CASO CLÍNICO/CASE REPORT

Unverricht-Lundborg Disease: Tackling the Challenges of a Complex Clinical Picture

Doença de Unverricht-Lundborg: Enfrentando os Desafios de um Quadro Clínico Complexo

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DOI: https://doi.org/10.46531/sinapse/CC/220078/2023

Abstract

Unverricht-Lundborg disease (ULD), also called progressive myoclonic epilepsy type 1, is characterized by stimulus-induced myoclonus and seizures without major progressive cognitive deficit, usually presenting during late childhood and early adolescence. It is an autosomal recessive disease, and, so far, only pathogenic variants in the gene encoding cystatin B (*CSTB*) have been described. We report the case of a 9-year-old boy who presented with generalized tonic-clonic seizures and developed paroxysmal myoclonic events over several years. The patient was started on antiseizure medication, but disease progression resulted in several changes to the therapeutic scheme, with highly variable clinical responses. The genetic study detected the pathogenic variant c.67-1G>C p.(?) in heterozygosity in the *CSTB* gene, after having identified the typical dodecameric expansion in the other allele, confirming the diagnosis of ULD.

Resumo

A doença de Unverricht-Lundborg, também chamada de epilepsia mioclónica progressiva tipo 1, é caracterizada por mioclonias induzidas por estímulo e crises epiléticas sem défice cognitivo progressivo importante, geralmente apresentando-se no final da infância e início da adolescência. É uma doença de hereditariedade autossómica recessiva e, até ao momento, foram descritas variantes patogénicas causadoras da doença apenas no gene que codifica a cistatina B (*CSTB*). Descrevemos o caso de um menino de 9 anos que começou por apresentar crises tónico-clónicas generalizadas e desenvolveu eventos mioclónicos paroxísticos progressivamente, ao longo de vários anos. Foi submetido a tratamento com fármacos anti-crise epilética, mas a progressão da doença ao longo do tempo resultou em várias mudanças no esquema terapêutico, com respostas clínicas altamente variáveis. O estudo genético identificou a variante patogénica c.67-1G>C p.(?) em heterozigotia no gene *CSTB*, após se ter identificado a típica expansão dodecamérica no outro alelo, confirmando o diagnóstico de ULD.

Informações/Informations:
Caso Clínico, publicado em Sinapse, Volume 23, Número 4, outubro-dezembro 2023. Versão eletrónica em www.sinapse.pt;
Case Report, published in Sinapse, Volume 23, Number 4, October-December 2023. Electronic version in www.sinapse.pt

Keywords:
Child;
Unverricht-Lundborg Syndrome.

Palavras-chave:
Criança;
Síndrome Unverricht-Lundborg.

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Recebido / Received: *2022-12-02*
Aceite / Accepted: *2022-12-14*
Publicado / Published: *2024-01-22*

Introduction

Progressive myoclonic epilepsies (PME) are a rare group of syndromes characterized by epileptic myoclonus, typically action-induced, neurological regression, refractory epilepsy and a variety of other signs and symptoms depending on the specific syndrome.[1] Unverricht-Lundborg disease (ULD), or progressive myoclonic epilepsy type 1 (PME1, OMIM254800) is an autosomal recessively inherited disorder and represents the most common and least severe type of PME.[2] ULD is considered an underdiagnosed condition[3]; its reported prevalence varies, but seems to be highest in Finland (4:100 000).[4] This condition is caused mostly by biallelic dodecamer repeat expansions in the promoter region of the *CSTB* gene,[5] responsible for encoding cystatin B (CSTB), a cysteine protease inhibitor. This protein reduces the activity of cathepsins, which are involved in the degradation of proteins in the lysosomes.[6] ULD is characterized by onset at age 6–16 years, progressively incapacitating stimulus-sensitive myoclonus, generalized tonic-clonic seizures and only mild cognitive dysfunction. Patients may develop ataxia, intentional tremor, and dysarthria, usually years after the onset.[5-9]

Case Report

We present the case of a 9-year-old obese boy, the second child of nonconsanguineous parents. There was a family history of paternal epilepsy up to the age of 11, and a sister was also diagnosed with epilepsy at age 16.

