Original article

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Long-term follow-up of two siblings with adult-onset neuronal ceroid lipofuscinosis, Kufs type A

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ABSTRACT – *Aim.* Reports on the clinical presentation of adult-onset neuronal ceroid lipofuscinoses (NCL) are scarce compared to infantile- and childhood-onset forms. Here, we aimed to present detailed temporal evolution of clinical and electrophysiological features of two siblings with adult-onset NCL and homozygous mutation in the *CLN6* gene.

Methods. We retrospectively analysed medical records and electrophysiological data in order to delineate evolution of clinical and electrophysiological findings. Electrophysiological studies included routine EEG and video-EEG, as well as polymyographic analysis of myoclonus and brainstem reflex studies.

Results. Both patients had seizures and cerebellar signs. Despite the slow progression of ataxia, they developed no mental deterioration, but had severe obsessive compulsive disorder and depression. EEG revealed frequent generalized spikes, polyspikes, and waves, prominent on awakening and during photic stimulation without significant change throughout the clinical course. Abnormalities concerning the blink reflex, auditory startle response, and startle response to somatosensory inputs manifested within four years. The patients underwent transient and mild improvement with valproate, whereas ataxia and seizures were dramatically ameliorated following high-dose piracetam.

Conclusions. Patients with adult-onset NCL may present with slowly progressive ataxia, persistent photosensitivity, and seizures without dementia or extrapyramidal findings. Brainstem abnormalities become more evident with time, in line with ataxia. Piracetam is effective for both seizures and ataxia.

Key words: neuronal ceroid lipofuscinosis, electrophysiology, clinical course, *CLN6*

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Reports on the clinical presentation of adult-onset neuronal ceroid lipofuscinoses (NCL) are scarce compared to the infantile- and childhood-onset forms. Here, we aimed to present detailed temporal evolution of clinical findings, drug responses, and electrophysiological features of two siblings with adult-onset NCL (homozygous mutation in the *CLN6* gene; CLN6 disease) after a long follow-up by the same clinician. These patients were previously included in a multicentre genetic study (Muona *et al*., 2015) and in two electrophysiological analysis studies at our centre (Coşkun *et al*., 2015; Kızıltan *et al*., 2016), however, their clinical details were not reported in detail.

Patients

The two Turkish siblings were born from a consanguineous marriage (first-degree cousins).

Patient 1 (index case)

A girl was admitted to an emergency department after having two generalized tonic-clonic seizures (GTCS) at the age of 18 years. The first seizure occurred as she fell asleep during an afternoon nap and recurred 12 hours later. Both seizures started with irregular jerks of the upper extremities and lasted for five minutes. After these seizures, she remembered that she had experienced some short absence-like spells a few days before the seizures. Her personal history was uneventful. EEG during wakefulness at that time revealed bitemporal sharp waves, predominant on the left, and sharp waves during photic stimulation at electrodes indicating the parieto-occipital regions. Temporal sharp and slow waves increased in number and tended to generalize during sleep. MRI and neuropsychological tests were normal. Although the patient was started on carbamazepine at 600 mg/day, the treatment was not an appropriate choice and was changed to valproate (VPA) at 500 mg/day after absence-like episodes and the determination of generalized spike, polyspike, and wave abnormalities with prominent photosensitivity which increased with eye closure (*figure 1A, B*). VPA treatment provided another seizure-free year until she had a GTCS that started with an "electric lightning-like" feeling on a very bright and sunny day. In the following year, despite a high VPA dose (2,500 mg/day), both the generalized seizures and eyelid myoclonia occurred during menstruation, infectious diseases, taking a bath, and upon awakening, especially if directly exposed to daylight. She used several other antiepileptic drugs without success (*figure 2*). Because of the occurrence of different types of seizures, myoclonia, photosensitivity, and progressive ataxia, she underwent further evaluation for progressive myoclonus epilepsy (PME)-related disorders with similar symptomatology and clinical features. However, an axillary biopsy for Lafora disease (LD) and genetic analyses for Unverricht-Lundborg disease (ULD) revealed no pathology. Relying on previous clinical experience and literature knowledge (Koskiniemi *et al*., 1998; Vural *et al*., 2003), she was administered piracetam, which was gradually increased up to 60 g/day with dramatic recovery of gait ataxia. She was also treated for obsessive-compulsive disorder with citalopram. The gait ataxia progressed slowly and the myoclonia increased in frequency, and high-dose piracetam infusion was repeated. On the last visit, she had hesitation in initiating walking and some problems in turning, and she was still very sensitive to photic stimulation. She continued oral piracetam at 32 mg/day, topiramate at 75 mg/day, and VPA at 1,000 mg/day. Her recent brain MRI at the age of 37 years demonstrated prominent global cortical atrophy (*figure 1C, D*).

