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# Seizure control in Unverricht-Lundborg disease: a single-centre study

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**ABSTRACT** – New antiepileptic drug (AED) options for generalised seizure types have been adopted for use as treatment for Unverricht-Lundborg disease. Whether this has led to improved seizure control or functional outcome in ULD patients remains obscure. We retrospectively identified all patients seen at Helsinki University Hospital due to Unverricht-Lundborg disease during 2003-2008 in order to determine which AED treatments had been retained for long-term use. The majority of the patients had severe functional disabilities. In the year preceding the last hospital visit, all patients (*n*=20) were receiving polytherapy and 14 patients had been free of tonic-clonic seizures. During follow-up, improvement in myoclonia had been recorded for the majority of patients with either add-on piracetam, topiramate, or levetiracetam, but valproate was still in use by all patients. Treatment with lamotrigine had been started and retained less often relative to other AEDs. Add-on AED treatment was often associated with significant adverse effects. Unverricht-Lundborg disease patients may benefit from add-on treatment with levetiracetam or topiramate for seizure control. Treatment of eventual comorbidities with other than AEDs is also discussed.

**Key words:** progressive myoclonic epilepsy, antiepileptic drug treatment, prognosis, adverse effect

Unverricht-Lundborg disease (ULD), a progressive myoclonic epilepsy, is an autosomal recessive disease caused by mutations in the cystatin B (CSTB) gene located on chromosome 21q22.3 (Shahwan *et al*., 2005). Onset of symptoms typically occurs at 6-15 years of age. Severity of progressive ataxia varies. Tonic-clonic seizures occur, but the main seizure type is multifocal myoclonic jerks, provoked by action and different external stimuli.

Phenytoin (PHT) may worsen myoclonus and precipitate cerebellar signs and atrophy. Introduction of therapy with sodium valproate (VPA) and clonazepam (CZP) is reported to improve both seizure control and coordination in ULD patients (Shahwan *et al*., 2005; Iivanainen *et al*., 1982). Other antiepileptic drugs (AEDs) that can be used for the treatment of generalised seizure types have been adopted for use in ULD patients.

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A positive response to piracetam (PIR) was found in a controlled study (Koskiniemi *et al*., 1998). Open case series suggest a benefit of topiramate (TPM) (Aykutlu *et al*., 2005), levetiracetam (LEV) (Magaudda *et al*., 2004; Crest *et al*., 2004), and zonisamide (ZON) (Kyllerman and Ben-Menachem, 1998; Vossler *et al*., 2008).

We retrospectively assessed medical records of ULD patients from Helsinki University Central Hospital (HUCH) in order to determine whether different add-on AED treatments led to improved seizure control and which AEDs had been adopted for long-term use. We also attempted to describe potential exacerbatory factors, such as comorbidities and use of other drugs.

## Methods

We retrospectively identified all ULD patients (*n*=23) attending HUCH during 2003-2008. HUCH serves as a tertiary epilepsy centre for a population of one million. In 2 patients, diagnosis had been confirmed by decreased cellular mRNA encoded by the gene cystatin B (*CSTB*). In all other patients, clinical diagnosis had been confirmed by detection of dodecamer repeat expansion mutations in the *CSTB* gene, in homozygous form. We excluded 3 patients with a clinical picture of late-stage, severe ULD lacking genetic confirmation.

Previous hospital records were collected from time of symptom onset and diagnosis, including data on brain imaging and EEG. Follow-up data included concomitant disease, medication, occurrence of tonic-clonic seizures, and change reported in myoclonia during treatment. Emergency room visits, living arrangements, and need of assistive devices were recorded for the last year of follow-up.

The study was considered observational and was approved by the HUCH institutional review board.

## Results

Patients' mean age at the end of follow-up (2005-2008) was 36 years (range: 18-58 years), with a mean age at symptom onset of 10 years (range: 7-16 years). The last hospital visit was in 2005 for 1 patient who moved to another hospital district, and 2007 for 5 patients taking part in a brivaracetam or ropinirole study in 2008. Demographic data along with functional state relative to age, sex, and use of AEDs are shown in *table 1*.

### Medication use and seizures

At the last visit recorded, all patients were receiving polytherapy (*table 1*). One patient was also administered vagus nerve stimulation. During the last year of follow-up, 14 patients had been free of tonic-clonic seizures. Of these 14 patients, 8 patients had been free of tonic-clonic seizures since initiating treatment with VPA and CZP. Add-on therapy with TPM or LEV coincided with cessation of tonic-clonic seizures in 3 patients.

