■ Clinical commentary

Epileptic Disord 2022; 24 (1): 163-170

Epileptic Disorders

Major intra-familial variability in Unverricht-Lundborg disease

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Received October 13, 2020;
Accepted July 30, 2021

ABSTRACT

Unverricht-Lundborg disease (ULD), also called progressive myoclonic epilepsy type 1, is usually characterized by the presence of ataxia associated with myoclonus and epileptic seizures without progressive cognitive deficit, presenting during late childhood and early adolescence. Currently, there is a growing body of evidence for atypical presentations of the disease with a milder phenotype or without the full symptomatology. We describe a case report of a late-onset phenotype with progressive myoclonus-ataxia syndrome accompanied by initial recurrent falls, resulting in specific phobia and agoraphobia starting at the age of 50 years old. The examination revealed multifocal myoclonus with cerebellar ataxia and electroencephalogram showed generalized polyspikes and spike-wave discharges. Electromyogram revealed positive myoclonus of 60-ms duration in the face and the presence of C reflex. A genetic study confirmed the diagnosis of ULD in the patient and other additional family members, presenting a wide range of intra-familial variability. We discuss the challenging differential diagnosis for such a misleading presentation and its possible underlying pathophysiological mechanisms. Our case report may contribute to broadening the age and clinical boundaries for this disease and emphasizes the intra-familial age and symptom variability. Based on a suggestive family history, the diagnosis of ULD should be considered in this context, even in older patients.

Key words: Unverricht-Lundborg, psychiatric, phobia, late-onset, familial variability

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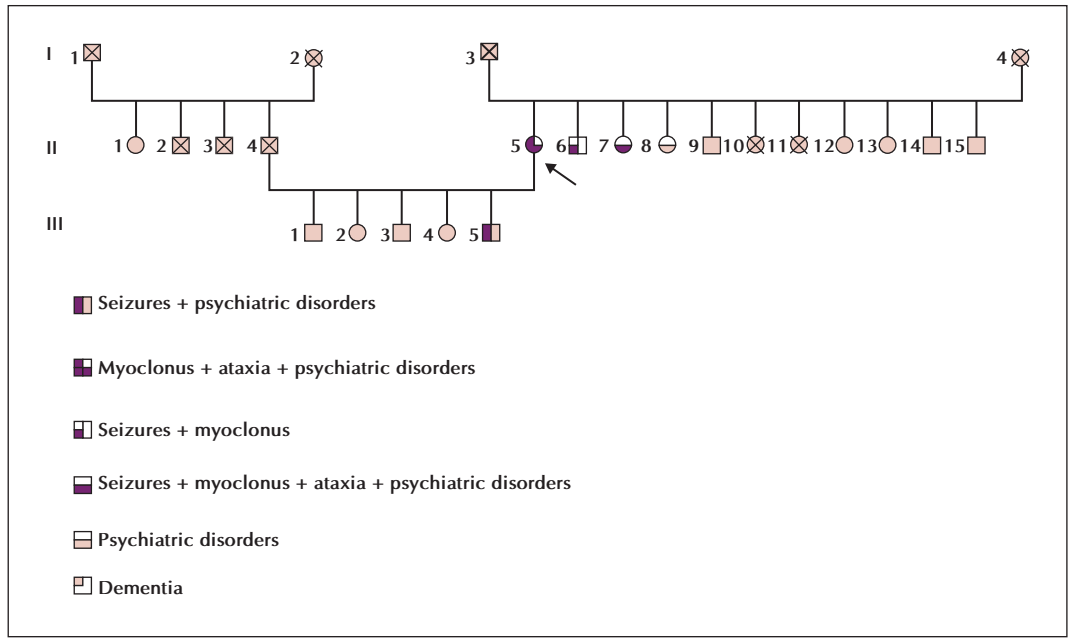
doi:10.1684/epd.2021.1372

