Myoclonus

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MYOCLONUS

A DIAGNOSTIC CHALLENGE

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Myoclonus

A diagnostic challenge

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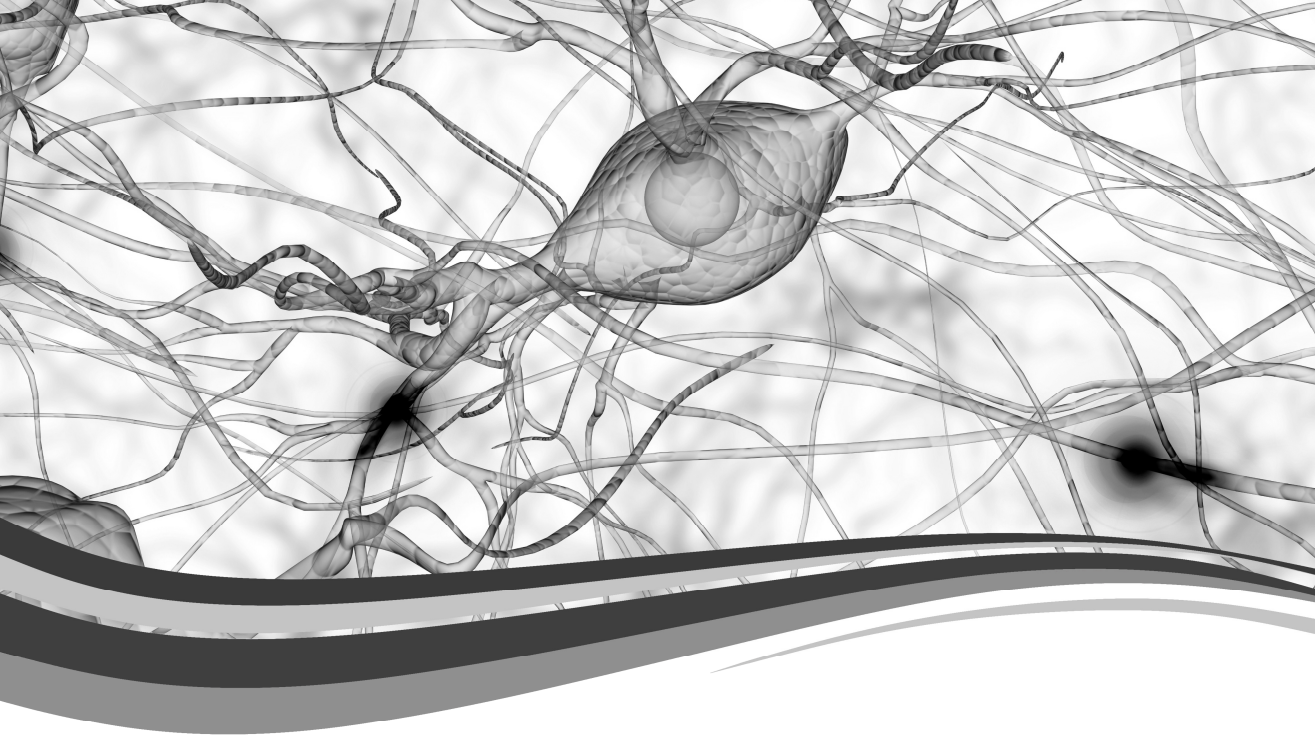
Vivat, crescat, floreat
'Leef, groei en bloei'

In dierbare herinnering aan mijn vader
Gerard Zutt (1950-2011),
van wie ik veel heb geleerd en
die mij deze levensspreuk meegaf.

CONTENT



Chapter 1 Introduction and Aims

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1.1 Definition and classification

Myoclonus is characterized by sudden, brief, involuntary jerks of a muscle or group of muscles. It can be caused by muscle contraction (positive myoclonus) or by interruptions of tonic muscle activity (negative myoclonus). Myoclonus was first described in 1881 by Friedreich using the term “paramyoclonus multiplex”.[1] In 1963, Lance and Adams described negative myoclonus in patients with post-hypoxic myoclonus.[2]

Myoclonus can be classified according to the origin of the myoclonic jerks: generation from the cortex, the subcortical areas (including brainstem), the spinal cord or peripheral nerves. Each anatomical category has its own clinical and electrophysiological characteristics, aetiology and treatment options.

1.2 Epidemiology

Little is known about the epidemiology of myoclonus, as it has a wide clinical spectrum with numerous causes, persons with mild myoclonus may not consult a physician, physicians may not always recognize myoclonic jerks, and most importantly, myoclonus can be overshadowed by other neurological features. For these reasons, the prevalence of myoclonus is likely to be underestimated. There is one study, carried out in a defined population in Olmsted Country from 1976 to 1990, showing an average annual incidence of myoclonus of 1.3 cases per 100,000 and a lifetime prevalence of persistent and pathological myoclonus in 1990 of 8.6 cases per 100,000. In 72% of cases, the cause of myoclonus was symptomatic, followed by 17% with an epileptic origin, and 11% essential myoclonus.[3,4] In patients presenting at the emergency room with movement disorders, 27.6% suffered from myoclonus, mostly provoked by a metabolic disturbance or drugs.[5]

1.3 Clinical presentation

The clinical presentation of myoclonus has different aspects, including the circumstances of appearance, the distribution, and the division into positive and negative myoclonus.

The relation to motor activity can be classified as myoclonus at rest or during voluntary activity such as action or intention. Action myoclonus is frequently seen in patients with cortical myoclonus. Reflex myoclonus can be provoked by unexpected tactile, visual or auditory stimuli. Usually, the fingers and toes are the most sensitive areas to a tactile stimulus, which can induce a series of

myoclonus.[6] Reflex myoclonus is an important feature of cortical and brainstem myoclonus.

The distribution of myoclonus can be focal, segmental, axial or generalized. In focal myoclonus the jerks are restricted to a defined body part and are most frequently generated in the cortex. Segmental myoclonus involves adjacent areas of one segment of the body (for example one limb) and usually reflects spinal myoclonus. Multifocal myoclonus involves two or more nonadjacent areas of the body. Multifocal myoclonus can be seen in subcortical or cortical myoclonus for instance in progressive and static myoclonus encephalopathy or metabolic disorders. Generalized myoclonus involves synchronous jerks of multiple segments and is usually an expression of (propio-) spinal or brainstem myoclonus such as reticular reflex myoclonus or excessive startle reflexes.

The temporal pattern of myoclonus is generally arrhythmic, but it can be rhythmic (in segmental myoclonus or palatal myoclonus - therefore, the latter is also referred to as palatal tremor). In rare cases, the pattern is oscillatory and resembles fast tremor. Myoclonus can be synchronized (in brainstem reticular reflex myoclonus) or non-synchronized.

Myoclonus is the result of muscular contractions (positive myoclonus) or on an interruption of muscle tone (negative myoclonus). Both cortical and subcortical mechanisms may be involved in the generation of negative myoclonus.[7] Three forms of negative myoclonus have been described.[8] First, ‘asterixis’, also called flapping tremor, probably has a subcortical generator and can be seen in patients with a toxic-metabolic encephalopathy, for instance in liver failure.[9] This negative myoclonus is caused by a sudden interruption of ongoing muscle contraction and a brief lapse in limb posture. It is usually bilateral and rhythmic. Unilateral asterixis can be seen in patients with thalamic lesions.[10] The second form of negative myoclonus involves the axial and proximal lower limbs, resulting in patients losing their posture. For example in Lance-Adams post-anoxic syndrome, this can cause a person to fall. The third form of negative myoclonus is epileptic negative myoclonus, defined as an interruption of muscle activity time-locked to an epileptic EEG abnormality without antecedent appearance of positive myoclonus, seen in epileptic disorders.[7,11]

1.4 Myoclonus assigned to its anatomical classification

1.4.1 Cortical myoclonus

1.4.1.1 Pathophysiology

Cortical myoclonus is the result of abnormal firing of the sensorimotor cortex. This generated activity travels through the fast corticospinal pathways, resulting in short-lasting myoclonic jerks in muscles.[12,13] Neuropathological studies however show broader involvement of other brain areas including the cerebellum, fronto-temporal cortex, hippocampus, and thalamus, among other areas.[14,15] The exact mechanisms that induce cortical hyperexcitability and their localization in the brain are not fully known. A generator in the primary motor cortex is suggested by cortical lesions inducing myoclonus and supported by magnetoencephalography (MEG) studies.[16] An alternative hypothesis includes functional cortical changes due to a channelopathies, as recognized in the inherited myoclonic epilepsy syndromes. Finally, changes in sensory input may also be an important factor in the generation of cortical myoclonus, as suggested by its stimulus sensitivity and the giant somatosensory evoked potentials (SSEPs) which can be found on electrophysiological examination. Based on the cerebellar changes in patients with celiac disease and those with familial cortical myoclonic tremor and epilepsy (FCMTE), both presenting with cortical myoclonus, it has been hypothesized that decreased cortical inhibition via the cerebello-thalamo-cortical loop is yet another cause of cortical myoclonus.[14]

1.4.1.2 Clinical presentation

Jerks manifest predominantly (multi)focally and are often exacerbated by voluntary movements, although they can also occur spontaneously. Myoclonus can often be auditory, somasthetic, or provoked by a verbal stimulus (reflex myoclonus).[17,18] Because of the somatotopic distribution of the cortex, body parts with large cortical presentation, like mouth, face and hands, are more affected than other parts.[17,18]

1.4.1.3 Electrophysiological testing

Video-polymyography in cortical myoclonus reveals short EMG bursts (usually 50-100 ms). [19,20] On the SSEP, enlarged (giant) cortical amplitude reflects a decreased intra-cortical inhibition. Hereby, the P27 and N35 peaks have large amplitudes (> 5uV).[16]

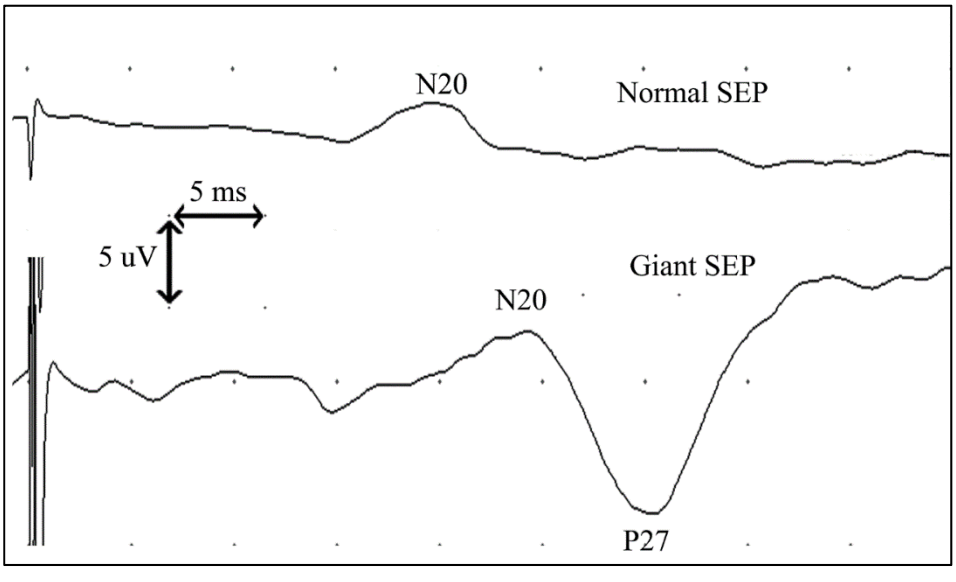

Figure 1 - Giant SSEP

Example of a giant somatosensory evoked potential (SSEP). Upper trace: a normal SSEP response showing a normal voltage N20 response at appropriate latency. Lower trace: Giant SSEP response in a patient with mitochondrial encephalopathy and cortical myoclonus. The N20 is slightly delayed, and the late potential complex (P27/N30) is enlarged.

In patients with cortical myoclonus, a C-reflex can be present. It can be seen in the ipsilateral thenar muscle with a latency of around 45 ms, and sometimes contralateral with a delay of 10-15 ms pointing to interhemispheric spread.[20] With the use of EEG back-averaging, a “time-locked” biphasic potential can be revealed on the contralateral sensory cortex preceding the jerks seen on the EMG.[19] The biphasic potential precedes the EMG activity by 15-25 ms for jerks in the arms and by 40 ms for jerks in the legs.[19] In high-frequency or continuous myoclonus, back-averaging is technically not possible, and coherence analysis can be performed to reveal the correlation between cortical and muscle activity and between muscles.[21] In cortical myoclonus, an exaggerated corticomuscular and intermuscular coherence in the alpha and beta band can be detected with a phase difference consistent with a cortical drive.[21-24]

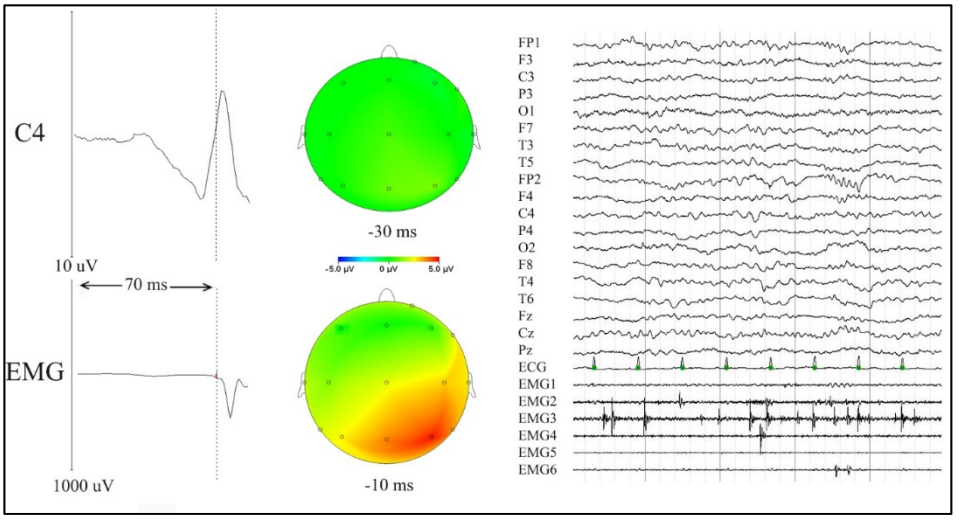

Figure 2 - Backaveraging in cortical myoclonus

Example of a cortical potential preceding the myoclonus in a patient with cortical myoclonus due to encephalitis associated with anti-voltage-gated potassium channel (VGKC) antibodies. Right panel: 5 seconds of raw EEG and EMG data of muscles of the left arm. Note the short duration of the EMG bursts. The EEG shows generalized slowing but no epileptic abnormalities. Left panel: after backaveraging of 162 epochs of myoclonus, a clear positive-negative potential can be seen in the right centroparietal electrodes which starts at approximately 25 ms before myoclonus onset. Middle panel: Topographic mapping: at 30 ms before myoclonus onset, no cortical potential is visible, while at 10 ms before myoclonus onset, the right centroparietal field distribution can be appreciated.

All the described electrophysiological findings support the clinical diagnosis of cortical myoclonus. However, the sensitivity and specificity of electrophysiological testing in unselected patients with myoclonus is largely unknown with most evidence to date involving only small patient cohorts, highly selected patients with a specific underlying etiological disorder, or reliant on expert opinion.[25-27]

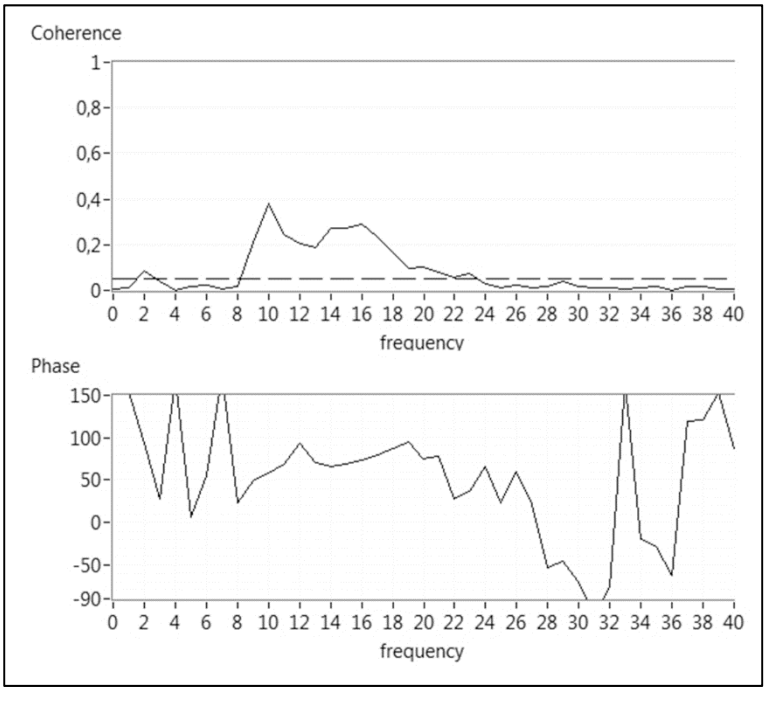

Figure 3 - EEG-EMG coherence analysis in cortical myclonus

Example of coherence analysis in a patient with high frequency cortical myoclonus. EEG channel: C3 EMG channel: first dorsal interosseus muscle on the right side (raw data not shown). Analysis of a 60 seconds duration epoch in which high frequency myoclonus of 7-10 Hz was present. Averaging of 60 epochs of 1000 ms duration. Upper panel: Coherence vs frequency plot. The dotted line indicates the level above which coherence can be considered significant. Significant coherence is present in the 9-23 Hz frequency range. Lower panel: Phase plot which shows an increasing phase difference with increasing frequency. This means that EEG leads phase with a calculated lead time of 19 ms, compatible with the expected cortico-muscular conduction time.

1.4.1.4 Etiology of cortical myoclonus

A wide variety of acquired and genetic disorders can manifest as cortical myoclonus. In general, acute or subacute onset and / or a fast progression of myoclonus are important clues for an acquired cause, whereas an early-onset disease with a slower progression is more characteristic for a genetic disorder. Specific clinical features that co-exist with myoclonus often provide important information regarding the underlying disorder.

In daily clinical practice, drug-induced myoclonus is one of the most important causes. Alternative acquired causes include toxins or metabolic derangements, infections or autoimmune disorders. If these acquired causes of cortical myoclonus are unlikely, myoclonus can be the manifestation of progressive myoclonic and static myoclonic encephalopathies. In patients with progressive

myoclonic encephalopathies, it is usually difficult to make the exact diagnosis, but by using subgroups based on associated neurological symptoms such as the presence or absence of epilepsy, ataxia and / or dementia, a more focused diagnostic strategy is possible. In clinical practice it is therefore important to determine the most prominent clinical symptoms. In late-onset, progressive myoclonic encephalopathy with dementia or parkinsonism, one must consider a neurodegenerative disorder. The differential diagnosis includes Alzheimer's disease, Parkinson's disease, multiple system atrophy (MSA), and less commonly dementia with Lewy bodies, Huntington's disease, and corticobasal degeneration (CBD).[25,28,29] In case of myoclonic encephalopathy with a rapidly progressive dementia, a prion disease must be considered.[30]

Static, i.e. non-progressive myoclonic encephalopathy mainly occurs in patients with post-anoxic encephalopathy. Post-anoxic myoclonus can be divided into early myoclonus developing within 72 hours after the event, and late onset (>72 hours) myoclonus.[31]

1.4.2 Subcortical myoclonus

Subcortical myoclonus is generated between the cortex and spinal cord, a part of these cases originate from the brainstem but in the majority the origin of this type of myoclonus is undetermined. Therefore, recently, experts on the field of myoclonus argued against the term subcortical myoclonus. However, due to the absence of accurate alternative terminology, the term subcortical myoclonus will be applied in this thesis, keeping in mind the new considerations.

The next paragraphs describe the different forms of brain stem myoclonus and Myoclonus Dystonia, considered subcortical myoclonus.

1.4.2.1 Brainstem myoclonus

Brainstem myoclonus can present with different phenotypes including, physiological myoclonus (hiccups and hypnagogic myoclonus), reticular reflex myoclonus, startle disease, opsoclonus myoclonus,[30,32] and orthostatic myoclonus.[33,34] Reticular reflex myoclonus and startle disease are characterized by generalized, synchronized, predominantly axial jerks. In both disorders myoclonus can be easily provoked by external stimuli.[35,36]

In brainstem myoclonus, polymyography show muscle contraction starting in the muscles innervated by the caudal brainstem (e.g. sternocleidomastoideus

and trapezius muscles) with a rostral and caudal activation of muscles.[37] In contrast to reticular reflex myoclonus, the EMG responses in the intrinsic hand and foot muscles in startle syndromes are relatively delayed. Furthermore, the latency of muscle activity after auditory stimuli in reticular reflex myoclonus are compatible with the pyramidal tract, while the startle reflex latency is longer as it travels through the reticulo-spinal pathways.

Reticular reflex myoclonus can be caused by post-hypoxic encephalopathy, encephalitis, and metabolic derangements (e.g. uraemia). The most common form of startle syndrome is hyperekplexia characterized by startling from birth, short periods of startle-induced stiffness during which voluntary movements are impossible, and generalized stiffness at birth. Hyperekplexia has an autosomal dominant inheritance most commonly caused by mutations in the *GLRA1*, *SCL6A56*, and *GLRB* genes.[38-40] In rare cases hyperekplexia can have an acquired cause including brainstem encephalitis, or a lesion in the brainstem (e.g. Multiple Sclerosis, vascular lesion).[37,41]

1.4.2.2 Myoclonus-Dystonia

The most common form of subcortical myoclonus is Myoclonus-Dystonia. Myoclonus-Dystonia is characterized by multifocal myoclonus combined with mild to moderate dystonia. Myoclonus predominantly affect the upper body, although also involve the lower limbs, face and larynx in approximately 25% of cases.[42,43] Dystonia usually involves the neck and upper limbs (writer's cramp). Both the myoclonus and dystonia can exacerbate by posture, action or stress, with myoclonus typically improving with alcohol.[43-45] Myoclonus-Dystonia is often accompanied by psychiatric co-morbidity including anxiety, panic attacks and obsessive-compulsive disorder.[46]

Polymyographic recordings show arrhythmic with EMG bursts ranges from 50 to 250 ms, with longer jerks being probably part of dystonic jerks. Local field potential recordings from the globus pallidus internus (GPi) in Myoclonus-Dystonia patients showed significant coherence between GPi and dystonic muscle activity in the 4-7 Hz 'dystonic band'. The cerebellum also seems to play an important part in the pathogenesis. In an eye movement study, impaired saccadic adaptation in patients with Myoclonus-Dystonia was associated with cerebellar dysfunction. Another clue in this regard is the fact that a major brain-specific *SGCE* isoform has a high expression in the cerebellum.[47] Electrophysiological studies including (EMG-) EEG, and SSEP

reveal no changes in cortical excitability. Cortical functional changes as detected in a transcranial magnetic stimulation study are thought to be secondary to basal ganglia pathology.[45,48]

1.4.3 Spinal myoclonus

Spinal myoclonus is generated in the spinal cord. Spinal jerks can be subdivided into segmental or propriospinal myoclonus.

1.4.3.1 Segmental myoclonus

Segmental myoclonus is characterized by continuous, rhythmic jerks, unaffected by voluntary movement. The jerks are not stimulus-sensitive. Segmental myoclonus often persists during sleep. The myoclonus results from abnormal discharges from one or two contiguous spinal segments. It is hypothesized that spinal segmental systems become hyperexcitable, resulting in jerks in muscles innervated by the particular segment(s). Polymyographic recordings show jerks with a frequency ranging from 1 to 200 per minute, and burst duration up to 1000 ms. Segmental myoclonus is mostly caused by a lesion in the spinal cord, such as a neoplasia, syringomyelia, myelitis or ischemia.

1.4.3.2 Propriospinal myoclonus

Propriospinal myoclonus is characterized by rhythmic, spontaneous and sometimes stimulus-sensitive jerks.[49,50] Lying down often provokes propriospinal myoclonus. These jerks mainly affect the axial muscles (trunk and abdominal muscles), sometimes expanding to the distal limbs but excluding the cranially innervated muscles.[49,50]

Propriospinal myoclonus is presumed to be caused by a spinal generator that induces muscle activity spreading up and down the spinal cord. Polymyographic recordings show initially bursts in the midthoracic segments followed by distribution up and down the spinal cord via propriospinal pathways.[50] There is a fixed pattern of muscle activation with slow spreading of activity with repetitive bursts (frequency 1-7 Hz) with a long duration (up to several 100 ms). In some patients with propriospinal myoclonus, lesions of the spinal cord have been reported, but usually no cause can be detected.[51] In the last few years, psychogenic-induced propriospinal myoclonus is being increasingly recognized. In a study of 20 patients with idiopathic propriospinal

myoclonus, a definite Bereitschaftspotential (BP) was detected in six patients and a possible BP in nine patients, suggesting a psychogenic origin.[52]

1.4.4 Peripheral myoclonus

Peripheral myoclonus is characterized by jerks limited to one segment of the body, usually the proximal part of a limb or the trunk. Myoclonus can be triggered by voluntary movement.[53] In most cases peripheral myoclonus is caused by damage to the peripheral nerve system (PNS), and the EMG shows varied burst duration.[53]

Any peripheral nerve lesion that is accompanied by fasciculations or myokymia may result in small myoclonic movements, especially if enlarged motor units are involved, since this will result in an increase in the mechanical effect of axonal discharges. Often, clear signs of peripheral nerve dysfunction are present, and the diagnosis of peripheral myoclonus is evident. With more complex nerve lesions such as multiple radiculopathy, the diagnosis may be more difficult, and EMG may be required to confirm the presence of a chronic neurogenic lesion. Other examples of causes of damage of the peripheral nervous system (PNS) inducing peripheral myoclonus include lesions of the brachial plexus[54], spinal root[55], the long thoracic nerve or after amputation ("jumping stump").[53,56]

1.4.5 Functional myoclonic jerks

In approximately 10-20% of functional movement disorders, patients suffer from functional (psychogenic) myoclonic jerks.[57,58] In a study of 212 patients with myoclonus, 8.5% were defined as functional.[58] Functional myoclonic jerks are often variable and distractible. Patients have myoclonic jerks at rest, and in most patients, the jerks increase with movement. Frequently, the onset of functional jerks is acute with a fast progression and improvement of motor function by distraction and suggestibility of symptoms.[52,57] Entrainment is often present; when executing a repetitive movement with a different body part, the functional myoclonic jerks adopt the same frequency. Functional myoclonic jerks are mostly segmental, but can be focal or generalized. Patients often suffer from a coexisting psychiatric disease like depression, anxiety or panic disorders. In case of diagnostic uncertainty, electrophysiological testing can be useful to differentiate from alternative diagnoses. In case of functional myoclonic jerks, the burst duration and / or recruitment order of the affected

muscles is often highly variable. Furthermore, a consistent characteristic pre-movement potential (BP) can be detected in the EEG on back-averaging. However, one has to be cautious, because it has been demonstrated that tics can also be preceded by a BP, and the absence of this potential does not exclude a functional origin.[52,59]

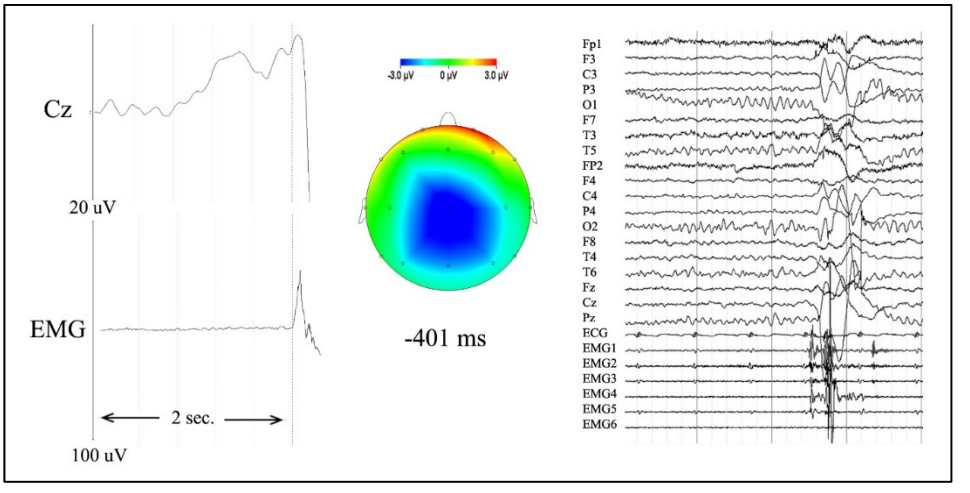

Figure 4 - Bereitschaftspotential

Example of a Bereitschaftpotential (BP) in a young woman with generalized myoclonic jerks of functional origin. Right panel: 4 seconds of raw EEG and EMG data. Note the long duration EMG bursts (+/- 500 ms), and the artefact in the EEG as the consequence of the jerks. Prior to the jerk, no EEG abnormalities can be seen. Left panel: After back-averaging of 63 epochs of jerks, a BP can be seen, which starts approximately 1 second before jerk onset. Middle panel: Topographic mapping of the BP at 401 ms prior the functional myoclonic jerk onset. View from the top. Note the centroparietal field distribution.