Patient 2

The male sibling experienced his first GTCS at the age of 26 years. He also had myoclonia, which were very sensitive to photic stimulation. Slowly progressive truncal and extremity ataxia developed in the first year of the disease. Neurological examination on admission revealed dysarthria, irregular jerking of the upper extremities, and truncal cerebellar ataxia. Because his sister was known to have benefited from VPA, he was also started on VPA at 500 mg/day. As the seizures continued, piracetam at 9.6 g/day and TPM at 100 mg/day were added to the regimen with improvement of his seizures. His cognition was totally normal. Brain MRI was normal at onset and mild atrophy developed based on recent MRI follow-up when he was 33 years old (*figure 1E*).

Electrophysiological findings

Polymyographic analyses were performed twice with a four-year interval, for both siblings. The following parameters were evaluated: myoclonus, the long-latency reflex (LLR), the segmental reflex of the median nerve, the blink reflex (BR) after supraorbital electrical stimulation, the auditory startle response (ASR), and startle response to somatosensory inputs (SSS). Both positive and negative myoclonia, which were more prominent on the distal muscles of the upper extremities during rest, posture, or action, were observed during all recordings. Both patients had high-amplitude C reflex or high-amplitude LLR I during active contraction. At first examination, R1 responses of the BR were normal in both patients, whereas R2 was prolonged and R2c was absent in Patient 1. The BR

