Neurophysiology of myoclonus and progressive myoclonus epilepsies

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ABSTRACT – The high temporal resolution of neurophysiological recordings makes them particularly suited to faithfully describing the time course of rapid events such as myoclonus and to precisely measure its time relationship with other related activities. In progressive myoclonus epilepsies (PMEs) polygraphy with simultaneous EMG-EEG recordings is a crucial tool for defining the characteristic of myoclonic jerks their topography over different muscles (namely antagonists), their time course and relationship with vigilance muscle activation and stimulations. Moreover on polygraphic recordings it is possible to detect EEG activities associated to myoclonic jerks and define their time relationship with myoclonus thus differentiating cortical types of myoclonus from subcortically generated ones. Thanks to the back averaging technique non obvious time-locked EEG potentials can be detected on polygraphy, furthermore in stimulus sensitive myoclonus the analysis can include the potential evoked by the somatosensory stimulus (SEP). The polygraphic recording also gives information on muscle activity suppression occurring after jerk or as pure negative myoclonus. Besides the time domain analysis, techniques based on frequency analysis have been developed to evaluate EEG-EMG coherence. The neurophysiological techniques provide investigators and clinicians with an invaluable information to define the type of myoclonus and its generating circuitry thus substantially contributing in the diagnosis and management of PMEs.

Key words: progressive myoclonus epilepsies, neurophysiology, EEG-EMG polygraphy, cortical myoclonus, coherence analysis

Neurophysiological features associated with myoclonus in progressive myoclonus epilepsies

Neurophysiological recordings may be conducted over a relatively long period of time, making them particularly suited to faithfully describing the time course of the shock-like muscle contractions which characterize myoclonus. Moreover, the combination of electroencephalographic (EEG) and electromyographic (EMG) recordings allows detection of any EEG correlates of myoclonus and high
Figure 1. Patient with Unverricht-Lundborg disease. Polygraphic recording with the patient at rest showing fragmentary multifocal myoclonus without overt EEG correlate (EMG artefacts due to myoclonic jerks involving the face are superimposed onto the EEG trace).

precision measurement of their time relationship to muscle jerks. For these reasons, neurophysiological analysis is a first-line approach to myoclonic syndromes, both in terms of clinical characterization and pathophysiological investigation.

The first section of this article deals with the neurophysiological techniques suitable for characterizing different types of myoclonus, while the second section addresses the value of neurophysiology in defining the clinical presentation of some progressive myoclonus epilepsies (PMEs) (Minassian et al., 2016).

Neurophysiological analysis of myoclonus

The correlation between EEG and EMG activities associated with myoclonus is the basis for investigating the pathophysiology of myoclonus as well as the clinical diagnosis of PMEs. Several signal analysis techniques relating to time and frequency domains, which are currently employed to detect EEG correlated with myoclonus and used to investigate its pathophysiology, will be highlighted in this first section.

Polygraphic recordings and EEG-EMG correlations in progressive myoclonus epilepsy

In epileptic disorders, polygraphy with simultaneous recording of EEG-EMG activity can provide relevant information for defining the characteristics of a motor manifestation and the relationship with concomitant EEG activity. Moreover, it can be useful to identify subtle and apparently subclinical manifestations, and is necessary for precise investigation of the temporal relationship between EEG and EMG phenomena (Tassinari and Rubboli, 2008).

In PMEs, polygraphic recording can be a crucial tool for the investigation and definition of the characteristics of myoclonic phenomena, which represent one of the cardinal features of this vast group of diseases. EMG is usually recorded using surface electrodes placed on the skin overlying the muscles involved in myoclonic activity, which should be clearly identified by clinical examination (figure 1 figure 1). The cortical correlates of myoclonus have also been analyzed using magnetoencephalography (MEG), which can complement the
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EEG information in terms of the cortical generators of myoclonus (Mima et al., 1998).

Myoclonus is an essential and defining feature of PMEs. It can occur spontaneously or be induced or exacerbated by a variety of stimuli (such as light, sound, touch and emotional strain) and active movement or posture maintenance. At rest, in PMEs, myoclonus is commonly fragmentary and multifocal, and is particularly apparent in the musculature of the face and distal limbs (figure 2, left panel). Action myoclonus, in which movement (as an attempt or intention to move) initiates jerking, is a common feature in almost all the conditions underlying PMEs, and can be extremely disabling. At rest, the EMG expression of myoclonus is a burst of myoclonic potentials of brief (100 ± 50 ms) duration, typically occurring synchronously in agonist and antagonist muscles. If myoclonus occurs in a contracting muscle, then after the myoclonus there is a brief (50-100 ms) suppression of muscle activity. A period of suppression of muscle activity without a preceding myoclonus can also produce a negative jerk, due to a sudden interruption and resumption of ongoing muscular activity. This latter phenomenon is referred to as ‘negative myoclonus’ and is related to a mechanism of supraspinal inhibition lasting from 100 to 500 ms. In PMEs, a mixture of positive and negative myoclonus is common in the same patient. The EMG correlate of a single action myoclonus is an EMG potential of short duration (20 to 30 ms), which appears synchronously in agonist and antagonist muscles (figure 3). It is usually followed by an EMG-silent period lasting 40 to 120 ms (in rare cases up to 300 ms). The myoclonic bursts and silent periods...
are seldom related to EEG spike and waves or polyspike and waves (Tassinari et al., 1974). More often, the EEG correlate is small in transient amplitude, merging with spontaneous EEG activity. The cortical nature of the myoclonic event can be assumed when a time-locked spike or other EEG paroxysmal event is detected on EEG-EMG polygraphic recordings either by visual inspection (figure 1) or by the back-averaging techniques that will be described in detail below. Cortical myoclonus, regardless of whether it is positive or negative, is attributed to a pathologically enhanced excitability of the primary sensorimotor cortex (Obeso et al., 1985), although negative myoclonus may also originate from the pre-motor or supplementary motor area (Rubboli et al., 2006). Additionally, increased excitability of subcortical circuits is considered to be the causative mechanism of subcortical myoclonus which may coexist with cortical myoclonus in PMEs. Additional findings that support the cortical or subcortical origin of myoclonus and their pathophysiological implications will be discussed in detail below.