Unverricht-Lundborg disease (ULD) is an autosomal recessive progressive myoclonus epilepsy (PME), also called progressive myoclonic epilepsy type 1 (PME1). Diagnosis can either be confirmed by the presence of an expansion, or less commonly a mutation affecting the gene coding for cystatin B (*CSTB*), including "CCCCGCCCCGCG" dodecamer repeats localized on chromosome 21q22.3. It is characterized by the presence of only a few symptoms associated with myoclonus and epileptic seizures without progressive cognitive deficit. It usually manifests during late childhood and early adolescence, ranging from age 8 to 15 years and peaking at around 12 to13 years old [1]. Currently, there is a growing body of evidence for atypical presentations of the disease with a milder phenotype or without the full symptomatology. These forms include patients with a juvenile myoclonic epilepsy-like phenotype [2], late-onset myoclonus or progressive myoclonic ataxia (PMA) without epileptic seizures [3]. We hereby describe a case report of ULD with a late-onset phenotype revealed by recurrent falls and PMA without epileptic seizures,

complicated by psychiatric features. We discuss the broad intra-familial variability and the challenging differential diagnosis of this presentation.

Case study

A 67-year-old woman sought care at our department at the age of 60 suffering from stuttering and a gait disorder. She was born to non-consanguineous parents, and had no personal history. She had a family history of seizures, myoclonus and psychiatric disorder, all starting before the age of 25, as well as late-onset dementia (*figure 1*, *table 1*). Since the age of 51, and as a result of recurrent falls occurring during the past year, she developed a specific phobia with a fear of falling down the stairs. Her symptoms progressively worsened and she became unable to walk by herself without assistance. Additionally, she developed agoraphobia and phobia of wheelchairs. She had initially been followed in a psychiatric department since the age of 57, and she had received benzodiazepines (alprazolam, clonazepam and prazepam) and antidepressants (venlafaxine and sertraline) alternately. A year later, she developed additional anxio-depressive symptoms following her husband's death and started to show stuttering with perioral jerks, and then shock-like movements of the limbs. Her gait disorder deteriorated with daily traumatic falls without associated seizures or loss of consciousness. Her examination revealed multifocal myoclonus affecting the face, the trunk and the limbs, proximally and distally, associated with cerebellar ataxia. She also had dysarthria with pseudo-stuttering associated with velar myoclonus. The baseline Unified Myoclonus Rating Scale (UMRS) score was 95. The Tinetti score was 23/28 corresponding to a very high risk of falls. The neuropsychological assessment revealed preserved cognitive functions with a Mini Mental State Examination score of 26/30, Frontal Assessment Battery score of 18/18, and severe anxio-depressive syndrome with BECK score of 26. Ophthalmic examination including investigation of the ocular fundus showed no abnormalities, in particular, the absence of red cherry spot or retinitis pigmentosa. Haematological and biochemical tests (including liver, renal, and thyroid tests, lactic acid and lactate to pyruvate molar ratio [L:P]) were normal. Immunological tests (anti-nuclear, anti-native DNA, anti-extractable nuclear antigen [ENA], anti-neutrophil cytoplasm [ANCA], anti-phospholipid, anti-thyroglobulin, anti-thyroperoxydase, anti-gliadine, anti-endomysium and anti-glutaminase antibodies), tumour markers (carcinoembryonic antigen [CEA], α-fetoprotein [AFP], CA19-9 and CA-125), antineuronal antibodies (anti-Cv2, anti-PNMA2, anti-Ri, anti-Yo, anti-Hu, anti-recoverin, anti-SOX1, anti-titin) and infectious serologies (B and C hepatitis, HIV and syphilis) were all negative. Electroencephalogram-electromyogram (EEG–EMG) polygrapher records demonstrated normal background rhythm with generalized polyspikes and spike-wave discharges, however, no myoclonus was registered (*figure 2*). EMG revealed positive myoclonus of 60-ms duration in facial muscles (orbicularis or is and depressor labbi



■ **Figure 1.** Family pedigree.