1.5 Differential diagnosis

Myoclonus must be differentiated from other hyperkinetic movement disorders. Alternative diagnoses include tremor, dystonia, tics, chorea, and simple partial seizures. During the neurological examination, one should search for specific symptoms differentiating myoclonus from these other movement disorders. For example, cortical myoclonus or brainstem myoclonus is characterized by its stimulus sensitivity, not present in other movement disorders. In contrast to tics, myoclonus is not suppressible, often interferes with voluntary movements and increases with muscle activation. In case of a tremor, there is a rhythmic oscillatory movement, while myoclonus is generally arrhythmic. In dystonic jerks, the dystonic posture can often be relieved by a sensory trick, not occurring in myoclonus. In chorea the movements are more fluent and show usually a more random-like pattern and patient incorporate

movements in seemingly purposeful movements. However, it should be noted that of course myoclonic jerks can co-occur in patients together with other movement disorders.

1.6 Treatment

The first focus of treatment in myoclonus should be aimed at treating the underlying cause, such as stopping drugs likely to cause myoclonus, removal of toxins, or correction of metabolic disturbances.[35] However, in the majority of patients, causal treatment of the underlying disorder is not possible, and symptomatic treatment is required. Symptomatic treatment can also be a challenge. The commonly used drugs are only effective in a proportion of patients and therapy is often limited by side effects. For this reason, initial low doses with a slow increase are recommended for almost all drugs used in myoclonus. Several drugs may be explored to find the optimal treatment in individual patients and polytherapy is generally more effective than monotherapy, especially for cortical myoclonus.[60] Table 1 provides an overview of the treatment options according to the anatomical subtype of myoclonus.

1.6.1 Cortical myoclonus

Cortical myoclonus is traditionally treated with drugs, which are beneficial in epilepsy due to the pathophysiological relationship between cortical myoclonus and epilepsy. In a cross-over trial in 21 patients with different causes of cortical myoclonus, piracetam significantly improved myoclonus. However, a high daily dose is required (up to 24 g/day). Because of its similarity to piracetam, the better tolerated levetiracetam is now considered the standard initial treatment of cortical myoclonus (daily dose up to 3000mg). Levetiracetam may be effective in both epileptic and non-epileptic cortical myoclonus. There is a long clinical experience of cortical myoclonus treatment with valproic acid and clonazepam. In a very small trial, milacemide seemed beneficial. Treatment of cortical myoclonus generally necessitates polytherapy, consisting of clonazepam, valproic acid and levetiracetam.[60]

1.6.2 Subcortical myoclonus

In the treatment of brainstem reticular reflex myoclonus, L-5-HTP may be effective, but this compound is often not well tolerated because of gastrointestinal side effects and, therefore, should be started at a low dose and increased slowly as well. Patients with hyperekplexia can be effectively

treated with clonazepam, and with this the stiffness may be more responsive than the startle reflexes and usually prevent patients from severe falls.

In opsoclonus myoclonus syndrome, myoclonus can also respond to clonazepam. If appropriate, treatment of the underlying disease with rituximab, ACTH or intravenous immunoglobulin therapy should be considered. Palatal myoclonus is difficult to treat. Clonazepam, carbamazepine, phenytoin, barbiturates and valproic acid can be tried, all with limited results. Other treatments include botulinum toxin and a tinnitus masking device. Regarding the treatment of orthostatic myoclonus, some beneficial effect was reported with clonazepam and gabapentin.[60]

Clonazepam is a first choice treatment for Myoclonus-Dystonia, but recently Zonisamide proved to be well-tolerated and effective for myoclonus in Myoclonus-Dystonia as well.[61]

1.6.3 Spinal myoclonus

In the symptomatic treatment of spinal myoclonus clonazepam is the first drug of choice.[51] Other options for treatment are carbamazepine, tetrabenazine, zonisamide and botulinum toxin.[60]

1.6.4 Peripheral myoclonus

Peripheral myoclonus sometimes can be effectively treated with clonazepam. In some cases botulinum toxin can also be considered as symptomatic treatment.

Table 1 - Treatment of myoclonus

	First choice of treatment	Alternative treatment	Other therapy
Cortical myoclonus			
In general	Levetiracetam Piracetam	Valproic acid, Clonazepam	Add on therapy with: Primidone, Phenobarbital
Posthypoxic cortical reflex myoclonus	Clonazepam Valproic acid		
Subcortical myoclonus			
Myoclonus dystonia	Clonazepam Trihexyphenidyl	Levodopa, L-5-HTTP*,Sodium oxybate	Deep brain stimulation
Opsoclonus myoclonus syndrome	Clonazepam		Treatment of underlying syndrome: Rituximab, ACTH, iv immunoglobulin
Hyperekplexia	Clonazepam		
Reticular reflex myoclonus	L-5-HTTP*		
Palatal myoclonus	Clonazepam, Carbamazepine Botulinum toxin		Tinnitus masking device
Ortostatic myoclonus	Clonazepam	Gabapentin	
Spinal myoclonus			
Segmental myoclonus	Clonazepam	Carbamazepine, Tetrabenazin, Botulinum toxin	
Propriospinal myoclonus	Clonazepam	Zonisamide	
Peripheral myoclonus			
Hemifacial spasm	Botulinum toxin	Carbamazepine Clonazepam	Microsurgical vascular decompression
Others	Botulinum toxin		

** = in combination with a decarboxylase inhibitor*

1.6.5 Functional myoclonic jerks

The treatment of functional myoclonic jerks consist of specialised physiotherapy and rehabilitation, combined when necessary with pharmacological treatment of comorbid psychiatric disorders.[62,63] Treatment of functional jerks must be initiated soon after diagnosis, because a longer duration of the syndrome is related to poor outcome.[57]

1.7 Aims of the thesis

As outlined above, myoclonus is a common and varied phenomenon in clinical practice, the anatomical sub-classification of which is often complex and difficult to disentangle. However, accurate diagnosis and determination of subtype is essential in delineating a differential diagnosis, as well as guiding appropriate management strategies. This thesis aims to explore the clinical diagnosis and anatomical subtyping of myoclonus, which investigative tools are most useful in aiding this process and how these may be combined in determining diagnosis.

1.7.1 Development of a novel diagnostic algorithm for patients with myoclonus (Chapter 2)

In recent years, next-generation sequencing (NGS) has revolutionised molecular genetic diagnostics, allowing simultaneous analysis of several hundred genes. When applied to well phenotyped clinical cohorts, NGS can vastly improve the yield of genetic diagnoses in clinical heterogeneous disorders, such as myoclonus.[64] As such, these techniques are increasingly being incorporated into clinical practice, but often lack a defined clinical framework within which they should be applied. The first piece of work for this thesis focuses on developing a novel and currently applicable diagnostic approach to patients with myoclonus, including implementation of these newer molecular diagnostic techniques. To demonstrate the potential application of the algorithm, Chapter 2A illustrates its implementation in aiding diagnosis in a patient with an atypical Progressive Myoclonus Epilepsy (PME).

1.7.2 The importance of clinical phenotyping in diagnosis and classification of myoclonus

Clinical phenotyping: clinical predictors of mutation status (Chapter 3)

Although Chapter 2 highlights the potential impact of NGS, the data generated using these techniques is vast, often complex, and frequently requires an understanding of the clinical context to allow their interpretation.[64] Core to the algorithm in Chapter 2 is the importance of accurate and detailed clinical phenotyping. Myoclonus Dystonia is a common myoclonus syndrome characterized by young onset myoclonus and dystonia with mutations in the epsilon sarcoglycan (*SGCE*) gene observed in a proportion of cases. Although several clinical factors have been proposed as predictor of an *SGCE* mutation,

discrimination of *SGCE* mutation positive from mutation negative M-D cases remains difficult. Chapter 3 reviews the possibility to use specific motor characteristics to identify those patients most likely to have an *SGCE* mutation.

Clinical phenotyping: the importance of non-motor characteristics (Chapter 4)

Psychopathology appear to be present in a large part of patients with a functional movement disorder.[65] However, also organic movement disorders are frequently accompanied by psychopathology.[46,66] Furthermore, quality of life seems to be equally impaired in functional as in organic movement disorders.[67] Little is known about psychopathology in functional jerks and no comparison has been made with an appropriate control group. In Chapter 4, a systematic comparison is made to examine the presence of depressive symptoms, anxiety, and quality of life in a cohort of adult patients with functional myoclonic jerks and cortical myoclonus.

1.7.3 The role of electrophysiological testing to aid diagnosis and sub-classification of myoclonus

Although a variety of electrophysiological testing methods are often employed in clinical practice, their sensitivity and specificity in aiding diagnosis in myoclonus remains largely unknown. The next two chapters focus on determining the contribution of electrophysiological testing, in isolation and in conjunction with clinical phenotyping, in aiding diagnosis and sub-classification.

a) Retrospective case review (Chapter 5)

This chapter explores the combination of clinical phenotypic detail and electrophysiological findings in determining diagnostic accuracy in a heterogeneous cohort of myoclonus patients retrospectively. Patients with myoclonus as initial clinical diagnosis and in whom video-polymyography was part of the diagnostic work-up were included. In this study, the electrophysiological diagnosis was used as final diagnosis. The number of cases were evaluated in which the clinical diagnosis was confirmed or changed after electrophysiological testing. In addition, the clinical characteristics were examined to explore if these could discriminate between the different anatomical myoclonus subtypes.

b) Prospective approach (Chapter 6)

The retrospective study suggested that electrophysiological testing was important to verify the clinical diagnosis of myoclonus and its subtype. However, the value of this result was limited due to the retrospective study design and absence of an indisputable etiological diagnosis or gold standard. For this reason, a prospective study was initiated and to increase the certainty of the final diagnosis, the diagnosis was evaluated after clinical examining, electrophysiological testing, review by a movement disorder specialist, and after at least six months of follow-up.

1.7.4 The contribution of novel electrophysiological techniques to diagnostic testing (Chapter 7)

Here it will be evaluated whether a novel electrophysiological biomarker 'event-related EEG desynchronization' (ERD) can be applied to distinguish functional myoclonic jerks and cortical myoclonus, and whether the combination of electrophysiological biomarkers (BP and ERD) can improve the electrophysiological identification of functional myoclonic jerks.

Finally, Chapter 8 summarises the findings from each of these chapters, as well as suggests areas of exploration for future studies.

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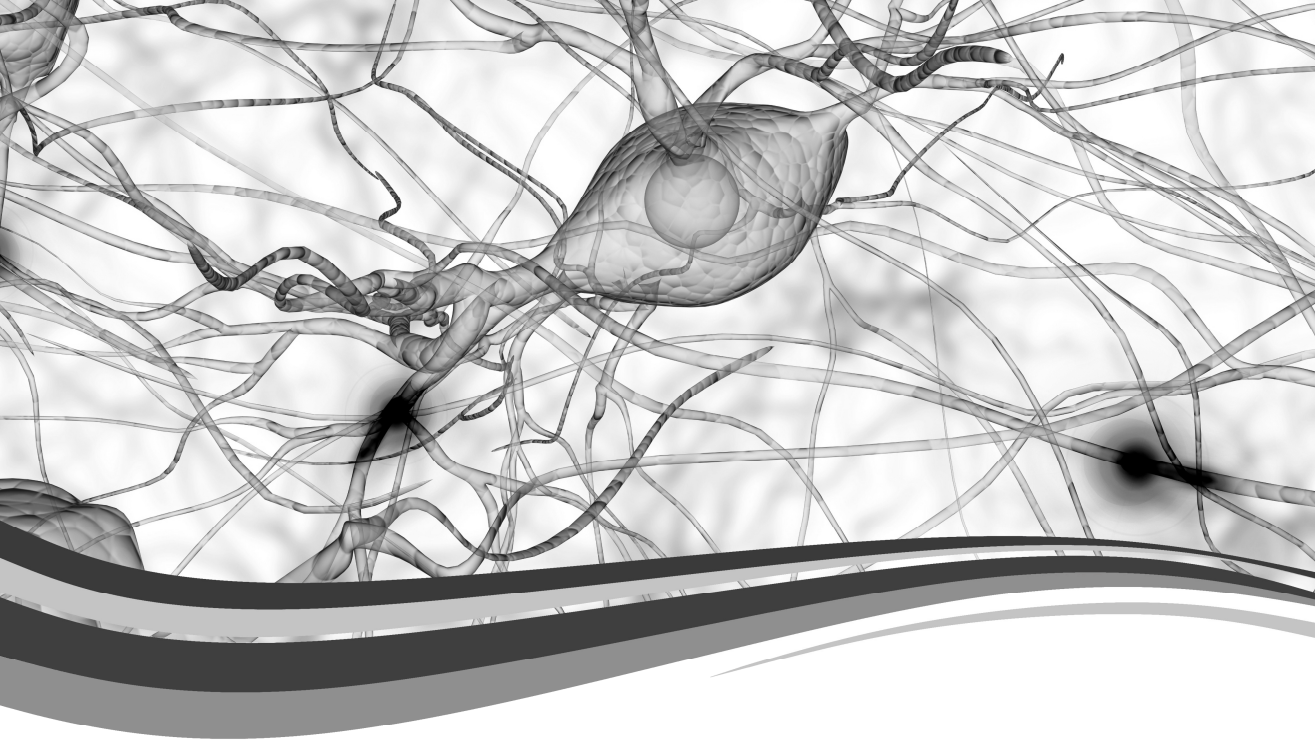

Chapter 2 A novel diagnostic approach to patients with myoclonus

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2.1 Abstract

Myoclonus is a hyperkinetic movement disorder characterized by brief, involuntary muscular jerks. Recognition of myoclonus and determination of the underlying aetiology remains challenging given that both acquired and genetically determined disorders have varied manifestations. The diagnostic work-up in myoclonus is often time-consuming and costly, and a definitive diagnosis is reached in only a minority of patients. On the basis of a systematic literature review up to June 2015, we propose a novel diagnostic eight-step algorithm to help clinicians accurately, efficiently and cost-effectively diagnose myoclonus. The large number of genes implicated in myoclonus and the wide clinical variation of these genetic disorders emphasize the need for novel diagnostic techniques. Therefore, and for the first time, we incorporate next-generation sequencing (NGS) in a diagnostic algorithm for myoclonus. The initial step of the algorithm is to confirm whether the movement disorder phenotype is consistent with, myoclonus, and to define its anatomical subtype. The next steps are aimed at identification of both treatable acquired causes and those genetic causes of myoclonus that require a diagnostic approach other than NGS. Finally, other genetic diseases that could cause myoclonus can be investigated simultaneously by NGS techniques. To facilitate NGS diagnostics, we provide a comprehensive list of genes associated with myoclonus.

2.2 Introduction

Myoclonus is a complex hyperkinetic movement disorder characterized by sudden, brief, involuntary jerks of a single muscle or a group of muscles. Diagnosis of jerky movement as myoclonus can be difficult, as was shown in a recent study by movement disorder specialists.[1]

Little is known about the epidemiology of myoclonus, mainly because this disorder has a wide spectrum of clinical manifestations and numerous causes. The only available epidemiological study of myoclonus comprised a defined population recruited in Olmsted County from 1976 to 1990, and revealed a lifetime prevalence of persistent and pathological myoclonus of 8.6 cases per 100,000 people.[2]

Three approaches to the classification and diagnosis of myoclonus exist: clinical, aetiological and anatomical. The clinical classification is based on clinical signs, including the distribution and temporal pattern of jerks and their relationship to motor activity. The aetiological classification is divided into four subgroups: physiological myoclonus, essential myoclonus, epileptic myoclonus, and symptomatic myoclonus.[3] In clinical practice, the initial approach is guided by the anatomical classification. Myoclonus can be generated in the cortex, in subcortical areas, in the spinal cord, or in the peripheral nerves. No epidemiological studies have been conducted on the anatomical subtypes of myoclonus. Cortical myoclonus is the most common type of myoclonus,[4,5] whereas spinal myoclonus and peripheral myoclonus are rare.[6] The anatomical locus of myoclonus is associated with clinical and electrophysiological characteristics that can be linked to an aetiological differential diagnosis, thereby guiding the selection of treatment.[7]

The next challenge in myoclonus diagnostics is to determine the cause. A wide variety of acquired and genetic disorders can manifest as myoclonus. As some of these disorders are treatable, it is important to identify the aetiology. For example, many commonly used drugs can cause myoclonus, and discontinuation of the drug often leads to immediate cessation of the condition. Other treatable causes include infections, systemic metabolic derangement, autoantibody disorders, and certain inborn metabolic abnormalities.

In cases where the myoclonus is likely to be of genetic origin, conventional Sanger sequencing and new molecular diagnostic techniques, including next-

generation sequencing (NGS), can be used to identify the cause. NGS has enabled a shift from targeted single gene mutation analysis to massively parallel sequencing of hundreds of genes in a single assay.[8] The types of NGS include whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted resequencing (TRS) panels which focus on a selection of genes.[9] Both established and potential genetic causes of myoclonus-associated diseases can be tested simultaneously with NGS. This approach has already proved effective in highly heterogeneous neurological disorders such as epilepsy.[10] In patients with movement disorders (hereditary spastic paraplegia, cerebellar ataxia and dystonia), NGS increased the diagnostic yield four-fold (from 5% to 20%) compared with Sanger sequencing.[11] The number of genes associated with myoclonus-inducing disease has grown substantially, and will continue to increase in the coming years. Moreover, costs and turnaround time of the various NGS techniques are decreasing rapidly. Thus, we expect that NGS will largely replace specific biochemical analyses and conventional Sanger sequencing in the diagnostic approach to myoclonus.

Here, we present a novel diagnostic algorithm for myoclonus. This algorithm is based on a systematic review (Supplementary Appendix 1) of all the causes of myoclonus, and includes-for the first time-the systematic use of targeted NGS. We also provide a comprehensive overview of genes reported to be associated with myoclonus, together with their key clinical features, to facilitate the use of targeted NGS.

2.3 Clinical approach to myoclonus

In this section, we propose a new diagnostic algorithm for myoclonus consisting of eight consecutive steps (Figure 1).

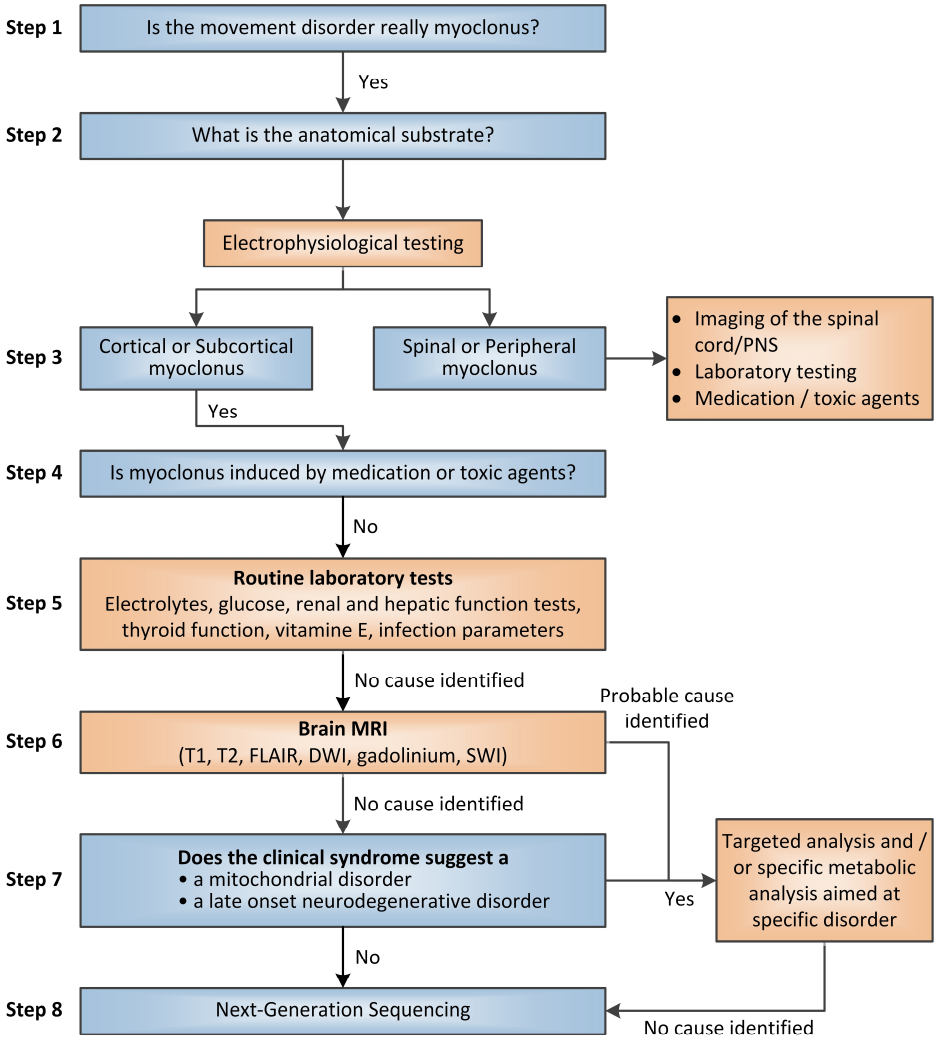


Figure 1 - New diagnostic myoclonus algorithm consisting of eight consecutive steps

2.3.1 Step 1: is the symptom really myoclonus?

Myoclonus is characterized by sudden, brief, involuntary jerks of a muscle or a group of muscles, caused by muscular contraction (positive myoclonus) or interruption of muscle activity (negative myoclonus).[12,13] Three types of negative myoclonus have been described: asterixis (flapping tremor of the hands when the wrist is extended) in patients with a toxic-metabolic encephalopathy;[14] negative myoclonus involving the axial muscles and lower limbs, which results in a wobbling gait and sudden falls;[15] and epileptic

negative myoclonus. Epileptic negative myoclonus is defined as an interruption of muscle activity time-locked to an epileptic EEG abnormality, without evidence of antecedent positive myoclonus. Epileptic negative myoclonus can be observed in a heterogeneous range of epileptic disorders.[16,17]

Myoclonus must be distinguished from other hyperkinetic movement disorders on the basis of a combination of clinical features and electrophysiological characteristics (Table 1). Alternative diagnoses include tremor, motor tics, chorea, dystonic jerks, and functional (psychogenic) jerks.

Table 1 - Mimics of myoclonus

Hyperkinetic movement disorder	Clinical characteristics	Electrophysiological characteristics
Functional (psychogenic) jerks	Inconsistent Reduces with distraction Entrainment	Variation in muscle involvement Variation in muscle recruitment order Variation in burst duration and/or amplitude Pre-movement potential on back-averaging
Chorea	Dance-like movements Non-patterned Iintegrated with normal movement	Variation in burst duration Variation in muscle recruitment order
Motor tics	Stereotypic or repetitive movements Onset in childhood Coexistence of other tics Can be voluntarily suppressed Premonitory sensations (urge) Relief after movement	Burst duration >100 ms Pre-movement potential on back-averaging
Dystonic jerks	Jerks together with dystonia Sensory tricks (geste antagoniste) can alleviate	Co-contraction agonist and antagonist Burst duration >100 ms Overflow (unintentional muscle contractions that accompany jerks, but is anatomically distinct from the primary dystonic movements]
Tremor	Sinusoidal and rhythmic	Alternating contractions of antagonistic muscles Steady frequency on accelerometry

2.3.2 Step 2: anatomical substrates of myoclonus

Myoclonus can be classified into peripheral, spinal (segmental and propriospinal), subcortical and cortical forms. Table 2 provides an overview of the important clinical and electrophysiological features of these myoclonus subtypes.

Table 2 - Characteristics that differentiate anatomical subtypes of myoclonus

Subtype of myoclonus	Clinical characteristics	Electrophysiological characteristics
Cortical	(Multi)focal or generalized Affects face, distal limbs Spontaneous, action-induced or stimulus-sensitive Negative myoclonus	Burst duration <100 ms Positive back-averaging Positive coherence Giant somatosensory evoked potentials C reflex
Subcortical		
Brainstem	Generalized or synchronous Axial Affects proximal limbs Spontaneous or stimulus-sensitive	Burst duration >100 ms Simultaneous rostral and caudal muscle activation Habituation
Myoclonus - Dystonia	(Multi)focal Axial, affects proximal limbs Spontaneous or action-induced	Burst duration >100 ms
Spinal		
Segmental	Focal or segmental Spontaneous (sometimes action-induced)	Burst duration >100 ms Distribution of bursts depends on the affected segment
Propriospinal	Fixed pattern Affects axial muscles Spontaneous or stimulus-sensitive (lying down can be a provoking factor)	Burst duration >100 ms Initiation in midthoracic segments followed by rostral and caudal activation Slow propagation velocity (5-10 m/s)
Peripheral	Focal Affects distal limbs Spontaneous or action-induced Can be accompanied by weakness and/or atrophy	Burst duration <50 ms Large motor unit action potentials Minipolymyoclonus Fasciculations/myokymia

Peripheral

Peripheral myoclonus has a focal distribution affecting the distal limbs, sometimes presenting as minipolymyoclonus owing to damage of the PNS.[18] Polymyography shows a short burst (<50 ms) duration, and electromyography (EMG) can help to detect and assess the severity of PNS damage.

Spinal

Spinal myoclonus can be divided into segmental myoclonus, in which adjacent body areas (for example, muscles in one arm, or muscles in the neck and proximal muscles in one arm) are involved, and propriospinal myoclonus, which is characterized by myoclonus of the trunk and abdominal muscles with

a fixed up-and-down pattern of muscle activation. Though sometimes organic, propriospinal myoclonus often has a psychogenic origin.[19]

Subcortical

The electrophysiological characteristics of subcortical myoclonus are a burst duration of >100 ms, and absence of cortical excitability (see below). Important subgroups of subcortical myoclonus are myoclonus-dystonia and brainstem myoclonus. The exact pathophysiology of myoclonus-dystonia is unclear. The neurophysiological features are not consistent with cortical myclonus, as the giant somatosensory evoked potential is absent, and no EEG-EMG correlation can be detected. A subcortical origin is suggested by improvement of myoclonus on deep brain stimulation of the globus pallidus internus.[20,21] As deep brain stimulation interferes with a network, this finding does not directly imply that the origin of the myoclonus is in the basal ganglia. The cerebellum also seems to have an important role in Myoclonus-Dystonia.[22]

The myoclonus in myoclonus-dystonia is multifocal, mostly affects the upper limbs, and is exacerbated by posture and action. Brainstem myoclonus is characterized by abnormal activity starting in the brainstem and spreading in both rostral and caudal directions, resulting in generalized myoclonus that is often stimulus-sensitive.