Polygraphic recordings of PMEs can be complemented with stimulation procedures aimed at revealing their stimulus sensitivity. Photic stimulation should always be applied due to the high frequency of photic reflex myoclonus and/or EEG photosensitivity. Intermittent photic stimulation (IPS) may induce bursts of polyspike-wave discharges associated with massive myoclonic jerks. If the triggering stimulus is prolonged, the clinical response may progress to a generalized convulsion. The mechanism of photic reflex myoclonus involves both occipital and motor cortices, with bilateral spread, presumably mediated by transcallosal connections and propagation down the spinal cord via fast-conducting cortico-spinal pathways (Rubboli et al., 1999).

Although cortical positive myoclonus usually occurs irregularly, it may appear fairly rhythmic, and may even resemble a tremor (hence the term ‘cortical tremor’) in some cases of PME (Toro et al., 1993). Brown & Marsden (1996) reported repetitive myoclonus, both spontaneous and stimulus-evoked, at short intervals of around 20 ms in patients with cortical reflex myoclonus. This was associated with repetitive EEG discharges of the same frequency. Enhanced motor cortex hyperexcitability, as the result of loss of intracortical inhibition, possibly due to abnormal GABA-B mediated inhibitory circuits, has been postulated to underlie the susceptibility to generate rhythmic myoclonic activity (Valzania et al., 1999). Rhythmic cortical myoclonus, at a frequency of around 12-20 Hz has also been reported in the recently described PME associated with SCARB2 mutations (Berkovic et al., 2008; Rubboli et al., 2011) (figure 2, right panel). This rhythmic myoclonus, reminiscent of postural tremor, can be evident at disease onset. Its cortical origin has been demonstrated mainly by coherence and phase analysis of EEG-EMG signals, indicating a significant EEG-EMG coupling and a direct corticospinal transfer (Rubboli et al., 2011). Rhythmic jerks in the beta band have also been described in some PMEs associated with rare storage diseases (Brown et al., 1999; Panzica et al., 2003; Canafoglia et al., 2006).

Additional information can be drawn from sleep recordings which should be performed in the PME work-up whenever possible. The results of sleep studies in different PMEs will be discussed in the second section of this article.

**Coherence study of EEG-EMG relationship in progressive myoclonus epilepsies**

Since synchronization between muscles and cortical activities was demonstrated in the 1990s (McLachlan & Leung, 1991; Farmer et al., 1993), methods of analysis relating to the frequency domain have become an important tool for investigating the human motor system, particularly in terms of studying whether specific patterns of neuronal synchrony may be of diagnostic value (Brown et al., 1999; Grosse et al., 2003).

In the last decade, spectral analysis, namely coherence and phase analysis, has been increasingly applied to investigations of the relationship between rhythmic or quasi-rhythmic myoclonic events and EEG oscillations. Indeed, the relationship between EEG or MEG activity and voluntary or involuntary muscle contraction can be studied by calculating the linear cross-correlation over certain frequency bands (coherence) during sustained muscle contraction (cortico-muscular coherence) (Conway et al., 1995; Salenius et al., 1997; Halliday et al., 1998; Mima & Hallett, 1999).

Spectral analysis appears to be a powerful method for detecting EEG-EMG coherence (Mima & Hallett, 1999) and MEG-EMG (Salenius et al., 1997; Silen et al., 2000) or EMG-EMG relationships in cortical myoclonus, and has several advantages over the more commonly used jerk-locked back-averaging technique (see below) for a number of reasons. High-frequency myoclonic discharges do not prevent the analysis, no arbitrary trigger level has to be chosen, results can be evaluated from a statistical point of view, and the technique can be automated, such that long sections of signal traces can be analyzed over a short epoch. However, the estimation of EEG-EMG coherence requires relatively artefact-free EEG/MEG epochs, and the recording itself, particularly in children with myoclonus or involuntary jerks, may be difficult and time-consuming.

