Electroclinical spectrum of the neuronal ceroid lipofuscinoses associated with *CLN6* mutations

Laura Canafoglia, MD
Isabella Gilioli, MD
Federica Invernizzi, PhD
Vito Sofia, MD
Valeria Fugnanesi, PhD
Michela Morbin, MD
Luisa Chiapparini, MD
Tiziana Granata, MD
Simona Binelli, MD
Vidmer Scaioli, MD
Barbara Garavaglia, PhD
Nardo Nardocci, MD
Samuel F. Berkovic, MD,
FRS
Silvana Franceschetti,
MD, PhD

Correspondence to
Dr. Canafoglia:
canafoglia@istituto-besta.it

ABSTRACT

Objectives: To describe the clinical and neurophysiologic patterns of patients with neuronal ceroid lipofuscinoses associated with *CLN6* mutations.

Methods: We reviewed the features of 11 patients with different ages at onset.

Results: Clinical disease onset occurred within the first decade of life in 8 patients and in the second and third decades in 3. All children presented with progressive cognitive regression associated with ataxia and pyramidal and extrapyramidal signs. Recurrent seizures, visual loss, and myoclonus were mostly reported after a delay from onset; 7 children were chairbound and had severe dementia less than 4 years from onset. One child, with onset at 8 years, had a milder course. Three patients with a teenage/adult onset presented with a classic progressive myoclonic epilepsy phenotype that was preceded by learning disability in one. The EEG background was slow close to disease onset in 7 children, and later showed severe attenuation; a photoparoxysmal response (PPR) was present in all. The 3 teenage/adult patients had normal EEG background and an intense PPR. Early attenuation of the electroretinogram was seen only in children with onset younger than 5.5 years. Somatosensory evoked potentials were extremely enlarged in all patients.

Conclusions: In all patients, multifocal myoclonic jerks and seizures were a key feature, but myoclonic seizures were an early and prominent sign in the teenage/adult form only. Conversely, the childhood-onset form was characterized by initial and severe cognitive impairment coupled with electroretinogram and EEG attenuation. Cortical hyperexcitability, shown by the PPR and enlarged somatosensory evoked potentials, was a universal feature. *Neurology*® 2015;85:316–324

GLOSSARY

CP = curvilinear profile; **ERG** = electroretinogram; **FP** = fingerprint profile; **GROD** = granular osmiophilic deposit; **LINCL** = late-infantile neuronal ceroid lipofuscinosis; **NCL** = neuronal ceroid lipofuscinosis; **PME** = progressive myoclonic epilepsy; **PPR** = photoparoxysmal response; **SEP** = somatosensory evoked potential; **SW** = spike and wave; **vLINCL** = variant late-infantile neuronal ceroid lipofuscinosis.

Neuronal ceroid lipofuscinoses (NCLs) are a family of hereditary diseases causing progressive neuronal degeneration and often retinal dystrophy. Clinically, there are variable associations of loss of cognitive skills, progressive visual impairment, refractory epilepsy, and movement disorders, presenting at different ages with varying time courses.

The neuropathologic marker is the intracellular storage of abnormal autofluorescent lipopigments, which accumulate in neurons and in other cells, characterized by electron microscopy as granular osmiophilic deposits (GRODs), curvilinear profiles (CPs), or fingerprint profiles (FPs). Classically, the coupling of onset age with specific neuropathologic patterns resulted in 4 main groupings: infantile, typically associated with GRODs; late-infantile (LINCL) associated with CPs; juvenile, associated with FPs; and adult (Kufs disease) with mixed neuropathologic patterns. Besides typical forms, many variants were recognized and the identification of molecular genetic abnormalities opened new prospects for NCL characterization, but also pointed to the

Supplemental data
at Neurology.org

From the Neuropathology and Epilepsy Centre (L. Canafoglia, I.G., S.B., V. Scaioli, S.F.), Neuropathology-Neurology 5 (V.F., M.M.), Neuroradiology (L. Chiapparini), and Child Neurology and Psychiatry (T.G., N.N.), IRCCS Foundation C. Besta Neurological Institute, Milan; Molecular Neurogenetics (F.I., B.G.), IRCCS Foundation C. Besta Neurological Institute-Bicocca, Milan; G.F. Ingrassia Department (V. Sofia), University of Catania, Italy; and Epilepsy Research Center (S.F.B.), Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Australia.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

problem of matching specific mutations with definite NCL phenotype.¹ This led to development of a new NCL classification based on several axes, including clinical, morphologic, and genetic data.²

Mutations in *CLN6*, encoding a protein of unknown function localized to the endoplasmic reticulum, were first identified in families denoted as variant LINCL (vLINCL).^{3,4} Recently, other mutations of the same gene were found in patients with the recessive adult form of NCL known as Kufs disease.^{5–7} We describe here the spectrum of clinical and neurophysiologic features associated with mutations of *CLN6* in a series of 11 patients, in order to identify common features that could suggest the diagnosis.