He was observed at the Emergency Department (ED) due to the occurrence of abnormal movements during sleep with 4 months of evolution, very suggestive of corresponding to tonic-clonic seizures of unknown onset. Frequent jerks of the upper limbs were also described during the day, in addition to excessive sleepiness, which led to a high degree of school absenteeism. The neurological examination showed no focal deficits. At the ED, a complete blood count, biochemistry and thyroid function analyses were performed, all with normal results. An electroencephalogram (EEG) showed a posterior dominant rhythm (7 Hz), with epileptiform interictal activity observed (sharp- and sharp-and-slow-waves), sensitized by sleep and a brain magnetic resonance imaging (MRI) was also requested, which turned out to be normal. The patient was hospitalized for a more accurate evaluation, but no suspicious episodes were identified. Nevertheless, due to frequent periods of sleep apnea registered during his stay in the ward, he underwent a nocturnal sleep record, which revealed a diagnosis of obstructive sleep apnea (it did not include a complete EEG montage and did not show the presence of epileptiform activity). Treatment with continuous positive airway pressure (CPAP) was started, with reported gradual clinical improvement. Considering the phenomenology initially described the use of antiseizure medication (ASM) was discussed with parents, and, given the recent diagnosis of obstructive apnea and the improvement being documented under non-invasive ventilation, it was decided to postpone the introduction of any drug.

He was discharged and was referenced for Neuropediatrics, Otorhinolaryngology and Pneumology appointments. Adenotonsillectomy was performed 3 months later, and at his first Neuropediatrics consultation, no reference to other paroxysmal events was made.

Nine months later, the patient started complaining of paroxysmal events characterized by decreased motor activity and subsequent somnolence, up to 2–3 times a week. The EEG was repeated, revealing scarce epileptiform activity (spike-and-slow-wave type) of bifrontal predominance and allowing the identification of an episode of bizarre motor semiology not compatible with an epileptic seizure. It was repeated shortly after, identifying the same epileptiform activity, again with frontal predominance, in relation to the record of myoclonic jerk-like movements (**Fig. 1**). Additionally, a generalized

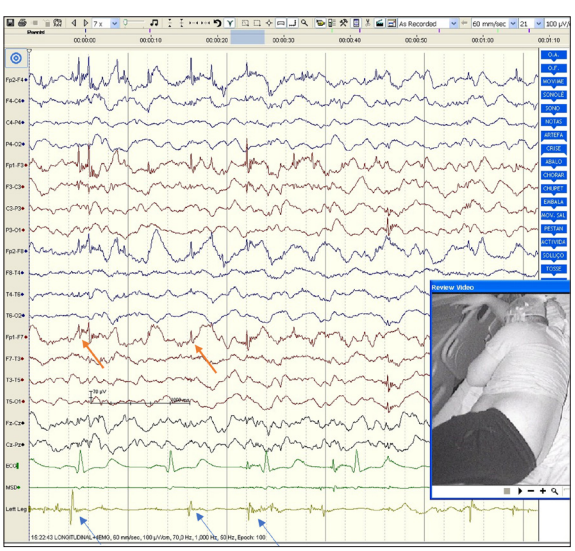

Figure 1. Epileptiform activity observed in the left frontal region (orange arrows) going along with myoclonic jerk-like movements recorded on the electromyography electrode placed on the left lower limb (blue arrows). The electroencephalographic setting follows the International 10-20 System.

tremor was clinically perceptible, as corroborated by the record made by the electromyography (EMG) electrode placed on the left lower limb (**Fig. 2**). An evident

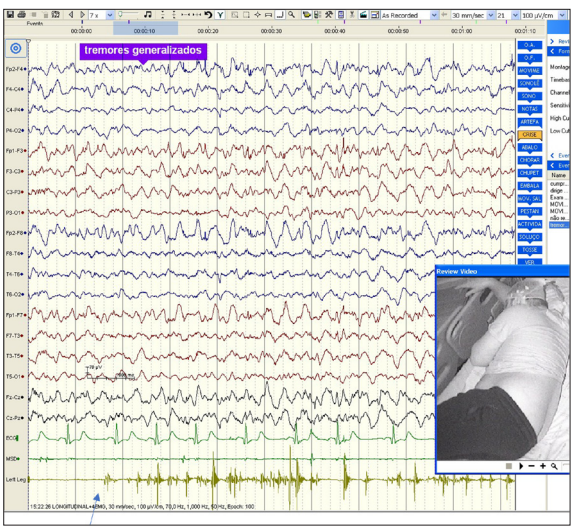

Figure 2. The patient had a generalized tremor, easily identifiable and corroborated by the recording of the EMG electrode placed on the left lower limb (starting with the blue arrow at the bottom). The electroencephalographic setting follows the International 10-20 System.

photoparoxysmal response was also observed (**Fig. 3**). In this context, levetiracetam (LEV) at 20 mg/kg/day was started, resulting in a decrease in the frequency of those events. Genetics consultation was requested, which the patient and the family repeatedly missed.

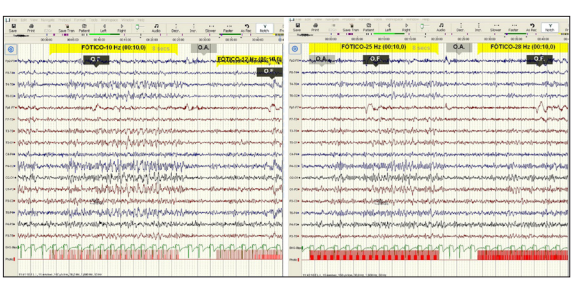

Figure 3. Photoparoxysmal response to different stimulation frequencies. The electroencephalographic setting follows the International 10-20 System.