Brown et al. (1999) demonstrated cortical activity related to myoclonic jerking through frequency analysis in five patients in whom jerk-locked back-averaging
failed to show any clear EEG transient associated with myoclonic jerks. To estimate coherence and phase spectra, couples of channels are usually investigated by means of cross-spectral analysis based on traditional Fast Fourier Transform (FFT). Selected data are usually divided into consecutive non-overlapping segments, transformed in the frequency domain and then averaged. A trade-off should be considered in the FFT approach between frequency resolution and spectral variance. As window length decreases, variance also decreases, but spectral resolution becomes poorer.

An alternative approach is based on parametric autoregressive (AR) models. The main advantages of spectral AR estimates over FFT-based methods are that they significantly improve frequency resolution since parametric spectra can be evaluated numerically at any number of frequencies and do not require any averaging to obtain a smoothed spectrum (Gath et al., 1992; Pardey et al., 1996; Spyers-Ashby et al., 1998). Conversely, the FFT-based spectra can be evaluated only on the number of samples (N) with harmonically related frequencies. This advantage is particularly important for the analysis of short sequence lengths or epochs characterized by rapid dynamic changes. Moreover, AR spectra can be obtained without windowing the data since no assumptions about samples outside the data sequence are needed. In addition, the inclusion of a noise term in the AR model means that the estimated spectrum is smooth, since its shape depends only on the values of the coefficients used to model the signal. In contrast, in the FFT-based analysis, random fluctuations due to noise can be reduced only by the averaging procedure. The improvement is related to the number of degrees of freedom of the AR model, which is given by N/p where N is the number of samples and p is the model order (Gath et al., 1992). Using the AR model, the number of AR parameters needed to model a time series is typically much lower than the total number of data points composing the signal, and this therefore gives a statistically desirable compact representation of the signal. For FFT methods, by comparison, it is necessary to determine as many coefficients as there are points in a particular data segment. In itself, this is statistically undesirable and this is the reason why one needs to average over a large number of data segments in order to obtain an appropriate spectrum. As a result, it is commonly claimed that AR spectral estimates tend to be more robust than FFT estimates when working with a small data set. These characteristics make it possible to estimate the myoclonic bursts that need to be isolated from periods of normal muscle contractions (as is the case with Unverricht-Lundborg patients), or from the spontaneous ‘epileptic’ myoclonus associated with diffuse spike-wave discharges (as is the case with Lafora patients) (Panzica et al., 2003). The main problem with AR models is the choice of model order. It is important to stress that the model order determines the number of frequency components contained in the spectra (in a univariate model, the maximum number of peaks in the power spectrum is half of that of the model order and thus determines the “frequency resolution of the spectrum” (Schlogl & Supp, 2006). The main advantage of the FFT over AR spectral estimation is its computational efficiency.

Using a parametric approach, multivariate AR models can be used to provide a multivariate representation of the signals, from which appropriate measures of coupling can be estimated. In 1991, Kaminski and Blinowska proposed the Directed Transfer Function (DTF) (Kaminski & Blinowska, 1991), a multichannel estimator of the intensity and direction of activity flow, based on a multichannel autoregressive model between couples of channels as a function of the frequency (Mima et al., 2001; Cassidy & Brown, 2003).

In 2001, Baccalá and Sameshima proposed a different multichannel approach, the partial directed coherence (PDC), which allows the direction of information flow between any of the two channels to be estimated by subtracting the interactions and possible common influences due to other remaining simultaneously observed time series (Baccalá & Sameshima, 2001; Meng et al., 2008). By applying this approach, Panzica et al. (2014) were recently able to demonstrate, in patients with cortical myoclonus, a significant increase in cortical outflow towards activated muscles, in comparison to healthy controls. Moreover, they showed a more robust EMG outflow toward ipsi and contralateral cortical areas which could maintain jerk recurrence.

In addition, non-stationary or time-varying multivariate AR models have recently been developed and can be applied to study dynamical changes associated with cortico-muscular coupling in patients with myoclonus, when the statistical properties of the signals change substantially over time. Panzica et al. (2010) studied myoclonus-related EEG changes in patients with two forms of progressive myoclonus (Unverricht-Lundborg disease and sialidosis) using bivariate time-varying autoregressive models (TVAR). The results indicated that it was possible to detect the presence of prominent peaks of EEG-EMG coherence between the EMG and contralateral frontal-EEG derivation by TVAR analysis in all patients and, most importantly, differences were disclosed relating to time-frequency spectral profiles correlated with the severity of myoclonus (figure 4).

