Chapter 5

AD-ANCL neurophysiology
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 (GPEPs, or GPD+).

Significance: GPD/GPEPs 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 background activity, 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 highvoltage (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.
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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 andchin 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 family members 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 high-voltage 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


