Epilepsy & Behavior 94 (2019) 59–64

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Epileptological aspects of juvenile neuronal ceroid lipofuscinosis (CLN3 disease) through the lifespan

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ARTICLE INFO

Article history:
Received 14 December 2018
Revised 22 February 2019
Accepted 22 February 2019
Available online 16 March 2019

Keywords:
Juvenile neuronal ceroid lipofuscinosis
CLN3 disease
Epilepsy
EEG
Cardiac conduction abnormalities
Paroxysmal sympathetic hyperactivity

ABSTRACT

Purpose: Juvenile neuronal ceroid lipofuscinosis (CLN3 disease) is the most common neurodegenerative disorder in childhood with survival until young adult age. Visual loss is followed by epilepsy, cognitive, neuropsychiatric, and motor symptoms. We have studied the evolution of electroencephalographic (EEG) and seizure characteristics.
Methods: Twenty-four patients were recruited via the Norwegian CLN3 disease parent association. Parents were interviewed. Medical records and EEG reports/recordings were collected. Electroencephalographic elements were classified according to Standardized computer-based organized reporting of EEG (SCORE). The evolution of EEG features along with seizure types was assessed by testing the difference in proportions with standardized normal deviate comparing findings below and above 15 years of age.
Results: Mean age at study or death (n = 12) was 21.2 (10–39) years. Twenty-two patients had experienced seizures; the first was usually bilateral tonic–clonic (TC). Later, focal motor seizures frequently occurred, often with increasing multifocal and polymorphic features. Paroxysmal nonepileptic motor and autonomous symptoms were also suspected in several patients. Distinct myoclonic seizures were uncommon. In four patients, we identified episodes of bradycardia/sinus arrest. Electroencephalography showed progressive slowing of the background activity ($p = 0.029$). Focal epileptiform discharges were rare and mainly seen at age <10. Combined multifocal and bilateral epileptiform discharges increased in adolescence ($p = 0.002$).
Conclusion: Seizure and EEG characteristics change with time in CLN3 disease. Tonic–clonic seizures are common at onset, and multifocal motor seizures increase with age. In contrast, focal epileptiform abnormalities are more common in childhood, compared to later multifocal and bilateral discharges. This seizure disorder belongs to the *combined generalized and focal epilepsies*. Paucity of myoclonic seizures does not warrant classification as a classic *progressive myoclonic epilepsy*. When attacks with only behavior arrest occur, cardiac conduction abnormalities should be considered.

1. Introduction

Juvenile neuronal ceroid lipofuscinosis (CLN3 disease) (Spielmeyer–Vogt disease or Batten disease) is the most common neurodegenerative disease in children with survival until young adult age. It is an autosomal recessive disorder; the responsible gene, CLN3, was identified in 1995. It codes for a lysosymal transmembrane protein. The genetic defect leads to intracellular accumulation of a lipopigment, which can be microscopically visualized in various tissues [1].

The epidemiological distribution of CLN3 disease is geography-related. It appears to be particularly common in Northern Europe, especially in Finland [1,2]. In Norway, the prevalence has been estimated to 8.3 per million inhabitants [3]. Apparently, CLN3 disease was first described in 1826 in the Norwegian medical journal Eyr by O.C. Stengel, a physician serving in the copper mining community at Røros within the catchment area of St. Olav Hospital in Trondheim [1,4].

The presenting manifestation is a progressive visual loss starting around the age of 6–8 years, eventually a slowing of cognitive development occurs, followed by dementia and frequently behavioral problems and psychosis. Seizures usually start at the age of 10–11 [5]. The seizure disorder has been classified among the *progressive myoclonic epilepsies* [6,7], although recently, myoclonic seizures have been found to be infrequent [8]. Motor symptoms in the form of pyramidal, extrapyramidal, and cerebellar deficits occur from adolescence, sometimes with parkinsonian features. Patients with CLN3 disease are prone to cardiac conduction abnormalities [9,10]. Recently, an autonomic nervous system involvement in the form of paroxysmal sympathetic hyperactivity has been suggested [11].