METHODS We performed a retrospective analysis of patients with NCL and known mutations of *CLN6*, observed between 1990 and 2014 at a single center.

We evaluated their clinical histories to detect initial, intermediate, and late symptoms of the disease. We considered as “earliest” the symptom occurring within 6 months from the recognition of neurologic abnormalities, as “intermediate” symptoms emerging between 6 months and 4 years, and “late” those emerging after 4 years (see table 1).

We evaluated the neurophysiologic and imaging findings obtained in proximity to the disease onset (0–2 years) and those obtained after a follow-up lasting 4 to 13 years.

EEG, somatosensory evoked potentials (SEPs), flash-evoked visual potentials, and electroretinogram (ERG) were performed according to standard procedures⁸ as is our standard protocol in evaluating patients with putative progressive neurologic disorders. All patients or their parents signed the informed consent for all procedures performed in the study, including genetic evaluation.

The amplitude of N20-P25 SEP component was regarded as “giant” when exceeding 25 μ V (normative laboratory values: 5.1 $\pm$ 2.4 μ V). ERG was recorded using surface electrodes, with flashes administered at 0.5 Hz, 1 J. Flash-evoked visual potentials were recorded in the same session of ERG recording, from O1 and O2 referred to Fz; N1-P1 potentials exceeding 10 μ V and N2-P2 potentials exceeding 30 μ V were regarded as giant.

Ultrastructural examination of skin, lymphocytes, and CNS was done as previously reported.⁹ All of the specimens were evaluated at the C. Besta Institute (M.M.), with the exception of the rectal biopsies (patients 9 and 10), which were performed in other hospitals.

RESULTS We included 11 patients from 10 families. Eight had a childhood onset (3–8 years) and 3 a teenage/adult onset (16–28 years). Nine were the only affected members of the family, and 2 children were brothers (patients 2 and 4); one child (patient 1) and one adult patient (9) had affected brothers not included in the series because of insufficient information. All children were first observed at the C. Besta Institute at the median age of 5.5 years; adults were

observed at C. Besta Institute (patients 9 and 11) or Catania University (patient 10) at the median age of 29 years. Follow-up (from onset) lasted for 5 years for children and 22 years for adults (see table 1).

The 11 patients had a variety of *CLN6* mutations (8 homozygous, 3 compound heterozygous) (table 1). The mutations have been previously described,^{5,10,11} with the exception of a novel mutation in patient 7.

Clinical data in children. Early disease presentation. In 7 children, the disease manifested between 3 and 5.5 years, while in the remaining case, onset was at 8 years (median 5.0 years). Cognitive abnormalities (table 1) were the earliest detected sign in 6 children, and defective language skills indicated a delay of language acquisition. Ataxia was the first detected sign in patient 4 who was repeatedly observed in the preclinical stages. In patient 8, with a relatively late onset, the disease presented with prominent extrapyramidal signs.

Seizures occurred at the onset in only one child, which appeared in the course of a febrile illness. Examination of the fundus oculi performed in 7 children (patients 1–7) did not reveal any abnormalities.

Intermediate and late stages. A few months after disease onset, worsening motor defects became obvious in all children, including prominent ataxia (patients 1–5) or pyramidal and/or extrapyramidal signs (patients 6–8). Four children had a clinically detectable progressive visual decline (patients 1, 3, 4, and 7); the others apparently did not. Repeated examinations of the eye fundus consistently showed normal findings.

Seven children had seizure onset at these later stages: 2 had absence seizures more than 4 years from the disease onset. Multifocal myoclonus, elicited or enhanced by movements, occurred in 4 patients (2, 3, 6, and 7); the delay between disease onset and appearance of myoclonus ranged from 0.5 (patient 6) to 7 years (patient 7) at ages 5.5 to 12 years.

