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Unverricht-Lundborg disease: Clinical course and seizure management based on the experience of polish centers

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A B S T R A C T

The purpose of this paper was to present our experience following the longterm treatment of 11 patients with Unverricht-Lundborg disease (ULD) confirmed by molecular testing.

Methods: We analyzed the clinical course, cognitive state, neuroimaging and neurophysiology results.

Results: The data were collected from 9 unrelated families (F/M: 4/7) aged 25-49. The most frequent early manifestations of ULD include generalized tonic-clonic seizures (GTCS) accompanied by myoclonus 2 years later. Myoclonus was observed in all of the patients; its severity made it impossible for 91% to move independently. In two patients- mild atrophy of brain were observed in the MRI. More than half of the patients who underwent evoked potential presented no abnormalities. The dominant EEG-change was slow background activity in all of the patients. Seven patients had generalized seizure activity. The patients received antiepileptic therapy modifications depending on the severity of symptoms and stage of the disease. Five patients received N-acetyl-cysteine.

Conclusions: ULD patients require anti-epileptic polytherapy, mostly benefitting from managing GTCS and myoclonus with valproic acid and clonazepam treatment. Patients may benefit from add-on therapy with levetiracetam or topiramate. An increase in myoclonus, resulting from the progressive nature of the disease leads to significant disability in the majority of patients.

1. Introduction

Unverricht—Lundborg disease (ULD) is a type of autosomal recessive progressive myoclonus epilepsy (PME). The molecular basis for ULD involves mutations in the gene encoding cystatin B, a cysteine protease inhibitor. The gene is located on chromosome 21 at q22.3 [1]. This mutation leads to the multiplication of the C4GC4GCG minisatellite sequence repeats. The normal range of repeats is 2—3, with a premutation range of 12—17, and a causative disease range of 30—80 repeats. However, the number of repeats does not correlate with the disease phenotype.

ULD shows quite a distinctive clinical picture, involving onset in childhood or early adolescence (< 15 years of age) with generalized tonic-clonic seizures (GTCS), with rapid development of myoclonus, which is further aggravated during the course of the disease [2]. Patients also present with progressive ataxia and low-to-moderate cognitive disorders. The various symptoms can fluctuate during the day, and typically increase in the morning and evening. Patients require antiepileptic polytherapy, which generally provides good management of the tonic-clonic seizures and, to a lesser extent, of the myoclonus; this is the most burdensome symptom, and can lead to significant disability.

In the present study, we report our experience following a long-term observation and treatment of 11 patients with ULD confirmed by molecular testing. We also present the results of the neurophysiological and imaging testing as well as the screening of the cognitive impairment of these patients, and the efficacy of chronic antiepileptic therapy.

2. Methods

In the period between 2005 and 2018, data from 11 patients were collected from nine unrelated families (four women, seven men) who were 25—49 years old (mean age: 38.27 years). The patients were diagnosed with ULD based on clinical observation and testing results. All patients had ULD confirmed by molecular diagnostics involving detection of a homozygous expansion of dodecamer repeat mutations in the cysteine protease inhibitor gene. Genetic testing was performed at The Institute of Psychiatry and Neurology (10 patients) and GENOMED (1) in Warsaw. The remaining data were collected from causal diagnostic procedures at the three neurology centres to which the authors of this study are affiliated. Currently, the patients remain under prospective observation and therapy in the various centres.

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Table 1
Demographical and clinical characteristic of Unverricht—Lundborg disease (ULD) patients.

