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Original article

A clinical and neurophysiological motor signature of Unverricht–Lundborg disease

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ABSTRACT

Objectives. – Unverricht–Lundborg disease (ULD) is the most common form of progressive myoclonus epilepsy. Cerebellar dysfunction may appear over time, contributing along with myoclonus to motor disability. The purpose of the present work was to clarify the motor and neurophysiological characteristics of ULD patients.

Methods. – Nine patients with genetically proven ULD were evaluated clinically (medical history collected from patient charts, the Scale for the Assessment and Rating of Ataxia and Unified Myoclonus Rating Scale). Neurophysiological investigations included EEG, surface polymyography, long-loop C-reflexes, somatosensory evoked potentials, EEG jerk-locked back-averaging (JLBA) and oculomotor recordings. All patients underwent brain MRI. Non-parametric Mann-Whitney tests were used to compare ULD patients' oculomotor parameters with those of a matched group of healthy volunteers (HV).

Results. – Myoclonus was activated by action but was virtually absent at rest and poorly induced by stimuli. Positive myoclonus was multifocal, often rhythmic and of brief duration, with top-down pyramidal temporospatial propagation. Cortical neurophysiology revealed a

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Abbreviations: Acc, accelerometer; EEG JLBA, EEG jerk-locked back-averaging; HV, healthy volunteers; JME, juvenile myoclonic epilepsy; LLCR, long-loop C-reflex; PME, progressive myoclonus epilepsy; PORM, perioral reflex myoclonus; SARA, scale for the Assessment and Rating of Ataxia; SEP, somatosensory evoked potential; SWJF, square-wave jerk frequency; ULD, Unverricht–Lundborg disease; UMRS, unified Myoclonus Rating Scale; V_{Peak}, peak velocity.

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transient wave preceding myoclonus on EEG JLBA ($n = 8$), enlarged somatosensory evoked potentials ($n = 7$) and positive long-loop C-reflexes at rest ($n = 5$). Compared with HV, ULD patients demonstrated decreased saccadic gain, increased gain dispersion and a higher frequency of hypermetric saccades associated with decreased peak velocity.

Conclusion. – A homogeneous motor pattern was delineated that may represent a ULD clinical and neurophysiological signature. Clinical and neurophysiological findings confirmed the pure cortical origin of the permanent myoclonus. Also, oculomotor findings shed new light on ULD pathophysiology by evidencing combined midbrain and cerebellar dysfunction.

1. Introduction

Progressive myoclonus epilepsy (PME) refers to a heterogeneous group of degenerative diseases of the central nervous system that share core features of myoclonus, epileptic seizures, cerebellar dysfunction and cognitive impairment, along with gradual neurological deterioration. The severity of each symptom depends on both the underlying etiology and stage of disease [1–4]. More than 20 culprit genes have been identified in PME [5].

Timing and course of the disease, associated signs, laboratory findings and radiological features display clues to help select a specific genetic test. However, despite extensive investigations, it is so far, not uncommon that a final diagnosis is not established. Although new genetic technologies, such as whole-exome sequencing allow extensive genetic testing, some diseases may still fail to be diagnosed due to the inability of such techniques to detect particular genetic abnormalities. Thus, accurate characterization of the phenotype remains of major importance.

Unverricht–Lundborg disease (ULD) is the most common form of PME. It is autosomal-recessive and caused by mutations in the gene encoding cystatin B (CSTB). The disease starts late in childhood with generalized tonic–clonic seizures, absences, myoclonic seizures and multifocal myoclonus [6–8]. Myoclonus is activated by either action or sensory stimuli and worsens over time. While seizures are generally well controlled by appropriate treatment, myoclonus is very often drug-resistant and disabling. Neuropsychological impairment and cerebellar ataxia are usually considered mild in ULD [7] compared with other PMEs. However, cerebellar signs may be difficult to identify and estimate due to action myoclonus. Dystonia has also been reported as an additional atypical motor sign in ULD [6].

The electroencephalography (EEG) features of ULD related to epilepsy are well known. At its onset, EEG shows generalized spike–wave activity and photosensitivity and the background is often moderately slow [9]. EEG abnormalities tend to improve over the course of the disease [10]. Previous neurophysiological studies of genetically defined ULD were more often focused on cortical changes and corticomuscular correlates [11–14] than on detailed polymyography descriptions and the findings were indeed suggestive of a cortical origin of myoclonus [15]. Cortical neurophysiological markers further supported this hypothesis. Yet, to our knowledge, myoclonus recordings are very limited in this disease. In addition, there has been no systematic polymyography research into the associated dystonia features and subcortical myoclonus patterns.

Radiological and neuropathological findings suggest the possible involvement of the cerebellum and brainstem in the disease pathogenesis [16–20]. However, clinical identification of cerebellar syndrome may be challenging in the context of action myoclonus, although neurophysiological investigations may further support the presence of brainstem or cerebellar involvement in patients. In particular, oculomotor recordings are a simple and non-invasive approach that can detect both cerebellar and brainstem dysfunction [21].

The purpose of the present work was to clarify the motor and neurophysiological characteristics of ULD by performing a detailed clinical and neurophysiological study of nine consecutive ULD patients.

2. Methods

Nine consecutive patients (six women, three men) with genetically proven ULD were prospectively enrolled in our study between December 2011 and March 2014. Local ethics committees approved the study and all participants gave their written informed consent.

2.1. *Clinical examination*

Patients underwent a standardized interview and neurological examination focused on the phenomenology and course of the motor signs and epilepsy. Neurological examination included the Scale for the Assessment and Rating of Ataxia (SARA) [22] and the Unified Myoclonus Rating Scale (UMRS) [23].

2.2. *Neurophysiology of myoclonus*

Myoclonus was characterized by surface polymyography (EMG), long-loop C-reflex (LLCR), somatosensory evoked potentials (SEPs) and EEG jerk-locked back-averaging (JLBA) using a neuropack system (Nihon Kohden, Tokyo, Japan). All recordings were made using surface silver/silver electrodes, with scalp electrodes positioned according to the international 10–20 system.

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