Cortical

Cortical myoclonus is the most frequent form of myoclonus,[4,23] and is characterized by multifocal myoclonus predominantly affecting the face and distal limbs (areas with large cortical representation). Cortical myoclonus is often exacerbated by voluntary movements, and is sometimes provoked by unexpected stimuli (referred to as reflex myoclonus or startle myoclonus). The clinical manifestations of cortical myoclonus include polyminimyoclonus, especially in parkinsonian syndromes, such as multiple system atrophy or corticobasal degeneration.

In cortical myoclonus, a short burst duration (<100 ms) is seen on polymyography. In terms of somatosensory evoked potentials, a giant potential often is detected.24 No definitive criteria for electrophysiological diagnosis of cortical myclonus have been accepted, but it is generally assumed that the P27 peak has an amplitude >5 mV and N35 peak has a suitable shape or amplitude >10 mV. Back-averaging of simultaneous EMG and EEG recordings can reveal that cortical discharges on EEG precede the jerks seen on

EMG.[25] In high-frequency myoclonus, coherence analysis demonstrates a correlation between cortical and muscle activity.[26] In cortical reflex myoclonus, a C reflex is often present, suggesting that the polysynaptic (long-loop) reflex mediated by the sensorimotor cortex is stronger than usual.[25,27,28] These electrophysiological features prove the existence of enhanced cortical excitability, but the exact pathogenesis of cortical myoclonic syndromes remains unclear. Although clinical symptoms arise from dysfunction of the cortex, neuropathological changes in the cerebellum have been detected in many patients with confirmed cortical myoclonus,[29,30] suggesting an important role for this structure.

2.3.2.1 Defining the anatomical locus

Unfortunately, differentiation of subtypes of myoclonus can be difficult in clinical practice, for several reasons. Little is known about the sensitivity and specificity of clinical features and electrophysiological tests in the heterogeneous myoclonus disorders. Moreover, more than one anatomical subtype can coexist in a given patient.

Different types of myoclonus have different aetiologies and, therefore, require different clinical approaches. Cortical and subcortical myoclonus can either be acquired or result from genetic disorders, warranting genetic testing in addition to MRI and laboratory tests, whereas spinal and peripheral myoclonus are usually acquired. The subsequent steps of the diagnostic algorithm aim at elucidating the underlying cause of the myoclonus by separating spinal and peripheral myoclonus (see step 3 in Figure 1) from cortical and subcortical myoclonus.

2.3.3 Step 3: defining the aetiology

Spinal or peripheral myoclonus

If the anatomical locus of the myoclonus has been established as peripheral or spinal, signs of muscle denervation and structural lesions must be assessed by appropriate electrophysiological testing and/or imaging. Furthermore, acute or subacute, fast progression, radiculopathy or polyradiculopathy, and systemic features (fever, skin rash, or joint involvement) suggest infectious or autoimmune cause, which should be confirmed with appropriate laboratory testing.

Peripheral myoclonus usually results from damage to the PNS, for example, brachial plexus lesions,[31] spinal root lesions,[32] or amputation of a distal limb ('jumping stump').[33] Discussion of the various disorders that can cause damage to the PNS is outside the scope of this Review.

Damage to the spinal cord can induce spinal myoclonus.[34-36] Segmental myoclonus is very rare, and is almost always caused by a structural spinal cord lesion. It is important to note that the vast majority of cases of propriospinal myoclonus are now considered to be functional movement disorders.[19] Furthermore, in rare cases, spinal myoclonus can be induced by medication[37-39] or infections,[40] underlining the need for careful evaluation of patients with this type of myoclonus.

Cortical and subcortical myoclonus

Cortical and subcortical myoclonus have a broad differential diagnosis. In general, acute or subacute onset and/or fast progression of myoclonus are important clues for an acquired cause, whereas an early-onset disease with a slower progression is more characteristic of a genetic disorder. Specific clinical features that coexist with myoclonus often provide important information regarding the underlying disease.

The next steps of the algorithm systematically evaluate the aetiological causes of cortical and subcortical myoclonus.

2.3.4 Step 4: are medications or toxic agents involved?

Drug-induced myoclonus usually begins more or less acutely at the start of treatment, but can also occur after chronic use, especially with intercurrent illness. Drug-induced myoclonus vanishes within a brief period after withdrawal of the drug.

5-hydroxytryptamine reuptake inhibitors and antiepileptic drugs, acting through serotonergic and GABAergic neurotransmitter systems, are commonly involved in drug-induced myoclonus,[41] but other drugs, such as levodopa and tricyclic antidepressants, can also induce myoclonus.[42] Other toxic causes of myoclonus include chronic alcohol abuse as well as alcohol withdrawal, aluminium toxicity in patients with dialysis syndrome, and exposure to certain insecticides, such as methyl bromide.[42] It is important to recognize these acquired causes of myoclonus, because cessation of the drug or detoxification will ameliorate the symptoms.

An overview of medications and toxic agents associated with myoclonus[41-43] is provided in Table 3.

Table 3 - Overview of medications and toxic agents associated with myoclonus

Drug/toxic agent group	Specific substances
Prescription drugs	
Anticonvulsants	Phenytoin, carbamazepine, sodium valproate, gabapentin, pregabalin, lamotrigine, phenobarbital, vigabatrin, oxcarbazepine, levetiracetam
Antipsychotics	Haloperidol, chlorpromazine, sulpiride, clozapine, olanzapine, metoclopramide
Antidepressants	Lithium, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, fluoxetine, imipramine
Antihypertensives	Verapamil, caverdilol, furosemide
Cardiovascular drugs	Propafenone, flecainide, diltiazem, nifedipine, buflomedil, veratramine, amiodarone
Antiparkinson drugs	Levodopa, bromocriptine, amantadine, entacopone, selegiline
Antibiotics	Quinolones, penicillin, cefepime, ceftazidime, moxalactam, ciprofloxacin, imipenem, carbenicillin, ticarcillin, piperacillin, cefuroxime, β-lactam antibiotics, gentamicin
Other anti-infective drugs	Piperazine, isoniazid, acyclovir
Antineoplastic drugs	Chlorambucil, prednimustine, busulphan plus cyclophosphamide, ifosfamide
Opiates	Morphine, tramadol, fentanyl, methadone, pethidine, norpethidine, hydrocodone
Anxiolytics	Buspirone, lorazepam, midazolam, zolpidem, zopiclone, carisoprodol, benzodiazepine withdrawal
Antidementia drugs	Cholinesterase inhibitors
Anaesthetic agents	Enflurane, etomidate, propofol, choralose
Others	Bismuth salts, contrast media, domperidone, omeprazole, antihistamines, prednisolone, ketoprofene, physostigmine, tryptophan, diclofenac, cobalamine supplementation, cimetidine, salicylates, tetanus toxin, dextromethorphan, tacrolimus
Toxic agents	
Psychoactive substances	Alcohol, cannabis, amphetamine, cocaine, ecstasy, toluene, intoxicating inhalants (for example, gasoline), heroin
Heavy metals	Aluminium, manganese, bismuth, mercury, tetra-ethyl lead
Insecticides	Methyl bromide, dichlorodiphenyltrichloroethane
Others	Baking soda, carbon monoxide, chloralose, colloidal silver

2.3.5 Step 5: routine laboratory tests

Homeostatic imbalance, organ failure or infection can cause cortical or subcortical myoclonus. Common examples include acute or chronic renal failure, acute or chronic hepatic failure, chronic respiratory failure with hypercapnia, disturbances of glucose homeostasis, hyperthyroidism, and

metabolic alkalosis or acidosis. Treatment of the underlying organ dysfunction and restoration of homeostasis generally leads to the disappearance of myoclonus.

Careful evaluation of a potential infectious or immune-mediated cause for myoclonus is warranted. If systemic signs of infection are present, the next step is serum and/or cerebrospinal fluid (CSF) analysis to test for immune-mediated disorders and to identify infectious agents. Immune-mediated disorders, such as anti N-methyl D-aspartate receptor (anti-NMDAR) encephalitis, stiff-person syndrome (SPS), progressive encephalomyelitis with rigidity and myoclonus (PERM), and opsoclonus-myoclonus syndrome (OMS), can be accompanied by acute or subacute onset of myoclonus. Early recognition of these disorders is important, because treatment-particularly when started early after symptom onset-can suppress the autoimmune response effectively.

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is characterized by a combination of psychiatric symptoms, seizures, movement disorders, and encephalopathy.[44] EEG usually reveals slow and disorganized activity or the unique extreme delta-brush pattern.[45] In CSF, moderate pleiocytosis with CSF-specific oligoclonal bands and NMDAR antibodies can be detected. Patients with anti-NMDAR encephalitis should be carefully tested for solid tumours, in particular, ovarian teratoma, which is present in over 50% of adult female patients with anti-NMDAR encephalitis.[46] In younger patients (<18 years), the occurrence of underlying tumours is less likely.[44,47]

Other autoimmune causes

SPS and PERM usually have a subacute onset (weeks) and are characterized by limb and truncal rigidity, painful muscle spasms, hyperekplexia, and brainstem symptoms. A substantial number of SPS and PERM cases are associated with glutamic acid decarboxylase, amphiphysin, and glycine receptor subunit α 148 antibodies, and PERM can also be associated with dipeptidyl peptidase-like protein 6 antibodies.[49]

Opsoclonus-Myoclonus syndrome

OMS is characterized by involuntary, arrhythmic, chaotic, multidirectional, fast eye movements, in combination with brainstem myoclonus involving the axial muscles and limbs. It is important to note that OMS is usually a manifestation

of a paraneoplastic syndrome, and is associated with breast cancer or small-cell lung carcinoma in adults[50] and neuroblastoma in children.[51,52]

Whipple disease

Of particular interest is Whipple disease, a rare but treatable bacterial multisystem infection characterized by systemic symptoms such as gastrointestinal complaints, fever, weight loss, and joint involvement in combination with CNS involvement. The triad of dementia, ophthalmoplegia (supranuclear gaze palsy and characteristic oculomasticatory myorrhythmia) and myoclonus is highly suggestive of Whipple disease. The diagnosis is based on PCR-based detection of Tropheryma whipplei in a CSF or duodenal biopsy sample.

2.3.6 Step 6: brain MRI

MRI can be helpful in identifying the acquired causes of myoclonus discussed in the previous step, and is probative in detecting structural lesions. Abnormalities seen on brain MRI can also indicate a genetic cause, such as neurodegeneration with brain iron accumulation (NBIA) disorders, leukodystrophy, or mitochondrial disorders. The recommended MRI protocol comprises T1-weighted and T2-weighted imaging, fluid-attenuated inversion recovery, and diffusion-weighted imaging (DWI), with administration of gadolinium contrast. Diagnosticians should also consider susceptibility-weighted imaging to assess iron accumulation. When detected, iron accumulation strongly raises a suspicion of pantothenate kinase-associated neurodegeneration[53,54] or other forms of NBIA.[55]

Structural lesions can indicate posthypoxic, post-ischaemic or post-traumatic brain injury, tumours, demyelinating diseases, or spongiform encephalopathies. Abnormal T2 hyperintensity of the grey matter and/or white matter or the deep grey nuclei can indicate infection, autoimmune encephalopathy or a paraneoplastic disorder. DWI can detect lesions at an earlier stage than can T2-weighted imaging.

If white matter abnormalities are present, leukodystrophies should be considered. One example is Alexander disease, an autosomal dominant inherited leukodystrophy caused by mutations in the glial fibrillary acidic protein (*GFAP*) gene.[56] Palatal myoclonus is a common feature of Alexander disease. In typical infantile cases, brain MRI shows extensive white matter T2

hyperintensities that are especially marked in frontal regions; a rim of periventricular T2 hypointensity; T2 hyperintensity involving the basal ganglia, thalamus and brainstem; and contrast enhancement, particularly of periventricular regions and brainstem.[57] Brainstem and cerebellar lesions and ventricular garlands with contrast enhancement are seen in the juvenile form.[58] In the adult form, MRI shows progressive atrophy of the medulla oblongata and cervical spinal cord (the so-called 'tadpole sign'), accompanied by T2 hyperintensity in these areas.[56]

An overview of the acquired causes of myoclonus, together with the recommended diagnostic investigations, is provided in Table 4.

Table 4 - Recommended investigations for acquired causes of myoclonus

Disorders and key features	Diseases causing myoclonus	MRI findings (the best diagnostic aid)	Recommended investigations
Metabolic			
(Sub)acute onset Negative myoclonus Encephalopathy Systemic involvement	Hyperthyroidism Hepatic failure Renal failure Dialysis syndrome Hyponatraemia Hypocalcaemia Hypomagnesaemia Hypoglycaemia Vitamin E deficiency Metabolic alkalosis or acidosis	No indication for neuroimaging	Basic laboratory tests, including electrolytes, glucose, renal and hepatic function tests, thyroid function, vitamin E (blood gas analysis)
Infectious or postinfectious			
(Sub)acute onset Fast progression Fever Encephalopathy Skin rash Joint or systemic involvement Radiculopathy Cranial nerve palsy	All infectious causes of myoclonus Arbovirus Epstein-Barr virus Enterovirus Coxsackie virus Herpes simplex virus Herpes zoster virus West Nile virus HTLV-1 Miscellaneous bacteria (e.g. *Streptococcus*,	T2-weighted imaging can detect abnormal hyperintensity of GM, WM or deep grey nuclei in the following structures: BG (bilaterally),thalamus and BS BG (symmetric pattern), thalamus, cortex, or BS Posterior medulla, pons, midbrain, DN, SC Midbrain, anterior SC LS Multifocal areas of cortex, BS, GM, CN BG, thalamus, BS, WM, SN, cerebellum, SC Deep WM Meningitis, cerebritis, vasculitis, pus collections; T2-	Serum and/or CSF testing for infection parameters: specific antigens/antibodies, PCR aimed at the specific agent, biopsy of the involved tissue

Disorders and key features	Diseases causing myoclonus	MRI findings (the best diagnostic aid)	Recommended investigations
	Clostridium)	hyperintense BG	
	Shiga-toxin-producing *Escherichia coli*	BS, BG, deep WM	
	Whipple disease	(Multi)focal lesion(s) in the(fronto)temporal lobe, PV WM, BS (on contrast enhancement)	
	HIV	Atrophy and bilateral PV/centrum semiovale WM, BG, cerebellum, BS	
	Malaria	Multiple cortical and thalamic infarcts with or without haemorrhages	
	Syphilis	Basilar meningitis	
	Cryptococcus	Dilated PVSs in deep grey nuclei, typically no contrast enhancement, miliary-enhancing or leptomeningeal-enhancing nodules or cryptococcomas	
	Borrelia burgdorferi	MS-like lesions + cranial neuritis and meningoradiculoneuritis (Bannwarth syndrome)	
	Progressive multifocal leucoencephalopathy (PML)	Asymmetrical T2 hyperintensity of SC areas	
	Subacute sclerosing panencephalitis	T2 hyperintensities in PV or SC WM (frontal>parietal>occipital lobes)	
Prion diseases			
Progressive (sub)acute dementia Psychiatric symptoms Vision loss	CJD: Variant CJD	Progressive hyperintensity of BG, thalamus, and cerebral cortex seen on DWI/T2 'Pulvinar' sign: bilateral symmetrical hyperintensity of pulvinar (posterior) nuclei of thalamus relative to anterior putamen; 'hockey stick' sign: symmetric pulvinar and dorsomedial thalamic nuclear hyperintensity	RT-QuIC testing of nasal brushings;[79]*, CSF 14-3-3 and tau proteins, EEG
	Sporadic CJD	Cortical hyperintensity	
	Heidenhain variant CJD	Occipital lobe hyperintensity	
	Gerstmann-Straussler-Scheinker syndrome (GSS)	No abnormalities; DWI hyperintensities LS and atrophy	CSF 14-3-3 and tau proteins, EEG

Disorders and key features	Diseases causing myoclonus	MRI findings (the best diagnostic aid)	Recommended investigations
Autoimmune or paraneoplastic			
(Sub)acute onset Fast progression Encephalopathy Epilepsy Psychiatric symptoms	Hashimoto encephalitis (steroid-responsive autoimmune encephalopathy associated with autoimmune thyroiditis)	Diffuse/focal cortical, SC WM T2-hyperintensity with relative sparing of occipital lobes	Antithyroperoxidase and antithyroglobulin antibodies
Other movement disorders	Anti-NMDA receptor encephalitis	T2 hyperintensities and atrophy in the LS	NMDA receptor antibodies
	Progressive encephalomyelitis with rigidity and myoclonus (PERM)	No abnormalities/T2 hyperintensity in MTLs and LS	Amphiphysin, LGI1, Caspr2, GAD, DPPX, and GLyR antibodies
	Stiff person syndrome	T2 hyperintensity in MTLs and LS	Paraneoplastic antibodies (anti-Hu, anti-Ri)
	Rasmussen encephalitis	Early unilateral swelling of gyri, followed by (predominantly frontal and parietal) progressive cortical atrophy	EEG, in certain cases brain biopsy
	Coeliac disease	WM T2 hyperintensities; cerebral and cerebellar atrophy	Anti-endomysial, anti-tissue transglutaminase, anti-reticulin and anti-gliadin antibodies Tissue biopsy of the small intestine
CNS lesions			
(Sub)acute onset Features depend on location of lesion	Neoplasia Ischaemia Amyloid angiopathy Demyelinating diseases Posthypoxic encephalopathy (Lance-Adams syndrome)	Variable	Variable

Abbreviations: BG, basal ganglia; BS, brainstem; Caspr 2, contactin-associated protein-like 2; CJD, Creutzfeldt-Jakob disease; CN, cranial nerves; CSF, cerebrospinal fluid; DN, dentate nucleus; DPPX, dipeptidyl-peptidase-like protein-6; DWI, diffusion-weighted imaging; GAD, glutamic acid decarboxylase; GM, grey matter; HTLV-1, human T-lymphotropic virus 1; LGI1, leucine-rich glioma-inactivated 1; GLyR, glycine receptor; LS, limbic system; MTL, mesial temporal lobe; NMDA, *N*-methyl-D-aspartate; PV, periventricular; PVS, perivascular space; RT-QuIC, real-time quaking-induced conversion; SC, subcortical; SN, substantia nigra; WM, white matter. *RT-QuIC testing of nasal brushings is a promising diagnostic test in diagnosing CJD, but must be validated before the test can be used in clinical practice.

2.3.7 Step 7: mitochondrial or neurodegenerative?

Although NGS is usually indicated in myoclonus, in two groups of patients-those with suspected mitochondrial disorders or late-onset neurodegenerative disorders-an initial approach other than NGS should be considered. Here, we will briefly discuss these two groups of disorders.

Mitochondrial disorders

In addition to genetic disorders caused by mutations in nuclear genes, one must be aware of mitochondrial disorders caused by mutations in mitochondrial DNA (mtDNA), which are associated with myoclonus including MERRF (myoclonic epilepsy with ragged red fibres) syndrome,[59,60] Leigh syndrome,[59] and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome.[59] Clinical clues for a mitochondrial disorder are multiorgan involvement, ophthalmoplegia, muscle involvement, neuropathy, ataxia, deafness, specific MRI brain findings, and maternal inheritance.

Targeted analysis of mtDNA is strongly advised if a mitochondrial disorder is suspected, because in many diagnostic laboratories, NGS analysis only reports mutations in nuclear genes (including mitochondrial DNA polymerase genes), and does not consider mtDNA mutations.

It is important to keep in mind that the mtDNA testing results obtained from peripheral blood samples can be falsely negative. Thus, testing of samples from different types of tissue, including cells isolated from urine, skin and muscle tissue, could be required.

Late-onset neurodegenerative disorders

Late-onset neurodegenerative disorders that are often accompanied by myoclonus include Alzheimer disease, Parkinson disease (PD), multiple system atrophy (MSA) and-less commonly-dementia with Lewy bodies, Huntington disease, and corticobasal degeneration. Myoclonus in PD and MSA usually manifests as irregular, small-amplitude, often stimulus-sensitive myoclonic jerks of the fingers during muscle activation (cortical polyminimyoclonus).[61-64] Neurodegenerative disorders can also be accompanied by orthostatic myoclonus that contributes to gait problems.[65,66] Diagnosis of neurodegenerative disorders is based on clinical criteria together with, for example, neuroimaging or CSF biomarker diagnostics and, in rare cases, DNA analyses.

2.3.8 Step 8: next-generation sequencing

If the previous diagnostic steps have not revealed the cause of the myoclonus, the next step is NGS, which comprises several massively parallel sequencing techniques, including WGS and WES, and TRS, which focuses on known disease-associated genes. The technical details of these techniques are reviewed elsewhere.[9]

Strengths and limitations of NGS

WGS and WES are particularly useful for identification of new disease-causing genetic variants, and WES of patient-parents trios is a particularly good strategy to detect de novo mutations in affected patients.[67] However, NGS diagnostics have some limitations. One important disadvantage of WGS and WES is the ethical dilemma associated with detection of unsolicited findings.

Most of the current NGS techniques miss repeat expansions, large structural rearrangements, and mutations in noncoding regions (deep intronic mutations and mutations in promoter regions). In addition, mutations in mtDNA often escape detection. For this reason, and because of the difficulties in recognizing mitochondrial disorders, targeted mtDNA analysis should be considered in cases that remain unsolved after completion of the diagnostic algorithm.[59]

WGS and WES can involve extensive data processing and confirmation of the detected variants, hence conferring higher costs than TRS. Another advantage of TRS over WGS and WES is that it avoids the interpretation of genetic variants with no relationship to the patient's phenotype. One crucial step-adequate data filtering and assessment of pathogenicity of all variants observed in NGS analyses-remains a challenge. Indeed, the main drawback of TRS diagnostic panels compared with WGS and WES is the need to consistently monitor all variants reported, collect all relevant information on newly defined disease genes, and continuously update the list of genes associated with myoclonus.[9]

NGS in myoclonus diagnostics

NGS can be a highly efficient tool to diagnose the disease that underlies myoclonus, because the list of disorders-and, hence, individual genes to be considered-in an individual patient is long. NGS is cost-effective in this respect, and can shorten the diagnostic process and avoid unnecessary diagnostic evaluations. The costs of all NGS techniques are rapidly falling, and the cost of

WES or TRS is currently comparable to that of sequencing three individual genes.[10,11]

The advantage of all NGS techniques is that mutations associated with an unusual clinical phenotype will also be detected. Even in monogenic disorders, patients often do not present with the classic phenotype and, as in other genetic disorders of the CNS, mutations in myoclonus-associated genes can cause a whole spectrum of symptoms. NGS is the only technique that enables screening of all the genes known to be related to myoclonus; using this approach, both 'typical' and 'atypical' presentations of gene defects can be diagnosed.

The clinical presentation of myoclonus disorders is very heterogeneous, and clear genotype-phenotype correlations are often lacking. For example, in six patients from two unrelated families with late-onset cortical myoclonus owing to sialidase-1 (*NEU1*) mutations, neither the canonical clinical phenotype nor the typical laboratory findings were evident, that is, macular cherry-red spots were absent, and urinary sialic acid excretion was not increased.[68] The involvement of *NEU1* would never have been suspected on clinical grounds or on the basis of laboratory test results, illustrating the power of NGS diagnostics. In this case, the mutations were detected with WES, but other NGS approaches would also have been successful.

Myoclonus-linked genes and genetic syndromes

The genetic disorders associated with myoclonus include five treatable inborn errors of metabolism: Niemann-Pick type C,[69,70] Wilson disease,[71,72] glucose transporter type 1 (GLUT1) deficiency,[73,74] cerebrotendinous xanthomatosis,[75,76] and tyrosine hydroxylase deficiency.[77] Identification of these disorders is crucial, because early treatment can prevent, stabilize or even improve symptoms. In general, these syndromes have additional defining symptoms that can support the diagnosis, but they are all associated with myoclonus. In the event of clinical suspicion of one of these disorders, the choice of diagnostic work-up depends on the facilities for biochemical testing and NGS available in the medical centre concerned (Table 4). A comprehensive overview of genes associated with myoclonus is provided in Supplementary Table 1. For use in clinical practice, we have classified these genes according to the key clinical feature (dystonia, epilepsy, spasticity, ataxia, dementia or parkinsonism) that is present in addition to myoclonus.

At present, the most common genetic causes of myoclonus remain unknown, because genetic diagnosis in myoclonus is a new advance and, therefore, prevalence data are not yet available. Moreover, the prevalence of genetic causes of myoclonus is likely to vary depending on the population characteristics (for example, the ethnic background). At present, we encourage multicentre collaboration to collect genetic data, so that the genetic background of myoclonus can be fully elucidated.

2.4 From diagnosis to treatment

Ideally, the underlying cause of myoclonus should be treated. Treatment can include withdrawal of drugs or toxic agents, correction of homeostasis or organ failure, or treatment of infections or autoimmune disorders. We have also stressed the importance of early treatment of the five inborn errors of metabolism, in which progression of the disease is potentially preventable (Table 5). However, symptomatic treatment needs to be considered in all patients with myoclonus, and the choice of treatment should be guided by the anatomical classification of their myoclonus. Symptomatic treatment of myoclonus can be difficult because of adverse effects, and polytherapy is often required for effective treatment.[7,78] Levetiracetam and valproic acid are generally considered to be the first choices of treatment in cortical myoclonus, whereas clonazepam is the first choice in subcortical, spinal and peripheral myoclonus.[78] Details of current treatment options for myoclonus have been reviewed elsewhere.[78] Future treatments might include gene therapy and enzyme replacement to modify and improve the prognosis in genetic disorders.

Table 5 - Investigation and treatment of five treatable inborn errors of metabolism

Disorder	MRI findings	Recommended investigations	Treatment
Inborn errors of metabolism			
Tyrosine hydroxylase deficiency	None	CSF analysis (homovanillic acid, 3-methoxy-4-hydroxyphenylglucol, and homovanillic acid/5-hydroxyindoleacetic acid ratio)	Levodopa (deep brain stimulation should be considered only in severe cases)
Cerebrotendinous xanthomatosis	Symmetrical abnormalities in dentate nucleus (T2 hyper/hypointensities) T2 hyperintensities in substantia nigra, globus pallidus, inferior olives and periaqueductal nuclei	Specialized laboratory analysis (plasma cholestanol concentration, bile acid and alcohol levels in serum and urine, plasma 5-α-cholestanol concentration); CSF analysis (cholestanol and apolipoprotein B)	Chenodeoxycholic acid
Niemann-Pick type C disease	Brain atrophy with cerebellar predominance and diffuse white matter disease Delayed myelination in infants	Specialized laboratory analysis (thrombocytes, transaminases [ASAT/ALAT], LDL- and HDL cholesterol, plasma triglycerides, chitotriosidase, oxysterol profile)	Miglustat
GLUT1 deficiency	Wide opercula and symmetrical T2 hyperintense basal ganglia (caudate/putamen>globus pallidus)	CSF analysis (glucose and lactate levels, CSF:blood glucose ratio commonly <0.4)	Ketogenic diet
Metal storage disorders			
Wilson disease	Symmetrical T2 hyperintensity or mixed intensity in putamen, caudate nucleus, thalamus, and globus pallidus Characteristic 'face of giant panda' sign at midbrain level	Laboratory analysis (24 h urine copper test, ceruloplasmin) Consult ophtalmologist (Kayser-Fleischer ring)	Zinc acetate, copper chelators (penicillamine, trientine, and tetrathiomolybdate)

Abbreviations: CSF, cerebrospinal fluid; GLUT1, glutamine transporter type 1.

