
ABR showed only cochlear microphonics and a delayed wave I (1,92 ms) at the age of 45, while several ABR between age 46 and 48 showed no waves at all.

Patient 4

This brother of patients 2 and 3 had myoclonic jerks of the arms since the age of 36 years. Progressive memory impairment, depressive episodes and visual hallucinations, parkinsonism and generalized tonic clonic epileptic insults led to severe disability, he died at the age of 56 years. He had moderate hearing difficulty. ABR at the age of 48 showed cochlear microphonics only at the left, with hardly discernible delayed waves IV and V at the right. A year later hearing threshold was 40 dB. With 103 dB stimulation at the right ear, cochlear microphonics were

seen, but no wave I or II, while wave III had a latency of 5 ms; latency of wave V was 6.5 ms (contralaterally 6,6 ms). At the left a similar pattern was seen but without cochlear microphonics (III en V latencies of 5.3 and 6.8 ms). Electronystagmography at the age of 54 showed no caloric response on both sides (30 and 44C).

Patient 5

This daughter of patient 2 had migraine attacks without aura from the age of 19 years. Neurological examination at the age of 24 years was normal. During pregnancy at the age of 32, she had myoclonus of the right arm. She has progressive memory difficulties and generalized tonic clonic seizures. She has had six ABR 's between the age of 24 and 41 years old (fig 2), with progressively increasing latencies. ABR at the age of 38 showed no abnormalities except for a delay of wave I latency at the right side.

Patient 6

This son of patient 4 has had myoclonus of the thumb and arms from the age of 25. From the age of 31 he has epilepsy, parkinsonism, polyminimyoclonus and visual dysfunction. He has had eight ABR's between age 25 and 38, which show increasing latencies of all waves with increasing age, but less severe than patient 5(fig 2).

Conclusions

The large NCL literature has only a few reports on auditory symptoms: auditory hallucinations[6] were reported in a single Late Infantile NCL (LINCL) case; impaired auditory attention[7], and decreased auditory memory span[8] were observed in Juvenile NCL (JNCL).

ABR has been studied scarcely in NCL, with normal responses in a case of JNCL[9] and a case of LINCL[10], while ABR was enhanced in a case of LINCL[11]. Abnormal brainstem auditory evoked potentials were found in 35% of individuals with Northern epilepsy[12].

We have previously reported storage of lipofuscin and neurodegeneration in the brainstem of patients 2 and 3 [5], which may explain the progressively abnormal late ABR waves, but the obvious delay of early ABR waves indicates co-occurrence of peripheral pathology. This has not been previously reported in adult NCL, but in JNCL, Elleder et al [13] studied inner ear cells, showing ultrastructural intralysosomal curvilinear and fingerprint patterns in several cell types including the receptor cells of the organ of Corti and sensory cells of crista ampullaris. We hypothesize a similar mechanism in autosomal dominant ANCL. This is supported by absent caloric electronystagmography responses in patient 4.

Our study indicates that in contrast to other NCL forms, auditory dysfunction and abnormal Auditory Brainstem Evoked Responses are a common feature of autosomal dominant adult NCL. Unlike EEG[14] , ABR seems to be progressively abnormal in later disease stages.

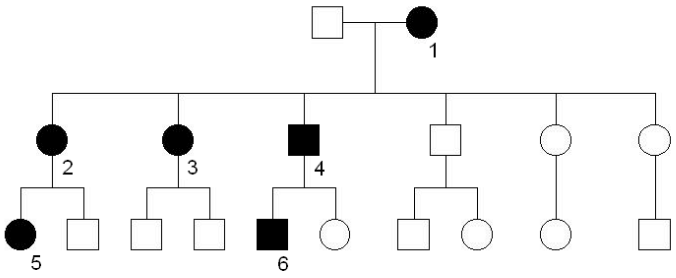

Fig 1. Family pedigree

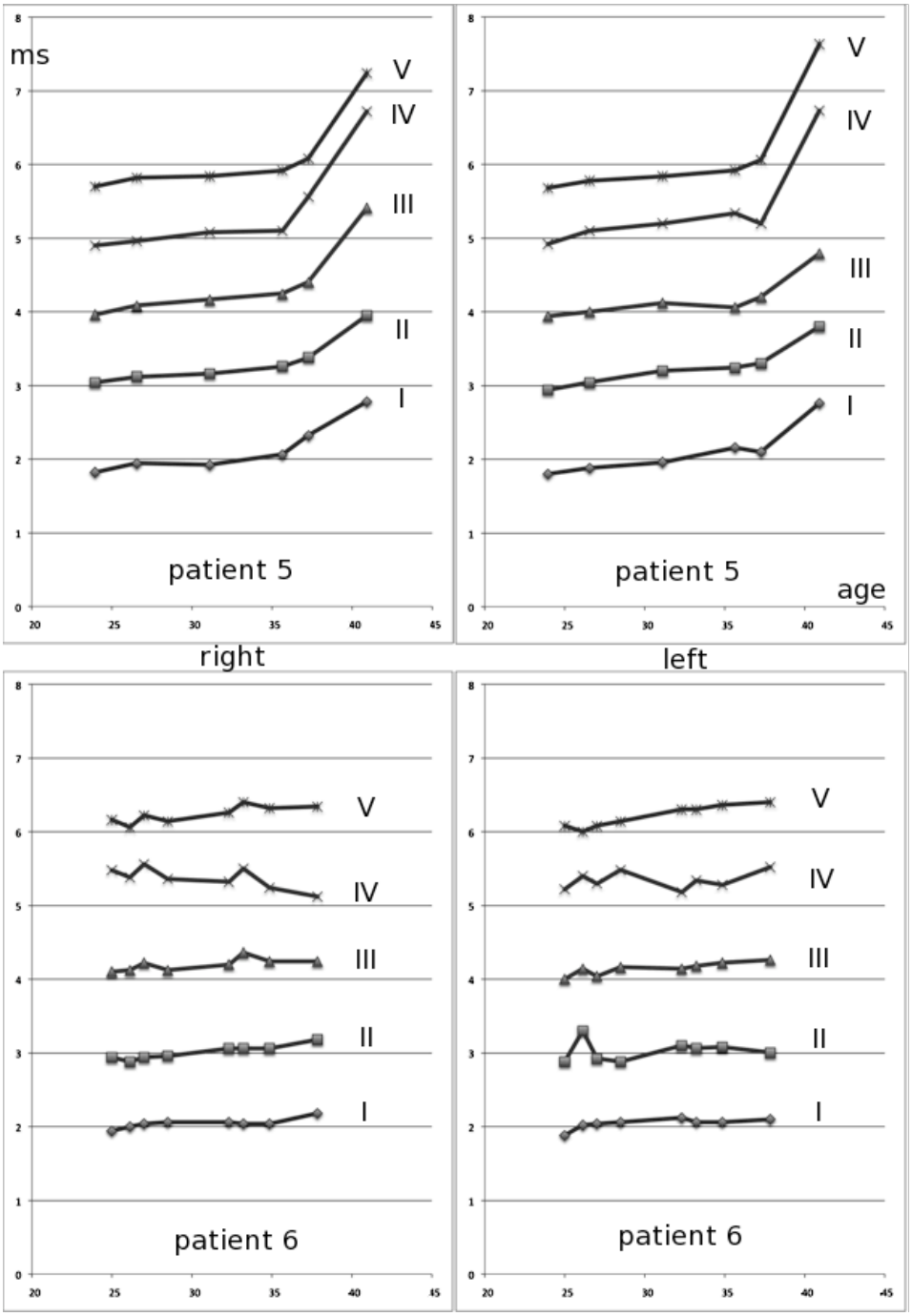

Fig 2. ABR latencies of waves I-V versus age (top panels: patient 5 (right/left), lower panels: patient 6 (right/left)

References

1.Mitchison HM, Mole SE. Neurodegenerative disease: the neuronal ceroid lipofuscinoses (Batten disease). Curr Opin Neurol 2001;14:795-803.