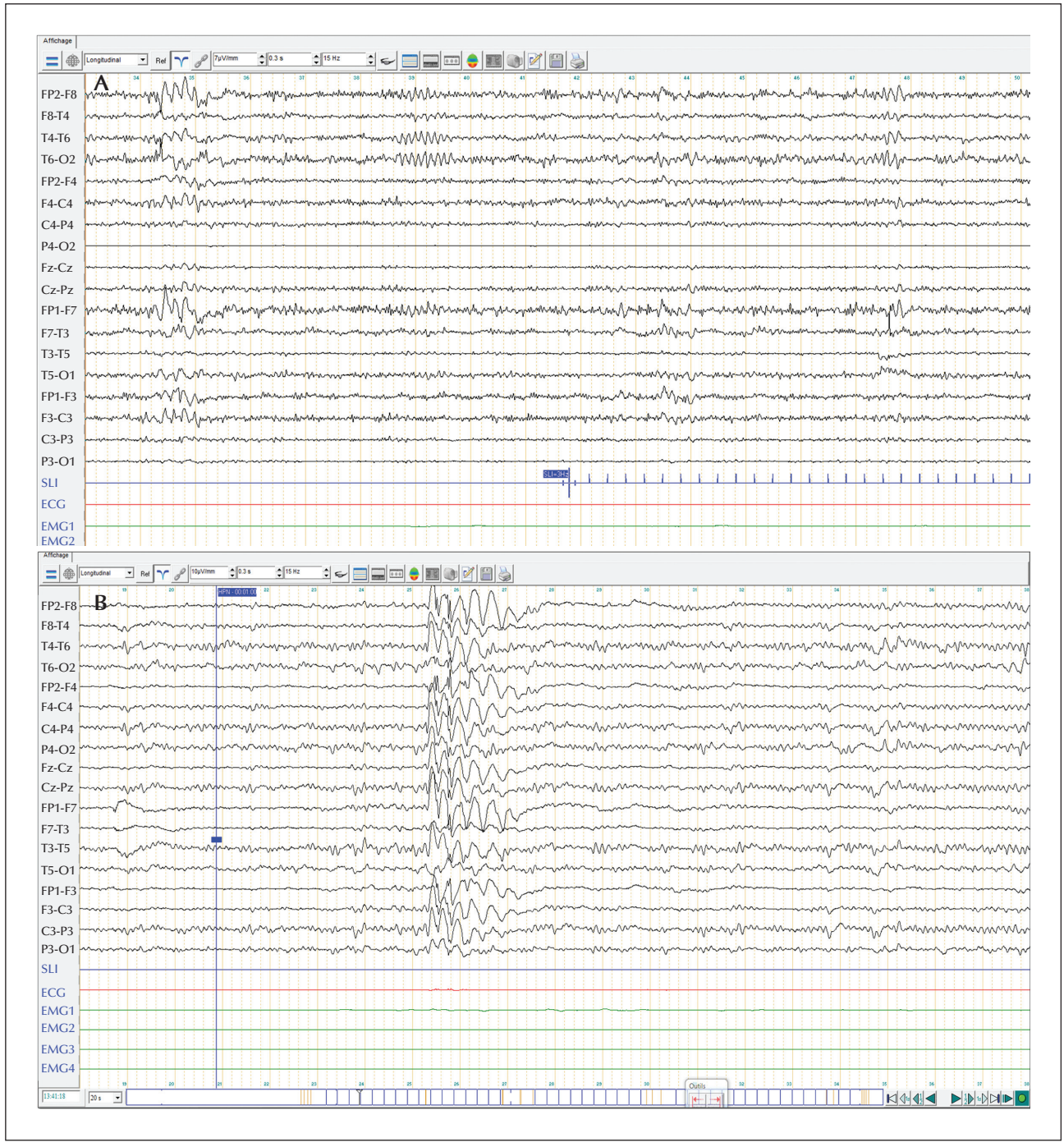
▼ **Table 1.** Clinical characteristics of affected members with confirmed ULD.