2.5 Conclusions

In this Review, we have proposed a novel diagnostic algorithm (Figure 1) to guide clinicians in detecting myoclonus, assessing its anatomical subtype and diagnosing its underlying cause. Moreover, we provide a comprehensive overview of the acquired and genetic causes of myoclonus.

The traditional clinical and anatomical classifications are included in this new algorithm. Careful clinical and electrophysiological phenotyping is important, because it provides clues to the anatomical subtype and facilitates diagnostic testing. Distinction of myoclonus subtypes (step 2) remains challenging, and further studies are necessary to establish the diagnostic value (in particular, the sensitivity) of electrophysiological features of myoclonus in clinical practice.

The formal aetiological classification of myoclonus includes a long list of possible causes. In our eight-step algorithm, we define steps to rule out acquired causes, mitochondrial disorders and late-onset neurodegenerative disorders, so as to identify the subgroup of patients in whom NGS diagnostics are highly recommended for the simultaneous analysis of all potential myoclonus-associated genes.

We believe that our diagnostic algorithm is useful for all practising clinical neurologists and paediatricians, including experts in the fields of movement disorders and epilepsy. The interesting genetic borderland of myoclonus between movement disorders and epilepsy leads to an ensemble of genetic causes, some of which have been previously linked with either epilepsy or movement disorders.

We expect that the new approach presented in this article will increase the diagnostic yield in myoclonus. Moreover, in the coming years, the systematic use of NGS diagnostics will lead to further discoveries of new myoclonus-associated genes and uncommon myoclonus phenotypes.

2.6 Supplementary Appendix 1

Full electronic search strategy for a systematic review of causes of myoclonus
We systematically reviewed all papers regarding myoclonus and its acquired and genetic causes. References for this review were identified by PubMed, OMIM and Text book search up to June, 2015, as well as searching for the references cited in the relevant articles. The key search terms used were 'myoclonus' and 'myoclonic jerks' combined with terms indicating possible etiologies including: 'genetic causes', 'acquired causes', 'metabolic diseases', 'inborn errors metabolism', 'etiology', 'causality', 'drug', 'toxin', 'autoimmune', 'paraneoplastic', and 'epilepsy'. All the papers and abstracts we reviewed were published in English. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[1] could not be applied in selecting cases, because disorders causing myoclonus are rare and the available evidence consisted of small clinical trials, case series and expert opinion. For the same reason not all items of the PRISMA Statement checklist were applicable (1A and 1B). Only causes presented in at least two patients with myoclonus were included in the review. Molecular defects had to be described in more than one family with myoclonus. The final reference list was generated on the basis of uniqueness and relevance to the topic.

1. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011 Oct 18;155(8):529-536.

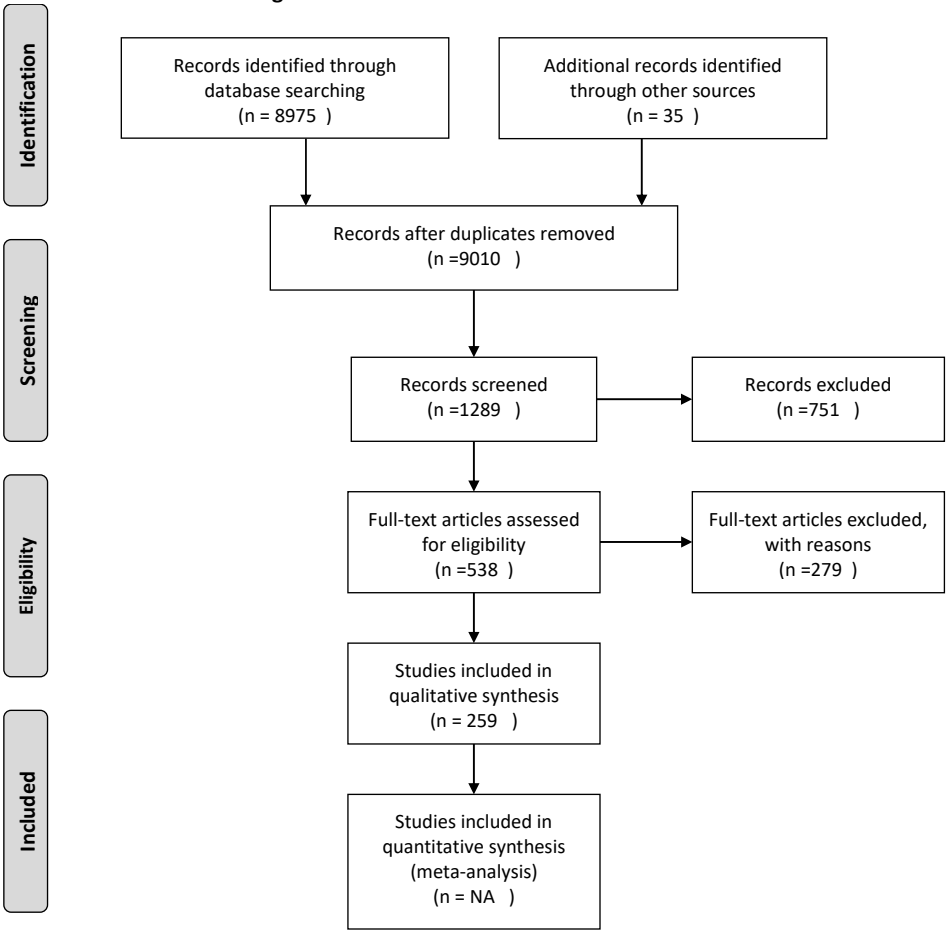
1A - PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	NA
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 / 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	NA
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 / suppl 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional	5 / suppl 1

		studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 / suppl 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	NA
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Prisma flow chart
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17/18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

1B - PRISMA 2009 Flow Diagram



2.7 Supplementary Table 1 - Comprehensive overview of genes associated with myoclonus

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Startle response		Hyperekplexia	Autosomal dominant or autosomal recessive	Infancy	149400	*GLRA1*	Excessive startle responses Startle-induced stiff falls Generalized stiffness at birth
			Autosomal recessive		614618	*SCL6A5/ GlyT2*	
			Autosomal recessive X-linked		614619 300429	*GLRB* *ARHGEF9*	
Dystonia		Myoclonus dystonia	Autosomal dominant	First or second decade	604149	*SGCE*	Myoclonus predominantly of the upper body Dystonia (Neck, writer's cramp) Psychiatric disorders
			Autosomal dominant		601012	*CACNA1B*	
			Autosomal dominant		600514	*RELN*	
			Autosomal dominant		616386	*KCDT17*	
			Autosomal dominant		610110	*ANO3*	Craniocervical dystonia Tremor
		'Russell-Silver syndrome'	Maternal uniparental disomy		180860	*mUPD7*	Myoclonus Dystonia Growth retardation Craniofacial dysmorphism
		Tyrosine hydroxylase deficiency	**Autosomal recessive**		**191290**	***TH***	**Levodopa-responsive Myoclonus Dystonia**
		Benign hereditary chorea	Autosomal dominant		600635	*NKX2-1/ TITF1*	Myoclonus Dystonia presentation Chorea Hypothyroidism Pulmonary abnormalities
		Neurodegener a-tion with brain iron accumulation-1 (NBIA1) (Hallervorden-Spatz)	Autosomal recessive	childhood - adolescence	606157	*PANK2*	Dystonia Pyramidal syndrome Cognitive decline Psychiatric symptoms
		Familial dyskinesia with facial myokymia	Autosomal dominant	childhood	600293	*ADCY5*	Periorbital and perioral facial dyskinesia Chorea Dystonia Axial hypotonia Movements worsened by anxiety
		Wilson's disease	**Autosomal recessive**	**early childhood - 60 years**	**606882**	***ATP7B***	**Tremor** **Dystonia** **Parkinsonism** **Hepatic signs** **Psychiatric symptoms**

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Epilepsy	**Generalized epilepsies**	Juvenile myoclonic epilepsy	Autosomal dominant	Onset around puberty	611136	*GABRA1*	Myoclonus mainly in arms, especially in the morningTonic-clonic seizures especially at night. Absences
			Autosomal dominant		601949	*EJM6/ CACNB4*	Juvenile myoclonic epilepsy Episodic ataxia
			Autosomal dominant		600570	*CLCN2*	
			Autosomal dominant		137163	*EJM7/ GABRD*	
			Autosomal recessive		604827	*EJM2/ CHRNA7*	
			Autosomal dominant		600235	*SCN1B*	Generalized epilepsy Febrile seizures Juvenile myoclonic epilepsy
			Autosomal dominant		254770	*EJM1/ EFHC1*	
			X-linked		300817	*EFHC2*	
			Autosomal dominant		612899	*CASR*	
			Autosomal recessive		607058	*Cx-36*	
			Autosomal dominant		601540	*BRD2*	
			Autosomal dominant		154270	*ME2*	
			Autosomal recessive		190197	*CNTN2*	
	Epileptic encephalo-pathies	Doose syndrome (myoclonic astatic epilepsy EM-ASs))	unknown	7 months - 6 years		*unknown (SCN1A, SLCA1?)*	Seizures (myoclonic-astatic/atonic, absences, tonic-clonic, tonic seizures) Cognitive disability
		Dravet (severe myoclonic epilepsy of infancy)	Autosomal dominant	first year of life (peak at 5 months)	607208	*SCN1A*	(Febrile) Seizures (focal, myoclonic seizures, atypical absences) Developmental delay
			X-linked		300088	*PCDH19*	
			Autosomal dominant		137164	*GABRG2*	
			Autosomal dominant		182390	*SCN2A*	
			Autosomal dominant		600235	*SCN1B*	
			Autosomal dominant		603415	*SCN9A*	
			Autosomal dominant		602926	*STXBP1*	
		SCN8A encephalopathy	Autosomal dominant	0-18 months	600702	*SCN8A*	Epilepsy Intellectual disability Hypotonia Dystonia
		Lennox-Gastaut syndrome	Autosomal recessive	1-7 years	600173	*JAK3*	Seizures (tonic-axial, atonic, absence seizures, myoclonic, generalized tonic-clonic, partial seizures) Mental retardation
			Autosomal dominant		602119	*CHD2*	
		Aicardi-Goutières syndrome	Autosomal dominant / autosomal recessive	Within first year of life	606609	*TREX1*	Severe developmental delay Seizures Progressive microcephaly

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
							Spasticity Dystonia
			Autosomal recessive		610326	*RNASEH2B*	
			Autosomal recessive		610330	*RNASEH2C*	
			Autosomal recessive		606034	*RNASEH2A*	
			Autosomal recessive		606754	*SAMHD1*	
		Infantile spasm syndrome	X-linked dominant	First months of life	300203	*CDKL5*	Epilepsy Mental retardation Lack of speech development Dysmorphic facial features
	Metabolic	Non-ketotic hyperglycinemia	Autosomal recessive	neonatal period (milder form adult onset)	238300	*GLDC*	Lethargy Hypotonia Apnea Early myoclonic epilepsy Mental retardation
			Autosomal recessive		238330	*GCSH*	
			Autosomal recessive		238310	*AMT*	
			X linked recessive	First two years of life	300011	*ATP7A*	Developmental delay Growth retardation Kinky hair Cerebral and cerebellar degeneration Seizures (infantile spasms) Myoclonus
		GLUT 1 deficiency	Autosomal dominant	early childhood	138140	*SLC2A1*	Paroxysmal exertional dyskinesia Ataxia Epilepsy Developmental delay Spasticity
		Menkes disease	X linked recessive	First two years of life	300011	*ATP7A*	Developmental delay Growth retardation Kinky hair Cerebral and cerebellar degeneration Seizures (infantile spasms) Myoclonus
		Tay-Sachs disease Gangliosidosis (GM2 gangliosidosis type 1)	Autosomal recessive	Childhood	606869	*HEXA*	Develepmental delay and/or regression Seizures Loss of vision (cherry red spot)
		Sandhoff's disease Gangliosidosis (GM2 gangliosidosis type 2)	Autosomal recessive	Childhood	606873	*HEXB*	Psychomotor retardation Seizures Visual loss (macular cherry-red spot) Ataxia

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
		Alpers-Huttenlocher syndrome (AHS)	mitochondrial	early childhood	174763	*POLG*	Epilepsia partialis continua Developmental regression Refractory focal motor or myoclonic seizures Liver dysfunction
		Leigh syndrome	mitochondrial	birth - adolescence	*	*	Psychomotor retardation Retinitis pigmentosa Ataxia Neuropathy Seizures
		Neuropathy, ataxia, and retinitis pigmentosa (NARP syndrome)	mitochondrial	Childhood	516060	*MTATP6*	Develepmental delay Retinitis pigmentosa Seizures Ataxia Sensory neuropathy
		Kearns-Sayre syndrome	mitochondrial	Onset before age 20	590050	*MTTL1 / **	Progressive external ophthalmoplegia Pigmentary retinopathy Cardiac conduction block
		Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome)	mitochondrial	Childhood	***	***	Stroke-like episodes at a young age Encephalopathy Epilepsy Cognitive decline
	Syndromic	Angelman syndrome	****	6 - 12 months	601623	*UBE3A*	Mental retardation Absent or lack of speech Behavioral problems Seizures Ataxia
		Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 2; MCAHS2	X-linked recessive	Early infancy	311770	*PIGA*	Facial dysmorphism Intellectual disability Seizures Neonatal hypotonia
		Rett syndrome	X-linked dominant	First year of life	300005	*MECP2*	Psychomotor retardation Impaired language development Hand stereotypies Seizures
		Coffin-Lowry syndrome	X-linked	childhood	300075	*RPS6KA3*	Psychomotor and growth retardation Facial and digital abnormalities Skeletal anomalies Seizures

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Progressive myoclonic epilepsies (PME)	Myoclonic epilepsy with ragged red fibers (MERRF syndrome)	mitochondrial	5 - 42 years	590060	*MTTK*	Seizures (tonic-clonic) Dementia Neuropathy Myopathy
			mitochondrial		590050	*MTTL1*	
			mitochondrial		590040	*MTTH*	
			mitochondrial		590080	*MTTS1*	
			mitochondrial		590085	*MTTS2*	
			mitochondrial		590070	*MTTF*	
		Sialidosis type I	Autosomal recessive	8 - 38 years	608272	*NEU1*	Gradual visual failure; cherry red spot Seizures (tonic clonic) Ataxia
		Sialidosis type II	Autosomal recessive	10 - 30 years	608272	*NEU1*	Dysmorphic features Seizures (tonic clonic) Hepatosplenomegaly Mental retardation
		Lafora disease	Autosomal recessive	11 - 18 years	607566	*EPM2A*	Progressive dementia Epilepsy Ataxia Visual hallucinations
			Autosomal recessive		608072	*EPM2B (NHLRC1)*	less severe clinical course compared to the EPM2B variant
		Gaucher disease (mainly type III)	Autosomal recessive	5 - 15 years	606463	*GBA*	Hepatosplenomegaly Skeletal disorders Supranuclear gaze palsy (horizontal) Cognitive impairment Seizures Ataxia
			Autosomal recessive		610539	*saposin C/ PSAP*	
		Niemann-Pick type C disease	**Autosomal recessive**	**childhood - adolescence**	**607623**	***NPC1***	**Ataxia** **Dystonia** **Cognitive decline** **Supranuclear gaze palsy (vertical)** **Psychiatric symptoms** **Hepatosplenomegaly**
			Autosomal recessive		**601015**	***NPC2/HE1***	
	Neuronal ceroid-lipofuscinoses	Santavuori-Haltia	Autosomal recessive	infantile onset (8-18 months)	256730	*CLN1/ PPT1*	Progressive loss of motor milestones Dementia Visual loss Seizures
		Jansky-Bielschowski	homozygous or compound heterozygous mutation	late infantile onset (2.5 -4 years)	204500	*CLN2/ TPP1*	Seizures Intellectual deterioration Progressive visual loss (macula degeneration)

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
							Ataxia Spasticity
		Batten's disease (Spielmeyer-Vogt-Sjogren-Batten disease)	Autosomal recessive	juvenile onset (4-10 years)	607042	*CLN3*	Visual loss (pigmentary retinopathy) Dementia Seizures Myoclonus Behavioral disorders
		Parry's disease	Autosomal dominant	adult onset (11-50 years)	611203	*CLN4/ DNAJC5*	Dementia with motor disturbances Behavioural disorders Ataxia
		Kufs disease type A	Autosomal dominant / autosomal recessive	late infantile / adult onset (11-50 years)	606725	*CLN 6*	Myoclonus Ataxia Dementia Seizures
			Autosomal recessive	late infantile	608102	*CLN5*	Hypotonia Seizures Visual loss Myoclonus
			Autosomal recessive	late infantile	610951	*CLN7/ MFSD8*	
			Autosomal recessive		607837	*CLN8*	Epilepsy Progressive mental retardation
			Autosomal recessive		614706	*CLN 11/ GRN*	
	Progressive myoclonic ataxia (PMA) / Ramsay Hunt syndrome	North sea progressive myoclonus epilepsy	Autosomal recessive	Childhood	614018	*GOSR2*	Ataxia Areflexia Generalized seizures Cortical reflex myoclonus
		Action myoclonus renal failure syndrome (AMRS)	Autosomal recessive	9 - 30 years	602257	*SCARB2/ LIMP2*	Ataxia Tremor Generalized tonic-clonic seizures Proteinuria and progressive renal failure (AMRS may occur without renal failure)
		Cerebrotendinous Xanthomatosis	Autosomal recessive	childhood - adult onset	606530	*CYP27A1*	Tendinous/tuberous xanthomas Juvenile cataract Cerebellar ataxia Chronic diarrhoea Peripheral neuropathy Psychiatric disoders Mild mental retardation

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
		Others in category of PME /PMA	Autosomal recessive		608500	*PRICKLE1*	
			Autosomal recessive		606919	*CERS1*	
			Autosomal recessive		613468	*ASAH1*	Spinal muscular atrophy Progressive myoclonic epilepsy
			Autosomal recessive		611725	*KCTD7*	Progressive myoclonic epilepsy Dystonia Ataxia
			Autosomal dominant		176258	*KCNC1*	
		Dentato-rubro-pallido-luysian atrophy (DRPLA)	Autosomal dominant	Mean age of onset 30 years (range first to seventh decade)	607462	*ATN1*	Seizures (tonic-clonic) Cerebellar ataxia Choreoathetosis Dementia
		Unverricht Lundborg disease (Baltic myoclonus)	Autosomal recessive	childhood-adolescence	601145	*EPM1/ CSTB*	Seizures Myoclonus Mild cognitive dysfunction Cerebellar signs
Spasticity		Leucoencephalopathy with vanishing white matter	Autosomal recessive	childhood	603945	*EIF2B5*	Cerebellar ataxia Spasticity (Myoclonic) Seizures
		Krabbe's leuco-dystrophy	Autosomal recessive	birth - adolescence	606890	*GALC*	Spasticity Seizures Loss of vision Dementia Peripheral neuropathy
		Alexander's disease	Autosomal dominant	infantile, juvenile, adult	137780	*GFAP*	Seizures Spasticity Cerebellar ataxia Bulbar or pseudobulbar symptoms Palatal myoclonus
		Kufor-Rakeb syndrome	Autosomal recessive	Average age of onset 13 years	610513	*ATP13A2*	Parkinsonism Supranuclear gaze palsy Spasticity Dementia
Ataxia		Friedreich ataxia	Autosomal recessive (GAA repeat)	First or second decade	606829	*FXN*	Progressive ataxia Limb muscle weakness Decreased vibratory perception & proprioception Scoliosis Cardiomyopathy and arrhythmias
		Ataxia telangiectasia	Autosomal recessive	early childhood	607585	*ATM*	Cerebellar ataxia Oculocutaneous telangiectases Ataxia Immune defects

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
							Endocrinopathy Predisposition to malignancy
		SCA 1	Autosomal dominant (CAG repeat)	third or fourth decade	601556	*ATXN1*	Cerebellar ataxia Spastic paraplegia Supranuclear gaze palsy
		SCA2	Autosomal dominant (CAG repeat)	Mean age of onset in third decade	601517	*ATXN2*	Slowed ocular movements Tremor Myoclonus Parkinsonism Cognitive impairment
		SCA3 (Machado-Joseph disease)	Autosomal dominant (CAG repeat)	3-4th decade	607047	*ATXN3*	Ataxia Pyramidal signs Pheripheral neuropathy Rigidity and bradykinesia
		SCA6	Autosomal dominant (CAG repeat)	20 - 65 years	601011	*CACNA1A*	Ataxia Impaired smooth pursuit eyes, nystagmus (downbeat) Episodic exacerbations
		SCA 7	Autosomal dominant (CAG repeat)	adult onset	607640	*ATXN7*	Ataxia Pigmental macular dystrophy Supranuclear ophthalmoplegia
		SCA8	Autosomal dominant (CAG repeat)	18 - 65 years	613289	*ATXN8*	Ataxia Nystagmus Mild pyramidal features
			Autosomal dominant (CTG repeat)	18 - 65 years	603680	*ATXN8OS*	
		SCA14	Autosomal dominant	childhood - sixth decade	176980	*PRKCG*	Myoclonus Ataxia Gaze-evoked nystagmus Sensory loss
		SCA17	Autosomal dominant (CAG repeat)	median age at onset 23	600075	*TBP*	Parkinsonism Psychiatric symptoms Cognitive impairment Ataxia
		SCA19 / SCA 22	Autosomal dominant	Variable age at onset	605411	*KCND3*	Ataxia (often pure)
Late onset dementia or parkinso-nism		Creutzfeld-Jakob disease (CJD)	Autosomal dominant	third to ninth decade	176640	*PRNP*	Progressive myoclonus Rapidly progressive dementia Behavioural disturbances Cortical visual disturbances
		Gerstmann-Straussler-Scheinker syndrome (GSS)	Autosomal dominant	19 - 66 years	176640	*PRNP*	Rapidly progressive dementia Seizures Pyramidal and extrapyramidal features
		Fatal familial insomnia (FFI)	Autosomal dominant	20-60 years	176640	*PRNP*	Insomnia Ataxia

Key feature (besides myoclonus)	Sub-category	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
							Rapidly progressive dementia
		Huntington's disease	Autosomal dominant (CAG repeat)	depends on number of CAG repeats	613004	*HTT*	Chorea Ataxia Dystonia Behavioural disturbances Cognitive decline
		Parkinsonism (PARK1)	Autosomal dominant	30-60 years	163890	*SNCA*	Parkinsonism Dystonia Cognitive decline
		Alzheimer's disease	Autosomal dominant	3th - 4th decade	104311	*PSEN1*	Dementia
		Pallido-ponto-nigral degeneration (PPND) (FTDP-17)	Autosomal dominant	Mean age of onset 45 years	157140	*MAPT*	Progressive parkinsonism Dementia Psychiatric symptoms
		Frontotemporal Dementia	Autosomal dominant	Mean age of onset 62 years	138945	*GRN*	Frontotemporal dementia Language deterioration Behavioural / Psychiatric disturbances

The diseases in bold are the five treatable inborn errors of metabolism mentioned in Step 8 of the manuscript, see Table V for an overview of the possibilities of diagnostic investigations other than NGS and information about the treatment

* Unknown which gene mutations are accompanied by myoclonus. Genes causing Leigh syndrome: *BCS1L* (603647), *NDUFA10* (603835), *SDHA* (600857), *NDUFS4* (602694), *NDUFS7* (601825), *NDUFAF2* (609653), *NDUFA2* (602137), *NDUFAF5* (612360), *NDUFAF6* (612392), *SURF1* (185620), *COX15* (603646), *NDUFS3* (603846), *NDUFS8* (602141), *FOXRED1* (613622), *NDUFA9* (603834), *NDUFA12* (614530), *COX10* (602125), *SURF1* (185620), *TACO1* (612958), *MTATP6* (516060);

** Caused by deletion of multiple genes in the mitochondrial DNA;

*** Unknown which gene mutations are accompanied by myoclonus.

**** Loss of maternally derived *UBE3A* allel (de novo dominant, paternal uniparental disomy (UPD) or other rare causes).

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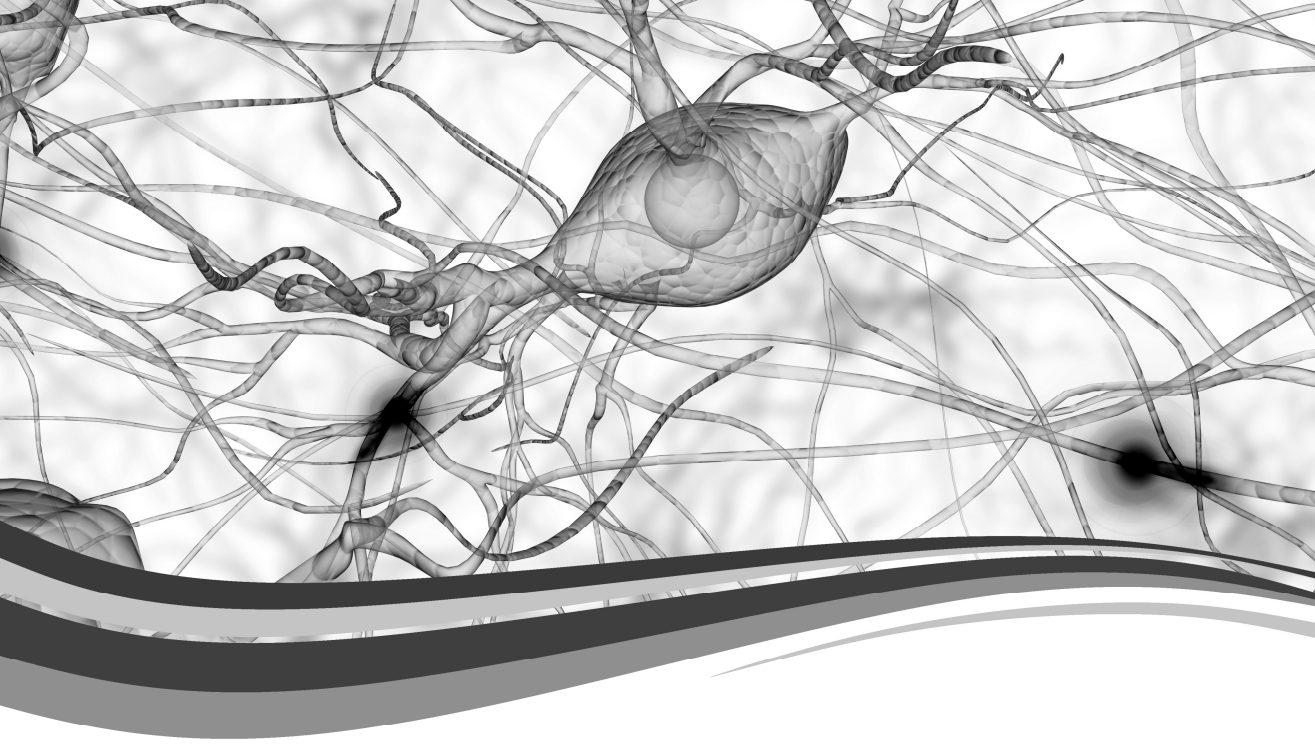

2.9 Chapter 2A Unusual course of Lafora disease

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2.9.1 Abstract

A 42-year-old male was admitted for refractory status epilepticus. At the age of 25, he had been diagnosed with juvenile myoclonic epilepsy. He had a stable clinical course for over a decade until a recent deterioration of behavior and epilepsy. After exclusion of acquired disorders, diagnostic work-up included application of next generation sequencing (NGS), i.e. a gene panel targeting progressive myoclonic epilepsies. This resulted in the diagnosis Lafora disease due to compound heterozygous *NHLRC1* pathogenic variants. Although these pathogenic variants may be associated with a variable phenotype including both severe and mild clinical course, the clinical presentation of our patient at this age is very unusual for Lafora disease. Our case expands the phenotype spectrum of Lafora disease due to pathogenic *NHLRC1* variants and illustrates the value of using next generation sequencing in clinical practice leading to a rapid diagnosis and guiding therapeutic options.