2.Siintola E, Lehesjoki AE, Mole SE. Molecular genetics of the NCLs -- status and perspectives. Biochim Biophys Acta 2006;1762:857-64.

3.Wisniewski KE, Zhong N, Philippart M. Pheno/genotypic correlations of neuronal ceroid lipofuscinoses. Neurology 2001;57:576-81.

4.Nijssen PC, Brusse E, Leyten AC, Martin JJ, Teepen JL, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: parkinsonism due to both striatal and nigral dysfunction. Mov Disord 2002;17:482-87.

5.Nijssen PC, Ceuterick C, van Diggelen OP et al. Autosomal dominant adult neuronal ceroid lipofuscinosis: a novel form of NCL with granular osmiophilic deposits without palmitoyl protein thioesterase 1 deficiency. Brain Pathol 2003;13:574-81.

6.Iannetti P, Messa C, Spalice A, Lucignani G, Fazio F. Positron emission tomography in neuronal ceroid lipofuscinosis (Jansky-Bielschowsky disease): a case report. Brain Dev 1994;16:459-62.

7.Adams HR, Kwon J, Marshall FJ, de Blieck EA, Pearce DA, Mink JW. Neuropsychological symptoms of juvenile-onset batten disease: experiences from 2 studies. J Child Neurol 2007;22:621-27.

8.Kristensen K, Lou HC. Central nervous system dysfunction as early sign of neuronal ceroid lipofuscinosis (Batten's disease). Dev Med Child Neurol 1983;25:588-90.

9.Davis SL, Aminoff MJ, Berg BO. Brain-stem auditory evoked potentials in children with brain-stem or cerebellar dysfunction. Arch Neurol 1985;42:156-60.

10.Wu JM, Young C, Wang PJ, Cheng CJ, Shen YZ. Late infantile type neuronal ceroid lipofuscinosis: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1996;37:376-80.

11.Kira J, Tabira T, Tsuji S, Shibasaki H, Goto I. [A case of neuronal ceroid-lipofuscinosis (Jansky-Bielshowsky type): morphological, biochemical and electrophysiological studies (author's transl)]. Rinsho Shinkeigaku 1981;21:706-13.

12.Lang AH, Hirvasniemi A, Siivola J. Neurophysiological findings in the northern epilepsy syndrome. Acta Neurol Scand 1997;95:1-8.

13.Elleder M, Voldrich L, Ulehlova L, Dimitt S, Armstrong D. Light and electron microscopic appearance of the inner ear in juvenile ceroid lipofuscinosis (CL). Pathol Res Pract 1988;183:301-07.

14.Nijssen PCG, Brekelmans GJF, Roos RAC. Electroencephalography in autosomal dominant adult neuronal ceroid lipofuscinosis. Clin Neurophysiol 2009, 120(10):1782-6.

Chapter 7

AD-ANCL visual

Chapter 7

Visual symptoms in autosomal dominant adult neuronal ceroid lipofuscinosis

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Abstract

Objective: to study visual problems in six patients from three generations of a family with autosomal dominant adult neuronal ceroid lipofuscinosis (AD-ANCL).
Methods: We surveyed their records for any data related to vision.
Results: In five patients visual dysfunction was obvious, with both positive visual symptoms (sometimes in temporal relation with epileptic attacks) and decreased visual acuity with abnormal VEP and ERG. Bull's eye maculopathy was seen in one patient, who also had a hyperintense lesion of the optic radiation on MRI.
Conclusion: visual problems are common in AD-ANCL, due to retinal pathology, optic nerve atrophy, optic radiation degeneration, cortical dysfunction and epilepsy.

Introduction

Progressive loss of vision leading to blindness is one of the major manifestations in childhood forms of neuronal ceroid lipofuscinosis (NCL), which show recessive inheritance.
Adult NCL has a rare recessive form (Kufs' disease), and a very rare autosomal dominant form (Parry disease). Ophthalmological findings in recessive adult NCL are reported to be normal{Berkovic et al., 1988, Brain, 111 , 27-62}, in sharp contrast to childhood forms. Here we report on visual problems in a family with the autosomal dominant adult form of NCL (AD-ANCL).

Methods

Descriptive and retrospective. We have carefully screened all medical records of our six patients from a known family with AD-ANCL {Nijssen et al., 2002, Mov Disord, 17, 482-7} for any clinical, neurophysiological, ophthalmological, and imaging data related to vision. Diagnosis was confirmed by electronmicroscopy as described previously {Nijssen et al., 2003, Brain Pathol, 13, 574-81}. The cases will be described briefly.

Results

Patient 1
This woman with tonic clonic seizures from the age of 44 years, had progressive cognitive decline, myoclonus and parkinsonism. She died at the age of 51.
No visual symptoms or signs were found in her medical records.

Patient 2

This woman is a daughter of patient 1. She had myoclonus of arms and face from the age of 46 years, followed by progressive dementia, parkinsonism, tonic clonic seizures and psychotic episodes. She died at the age of 59 years. At the age of 46 years old, she mentioned flashes in both eyes. Several months later she described seeing all kinds of colors. No other visual symptoms could be found in her extensive medical records. Neuropsychological testing showed severe difficulties in a trail making test and also in copying complex figures, but no visual problem were reported.
Visual evoked potential (VEP) at the age of 46 years old showed a P100 latency of 115 ms on both sides (normal <117 ms). Two VEP's in the next 2 years were similar.

Patient 3

This sister of patient 2 had depressive and psychotic episodes, epileptic seizures, parkinsonism, myoclonus and dementia. She died at the age of 56.
At the age of 47 she mentioned seeing flashes frequently. A year later she reported colorful optic sensations, which were hard to describe in more detail. In the next two years she complained of blurred vision, and progressively decreasing visual acuity.
VEP at the age of 48 showed delayed P100 latencies of 136 and 146 ms. Four years later VEP showed no discernable responses anymore.

Patient 4

This brother of patients 2 and 3 had myoclonic jerks of the arms since the age of 36 years. He had progressive memory impairment, depressive episodes, parkinsonism, facial dyskinesias and tonic clonic epileptic insults. He died at the age of 56 years.

He mentioned seeing stars and black patches at the age of 43. Five years later a tonic clonic epileptic seizure had a prodrome consisting of seeing stars. In the last months of his life he had an episode with visual hallucinations of persons.
Electronystagmography at the age of 54 showed saccadic pursuit movements, hypometric and overshoot saccades and absent caloric responses (indicating peripheral as well as central vestibular dysfunction). Electrooculography and electroretinography at the age of 54 showed a low normal Lp/Dt ratio, low scotopic amplitudes, while photopic responses were normal, indicating rod-dysfunction. At the age of 61 findings were similar. VEP at the age of 53 showed a delayed P100 of 145 ms at the right side, and no response at the left.

Patient 5

This daughter of patient 2 had tension-type headache and migraine attacks without aura from the age of 19 years. Neurological examination at the age of 24 years was normal. Since the age of 32, she has had progressive myoclonus and slight memory difficulties.
Since the age of 37 she had frequent attacks of colorful visual sensations, which were described as caleidoscopic speckles in the whole visual field, without impairing vision. The sensations were often the first symptoms of an epileptic attack with loss of consciousness. She saw hundreds of yellow or orange dots in a week of not taking her antiepileptic drugs. During a psychotic episode she saw spiders and magicians. She had several short attacks seeing indefinable colorful objects, which diminished after addition of levetiracetam. Since the age of 45 she complains of progressively worsening visual acuity, which decreased to 0.7 vs 0.5 at age 46. Fluorescein fundus angiogram showed slightly altered macular pigment distribution, but no Bulls eye maculopathy. Optical coherence tomography (OCT) was normal.