Patient	II5	II6	II7	III5
Sex	F	M	F	M
Age	67	63	61	26
Age at onset	50	23	17	11
Disease duration (years)	16	40	44	15
First symptom	Myoclonus	GTCS	GTCS	GTCS
GTCS	-	+	+	+
Cerebellar syndrome	+	-	+	-
Myoclonus	+	+	+	+
Cognitive impairment	-	-	-	-
Psychiatric signs	Specific phobia and agoraphobia	-	Anxiety Depression	Anxiety Depression
EEG BR	Normal	Normal	Normal	Normal
EEG PA	PS, SW	PS, SW	PS, SW	PS, SW
EEG CM	-	+	+	-
Anti-epileptic drugs	PIR+ CLZ+LEV	PB then CBZ then LEV	PB then VPA then LEV	LEV

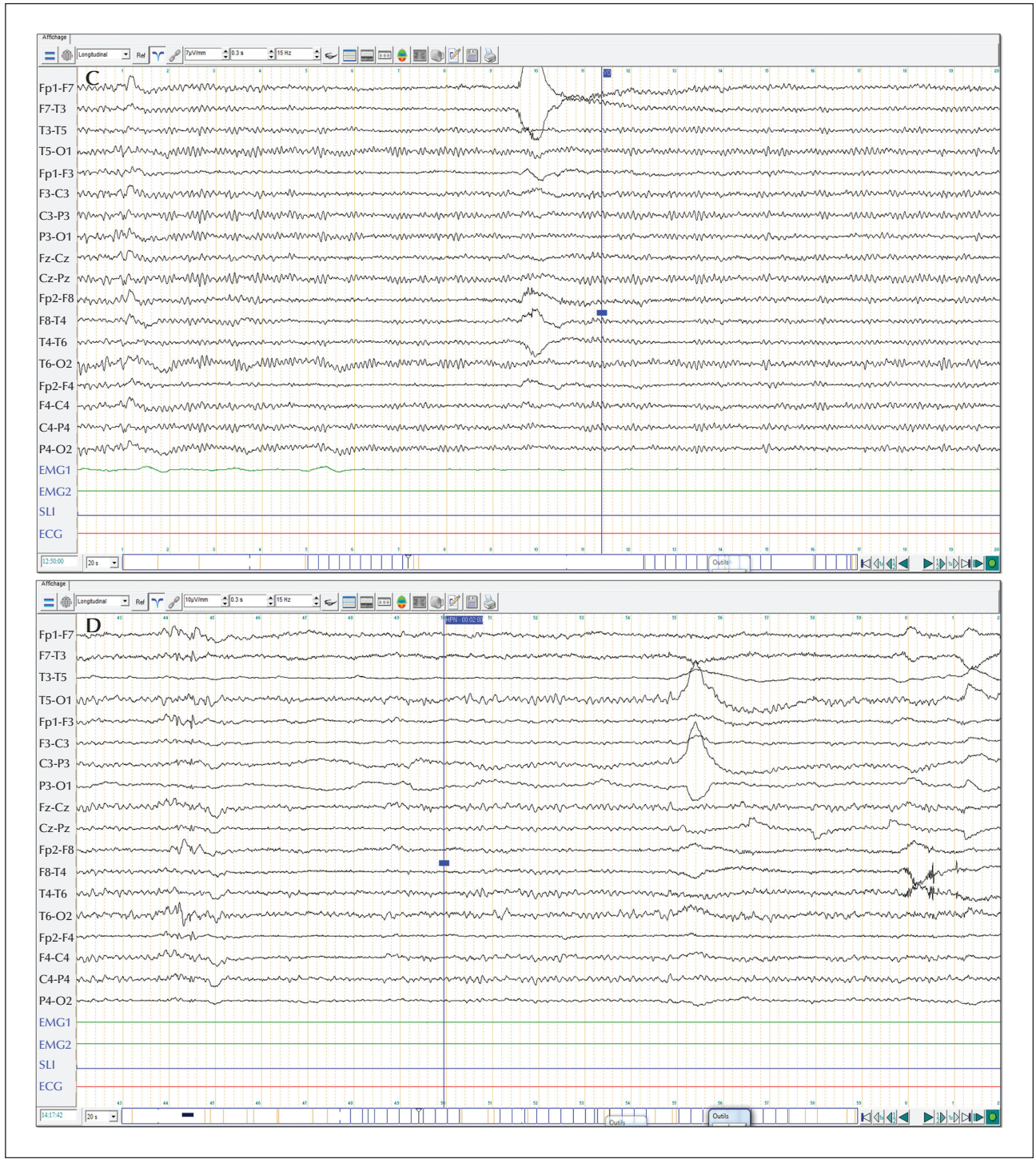
BR: background rhythm; CM: cortical myoclonus; GTCS: generalized tonic-clonic seizures; PA: paroxysmal abnormalities; PS: polyspikes; SW: spike-wave; ULD: Unverricht-Lundborg disease; CBZ: carbamazepin; CLZ: clonazepam; LEV: levetiracetam; PB: phenobarbital; PIR: piracetam; VPA: valproate.

