Autosomal dominant adult neuronal ceroid lipofuscinosis

Nijssen, P.C.G.

Chapter 2

AD-ANCL Clinical

Autosomal Dominant Adult Neuronal Ceroid Lipofuscinosis:

parkinsonism due to both striatal and nigral dysfunction

Peter C.G. Nijssen

Esther Brusse

Antonius C.M. Leyten

Jean-Jacques Martin

Johannes L.J.M. Teepen

Raymund A.C. Roos

published in Movement Disorders Vol. 17, No. 3, 2002, pp. 482–487

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

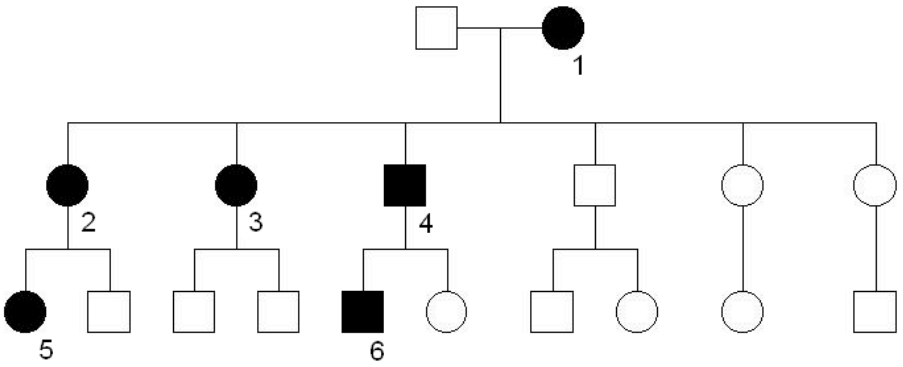

FIG. 1. Family pedigree (square, male; solid, affected).

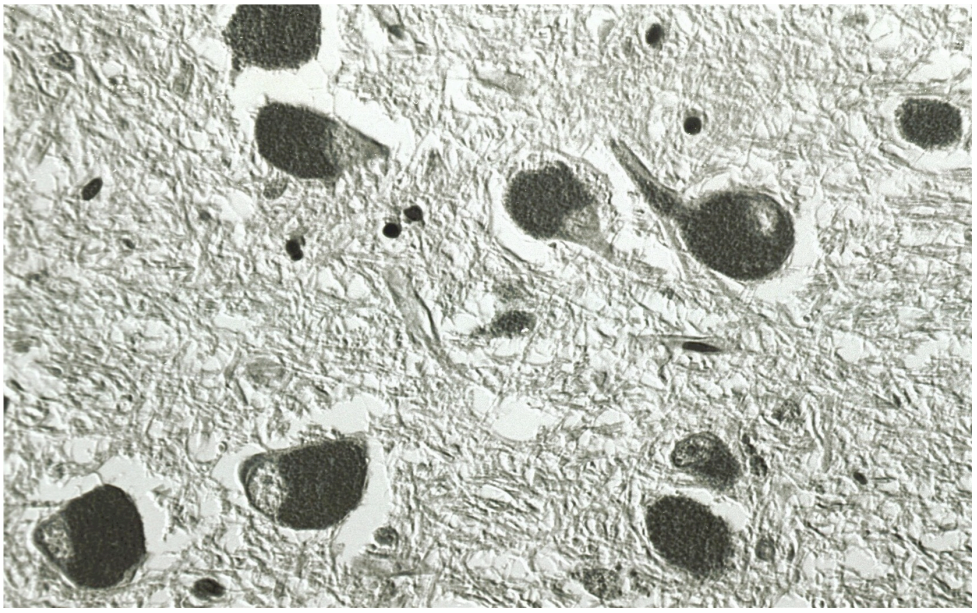

FIG. 2. Extensive intraneuronal storage is seen throughout the brain, with ballooned neurons and distended axon hillocks. Patient 2, pontine nuclei. Periodic acid–Schiff stain. Magnification, 440×.

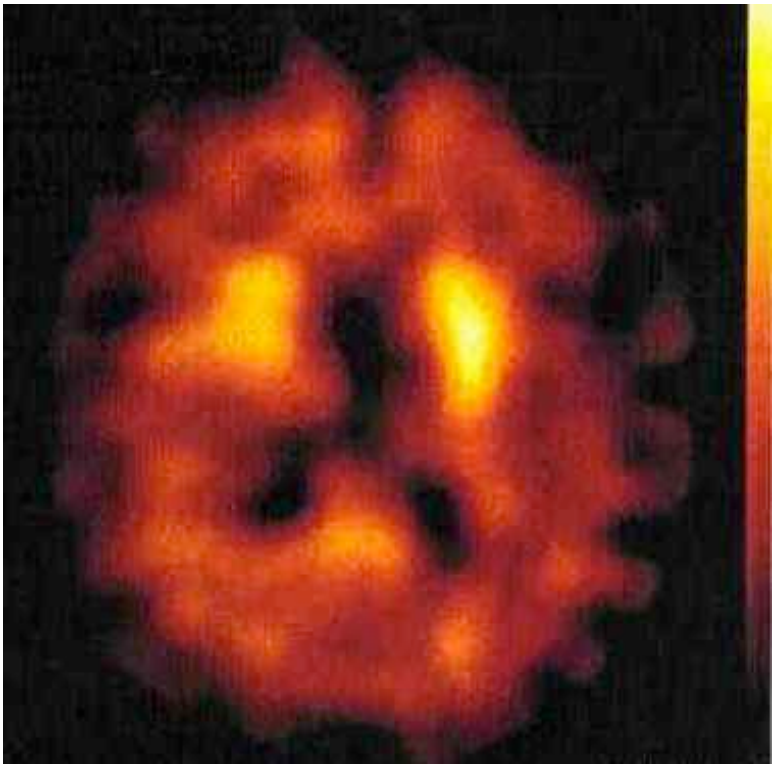

FIG. 3. 123I-IBZM SPECT of Patient 4 shows decreased striatal uptake, indicating loss of striatal D2 receptors

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.