Patient 6

This son of patient 4 has had myoclonus of the thumb and arms from the age of 25, and frequent tonic clonic seizures since age 31.
Pattern VEP at the age of 31 showed delayed P100 latencies of 132 ms (right) and 134 ms (left). Six years later responses were extremely delayed (239 and 242 ms).
At the age of 38 he reported blurred vision, when visual acuity of the right eye was 3/6, 1/30 at the left. He then had attacks for 10 minutes, three times a week, seeing colorful images. A year later he reported an attack where he saw images of melting snow, blue patches, lots of hair, greyish faces, and a parade of people passing by. Visual acuity was 0.1 vs 0.16. Fluorescein fundus angiogram showed a Bull's eye maculopathy (fig. 2). Cerebral MRI showed optic nerve atrophy, and paraventricular T2 hyperintensity, extending in a thin line (cross-secting a plane parallel to the lateral ventricle wall) into the optic radiation (fig. 3). Later he had several attacks with images of hundreds of black hairs randomly scattered like mikado sticks on a white background, stripes in different colors, or more complex images like dolphins in an aquarium. After levetiracetam was added to his anti-epileptic drug regimen, positive visual sensations vanished. At age 44 visual acuity had decreased to 0.05 vs 0.01.

Optical coherence tomography (OCT) (fig 4A) showed severe retinal abnormalities, consisting of an atrophic retina on an intact Bruch membrane, with disturbed retinal layer morphology, merely due to thinning of the outer nuclear layer and outer segment layer (along with its hyperintense borders), and maybe also retinal pigment epithelium atrophy. Where the outer segment layer and retinal pigment epithelium were expected, granular bead-like structures were seen with a diameter of 20 to 50 µm.

Discussion

Visual dysfunction is a hallmark of most NCL forms, but not in Kufs' disease.
In Infantile NCL (CLN1) visual symptoms occur in the first 2 years {Wisniewski et al., 1988, Am J Med Genet Suppl, 5, 27-46}, with retina degeneration, involution of retinal vessels, brownish macula discoloration and optic atrophy. VEP amplitudes decrease from the age of 2.5 years old, and extinction of VEP and Electroretinography (ERG) occur before the age of 4 years{Vanhanen et al., 1997, Dev Med Child Neurol, 39, 456-63}.
In classic Late Infantile NCL (CLN2) onset between age 2 and 4 progresses to blindness at the age of 5 or 6 years old, with retina atrophy and centrifugally progressive loss of photoreceptors. ERG is diminished early, and finally extinguishes. Giant VEP (with amplitudes of around 350 V) is persistent, only to diminish in a preterminal stage {Pampiglione and Harden, 1977, J Neurol Neurosurg Psychiatry, 40, 323-30}.
In CLN3 visual failure presenting between 4 to 7 years old is often the presenting symptom, with rapid progression due to diffuse retinal pigment epithelium atrophy with stippled hyperfluorescence {Hainsworth et al., 2009, Retina, 29, 657-68} and optic nerve atrophy. Bull's eye maculopathy occurs in 1 in 4 {Hainsworth et al., 2009, Retina, 29, 657-68}{Collins et al., 2006, Br J Ophthalmol, 90, 1119-24}. VEP shows markedly reduced amplitudes, and early extinction {Tackmann and Kuhlendahl, 1979, Eur Neurol, 18, 234-42} .
In CLN5 (Finnish v LINCL) giant VEPs are seen at 7-10 years of age {Lauronen et al., 2002, Clin Neurophysiol, 113, 1491-500}, while in CLN6 diminished or absent VEP were reported {Williams et al., 1999, The neuronal ceroid lipofuscinoses , 102 - 13}. In Northern epilepsy

visual evoked potentials were abnormal in 44% {Lang et al., 1997, Acta Neurol Scand, 95, 1-8}.
Despite evident retinal abnormalities in a member of our ANCL family and other NCL forms, some studies indicate that other factors than retinal pathology may contribute to visual deterioration in NCL. In a mouse PPT-1 gene knockout model progressive accumulation of autofluorescent storage material in all layers of the retina was observed, but only a modest loss of nucleated cells in the outer and inner nuclear layers. Retinal function was severely impaired by 8 months, despite only modest changes in retinal morphology {Lei et al., 2006, J Neurosci Res, 84, 1139-49}. In Cln3(-/-) mice decreased optic nerve axonal density and decreased nerve conduction were found, with loss of neurons in the dorsal lateral geniculate nucleus (LGNd). Reduced transport of amino acids from the retina to the LGN suggested an impediment in communication between the retina and projection nuclei {Weimer et al., 2006, Neurobiol Dis, 22, 284-93}.

The granular bead-like structures with a diameter of 20 to 50 m which were seen on OCT in the outer segment layer and retinal pigment epithelium in patient 6 may represent degenerated retinal cells or clustered aggregates of storage material. It is not likely that these beads represent individual GRODs, since the size of ultrastructural granular osmiophilic deposits (GRODs) in CLN1 is usually up to 0.5 µm, forming aggregates of up to 5 µm {Elleder et al., 1999, The neuronal ceroid lipofuscinoses , 5-15}. GRODs found in neurons throughout the CNS in this family varied from 0.5 to 2.5 µm ø, while glial inclusions up to 4 µm ø were seen filled with numerous dense osmiophilic granules {Nijssen et al., 2003, Brain Pathol, 13, 574-81}. Early ultrastructural studies of the retina in human childhood NCL showed storage material in almost every type of retinal cells, loss of photoreceptors, atrophy of pigment epithelium and displacement of melanin into inner layers of the retina

{Goebel et al., 1974, Am J Ophthalmol, 77, 25-39} {Goebel, 1977, Fortschr Med, 95, 2432-6}.

In Kufs' disease, the autosomal recessive adult NCL form, vision remains normal, and no retinal pigmentary degeneration occurs {Berkovic et al., 1988, Am J Med Genet Suppl, 5, 105-9} {Berkovic et al., 1988, Brain, 111 , 27-62}. A few case reports focus on the exceptions to this rule. Martin et al. reported storage in retinal ganglion cells in a single Kufs case {Martin et al., 1987, Clin Neuropathol, 6, 231-5}. Goebel et al. found granular lipopigment storage in nerve cells in different layers of the retina of a 33-year-old woman with biopsy-proven Kufs' disease who had never had visual impairment, nor electroretinographic abnormalities {Goebel et al., 1998, Acta Anat (Basel), 162, 127-32}. Ikeda et al. report a case of Kufs' disease with retinal lesions which resulted in total blindness, with retinal thinning with severe loss of rods, cones, and outer nuclear and outer plexiform layers. Ganglion cells of the retina were ballooned and contained lipopigments {Ikeda et al., 1984, Clin Neuropathol, 3, 237-9}. Armstrong et al. reported abnormal functioning of the amacrine and horizontal cell systems of lateral inhibition in a patient with Kufs' disease {Armstrong et al., 1985, Int Ophthalmol, 8, 37-42} {Dawson et al., 1985, Doc Ophthalmol, 60, 163-71}. Charles et al. found asymptomatic pigmentary retinal degeneration in a patient with questionable Kufs' disease {Charles et al., 1990, Rev Neurol (Paris), 146, 752-6}. Alonso-Navarra observed a single case of Kufs' disease with probable visual agnosia, hypermetamorphopsia {Alonso-Navarro et al., 2005, Rev Neurol, 40, 93-8}. Zini described a case of Kufs' disease with focal occipital seizures with visual hallucinations where MRI showed cortical atrophy and, on T2-weighted images, hyperintensity and reduction of the deep white matter {Zini et al., 2008, Neurology, 71, 1709-12}. However, according to Berkovic, the reported diagnosis of Kufs' disease is often doubtful after critical reassessment (including