inferioris) and the presence of C reflex via median and ulnar nerves (*figure 3*). Visual evoked potentials were normal. Brain and spinal MRI showed diffuse cortical-sub-cortical atrophy with mild cerebellar atrophy. She received piracetam at 2,400 mg/day and clonazepam at 4 mg/day, sertralin at 50 mg/day and naproxen at 550 mg/day. This resulted in an initial partial improvement of the myoclonus, gait disorder, stuttering, and her psychiatric disorder. The evolution was marked by a progressive worsening of myoclonus, later partially controlled by the addition of levetiracetam at a dose of 1,500 mg/day.

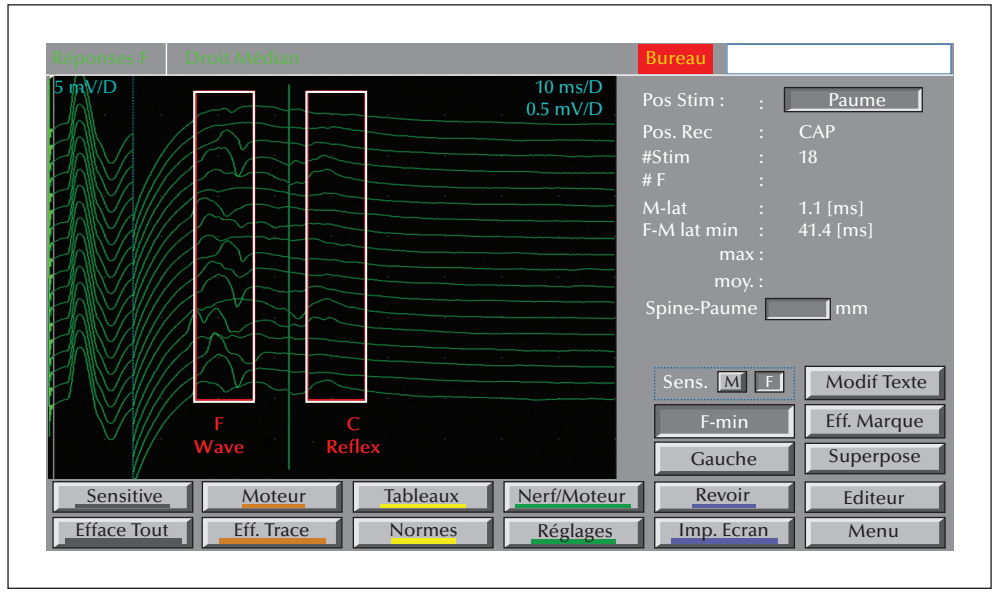
Other family members were summoned for clinical and genetic assessment. For the genetic study, genomic DNA was extracted from the proband and her available family members using the salting-out method. Detection of the expanded *CSTB* dodecamer repeat mutation was performed by polymerase chain reaction (PCR). This indicated the presence of about 36 copies of the dodecamer, confirming the diagnosis of ULD in our patient (*figure 4*). The genetic study using the same procedure confirmed the diagnosis of ULD in her brother (II6), her sister (II7) and her son (III5). The phenotypic analysis of these affected members, all examined by the same neurologists, showed a heterogeneous age at onset, ranging from 11 to 23 years old, with a disease duration ranging from 15 to 44 years. All the other patients had generalized tonic-clonic seizures (GTCS) and myoclonus. Her son, in particular, has had prominent myoclonus since the age of 11 years old which had been aggravated at the age of 14. This affected the four limbs, occurring at any time during the day, predominantly in the morning, causing the dropping of objects and frequent falls. He only had one isolated generalized tonic-clonic seizure at the age of 26. A careful examination of all affected family members revealed that, besides the proband, only her sister developed cerebellar ataxia, and no further, even mild cerebellar features were detected in both her son and her brother. Psychiatric symptoms associated with anxiety and depression were reported in her son and her sister. All the affected family members were able to work normally. EEG recordings revealed generalized spike-waves and polyspikes in all the other affected members as well as cortical myoclonus in her siblings (*figure 2*). They received different antiepileptics sequentially.