Add-on AED treatment was mainly used with the aim to control myoclonia. Improvement in myoclonia leading to a described ease of movement or speech had been recorded for the majority of patients with add-on treatment (*table 2*). Treatment was discontinued in several patients due to different adverse effects, such as kidney dysfunction (PCT), rash or fear (LTG), depression or memory complaint (LEV), somnolence, speech impairment or depression (TPM). Adverse effects did not always lead to AED withdrawal. TPM was continued despite recognised adverse effects (aggression, depressive symptoms, and weight loss) due to significant worsening on withdrawal. In 3 patients, attempts had been made to replace VPA with other AEDs. All 3 patients were re-introduced to VPA, but the most successful replacement with a combination of LEV, TPM, and CZP lasted from 1999 to 2005.

### Causes of seizure exacerbation

Alcohol or other drug abuse was referred to as a reason for inadequate seizure control in 2 patients. In 1 patient, re-appearance of tonic-clonic seizures led to controlled brain imaging and discovery of a corpus callosum cavernoma. Seven pregnancies in 3 female patients were uneventful regarding seizures. Nine patients consistently reported exacerbation of myoclonia during menstrual period.

Treatment of concomitant disease with corticosteroids, thyroxine, lynestrenol, desorgerstel, propranolol, metoprolole, enalaprile, bezafibrate, or simvastatin was not associated with change in myoclonia during clinical follow-up.

In 2 patients with type II diabetes, treatment and normalisation of blood glucose values with insulin and metformin coincided with improved control of myoclonias.

Five of 9 patients with diagnosed depression had received antidepressants, including escitalopram, citalopram, venlafaxine, and fluoxetine, with no seizure exacerbation. One patient reported worsening with either mirtazapine or mianserine while tolerating high-dose (60 mg) citalopram.

### Emergency treatment

During the preceding year, emergency room treatment had been required for 1 patient due to repeat

**Table 1.** Functional staterelative to age, sex, and previous use of AEDs.

| Sex and age (years) in 2008 | AEDs, dose (mg) at end of follow-up | Previous use of PHT, CBZ or OXCBZ | Living arrangement | Assistive devices for ambulation |
|---|---|---|---|---|
| M (19) | VPA 1000, CLB 40, LEV 1000 | - | independently with parents | - |
| F (24) | VPA 1600, CZP 4.5 | - | alone; personal aid | - |
| F (26) | VPA 1200, CZP 3, TPM 50, LEV 3000 | - | sheltered housing | wheelchair |
| F (26) | VPA 3000, CLB 20, TPM 500, LEV 3000, PRM 375 | 3 months | sheltered housing | wheelchair |
| F (27) | VPA 2100, CZP 3, LEV 3500 | - | sheltered housing | wheeled walker |
| F (29) | VPA 1200, LEV 1000 | - | independently | - |
| F (31) | VPA 1500, CLB 30, TPM 200, LEV 3000 | 1 month | personal aid | wheelchair |
| F (33) | VPA 1800, CZP 1, LEV 1000, LTG 200 | 7 years | independently | - |
| F (34) | VPA 2000, CZP 3, TPM 175, LEV 3000 | 3 months | independently, with husband | - |
| M (35) | VPA 1200, CZP 1.5, LEV 2000 | 3 months | alone, aid from mother | wheeled walker |
| F (36) | VPA 600, CZP 4 | | with family, personal aid | walking stick |
| F (38) | VPA 1100, CZP 1.5, TPM 200, LEV 2000 | | sheltered housing | - |
| F (39) | VPA 200, CZP 3, TPM 150, LEV 3000 | - | sheltered housing, personal aid | wheeled walker |
| F (41) | VPA 1500, CZP 1.5, LEV 2000, LTG 50 | 1 month | independently, with 2 children | - |
| M (42) | VPA 1300, CZP 4, PIR 16800 | - | sheltered housing | wheeled walker |
| M (42) | VPA 1500, CZP 6, TPM 200, PIR 24000 | 2 years | sheltered housing | wheelchair |
| M (44) | VPA 1800, TPM 50, CZP 10 | 2 years | sheltered housing | wheelchair |
| F (50) | VPA 1600, CZP 5, LEV 3000, PB 100 | 3 years | nursing home | wheelchair |
| F (52) | VPA 3500, CZP 8, PIR 9600, PB 100 | 6 years | nursing home | wheelchair |
| M (58) | VPA 1000, CZP 4, TPM 100, LEV 2000 | 10 years | with help from wife | uses furniture for support |

CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; LEV: levetiracetam; LTG: lamotrigine; OXCBZ: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PIR: piracetam; PRM: primidone; TPM: topiramate; VPA: valproate.
None of the patients received tiagabine, vigabatrine, gabapentin, pregabaline, or zonisamide.

tonic-clonic seizures and for 5 patients due to prolonged myoclonias. Four patients had several emergency room visits. Contributing reasons included urinary infection in a diabetic patient, biliary attack, emotional stress due to change in living arrangements, and depression with poor medication compliance. One patient was investigated further during follow-up and all others received *i.v.* clonazepam, diazepam, or lorazepam. In addition, 2 patients were given *i.v.* VPA, and in 1 patient, long-term LEV treatment was started with a 1,000-mg *i.v.* loading dose.