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https://doi.org/10.1016/j.yebeh.2019.02.020
1525-5050/

Table 1
Clinical milestones in patients with CLN3 disease.

	Patients (n)	Mean age, years (range)
Visual failure	24	6.0 (3–10)
Diagnosis established	24	7.3 (3–13)
Seizures	22	10.6 (6–15)
Psychotropic drug use	16	14.5 (7–22)
Wheelchair-bound	9	21.8 (18–29)
Sick sinus syndrome	4[a]	31 (28–35)
Death	12	27.7 (20–39)

[a] Sudden unexpected death in one additional patient.

Because of the low prevalence of the disorder, as well as the multiple progressing symptoms, studies with particular focus on the epilepsy are few and are mostly based on observational surveys of rather small numbers of patients at a relatively young age. Little attention has been given to the course of CLN3 disease above childhood and adolescent age up to the terminal phase. The aim of the present study was to address the long-term evolution of the electroencephalography (EEG) along with clinical issues related to the seizure disorder in CLN3 disease.

2. Methods

Invitations to participate were distributed to 46 affected families through the Norwegian CLN3 disease parent association in 2008. Consent to collect medical records from hospitals and institutions was requested. A questionnaire concerning the onset and development of key clinical symptoms was enclosed. Twenty families responded, and 24 patients (5 sibling pairs) were included. Reminders were not sent to nonresponders. A semistructured interview by telephone or in the outpatient clinic was performed. The questionnaire data were discussed, and medical records were reviewed with a particular focus on seizure types and EEG characteristics from various stages of the disease. Collection of clinical and EEG data could be extended up to 2018 from patients residing in the Central Norway Health Region. In addition, the use of antipsychotic, antidepressant, anxiolytic, and hypnotic drugs was evaluated for all patients.

The clinical diagnosis of CLN3 disease was made by the onset age of typical symptoms and the progression of the disorder, and supported by the occurrence in siblings or by lipopigment inclusions in various tissues (lymphocytes, n = 13; appendix, n = 4; conjunctiva, n = 4; rectum, n = 1; skin, n = 1), as well as ascertained by CLN3 mutations (n = 15).

Seizures were reclassified according to the current operational classification of the International League Against Epilepsy (ILAE) [12]. Electroencephalographic findings were rescored for slowing, focal abnormality, asymmetries, and epileptiform discharges in all patients. Morphology of epileptiform discharges was categorized based on definitions suggested by the SCORE group and a recently revised glossary of terms [13,14]. The evolution of EEG features along with seizure types was investigated.

The study was approved by the regional ethics committee.

2.1. Statistical methods

We assessed the development of seizure types and EEG abnormalities with age, defined as number of patients with at least one seizure type and abnormal EEG respectively within each age category. We tested the difference in observed proportions with a standardized normal deviate. Both seizure type proportions and EEG abnormality proportions in younger and older groups were accordingly compared.

Table 3
Seizure types in relation to age in 22 patients with CLN3 disease.

Seizure types	Number of patients N = 22	Mean onset age, years (range)	≤15 years n = 22	>15 years n = 15
Tonic–clonic	21 (95.5%)	10.8 (6–15)	20 (91%)	14 (93.3%)
Nonmotor	14 (63.6%)	14.0 (6–28)	10 (45.5%)	9 (60%)
Focal motor	13 (54.5%)	17.2 (10–30)	5 (22.7%)*	10 (66.7%)*
Drop attacks	6 (22.7%)	19.8 (13–28)	1 (4.5%)	5 (33%)
Myoclonic	3 (13.6%)	17.6 (17–19)	0	3 (20%)
Unclassified or poorly described	11 (50%)	18.8 (10–31)	5 (22.7%)	7(46.7%)

* $p = 0.008$ for difference in proportions comparing ≤15 and >15 year groups.

3. Results

3.1. Demographics and clinical milestones

Mean age at study completion or death was 21.2 (10–39) years. Thirteen patients were males. Two patients, aged 11 and 13 years, had not developed epilepsy. Table 1 shows the chronological distribution of key clinical milestones in all patients. Twelve patients had died; known clinical circumstances and the probable immediate cause of death are shown in Table 2.