Three children (patients 4–6) were lost to follow-up. Among the 5 observed for at least 4 years (4.5–12) from onset, disease progression was fast with profound mental decline. Gait loss occurred at 7.8 ± 2.7 years (after 3.5 ± 1.7 years from the disease onset). Patient 8 with a delayed disease onset had a milder course and, after 4.5 years, still retained some verbal abilities (total IQ 37, verbal IQ 51, performance IQ 36), was able to walk despite prominent extrapyramidal signs, and had normal visual acuity and fundal examination.

Clinical data in teenage/adult patients. The disease presented in the second (patients 9 and 10) or third decade. Patient 10 manifested poor learning ability since the age of 12 years, before the obvious appearance of seizures at age 17. All patients showed prominent myoclonic jerks with the characteristic of cortical myoclonus from the age of 16 to 28 years. Myoclonus

Table 1 Patients with NCL and known mutations of *CLN6*

Patient no./sex	Onset age, y	Symptoms			Last obs., y	Seizures	Histology	Mutations	Protein
		Earliest	Intermediate	Last (> 4 y)					
1/F	3	Cognitive decline, ataxia	Low vision, seizures	Pyr	11	Clonic, myoclonic	Lymph: normal; skin: FPs, CPs	c.560T>C	p.Leu187Pro
2 ^a /F	4	Cognitive decline, ataxia	Seizures	Pyr, extrapyr, myoclonus	9.5	Clonic, myoclonic	Lymph: GBs, FPs; skin: FPs, CPs	c.184C>T; c.662A>G	p.Arg62Cys; p.Tyr221Cys
3/F	5	Cognitive decline, ataxia	Low vision, seizures	Pyr, extrapyr, myoclonus	12	TC	Lymph: FPs, GBs; skin: FPs, CPs	c.776G>T	p.Gly259Cys
4 ^a /M	5	Ataxia	Cognitive decline, low vision, pyr, extrapyr, seizures	—	6	Absences	Lymph: FPs; skin: n.e.	c.184C>T; c.662A>G	p.Arg62Cys; p.Tyr221Cys
5/M	5	Cognitive decline, ataxia	Pyr, seizures	—	6	Atonic	Lymph: n.e.; skin: FPs, CPs	c.248A>T	p.Asp83Val
6/F	5	Cognitive decline, extrapyr	Myoclonus, seizures	—	6	Clonic, myoclonic	Lymph: GBs, CBs; skin: FPs, CPs	c.896C>T	p.Pro299Leu
7/M	5.5	Cognitive decline, seizures	Low vision, pyr, extrapyr	Myoclonus	17.5	TC	Lymph: FPs; skin: FPs, CPs	g.5'UTR-3518, IVS1+450del4040	—
8/M	8	Pyr, extrapyr	Cognitive decline	Ataxia, seizures	12.5	Absences + eyelids myoclonus	Lymph: GBs; skin: FPs	c.700T>C	p.Phe234Leu
9/F	16 ^b	Myoclonus	Seizures, cognitive decline	Pyr, extrapyr	47	TC, myoclonic	Skin: normal ^c	c.200T>C; c.308G>A	p.Leu67Pro; p.Arg103Gln
10/F	17 ^d	Myoclonus ^e	Seizures, ataxia, cognitive decline	Pyr, extrapyr	31	TC, myoclonic	Skin: normal; rectal: GRODs	c.712T>A; 713T>C	p.Phe238Thr
11/F	28 ^f	Myoclonus, seizures	Cognitive decline, ataxia	—	50	TC, myoclonic	Skin: normal; cerebral: FPs, CPs	c.139C>T	p.Leu47Phe

Abbreviations: CB = condensed body; CP = curvilinear profile; extrapyr = extrapyramidal signs; FP = fingerprint profile; GB = granular body; GROD = granular osmiophilic deposit; NCL = neuronal ceroid lipofuscinosis; n.e. = not examined; obs. = observation; pyr = pyramidal signs; TC = tonic-clonic.

^a Patients 2 and 4 were siblings.

^b Ku1 pedigree reported by Arsov et al., 2011.⁵

^c FPs were demonstrated in a rectal biopsy of the affected brother, studied in another hospital.

^d Ku6 pedigree reported by Arsov et al.⁵

^e Myoclonus was preceded by cognitive regression at 12 years.

^f Ku2 pedigree reported by Arsov et al.⁵

progressively worsened, becoming a dominant symptom and causing severe motor impairment.