In patients with cortical myoclonus, regardless of aetiology, frequency analysis showed the presence of an exaggerated coherence peak in the beta band (mainly at 15-20 Hz) between sensorimotor cortex activity and EMG activity that is normally rectified, recorded from muscles co-activated by myoclonic jerks. In this

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frequency range, often the cortical activity precedes EMG by a time period which is appropriate for conduction in the fast conduction pyramidal pathway (Brown & Marsden, 1996; Brown et al., 1999; Valzania et al., 1999; Silen et al., 2000; Grosse et al., 2003; Panzica et al., 2003). Sometimes, however, the phase difference indicates a time lag that is lower than expected for the fastest conducting pathway (Brown et al., 1998; Ohara et al., 2000). This phenomenon may be due to the presence of multidirectional activities which contribute to the cortico-muscular coherence between muscle and cortex (efferent control from the primary motor cortex to muscle and afferent feedback from the periphery) (Panzica et al., 2012). These findings support the idea that myoclonus may be due to an exaggeration of the cortico drive to muscle observed during voluntary contractions in healthy subjects (Brown et al., 1999). Unlike coherent beta activity, a coherent gamma peak is not a consistent feature. In healthy subjects, a similarly inconsistent presence of coherent gamma activity has been hypothetically attributed to the variable cortical activation associated with attention or differences in functional cortical-muscular coupling depending on the strength of the muscle contraction (Brown et al., 1998; Mima & Hallett, 1999). Panzica et al. (2003), based on a study of patients with different types of PMEs, found constant coherent gamma coherence only in the patients with sialidosis (figure 4). In these patients, myoclonic jerks entirely replaced the physiological muscle contractions, which occurred at the
Neurophysiological investigation of brain circuitry sub-serving myoclonus

In this section, we review some neurophysiological techniques in the time domain that may complement the frequency analysis of EEG-EMG polygraphic recordings to investigate whether muscle jerk is associated with any EEG activity and to define their reciprocal time relationship. The first important point concerns the existence of myoclonus-associated scalp electrophysiological events that precede the myoclonic jerk, thus supporting a cortical origin of myoclonus.

Jerk-locked back-averaging

The potential of this technique to detect non-obvious EEG correlates of myoclonus was first reported by Shibasaki and Kuroiwa (1975) and has been widely employed since then to study involuntary movements. The principle upon which it is based is that of averaging the EEG (or MEG) recording preceding the muscle jerk such that all activities which are not consistently time related to the jerk are subtracted from one another, while the time-locked EEG potentials preceding myoclonus will summate, resulting in easily recognizable transients which are well-suited to morphological analysis and time relationship calculation (figure 5).

According to Kornhuber and Deecke (1965) in their original study of movement-related EEG activities, the backward analysis could be performed by playing back a magnetic tape where polygraphic the EEG-EMG recording has been stored or by introducing a delay-line analogue circuit into the EEG recording system (Franceschetti et al., 1980). With the increased availability of digitized recordings, analysis of the EEG

![Figure 5](image-url)
preceding the myoclonic jerk can be easily obtained by setting the analysis window at 200 ms before and 200 ms after the myoclonus onset. The trigger pulse is generated by the myoclonus-related EMG potential either in its original or rectified shape. The definition of the true onset of the EMG potential is crucial to ensure reliable results. The method can also be applied to the study of the negative myoclonus of cortical origin, in which the onset of the EMG silent period is used as a trigger for back-averaging EEG (Ugawa et al., 1989).

An EEG potential preceding the muscle jerk by 15-20 ms may express a cortical discharge responsible for the myoclonus and is therefore considered to be compatible with its cortical origin. Shorter intervals or an inverted time relationship with the jerk preceding the EEG potential would rather support a cortical response evoked by the muscle jerk originating in some subcortical structure.

Electrophysiological study of reflex myoclonus

In 1939, Adrian and Moruzzi showed that the stimulus-evoked myoclonus observed in cats anaesthetised with chloralose was due to a discharge travelling in the pyramidal tract and time-locked to a cortical wave (Adrian & Moruzzi, 1939). This “cortical reflex myoclonus” did not fully account for the muscle jerk observed in the anaesthetised animals, as decortication did not eradicate it completely. The origin of the residual component was found to be in the reticular formation. The observation of stimulus-sensitive myoclonus in different human diseases made it possible to characterize cortical versus reticular reflex myoclonus in several pathological disorders, including PMEs. Their main features are summarized here, in line with the work by Shibasaki and Hallett (2005) and Shibasaki (2012).

Cortical reflex myoclonus

Cortical reflex myoclonus, evoked by electrical shocks delivered to the median nerve at the wrist, is associated with a giant somatosensory evoked potential (SEP), first reported by Dawson in 1947 (Dawson, 1947), with an extreme enlargement of P25 and subsequent components (up to 10 times as large as the normal value), whereas the initial components N20 and P20 are normal or only slightly enhanced (figure 6).

However, the studies of somatosensory evoked magnetic fields (Karhu et al., 1994; Mima et al., 1998) shows that M20 is also slightly enhanced in some cases, suggesting hyperactivity of the sensorimotor thalamocortical loop. Moreover, these studies demonstrate that the hyperactivity involves the primary somatosensory cortex but not the second somatosensory area, which is not hyperexcitable.

Giant potentials can also be evoked by flash stimulation in photosensitive myoclonus, which is also considered a type of cortical reflex myoclonus (Shibasaki & Neshige, 1987). The areas of enhanced excitability include the occipital and frontal cortices, in which hyperexcitability is considered to account for photo-induced muscle jerks.