2.9.2 Introduction

Early-onset myoclonic epilepsy points toward a genetic disorder.[1] The most common epileptic myoclonus syndrome is juvenile myoclonic epilepsy (JME) which is occasionally associated with pathogenic variants in *GABRA1*, *CLCN2* or *EFHC1*.[2, 3] It appears around puberty, remains stationary over time, and is characterized by bilateral irregular myoclonic jerks of predominantly the arms, particularly on awakening while generalized tonic-clonic seizures (GTCS) or absences may occur.[4] Other epilepsy syndromes with myoclonus with a progressive course include progressive myoclonic epilepsies (PMEs)[1] and inborn errors of metabolism including mitochondrial disorders. Lafora disease, a common form of PMEs, is characterized by adolescent onset (between 8 and 18 years) of progressive myoclonus combined with seizures, visual hallucinations and cognitive decline. Lafora disease is inherited in an autosomal recessive fashion and caused by pathogenic variants in the *EPM2A* or *NHLRC1* (also called *EPM2B*) genes, encoding the interacting proteins laforin and malin. Death occurs usually within 10 years after onset, although pathogenic *NHLRC1* variants are sometimes associated with a later age at onset and milder clinical course.[5-7] Diagnosis of Lafora disease can be made by detection of polyglucosan aggregates in myoepithelial cells surrounding sweat glands, also called Lafora bodies.[8] However, distinguishing Lafora bodies from normal apocrine cell granules may be difficult[9], making genetic testing the preferred diagnostic method. Genetic analysis with targeted NGS has changed diagnostic strategies of heterogeneous diseases associated with a broad phenotype as epileptic myoclonus syndromes.[10] It enables screening for pathogenic variants associated with PMEs, with results available in four weeks. Costs are comparable to those of sequencing three individual genes.[11,12] Here, we describe a 42-year-old male patient, initially diagnosed with JME, who appeared to have Lafora disease. Most remarkable was the unusual clinical course with very late adult onset and disease progression only after 17 years.

2.9.3 Case report

This 42-year-old male was admitted with a generalized convulsive status epilepticus. Aged 25, he had had a single unprovoked GTCS, followed by mild multifocal myoclonic jerks, mainly distally in his arms, two years later. Family history was negative for epilepsy. EEG at that time showed frequent generalized 2-3Hz (poly)spike-waves without photosensitivity and a diagnosis

of JME was made. With valproate treatment, myoclonic jerking persisted without seizures. Personal and social functioning appeared normal until a few weeks before admission when friends noticed manic behavior.

Despite standard anti-epileptic drug treatment, seizures persisted requiring intubation and sedation with propofol and midazolam. After tapering sedation, tonic-clonic seizures and myoclonus of his feet reappeared. EEG showed continuous generalized spikes and high voltage sharp waves with a bifrontocentral maximum. Sedation was restarted to induce electrographic burst suppression and lacosamide was added. After 48 hours of burst suppression, tapering of sedation again led to myoclonus of the feet and reappearance of epileptic paroxysms in the EEG. Subsequently, burst suppression with thiopental was maintained for another 48 hours. After regaining consciousness five days later, the patient developed action provoked and stimulus sensitive multifocal myoclonus in his face (predominant left-sided) and distal limbs. Without an obvious EEG correlate, their cortical origin was substantiated with back-averaging (Figure 1a). Somatosensory evoked potentials (SSEP) showed no enlarged late potential complex (P27/N30), possibly due to medication. The following days, still artificially ventilated, he responded adequately with normal facial and oculomotor functions while voluntary limb control was strongly impaired. This progressed into tetraparalysis with continuously myoclonic limb jerking.

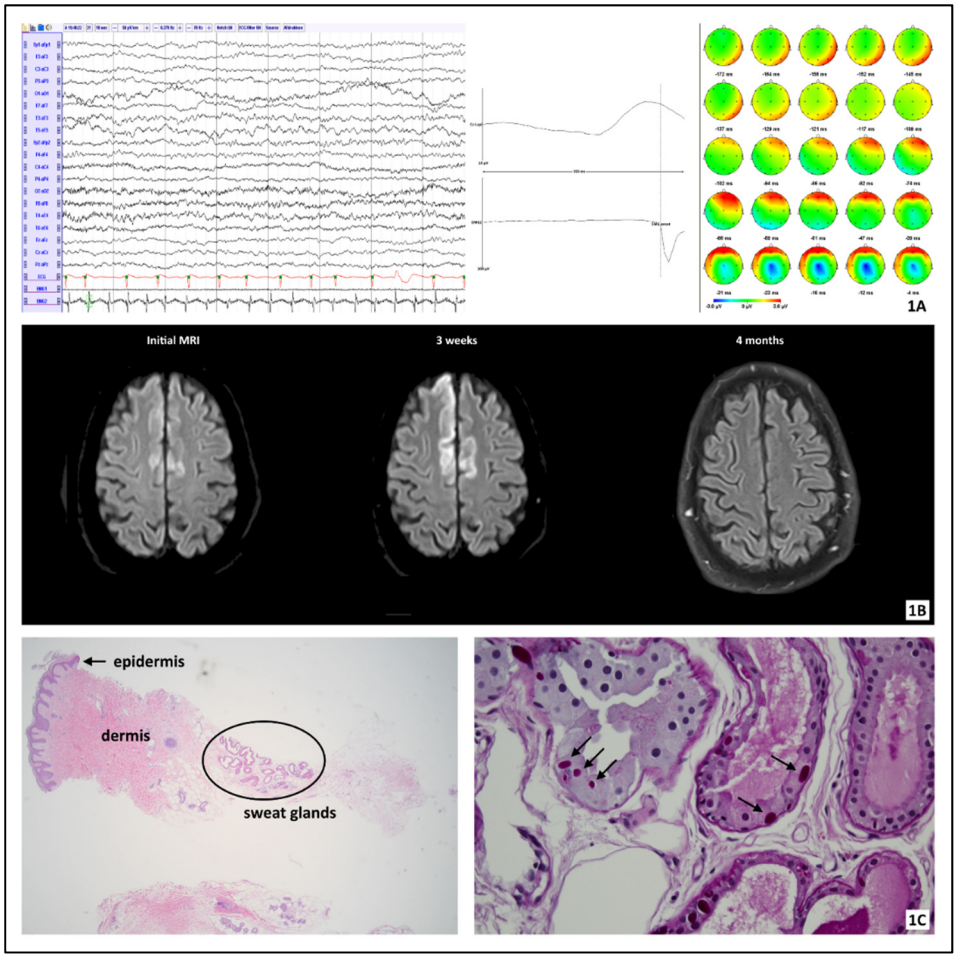

Figure 1

1A: The left panel shows 10 seconds of raw EEG and EMG data of muscles of the right leg. Note the short duration of the EMG bursts. The EEG shows no epileptic abnormalities. The middle panel shows a clear positive-negative potential in the central electrode after back-averaging, which starts approximately 40 ms before myoclonus onset. Right panel: Topographic mapping of the cortical potential.

1B: Three consecutive Brain MRI's (transversal sections). The left and middle slices show Diffusion Weighted Images (DWI); the right image is based on Fluid Attenuation Inversion Recovery (FLAIR) sequences. The first MRI shows hyperintensity of the gyrus cinguli corresponding to the maximum of seizure activity. The second MRI shows extension of the grey matter abnormalities likely associated with repeated periods of epileptic seizure activity. The third MRI shows complete disappearance of the abnormal T2 hyperintensity of the grey matter.

1C: The left panel shows a haematoxylin and eosin (H&E) stain overview of the axillary biopsy. The right panel shows a detailed periodic acid -Schiff staining with multiple Lafora bodies (arrows) in the myoepithelial cells surrounding the glands.

A week later, convulsive status epilepticus reappeared with facial myoclonus and tonic-clonic seizures. EEG showed continuous generalized spikes and high voltage sharp waves with a (right) frontocentral maximum. Under propofol, valproate was switched to gabapentin in addition to continued phenytoin, clonazepam, levetiracetam and lacosamide treatment. His epilepsy became finally controlled and limb motor function gradually improved with residual cognitive impairment including mild expressive aphasia.

Initially, the status epilepticus was assumed to be related to JME. His long-lasting stable clinical course seemed a strong argument against PME. The differential diagnosis of refractory seizures preceded by behavioral changes included infectious or immune-mediated (paraneoplastic) encephalopathy or an inborn metabolic error. Serum and cerebrospinal fluid analyses excluded infectious or immune-mediated etiologies. Brain MRI, made five days after admission, showed brain atrophy with T2 hyperintensity of mid-cingulate gray matter. Three weeks later, MRI abnormalities extended frontally (right) and occipito-temporal. This suggested a local consequence of epileptic activity, which was supported by T2 normalization on three-month follow-up MRI (Figure 1b). With a targeted next generation sequencing epilepsy panel (NGS), 19 monogenic PME-associated disorders including Unverricht-Lundborg disease, Lafora disease and neuronal ceroid lipofuscinoses, were screened. We identified two pathogenic variants in the *NHLRC1* gene (NM_198586.2) on chromosome 6p22, c.386C>A p.(Pro129His) and c.361G>A p.(Gly121Ser), pointing towards Lafora disease. The parents were not available to check their mutation status. Due to the fact that the variants are close to each other, that the gene is analyzed by reads of about 150 basepairs long and that both alleles are sequenced, we could assign the variants to different alleles. Besides, the diagnosis was confirmed by an axillary biopsy showing pathognomonic inclusion bodies in myoepithelial cells surrounding the sweat glands (Figure 1c).

2.9.4 Discussion

This case report describes a patient with Lafora disease following an atypical clinical course with late onset and long-lasting clinically stabile course with sudden deterioration into refractory status epilepticus at the age of 42 years. The *NHLRC1* gene variants detected in our patient are considered pathogenic based on a number of arguments. Both variants are found only once in the

publicly available control population database (Exome Aggregation Consortium; http://exac.broadinstitute.org/): p.Pro129His 1/116492 alleles and p.Gly121Ser 1/112232 alleles. The variants are part of one of the six NHL domains of the protein, a conserved domain probably involved in protein-protein interaction. Pro129 and Gly121 are both highly conserved amino acids. Alamut (version 2.6) from Interactive Biosoftware (http://www.interactive-biosoftware.com) was used to predict pathogenicity. It includes Align GVDG, SIFT, PolyPhen-2 and Mutation Taster. All four programs predicted the variants damaging. Finally, both variants are published previously in patients with Lafora Disease.[5,6,13] Since segregation analysis in the family of our patient was not possible, the diagnosis of Lafora disease was confirmed by immune histochemical testing.

Later age at onset and milder clinical course are described in patients with pathogenic *NHLRC1* variants resulting in a lower neurologic disability score and less severe seizure phenotype compared to patients with pathogenic *EPM2A* variants.[5,14] However, to our

knowledge, no patient with an initially mild disease presentation, suddenly deteriorating towards refractory status epilepticus after more than 15 years has been described before.

The characteristic visual hallucinations were not present in our case which, on the other hand, is in accordance with the study of Ferlazzo et al.[5]

Mild brain atrophy has been described in 35-40% of patients with typical and mild Lafora disease with normal MRI in the remaining patients.[5,14] The transient MRI abnormalities of our patient may well have been caused by the intensive seizure activity as they were localized in the area with the highest seizure activity registered on EEG and had normalized after three-month follow-up. Transient MRI abnormalities with diffusion restriction has been described previously in patients with focal status epilepticus.[15]

Our case thus expands the phenotypic spectrum of Lafora disease due to pathogenic *NHLRC1* variants and highlights the importance of NGS in epileptic myoclonus syndromes.

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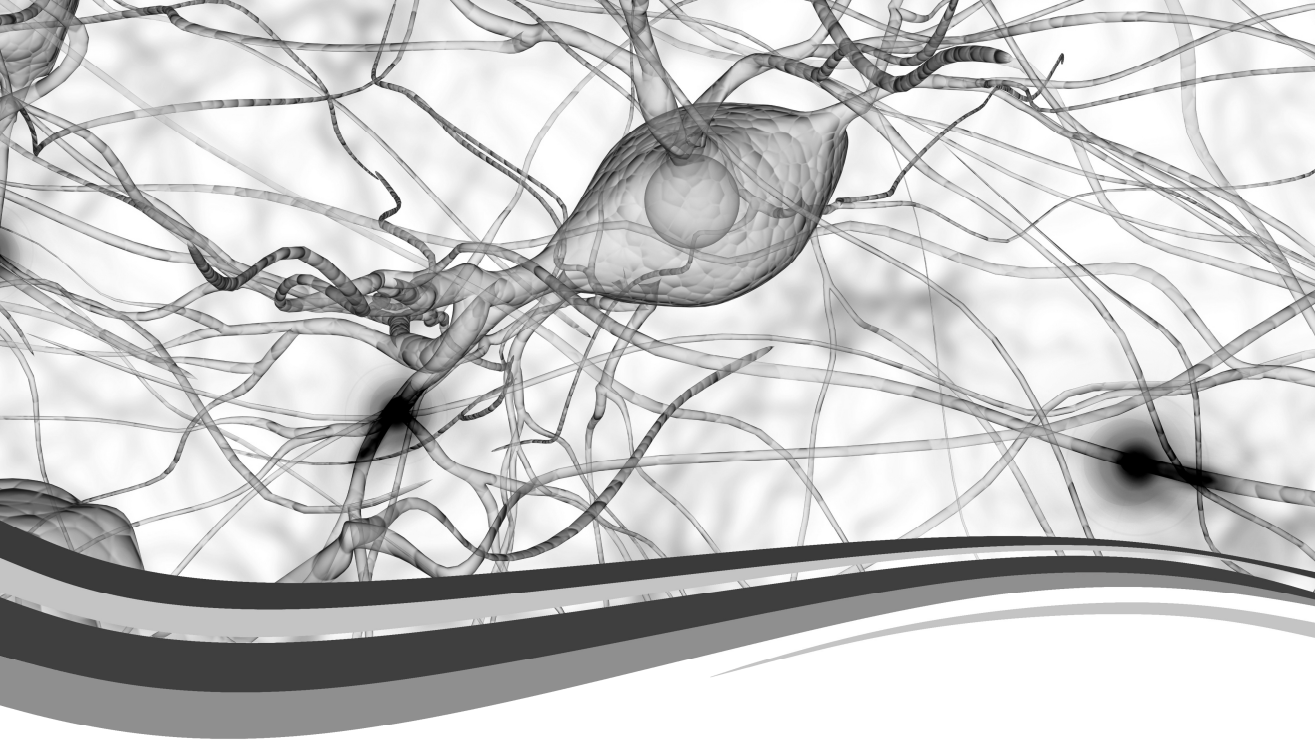

Chapter 3 Distribution and co-existence of myoclonus and dystonia as clinical predictors of *SGCE* mutation status: a pilot study

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3.1 Abstract

Introduction | Myoclonus-Dystonia (M-D) is a young onset movement disorder typically involving myoclonus and dystonia of the upper body. A proportion of cases are caused by mutations to the autosomal dominantly inherited, maternally imprinted, epsilon-sarcoglycan gene (*SGCE*). Despite several sets of diagnostic criteria, identification of patients most likely to have an *SGCE* mutation remains difficult.

Methods | Forty consecutive patients meeting pre-existing diagnostic clinical criteria for M-D underwent a standardised clinical examination (20 *SGCE*-mutation positive and 20 negative). Each video was reviewed and systematically scored by two assessors blinded to mutation status. In addition, the presence and co-existence of myoclonus and dystonia was recorded in four body regions (neck, arms, legs and trunk) at rest and with action.

Results | Thirty-nine patients were included in the study (one case was excluded owing to insufficient video footage). Based on previously proposed diagnostic criteria patients were subdivided into 24 'definite', 5 'probable' and 10 'possible' M-D. Motor symptom severity was higher in the *SGCE* mutation negative group. Myoclonus and dystonia were most commonly observed in the neck and upper limbs of both groups. Truncal dystonia with action was significantly more seen in the mutation negative group ($p<0.05$). Co-existence of myoclonus and dystonia in the same body part with action was more commonly seen in the mutation negative cohort ($p<0.05$).

Conclusion | Truncal action dystonia and co-existence of myoclonus and dystonia in the same body part with action might suggest the presence of an alternative mutation in patients with M-D.

3.2 Introduction

Myoclonus-Dystonia (M-D) is a rare movement disorder, characteristically with onset in the first two decades of life.[1] Motor features are typically of myoclonic jerks, predominantly involving the upper body, although also involve the lower limbs, face and larynx in up to a quarter of cases.[2-4] The dystonic component most frequently involves the neck and upper limbs (writer's cramp).[5,6] Both the myoclonus and dystonia may be exacerbated by posture, action or stress. Presentation and progression of motor symptoms may vary, ranging from an early childhood-onset form starting with upper body or lower limb involvement and progressing to upper limbs involvement, to a later-onset form, with predominant upper body symptoms and frequent cervical involvement. The clinical course can be stable or show a progressive course, with increasing severity and/or spreading of symptoms.[7] Alcohol consumption is widely reported to improve motor symptoms, particularly the myoclonus, resulting in excess alcohol consumption in some cases.[8,9] Several studies have also identified psychiatric symptoms in M-D cohorts, including anxiety, panic attacks and obsessive-compulsive disorder.[10-12]

M-D is inherited in an autosomal dominant fashion with mutations in the maternally imprinted epsilon sarcoglycan (*SGCE*) gene (DYT11) observed in a proportion of cases.[13-15] At present, clinical discrimination of *SGCE* mutation positive from mutation negative M-D cases remains difficult. Previous studies have shown the frequency of *SGCE* mutations in M-D cohorts to vary between 21% and 85% dependent on the inclusion criteria employed.[3,4,6,16-19] Several factors have been proposed as predictors of an *SGCE* mutation, including motor symptom onset <20 years, a positive family history of a similar movement disorder and co-morbid psychiatric symptoms.[19-21]

A classification system has been developed to determine the likelihood of an *SGCE* mutation in individual cases, with subgroups 'definite', 'probable' or 'possible', based on the distribution of motor symptoms, age at onset, and presence or absence of a family history (Supplementary Table 1).[18]

Supplementary Table 1: Grunewald criteria

Grunewald criteria[15]		
Definite' M-D		Early onset myoclonus and dystonia
	OR	Isolated myoclonus predominantly in the upper body half
	AND	Positive family history for myoclonus and/or dystonia
Probable' M-D		Early onset myoclonus and dystonia
	OR	Isolated myoclonus predominantly in the upper body half
Possible' M-D		'Jerky dystonia' of neck
	OR	Isolated jerky movements of variable distribution
	OR	Signs of dystonia and/or myoclonus in lower body half
	OR	No response to alcohol

Refinement of these diagnostic criteria has been proposed to include a positive family history with specific paternal transmission and normal brain imaging,[5] or the combination of young onset motor symptoms with psychiatric features.[20] However, it remains difficult to identify those patients most likely to have an *SGCE* mutation.

The aim of this study is to determine whether the characteristics of motor signs observed during clinical examination can be of help in identifying carriers of a *SGCE* mutation. Particular emphasis was placed on whether co-existence of myoclonus and dystonia in the same body part was helpful in distinguishing those with and without an *SGCE* mutation. We hypothesized that *SGCE* mutation negative patients with "jerky dystonia" would more often present with jerky movements superimposed on the dystonic posture in the same body part, whereas for those with an *SGCE* mutation the myoclonus and dystonia would be evident independently and in different body regions.

3.3 Methods

Following informed consent, forty consecutive M-D patients from the movement disorders service at the Academic Medical Center, Amsterdam, The Netherlands were recruited for the study (20 *SGCE* positive and 20 *SGCE* negative). Participants were divided into one of three diagnostic categories, 'definite', 'probable' and 'possible', according to previously proposed diagnostic criteria (Supplementary Table 1). All participants underwent a video taped clinical examination, which in the majority of cases followed a standardised protocol (n=31), the remaining cases were examined as part of routine clinical practice (n=9). Each videotaped examination was subsequently assessed by two of the three independent movement disorder experts (MFC, HS, JMD), blinded to the genetic status of the participant.

The motor section of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and sections 2 (myoclonus at rest) and 4 (action myoclonus) of the Unified Myoclonus Rating Scale (UMRS) were used to assess motor symptom severity.[22] In addition, the presence and co-existence of myoclonus and dystonia was recorded in four body regions (neck, arms, legs and trunk), at rest and with action. In the absence of adequate video footage to allow evaluation of a specific body region in individual patients, the score for this region was omitted.

The Ethical Board of the Academic Medical Centre of Amsterdam approved the study.

3.3.1 Statistical analysis

Clinical features were analysed using the Fisher's exact test or Student's t test where appropriate. Inter-rater reliability was assessed using intra-class correlation coefficients (ICC) (Two way mixed, consistency, average measures). ICC results were further classified as; 0.91-1: excellent, 0.71 and 0.9: good, 0.51 and 0.70: moderate, < 0.5: poor, < 0.3: very poor.[23] The inter-rater reliability of the new evaluation tool was reported both in absolute agreement and percentage of agreement between raters.

3.4 Results

3.4.1 Demographic characteristics

A full summary of the demographic characteristics of this cohort is reported in Table 1. Due to the consecutive nature of recruitment, mutation positive and negative groups were not matched for gender and age at onset of motor symptoms. The *SGCE*-mutation positive cohort included a greater number of cases with motor symptom onset <20 years and a positive family history. There were no significant differences in demographic characteristics between the groups.

Table 1 - Demographic characteristics

	SGCE **Mutation positive Proband only cohort** (n=13)	***SGCE*** **Mutation positive All patients** (n=19)	***SGCE*** **Mutation negative cohort** (n=20)	***SGCE*** **positive vs.** ***SGCE*** **negative** ***(p-value)***
Gender				
Male/female	5/8	9/10	5/15	0.19
Age median (range)	40 (15 - 60)	41 (15 - 75)	36 (14 - 61)	0.56
Age at onset				
≤ 20 years/>20 years	12/1	17/2	12/8	0.07
Symptom at onset				
Myoclonus	9	13	15	0.73
Dystonia	1	3	5	0.70
Myoclonus & Dystonia	3	3	0	0.11
Alcohol responsiveness				
Responsive	5	5	6	0.23
Unresponsive	0	0	4	
Unknown	8	14	10	
Family history				
Positive/Negative	13/0	…	8/12	0.00
"Grunewald Classification"				
"Definite"	12	17	7	0.00
"Probable"	0	1	4	0.34
"Possible"	1	1	9	0.01

Overall 39 patients (25F: 14M) with a clinical M-D phenotype were included in the study. Nineteen had an *SGCE* mutation (one mutation positive case was excluded owing to insufficient video footage) and 20 patients were mutation negative. Median age at examination was 39 years (range: 14-75). Myoclonus was the presenting feature in 28 cases, dystonia in eight and both myoclonus and dystonia were observed at symptom onset in three. Details of the cognitive and psychological characteristics of this cohort have been published elsewhere.[12]

The *SGCE*-mutation positive cohort (n=19, 10F: 9M) included 13 probands and had a median age at examination of 41 years (range: 15-75). Seventeen cases had onset of symptoms <20 years of age, with single cases developing motor symptoms in each of the 30-40 year and 40-50 year age brackets. Applying Grunewald diagnostic criteria this group was further sub-divided into 17 'definite', 1'probable' and 1'possible' cases.

The *SGCE*-mutation negative cohort (n=20, 15F: 5M) had a median age at examination of 36 years (range: 14-61). Motor symptom onset was <20 years in 12 cases, 30-40 years in 4 cases, 40-50 years in 3 cases and >50 years in a single participant. With application of the same diagnostic criteria this group was sub-divided into 7 'definite', 4 'probable' and 9 'possible'.

Due to a sub-optimal video footage, 11/76 (at rest) and 11/76 (with action) dystonia and 2/76 (at rest) and 3/76 (with action) myoclonus video assessment sections were scored as missing in the *SGCE*-mutation positive cohort. In the mutation negative group, 2/80 (at rest) and 3/80 (with action) dystonia while none of the myoclonus assessment sections incomplete.

3.4.2 Distribution of symptoms

Myoclonus and dystonia were most commonly observed in the neck and arms in both mutation positive and negative groups. Comparison of the *SGCE* mutation positive probands and the mutation negative group identified significant difference with truncal dystonia during action (8/19 (*SGCE* mutation negative) 0/13 (*SGCE* positive probands only); (p=0.01, OR=0.01, 95% CI (0.00, 0.74). This difference was preserved when extended to include the entire mutation positive group: truncal dystonia (8/19 (*SGCE* mutation negative) 1/17 (*SGCE* mutation positive); p=0.02, OR=0.09, 95% CI (0.00, 0.88). (Tables 2 and 3, Supplementary Figure 1).

Table 2 - Distribution of myoclonus at rest and with action

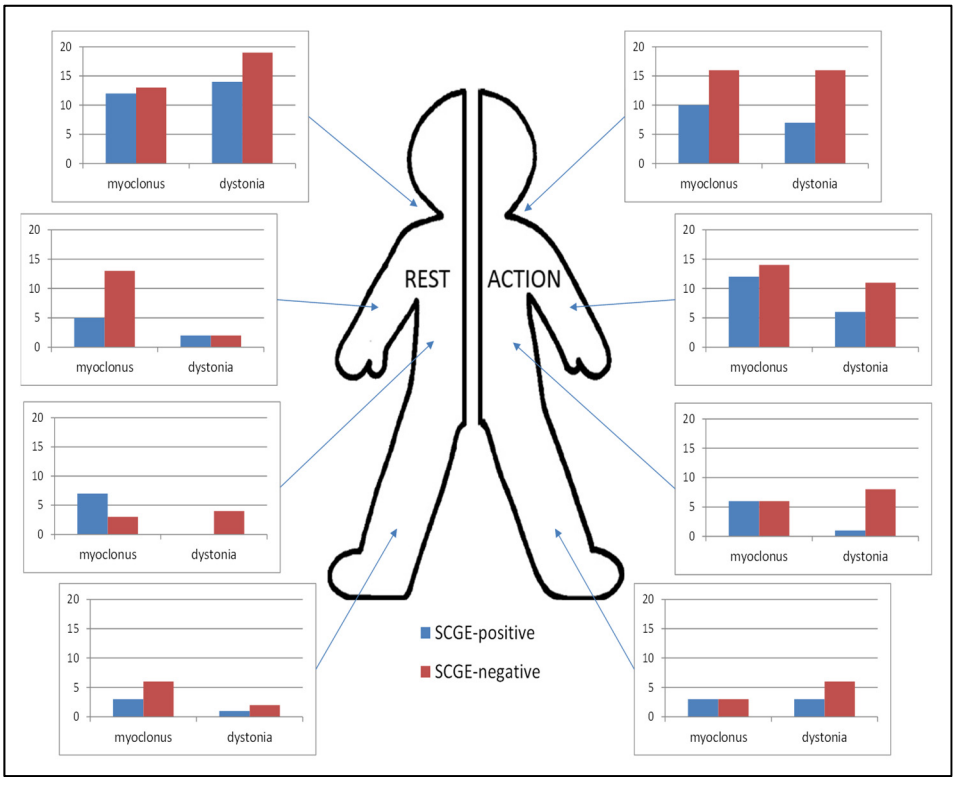
Myoclonus	***SGCE positive All*** *(n=19)*	***SGCE positive Proband only*** *(n=13)*	***SGCE negative*** *(n=20)*	Statistical comparison **All / negative** p-value (OR; 95% CI)	Statistical comparison **Proband only / negative** p-value (OR; 95% CI)
Rest					
Neck	12	9	13	1.00 (0.92; 0.21, 4.15)	1.00 (1.21; 0.22,6.97)
Upper Limbs	5	4	13	0.05 (0.22; 0.04, 1.09)	0.08 (0.24; 0.04,1.32)
Trunk	7	5	3	0.07 (4.41; 0.74, 29.07)	0.12 (4.05; 0.59,30.64)
Lower Limbs	3	2	6	1.00 (0.70; 0.10, 4.41)	0.68 (0.52; 0.06,4.00)
Action					
Neck	10	8	16	0.29 (0.42; 0.07, 2.30)	0.43 (0.50; 0.07,3.30)
Upper Limbs	12	9	14	1.00 (0.86; 0.18, 4.14)	1.00 (0.96; 0.17,5.68)
Trunk	6	4	6	1.00 (1.27; 0.26, 6.29)	1.00 (1.04; 0.18, 6.02)
Lower Limbs	3	2	3	0.67 (1.55; 0.20, 12.33)	1.00 (1.13; 0.11,10.83)

Key: Statistically significant differences (p<0.05) between *SGCE* mutation positive and negative groups are highlighted in bold. Fisher's exact test was used for Statistical comparison.

