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Autosomal dominant adult neuronal ceroid lipofuscinosis

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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 material¹. Most forms have an autosomal recessive mode of inheritance² and present at childhood with prominent visual loss, epilepsy, cognitive decline and movement disorders³. 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 autopsies⁵, 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 hallucinations⁶ were reported in a single Late Infantile NCL (LINCL) case; impaired auditory attention⁷, and decreased auditory memory span⁸ were observed in Juvenile NCL (JNCL).

ABR has been studied scarcely in NCL, with normal responses in a case of JNCL⁹ and a case of LINCL¹⁰, while ABR was enhanced in a case of LINCL¹¹. Abnormal brainstem auditory evoked potentials were found in 35% of individuals with Northern epilepsy¹².

We have previously reported storage of lipofuscin and neurodegeneration in the brainstem of patients 2 and 3⁵, 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 al¹³ 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 EEG¹⁴, ABR seems to be progressively abnormal in later disease stages.

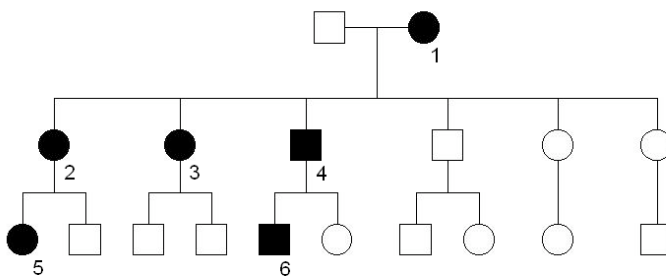


Fig 1. Family pedigree

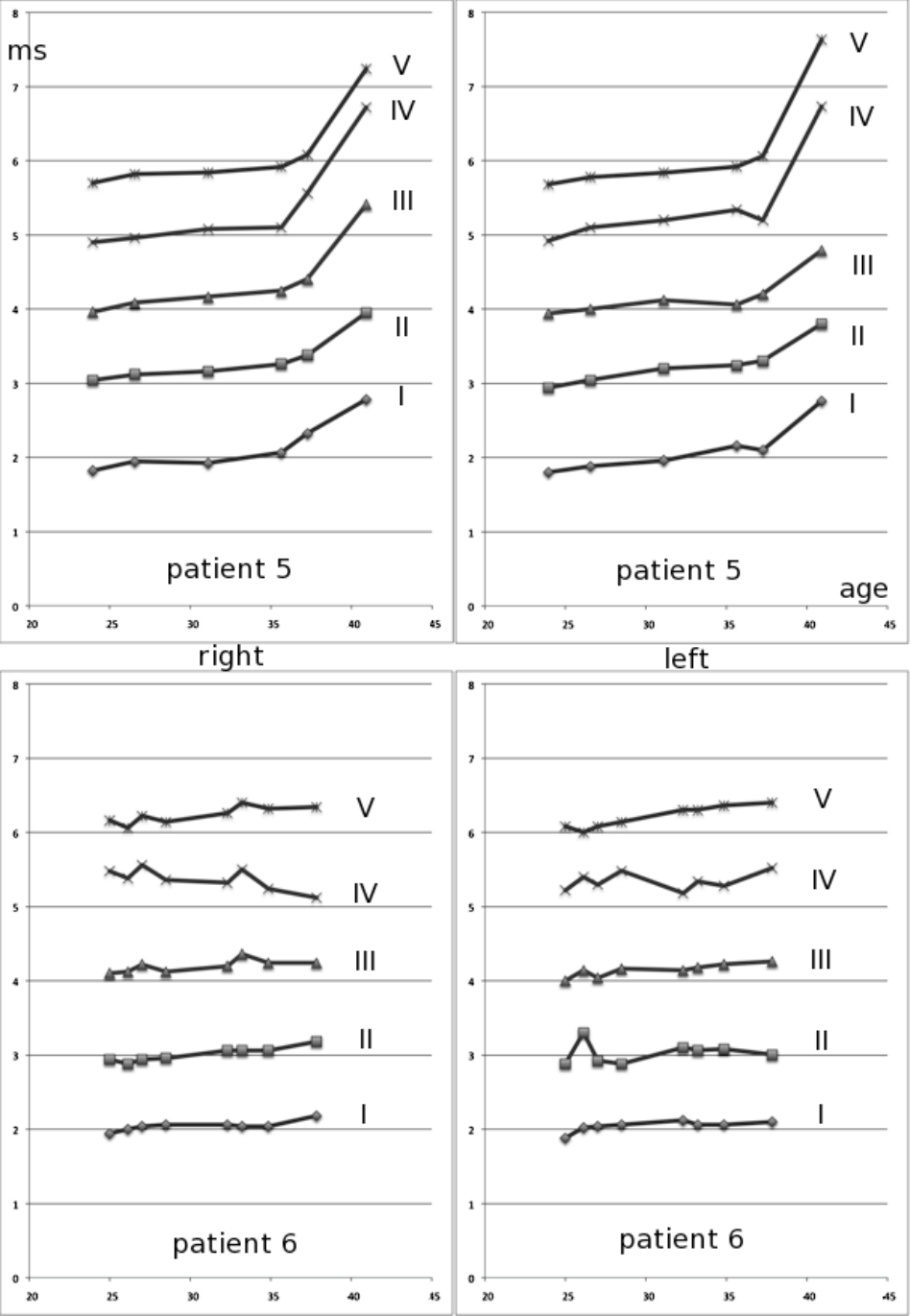


Fig 2. ABR latencies of waves I-V versus age (top panels: patient 5 (right/left), lower panels: patient 6 (right/left))

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.