The somatosensory stimulus-induced cortical reflex myoclonus is readily evoked in the thenar muscle by stimulating the median nerve at the wrist with a latency of 45 ms, which corresponds to that of the long-loop reflex known as the C reflex (C for ‘cortical’), as reported by Sutton and Mayer (1974). The P25 peak of giant SEP and cortical potential preceding the muscle jerk, as revealed by jerk-locked back-averaging, show a similar topography and time interval relationship to myoclonus and are considered to be related to the same pathophysiological mechanisms, i.e.
cortical hyperexcitability (Shibasaki et al., 1978). Analysis of the latencies of the cortical reflex myoclonus recorded from different muscles shows a rostro-caudal order of activation, compatible with a cortical origin of the myoclonus, generating a signal which travels down the brainstem (Hallett et al., 1979).

Reticular reflex myoclonus

Reticular reflex myoclonus differs from cortical reflex myoclonus in terms of SEP, which is not enhanced, and order of activation of muscles; bulbar muscles are activated first and rostral cranial (i.e. facial muscles) muscles and caudal muscles (i.e. limb muscles) are involved only subsequently (Hallet et al., 1977). Cortical and reticular reflex myoclonus can coexist in the same patients with PME. The coexistence of subcortical and cortical myoclonus has been demonstrated on the basis of the discrepancies between the latency of reflex myoclonus and the sum of afferent and efferent times to and from the cortex, as evidenced by TMS studies (Cantello et al., 1997).

Neurophysiological findings in different progressive myoclonus epilepsy forms

PMEs share common neurological signs that include progressively worsening cortical myoclonus and epileptic seizures, with classic onset in late childhood and adolescence. Other neurological symptoms, namely dementia and ataxia, are typically associated with myoclonus-epilepsy syndromes, and occasionally further signs and symptoms are due to the specific impairment of nervous or other systems (Marseille Consensus Group, 1990).

The PME phenotype includes a ‘core’ symptom: multifocal reflex (action-induced) myoclonus. This type of myoclonus is assumed to be cortically generated, since it is typically associated with ‘subtle’ central EEG changes that can be studied using EEG-EMG relationship analysis (including jerk-locked back-averaging and other techniques). Moreover, cortical myoclonus is coupled with neurophysiological features reflecting neocortical hyperexcitability, such as ‘giant’ evoked potentials and enhanced long-loop reflexes (Shibasaki, 1988; Shibasaki & Thompson, 2011).

PMEs are derived from heterogeneous genetic disorders (Serratosa et al., 1999; Ramachandran et al., 2009; de Siqueira, 2010), probably with distinct pathological mechanisms, including neural degeneration (Unverricht-Lundborg and dentatorubral-pallidoluysian atrophy), storage disorders (Lafora disease, neural-geroid-lipofuscinoses, sialidoses, Gaucher III, Niemann Pick type C, and action myoclonus-renal failure syndrome), mitochondrial disorders (myoclonic epilepsy associated with ragged-red fibres), and ion channel dysfunction (Azizieh et al., 2011). Advances in biomolecular research continuously enrich our knowledge of the genetic background of PMEs and their pathogenesis.

Since the causes of PMEs are heterogeneous, they can be expected to affect cortical and subcortical brain structures in varying ways and probably by different mechanisms.

Due to different pathogenetic/neuropathological mechanisms, PME syndromes may present partially different neurophysiological features, which can reflect the prominent dysfunction of distinct cerebral areas or the occurrence of associated symptoms (for instance, the involvement of the peripheral nervous system). Specific neurophysiological findings may be important for diagnostic assessment and phenotypic classification (Kasai et al., 1999; Panzica et al., 2003; Canafoglia et al., 2004; Canafoglia et al., 2010) and may help quantify the severity of the clinical disorder (Garvey et al., 2001) at diagnosis and during follow-up. Indeed, changes in neurophysiological findings relating to the disease course may reflect spontaneous evolution or relate to therapeutic interventions (Kobayashi et al., 2011).

In this section, we address the differences between neurophysiological findings in the main PME forms, Unverricht-Lundborg (EPM1) and Lafora body disease (EPM2), and in some rarer diseases: sialidoses and neuronal-geroid-lipofuscinoses (NCL) in adults (Kufs disease). With this aim, we report on the EEG-EMG features and neurophysiological findings obtained using somatosensory evoked potentials (SSEPs), long-loop reflexes (LLR) and transcranial magnetic stimulation in these diseases and their changes over time.

EEG-EMG findings may be useful to differentiate between different PMEs

EEG-EMG polygraphy

Unverricht-Lundborg (EPM1)

The EEG-EMG features of EPM1, originally described in patients with Baltic myoclonus from a restricted geographical area (Koskiniemi et al., 1974; Norio & Koskiniemi, 1979), highlight diffuse EEG background slowing with recurrent paroxysms of spike and polyspike and waves, focal spikes in the central region, and marked photosensitivity. A different disease course, probably resulting from more effective treatment (usually including valproate), emerged in more recent observations of large case series. Indeed, EPM1 patients observed in recent years have generally demonstrated normal to slightly slow EEG background and brief and rare epileptic paroxysms of spikes
or polyspikes, occasionally associated with spontaneous isolated myoclonic jerks (Canafoglia et al., 2004; Ferlazzo et al., 2007). Segmental myoclonic jerks occurring with voluntary or passive movements (action myoclonus), unrelated to obvious EEG ‘epileptic’ paroxysms, remain the prominent symptom. Epileptic paroxysms and photosensitivity tend to disappear over the years, together with a relatively stationary phase of the disease (Magaudda et al., 2006; Kälviäinen et al., 2008; Genton, 2010), while some observations indicate progressive impairment of the physiological EEG sleep pattern (Ferlazzo et al., 2007).