All 3 patients had generalized seizures. Patient 9 had myoclonic seizures with the characteristics of “vibrating” attacks, induced by voluntary movements or somatosensory and visual stimuli. She died at 47 years after the occurrence of repeated epileptic status. The other 2 patients, now aged 31 and 50 years, are still alive after 14 and 22 years from the onset of symptoms. Patient 10 was bedridden since age 26 years, with continuous myoclonic attacks induced by any movement attempt. Patient 11 has less than monthly tonic-clonic seizures sometimes induced by visual stimuli.

Gait loss, leading to wheelchair use, occurred 17 years after onset in patient 9 and 7 years after onset in patient 10, while patient 11 is still able to walk with help. Patients 9 and 10 developed moderate pyramidal and extrapyramidal signs. All 3 showed slow cognitive decline but remained able to speak until last follow-up, 13 to 25 years from onset.

MRI. Six children (patients 2–7) were evaluated within 2 years from onset. Five children (patients 1, 2, 3, 7, and 8) were evaluated more than 4 years after the onset. All adults were evaluated more than 4 years from the onset.

At our first evaluation, cerebral cortical atrophy was already detectable in all patients, which was associated with white matter periventricular T2 hyperintensity in all except for one adult (patient 10). In addition, cerebellar atrophy was observed in 7 children (patients 1–7) and one adult (patient 11).

Morphologic diagnosis. In children, skin biopsy showed storage material characterized by FPs and CPs (figure e-1, B and E, on the *Neurology*[®] Web site at Neurology.org). Lymphocyte evaluation showed storage material with more heterogeneous features (figure e-1, A and D; see table 1).

The storage material in adult patients in brain (figure e-1, C and F) or rectal biopsies was predominantly FPs. The histologic diagnosis in patient 9 was based on the finding obtained in a rectal biopsy of her brother (not included in the series). Skin evaluation was consistently negative in the 3 adults.

Neurophysiologic data. Children. *EEG/polygraphy.* Shortly after clinical onset, all children showed a slow (theta-delta) and poorly organized EEG background. All had interictal EEG discharges of irregular, slow spike and waves (SWs) (at about 2.5 Hz) (figures 1A, 2A, and 3A), although clinical seizures were not reported.

Sleep was already disorganized: light sleep showed an excessive rhythmic alpha-beta activity, while slow sleep showed diffuse delta waves with rare multifocal (either frontocentral or posterior) spikes (figure 1, B and C).

All children already showed photoparoxysmal responses (PPRs) at 15-Hz stimulation, while 3

(patients 3, 5, and 7) showed PPR also to lower frequency stimuli and 2 (patients 3 and 5) responded with 1:1 spike to 1-Hz stimuli (figure 1, D and E).

Four years after the disease onset, all children except patient 8 had an extremely slow and low-voltage EEG, and SW discharges became rare, often replaced by individual spikes with multifocal location (figure 2B).

Myoclonus could present either time-locked with SW, leading to a myoclonic seizure (figure 2B), or without any visible EEG correlate.

In contrast to the other children, patient 8 had preserved alpha-theta background 4 years after disease onset. Spontaneous epileptic paroxysms occurred during the EEG recording (figure 3A) and there was a marked PPR, similar to that seen in adult patients (figure 3, B and C).

Evoked responses. ERG waves were attenuated from our first measurement in 6 children (nearly extinct in 3) (figure 1F). In patient 2, ERG was initially considered normal but became attenuated 2 years later. Patient 8, at our last observation 4.5 years from onset, had a normal ERG waveform.

Visual evoked potentials showed heterogeneous features: at our first observation, P1 component (latency: 66 milliseconds) was enlarged in patients 3 and 5 (33 and 156 μ V) (figure 1F), while it became slightly enlarged 4 years after onset in patients 1 and 8 (20 and 26 μ V).

SEP amplitude was giant in all patients with an average value of 45.3 ± 6.5 μ V, with normal or minimally delayed N20 latency. The amplitude remained consistently enlarged during follow-up (figure 2, C and D).

Adults. The EEG recorded at the average age of 28.6 ± 5.5 years (8.3 ± 4.0 years from onset) showed a preserved background organization with dominant frequencies at the lower limits of the alpha band. Brief discharges of S, SW, or fast activity rarely occurred on posterior derivations (see figure 3D). Myoclonus regularly occurred with active movements, and was associated with occipital spikes at the time of intermittent photic stimulation. Both jerks and occipital spikes followed with a 1:1 ratio the stimuli administered at 1 to 5 Hz (see figure 3E) and became extreme in response to higher-stimulus frequencies when EEG spikes tended to spread toward other EEG derivations (see figure 3F). Abnormal PPR persisted until the advanced disease stage. The 3 adult patients had normal ERG and visual evoked potentials, but giant SEPs were seen.