Patient number	Age in 2018 / sex	Onset (age) / symptoms	Current myoclonus intensification	TCS frequency (last 5 years)	Assistive ambulation devices	Family history	Therapy (daily dose; mg) during last evaluation	Other previous therapies
1	43 / F	7 / GTCS	+ + +	0	Wheel-chair	Negative	CLZ 12 VPA 2500 PRM 750 NTZ 20	NAC TPM PIR
2	43 / M	9 / GTCS	+ + +	0	Wheeled walker	Negative	LEV 1500 CLZ 4 PRM 125 VPA 1300	NAC PIR
3	49 / M	13 / GTCS	+ + +	0	Wheel-chair	Negative	LEV 1500 PRM 750 VPA 900	NAC CLZ
4	42 / M	12 / GTCS	+ + +	0	Wheel-chair	Unknown	CLZ 27 VPA 900 NTZ 15 PRM 750 LEV 1500	NAC PIR
5	31 / M	12 / GTCS	+ + +	0	Caregiver's help	Negative	VPA 2500 LEV 3000 TPM 600 CLB 6 CLZ 20 PIR 3600	CBZ PGB
6	26 / M	8 / GTCS	+ +	5 / years	Independent	Sister with ULD (patient 7), ULD in cousin and uncle-carrier (family genogram in Fig. 1)	LEV 2000 CLZ 4 VPA 1500	Unknown
7	34 / F	5 / GTCS	+ + +	0	Wheel-chair	Brother with ULD (patient 6)	LEV 1500 CLZ 4 VPA 1,000	CBZ TPM PGB PIR
8	25 / M	9 / GTCS	+ +	10 / years	Wheel-chair	Negative	VPA 2500 CLZ 14 LEV 3000 TPM 350 FLB 1200	OXC PRM GBP ENC PHT
9	39 / F	8 / GTCS, M[a]	+ +	8 / years	Wheeled walker	Sister with ULD (patient 10)	VPA 2000 LEV 1000 LTG 300 CLZ 1 DZP 7	LCS CBZ
10	48 / F	11 / GTCS	+ + + +		Bedridden	Sister with ULD (patient 9)	VPA 1000 CLZ 15 PIR 12,000 CBZ 600	Unknown
11	Died at 41 years (2010)	10 / GTCS, M[a]	+ + + +	0 / last 5 years of life	Bedridden	Patient's brother died at 39, bedridden, TCS, massive myoclonus	CLZ 12 VPA 1500 PRM 750 NTZ 20	NAC PIR

Degrees of myoclonus severity: from + to + + + + (+: single myoclonus during the day, not affecting function, triggered by movement; + +: bilateral myoclonus, occurring with emotions/movement but not disturbing gait, unrelated to the risk of injury; + + + +: myoclonus affecting function (e.g., preventing from sitting in stable upright position); + + +: between + + and + + + +.
ULD: Unverricht—Lundborg disease; GTCS: generalized tonic-clonic seizures; M: myoclonus; CLZ: clonazepam; VPA: valproic acid; PRM: primidone; NTZ: nitrazepam; NAC: N-acetyl-cysteine; TPM: topiramate; PIR: piracetam; LEV: levetiracetam; CBZ: carbamazepine; CBZ: clobazam; FLB: felbamat; DZB: diazepam; OXC: oxcarbazepine; GBP: gabapentin; ENC: encorton; PGB: pregabalin; PHT: phenytoin; LCS: lacosamide.
[a] Myoclonus within 1 year from disease onset.

3. Results

3.1. Disease onset and clinical course

The onset of a progressive neurological syndrome occurred between 5—12 years of age (mean: 9.45 years). No significant antecedent factors for epilepsy were identified, and the mental state of all patents was reported as normal prior to disease onset. The most frequent early manifestations of ULD include generalized tonic-clonic seizures accompanied by myoclonus 2 years later. Four patients were initially diagnosed with juvenile myoclonic epilepsy. A further clinical course for each patient, as well as symptomatology of epileptic seizures and results of electroencephalography (EEG) monitoring, suggested progressive myoclonus epilepsy. In the last 5 years of follow-up, the majority of patients (63.63%) were free of GTCS. Myoclonus was observed in all patients, the severity of which made it impossible for 10 patients (90.90%) to move independently.