3.2. Ictal and episodic events

Epileptic seizure types related to age group are shown in Table 3. The first reported seizure type was tonic–clonic (TC) in 20 of 22 subjects with seizures. In one patient, the first seizure was nonmotor, while it was unclassifiable in another. Nonmotor seizures of unknown onset were common (>50% of the patients; n = 14). Nonconvulsive status epilepticus was verified by video-EEG in one patient with prolonged unresponsiveness. Focal motor seizures clearly increased with age ($p = 0.008$, Table 3). The seizure semiology was characterized by multiple, diverse, and polymorphic seizures. A differentiation between

Table 2
Clinical course of entire lifespans in 12 patients with CLN3 disease.

	Age (years)						Clinical circumstances at death
	Visual failure	Diagnosis	Seizures	Wheelchair	Sick sinus	Death	
1	5	6	9	29	35	39	Congestive heart failure, infection
2	3	8	13	28	32	34	Congestive heart failure, infection
3	4	7	15	22	29	33	Congestive heart failure, infection
4	7	7	10	24	Likely	31	Sudden death during general anesthesia
5	5	7	12	25	28	31	Unknown
6	5	8	7	18	No	25	Clinically suspected SE/autonomous symptoms, infection
7	5	7	14	20	No	25	Serial seizures/autonomous symptoms, infection
8	7	7	12	Unknown	No	24	Infection
9	5	9	9	21	No	23	Clinically suspected SE/autonomous symptoms, infection
10	5	7	12	No	No	23	Unknown
11	5	8	12	22	No	23	Infection
12	7	10	9	18	No	20	Serial seizures/autonomous symptoms, infection

SE, status epilepticus.

Table 4
EEG data in 21 patients with CLN3 disease.

	Number of recordings (number of pts)
All	98 (21)
Digital recordings	32 (7)
Selected segments of paper	22 (7)
Reports without preserved recordings	44 (14)
Standard recordings	94 (21)
Recordings after sleep deprivation	2 (2)
Long-term monitoring	2 (2)
Recordings with video	6 (3)
Recordings without activations	34 (10)
Recordings with only photostimulation	18 (9)
Recordings with only hyperventilation	6 (3)
Recordings with hyperventilation and photostimulation	18 (12)
Recordings without known activation procedures	22 (8)

nonmotor focal seizures with behavioral arrest and atypical absences was usually impossible on clinical grounds. The tendency to short-lasting serial jerks increased with age. In the majority, these were side-shifting and rhythmic with an apparent character of focal clonic seizures, predominantly in the arms and face. Bilateral massive myoclonus or serial myoclonic jerks (less regularly repetitive and sustained than clonic seizures) were not a predominant seizure type. Action myoclonus was not reported. Drop attacks, described as short-lasting loss of consciousness and body tone, sometimes only as nodding, were reported in some patients, sometimes occurring in multiple series several times a day.

In four patients, episodes of bradycardia and sinus arrest were identified by electrocardiography (ECG) (Table 2). These episodes were first thought to be epileptic manifestations. A pacemaker was implanted in one patient; during the procedure, cardiac arrest occurred. Resuscitation was successful, and head drops were no longer reported. Pacemaker was not advised in the three other patients because of terminal stage of the disorder. Another patient without previously confirmed sick sinus syndrome died unexpectedly from cardiac arrest during general anesthesia for dental treatment at the age of 31 years (Table 2).

Moreover, by retrospective review of medical records, episodic symptoms suggestive of *paroxysmal sympathetic hyperactivity* [11] were identified in 10 subjects following adolescence. In these patients, episodes of agitation, restlessness, grimacing, and other unspecific motor symptoms were reported from mean age 17 years (range: 14–27). Anxiety with clinging to the bed was described, as well as sweating and elevated temperature without signs of infection. The episodes increased during the late stage of the disorder and lasted up to hours and days. In one subject, nonconvulsive status epilepticus was ruled out by video-EEG; the findings rather suggested an aroused pattern. In four other patients, atypical status epilepticus/serial subtle motor seizures were clinically suspected, and treated as such, albeit not supported by distinct ictal patterns in standard EEGs (Table 2).