Table 3 - Distribution of dystonia at rest and with action

Dystonia	*SGCE positive All* *(n=19)*	*SGCE positive Proband only* *(n=13)*	*SGCE negative* *(n=20)*	Statistical comparison **All / negative** p-value (OR; 95% CI)	Statistical comparison **Proband only / negative** p-value (OR; 95% CI)
Rest					
Neck	14	11	19	0.17 (0.18; 0.01, 2.14)	0.55 (0.29; 0.01,4.90)
Upper Limbs	2	2	2	1.00 (1.20; 0.10, 14.07)	1.00 (1.64; 0.14,19.91)
Trunk	0	0	4	NA	NA
Lower Limbs	1	1	2	1.00 (0.71; 0.02, 12.05)	1.00 (0.85; 0.03,14.84)
Action					
Neck	7	5	16	0.04 (0.19; 0.03, 1.04)	0.05 (0.18; 0.03,1.10)
Upper Limbs	6	5	11	0.21 (0.41; 0.09, 1.84)	0.48 (0.51; 0.10,2.63)
Trunk	1	0	8	**0.02 (0.09; 0.00, 0.88)**	**0.01 (0.00; 0.00, 0.74)**
Lower Limbs	3	3	6	1.00 (0.73; 0.11, 4.43)	0.69 (0.55; 0.08,3.44)

Key: Statistically significant differences (p<0.05) between *SGCE* mutation positive and negative groups are highlighted in bold. NA= not applicable. Fisher's exact test was used for Statistical comparison.



Supplementary Figure 1 - Body distribution of myoclonus and dystonia

3.4.3 Co-existence of myoclonus and dystonia

At rest, there was no significant difference between the proband-only mutation positive group and those without an *SGCE* mutation in the co-existence of myoclonus and dystonia in the same body part, either overall or by individual body part. Overall assessment with action showed a significant difference between the two groups (p= 0.01, OR=0.11, 95% CI (0.01, 0.73), being the co-existence more common in the mutation negative group, although no difference was observed between individual body parts. Inclusion of the entire mutation positive cohort showed similar results overall (p=0.01, OR=0.13, 95% CI (0.02, 0.71)) and a trend towards significance when examining the cervical region (p=0.09, OR=0.26, 95% CI (0.05, 1.26)). A full summary of the rates and distribution of co-existent myoclonus and dystonia can be seen in Table 4.

Table 4 - Comparison of co-existent myoclonus and dystonia in the same body region in *SGCE* mutation positive and negative cohorts

Myoclonus & Dystonia	***SGCE positive All*** *(n=19)*	***SGCE positive Proband only*** *(n=13)*	***SGCE negative*** *(n=20)*	Statistical comparison **All / negative** p-value (OR; 95% CI)	Statistical comparison **Proband only / negative** p-value (OR; 95% CI)
Rest					
Overall	10	8	15	0.19 (0.37;0.08, 1.73)	0.46 (0.53; 0.09,3.05)
Neck	10	8	13	0.74 (0.67;0.15, 3.01)	1.00 (0.86; 0.16,4.63)
Upper Limbs	0	0	2	NA	NA
Trunk	0	0	0	NA	NA
Lower Limbs	1	1	1	1 .00 (1.50;0.04, 62.14)	1.00 (1.80; 0.04,75.80)
Action					
Overall	8	5	17	**0.01 (0.13; 0.02,0.71)**	**0.01 (0.11; 0.01,0.73)**
Neck	6	5	14	0.09 (0.26;0.05, 1.26)	0.15 (0.31; 0.05,1.71)
Upper Limbs	5	4	8	0.51 (0.58; 0.12, 2.74)	0.72 (0.67; 0.12,3.65)
Trunk	1	0	4	0.34 (0.23; 0.01, 2.75)	0.13 (0.00; 0.00, 2.21)
Lower Limbs	0	0	0	NA	NA

Key: Statistically significant differences (p<0.05) between *SGCE* mutation positive and negative groups are highlighted in bold. NA= not applicable. Fisher's exact test was used for Statistical comparison.

3.4.4 Severity of myoclonus and dystonia with use of BFMDRS and UMRS rating scales

The median total BFMDRS score was significantly higher in the *SGCE* mutation negative group (6/120 (range: 4-47)) vs. 3.5/120 (range: 0-11) than in the mutation positive group ($p<0.05$). A higher median UMRS total score was also observed in the *SGCE*-negative patients (25/240 (range: 0-92)) compared to 14.5/240 (range: 0-80) in the mutation positive group ($p>0.05$), although this difference was not statistically significant.

3.4.5 Inter-rater agreement

Two assessors evaluated the *SGCE* mutation negative group using both BFMDRS and UMRS rating scales, achieving an inter-rater concordance of "good" (ICC BFMDRS = 0.91 (95% CI: 0.74 - 0.97) / ICC UMRS = 0.87 (95% CI:0.60 - 0.96)). Each rating scale was scored by a single assessor during evaluation of the mutation positive patients (Supplementary Table 2). In evaluating co-occurrence of myoclonus and dystonia, overall-agreement between the two assessors was 88% at rest and 84% with action. Evaluation of individual body parts showed the strongest concordance when assessing the truncal region (94%, 34/36) and the lowest rate of agreement when evaluating movements of the neck with action (64%, 23/36). A summary of the positive agreement between assessors can be seen in Supplementary Table 3.

Supplementary Table 2 - Comparison of assessor BFMDRS and UMRS scores in SGCE mutation positive and negative cohorts

	Median	Range	SD	ICC (95% CI)
BFMDRS				
Rater 1				
Overall	6,00	0 - 47	9,54	
SGCE-positive	3,50	0 - 11	3,25	
SGCE-negative	6,00	4 - 47	12,16	
Rater 2				
SGCE-negative	7,50	2 - 32	7,20	0,91 (0,74 - 0.97)
UMRS				
Rater 1				
Overall	21,00	0 - 92	23,22	
SGCE-positive	14,50	0 - 80	18,31	
SGCE-negative	25,00	0 - 92	25,16	
Rater 2				
SGCE-negative	16,50	0 - 73	20,16	0,87 (0,60 - 0,96)

Supplementary Table 3 - Inter-rater agreement of the co-existence of myoclonus and dystonia

Rater 1 vs Rater 2	Neck		Arms		Trunk		Legs		Total	
	absolute agreement	%	absolute agreement	%	absolute agreement	%	absolute agreement	%	absolute agreement	%
Rest	31/38	82%	32/37	86%	33/35	94%	29/32	91%	125/142	88%
Action	23/36	64%	32/38	84%	34/36	94%	30/32	94%	119/142	84%

3.5 Discussion

This study examined the distribution and co-existence of myoclonus and dystonia, at rest and with action as a predictive factor in determining the presence of an *SGCE* mutation in patients with an M-D phenotype. We have demonstrated that truncal dystonia and co-existence of myoclonus and dystonia in the same body region with action are more frequently observed in those without an *SGCE* mutation.

Application of the Grunewald diagnostic criteria to this study cohort didn't clearly distinguish between those with and without an *SGCE* mutation. Seven on those without a mutation were deemed to be in the 'definite' diagnostic category, while a two individuals with mutations were placed, one each, in the 'probable' and 'possible' groups. In keeping with the current diagnostic criteria, myoclonus and dystonia were most frequently observed in the neck and arms of both mutation positive and negative cohorts, with onset of symptoms <20 years being more frequent in those with an *SGCE* mutation (17/19 vs. 12/20).[5,18] A positive family history was more frequently observed amongst those with an *SGCE* mutation and therefore increased the number of cases in the 'definite' diagnostic category. The mutation positive cohort consisted of 13 probands with an additional six affected cases recruited from two families, reflecting an inherent recruitment bias from a specialist tertiary movement disorder service. It could also be argued that by recruiting multiple members of the same kindred additional genetic and environmental factors may also be contributing to their motor phenotype. However, little difference in results was observed when comparing both the proband only and complete *SGCE* mutation positive cohort to the mutation negative group, suggesting that any potential additional factors had little effect in the outcome of this study. In addition, multiple case reports and case series have demonstrated significant intra-familial motor variability amongst those with *SGCE* mutations.[4]

It is worth mentioning that mutations in other genes, including *KCTD17*, *THD* and *RELN*, have been recently associated with M-D, although confirmation in a larger number of families is still needed.[24-26] Available data suggest that the phenotype associated with these mutations might slightly differ from that associated with *SGCE* mutation. For example the *KCTD17* gene mutation is characterized by a milder myoclonus affecting the upper limbs and progressive dystonia spreading from the cranio-cervical region to other sites. The patients in our cohort were not screened for these mutations, which could potentially account for some of the *SGCE*-negative cases.

Although multiple previous reports have commented on worsening of motor features with action in M-D cohorts, none of the previous studies have directly compared the nature and frequency of the movement disorder between an *SGCE* mutation positive cohort and a suitable mutation negative control group, both at rest and with action. Overall, no difference between the two groups was observed at rest, however, co-existence of myoclonus and dystonia in the same body area was significantly more frequent with action in the mutation negative cohort ($p<0.05$) with a trend towards significance observed in the cervical region with action ($p=0.09$). These observations of co-existent myoclonus and dystonia in the same body region in those without an *SGCE* mutation may reflect a 'jerky' dystonia rather than myoclonus. These two forms of hyperkinesias are known to be difficult to differentiate, both in clinical practice and assessment of videotaped examination. It may be contributory to include neurophysiological testing in future studies to aid in differentiating between these two forms of movement disorder.[27]

Multi-rater comparison of clinical cases can potentially result in significant variability of clinical opinion. Overall inter-rater agreement between the movement disorders specialists involved in this study was good. Disparities in scoring were predominantly observed in the cervical region where dystonic 'overflow' or movement of other body parts can cause diagnostic difficulty. These results highlight the notoriously difficult task of hyperkinetic movement disorder phenomenology, particularly when two or more movement disorder subtypes may co-exist in the same body region. This study can be regarded as a pilot study due to the relatively small number of patients in each study group ultimately preventing further and more elaborate statistic analysis of the available results. Future studies will require large, multi-centre collaboration in

order to enable recruitment of sufficiently large and diverse cohorts to allow definitive conclusions to be drawn.

3.6 Conclusion

The results of this pilot study suggest that the presence of truncal dystonia and the co-existence of myoclonus and dystonia in the same body region with action reduce the likelihood of *SGCE* mutation in patients with a M-D phenotype. Larger series are needed to confirm our preliminary findings before they can be translated into clinical practice. These results highlight the importance of examining movement disorders both at rest and with action during clinical assessment, particularly when selecting those patients to undergo specific genetic testing.

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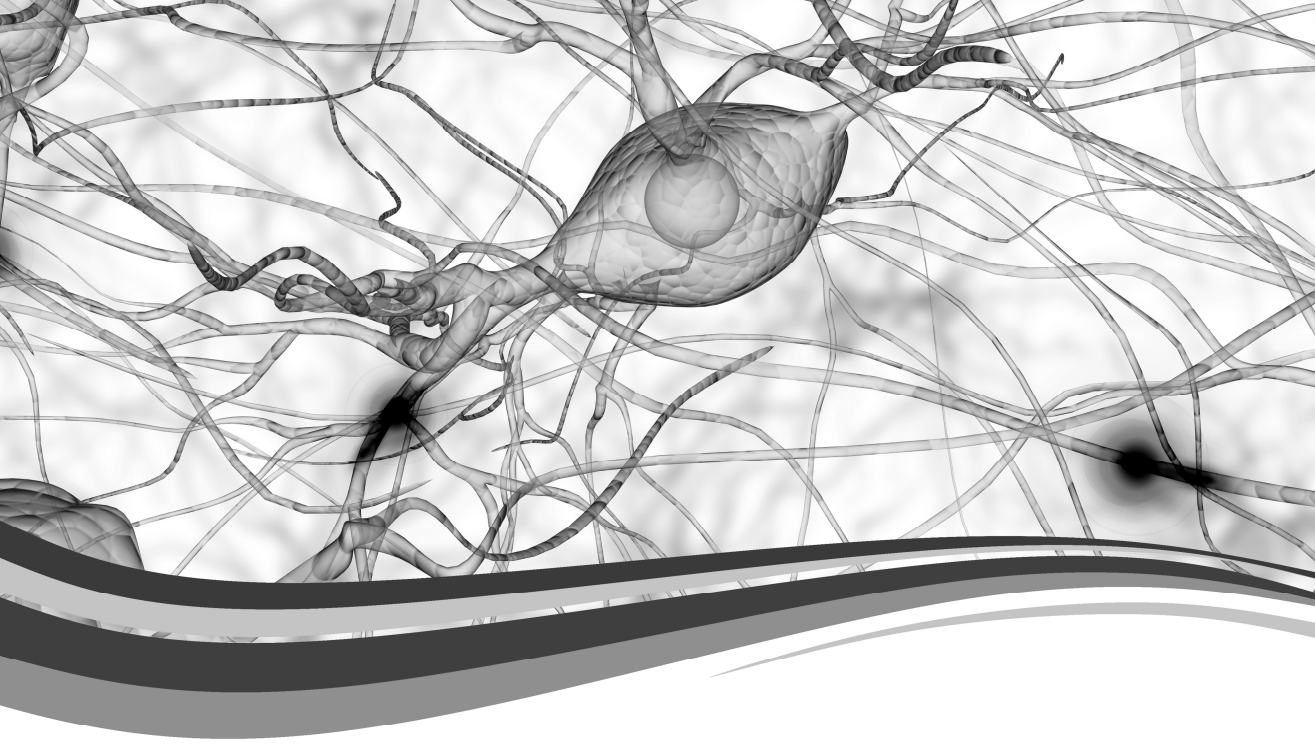

Chapter 4 The presence of depression and anxiety do not distinguish between functional myoclonic jerks and cortical myoclonus

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4.1 Abstract

Introduction | Functional movement disorders are accompanied by a high occurrence of psychopathology and cause serious impairments in quality of life. However, little is known about this in patients with functional jerks and no comparison has been made between patients with functional jerks and organic myoclonus. This case control study compares the occurrence of depression, anxiety and quality of life (HR-QoL) in patients with functional jerks and cortical myoclonus.

Methods | Patients with functional jerks and cortical myoclonus, consecutively recruited, were compared on self-rated anxiety (Beck Anxiety Inventory), depression (Beck Depression Inventory), health-related quality of life (RAND-36), and myoclonus severity (UMRS and CGI-S rating scales).

Results | Sixteen patients with functional jerks and 23 with cortical myoclonus were evaluated. There was no significant difference in depression (44% vs. 43%) or anxiety (44% vs. 47%) scores between groups. The HR-QoL was similarly impaired except that functional jerks patients reported significantly more pain ($p<0.05$). Only in the functional jerks group myoclonus severity correlated with depression and anxiety.

Conclusion | Depression and anxiety scores are high and do not discriminate between functional jerks and cortical myoclonus. Quality of life was equally impaired in both sub-groups, but pain was significantly worse in patients with functional jerks.

4.2 Introduction

Functional movement disorders (FMD) are disabling involuntary movements, which can be defined by incongruence with known neurological pathology and the influence maneuvers like distraction and suggestion. One of the manifestations of FMD is functional myoclonic jerks (FJ), which has a prevalence amongst FMD of approximately 15%.[1]

FJ is characterized by an acute onset of jerks with a slow or variable burst duration, an inconsistent distribution, and reduction with distraction.[2] Clinical discrimination between FJ and organic myoclonus can be very difficult, even for world class experts.[3] In these cases, electrophysiological testing aids in the diagnosis of FJ, especially with the finding of a pre-movement or Bereitschaftspotential with back-averaging. Accurate and early diagnosing of FJ is important as prompt treatment improves patient's outcome.[4] There is no evidence on specific therapy for FJ, but patient education and specialized physiotherapy are considered increasingly important in the treatment of FMD.[5]

Symptoms of depression and anxiety are more common in FMD than in healthy controls, with 37,1%-61% lifetime depression and 20% - 21% generalised anxiety disorder in two key publications.[6] Although psychopathology has been found to be high in FMD,[7] this is not unique for FMD as organic movement disorders are also often accompanied by psychopathology.[8-10] Studies comparing FMD with organic neurological disorders found either more affective disorders and anxiety in FMD, or equal prevalences.[6] Furthermore, previous studies reported a similar level of impairment of the quality of life and daily functioning, for example when comparing FMD with Parkinson's Disease.[7-11] In multiple movement disorders there is an ongoing discussion whether psychiatric co-morbidity are primary and part of the phenotype or a secondary consequence of the motor disorder.[8-12]

Little is known about the psychiatric co-morbidity in patients with FJ, and, to date, there has been no systematic comparison with an appropriate control group. In our study we explored the depression and anxiety rate, and whether these psychiatric symptoms and the perceived health related quality of life could discriminate between FJ and cortical myoclonus (CM). Based on the literature, our hypothesis is that patients with FJ experience more symptoms of depression, anxiety, and have a greater impairment of their quality of life.

4.3 Methods

4.3.1 Recruitment

Adult patients with FJ and CM were consecutively recruited from both the outpatient clinic and the ward of the Neurology department of our tertiary referral centre between May 2014 and June 2016. Patients were excluded if they were aged less than 16, or were judged to have significant cognitive impairment interfering with ability to complete measures. In all patients a comprehensive history was taken, including age at onset, co-existing neurological symptoms, and non-neurological co-morbidity. All subjects previously participated in a study about the value of electrophysiological testing in determination of the myoclonus subtype (*article under review*).

The Ethical Board of the University Medical Center Groningen (UMCG) approved the study (Number M14.157933).

4.3.2 Motor assessment

All patients underwent a medical history, protocolled videotaped clinical examination and electrophysiological testing. The diagnosis CM or FJ was made by a movement disorder specialist (MT) based on clinical characteristics. Co-existing neurological symptoms including additional movement disorders were recorded.

Severity of myoclonus was scored by two independent experts using the modified versions of the Unified Myoclonus Rating Scale (UMRS)[13] and the 7 point Global Clinical Impression - Severity (GCI-S) scale.[14] The average score of the two experts was used.

4.3.3 Psychiatric and quality of life assessment

Participants were asked to fill out a questionnaire consisting of the Beck anxiety Inventory (BAI)[15], and the Beck depression inventory (BDI).[16] For the BDI, we used a cut-off score of 10 or higher to distinguish depressive from non-depressive patients, the range for mild depression was 10-19, moderate 19-29 and severe 30-63.[16] For the BAI the same scores were used to divide symptoms into no, mild, moderate and severe anxiety.[17] Three items on the BAI concerning trembling or shaking of several body parts were excluded from analysis, without adjustment of the marking of the BAI, as these questions are

inherent to the movement disorders studied. The RAND 36 questionnaire, a Dutch validated version of the SF36 was used for measuring quality of life.[18]

4.3.4 Statistical analysis

Chi-square tests were used for categorical variables and Mann-Whitney U tests for ordinal and continuous not-normally distributed data in SPSS 23. When differences between groups were found, odds ratios were calculated using binominal logistic regression analysis, to provide predictive value of the factor for being in one of the groups. Inter-rater reliability for video motor scoring was assessed using the intra-class correlation coefficient (ICC) (Two way mixed, consistency, average measures). Correlations between physical functioning (RAND-36 subscale), depression (BDI), anxiety (BAI) and symptom severity (CGI), were calculated using Spearman's correlation in both groups. No violations were noted of the completed statistical analyses. All statistical tests were two-sided. The p-values of <0.05 were considered as statistically significant.

4.4 Results

4.4.1 Participants characteristics

Forty-seven adult patients, including 27 with CM and 20 FJ were recruited. Three CM cases were excluded from the study due to cognitive problems and five cases (4FJ and 1CM) had not completed the questionnaires.

In total 39 patients; 16 FJ (69% female, median age at examination 32 years) and 23 CM patients (52% female, median age at examination 30 years) participated in the study.

The severity of myoclonus on the UMRS was significantly higher for FJ (FJ:16.5, CM: 5.7) without a significant difference in CGI-S (FJ:4, CM:3) with a good ICC between raters (ICC UMRS = 0.98 (95% CI: 0.95-0.99) / ICC GCI-S = 0.82 (95% CI: 0.67- 0.91)).

Co-existing neurological symptoms were detected in five of the 20 FJ and in nine of the 27 CM patients (Table 1).

In the CM group, in 15/23 cases an aetiological diagnosis was made; five had an acquired cause, 10 cases were thought to have a genetic origin of which a causative gene mutation was found in seven cases (see Supplementary Table 1). The demographic features are shown in Table 1.

Table 1 - Demographic features, psychiatric co-morbidity and quality of life in functional jerks versus cortical mycolonus patients

	CM (n=23)	FJ (n=16)
Female N (%)	12 (52%)	11 (69%)
Age at examination, median (IQR)	30 (32)	32 (38)
Age at onset of myoclonus, median (IQR)	17 (39)	25 (36)
Total UMRS, median (IQR)	**5,7 (15)**	**16,5 (14)***
Total GCI-S, median (IQR)	3 (4)	4 (4)
Medical history		
epilepsy	5	0
cognitive problems	4	0
structural brain damage	3	1
Other neurological symptoms		
dystonia	5	0
ataxia	4	0
spasticity	0	1
other functional symptoms	0	4
Median RAND-36 scores (IQR)		
Physical functioning	60 (56)	75 (63)
Social functioning	63 (38)	63 (59)
Role limitation physical	50(100)	12,5 (94)
Role limitation emotional	100 (100)	100 (50)
Mental health	76 (32)	78 (20)
Vitality	50 (30)	50 (30)
Pain	**80 (33)**	**49 (52)***
General health perception	40 (15)	50 (35)
Expected health change	50 (25)	50 (50)
Median BDI (range) (cut-off scores)	9 (0 - 25)	7 (0 - 43)
No depression (0-9)	13	9
Mild depression (10-18)	7	4
Moderate depression (19-29)	3	1
Severe depression (30-63)	0	2
Median BAI (range)	7 (0 - 26)	7 (3 - 28)
No anxiety (0-9)	12	9
Mild anxiety (10-18)	7	4
Moderate anxiety (19-29)	4	3
Severe anxiety (30-63)	0	0

Supplementary Table 1 - Aetiological diagnosis

Etiological diagnosis		CM (n=23)
Genetic disorder		
Genetic mutation identified	Wilson disease (mutation *ATP7B* gene)	1
	Niemann pick type C (*NPC1* mutation)	2
	Lafora disease (mutation *NHLRC1* gene)	1
	Ramsay Hunt syndrome (*GOSR* mutation)	1
	Mycolonus dystonia (*RELN* mutation)	1
	Myoclonus Dystonie (chromosome 18p-)	1
No genetic mutation identified	Juvenile myoclonus epilepsy	1
	Ramsay Hunt syndrome	1
	Mycolonus dystonia	1
Acquired disorder		
	Medication-induced	1
	Metabolic derangements	2
	Structural cerebral lesion	2
Unknown		8

4.4.2 Occurrence of depression, anxiety, and health related quality of life

As is shown in Table 1, in the FJ group, 7/16 (44%) met criteria for a mild to severe depression and in the CM group this was 10/23 (43%). The median depression score on the BDI was not significantly different between the FJ and CM groups (FJ: 7 (0-43), CM: 9 (0-25), p=0.72).

Seven of 16 (44%) FJ patients and 11/23 (48%) CM patients met criteria for mild to severe anxiety. The median BAI score was not significantly different for FJ (6 (0-28)) compared to CM patients (7 (0-26)).

On all subdomains of HR-QoL FJ and CM patients were equally impaired, except for the subdomain of pain. FJ patients reported significantly more pain (FJ vs CM median 49 (IQR 52) vs median 80 (IQR 33), $p<0.05$). Details about HR-QoL subdomains and severity of depression and anxiety can be found in Table 1.

As is shown in Table 2, myoclonus severity was correlated to both depression and anxiety in the FJ group, but not in the CM group. Pain was correlated to physical functioning in CM but not in FJ.

Table 2 - Correlations between myoclonus severity, psychiatric co-morbidity and HR-QoL

	Physical functioning (RAND36)		Myoclonus severity (mean CGI-S)	
	FJ	**CM**	**FJ**	**CM**
Myoclonus severity (mean CGI-S)	Rho -0,08 P=0.77	Rho -0,11 P=0.61	X	X
Depression (BDI)	Rho -0,27 P=0.33	Rho -0.12 P=0.60	**Rho 0.49, p = 0.05**	Rho 0.18, p = 0.42
Anxiety (BAI -corrected)	Rho -0,03 P=0,91	Rho -0.02 P=0.91	**Rho 0.73, p <0.05**	Rho 0.36, p = 0.09
Pain (RAND36)	Rho 0.40 P=0,12	**Rho 0.47 p <0.05**	Rho -0,25 P=0,34	Rho 0,31 P=0,14

BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, CGI-S: Global Clinical Impression - Severity, CM: cortical myoclonus, FJ: functional jerks. Statistically significant correlations using Spearman's Rho ($p<0.05$) are highlighted in bold.

4.5 Discussion

In this prospective study, we showed functional jerks and cortical myoclonus patients had equally high depression and anxiety scores and a similar impaired health related quality of life. Patients with FJ reported significantly more pain compared to the CM group.

The occurrence of mild to severe depression and anxiety in both FJ and CM found in our cohort is high compared to the normal population. In FJ, this confirms earlier findings in several types of functional neurological disorders.[7] Psychiatric co-morbidity in a heterogeneous group of CM has not been studied before, but our results are comparable with the rates of anxiety and depression reported in CM patients diagnosed with Familial Cortical Myoclonic Tremor and Epilepsy and Juvenile Myoclonus Epilepsy.[19,20] These findings might implicate that cortical myoclonus syndromes in general are associated with psychiatric co-morbidity. In myoclonus dystonia (M-D) psychiatric comorbidity has consistently been described.[10] However, as M-D has a subcortical anatomical origin rather than cortical, a direct comparison with CM cannot be made. All in all, the similar levels of depression and anxiety in FJ and CM underline current views that these symptoms are not diagnostically relevant for FJ. The findings do, however, emphasize the importance for treatment of looking for anxiety and depression in both patient groups.[5]

Health related quality of life was similarly impaired in FJ and CM patients, as was hypothesized based on the literature.[7,11] Pain was the only HRQoL subdomain significantly higher in the FJ group (median 49 (IQR 52) vs median 80 (IQR 33), $p< 0.05$). Pain has been reported to be high in other subtypes of

FMD, mainly functional (fixed) dystonia.[21] The relation between FJ and pain has not been studied before. Our finding implies that pain might be a promising diagnostic tool to discriminate FJ from other jerky movements, but this requires further studies in a larger prospective cohort.