There was a family history of ULD in four patients, and probable history in one patient (not confirmed by genetic testing). Our patients included two pairs of siblings (patient numbers 6 and 7, and 9 and 10). One patient had an ancestor from Finland, which may be important in the context of the geographical distribution of ULD. The demographic and clinical data are listed in Table 1. We also collected genealogical data from a pair of siblings (patient numbers 6 and 7) that allowed us to create a genogram of the family members burdened with ULD (i.e., the patients and carriers; Fig. 1). The clinical details were unknown from one family member with confirmed ULD (the cousin of one of our patients). One of the patients, who suffered from the disease for 31 years, died of pneumonia at 41 years old.

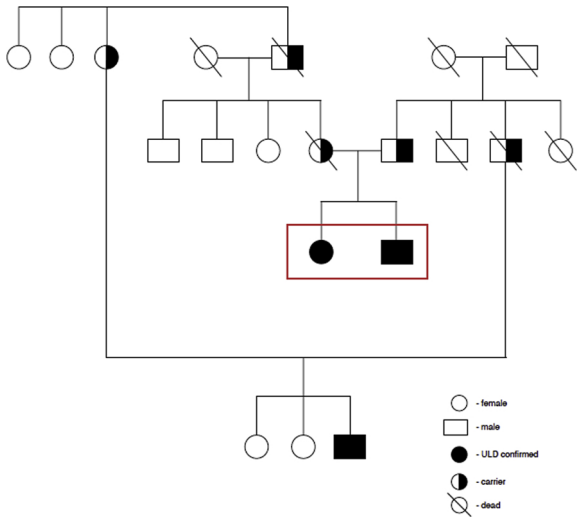

Fig. 1. The family genogram of patients 6 and 7 (boxed).

3.2. Brain magnetic resonance imaging (final evaluation)

Magnetic resonance imaging was available for all living patients between 25—48 years old, while in the deceased patient it was performed in their final year of life (at 41 years old). No brain pathology was observed in nine patients, while two patients (42 and 43 years old) showed mild cortical and cortico-subcortical atrophy.

3.3. Neurophysiology results

Of the nine patients who received evoked potential (EP) tests (visual EP, somatosensory EP [SEP], and brainstem auditory EP), five presented no abnormalities, while the remaining three showed high amplitude SEPs and visual EPs (Fig. 2).

EEG data were available for all 11 patients. The tests were performed repeatedly, and an abnormal result was obtained in each case. EEGs were recorded using surface electrodes placed on the scalp according to the international 10–20 system. Background activity was moderately or mildly slow in all patients. Background slowing was more pronounced in two patients receiving carbamazepine but was improved after treatment was switched to valproate. Generalized spike or polyspike and wave discharges were present in all patients. Three

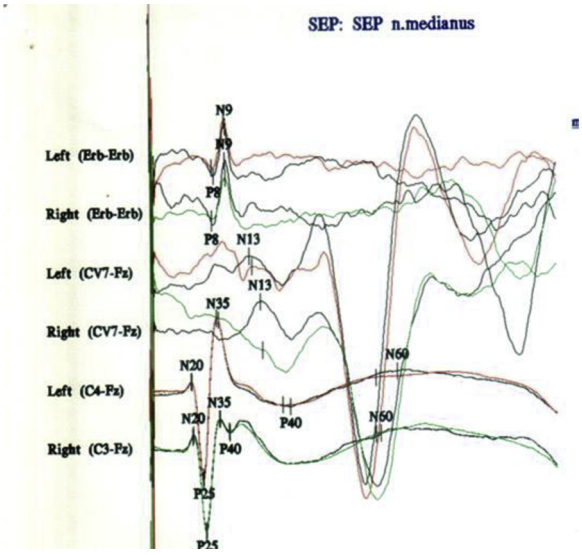

Fig. 2. The somatosensory evoked potentials. Note the high amplitude (45 μV).

Table 2
Neurophysiological results and cognitive state examination.