Dawson's case) {Berkovic et al., 1988, Am J Med Genet Suppl, 5, 105-9}{Berkovic et al., 1988, Brain, 111 , 27-62}. In the autosomal dominant ANCL family described by Boehme, no sensory disturbances were seen, but their patient IV/2 presented with 'a faint preceded by a visual aura of "bright spots" '{Boehme et al., 1971, Brain, 94, 745-60}. The single patient from an AD-ANCL family reported by Ferrer et al. had no reported visual problems{Ferrer et al., 1980, J Neurol, 222, 183-90}. In the AD-ANCL family described by Josephson et al. one patient had visuospatial deficits, one had 'a spell with micropsia' and visual hallucinations, in 3 others ophthalmologic examination was normal{Josephson et al., 2001, J Neurol Sci, 188, 51-60}. In the AD-ANCL family from Alabama, 2 patients saw flashing lights as an aura to their seizures. None had optic atrophy or retinal degeneration on fundoscopic examination{Burneo et al., 2003, Epilepsia, 44, 841-6}.

In our autosomal dominant ANCL family visual problems were frequent and diverse. Abnormal ERG's and Bulls eye maculopathy indicate retinal pathology. Bilaterally delayed VEP's may also indicate retinal, optic nerve, chiasma, tract or radiation dysfunction. Optic nerve atrophy was seen on MRI of patient 6, where cerebral MRI also showed optic radiation hyperintensity and atrophy of the visual cortex.
Abundant positive visual signs in patient 3,4,5 and 6 were most likely of temporo-occipital epileptic origin, because of a temporal relation with epileptic seizures and response to anti-epileptic drugs. In patient 6 more complex images occurred in later stages with severely impaired vision, which may resemble Charles-Bonnet syndrome.
The widespread visual pathology in this family with AD-ANCL is in contrast with the normal or minimal visual findings in Kufs' disease. This supports our view that the autosomal dominant and the recessive form of ANCL should be considered separate nosological entities.

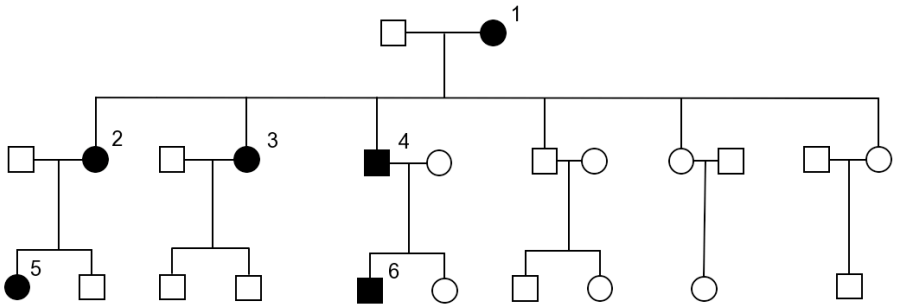


Fig.1: Family pedigree.

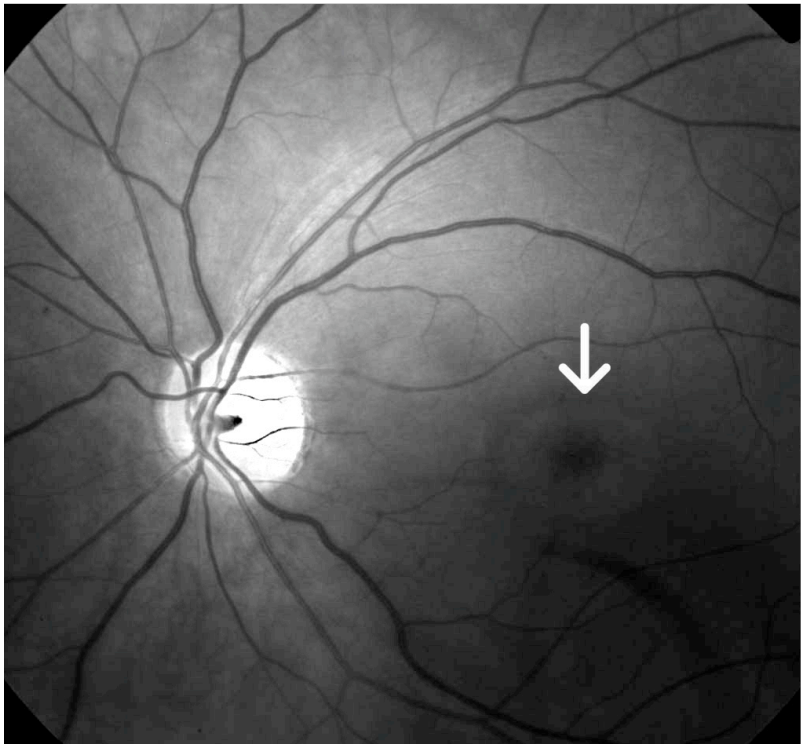


Fig. 2: fluorescein fundus angiogram of patient 6, showing a Bull's eye maculopathy (arrow).