DISCUSSION Recent data show that *CLN6* mutation may cause severe neurologic disorders beginning in both childhood and adult life. We evaluated

Figure 1 EEG and ERG pattern in children

Patient #3: 5 years and 2 months

EEG pattern in patient 3 close to disease onset: (A) wakefulness showing irregular spike-and-wave discharge; (B and C) abnormal light and deep EEG pattern. (D and E) Photoparoxysmal response evoked by slow and high-frequency IPS. (F) At the bottom, ERG pattern showing attenuated and inconsistent response. At the top, visual evoked potential showing increased P1. ERG = electroretinogram; IPS = intermittent photic stimulation.

the present series of 11 patients with NCL and *CLN6* mutations with the aim of describing the phenotypic spectrum of this disorder. Seven patients had a childhood onset; one had an intermediate or “juvenile” onset at 8 years. Moreover, among the 3 adults, all showing a typical progressive myoclonic epilepsy (PME) phenotype, one had learning disabilities detected at 12 years. The patient with disease onset at 8 years, together with the patient with cognitive impairment at 12 years, before the appearance of myoclonus and seizures, have an intermediate age at onset and suggest that *CLN6* does not present at 2 explicit age peaks but may occur at different ages.

Clinical presentation of the children in this series, in agreement with other reports of patients with *CLN6* mutations^{10,12–16} (see table e-1), included cognitive and motor regression, progressive cerebellar, pyramidal, and extrapyramidal signs, and seizures. In our children, cognitive regression was the most common presenting feature, often associated with ataxia. Moreover, the observation of delayed language skills preceding the overt presentation of the disease might suggest that mild defects in cognitive development could actually be the true presenting symptom in all. The following course of the disease was severe in all children and led to loss of independent gait at approximately 7 years.

A. Patient #2: 4 years and 8 months

B. Patient #2: 8 years and 2 months

Early (A) and late (B) EEG recorded in patient 2. Note in B the signal attenuation with persistence of frontal spike and wave associated with a myoclonic seizure. (C and D) SEP recorded at early and late stages. Note that N20-P25 and medium cortical components are giant and remained almost unchanged in the follow-up. SEP = somatosensory evoked potential.

It is important to note that in our patients, the ERG attenuation was an early and important feature suggesting the diagnosis of NCL. Although visual deficits were never an initial feature, and the examination of the fundus oculi never revealed specific pathologic findings, it is possible that the rapid and severe mental decline and motor impairments masked visual defects suggested by the impairment of ERG.¹⁷

Seizures were not an early feature but appeared during the intermediate or late disease stages; only one child had early seizures associated with a febrile illness. Seizures were mostly generalized myoclonic or tonic-clonic, while absences occurred in the late stage of the disease in only 2 children. Epilepsy onset was therefore later than observed in the “classic”

late-infantile *CLN2* form.¹⁸ Segmental myoclonus, enhanced by active movements, was present in a few children and resembles that seen with the adult *CLN6*-PME phenotype. This observation is further supported by the presence of extremely enlarged SEPs, which is a typical marker of PMEs.¹⁹

The child with onset at age 8 years (patient 8) had a milder phenotype.²⁰ His onset age is at the upper limit of that described for vLINCL¹ but the lack of retinal involvement prevents the inclusion as a typical juvenile NCL form.²¹ The prominent extrapyramidal phenotype without any evidence of myoclonus differs from the adult presentation, but the presence of giant SEPs and PPR in this patient confirms cortical hyperexcitability.

Patient #8; 10 years

Patient #11; 37 years

Patient 8, EEG: atypical absence in A and peculiar PPR in B and C, consisting of fast waves 1:1 related with flashes. Patient 11, resting EEG showing small occipital spikes in D; PPR showing fast waves 1:1 related with flashes in E and F. Parieto-occipital channels are magnified in insets. IPS = intermittent photic stimulation; PPR = photoparoxysmal response.