Patient number	Age in 2018 / sex	EEG	EP	MRI	MMSE	
1	43 / F	Slow background activity, generalized seizure activity spike-wave 5—7 Hz	High amplitude of SEP	Mild cortical atrophy	24 points	
2	43 / M	Slow background activity	High amplitude of SEP	Normal	29 points	
3	49 / M	Slow background activity	Normal	Normal	26 points	
4	42 / M	Slow background activity, generalized seizure activity	Normal	Mild cortico-subcortical atrophy	25 points	
5	31 / M	Slow background activity, generalized seizure activity, spike-wave 5—8 Hz	Normal	Normal	Mild mental retardation and further cognitive decline; 22 points / MMSE	
6	26 / M	Slow background activity, generalized seizure activity, spike-wave 6—8 Hz	Normal	Normal	25 points	
7	34 / F	Slow background activity, generalized seizure activity, spike-wave 6—8 Hz	Normal	Normal	24 points	
8	25 / M	Slow background activity, generalized seizure activity, spike-wave 5—8 Hz	Unknown	Normal	25 points	
9	39 / F	Slow background activity, multiple delta waves in all leads	Unknown	Normal	24 points	
10	48 / F	Slow background activity, spike-wave 5—7 Hz	Unknown	Normal	23 points	
11	Patient died at age 41 (2010)	Slow background activity, generalized seizure activity present	High amplitude of VEP and SEP	Normal	22 points	

F: female; M: male, EEG: electroencephalography; EP: evoked potential; VEP: visual EP; SEP: somatosensory EP; MRI: magnetic resonance imaging; MMSE: Mini Mental State Examination.

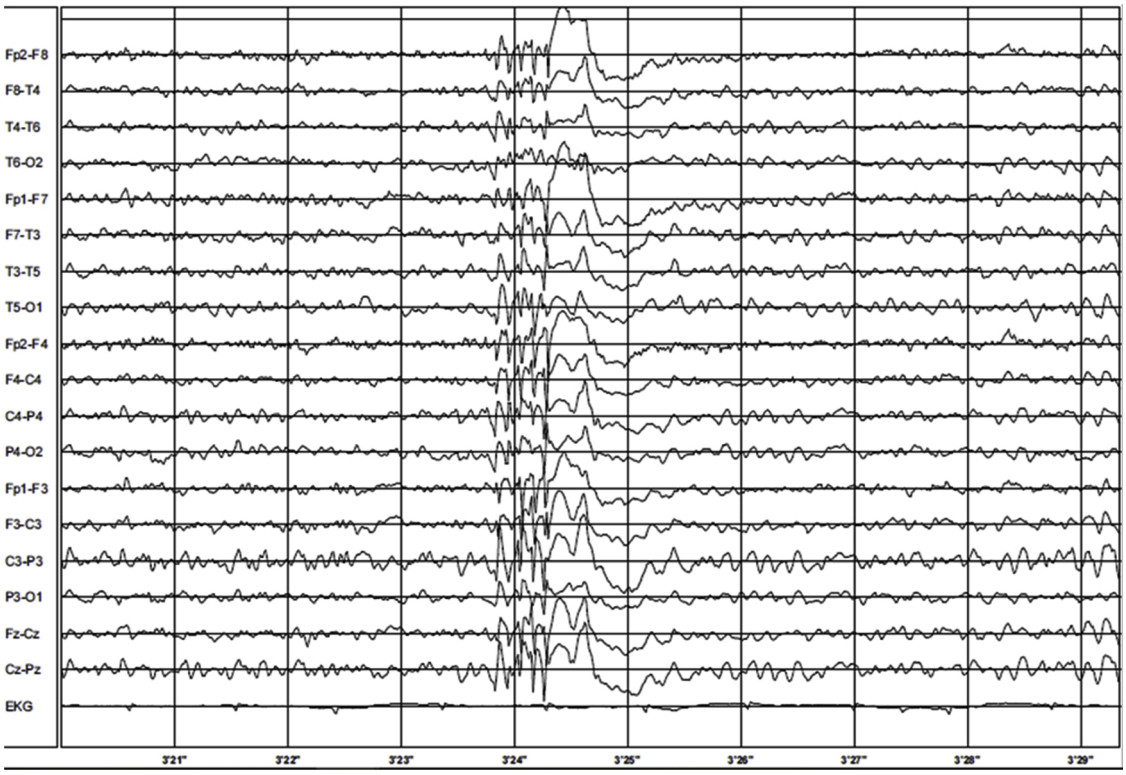

Fig. 3. Electroencephalogram showing a slightly slowed background activity with generalized spike-wave discharges.

patients also showed focal spikes or sharp waves. Photosensitivity was found in two patients. Myoclonic jerks were recorded in all subjects, although most of the jerks were not time-locked to EEG discharges. Beta activity excess was seen in patients receiving clonazepam (CLZ).