After two years on LEV, an increase in the frequency of generalized tonic-clonic seizures was mentioned by his parents. Given that the sister had a history of epilepsy with an excellent therapeutic response to lamotrigine (LMT), it was decided to associate this drug, starting at 1 mg/kg/day and later adjusted to 2 mg/kg/day.

At 12 years of age, the patient reported complaints compatible with myoclonic jerks and started therapy with zonisamide (ZNS) at a target dose of 2 mg/kg/day, with significant improvement. At the age of 13, he developed high-intensity episodes of myoclonus that did not allow him to hold objects. LEV was replaced by sodium valproate (VPA), while LMT and ZNS were weaned off, and clobazam (CLB) was started with an overall clinical improvement. In the following two years, the patient and his family did not come to the Hospital, a situation naturally complicated by the COVID-19 pandemic period. Thereafter, there were repeated absences from several appointments, and only after completing 15 years of age was the patient re-observed.

At this time, he was medicated with the combination of LEV and CLB, with the occurrence of sporadic myoclonic jerks described by the family. Due to the loss of autonomy for activities of daily living, hospitalization was proposed. The video-EEG revealed a mild diffuse brain alteration with bifrontal or generalized interictal epileptiform activity (**Fig. 4**); generalized myoclonic seizures

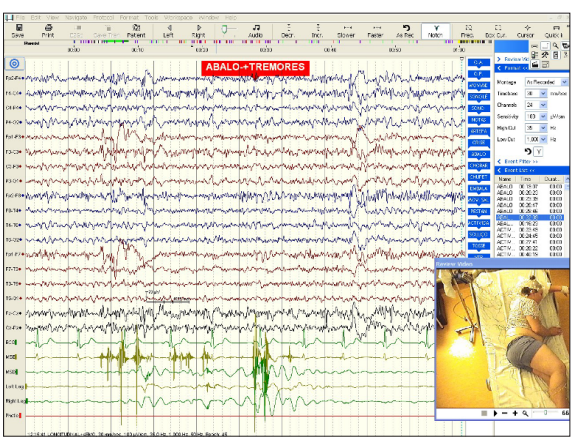

Figure 4. Generalized interictal epileptiform activity, with bifrontal predominance. Generalized myoclonic seizures were also recorded. The electroencephalographic setting follows the International 10-20 System.

were recorded, as well as appendicular and axial myoclonus without electroencephalographic translation. The MRI was then repeated, and the comparison with the previous examination showed a slight global increase in the volume of the cerebral and cerebellar cortical sulci, compatible with mild diffuse cortical atrophy. The cerebrospinal fluid examination was unremarkable, and, in view of the suspicion of progressive myoclonic epilepsy, the collaboration of Medical Genetics was requested. The hospitalization was used to carry out a formal cognitive assessment, and the main results in the Wechsler Intelligence Scale for Children – III Edition (WISC-III) were as follows: verbal intelligence quotient (IQ) of 73

(inferior); achievement IQ of 87 (lower middle); and full-scale IQ 77 (inferior). Perampanel (PER) 2 mg/day was added to the therapy, and clinical improvement was reported. By this time, the most significant findings in the neurological examination were a wide-based gait with significant scandic dysarthria, associated with exuberant stimulus-sensitive negative myoclonus.

The genetic study then requested allowed the detection of the dodecamer repeat expansion in the promoter region of the *CSTB* gene on one of the alleles. Since the diagnostic suspicion was ULD, the laboratory moved on to the full sequencing of the other allele, and a second pathogenic variant c.67-1G>C p. (?) in compound heterozygosity was detected. The parents were studied, and it was possible to confirm that the patient had the genetic variants in trans (each of the parents carried an allele with a pathogenic variant). These results made it possible to establish the diagnosis of ULD.

Discussion

Progressive myoclonic epilepsies are categorized genetically and phenotypically into five major diseases: ULD (or Baltic myoclonus), dentatorubropallidoluysian atrophy (DRPLA), Lafora disease, neuronal ceroid lipofuscinoses and sialidosis. ULD, although often debilitating, could be the clinically mildest PME, in part because the cognitive impairment is rarely severe and may be absent.[4,5,7,8] Generalized tonic-clonic seizures are usually grounds for an initial referral. They occur typically at awakening, just like with our patient, or during sleep.[9-11] While disease-specific therapy using genetic treatment, enzyme replacement or substrate reduction will be the future of these disorders, most children with ULD are managed symptomatically with ASM.[12] It is worth mentioning that our patient presents another variable on which it is possible to act in the sense of reducing the probability of the occurrence of epileptic seizures: obstructive sleep apnea. In a retrospective study by Segal *et al*, 37% of the children included became seizure-free three months after surgery (adenotonsillectomy, as in our patient) for their sleep apnea, and 11% demonstrated more than 50% seizure reduction.[13]