3.3. EEG

Data from 98 EEG recordings were available in 21 patients (Table 4), 44 in 20 patients <15 years, and 54 in 13 patients >15 years of age. Three of 24 patients had no available EEGs. The number of EEGs per patient ranged from 1 to 14 (mean = 5). Table 5 compares the EEG abnormalities between the two age groups. Electroencephalography showed progressive slowing of the background activity ($p = 0.029$). Distinct focal epileptiform activity was rare and mainly seen at age <10, only seen in one patient >20 years. Multifocal epileptiform discharges increased significantly after adolescence, often associated with bilateral synchronous and asynchronous features (Table 5, Fig. 1). Electroencephalographic photosensitivity was not a prominent feature.

3.4. Drug treatment

At recruitment or prior to death in previously deceased subjects, the following prophylactic antiepileptic drugs (AEDs) were used: carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, phenytoin, topiramate, and valproate. The mean number of AEDs that had been used in patients >18 years was 4.1 (range: 2–8).

Altogether, 16 patients used psychotropic drugs. Twelve were treated with antipsychotic drugs, four with one, and eight patients with two drugs, mostly haloperidol, risperidone, chlorprothixene, olanzapine, or thioridazine. Five patients used antidepressants, three of them used escitalopram/citalopram. Anxiolytics or hypnotics were used by 12 patients, often in combination, usually diazepam, alimemazine, oxazepam, nitrazepam, and zopiclone/zolpidem.

4. Discussion

In this study, the proportion of adult patients with CLN3 disease was high. Although the number of patients was limited, the age distribution and the proportion of advanced cases render this material unique. In half of the patients, available data from the entire lifespans, including the terminal phase and death, could be reviewed at study completion.

4.1. The seizure disorder in CLN3 disease

The course of the disorder in the present patients nicely demonstrates how seizure types and EEG abnormalities change with time in CLN3 disease (Tables 3 and 5). The first reported seizure was usually of bilateral TC type. In contrast, focal epileptiform abnormalities in the EEG were more common in young patients, whereas bilateral and multifocal epileptiform discharges in the EEG were significantly more prevalent in the later stages of the disease, along with a progressive slowing of the background rhythm. Other seizure types than TC increased during adolescence, particularly focal clonic seizures. Many patients had nonmotor seizures with behavior arrest, partly of subtle character. However, myoclonic seizures (jerks less regularly repetitive

Table 5
Epileptiform and slowing abnormalities in 98 EEG recordings in 21 patients with CLN3 disease.

	All patients	Patients < 15 years[a]	Patients > 15 years[a]	Standardized normal deviate (u) and p-value	
	Patients [number of EEGs (range per patient)]			u	p
Patients with EEG (number of EEGs)	21 [98 (1–14)]	20 [44 (1–5)]	13 [54 (1–11)]		
Slowing	17 [75 (1–12)]	14 [22 (1–4)]	13 [53 (1–11)]	−2.18	0.029
Focal epileptiform discharges	7 [14 (1–3)]	5 [11 (1–3)]	3 [3 (1)]	0.13	0.9
All with multifocal epileptiform discharges	11 [34 (1–7)]	5 [9 (1–3)]	10 [25 (1–7)]	−2.93	0.003
Subgroup with combined multifocal and bilateral synchronous/asynchronous epileptiform discharges	9 [24 (1–7)]	2 [3 (1–2)]	8 [21 (1–7)]	−3.15	0.002
Bilateral synchronous/asynchronous epileptiform discharges without focal features	8 [22 (1–10)]	5 [9 (1–4)]	5 [13 (1–7)]	−0.82	0.41

[a] Patients with at least one EEG with the respective abnormality.