Lafora body disease (EPM2)
The EEG-EMG picture observed in EPM2 patients is strikingly different from that of Unverricht-Lundborg, at least in the intermediate and advanced stages. As described by Tassinari et al. (1978), in the first disease period, EEG features may resemble those of primary generalized epilepsy due to preserved background activity and the occurrence of fast spikes, polyspikes, waves and photosensitivity. However, shortly after onset, despite advanced pharmaceutical treatments, the EEG background markedly slows and posterior or diffuse paroxysms of multiple spikes, associated with atypical (myoclonic-atonic) seizures or absences, sometimes resulting in a non-convulsive status (Fernández-Torre et al., 2012), recur with a high frequency.

Moreover, myoclonus in EPM2 patients shows rather peculiar features, including prominent negative EMG phenomena (Shibasaki, 1995). Voluntary motor activity consistently enhances the occurrence of myoclonic jerks on the activated segment, but it is often difficult to distinguish action myoclonus from the almost incessant spontaneous myoclonus (Canafoglia et al., 2004).

Sialidoses
EEG background activity is substantially preserved, although it may include a moderate amount of theta activity. Brief paroxysms of bilateral spikes and polyspikes and waves, with maximum amplitude on the central EEG regions, may be present, combined with rare spontaneous bilateral myoclonic jerks. Photosensitivity is mild or absent. Myoclonus mainly occurs during motor activity and typically takes a pseudo-rhythmic course (Rapin et al., 1978; Canafoglia et al., 2011). Rhythmic EEG fast activities are sometimes visible on central and vertex regions, occasionally associated with spikes. The movement-activated central fast rhythm (Kelly et al., 1978), sometimes intermingled with spikes, constitutes a rather typical correlate of the rhythmic myoclonus observed during motor activation.

Neuronal-ceroid-lipofuscinoses (NCL)
Clinical and electrophysiological features of adult-onset NCL (Kufs disease) were critically revised by Berkovic et al. (1988). Recently, CLN6 gene mutations have been found in PME patients with Kufs disease (Arsov et al., 2011). The EEG shows paroxysms of spike-and-slow-wave complexes (Berkovic et al., 1988) or multiple generalized spikes without any slow component (Binelli et al., 2000). Multiple spike discharges may be synchronized with myoclonus and the slow waves with brief EMG, silent in limb muscles (Berkovic et al., 1988). The photoparoxysmal and myoclonic response to photic stimulation is particularly strong both at slow and high (1 to 100 Hz) stimulus frequencies, and low-frequency photoparoxysmal response might be an early clue for diagnosis (Guellerin et al., 2012). Table 1 summarizes the information on EEG-EMG features.

Evolution of EEG-EMG findings during sleep
In Unverricht-Lundborg disease, sleep studies demonstrate:
– (1) a lack of activation of generalized paroxysmal discharges;
– (2) and the appearance of focal multiple fast spikes occurring in repetitive bursts, localized over the

### Table 1. EEG-EMG features (in treated patients).

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<th>Background Type</th>
<th>Epileptic paroxysms Type</th>
<th>Occurrence</th>
<th>PPR</th>
<th>Spontaneous myoclonus Occurrence</th>
<th>Action myoclonus Occurrence</th>
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<tr>
<td>EPM1</td>
<td>alpha-theta</td>
<td>Diffuse SW/PSW</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>EPM2</td>
<td>theta-delta</td>
<td>Diffuse SW/PSW</td>
<td>+/</td>
<td>+</td>
<td>+++</td>
<td>++</td>
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<td>and occipital SW</td>
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<tr>
<td>Sialidoses</td>
<td>alpha-theta</td>
<td>Diffuse SW/PSW</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Kufs</td>
<td>alpha-theta</td>
<td>Diffuse SW/PSW</td>
<td>++</td>
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midline and centroparietal regions, more frequently during REM sleep, particularly when eye movements are abundant. These fast spikes can be time-locked to myoclonic jerks, particularly in muscles which show a striking action myoclonus during wakefulness. In Lafora disease, sleep organization is radically altered, with the barely recognizable different stages. Paroxysmal activity does not appear to increase during sleep; diffuse multiple fast spikes show variable amplitude and topography and can be intermixed with fast activity, while posterior spikes persist during slow sleep and can appear enhanced during REM sleep (table 2).