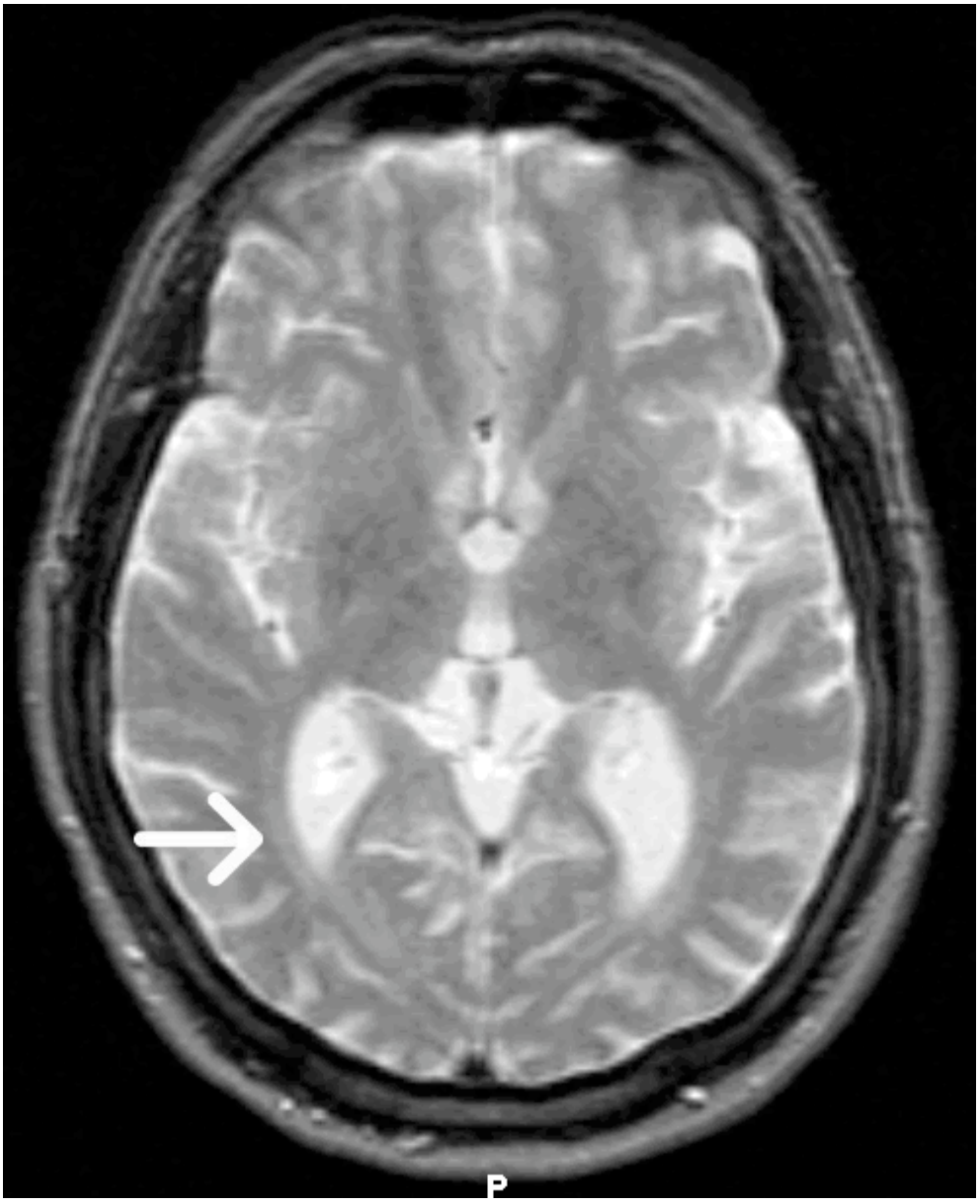


Fig. 3: T2 weighted cerebral MRI of patient 6, showing bilateral periventricular hyperintensity in the optic radiation (arrow).

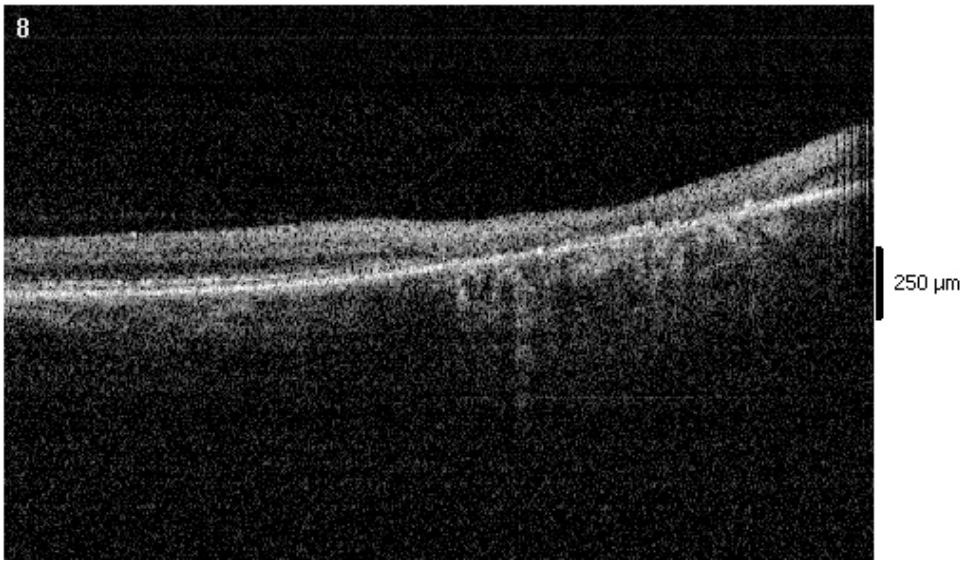
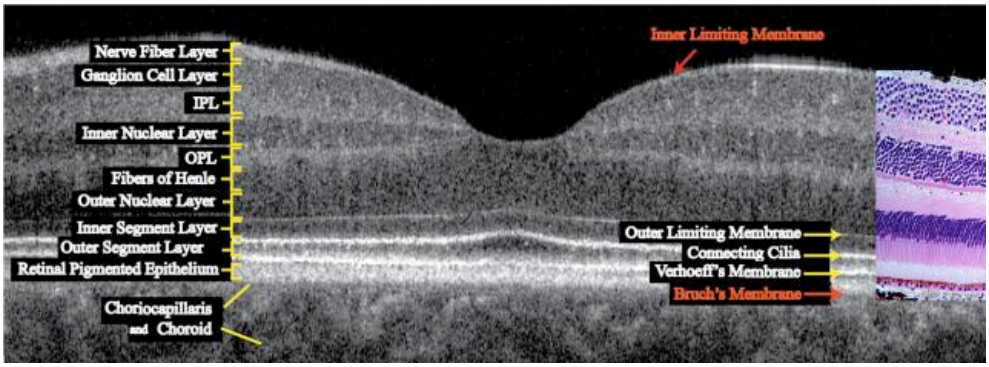


Fig. 4A: Optical coherence tomography (OCT) of patient 6. Retinal atrophy due to thinning of the outer nuclear layer and outer segment layer, and maybe also retinal pigment epithelium atrophy. Where the outer segment layer and retinal pigment epithelium were expected, granular bead-like structures were seen with a diameter of 20 to 50 m.



4B: normal OCT and normal retinal histology
(from http://vsri.ucdavis.edu , adapted from Optics ExpresNs, 2005; Expert Review of Ophthalmology, 2007)

References

1.Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kufs' disease: a critical reappraisal. Brain 1988;111:27-62.

2.Nijssen PC, Brusse E, Leyten AC, Martin JJ, Teepen JL, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: parkinsonism due to both striatal and nigral dysfunction. Mov Disord 2002;17:482-87.

3.Nijssen PC, Ceuterick C, van Diggelen OP et al. Autosomal dominant adult neuronal ceroid lipofuscinosis: a novel form of NCL with granular osmiophilic deposits without palmitoyl protein thioesterase 1 deficiency. Brain Pathol 2003;13:574-81.

4.Wisniewski KE, Rapin I, Heaney-Kieras J. Clinico-pathological variability in the childhood neuronal ceroid-lipofuscinoses and new observations on glycoprotein abnormalities. Am J Med Genet Suppl 1988;5:27-46.

5.Vanhanen SL, Sainio K, Lappi M, Santavuori P. EEG and evoked potentials in infantile neuronal ceroid-lipofuscinosis. Dev Med Child Neurol 1997;39:456-63.

6.Pampiglione G, Harden A. So-called neuronal ceroid lipofuscinosis. Neurophysiological studies in 60 children. J Neurol Neurosurg Psychiatry 1977;40:323-30.

7.Hainsworth DP, Liu GT, Hamm CW, Katz ML. Funduscopic and angiographic appearance in the neuronal ceroid lipofuscinoses. Retina 2009;29:657-68.

8.Collins J, Holder GE, Herbert H, Adams GG. Batten disease: features to facilitate early diagnosis. Br J Ophthalmol 2006;90:1119-24.

9.Tackmann W, Kuhlendahl D. Evoked potentials in neuronal ceroid lipofuscinosis. Eur Neurol 1979;18:234-42.

10.Lauronen L, Huttunen J, Kirveskari E et al. Enlarged SI and SII somatosensory evoked responses in the CLN5 form of

neuronal ceroid lipofuscinosis. Clin Neurophysiol 2002;113:1491-500.

11.Williams RE, Lake BD, Elleder M, Sharp JD. CLN6 Variant late infantile/early juvenile NCL. In: Goebel H-H, Mole SE, Lake BD, eds. The neuronal ceroid lipofuscinoses (Batten disease). Amsterdam ; Washington, DC Tokyo: IOS Press Ohmsha; 1999:102 - 13.

12.Lang AH, Hirvasniemi A, Siivola J. Neurophysiological findings in the northern epilepsy syndrome. Acta Neurol Scand 1997;95:1-8.

13.Berkovic SF, Andermann F, Andermann E, Carpenter S, Wolfe L. Kufs disease: clinical features and forms. Am J Med Genet Suppl 1988;5:105-09.