The clinical picture of our adult patients is in accord with the definition of PME,⁵ with cortical myoclonus as the most disabling symptom.²² All had normal vision and normal ERGs. All developed pyramidal and extrapyramidal signs in the advanced disease stages, a neurologic condition that is frequent in NCL^{6,7} but rare in the more common PME forms such as EPM1 and EPM2.^{22–24}

Morphologic evaluation of skin biopsy in children showed typical storage materials with the characteristics of FPs, CPs as reported in vLINCL^{12,25,26} suggesting that cytoplasmic vacuoles containing mixed CPs

and fingerprints are a common characteristic in children with *CLN6* mutations. Leukocyte examination is less invasive, but even if suggestive of NLCs does not show a specific pattern and can be negative.

Of note, none of the 3 adult patients showed storage material in the skin, so morphologic diagnosis needed invasive biopsies (deep rectal or brain). The rectal biopsies showed FP or GRODs in 2 of these adults; however, the reliability of the findings obtained in rectal specimen was recently questioned.²⁷ This confirms that neuropathologic diagnosis in adult patients can be challenging and underscores the value of

advances in molecular diagnosis for putative adult NCL cases.^{5,28,29}

Neurophysiologic findings revealed a link between the different age-dependent *CLN6* phenotypes. “Giant” SEPs, assumed to be a typical and specific marker of patients with cortical myoclonus, were present both in patients with Kufs with obvious PME and in our *CLN6* children, either in the presence or absence of myoclonus. This suggests that mutation of *CLN6* predisposes to cortical hyperexcitability irrespective of (or prior to) myoclonus or seizures. Another neurophysiologic marker of cortical hyperexcitability was the presence of a prominent PPR. This is characteristic of LINCL^{30–33} and has been recently reported in vLINCL associated with *CLN1*³⁴ but not in patients with *CLN8* mutation.³⁵ Our observation indicates that PPR was “extreme” in patients with Kufs disease, with a typical finding of 1:1 photomyoclonic response to low-frequency stimulation (as previously described⁷), but prominent PPRs were also present since the earliest observation in all of our children, thus representing a consistent and “connecting” marker in the different phenotypes.

A major difference between childhood and adult onset was the involvement of the retina; the ERG was attenuated only in patients with an onset younger than 5.5 years, as also reported in the classic late-infantile form caused by *CLN2* mutation and in juvenile Batten disease caused by *CLN3* (and less frequently *CLN1*) mutation. Another age-related neurophysiologic difference is the characteristic and time course of EEG background disruption, moderate in adults and in our child with a delayed onset but extremely severe in younger children, reminiscent of that described in the infantile NCL³⁶ and in the late-infantile form associated with *CLN1* mutation.³⁴

Certain clinical and neurophysiologic features link the different presentations of *CLN6* despite the variability in age at onset. Giant SEPs were a consistent marker of both childhood and adult presentation, and a PPR was present in all patients and extremely marked in adult cases. All these features revealed enhanced cortical (or corticothalamic) excitability in *CLN6*. Neurophysiologic findings have rarely been systematically evaluated in series of patients with *CLN6* mutations (see table e-1), but they appear to significantly orient the diagnostic workup. Indeed, the finding of giant SEPs is extremely rare in childhood and considered to be mostly associated with NCL.³⁷ On the basis of our observations, the concurrent presence of PPR and giant SEPs in childhood can be a feature suggestive of NCL, to which attenuated ERG can add further confidence in indicating the likelihood of finding a *CLN6* mutation.

Our data do not imply changes in the diagnostic algorithm necessary in suspected childhood NCLs,³⁸

but they are valuable in proposing a pathophysiologic link between childhood onset and adult *CLN6*-LINCL, revealed by strong and early cortical hyperexcitability even in the presence of dissimilar clinical presentation, namely, in early disease stages.

In adult and adolescent patients presenting with prominent cortical myoclonus,^{5,39} *CLN6* should be included in the genetic screening especially in the presence of extreme responses to intermittent photic stimulation at low and high frequencies (Kufs type A), since storage material is difficult to identify in skin, absent in lymphocytes, and problematic in rectal biopsy.^{26,27}