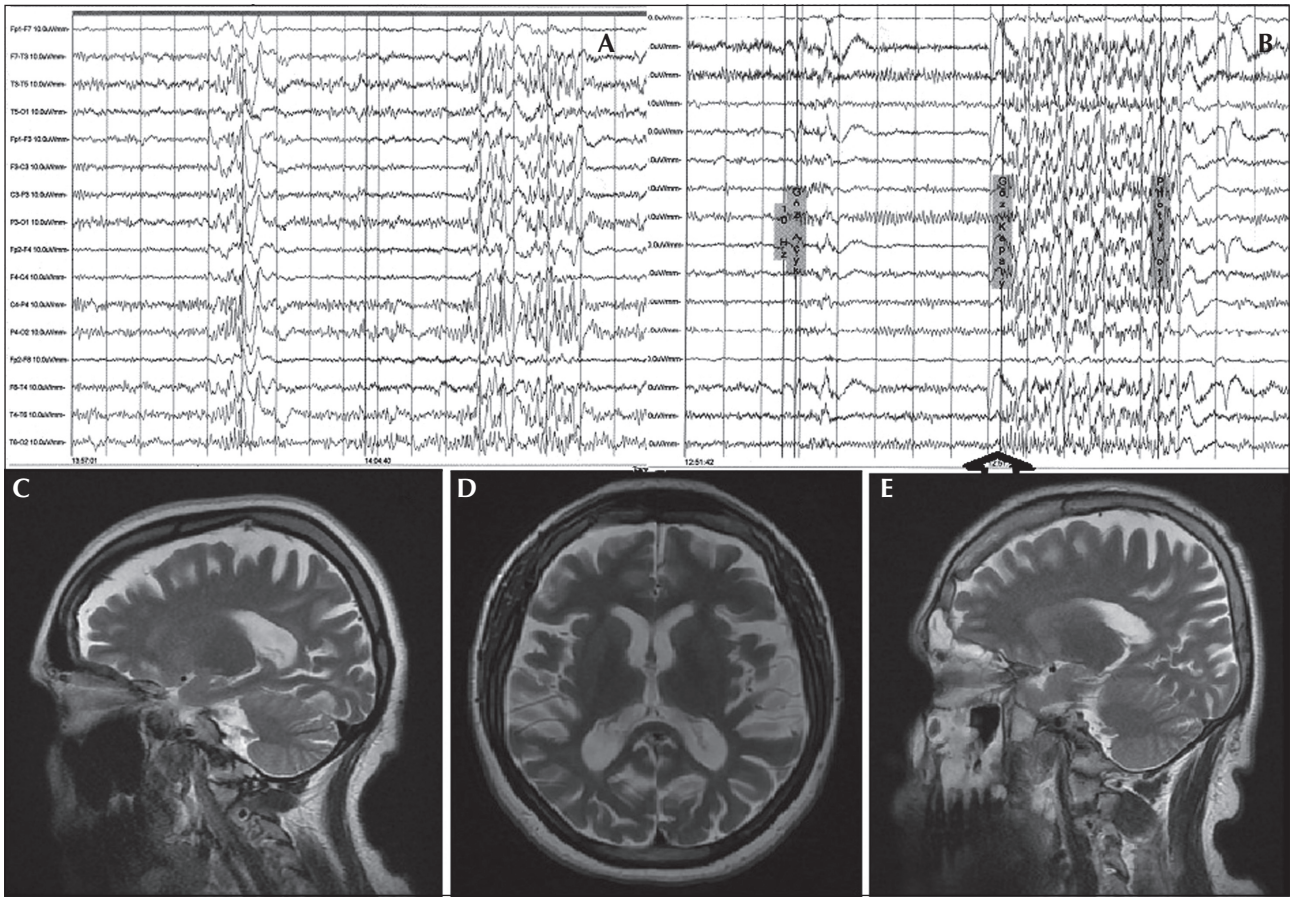

Figure 1. (A) EEG during wakefulness showing generalized spikes, polyspikes, and slow waves. (B) The discharges of generalized activity on EEG increased in number during eye closure in the same patient (arrow marks eye closure). (C, D) Prominent cortical atrophy on T2 sagittal and axial sections during brain MRI in Patient 1 at the last follow-up visit. (E) Mild atrophy on T2 sagittal section during brain MRI in Patient 2.

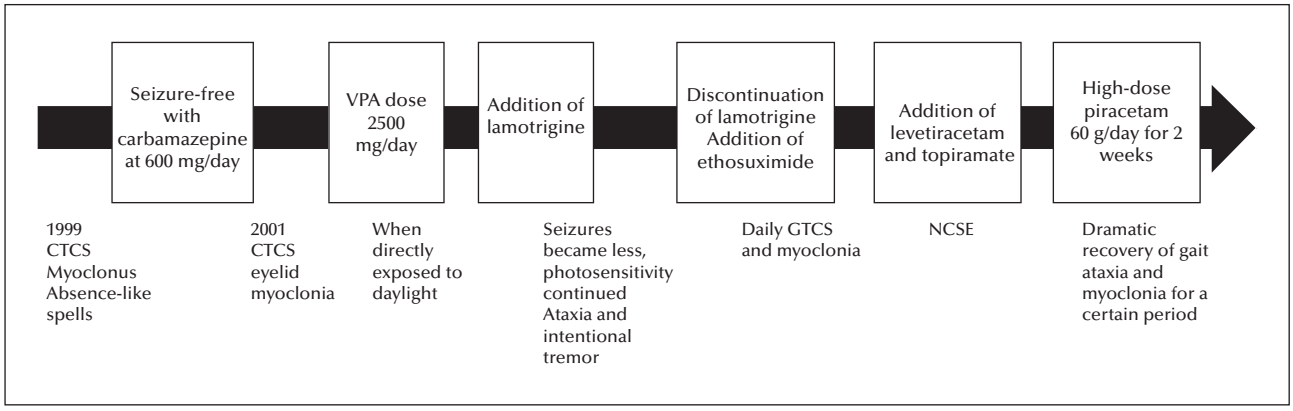

Figure 2. Timeline showing clinical course and response to antiepileptic drugs for Patient 1.

did not show remarkable changes in Patient 2, however, we could not elicit the BR in Patient 1 in the second examination. The recordings of the ASR and SSS revealed long latencies with decreased response rates at first and afterwards, the abnormalities manifested. Patient 1 exhibited almost no responses after auditory or somatosensory stimulation in the second examination.

Genetic findings

Whole-exome sequencing for Patient 2 revealed a novel homozygous mutation in the *CLN6* gene (c.509A>G, p.Tyr170Cys; mutation nomenclature based on GenBank transcript NM_017882.2). Sanger sequencing analysis showed that Patient 1 was also homozygous for the mutation, while both parents were heterozygous carriers. The genetic findings were originally reported by Muona *et al*. (2015).

Discussion

The clinical findings of GTCS and myoclonic seizures, which were sensitive to photic stimulus and eye closure, slowly progressive ataxia, psychiatric problems, and photosensitive response on EEG with generalized spikes, polyspikes, and slow waves, prominent on awakening, suggested that the most probable diagnosis in these patients was PME with a relatively mild clinical course. Genetic analysis confirmed NCL with homozygous mutation in the *CLN6* gene.