14.Martin JJ, Libert J, Ceuterick C. Ultrastructure of brain and retina in Kufs' disease (adult type-ceroid-lipofuscinosis). Clin Neuropathol 1987;6:231-35.

15.Goebel HH, Schochet SS, Jaynes M, Gutmann L. Ultrastructure of the retina in adult neuronal ceroid lipofuscinosis. Acta Anat (Basel) 1998;162:127-32.

16.Ikeda K, Kosaka K, Oyanagi S, Yamada K. Adult type of neuronal ceroid-lipofuscinosis with retinal involvement. Clin Neuropathol 1984;3:237-39.

17.Armstrong D, Benedetto M, Samuelson D. Amacrine and horizontal cell dysfunction in adult ceroid-lipofuscinosis (Kufs disease) and anatomical correlates in the ovine model. Int Ophthalmol 1985;8:37-42.

18.Dawson WW, Armstrong D, Greer M, Maida TM, Samuelson DA. Disease-specific electrophysiological findings in adult ceroid-lipofuscinosis (Kufs disease). Doc Ophthalmol 1985;60:163-71.

19.Charles N, Vighetto A, Pialat J, Confavreux C, Aimard G. [Dementia and psychiatric disorders in Kufs disease]. Rev Neurol (Paris) 1990;146:752-56.

20.Alonso-Navarro H, Jimenez-Jimenez FJ, Puertas-Munoz I, Rabano J, de Yebenes JG, Sarasa-Corral JL. [Kluver-Bucy syndrome as the initial symptom of adult-type ceroid lipofuscinosis (Kufs' disease)]. Rev Neurol 2005;40:93-98.

21.Zini A, Cenacchi G, Nichelli P, Zunarelli E, Todeschini A, Meletti S. Early-onset dementia with prolonged occipital seizures: an atypical case of Kufs disease. Neurology 2008;71:1709-12.

22.Boehme DH, Cottrell JC, Leonberg SC, Zeman W. A dominant form of neuronal ceroid-lipofuscinosis. Brain 1971;94:745-60.

23.Ferrer I, Arbizu T, Pena J, Serra JP. A golgi and ultrastructural study of a dominant form of Kufs' disease. J Neurol 1980;222:183-90.

24.Josephson SA, Schmidt RE, Millsap P, McManus DQ, Morris JC. Autosomal dominant Kufs' disease: a cause of early onset dementia. J Neurol Sci 2001;188:51-60.

25.Burneo JG, Arnold T, Palmer CA, Kuzniecky RI, Oh SJ, Faught E. Adult-onset neuronal ceroid lipofuscinosis (Kufs disease) with autosomal dominant inheritance in Alabama. Epilepsia 2003;44:841-46.

Chapter 8

Summary and concluding remarks

Summary and concluding remarks

Although the Neuronal ceroid lipofuscinoses (NCLs) form the most common inherited progressive childhood encephalopathies, adult NCL is very uncommon. NCLs show recessive inheritance, except for the extremely uncommon autosomal dominant adult form (AD-ANCL, also called Parry disease). Only 6 families with AD-ANCL have been reported in detail. A Dutch family with the dominant adult NCL form is the subject of this thesis.

In chapter 1 a review of the scarce literature on AD-ANCL is presented, and a brief review of the knowledge of childhood NCLs and recessive adult NCL (Kufs' disease). The classification of NCL is explained, which has changed from age related categories to genotypes.

Chapter 2 presents clinical aspects of our family with adult neuronal ceroid lipofuscinosis with autosomal dominant inheritance. Detailed case reports of 6 affected individuals in three generations indicate disease onset in the fifth decade, with myoclonus in face and arms, epilepsy, auditory symptoms, cognitive decline, or depression. Parkinsonism occurred a few years after disease onset. The disease evolves to severe handicap, with severe dementia, contractures, dysphagia, and dysarthria. The pathophysiology of parkinsonian symptoms is treated in more detail in this chapter.

In chapter 3 we describe the neuropathological and biochemical autopsy findings in three patients with AD-ANCL. Throughout the brain abundant intraneuronal lysosomal storage of autofluorescent lipopigment granules was seen. Striking loss of neurons in the substantia nigra was found. In contrast, little neuronal cell loss occurred in other cerebral areas, despite massive neuronal inclusions. Visceral storage was present in gut,

liver, cardiomyocytes, skeletal muscle, and in the skin eccrine glands. The storage material showed highly variable immunoreactivity with antiserum against subunit c of mitochondrial ATP synthase, but uniform strong immunoreactivity for saposin D (sphingolipid activating protein D). Protein electrophoresis of isolated storage material revealed a major protein band of about 14 kDa, recognized in Western blotting by saposin D antiserum (but not subunit c of mitochondrial ATPase (SCMAS) antiserum).
Electron microscopy showed ample intraneuronal granular osmiophilic deposits (GRODs), as occurs in CLN1 and congenital ovine NCL. These forms of NCL are caused by the deficiencies of palmitoyl protein thioesterase 1 and cathepsin D, respectively. However, activities of these enzymes were within normal range in our patients. Thus we propose that a gene distinct from the cathepsin D and CLN1-CLN8 genes is responsible for this autosomal dominant form of ANCL.

In chapter 4 we tried to identify the genetic defect in our family with AD-ANCL. We applied genome wide STR-based linkage analysis with subsequent fine-mapping of candidate loci. Under an autosomal dominant model, 8 loci were suggestive for linkage with a LOD-score > 1. Of these, three loci were most promising as two subsequent markers gave a LOD-score above 1 (on chr. 2 and chr. 21), while multipoint LOD-score calculations achieved a maximum score of 1.96 on chr. 12. These 3 loci were further analyzed by genotyping additional STR markers in the region. In the 3 loci a disease haplotype appeared to segregate with the disease. Markers in the proximity of the known NCL loci (1p32, 11p15, 16p12.1, 13q21, 15q21-33, 8p23, 11p15.5) were checked but none passed a LOD-score value of 1.

In chapter 5 we describe the findings in 59 EEGs from six patients of our AD-ANCL familiy, with a follow up of 9–21 years. EEGs were all severely

abnormal, with generalized or bilateral independent periodic epileptiform discharges (GPEDs, or GPD+) as the most common pattern. In a few EEGs periodic discharges were seen. Intraindividual EEG changes in the course of the disease were modest, despite severe clinical disease progression.

In chapter 6 we investigated the occurrence of auditory dysfunction in our family with AD-ANCL. Hearing impairment was common, and in all 5 affected siblings who had Auditory Brainstem Responses, waves I to V were delayed, with progressive abnormalities in later disease stages. Auditory symptoms have not been reported in other NCL forms.

In chapter 7 we studied visual problems in our family with AD-ANCL. In five patients visual dysfunction was obvious. They had positive visual symptoms (some of which appeared to be related to epileptic attacks) and also decreased visual acuity, with abnormal VEP and ERG. Bull's eye maculopathy was seen in one patient, who also had a hyperintense lesion of the optic radiation on MRI. His optical coherence tomogram showed retinal atrophy with granular lesions in retinal pigment epithelium. We conclude that visual problems are common in AD-ANCL, due to retinal pathology, optic nerve atrophy, optic radiation degeneration, cortical dysfunction or epilepsy. This finding is in contrast to general opinion which states that vision in adult NCL is normal.