AUTHOR CONTRIBUTIONS

Dr. Canafoglia conceived the study, clinically evaluated the patients, analyzed neurophysiologic findings, discussed the results, and drafted and revised the manuscript. Dr. Gilioli clinically evaluated the patients, analyzed neurophysiologic findings, discussed the results, and drafted the manuscript. Dr. Invernizzi performed genetic studies and discussed the results. Dr. Sofia clinically evaluated the patients and discussed the results. Dr. Fugnanesi performed neuropathologic studies and discussed the results. Dr. Morbin evaluated neuropathology, discussed the results, and drafted and revised the manuscript. Dr. Chiapparini evaluated neuroradiology and discussed the results. Dr. Granata clinically evaluated the patients, discussed the results, and revised the manuscript. Dr. Binelli clinically evaluated the patients, evaluated EEG recordings, and discussed the results. Dr. Scaioli evaluated evoked potentials and discussed the results. Dr. Garavaglia evaluated the genetic findings and discussed the results. Dr. Nardocci clinically evaluated the patients, discussed the results, and revised the manuscript. Dr. Berkovic evaluated genetic findings, discussed the results, and revised the manuscript. Dr. Franceschetti conceived the study, clinically evaluated the patients, analyzed neurophysiologic findings, discussed the results, and drafted and revised the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received November 3, 2014. Accepted in final form March 31, 2015.

REFERENCES

1. Kousi M, Lehesjoki AE, Mole SE. Update of the mutation spectrum and clinical correlations of over 360 mutations in eight genes that underlie the neuronal ceroid lipofuscinoses. *Hum Mutat* 2012;33:42–63.
2. Williams RE, Mole SE. New nomenclature and classification scheme for the neuronal ceroid lipofuscinoses. *Neurology* 2012;79:183–191.
3. Sharp JD, Wheeler RB, Lake BD, et al. Loci for classical and a variant late infantile neuronal ceroid lipofuscinosis map to chromosomes 11p15 and 15q21–23. *Hum Mol Genet* 1997;6:591–595.
4. Haines JL, Boustany RM, Alroy J, et al. Chromosomal localization of two genes underlying late-infantile neuronal ceroid lipofuscinosis. *Neurogenetics* 1998;1:217–222.
5. Arsov T, Smith KR, Damiano J, et al. Kufs disease, the major adult form of neuronal ceroid lipofuscinosis, caused by mutations in *CLN6*. *Am J Hum Genet* 2011;88:566–573.