The results of neurophysiological testing and cognitive state examination are shown in Table 2, while selected findings from the neurophysiological tests are shown in Fig. 2 (SEP) and Fig. 3 (EEG).

3.4. The screening for the cognitive impairment

The Mini Mental State Examination (performed in 2018 for all patients except no. 11 [performed in 2010]) revealed mild cognitive impairment in the majority of patients (91%).

3.5. Therapy

During the course of the disease, the therapy was modified according to exacerbation of symptoms and/or disease phase. At final evaluation, patients were on 3—5 antiepileptic drugs. Systematic evaluation of efficacy was not possible, although we observed that valproate was the most effective drug for treatment of tonic-clonic seizures and myoclonus. The clinical effect was evaluated retrospectively according to the ambulatory and hospital data describing significant improvement, little improvement, no improvement, or exacerbation. Valproic acid (VPA) and CLZ were used in all of the patients, while the majority (eight patients, 72.72%) also received levetiracetam (LEV). VPA was used (presently or previously) in daily doses of 900—4000 mg (most patients received a dose $\geq$1.5 mg). Half of the patients using CLZ required a daily dose > 10 mg (maximum 27 mg). LEV was typically administered at a minimum dose of 1.5 mg (maximum 3.0 mg). Most patients (63.63%) used piracetam (PIR) to reduce myoclonus (3.60—12.0 g daily). Four patients stopped PIR therapy because there was little benefit and side effects including tinnitus and headaches at a daily dose > 10.0 g. The other most commonly used drugs were primidone (daily dose 125—750 mg), nitrazepam (15—20 mg), and topiramate (TPM; 300—600 mg). In 2007, five patients were given n-acetyl-cysteine (NAC) in daily doses of 600—2400 mg for 12 months, with three patients experiencing a successful, yet transient, effect on management of myoclonus. NAC therapy was discontinued because of no effect in two patients, exacerbation of myoclonus in one patient, and poor tolerability (oral mucositis) in two patients. During treatment, all patients showed an increase in total serum glutathione concentration (up to 6.57—7.53 μmol/l; 8.4 μmol/l increase [27%] relative to pre-therapy concentration). NAC therapy had no effect on neurophysiological testing. The most common other side effects resulting in withdrawal or reduction of drug doses included weight gain, mild somnolence, dizziness, and anxiety. Drug administration data are presented in Table 1.

4. Discussion

PME is a distinctive epilepsy syndrome characterized by myoclonus, generalized tonic-clonic seizures, and progressive neurological deterioration. PME is caused by a number of genetic abnormalities, the majority of which are autosomal recessive conditions. The more frequent disorders include Unverricht—Lundborg disease, Lafora disease, and neuronal ceroid lipofuscinosis [3]. As PME is rare and its onset is generally non-specific, diagnosis may be delayed. Further, because of the age of first symptoms of PME and the type of seizures, it can be misdiagnosed as juvenile myoclonic epilepsy. Nevertheless, careful observation and correct interpretation of comorbid symptoms provides correct diagnosis in 70%—90% of PME patients [3–5].