■ **Figure 2.** EEG of the proband and family members. EEG-EMG polygraphic records showing bilateral frontal spike-and-wave complexes in the proband (II5) (A), generalized spike-and-wave discharges with frontal predominance in her son (III5) (B).



■ **Figure 2.** EEG of the proband and family members. EEG-EMG polygraphic records showing bilateral central spike-and-wave complexes in her brother (II6) (C), and bilateral frontal spike-and-wave complexes in her sister (II7) (D) (*continued*).



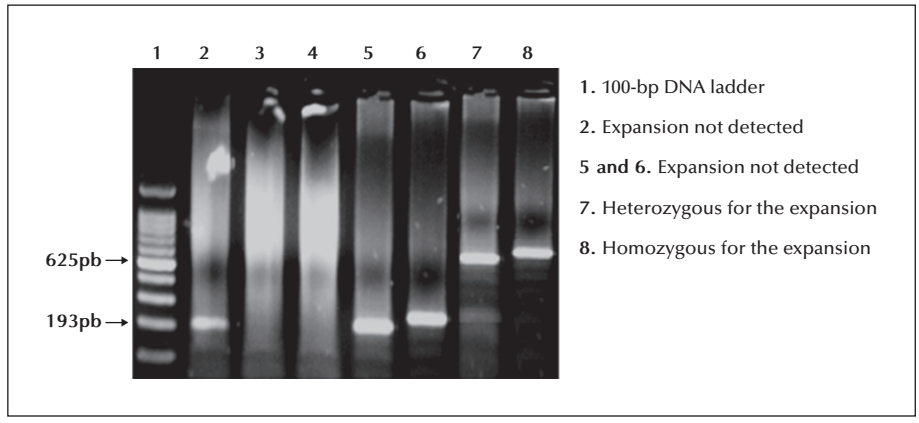
■ **Figure 3.** C-reflex on EMG (latency at 41.4 ms) following F wave on the median nerve in the proband.

However, all of the family members ultimately improved with levetiracetam (*figure 1*, *table 1*).

Discussion

We report an unusual case of late-onset progressive myoclonus-ataxia syndrome with initial recurrent falls resulting in specific phobia and agoraphobia, starting at the age of 50 and revealing ULD in a woman with family history of epilepsy, myoclonus, psychiatric disorder and dementia.

The very late age at onset, the absence of clinical features of epilepsy and the ushering psychiatric presentation were misleading in our patient. The differential diagnosis in this PMA presentation consisted mainly of acquired causes comprising autoimmune, paraneoplastic and infectious diseases, all ruled



■ **Figure 4.** Gel electrophoresis of *CSTB* dodecamer repeats. Detection of the expanded *CSTB* dodecamer repeat mutation was achieved by PCR, and amplified products were analysed on a 1% agarose gel against a 100-bp DNA ladder. In lanes 2, 5 and 6, the arrow indicates a fragment of approximately 193 bp, indicating the normal allele. In lane 7, the presence of two fragments of 193 bp and 625 bp confirms that this patient is a heterozygous expansion carrier. In lane 8, the presence of the fragment of approximately 625 bp confirms that this patient is a homozygous expansion carrier.

▼ **Table 2.** Literature review of ULD cases with age at onset >20 years.