Myoclonus severity was found to correlate with anxiety and depression scores in FJ but not CM. This might suggest that in the FJ group, there is a bidirectional relationship between anxiety/depression and myoclonus. Previous studies have shown that chronic pain negatively influences mood and quality of life.[22] However, in our cohort pain did not explain the relationship between anxiety/depression and myoclonus, as pain was not correlated to myoclonus severity. The lack of a relationship between anxiety/depression and myoclonus in CM suggest that these symptoms could be part of the CM phenotype or could be caused by other factors not taken into account in this study. To be able to determine whether the psychiatric symptoms have a primary or secondary cause, larger, preferably longitudinal, studies are required.

This study has limitations. As applies to all rare disorders, we had to study a small sample from a tertiary clinic, which improves diagnostic accuracy but might impair generalizability. Furthermore, using the BAI might have caused an overestimation of anxiety in both groups, as it largely measures the experience of physical complaints, which are partly influenced by having myoclonus. In order to minimize this overestimation, we have excluded questions directly related to jerky movements, while retaining the cut-off value.

In conclusion, this study showed high depression and anxiety scores and a comparable impairment of the quality of life in patients with FJ and CM, with significantly more pain in the FJ group. It is important for clinicians to be aware of the high appearance of depression and anxiety in myoclonic disorders as these symptoms often require treatment. Unfortunately, the presence of depression and anxiety cannot be used as a diagnostic tool for FJ, however, pain might be a significant marker of differentiation between organic myoclonus and functional jerks.

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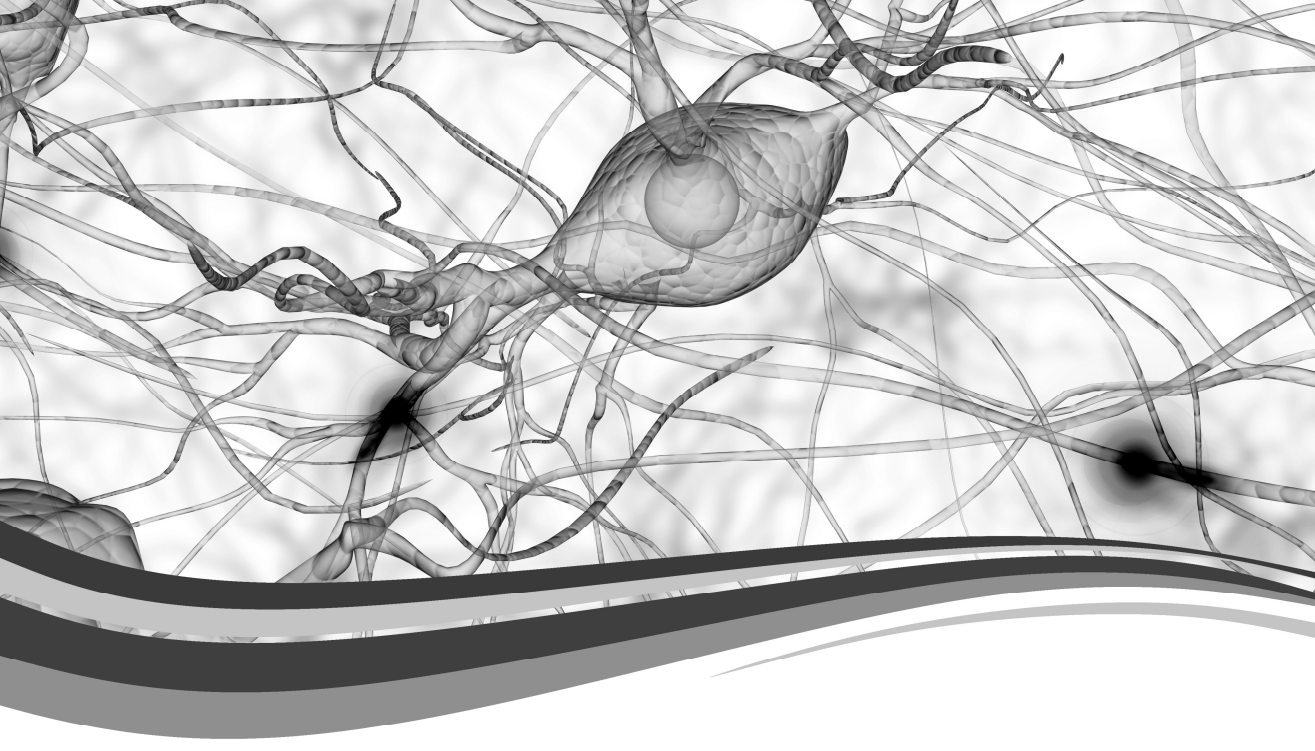

Chapter 5 Myoclonus subtypes in tertiary referral center Cortical myoclonus and functional jerks are common

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5.1 Abstract

Objective | To evaluate the accuracy of clinical phenotyping of myoclonus patients and to determine differentiating clinical characteristics between cortical (CM), subcortical (SCM), spinal (SM), peripheral (PM) myoclonus, and functional myoclonic jerks (FJ).

Methods | Clinical notes for all patients with myoclonus over an 8-year period (2006-2014) were reviewed retrospectively. We used the conclusion of electrophysiological testing as definite diagnosis of myoclonus or FJ.

Results | 85 patients were identified suffering from CM (34%), SCM (11%), SM (6%), PM (2%), and 47% FJ. The clinical diagnosis of myoclonus was confirmed by electrophysiological testing in 74% and its subtype in 78% of cases. CM was characterized by an early age of onset, facial myoclonus, and provocation by action. Differentiating features of FJ were an abrupt onset, preceding contributing events and provocation by a supine position.

Conclusion | The majority of clinical myoclonic jerk cases were functional in our heterogeneous tertiary clinic cohort. CM was the main anatomical myoclonic subtype. Clinical diagnosis was accurate in the majority of cases, although electrophysiological testing was important to verify the clinical classification.

Significance | In patients with jerky movements a functional diagnosis should be considered. Determination of the myoclonic subtypes is important to initiate tailored treatment.

5.2 Introduction

Myoclonus is a hyperkinetic movement disorder caused by an abrupt muscle contraction (positive myoclonus)[1] or interruption of muscle activity (negative myoclonus).[2]

Myoclonic jerks can be classified according to origin, i.e. generated in the cortex, subcortical areas (including basal ganglia and brainstem), spinal cord or peripheral nerves. In addition, myoclonus can also be the result of a functional movement disorder; i.e. FJ. CM is considered most frequent[3] but little is known about the epidemiology. Even less information is available on the sensitivity and specificity of clinical features in patients with myoclonus. Differentiating between subtypes of myoclonus is important, as each subtype can be linked to an etiological differential diagnosis and guides treatment selection.[4,5]

Accurate clinical diagnosis of myoclonus remains challenging[6] and electrophysiological tests are often required to distinguish myoclonus from other hyperkinetic movement disorders and subsequently, to define its anatomical subtype. Video-polymyography is the electrophysiological test in clinical practice to make the diagnosis of a jerky movement based on burst duration and muscle recruitment.[7] Additional, more sophisticated testing can be performed such as EEG-EMG back-averaging[7] or coherence analysis,[8,9] to detect a cortical origin in CM or a bereitschaftspotential in FJ.[10] Furthermore, somatosensory evoked potential (SSEP) can be useful to detect a giant potential pointing towards cortical hyperexcitability.[11]

The aim of this study is to evaluate the accuracy of clinical phenotyping in a heterogeneous cohort of myoclonus patients and to determine differentiating clinical characteristics.

5.3 Methods

A retrospective analysis was performed of patients who visited our tertiary referral centre between February 2006 and May 2014 and in whom video-polymyography was part of the diagnostic work-up. Patients were identified with the use of an electronic database from the department of Clinical Neurophysiology at the UMCG, the Netherlands. The database contains all electrophysiological test results since 2006. Registrations were analysed by two experienced clinical neurophysiologists (JWE and JvdH). The Ethical Board of the University Medical Center Groningen (UMCG) approved the study (Number M14.157933). We selected all cases with myoclonus as referring

clinical diagnosis for video-polymyography. The definite diagnosis used in our study was the diagnosis based on electrophysiological testing.

Electrophysiological tests included continuous recordings of surface EMG (maximum of nine channels) and video in all cases. In a subset of patients EMG-EEG back-averaging, coherence analysis and/or SSEP was applied.

EMG was recorded with Ag/AgCl pairs of surface electrodes placed at affected muscles. Myoclonus was measured during rest and action, action was defined by posture and specific tasks (finger to nose and knee to heel test).

The EEG was recorded with Ag/AgCl surface electrodes placed at the scalp according to the 10-20 International System and acquired by a computerized system (All data was recorded with BrainRT software (OSG BVBA, Rumst, Belgium) using a sample frequency of 1000Hz.

The electrophysiological characteristics of myoclonus and its subtypes were applied as described in literature and used in our laboratory to draw conclusions (Table 1).

Table 1 - Electrophysiological criteria of myoclonus and its subtypes used in this study

Myoclonus and its subtypes		Electrophysiological criteria based on polymyography	Impor-tance of criteria
Myoclo-nus		- Abrupt muscle contraction or interruption of tonic muscle activity - Synchronous contraction of agonists and antagonists muscles	required supportive
Cortical		- Burst duration of positive myoclonus <100ms - Multifocal/focal distribution - Presence of negative myoclonus	required supportive supportive
		- **Positive cortical spike back-averaging** (more reliable if >100 jerks, not performed if < 25 jerks) Presence of a “time-locked” biphasic potential >2SD above baseline on the contralateral motor cortex preceding the jerks seen on the EMG according to the conduction time of corticospinal pathways (15-25 ms for jerks in the arms and by +/- 40 ms for jerks in the legs)	diagnostic
		- **Positive cortico-muscular coherence** (frequencies > 10 Hz- 60 Hz) Occurrence of significant cortico-muscular coherence in the alpha and beta band with a phase difference	diagnostic

Myoclonus and its subtypes		Electrophysiological criteria based on polymyography	Impor-tance of criteria
		consistent with a cortical generator (i.e. cortex leads muscle) in coherence analysis.	
		- **Presence Giant SEP** The P27 and N35 peaks had large amplitudes above 5uV and had a suitable shape	diagnostic
Sub-cortical	**Brainstem**	- Burst duration >100ms - Simultaneous rostral and caudal muscle activation at brainstem level	supportive supportive
	Myoclonus-Dystonia	- Burst duration >100ms - Do not meet criteria other categories	supportive
Spinal	**Segmental**	- Burst duration >100ms - Distribution according to one or two contiguous spinal segments - Rhythmic (1-2/min to 240/min)	supportive required supportive
	Proprio-spinal	- Burst duration >100ms - Initiation in mid thoracic segments followed by rostral and caudal activation - Propagation with slow velocity (5-15 m/s) in cord	supportive required required
Peripheral		- Burst duration <50ms - Large MUAPs - Minipolymyoclonus or fasciculations/myokymia - Accompanied by weakness/atrophy	required required required supportive
Functional myoclonic jerks		- Variable muscle recruitment - Variable burst duration - Burst duration >100 ms - Distractibility and or/ entrainment (rhythmical myoclonus)	supportive supportive supportive supportive
		- **Presence Bereitschaftspotential** (performed if > 40 jerks, less than 1 every 5 s) Presence of a clear slow negative electrical shift over the central cortical areas that increased over time with amplitudes of at least 5uV 1-2 s before movement onset	diagnostic (ex.tics)

Besides the techniques of back-averaging and coherence analysis, all EEGs were analysed for epileptiform abnormalities.

If the EMG failed to detect mild myoclonus or pointed to another movement disorder, patients were excluded, as were patients with co-existence of multiple myoclonus subtypes (Figure I). For the included cases we systematically scored from their clinical records a number of clinical characteristics: gender, age at onset, age at examination, family history, rate of onset, preceding contributing event, distribution of myoclonus, provoking factors, stimulus sensitivity. We also systematically scored polymyography

features: burst duration, muscle recruitment, presence of negative myoclonus. If available we added results of back-averaging/coherence analysis/SSEP.

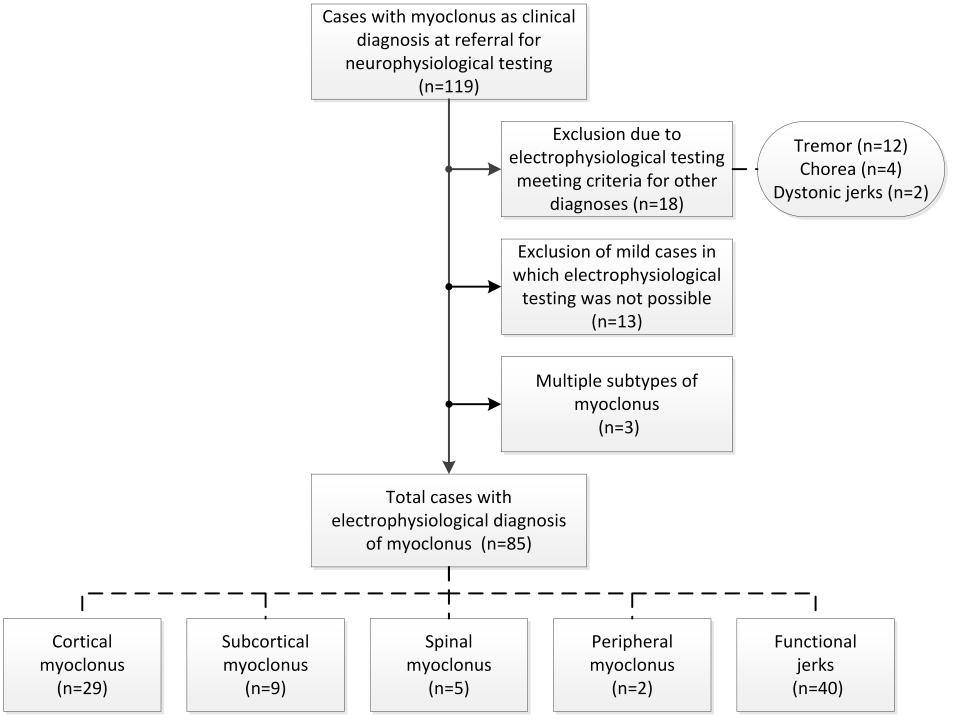

Figure 1 - Diagrammatic representation of patient inclusion

A complete overview of the inclusion and exclusion of myoclonus cases. A total of 85 myoclonus cases were included for retrospective analysis.

5.3.1 Statistical analysis

The clinical characteristics were analysed using Chi-square and Fisher's Exact tests for categorical variables and Kruskal-Wallis tests for continuous, not-normally distributed data in SPSS 20. In case of significant differences ($P<0.05$) between myoclonus subgroups, post-hoc testing was performed using Fisher's Exact and Mann-Whitney tests. To counteract the problem of multiple comparisons, in post-hoc testing $p<0.005$ were considered significant. For the agreement between clinicians and clinical neurophysiologists Cohen kappa was used. Kappa results were classified as; $k<0$ 'poor', 0-0.2 'slight', 0.21-0.4 'fair', 0.41-0.6 'moderate', 0.61-0.8 'substantial', >0.81 'almost perfect'.[12]

5.4 Results

5.4.1 Inclusion of patients

One hundred and nineteen patients were referred for video-polymyography with myoclonus as initial clinical diagnosis. Eighteen patients were excluded as the video-polymyography testing concluded other movement disorders: in 12 cases tremor, four chorea, and two dystonic jerks. The clinicians agreed with these definite electrophysiological diagnoses. Thirteen patients were excluded as myoclonus was too mild for adequate electrophysiological testing.

Three patients (3%) were considered to have multiple myoclonus subtypes and excluded for further analysis: i.e. organic (two SM/one SCM) together with FJ: in one the diagnosis of FJ was confirmed by the presence of a bereitschaftspotential and in the two based upon variable burst duration and muscle recruitment.

In total 85 video-polymyography diagnosed myoclonus patients (50 males: 35 females, with a median age of 31 year (0-80)) were studied. This group included 29 cases (34%) with electrophysiological diagnosed cortical, nine (11%) with subcortical, five (6%) with spinal, two (2%) with peripheral and 40 (47%) with FJ (Figure 1).

5.4.2 Correlation between Clinical and Electrophysiological diagnoses

The reason for referral for electrophysiological testing in our cohort was to confirm the clinical diagnosis of myoclonus together with determination of its subtype in 23, only determination of myoclonus subtype in 34, and confirmation of FJ diagnosis in 28 cases.

The clinical diagnosis of myoclonus was confirmed by video-polymyography in 88/119 (74%) patients, 13 cases had an inconclusive result due to mild myoclonus. Clinical judgement of the subtype of myoclonus or FJ was performed in 63 of the 85 cases, and in 48 (78 %) the anatomical subtype was confirmed by electrophysiological testing (17 CM, 5 SCM, 3 SM, 0 PM, 23 FJ).

The largest shift in diagnosis was made in the clinically defined SM subgroup; 6/9 cases were concluded to have FJ after electrophysiological testing. The additional 2 SM cases were not clinically recognized, but based on electrophysiological testing. Overall, Cohen kappa analysis showed a moderate

agreement (kappa=0.43) between clinicians and clinical neurophysiologists in diagnosing myoclonus subtypes.

5.4.3 Electrophysiological characteristics according to the anatomical subtypes

Table 2 gives an overview of the electrophysiological characteristics of the myoclonus subtypes.

Table 2 - Electrophysiological characteristics

Electrophysiological characteristics		CM	SCM	SM	PM	FJ	Total
Number		29	9	5	2	40	85
Burst duration (ms)	30 - 50	6	0	0	2	0	8
	50 - 100	19	1	0	0	0	20
	100 - 300	0	5	3	0	14	22
	> 300	0	0	1	0	15	16
	Variable	4	3	1	0	11	19
	NA	0	0	0	0	0	0
Distribution	Focal	1	0	0	0	1	2
	Multi focal	26	4	0	2	4	36
	Segmental	2	0	0	0	1	3
	Generalized	0	3	0	0	0	3
	Cranial to caudal	0	2	1	0	2	5
	Initially thoracic to cranial or caudal	0	0	4	0	0	4
	Variable	0	0	0	0	32	32
Negative myoclonus	Yes	15	1	0	0	0	16
	No	14	8	5	2	40	69
Bereitschaft potential	BP present	NA	NA	0	NA	8	8
	BP absent	NA	NA	2	NA	5	7
	BP not performed	NA	NA	1	NA	13	14
	BP unable to interpret	NA	NA	2	NA	14	16
Cortical spike preceding myoclonus	Present	5	0	NA	0	NA	5
	Absent	8	2	NA	1	NA	11
	Not performed	10	4	NA	0	NA	14
	Unable to interpret	6	3	NA	1	NA	10
Positive coherence	Present	4	0	0	0	0	4
	Absent	4	1	0	1	1	7
	Not performed	21	8	5	1	39	74
Giant SEP	Present	3	0	0	0	0	3
	Absent	8	3	0	0	2	13
	Not performed	16	6	5	2	38	67
	Unable to interpret	2	0	0	0	0	2

CM: Cortical myoclonus, SCM: Subcortical myoclonus, SM: Spinal myoclonus, PN: peripheral myoclonus, FJ: Functional jerks, NA: Not applicable

Cortical myoclonus

Twenty nine patients were diagnosed with CM. Twenty four patients had a classical presentation at electrophysiology with a burst duration of <100ms combined with a focal or multifocal distribution of myoclonus. One patient had a burst duration <100ms and segmental distribution, with myoclonus spreading from the trapezius muscle towards the limbs. The additional four patients had a burst duration <100ms combined with negative myoclonus with longer burst duration (up to 200ms). One of these four patients had a segmental distribution in his left leg, the others had a multifocal distribution.

Back-averaging was performed in 19/29 (66%) CM cases. In five cases a cortical spike preceding myoclonus was present, in eight cases the cortical spike was absent, and in six cases interpretation was not possible, due to infrequent myoclonus or major EEG artefacts. Coherence analysis was performed in 8/29 (28%) cases with high frequency myoclonus (including four cases in which back-averaging was uninterpretable), detecting a positive coherence in four cases. EEG showed generalized epileptic features (spikes, spike wave complexes, and/or sharp waves) in nine CM cases; generalized features in nine and focal or multifocal epileptic features in five. SSEP analysis was performed in 13/29 (33%) patients; a giant SSEP was present in three patients, in two cases analysis was limited by polyneuropathy.

Subcortical myoclonus

Nine patients were diagnosed with SCM, including five cases of brainstem myoclonus (BM) and four with a clinical Myoclonus-Dystonia syndrome. Three cases with BM had a burst duration of 100-300ms, one with <100ms and one had a variable burst duration. Three BM cases had a generalized distribution and the other two had craniocaudally spreading. Two Myoclonus-Dystonia cases had a burst duration of 100-300ms and the others had a variable burst duration. All had a multifocal distribution. Back-averaging was performed in 5/9 (3/9 uninterpretable), coherence analysis in 1/9, and SSEP in 3/9 cases, all with negative test results. EEGs showed no features of epilepsy.

Spinal myoclonus

Five patients were concluded to have SM, including four with propriospinal myoclonus (PSM) and one unclassified SM case. Between the PSM cases burst duration varied from 100ms up to >300ms. In all cases a fixed distribution was observed starting in thoracic muscles with a cranially and caudally

propagation. In the last patient myoclonus migrated unilateral from the upper to the lower limb with a burst duration of 100-300ms. Combined EEG-EMG recording was performed in 4/5 cases; a bereitschaftspotential was absent in two cases and analysis was uninterpretable in the other two cases. EEGs showed no features of epilepsy.

Peripheral myoclonus

Two patients were diagnosed with PM. Both patients had a burst duration from 30-50ms and a multifocal distribution. Damage of the peripheral motor nerve system was objectified with EMG in both cases. Back-averaging was performed in both cases and coherence analysis in 1/2. The test results were negative and back-averaging analysis was uninterpretable in one case because of EEG artefacts.

Functional myoclonic jerks

Forty patients were diagnosed with FJ. Thirty-six patients had a classical presentation with a variable burst duration and/or variable muscle recruitment. Four other patients were diagnosed with FJ because of complete disappearance of myoclonus during distraction.

Back-averaging was performed in 27/40 (68%) patients. A bereitschaftspotential was detected in eight patients and in 14/27 (52%) cases the result of back-averaging were uninterpretable because of infrequent myoclonus or major EEG artefacts. EEGs showed no features of epilepsy.

5.4.4 Differences in clinical characteristics between anatomical subtypes of myoclonus

A full summary of clinical characteristics of this cohort can be found in Table 3 and an overview of etiological diagnoses in Table S1.

Table 3 - Clinical characteristics of myoclonus

Clinical characteristics		CM (n=29)	SCM (n=9)	SM (n=5)	PM (n=2)	FJ (n=40)	Post-hoc analysis P<0.005
Gender	Male/Female	16/13	5/4	4/1	2/0	23/17	
Age at onset of myoclonus		**12 (2 - 80)**	**4 (0 - 55)**	35 (9 - 74)	13 (11 - 15)	**45 (12 - 77)**	CM < FJ SCM < FJ
Age at examination		21 (5 - 88)	15 (0 - 68)	38 (9 - 75)	16 (14 - 17)	50 (12 - 78)	
Positive Family history	Yes	8	5	0	1	2	
	No	13	3	4	1	25	
	Missing	8	1	1	0	13	
Rate of onset	acute/subacute	**5**	2	**3**	0	**22**	CM < FJ
	gradually	15	4	0	2	4	
	missing	9	3	2	0	14	
Preceding contributary event	Yes	**2**	**0**	4	0	**21**	CM < FJ SCM < FJ
	No	19	7	0	2	8	
	Missing	8	2	1	0	11	
Distribution	Face	13	3	0	0	3	
	Axial	10	4	4	0	21	
	Limbs	29	6	3	2	34	
Provoking factors	Action	**12**	1	1	1	**1**	FJ < CM CM < FJ
	Supine position	**1**	0	2	0	**13**	
	None	1	0	0	0	4	
	Missing	15	8	2	1	22	
Stimulus sensitive	Yes	10	1	1	0	5	
	No	4	4	0	1	1	
	Missing	15	4	4	1	34	

CM: Cortical myoclonus, FJ: Functional jerks, PM: peripheral myoclonus, SCM: Subcortical myoclonus, SM: Spinal myoclonus.

Table S1 - Etiological diagnoses according to the anatomical subtypes

Suptype of myoclonus	Etiological diagnosis or syndrome	n=
Cortical myoclonus (n=29)	Dravet syndrome *(SCN1A* mutation)	2
	Niemann pick type C (*NPC1* mutation)	1
	Progressive myoclonus epilepsy (unknown genotype)	3
	Ataxia telangiectasia	1
	Mutation *GOSR* gene	4
	Mutation mitochondrial DNA	2
	Postinfectious	1
	Medication-induced	2
	Strucural cerebral lesion	1
	Unknown	12
Subcortical myoclonus (n=9)	Hyperekplexia	2
	Structural lesion brainstem	2
	Mycolonus dystonia (*SGCE* mutation)	1
	Mycolonus dystonia (partial deletion chromosome 7Q)	1
	Mycolonus dystonia (unknown genotype)	2
	Myoclonus epilepsy (unknown genotype)	1
	Unknown	0
Spinal myoclonus (n=5)	Cervical spinal cord injury	1
	CHARGE syndrome with unknown cause	0
	Postinfectious	1
	Unknown	3
Peripheral myoclonus (n=2)	Neurofibromatosis type II	0
	Spinal muscle atrophy type III	1
	Motor neuron disease	1
	Unknown	0

The subgroup with CM (n=29) had a median age of onset of 12 years (2-80). Eight patients had a positive family history. Fifteen patients had a gradually rate of onset, while in five patients the onset was acute or sub-acute. Most patients suffered from myoclonus in the limbs (UL 27/LL 19), 13 in the face, 10 in the neck, and six had truncal myoclonus. Action was the major provoking factor (n=12). In 17/29 (59%) CM patients an etiological diagnosis was made. In four patients an acquired cause was identified, and 13 cases were thought to have a genetic origin of which a causative gene mutation was found in 9 cases. Nine patients had SCM with a median age of onset of four years (0-55), five had a positive family history. The rate of onset was acute in two patients and gradually in four. In one patient action was described as provoking factor. Of the patients with BM two suffered from hyperekplexia and two had a structural brain lesion (one tumour and one dolichobasilaris).[13] Four patients had the clinical Myoclonus-Dystonia syndrome confirmed by a causative gene

mutation in two. One patient suffered from myoclonus epilepsy without a known genetic origin.

The subgroup with SM (n=5) had a median age of onset of 35 (9-74), one patient had a positive family history. The rate of onset was acute in three patients and unknown in the others. In four cases a preceding contributory event was recorded (operation, pain, medication, and school problems). Supine position and action were provoking factors. A causative factor was found in two of the patients with SM, including cervical spinal cord injury and post infectious SM.

Two patients had PM with a median age of onset of 13 years (11-15), one had a positive family history. Myoclonus was located in the limbs and was provoked by action in one patient. One patient was diagnosed with spinal muscle atrophy type III, and the other patient the EMG pattern fitted the pattern of a chronic form of motor neuron disease.

In 40/85 patients (47%) the diagnose was FJ. The median age of onset was 45 years (12-77). Two patients had a positive family history. The rate of onset was acute/sub-acute in 22 patients and gradually in four. A preceding contributory event was present in 21 patients (10 pain, 6 trauma, 3 operation, 1 infection, 1 intensive gymnastics). Supine position was the major provoking factor, present in 13 patients.