Future perspectives on the study of autosomal dominant ANCL are dominated by an itching desire to find the gene behind this disease, which could pave the road for genetic counseling, and ultimately even gene therapy. Because this is the only autosomal dominant NCL form, knowledge of this gene will most likely also expand insight into the pathogenesis of other NCL forms. Further exploration of the pathogenesis of this genetic neurodegenerative disease could also

provide insights which may help to understand diseases like Alzheimer and Parkinson's. The clinical, pathological and neurophysiological similarity of reported and as yet unreported AD-ANCL families indicate an opportunity for genetic analysis by investigation of multiple families. This has led us to gather international efforts of genetic ANCL studies within the Rare NCL Gene Consortium (http://www.ucl.ac.uk/ncl/RNGC.shtml), which is coordinated by dr. Sara Mole from the University College London.

Samenvatting

Neuronale ceroid lipofuscinose (NCL) is een heterogene groep aandoeningen, waarbij stapelingsmateriaal in zenuwweefsel en netvlies gepaard gaat met blindheid, epilepsie, cognitieve achteruitgang en bewegingsstoornissen. NCL komt vooral voor op kinderleeftijd, en erft dan autosomaal recessief over.
Dit proefschrift beschrijft een familie met een zeer zeldzame adulte NCL vorm met autosomaal dominante overerving (AD-ANCL).

Hoofdstuk 1 beschrijft de literatuur over AD-ANCL, de diverse NCL vormen op kinderleeftijd en de classificatie van NCL.

Hoofdstuk 2 beschrijft de kliniek van de familie met AD-ANCL die het onderwerp is van dit proefschift: bij zes personen uit drie generaties begon de ziekte meestal na het 40e levensjaar, met myoclonus (schokken) in gelaat en armen, epilepsie, gehoorsproblemen, cognitieve achteruitgang of depressie. Het verloop van de ziekte en de achtergrond van Parkinson-achtige klachten wordt beschreven.

In hoofdstuk 3 worden neuropathologische en biochemische bevindingen in drie patienten met AD-ANCL beschreven. Een bijzonder stapelingsmateriaal (zogenaamde GRODs) dat kenmerkend is voor NCL werd aangetroffen in hersenen en in darm, lever, hart, spier en huid. In bepaalde regio's van de hersenen (met name in de substantia nigra, die ook aangedaan is bij de ziekte van Parkinson) werd een verlies van zenuwcellen gezien.
Stapelingsmateriaal bevatte subunit c van mitochondriaal ATP synthase en vooral saposine D (sphingolipide activerend proteïne D), twee eiwitten die ook in andere NCL vormen aangetroffen zijn.

In hoofdstuk 4 beschrijven we de resultaten van genetisch onderzoek naar de onderliggende genafwijking bij onze familie met AD-ANCL. Linkage analyse met STR-markers leverde 3 regio's op op chromosoom 2, 12 en 21 die bij alle patiënten met de ziekte aanwezig zijn. Dit onderzoek wijst er op dat de genen die verantwoordelijk zijn voor de kindervormen van NCL geen rol spelen bij deze familie.

In hoofdstuk 5 worden bevindingen bij electroencephalografie (EEG, 'hersenfilmpje') in deze familie beschreven, met patronen van sterk verstoorde electrische hersenactiviteit, zogenaamde gegeneraliseerde en bilateraal onafhankelijke periodieke epileptiforme ontladingen. Deze afwijkingen kunnen ook al optreden wanneer er nog geen symptomen van ziekte zijn.

In hoofdstuk 6 beschrijven we gehoorsproblemen bij AD-ANCL, die aantoonbaar zijn met zogenaamde Auditory Brainstem Responses, die toenemende vertraging lieten zien met toenemende leeftijd. Gehoorproblemen zijn niet eerder beschreven bij NCL.

In hoofdstuk 7 beschrijven we visuele problemen in onze familie met AD-ANCL. Hoewel ANCL bekend staat om normale visus, werd bij 5 patienten uit onze AD-ANCL familie een scala aan visusklachten gezien, met zowel verslechtering van het zien, als spontaan optredende visuele sensaties zoals het zien van kleurrijke flitsen. Dit was soms voorafgaand aan een epileptische aanval. Beelden van het netvies toonden een zogenaamde Bulls eye maculopathie. Recent ontwikkelde Optical Coherence Tomography toonde een beeld van retina atrofie en aanwezigheid van korrelige structuren in de pigmentlaag van het netvlies. Op MRI werden subtiele afwijkingen gezien in de occipitaalkwabben, in de radiatio optica.

Toekomstig onderzoek naar autosomaal dominante ANCL zal zich onder andere richten op voortzetting van de speurtocht naar het verantwoordelijke gen. Identificatie daarvan zal nieuwe mogelijkheden bieden voor genetische counseling en wellicht uiteindelijk zelfs voor gentherapie. Als de kennis van de pathofysiologie van deze ziekte toeneemt is het denkbaar dat ook het inzicht in de achtergrond van neurodegeneratieve ziektes zoals Alzheimer en Parkinson daardoor groeit. Inmiddels is een internationaal consortium in het leven geroepen om kennis en onderzoek rond de zeldzame ziekte ANCL te bundelen.

List of abbreviations

ABR: Auditory Brainstem Responses

AD-ANCL : autosomal dominant adult neuronal ceroid lipofuscinosis

ANCL: adult NCL

CLN 1 to 8: NCL genes

CNS: central nervous system

CONCL: congenital ovine NCL

CTSD: cathepsin D

EEG : electroencephalogram

EM: electron microscopy

EPMR: progressive epilepsy with mental retardation

FPs: fingerprint profiles

GRODs : granular osmiophilic deposits

IBZM: iodobenzamide

INCL: infantile NCL

JNCL: juvenile NCL

LAG1: longevity assurance gene 1.

LINCL : late-infantile NCL

MFSD8: major facilitator superfamily domain containing 8 gene

MIM: Mendelian inheritance of man

MRI: magnetic resonance imaging

NCL: neuronal ceroid lipofuscinosis

OCT: optical coherence tomography

PAS: periodic acid Schiff

PPT : palmitoyl protein thioesterase

SAPs : saposins

SCMAS : subunit c of mitochondrial ATPase

STR: short tandem repeat

TPP1: tripeptidyl peptidase 1

UBQ: ubiquitin

List of publications

Nijssen PC, Brekelmans GJ, Roos RA. Electroencephalography in autosomal dominant adult neuronal ceroid lipofuscinosis. Clin Neurophysiol. 2009 Oct;120(10):1782-6.

Venmans A, Nijssen PC, Sluzewski M, van Rooij WJ. Progressive supranuclear palsy. JBR-BTR. 2009 May-Jun;92(3):182-3.

Esselink RA, de Bie RM, de Haan RJ, Lenders MW, Nijssen PC, van Laar T, Schuurman PR, Bosch DA, Speelman JD. Long-term superiority of subthalamic nucleus stimulation over pallidotomy in Parkinson disease. Neurology. 2009 Jul 14;73(2):151-3.

van Laar T, Berendse H, Bloem BR, Boon AJ, van Hilten JJ, Hovestadt A, de Koning-Tijssen MA, Nijssen PC, Weber WE. Pergolide use and heart valve fibrosis. Yearly control in patients with Parkinson disease who use pergolide. Ned Tijdschr Geneeskd. 2009 Jan 17;153(3):87-90.

Weber WE, Nijssen PC. Impulse control disorder induced by the use of dopamine agonists. Ned Tijdschr Geneeskd. 2009 Jan 17;153(3):80-1.

Hanse MC, Gerrits MC, van Rooij WJ, Houben MP, Nijssen PC, Sluzewski M. Recovery of posterior communicating artery aneurysm-induced oculomotor palsy after coiling. AJNR Am J Neuroradiol. 2008 May;29(5):988-90.

Sluzewski M, van Rooij WJ, Beute GN, Nijssen PC. Balloon-assisted coil embolization of intracranial aneurysms: incidence, complications, and angiography results. J Neurosurg. 2006 Sep;105(3):396-9.

van Rooij WJ, Sluzewski M, Beute GN, Nijssen PC. Procedural complications of coiling of ruptured intracranial aneurysms: incidence and risk factors in a consecutive series of 681 patients. AJNR Am J Neuroradiol. 2006 Aug;27(7):1498-501.