ASM and piracetam alleviate the burden of seizures and myoclonus throughout the course of the disease. Unfortunately, this effect is partial in some cases, as drugs do not influence the natural course of the condition. Patients will usually receive an ASM after the first generalized tonic-clonic seizures, typically VPA. Mainly by increasing brain levels of gamma-aminobutyric acid (GABA), it is normally effective in suppressing for some time most of those seizures, photosensitivity, and some of the myoclonus.[12] LEV, which binds to the SV2A glycoprotein, reducing the activity of presynaptic calcium channels and, therefore, the availability of neurotransmitters in the synapse, seems to be effective for both myoclonus and generalized onset seizures and is increasingly used in adolescents with ULD, considering its adverse effect profile. Phenobarbital (PB) and primidone are effective by reducing the excitability of postsynaptic neurons, but produce cognitive side effects. Other useful drugs include topiramate (TPM) and ZNS, both with a significant effect on myoclonus control (they modulate the activity of voltage-sensitive ion channels, particularly sodium and calcium channels). Additional relief can be obtained with benzodiazepines (BZD), which, like barbiturates, increase GABAergic tone in postsynaptic neurons. The latter (usually clobazam, clonazepam, or diazepam) should be used with caution because of their marked initial effect followed by rapid tolerance.[12] PER, a noncompetitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-glutamate receptor antagonist, represents a valid antiseizure and symptomatic therapy, widening the restricted armamentarium available for progressive myoclonic epilepsies.[14]

For established ULD, ASM treatment leads to polytherapy with a combination of several of the drugs above, as we had to do in our case, even before the diagnosis was made. The most commonly used combinations are VPA+LEV or TPM or ZNS, with an additional BZD (a three-to-five drug combination is quite usual). One can switch between different BZDs in the event of tolerance.[15] There is no evidence that sodium channel blockers like carbamazepine (CBZ), oxcarbazepine (OXC), phenytoin, eslicarbazepine, gabapentin, pregabalin, vigabatrin or lacosamide are of any benefit. Often, withdrawal from one of these ASMs (especially CBZ or OXC) will bring some relief.[15] Using N-acetylcysteine in the treatment of ULD is also described in the literature, and the increase in serum levels of glutathione seems to be the mechanism by which the drug may promote clinical benefit.[16] Even so, these results do not seem to be consistent with the heterogeneity of responses coming from animal models of epilepsy.[17] For our patient, this was not tested.

In practice, some patients will evolve reasonably well with a limited drug regimen, while others will remain severely disabled. In such patients, vagal nerve stimulation has been tried with success in some individuals,[18] but the benefit is limited; deep brain stimulation has also been used in PME cases; combined subthalamic and thalamic high-frequency stimulation has brought some relief.[12,18,19]

Regarding the prognosis, the long-term evolution is characterized by limited progression after the first five to ten years[19,20]; the outcome in adults ranges from independent, active life with minimal impairment to wheelchair-bound and severe disability. Early death has a low incidence and may be due to suicide or accidents.[19]

Although nowadays ULD can be treated effectively (albeit only symptomatically), which has led to reduced severity, patients may experience significant disability. A precise molecular diagnostic technique is available, but it is necessary to consider that the most typical alteration (homozygosity for the dodecamer repeat expansion in the promoter region of the *CSTB* gene) attributable to the disease is not always found, since most Next Generation Sequencing panels in use do not assess the presence of nucleotide expansions. Indeed, in our case, it was the clinical orientation (and here the importance of a careful clinical evaluation is reinforced) that supported the need for sequencing the second allele, since the typical dodecameric expansion had only been identified in one of them. With the identification of the second variant, it was then possible to make the diagnosis, since ULD is a disease of autosomal recessive inheritance.

Major progress can be expected in the near future, as elucidation of the mechanisms causing seizures, myoclonus, and associated symptoms are likely to bring about pathogenetically oriented treatment for ULD.[20] Nevertheless, careful clinical assessment of patients, regular follow-up, documenting any phenotypic changes, improving semiology and treatment continue to be fundamental in practice. Despite the advances that molecular genetics can bring, navigating between different laboratory techniques will be much more fruitful and useful for the patient if there is clinical-based thinking, as it could not be otherwise. ■

Contributorship Statement / Declaração de Contribuição
MFS: Manuscript elaboration
ML and CR: Manuscript review and approval
FP: Manuscript elaboration, critical review and final approval.

Responsabilidades Éticas
Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures
Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

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