ULD is geographically concentrated in Finland and around the Mediterranean region. To the best of our knowledge, ULD has only been genetically confirmed in 16 patients in Poland, 11 of whom are described in the present study. ULD typically occurs before 15 years of age, with tonic-clonic epileptic seizures rapidly accompanied by myoclonus and ataxia. The progressive nature of ULD manifests in a consistent increase in myoclonus, with relative stabilization of GTCS. Generalized TCS are infrequent in treated adult ULD patients. Apart from myoclonus and ataxia, there are no other consistent neurological features of ULD. A proper differentiation between ataxia, intention

tremor, and myoclonus is difficult at an advanced stage of the disease. Our observations indicate a beneficial trend related to management of GTCS with an increased frequency and intensity of myoclonus. The increasing intensity of myoclonus is provoked by patients' movements and emotions, and by various external stimuli (e.g., physical factors and sounds). Myoclonus is now the main cause of disability in ULD patients, followed by ataxia. Indeed, the majority of patients in the present study (91%) required help with mobility and basic daily activities. Myoclonus increases over the course of disease, as previously reported [6].

In the present study, cognitive impairment was difficult to evaluate in patients with severe myoclonus, which is also influenced by the effects of long-term antiepileptic therapy and limited education because of disability. Nevertheless, patients appeared to show a slow cognitive decline following disease onset. The treatment of our patients was also challenging. Valproate, CLZ, and LEV appeared to be the most effective drugs, as previously reported [1,7–9]. TPM is also recommended as an add-on therapy to VPA and CLZ [10], although its efficacy was reported to decrease over longer periods of treatment, and withdrawal was associated with a rapid deterioration in condition in one case [7]. Half of our patients received TPM at various stages of their disease. We avoided lamotrigine therapy in our patients because of the potential for myoclonus exacerbation [11]. Other medications such as phenytoin, carbamazepine, oxcarbazepine, pregabalin, and gabapentin may also worsen myoclonus management [7]. Moreover, there is some evidence that these drugs may increase ataxia in ULD patients [12,13]. We did not have the opportunity to evaluate the efficacy of zonisamide or perampanel in the present study, which were reported to be beneficial for ULD patients [14,15].

GTCS in our patients were generally well controlled, although the effects of drug treatment on myoclonus action was modest. The myoclonus action was prominent in our patients, and correlated with myoclonic bursts in EEG, while spontaneous myoclonic jerks associated with polyspike and wave paroxysms in EEG were rare. According to the latest hypothesis, myoclonus action is provoked by an exaggeration in the physiological cortical drive to the muscles that control voluntary contractions in healthy subjects. A loss of intra-cortical inhibition resulting in motor cortex hyperexcitability is also postulated to underlie the susceptibility to generate rhythmic myoclonic activity in PME. Giant SEPs provide additional evidence of cortical hyperexcitability. Myoclonus in ULD may also be, at least in part, of subcortical origin, which may explain why antiepileptic drugs show reduced efficacy in such patients [16]. Apart from AEDs, high doses of PIR are also recommended for treatment of myoclonus, as demonstrated in an initial controlled study [17]. PIR was used in seven of our patients at various stages of the disease, and two patients are currently receiving PIR treatment.

Finally, there is evidence of a potential role of oxidative stress resulting from decreased intracellular glutathione levels in ULD patients. However, although we used NAC in several patients, they did not achieve permanent improvement with the safe NAC dose range. Nevertheless, because of the anti-oxidative stress action of NAC, its use in ULD patients may stabilize symptoms and decrease disease progression, although there are contrasting findings [18].

5. Conclusion

ULD patients require antiepileptic polytherapy, with the majority benefitting from managing GTCS and myoclonus with VPA and CLZ treatment. Patients may also benefit from add-on therapy with LEV or TPM. An increase in myoclonus, resulting from the progressive nature of the disease and moderate efficacy of medications, leads to significant disability in the majority of ULD patients. With regards to polytherapy in ULD, caution should be taken to avoid long-term adverse effects over a relatively short-term benefit. Our experience suggests that such detrimental effects are possible with the use of high doses of PIR and NAC. Future studies in a larger group of Polish patients with a genetically confirmed disease are required to further refine the optimal treatments for this rare disease in our population.

Conflicting interests

The all authors declare, that there is no conflict of interest.

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Ethical approval for this study

Not applicable.

Guarantor

Anetta Lasek-Bal, ALB, MD, PhD, Ass. Prof.

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