## Discussion

Phenytoin, carbamazepine, oxcarbazepine, tiagabine, vigabatrine, pregabalin, and gabapentin are

**Table 2.** Number of patients receiving different add-on AED treatments.

| AED | PIR | TPM | LEV | LTG |
|---|---|---|---|---|
| Number of patients started on AED | 12 | 17 | 17 | 8 |
| Reported improvement in myoclonias | 8 | 13 | 10 | 2 |
| AED replaced by other drug | 4 | 0 | 0 | 0 |
| AED discontinued due to adverse effects | 2 | 4 | 3 | 2 |
| AED discontinued due to lack of effect or worsening | 3 | 4 | 0 | 4 |
| AED continued at end of follow-up | 3 | 9 | 14 | 2 |
| Use of AED <1 year | 3 | 8 | 3 | 4 |
| Use of AED >1 year or continuing | 9 | 9 | 14 | 4 |

LEV: levetiracetam; LTG: lamotrigine; PIR: piracetam; TPM: topiramate.

avoided for the treatment of ULD due to possible worsening of myoclonia. It has been suggested that when PHT and other potentially exacerbatory drugs are avoided, patients do not develop worsening ataxia (Magaudda *et al*., 2006; Santoshkumar *et al*., 2008). In our patient population, moderate-to-severe ataxia, with need of assistive devices for ambulation, was seen in the majority of patients, including several young patients with no history of exacerbatory drug treatment. Possibly, more benign forms of ULD had not been referred to HUCH, causing selection bias. However, our patient population was large enough to represent a single-centre catchment area.

Several factors may confound the interpretation of AED response in our study. No quantitative method for evaluation of severity of myoclonia could be retrospectively applied. Subjective changes in myoclonia can be modified by AED mood effects or attributed to positive expectations of both clinician and patient. In addition to lack of controls, systematic withdrawal of add-on treatment had not been carried out. VPA remained in use in all patients, but discontinuation had only been attempted in 3 patients. Obviously, the use of a previous AED combination affects the potential effectiveness of a newly introduced AED. Lastly, the choice of treatment schedule reflects local clinical practice and preconceptions.

Improvement of myoclonia by TPM, LEV, and PIR in ULD patients is supported by our case series. Tonic-clonic seizures may also be controlled by add-on treatment with TPM or LEV. LTG, which is reported to provide limited benefit with possible major worsening of myoclonias (Genton *et al*., 2006), was less often retained in use, relative to TPM or LEV. In addition, duration of use of TPM was less than a year for nearly half of the patients receiving the AED. TPM, in continued use, was often interpreted to become less effective, but withdrawal was often associated with at least temporary worsening. Replacement of PIR with LEV for ease of administration was usually successful, leading to a low retainment rate for PIR. None of the patients had used zonisamide, which was reimbursed by the Finnish Social Insurance Institution in 2008.

Exacerbation of somnolence and impairment of balance can occur when aiming to minimise myoclonic jerks by polytherapy. Long-term effects of different AEDs in the treatment of ULD are poorly understood. Although development of drug resistance is possible, disease progression may also overcome the effect of add-on AEDs. Differentiation of myoclonia from ataxia and intention tremor in severe forms of the disease is difficult. The origin of myoclonia in ULD may be partly subcortical, reducing the potential effectiveness of AED therapy (Korja *et al*., 2007).

Special efforts should be made to identify concomitant disease and other causes of worsening in ULD patients. Catamenial seizures may warrant a trial with hormonal treatment. According to our experience, several antidepressants may be safely used, although addition of any psychotropic medication in ULD patients requires careful follow-up. Antiepileptic and other drug treatment should not aim to replace other forms of support or help in coping with the disease.

## Conclusion

ULD patients may benefit from add-on treatment with piracetam, topiramate, or levetiracetam. Intravenous forms of LEV and VPA can be used for emergency treatment of ULD. With regards to AED polytherapy,

caution should be taken in order to avoid long-term adverse effects in exchange for a relatively short-term benefit. □

**Disclosures.**
Reina Roivainen received speakers' fees from UCB Pharma and was an advisory board member for Eisai Pharma. Tarja Puumala received travel grants from Eisai.

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