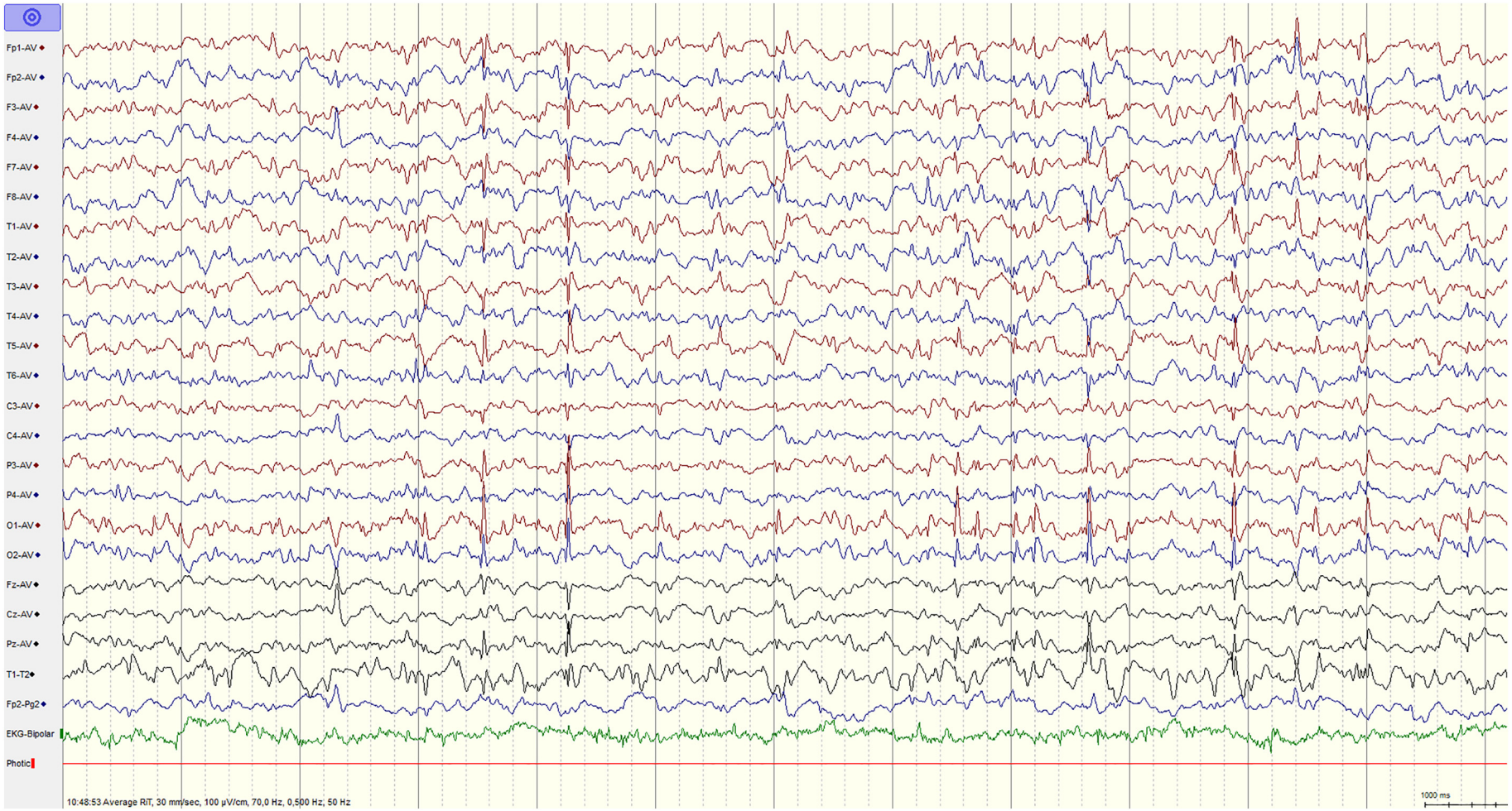

Fig. 1. Interictal EEG with combined multifocal and bilateral epileptiform discharges in a subject with CLN3 disease at age 24 years, 11 months prior to death.

and sustained than clonic) were rare and only suspected in four patients in the late course. Previously, the seizure disorder of CLN3 disease was lumped together with other forms of ceroid lipofuscinoses among the progressive myoclonic epilepsies [6,7,15]. This has now been questioned by other recent studies [8]. It has been emphasized that the various neuronal ceroid lipofuscinosis comprise genetically distinct disorders with a different clinical course [16]. In this study, bilateral myoclonic jerks were not reported as a predominant feature, but sometimes it was difficult to disentangle and classify minor motor symptoms in the terminal stage of the disorder [11]. Particular treatment recommendations for the progressive myoclonic epilepsies [17] do not appear to be relevant for patients with CLN3 without myoclonic seizures.