### Somatosensory evoked potentials

**Giant potentials**

In PME patients, early SEP components are typically enlarged, with major emphasis of the P25-N33 waves, which are thought to be connected to the occurrence of reflex myoclonus (Kakigi & Shibasaki, 1987). In a study performed in EPM1 and EPM2 patients (Canafoglia et al., 2004), the peak-to-peak amplitude of N20-P25 was abnormally enlarged in both groups, but N33 was often poorly defined in EPM2 patients, merging in a broad negative wave (N3, peaking between 43.8 to 66.6 ms). Moreover, the P25-N60 and N60 amplitudes were significantly larger in EPM2 patients in comparison to both controls and EPM1 patients (figure 7).

Increased SSEP amplitudes may also occur less consistently in patients with sialidosis and Kufs disease, however, they are unlikely to be useful in the differential diagnosis (Berkovic et al., 1988; Canafoglia et al., 2011).

The amplitude of the SSEP components may change over the course of the disease. A recent study (Kobayashi et al., 2011) suggested that in EPM1 patients, the reduction or disappearance of a middle-latency cortical component (labeled N40) is associated with a decrease in epileptiform discharges at the plateau stage of the disease. Conversely, in EPM2 patients, early and middle-latency SSEP components may increase during the disease, alongside the worsening course of the myoclonus and seizures.

### SEP latencies

Various studies indicate that the latencies of the early cortical SSEP components increase (Mervaala et al., 1984; Canafoglia et al., 2004) due to a delay in the central conduction pathway from the thalamus to the somatosensory cortex, while in EPM2 patients, the conduction studies gave normal results (Canafoglia et al., 2004) (figure 8A).

In patients with sialidosis, the possible co-occurrence of polyneuropathy is typically associated with prolonged latencies (Canafoglia et al., 2011).

### Long latency reflex (LLR)

LLR is the neurophysiological correlate of reflex myoclonus. A comparative study has suggested that facilitated LLRs are more common in EPM1 than EPM2 patients, probably reflecting the prominence of reflex myoclonus in this disorder. LLR latencies were briefer in EPM1 than in EPM2 patients (Canafoglia et al., 2004) (figure 8B).

In sialidoses patients, the shape of LLR often includes multiple waves, probably reflecting the rhythmic occurrence of the jerks (Franceschetti et al., 1980; Tobimatsu et al., 1985; Canafoglia et al., 2011).

### Cortical relay time (CRT)

According to a comparative study (Canafoglia et al., 2004) the CRT was significantly briefer in both EPM1 and EPM2 patients, in comparison to that of healthy controls. The CRT was particularly brief in EPM1 patients, due to their delayed N20 latency, together with short LLR latency (figure 8C).
Both healthy subjects and PME patients had larger MEP amplitudes after conditioning stimuli (R2) to peripheral mixed nerves, in comparison to basal (non-conditioned) MEP amplitudes (R1); this finding was more evident at inter-stimulus intervals (ISIs), ranging from 30 to 80 ms (Reutens et al., 1993; Cantello et al., 1997; Canafoglia et al., 2004). Digital stimulation markedly facilitated conditioned motor evoked potentials at ISIs ranging from 25 to 40 ms in all patients. This pattern was significantly different from the inhibition observed in controls at the same ISIs (Manganotti et al., 2001).

A comparative analysis of the results obtained in EPM1 and EPM2 patients (Canafoglia et al., 2004) indicated that the degree and time course of MEP facilitation was different for EPM1 compared to EPM2. Indeed, EPM2 patients maintained a significantly higher MEP facilitation at ISIs of between 40 and 60 ms, whereas EPM1 patients had a higher facilitation only at an ISI of between 20 and 40 ms (figure 9).

### Intracortical inhibition and facilitation tested with paired magnetic pulses

In patients with cortical myoclonus, short interval intracortical inhibition (SICI) is generally reduced (Brown et al., 1996; Manganotti et al., 2001; Hanajima et al., 2008). A comparative study in patients with EPM1 and EPM2 (Canafoglia et al., 2010) indicated that both the EPM1 and EPM2 patients showed significantly less inhibition than the healthy subjects, with no difference between the two patient groups, with the exception of an ISI of 6 ms; at this ISI there was a significant enhanced inhibition in EPM2 with respect to EPM1 patients. Intracortical facilitation (ICF) was normal in EPM1 patients, while there was a significantly reduced facilitation in EPM2 patients at an ISI of 10 ms.

Data obtained in sporadic patients with sialidosis (Brown et al., 1996; Manganotti et al., 2001) and in a homogeneous series of patients with sialidosis type I (Huang et al., 2008) indicated a reduced SICI. In those patients, ICF was normal.

Long interval intracortical inhibition (LICI) was generally impaired in patients with cortical myoclonus (Valzania et al., 1999). However, a comparative study in patients (Canafoglia et al., 2010) with EPM1 and EPM2 revealed significantly less inhibition in EPM2 patients with afferent stimuli (ISIs: 20 and 40 ms; ISIs: 30-80 ms).

### Cortical plasticity

Cortical plasticity may be tested by means of repetitive TMS protocols. A study performed using a paired associative stimulation protocol indicated altered plasticity of the sensorimotor cortex in EPM1 patients. These patients exhibited an average decrease of 15 per cent in motor-evoked potential amplitudes, 30 minutes after...
Figure 9. Graphic representation of interaction between peripheral somatosensory stimuli and transcranial magnetic stimulation (TMS). Note the different profiles between controls and both PME groups indicating the amplification of the effect of sensory stimulus on motor cortex excitability. Moreover, Lafora patients show a larger and long-lasting excitatory interaction.