Whereas the clinical features of childhood NCLs have been delineated relatively well, juvenile- or adult-onset NCLs may present without retinal involvement or with GTCS which may be well-controlled by AEDs at onset (Nita *et al*., 2016) and may lead to a diagnostic challenge (Berkovic *et al*., 2016). In Patient 1, irregular jerks were misdiagnosed as focal seizures at onset of a GTCS. However, irregular jerks in this case were indeed myoclonic seizures and, together with photosensitivity and EEG findings, raised the suspicion of syndromes with myoclonic seizures.

In these cases, the following disorders were considered in the differential diagnosis:

– Classic LD starting in early adolescence exhibits the most severe clinical course among patients with PME. However, there are exceptions starting at older ages (Baykan et *al*., 2005). Thus, we performed axillary skin biopsies with negative results for Lafora bodies.

– PRICKLE1-related PME was identified long after we had started to follow the index case (Patient 1), however, patients present first with ataxia and myoclonus and seizures follow afterwards (Fox and Bassuk, 2014).

– Early-onset NCL is the most frequent neurodegenerative disorder of childhood and is characterized by dementia, blindness, retinal pigmentation, and extrapyramidal findings. However, Kufs disease, the adult form of NCL, may present at any time before 40 years of age and may have a milder course than the early-onset forms, along with preservation of vision.

In our cases, onset in adulthood with the typical course of PME and no visual complications was consistent with Kufs type A disease. *CLN4* was initially designated gene for Kufs disease, however, the frequency of the disorder, the existence of related genes, and clinical findings of Kufs disease have complicated our understanding of the genetic basis. CLN6, a membrane protein resident in the endoplasmic reticulum (Heine *et al*., 2007) has been reported in both variant late infantile and adult-onset NCL (Gao *et al*., 2002; Wheeler *et al*., 2002; Arsov *et al*., 2011). Kufs disease associated with CLN6 occurs with an onset at around 30 years of age with PME, followed by dementia without vision loss (Arsov *et al*., 2011).

Arsov *et al*. (2011) identified patients with Kufs A disease with *CLN6* mutations, and most patients exhibited myoclonus, seizures, and dementia, followed by ataxia. However, neither our patients nor their relatives had dementia or extrapyramidal findings. The different type of mutations is likely the reason for the different clinical presentations.

Electrophysiological recordings of myoclonia or indirect indicators of increased cortical activation, such as the presence of the C reflex, did not show changes despite adequate control of seizures. Our patients provide evidence for the inhibition of various brainstem reflexes in NCL and establish that these abnormal findings deteriorate with time. The more severe electrophysiological abnormalities in Patient 1 suggest concordance with a more severe clinical course.

Brain MRI is initially normal in NCL patients, but nonspecific abnormalities, such as cerebral and cerebellar atrophy, thinning of the corpus callosum, and deep white matter hyperintensity, may develop with time (Nita *et al*., 2016). Similarly, the presented cases had normal MRI at onset and both developed cortical atrophy with time, which was more prominent in the patient with more severe clinical findings and longer disease duration.

Piracetam, which has a molecular structure very similar to levetiracetam, is not generally considered for epilepsy treatment. Levetiracetam has been reported to be of benefit in some patients with NCL (Augustine *et al*., 2015; Nita *et al*., 2016), whereas piracetam provided dramatic relief from myoclonic seizures and ataxia in the presented cases. Thus, piracetam may be considered for the palliative treatment of these patients. The major drugs for the treatment of myoclonic seizures are valproate, levetiracetam or benzodiazepines. There are also other drugs, such as zonisamide or a novel drug, brivaracetam, however, carbamazepine or phenytoin should be strictly avoided in patients with myoclonic epilepsies (Striano and Belcastro, 2017).

In conclusion, progressive myoclonic epilepsies are a group of heterogeneous disorders with a diverse age at onset presenting with various additional neurological findings. Adult-onset NCL associated with *CLN6* mutation is a rare form of PME in which

persistent photosensitivity is an important clinical feature for accurate diagnosis, which necessitates appropriate genetic investigation. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What are the characteristic findings of Kufs disease associated with *CLN6* mutation?

(2) What are the changes of the brainstem reflexes in Kufs disease associated with *CLN6* mutation?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".