Based on clinical and EEG features, the seizure disorder of CLN3 disease can be classified as *combined focal and generalized epilepsies* with both genetic and metabolic etiologies, according to the recently revised ILAE epilepsy classification [18].

CLN3 disease is a progressive *developmental encephalopathy* associated with regression and further slowing of the development, as well as epilepsy. An additional component of an *epileptic encephalopathy* caused by a negative impact of epileptic activity (Fig. 1) on the function of the adolescent brain is conceivable, emphasizing the importance of optimal antiepileptic treatment in CLN3 disease. International League Against Epilepsy now recommends that the epileptic encephalopathy concept should be utilized more widely and not only be restricted to severe epilepsies arising in early childhood [18].

In this retrospective study, crude seizure frequency was difficult to compare in the various stages of the disorder, but multiple seizure types as well as bilateral and multifocal epileptiform EEG elements increased. Difficult-to-treat epilepsy was reflected by the large number of AEDs that had been used following adolescence. Apparently, the age of seizure onset did neither correlate with the overall lifespan progression of the disorder, nor with the age of death (Table 3).

Dramatic complex symptoms with possible elements of both status epilepticus/serial subtle motor seizures and autonomous symptoms suggesting paroxysmal sympathetic overactivity were related to death in 4 patients. These patients tended to die at a younger age compared with those who passed away from infectious disease/congestive heart failure/cachexia (Table 2).

4.2. Cardiac involvement in CLN3 disease

Affection of the heart has long been acknowledged in CLN3 disease. Postmortem studies showed extensive lipopigment deposits in the sinus node, as well as in the atrioventricular node and the bundle of His [9,10]. A progressive cardiac involvement with repolarization disturbances, ventricular hypertrophy, and sinus node dysfunction may occur [19]. Severe bradycardias, including long periods of sinus arrest, which may mimic epileptic seizures, have been demonstrated [19,20]. In the present study, four patients had been diagnosed with manifest cardiac conduction abnormalities in the advanced stage of the disorder, which clinically were first thought to represent nonmotor/atonic seizures. Unfortunately, for most patients in this series, the ECG status could not be assessed. The potential cardiac manifestations of the disorder are of utmost importance for the differential diagnosis of paroxysmal events in CLN3 disease, a fact which should be brought to the attention of treating neurologists. The follow-up of these patients should include cardiac rhythm assessments. Consequently, sodium channel-blocking AEDs with potential adverse effects from the cardiac conduction system, such as carbamazepine [20] and its derivatives, as well as lacosamide [21], should be used with caution in CLN3 disease.

4.3. The concept of paroxysmal sympathetic hyperactivity

We believe that the recent reporting of an episodic autonomous imbalance suggesting *paroxysmal sympathetic hyperactivity* in CLN3 disease [11,22] has increased our understanding of the complex clinical picture during the late stage of the disorder. Prolonged episodes of severe behavioral, hypermotor, as well as autonomic symptoms were present in many patients. Such events caused concern and differential diagnostic difficulties. The episodes had been interpreted as merely psychiatric symptoms or seizure-related events. Stimulus sensitive restlessness, tremor, and myoclonic-like jerking occurred. However, during one episode, nonconvulsive status epilepticus was clearly excluded by EEG. The underlying mechanism of paroxysmal sympathetic hyperactivity is thought to represent an episodic release of sympathetic activity with an overreactivity to afferent stimuli, corresponding to what may occur in traumatic brain injury [11].

4.4. Behavioral and psychiatric comorbidities in CLN3 disease

Behavioral problems, extrapyramidal signs, sleep disturbances, and even psychotic symptoms may occur in the second decade of life [23]. When episodic behavioral changes occur, nonconvulsive status epilepticus as well as paroxysmal sympathetic overactivity should be considered.