Conclusions

The neurophysiological evaluation of patients with different PMEs demonstrates the presence of peculiar features that, although not strictly distinctive, suggest different mechanisms underlying the generation of myoclonus. Most patients who were included in the study protocols were treated with multiple drugs, mainly AEDs, which may have influenced some results. However, since the treatment was relatively similar in the various PME syndromes, the differences observed actually suggest different dysfunctions affecting the circuitries sustaining myoclonic jerks.

In EPM1 patients, myoclonus was regularly induced by action and was associated with exaggerated LLRs and early facilitation of the motor cortex by afferent stimuli. These findings, associated with the increased P25-N33 SSEP component, completely fit the definition of cortical reflex myoclonus (Shibasaki & Thompson, 2011). The finding of a short cortical relay time suggests the possibility of an alternative transcortical loop generating reflex myoclonus, passing through the thalamus directly to the motor cortex (Canafoglia et al., 2004). This hypothesis also agrees with the finding in EPM1 patients, of an early facilitation of the motor cortex by conditioning stimuli (possibly following premature invasion of the motor cortex by somatosensory afferent volleys).

The findings obtained with paired TMS stimulation clearly indicated a defective inhibition, probably due to defective GABA circuitry (Canafoglia et al., 2010), in line with the observation made in the CSTB mouse model, suggesting a prominent reduction in GABA-dependent inhibitory function in both the hippocampus and neocortex (Franceschetti et al., 2007; Buzzi et al., 2012).

The finding of abnormal cortical plasticity indicating defective sensorimotor integration may be associated
with the previously reported structural and physiological abnormalities of the primary motor cortex in EPM1 patients (Danner et al., 2011).

In EPM2 patients, neurophysiological findings differ from those found in EPM1 patients, suggesting a more complex circuitry sustaining the severe myoclonic presentation. LLRs are more often within the normal range, corresponding to a less significant reflex myoclonus. Conversely, the prolonged late facilitation of motor cortex found by applying sensory stimuli followed by magnetic stimuli, and the enhanced middle latency SSEP components can, conversely, match a more complex circuitry, generating the high propensity of these patients to show spontaneous epileptic myoclonus. The profile of cortical excitability revealed by paired pulse with TMS, showing multiple abnormalities, not limited to short-time interaction or even late interaction, revealed by ICF and LICI, may support this interpretation, suggesting a more complex, hyperexcitable network and a more extensive defect of the inhibitory mechanisms, possibly related to GABA-B mediation (Ziemann, 2004).

Polyglucosan accumulation in dendrites typically occurring in this disorder (Chan et al., 2004) may directly cause an imbalance between GABAergic and glutamatergic post-synaptic inputs to the dendrite tree or changes in the dendrite electrotonic properties capable of modifying the transfer of inputs to the neuronal soma.

In sialidoses, neurophysiological findings mainly overlap those observed in EPM1, since myoclonus prominently presents as a reflex phenomenon and as action-activated. The most characteristic feature is the rhythmic time course of action myoclonus, which substantially replaces the normal muscle contraction throughout the movement. In accordance with this finding, LLR mostly features repetitive components, probably reflecting pathological loops involving the motor cortex, leading to a reverberating circuitry and recurrence of jerks.

Although sialidoses are lysosomal disorders leading to neuron storage which may in turn lead to cell death, only mild spongiosis and lipofuscin granules have been found in the neocortical structures of patients with sialidosis (Allegranza et al., 1989).

Thus, the hyperexcitability sustaining myoclonus in this disorder probably arises from subtle circuitry rearrangements rather than from massive cell loss. The circuitry rearrangement resulting from sialidoses may lead to extreme synchronization of the neuronal pools sustaining action-activated jerks.

In conclusion, although PME presentations always include findings reflecting neocortical hyperexcitability, the recognition of subtle differences in diverse genetic disorders may help in designing the diagnostic work-up. Moreover, these differences suggest peculiar dysfunctions in the neuronal network responsible for myoclonus. At present, we can only hypothesize that different modulating mechanisms derived from extra cortical regions (possibly subcortical nuclei and cerebellum) or due to complex cortico-cortical interaction, potentially lead to these different presentations.

In this article, we report evidence obtained in the two more common PME forms (EPM1 and EPM2) and for sialidoses, in which different neurophysiological features reflect the different clinical presentation and severity of stimulus reflex vs. spontaneous myoclonus. However, this certainly also occurs for other, rarer PMEs, which are often reported in single cases or minimal case series, preventing an analysis of the comparability of the results obtained by the applied examination protocols. The opportunity to share similar examination procedures could significantly promote better recognition of the specific phenotypes and could better address significant hypotheses to explain genotype-phenotype relationships. □

Disclosures.
The authors have no conflict of interest to disclose.

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References


Neurophysiology of myoclonus and progressive myoclonus epilepsies