Smeding HM, Speelman JD, Koning-Haanstra M, Schuurman PR, Nijssen P, van Laar T, Schmand B. Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. Neurology. 2006 Jun 27;66(12):1830-6.

van Rooij WJ, de Gast A, Sluzewski M, Nijssen PC, Beute GN. Coiling of truly incidental intracranial aneurysms. AJNR Am J Neuroradiol. 2006 Feb;27(2):293-6.

Sluzewski M, van Rooij WJ, Beute GN, Nijssen PC. Late rebleeding of ruptured intracranial aneurysms treated with detachable coils. AJNR Am J Neuroradiol. 2005 Nov;26(10):2542-9

Roks G, Sistermans EA, de Vries LB, Nijssen PC. Progressive ataxia and cognitive deficits caused by premutation in the fragile-X gene. Ned Tijdschr Geneeskd. 2005 Oct 22;149(43):2418-22.

Nieuwkamp DJ, de Gans K, Algra A, Albrecht KW, Boomstra S, Brouwers PJ, Groen RJ, Metzemaekers JD, Nijssen PC, Roos YB, Tulleken CA, Vandertop WP, van Gijn J, Vos PE, Rinkel GJ. Timing of aneurysm surgery in subarachnoid haemorrhage - an observational study in The Netherlands. Acta Neurochir (Wien). 2005 Aug;147(8):815-21.

Esselink RA, de Bie RM, de Haan RJ, Lenders MW, Nijssen PC, Staal MJ, Smeding HM, Schuurman PR, Bosch DA, Speelman JD. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. Neurology. 2004 Jan 27;62(2):201-7.

Nijssen PC, Ceuterick C, van Diggelen OP, Elleder M, Martin JJ, Teepen JL, Tyynela J, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: a novel form of NCL with granular osmiophilic deposits without palmitoyl protein thioesterase 1 deficiency. Brain Pathol. 2003 Oct;13(4): 574-81.

Hanse MC, Nijssen PC. Unilateral palsy of all cranial nerves (Garcin syndrome) in a patient with rhinocerebral mucormycosis. J Neurol. 2003 Apr;250(4):506-7.

Lusseveld E, Brilstra EH, Nijssen PC, van Rooij WJ, Sluzewski M, Tulleken CA, Wijnalda D, Schellens RL, van der Graaf Y, Rinkel GJ. Endovascular coiling versus neurosurgical clipping in patients with a ruptured basilar tip aneurysm. J Neurol Neurosurg Psychiatry. 2002 Nov;73(5):591-3.

Nijssen PC, Brusse E, Leyten AC, Martin JJ, Teepen JL, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: parkinsonism due to both striatal and nigral dysfunction. Mov Disord. 2002 May;17(3):482-7.

Croes EA, Roks G, Jansen GH, Nijssen PC, van Duijn CM. Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone. J Neurol Neurosurg Psychiatry. 2002 Jun;72(6):792-3.

Nijssen PCG De ziekte van Parkinson, of toch iets anders ? Papaver 2002 Sept;25(5): 16-17.

Nijssen PCG Stereotactische operatie bij de ziekte van parkinson: wat mag u verwachten? Papaver 2002 Mei;25(3):16-18.

Nijssen PCG Comateus, soporeus of stuporeus ? Intensive Care Capita Selecta 2001 Red.: J. Bakker, B. de lange, J.H. Rommes Wetenschappelijke uitgeverij Venti-Care, Utrecht

Beekman R, Nijssen PC, van Rooij WJ, Wijnalda D. Migraine with aura after intracranial endovascular procedures. Headache. 2001 Apr;41(4):410-3.

Sluzewski M, Bosch JA, van Rooij WJ, Nijssen PC, Wijnalda D. Rupture of intracranial aneurysms during treatment with Guglielmi detachable coils: incidence, outcome, and risk factors. J Neurosurg. 2001 Feb;94(2):238-40.

Majoie CB, van Delden OM, Sluzewski M, Nijssen PC, Stam J, Reekers JA. [Neuroradiologic intervention in two patients with cerebral sinus thrombosis] Ned Tijdschr Geneeskd. 2000 Sep 16;144(38):1839-44. Dutch.

van Rooij WJ, Sluzewski M, Metz NH, Nijssen PC, Wijnalda D, Rinkel GJ,Tulleken CA. Carotid balloon occlusion for large and giant aneurysms: evaluation of a new test occlusion protocol. Neurosurgery. 2000 Jul;47(1):116-21

de Bie RM, de Haan RJ, Nijssen PC, Rutgers AW, Beute GN, Bosch DA, Haaxma, R, Schmand B, Schuurman PR, Staal MJ, Speelman JD. Unilateral pallidotomy in Parkinson's disease: a randomised, single-blind,multicentre trial. Lancet. 1999 Nov 13;354(9191):1665-9.

Lopes da Silva FH, Pijn JP, Velis D, Nijssen PC. Alpha rhythms: noise, dynamics and models. Int J Psychophysiol. 1997 Jun; 26(1-3):237-49. Review.

Nijssen PC, Deprez RH, Tijssen CC, Hagemeijer A, Arnoldus EP, Teepen JL,Holl R, Niermeyer MF. Familial anaplastic ependymoma: evidence of loss of chromosome 22 in tumour cells. J Neurol Neurosurg Psychiatry. 1994 Oct;57(10): 1245-8.

Nijssen PC, Sexton T, Childers SR. Opioid-inhibited adenylyl cyclase in rat brain membranes: lack of correlation with high-affinity opioid receptor binding sites. J Neurochem. 1992 Dec;59(6):2251-62.

Nijssen PC, Tijssen CC. Stimulus-sensitive paroxysmal dyskinesias associated with a thalamic infarct. Mov Disord. 1992 Oct; 7(4):364-6.

Nijssen PC, Childers SR. Characteristics of sodium-induced increase in opiate antagonist binding sites in rat brain membranes. Eur J Pharmacol. 1987 Mar 31;135(3):355-64.

Childers SR, Nijssen P, Nadeau P, Buckhanna P, Le PV, Harris J. Opiate-inhibited adenylate cyclase in mammalian brain membranes. NIDA Res Monogr. 1986;71:65-80.

Curriculum vitae

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In 1980 he participated in the Bessie F Lawrence summer program of the Weizmann Institute of Science, Rehovot, Israel. He studied chemistry in Utrecht, but switched to medicine.
In 1984-85 an exchange program consisted of a neuroscience program and neuropharmacology at the University of Florida, Gainesville, studying opiate receptors and second messengers with dr. S.R. Childers.
In 1986 neuropharmacological studies focussing on beta-endorphin and behaviour were performed at the Rudolf Magnus Institute, Utrecht (prof. dr. J. van Ree).
From 1989 – 1996 he was a neurology resident in Tilburg (dr. A.A.W. op de Coul and dr. C.C. Tijssen). He studied nonlinear analysis of electroencephalography in coma with prof. F.H. Lopes da Silva and prof. C.J. Stam.
Since 1996 he works as a neurologist specialised in Parkinsons disease, movement disorders and functional stereotaxy, in both St. Elisabeth hospital and Tweestedenziekenhuis, Tilburg, The Netherlands. He is a member of the medical advisory board of the Dutch Parkinson patient organisation, a boardmember of the Dutch movement disorders workinggroup of the Nederlandse Vereniging voor Neurologie and chairman of the Dutch Parkinson Genes and Environment Studygroup (PAGES).
He married Ruth Fleischeuer on may 29, 2010.