Assessment for psychiatric disorders was not part of this study, but comorbidities were evidenced by the high drug burden in these patients. Psychotropic drugs were used by the majority, often in combination. Antipsychotics and anxiolytics were most common. A range of pharmacokinetic and pharmacodynamic interactions between these drugs and AEDs may occur. Several AEDs can induce or aggravate behavioral problems, particularly drugs like levetiracetam, topiramate, and perampanel [24,25], whereas other AEDs may have mood stabilizing effects [26]. Antipsychotic drugs can induce seizures by a neurotoxic effect, and high doses and rapid dose increase should be used with caution [27]. Moreover, antipsychotics have extrapyramidal adverse effects which may aggravate motor impairments. Frequent intermittent use of benzodiazepines might contribute to seizures by withdrawal effects [26]. Subjects with CLN3 disease may be particularly vulnerable to many of these adverse drug effects and interactions. These considerations need attention in the epileptological approach to CLN3 disease.

4.5. Limitations and strengths

The lack of available results from molecular CLN3 genetic testing in some of these patients is a limitation to this study. However, typical symptoms, onset age, and course, along with characteristic lipopigment inclusions in lymphocytes and other extracerebral tissue were considered diagnostic in all patients. Nevertheless, this patient sample was too small for a meaningful geno-phenotype correlation.

The study was originally designed to be nationwide, but less than half of the invited member families of the Norwegian CLN3 disease association participated in the questionnaire study. Conceivably, the responder rate was low in families with children below the age of seizure onset, and when affected individuals had already passed away. Moreover, as pointed out by board members of the association, weariness and frustration were prevalent among the parents because of the facing of the progressive disorder and repeated requirements for filling in questionnaires and applications to meet the increasing demands of health, social, and educational services for their children. However, all known subjects with CLN3 disease in the Central Norway health region served by St. Olav University Hospital were included in the study.

The hypothesis of paroxysmal sympathetic hyperactivity in CLN3 disease was brought to our attention during the very end of the study [11]. The review of medical records supported the notion that this phenomenon occurs in CLN3 disease, but was obviously only based on anecdotes [11].

A strength of the study was the large number of EEG recordings available for objective rescoring by the novel standardized terminology according to the SCORE method for EEG assessment [13]. In contrast, retrospective seizure classification based on medical records and parental reporting was challenging. Multiple seizure types of partly

ambiguous and subtle character occurring in the later stages of the disorder were sometimes difficult to differentiate from other paroxysmal and episodic events occurring in these multimorbid individuals. Moreover, it is a fact that the distinction between clonic and myoclonic seizures sometimes may be somewhat arbitrary. In this study, clonic implied sustained, rhythmic stereotypical jerks, whereas myoclonic was less regularly spaced and occurring in briefer runs, according to the Instruction Manual for the ILAE operational classification of seizure types [12]. Unfortunately, ictal video-EEG recordings were scarce.

5. Conclusion

Seizure and EEG characteristics change with time in CLN3 disease. At epilepsy onset, bilateral TC seizures are common, whereas multifocal motor seizures increase with age. In contrast, focal epileptiform abnormalities are more common in childhood, compared to later multifocal and bilateral discharges.

According to the multilevel framework of the current ILAE epilepsy classification [18], the seizure disorder of CLN3 disease can be classified as *combined generalized and focal epilepsies* with multiple seizure types, with both genetic and metabolic etiologies, and associated with a progressive *developmental encephalopathy*. Uncommon occurrence of bilateral myoclonic seizures does not justify classification as a classic *progressive myoclonic epilepsy*; contrasting to some other types of neuronal ceroid lipofuscinoses. Care should be taken not to misdiagnose episodes of paroxysmal sympathetic hyperactivity as epileptic symptoms. When attacks with only behavior arrest occur, involvement of the cardiac conduction system should be considered.

The management of epilepsy in CLN3 disease represents a major challenge, as numerous other symptoms than the seizures require attention and intervention. The drug burden in these patients is often excessive; multiple adverse effects and interactions may have an impact on the seizure disorder. The pharmacological treatment in these subjects should be carefully tailored with all these obstacles in mind.

Conflicts of interest

The authors declare no conflicts of interest.

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