6. Kufs H. Über eine Spätform der amaurotischen Idiotie und ihre heredofamiliären Grundlagen. *Z Ges Neurol Psychiatr* 1925;95:169–188.
7. Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kufs' disease: a critical reappraisal. *Brain* 1988; 111:27–62.
8. Scaiola V, Nardocci N. A pathophysiological study of neuronal ceroid lipofuscinoses in 17 patients: critical review and methodological proposal. *Neurol Sci* 2000;21:S89–S92.
9. Nardocci N, Morbin M, Bugiani M, Lamantea E, Bugiani O. Neuronal ceroid lipofuscinosis: detection of atypical forms. *Neurol Sci* 2000;21:S57–S61.
10. Cannelli N, Garavaglia B, Simonati A, et al. Variant late infantile ceroid lipofuscinoses associated with novel mutations in CLN6. *Biochem Biophys Res Commun* 2009; 379:892–897.
11. Santorelli FM, Garavaglia B, Cardona F, et al. Molecular epidemiology of childhood neuronal ceroid-lipofuscinosis in Italy. *Orphanet J Rare Dis* 2013;8:19.
12. Sharp JD, Wheeler RB, Parker KA, Gardiner RM, Williams RE, Mole SE. Spectrum of CLN6 mutations in variant late infantile neuronal ceroid lipofuscinosis. *Hum Mutat* 2003;22:35–42.
13. Siintola E, Topcu M, Kohlschütter A, et al. Two novel CLN6 mutations in variant late-infantile neuronal ceroid lipofuscinosis patients of Turkish origin. *Clin Genet* 2005; 68:167–173.
14. Al-Muhaizea MA, Al-Hassnan ZN, Chedrawi A. Variant late infantile neuronal ceroid lipofuscinosis (CLN6 gene) in Saudi Arabia. *Pediatr Neurol* 2009;4:74–76.
15. Bouhouche A, Regragui W, El Fahime E, et al. CLN6 p. I154del mutation causing late infantile neuronal ceroid lipofuscinosis in a large consanguineous Moroccan family. *Indian J Pediatr* 2013;80:694–696.
16. Guerreiro R, Bras JT, Vieira M, et al. CLN6 disease caused by the same mutation originating in Pakistan has varying pathology. *Eur J Paediatr Neurol* 2013;17:657–660.
17. Birch DG. Retinal degeneration in retinitis pigmentosa and neuronal ceroid lipofuscinosis: an overview. *Mol Genet Metab* 1999;66:356–366.
18. Pérez-Poyato MS, Marfa MP, Abizanda IF, et al. Late infantile neuronal ceroid lipofuscinosis: mutations in the CLN2 gene and clinical course in Spanish patients. *J Child Neurol* 2013;28:470–478.
19. Shibasaki H, Yamashita Y, Neshige R, Tobimatsu S, Fukui R. Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. *Brain* 1985;108: 225–240.
20. Leuzzi V, Garavaglia B, Manti F, Bertino S, Nardocci N. Running apraxia as a presenting symptom of neuronal ceroid lipofuscinosis 6. *Mov Disord* 2014;29:277–278.
21. Mole SE, Williams RE, Goebel HH, editors. *The Neuronal Ceroid Lipofuscinoses (Batten Disease)*, 2nd ed. Oxford: Oxford University Press; 2011:24–34.
22. Franceschetti S, Michelucci R, Canafoglia L, et al; Collaborative LICE Study Group on PMEs. Progressive myoclonic epilepsies: definitive and still undetermined causes. *Neurology* 2014;82:405–411.
23. Genton P. Unverricht-Lundborg disease (EPM1). *Epilepsia* 2010;51:37–39.
24. Kälviäinen R, Khyuppenen J, Koskenkorva P, Eriksson K, Vanninen R, Mervaala E. Clinical picture of EPM1-Unverricht-Lundborg disease. *Epilepsia* 2008;49:549–556.
25. Topçu M, Tan H, Yalnizoglu D, et al. Evaluation of 36 patients from Turkey with neuronal ceroid lipofuscinosis: clinical, neurophysiological, neuroradiological and histopathologic studies. *Turk J Pediatr* 2004;46:1–10.
26. Anderson GW, Goebel HH, Simonati A. Human pathology in NCL. *Biochim Biophys Acta* 2013;1832:1807–1826.
27. Ferlazzo E, Gasparini S, Pasquinelli G, et al. Usefulness of rectal biopsy for the diagnosis of Kufs disease: a controlled study and review of the literature. *Eur J Neurol* 2012;19: 1331–1336.
28. Nosková L, Stránecký V, Hartmannová H, et al. Mutations in DNAJC5, encoding cysteine-string protein alpha, cause autosomal-dominant adult-onset neuronal ceroid lipofuscinosis. *Am J Hum Genet* 2011;89:241–252.
29. Smith KR, Dahl HH, Canafoglia L, et al. Cathepsin F mutations cause type B Kufs disease, an adult-onset neuronal ceroid lipofuscinosis. *Hum Mol Genet* 2013;22: 1417–1423.
30. Pampiglione G, Harden A. So-called neuronal ceroid lipofuscinosis: neurophysiological studies in 60 children. *J Neurol Neurosurg Psychiatry* 1977;40:323–330.
31. Barthez-Carpentier MA, Billard C, Maheut J, Santini JJ, Ruchoux MM. A case of childhood Kufs' disease. *J Neurol Neurosurg Psychiatry* 1991;54:655–657.
32. Sainio K. Neurophysiological findings in neuronal ceroid lipofuscinoses. *Neuropediatrics* 1997;28:70.
33. 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:S83–S87.
34. Simonati A, Tessa A, Bernardina BD, et al. Variant late infantile neuronal ceroid lipofuscinosis because of CLN1 mutations. *Pediatr Neurol* 2009;40:271–276.
35. Striano P, Specchio N, Biancheri R, et al. Clinical and electrophysiological features of epilepsy in Italian patients with CLN8 mutations. *Epilepsy Behav* 2007;10:187–191.
36. Santavuori P. EEG in the infantile type of so-called neuronal ceroid-lipofuscinosis. *Neuropadiatrie* 1973;4:375–387.
37. Schmitt B, Thun-Hohenstein L, Molinari L, Superti-Furga A, Boltshauser E. Somatosensory evoked potentials with high cortical amplitudes: clinical data in 31 children. *Neuropediatrics* 1994;25:78–84.
38. Schulz A, Kohlschütter A, Mink J, Simonati A, Williams R. NCL diseases: clinical perspectives. *Biochim Biophys Acta* 2013;1832:1801–1806.
39. Andrade DM, Paton T, Turnbull J, Marshall CR, Scherer SW, Minassian BA. Mutation of the CLN6 gene in teenage-onset progressive myoclonus epilepsy. *Pediatr Neurol* 2012;47:205–208.