Reference (authors, year)	Country of origin	Number of ULD patients in the study	Oldest age at onset reported in the study group (years)
Our study	Tunisia	4	50
Canafoglia *et al.*, 2004 [14]	Italy	10	8 patients (age of onset: 20-44 years)
Kälviäinen *et al.*, 2016 [16]	Multicentric study	50	34.7
Gargouri-Berrechid *et al.*, 2016 [1] and Gouider *et al.*, 1998 [9]	Tunisia	17	32
Satishchandra and Sinha, 2010 [18]	India	9 (NGC)	32
Khiari *et al.*, 2009 [17]	Italy, France, Tunisia, Serbia	19	28 (from Italy)
Hyppönen *et al.*, 2015 [12] and Koskenkorva *et al.*, 2012 [19]	Finland	66 53	25
Danner *et al.*, 2011 [15]	Finland	7	21

out by negative laboratory tests. Other inherited aetiologies including mitochondriopathies and sialidosis were considered. However, the typical red cherry spot or retinitis pigmentosa was not found on ophthalmologic examination, and the L:P ratio was normal. The preserved cognitive functions did not support the diagnosis of myoclonic epilepsy in Alzheimer's disease (AD) [4].

The initial phobic presentation in our patient complicating recurrent falls, probably due to negative myoclonus, was also disconcerting. Psychiatric disorders are common in ULD, affecting 40-85% of patients and consisting mainly of depression. Yet, agoraphobia has seldom been described in patients with ULD [5]. More recently, basophobia has been reported in a patient with severe postural and action myoclonus affecting all the limbs and an inability to stand and walk independently. Her psychiatric symptoms were lessened by the improvement of myoclonus by taking perampanel [6]. In our patient, a vicious cycle was established between myoclonus causing the first falls and the onset of agoraphobia. Moreover, the common cerebral hypofrontality due to frontal and prefrontal hypoactivity in both ULD [7] and agoraphobia [8] could explain the association of these conditions, although no prominent frontal impairment was noted in our patient upon assessment with the FAB.

In addition, intra-familial variability was a marked feature in this family in terms of the age at onset, ranging from to 11 to 50 years old, as well as the clinical features with different combinations of disease signs. Myoclonus was constant in all affected family members. However, no cerebellar features were detected in her brother despite the fact that he was older and he had the disease for a longer period of time. In fact, the severity of the various symptoms in ULD and the progression of the disease can widely vary from one case to another even within the same family [3, 9, 10]. In a previous study by Lakiotis *et al.*, the authors suggested that disease severity was not related to number of dodecamers [11]. However, in a large Finnish nationwide study, Hyppönen *et al.* concluded that the longer expansion of sequence at the *CSTB* allele was likely to have a modulating effect on cortical neurophysiology, age at disease onset and myoclonus severity [12]. These conflicting findings highly suggest that other factors could determine disease evolution. In their report, Analogia *et al.* found that a younger age at onset, early severe myoclonus, and seizure persistence were predictors of a more severe outcome [13]. In a study on 19 Maghreb ULD families, older age at onset was reported to be 32 years in one patient [9]. Other studies in the literature have reported possible onset over the age of 20 in ULD patients reaching 44 years old. To our knowledge, this case of ULD represents the latest onset in the literature (*table 2*) [1, 9, 14-19].

In conclusion, our case report illustrates the wide range of intra-familial variability in ULD. We also emphasize the challenging differential diagnosis of late-onset myoclonus-ataxia syndromes, mainly with unusual psychiatric presentation such as agoraphobia. The diagnosis of ULD should be considered in this context, even in older patients, broadening the age and clinical boundaries associated with this disease. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Acknowledgements and disclosures.
The authors thank all family members for their participation in this study.
The authors declare that they have no competing interests.

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TEST YOURSELF

(1) Do members of the same family have the same phenotype for Unverricht-Lundborg disease (ULD)?

(2) Does the absence of epilepsy rule out the diagnosis of ULD?

(3) Does the number of dodecamers of the cystatin B (*CSTB*) gene determine the severity of the ULD phenotype?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.