5.4.5 Comparison of clinical characteristics between anatomical subgroups

Patients with CM and SCM had a significantly earlier onset than those with FJ ($p<0.001$). There was no difference in gender distribution between the subgroups. Chi-square analysis showed significant differences between subgroups with the presence of positive family history, rate of onset, preceding contributory event, distribution in the face or axial muscles, and provoking factors. Post-hoc analysis showed significant differences in rate of onset; the onset was more frequently abrupt in patients with FJ compared to CM ($P<0.005$). Furthermore, FJ was preceded more frequently by a preceding contributory event compared to CM and SCM ($P<0.005$). There were no differences in distribution of myoclonus between subgroups, although facial myoclonus appeared more often in CM compared to FJ ($P=0.005$). CM was usually provoked by action ($P<0.001$) compared to FJ, while FJ was often induced by a supine position ($P<0.001$) (Table 2).

5.5 Discussion

This retrospective study examined a large unbiased myoclonus population in a tertiary referral movement disorder center. We evaluated the accuracy of the clinical classification of myoclonus including FJ based on electrophysiological diagnosis. Subsequently we evaluated the discriminative clinical features between myoclonus subtypes.

The clinical diagnosis of myoclonus was confirmed by electrophysiological testing in 88/119 (74%) cases. It is difficult to draw conclusions about the percentage of missed clinical myoclonus diagnosis as not all patients were referred for video-polymyography. In 63 myoclonus cases the anatomical subtype was defined by the clinician and this was supported by electrophysiological testing in 49 cases (78 %). The accuracy of clinical classification of myoclonus subtype is lower compared to that of tremor (87%).[14] This might be explained by a much higher prevalence of tremor,[15,16] and subsequently a higher familiarity with diagnosing the movement disorder. The moderate correlation (kappa 0.43) between clinical and electrophysiological testing illustrates that electrophysiological testing in addition to clinical judgement is valuable. It is important to determine the anatomical origin of the myoclonus as it guides treatment options.[4]

The main electrophysiological classified myoclonus subtypes were FJ (47%) and CM (34%), followed by SCM (11%) and SM (6%), while PM was rare (2%). It is of interest that almost half of the myoclonus patients were diagnosed with FJ. This is more frequent than the numbers described in the literature. Overall in the movement disorder clinics the frequency of functional disorders varies between 3 to 20% depending on the base population of the study.[17] The number of FJ in our cohort might even be higher because not all FJ patients were referred for video-polymyography. Part of the FJ patients might have had the referring diagnosis of epilepsy and these patients were seen at the epilepsy clinic and diagnosed with psychogenic nonepileptic seizures. The diagnoses FJ and psychogenic nonepileptic seizures have an profound overlap.[18] Therefore, it is recommended to check for epileptic abnormalities with the performance of an EEG in all patients with jerks. The unfamiliarity with rare myoclonus disorders makes it difficult in the general neurology practice to diagnoseFJ based on positive signs in history and physical examination and to decide that the myoclonus is incongruent.[19,20] This, combined with the special interest of

our tertiary referral center in jerky movements with many nationwide referrals, could account for the relatively higher number of FJ in our cohort.

Discrimination between PSM and FJ was the most difficult; of nine cases clinically diagnosed as SM, the conclusion was FJ in six. The additional two SM cases were not clinically recognized, but based on electrophysiological testing. This finding is in line with previous studies, describing the difficulties in clinically discriminating PSM and FJ.[21-23] Recently, insights have changed regarding the diagnosis of PSM. Many patients previous diagnosed with idiopathic PSM appeared to have FJ.[24,25] It is possible that PSM cases in our cohort might have been misclassified and actually be FJ, as a fixed invariable pattern has also been described in FJ.[22]

Differentiating clinical features of FJ were an abrupt onset, a preceding contributing event, and provocation with a supine position. On the other hand, CM was clinically characterized by an early age of onset, facial myoclonus, and provocation by action. Most of the clinical characteristics of subtypes found in our cohort are in concordance with those reported in the literature[5]. In contrast with other studies[26,27] our FJ patients had a significantly later age of onset compared to CM, and there was no predominance of the female gender. Van der Salm et al[24,25] also reported an equal distribution of FJ between men and women.

Back-averaging, coherence analysis, and SSEP were applied only in a subset of patients. For this reason, no firm conclusions can be drawn about the additional value of these electrophysiological tests. However, the applicability in our heterogeneous myoclonus subgroup and the additive diagnostic value was limited. Back-averaging analysis was possible in 13/19 (68%) CM cases (5/13 (38%) cortical correlate). Coherence analysis and SSEP were performed in a small number of CM patients with a positive result in 4/8 (50%) and 3/11 (23%) cases respectively. The analysis of back-averaging was interpretable in 13/27 (48%) FJ patients (8/13 (62%) bereitschaftspotential). The main reasons for the limited applicability of back-averaging and coherence analysis were infrequent occurrence of myoclonus, major EEG artefacts due to myoclonus, and/or non-stationarity and non-rhythmicity of myoclonic jerks (coherence analysis). A systematic application of these tests in a prospective cohort is required to determine the additional value in clinical practice. Furthermore, A recent paper showed that event-related EEG desynchronization might be more sensitive than back-averaging in predicting functional jerks. This is a promising

new technique, but before this is applicable in daily clinical practice confirmation in a larger cohort is required.[28]

A limitation of our study is the absence of an indisputable etiological diagnosis in a proportion of the patients with organic myoclonus. For this reason, the best option was to use the electrophysiological diagnosis as definite diagnosis to distinguish myoclonus and its anatomical subtypes. Misclassification is possible, but clinical and electrophysiological features in our patients are in concordance with literature. Another limitation, due to the retrospective nature of our study is that we only selected patients with a video-polymyography and this might have given a selection bias.

In conclusion, FJ counted for 47 % in our heterogeneous tertiary clinic myoclonus cohort. CM was the main anatomical myoclonus subtype. Clinical characteristics are helpful to discriminate between myoclonus subtypes and FJ. However, clinical diagnosis of myoclonus and its subtype remains challenging, and electrophysiological testing is important to verify the clinical classification. Optimal classification of myoclonus enables more tailored diagnostic strategies and treatment options for patients.

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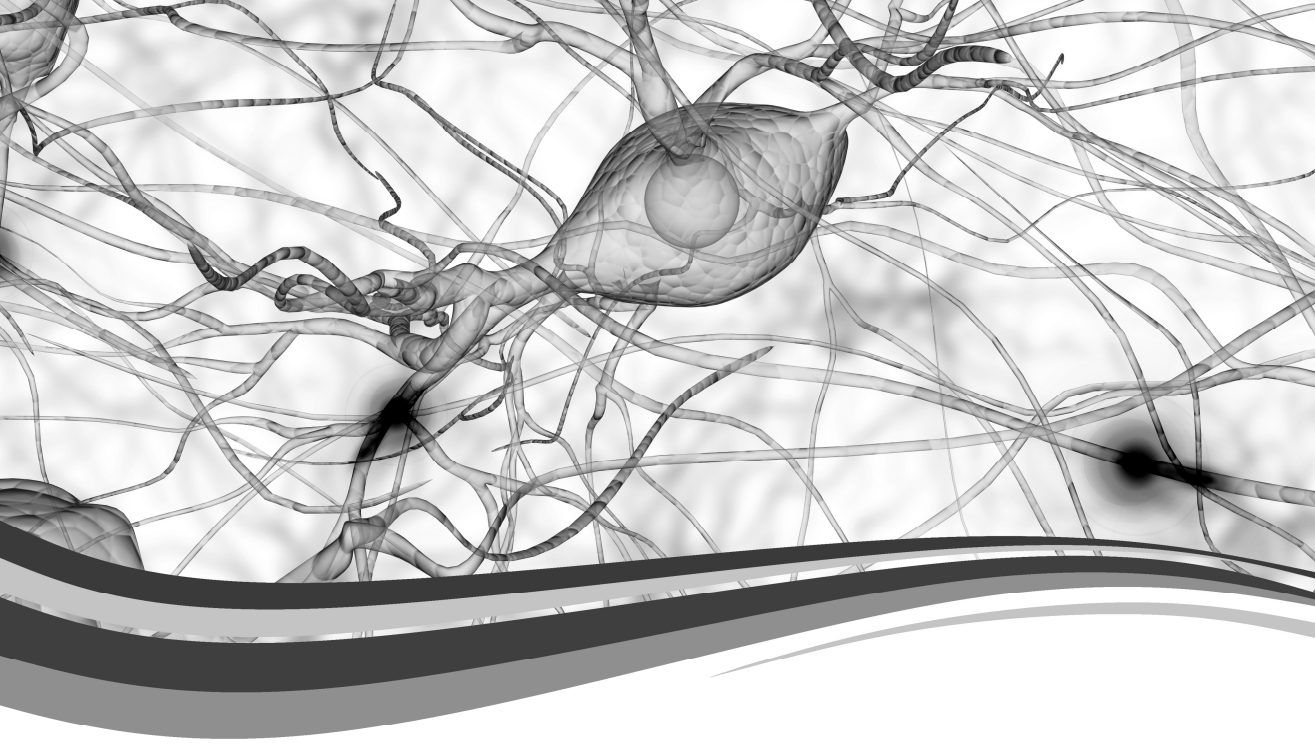

Chapter 6 Electrophysiological testing aids diagnosis and subtyping of myoclonus

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6.1 Abstract

Objective | To determine the contribution of electrophysiological testing in the diagnosis and anatomical classification of myoclonus.

Methods | Participants with a clinical diagnosis of myoclonus were prospectively recruited, each undergoing a videotaped clinical examination and battery of electrophysiological tests. The diagnosis of myoclonus and its subtype was reviewed after six months in the context of the electrophysiological findings and specialist review of the videotaped clinical examination.

Results | Seventy-two patients with myoclonus were recruited. Initial clinical anatomical classification included 25 cases with cortical myoclonus, 7 subcortical myoclonus, 2 spinal myoclonus, and 15 with functional myoclonic jerks. In 23 cases, clinical anatomical classification was not possible due to the complexity of the movement disorder. Electrophysiological testing was completed in 66, with agreement of myoclonus in 60 (91%) and its subtype in 28 (47%) cases. Subsequent clinical review by a movement disorder specialist agreed with the electrophysiological findings in 52/60, in the remaining eight electrophysiological testing was inconclusive.

Conclusions | Electrophysiological testing is an important additional tool in the diagnosis and anatomical classification of myoclonus, also aiding in the decision-making regarding therapeutic management. Further development of testing criteria is necessary to optimize its use in clinical practice.

6.2 Introduction

Myoclonus is a frequently observed hyperkinetic movement disorder, which is often classified according to its anatomical origin: cortical (CM), subcortical (SCM), spinal (SM), peripheral (PM) or functional myoclonic jerks (FJ) in case of a functional movement disorder.

Electrophysiological testing is frequently useful in distinguishing myoclonus from other hyperkinetic movement disorders, and in identifying its anatomical origin.[5-7] The tests used in the assessment of myoclonus include polymyography, EEG-EMG back-averaging, coherence analysis and somatosensory evoked potential (SSEP).[8-12] Table 1 summarises the electrophysiological criteria used in the diagnosis of myoclonus and its subtypes.

The sensitivity and specificity of electrophysiological testing in patients with myoclonus is largely unknown, with the majority of work to date being limited by small cohorts, highly selected patient populations, or reliant on expert opinion to determine the diagnosis.[13-15]

Our recent retrospective analysis of 85 patients with myoclonus demonstrated the key clinical and electrophysiological features in distinguishing myoclonus subtypes.[4] In 74% of cases the clinical diagnosis of myoclonus was confirmed with electrophysiological testing, and electrophysiological assessment of the myoclonus subtype aided diagnosis in 73% of cases. This study seeks to apply these principles to a prospectively recruited cohort of patients, evaluating the contribution of electrophysiological testing in the diagnosis and management of myoclonus.

Table 1 - Electrophysiological criteria of myoclonus and to aid diagnosis by anatomical subtype

Anatomical subtype	Video-polymyography	Back-averaging / Coherence analysis / SSEP	Importance of criterium
Myoclonus	Abrupt muscle contraction or interruption of muscle activity Synchronous contraction of agonists and antagonists muscles		Required Supportive
Cortical myoclonus	Burst duration positive myoclonus <100ms Multifocal/focal distribution		Required Supportive

Anatomical subtype	Video-polymyography	Back-averaging / Coherence analysis / SSEP	Importance of criterium
	Presence of negative myoclonus		Supportive
		Positive cortical spike Back-averaging *Presence of a "time locked" biphasic potential >2SD above baseline on the contralateral motor cortex preceding the jerks seen on the EMG according to the conduction time of corticospinal pathways (arms 15-25ms / legs +/- 40ms)*	**Diagnostic**
		Positive cortico-muscular coherence *Occurrence of significant cortico-muscular coherence in the alpha and beta band with a phase difference consistent with a cortical generator*	**Diagnostic**
		Presence of a Giant SSEP *The P27 and N35 peaks had large amplitudes above 5uV and had a suitable shape*	**Diagnostic**
Subcortical myoclonus			
Brainstem	Burst duration >100ms		Supportive
	Simultaneous rostral and caudal muscle activation at brainstem level		Required
M-D/other	Burst duration >100ms		Supportive
	Presence of negative myoclonus		Supportive
	Do not meet criteria other categories		Required
Spinal myoclonus			
Segmental	Burst duration >100ms		Supportive
	Distribution according to one or two contiguous spinal segments		Required
	Rhytmic (1-2/min-240/min)		Supportive
Propriospinal	Burst duration >100ms		
	Initiation in mid thoracic segments followed by rostral and caudal activation		Required
	Propagation with slow velocity (5-15 m/s) in cord		Required
Peripheral myoclonus	Burst duration <50ms		Required
	Large MUAP's		Supportive
	Minipolymyoclonus or fasciculations/myokymia		Supportive

Anatomical subtype	Video-polymyography	Back-averaging / Coherence analysis / SSEP	Importance of criterium
	Accompanied by weakness/atrophy		Supportive
Functional myoclonic jerks	Variable muscle recruitment		Supportive
	Variable burst duration (>100ms)		Supportive
	Distractibility and/or entrainment		Supportive
		Presence of a Bereitschaftspotential *Presence of a clear slow negative electrical shift (>5 uV)over the central cortical areas that increased over time 1-2 s before movement onset*	**Diagnostic**

6.3 Methods

6.3.1 Participants

Participants with a clinical diagnosis of myoclonus were identified prospectively from inpatient and outpatient settings (July 2014 - June 2016). Exclusion criteria included; on going inpatient care on the Intensive Care Unit (ICU), language and/or literacy barriers, and ≤6 years of age. All participants were followed-up for a minimum of six months, after which a final diagnosis was made.

6.3.2 Initial clinical classification

The initial clinical diagnosis of myoclonus and its anatomical subtype was provided by the participants' primary caring neurologist (adult or paediatric), with all participants undergoing a standardised and systematic assessment, including videotaped clinical examination.

6.3.3 Electrophysiological Testing

The standardised electrophysiological protocol included an initial polymyography, with participants excluded at this stage if the myoclonus was too subtle to adequately perform the assessment. For those meeting electrophysiological criteria for myoclonus, further investigations included EEG-EMG back-averaging (if > 25 jerks) or coherence analysis (if jerk frequency >3 Hz). Where possible those with CM and SCM underwent testing for SSEPs (Figure e-1).

Blinded to the original clinical diagnosis, an experienced neurophysiologist (JWE and JvdH) determined if the findings were consistent with myoclonus, and the likely myoclonus subtype. Table 1 summarises the electrophysiological criteria used in determining diagnosis.[4]

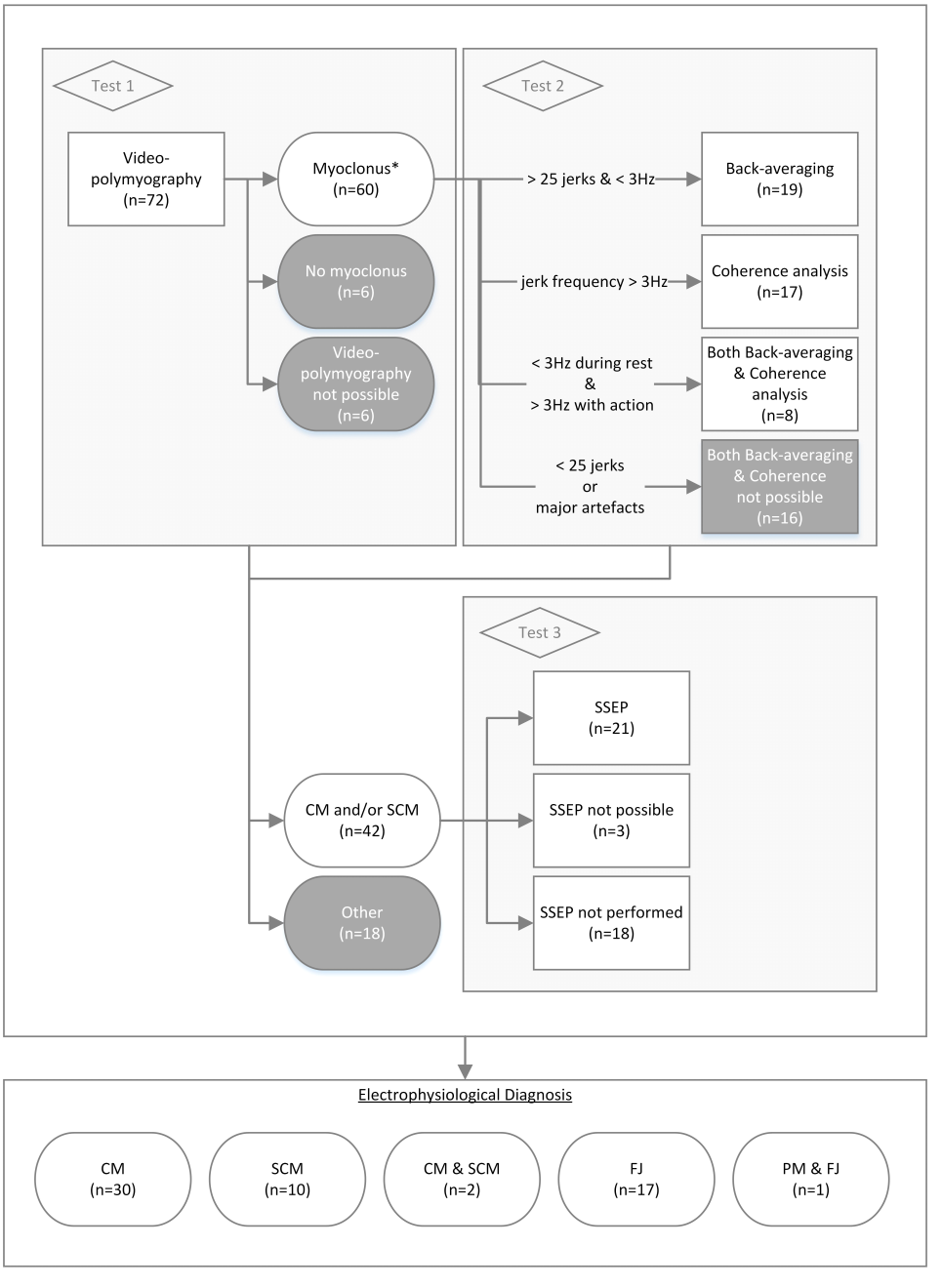


Figure e-1 - Diagnostic protocol of the electrophysiological tests to diagnose myoclonus and classify its anatomical subtype

All participants underwent a video-polymyography (test 1). If the diagnosis was myoclonus, Back-averaging or Coherence analysis was performed depending on the frequency of the myoclonus (test 2). Where possible those with CM and SCM underwent testing for SSEP's (test 3). CM: Cortical myoclonus, FJ: Functional jerks, PM: peripheral myoclonus, SCM: Subcortical myoclonus.

6.3.4 Diagnostic review and six-month follow-up

A neurologist with expertise in movement disorders (MT), blinded to the initial diagnoses reviewed the clinical details, videotaped clinical examination and results of the electrophysiological testing. Each patient was reviewed again six-months after their initial assessment to determine any changes to the clinical findings, with the final diagnosis being confirmed by the specialist (Figure 1).

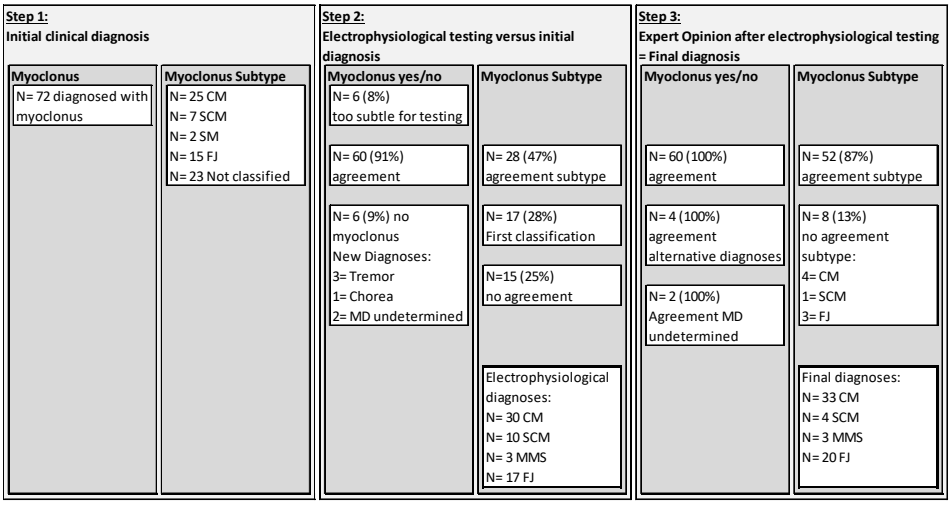


Figure 1 - Overview of the stages of clinical assessment and diagnosis undertaken in this study

CM: Cortical myoclonus, FJ: Functional jerks, MD: Movement disorder, MMS: Multiple myoclonus subtypes, SCM: Subcortical myoclonus, SM: Spinal myoclonus.

6.3.5 Severity of the myoclonus

The severity of the myoclonus was determined by two independent clinicians (RZ and JCvZ or JMG) following review of the videotaped clinical examinations, scoring sections 2 and 4 of the Unified Myoclonus Rating Scale (UMRS) and the 7-point Global Clinical Impression of Severity (GCI-S) scale.

6.3.6 Power Analysis

A power calculation was performed based on our previously reported retrospective analysis.[4] It was estimated that electrophysiological testing would support the clinical diagnosis of the myoclonus anatomical subtype in approximately 70%. A change in clinical classification of >20%, due to electrophysiological testing, was considered clinically relevant. Using the One Proportion Confidence Interval Formula: Exact (Clopper-Pearson), a 95% confidence level, 0.7 (proportion), 0.8 (upper limit), we estimated that a minimum of 56 participants would need to be recruited.

6.3.7 Statistical analysis

The clinical characteristics were analysed using Kruskal-Wallis tests for continuous, non-normally distributed data. Inter-rater reliability was assessed using the intra-class correlation coefficient (ICC) (Two way mixed, consistency, average measures)[16], or Cohen's kappa[17] where appropriate. A Chi-squared Automatic Interaction Detection (CHAID) (SPSS, parent nodes n<3, child nodes n>1) analysis was undertaken to generate a decision tree in order to quantify the importance of the clinical and electrophysiological criteria in the diagnosis of the myoclonic subtypes

6.3.8 Standard protocol approvals, registrations, and patient consents

Full written informed consent was obtained from all participants according to the Declaration of Helsinki. The study protocol was approved by the University Medical Centre Groningen ethics committee (Number M14.157933, approved July 2, 2014).

6.4 Results

6.4.1 Overall cohort

A total of 72 patients (32M; 40F) were recruited, with a median age of 29 years (range: 7-83 years), 59 from the outpatient setting and 13 from inpatient care.

The demographic details and clinical characteristics of this cohort are summarised in Table 2 and Table e-1 respectively.

Table 2 - Demographic features of the myoclonus cohort

Demographic features		CM (n= 33)	SCM (n= 4)	FJ (n= 20)	MMS (n= 3)	Total (n= 60)
Sex	Male/Female	15 / 18	2 / 2	7 / 13	1 / 2	25 / 35
Age at examination*		21(7-83)	19(15-48)	32(16-73)	63(18-73)	22(7-83)
Age at onset of myoclonus*		14(0-83)	11(10-14)	25(12-66)	60(4-73)	18(0-83)
Follow-up interval (months)**		21	22	22	15	20
UMRS*	rest	9(0-38)	14(9-23)	17(2-30)	9(6-18)	11(0-38)
	action	19(6-57)	15(7-23)	8(0-33)	16(0-31)	15(0-57)
	total	31(7-85)	31(19-42)	23(5-62)	28(6-49)	27(5-85)
GCI-S*		3(2-7)	4(3-5)	4(2-6)	4(3-5)	4(2-7)
Family history of a related disorder		7	3	2	1	13
Other neurological symptoms	eye movement disorder	8	0	0	0	8
	dystonia	9	4	0	1	14
	chorea	3	0	0	0	3
	ataxia	4	0	0	0	4
Comorbidity	psychiatric	5	0	4	0	9
	epilepsy	9	0	0	0	9
	cognitive problems	7	2	0	0	9
	liver or kidney disease	5	0	2	0	7
	structural damage brain	3	0	1	0	4
Treatment	No treatment	14	3	5	1	23
	clonazepam	9 (4)	0	0	2 (2)	11 (6)
	levetiracetam	9 (6)	0	0	0	9 (6)
	valproic acid	3 (1)	1 (0)	0	1 (0)	5 (1)
	multiple drug therapy	5 (4)	0	0	0	5 (4)
	physiotherapy	0	0	10 (5)	1 (1)	11 (6)
	explanation diagnosis	0 (0)	0 (0)	5 (5)	0 (0)	5 (5)
Side effects yes/no	clonazepam	5 / 4	0 / 0	0 / 0	0 / 2	5 / 6
	levetiracetam	7 / 2	0 / 0	0 / 0	0 / 0	7 / 2
	valproic acid	3 / 0	0 / 1	0 / 0	0 / 1	3 / 2
	multiple drug therapy	3 / 2	0 / 0	0 / 0	0 / 0	3 / 2

Classification of myoclonus is given as the final diagnosis following review at six months post-diagnosis.
Treatment: the number in brackets is the number of patients in whom the myoclonus improved with treatment.
*values are displayed as median (range). **value is displayed as mean.
CM: Cortical myoclonus, GCI-S: Global Clinical Impression MMS: Multiple myoclonus subtypes,
SCM: Subcortical myoclonus, FJ: Functional jerks, UMRS: Unified Myoclonus Rating Scale.

Table e-1 - Clinical characteristics of each subtype based on final diagnoses

Clinical characteristics		CM (n=33)	SCM (n=4)	FJ (n=20)	MMS (n=3)	Total (n=60)
Rate of onset	acute	6	0	8	2	16
	subacute	2	0	9	0	11
	gradually	25	4	3	1	33
Preceding contributary event	Yes	7	0	12	0	19
	No	26	4	8	3	41
Course	improved	0	0	2	0	2
	stable	13	1	4	1	19
	waxing and waning	5	0	2	0	7
	slowly progressive	14	3	5	1	23
	rapidly progressive	1	0	7	1	9
Distribution	face	19	3	1	0	23
	proximal	1	0	15	1	17
	distal	23	1	5	0	29
	both	9	3	0	2	14
Provoking factors	rest	4	0	10	1	15
	action	23	4	3	2	32
	supine position	0	0	3	1	4
	fatigue	14	2	5	1	22
	stress	15	1	6	0	22
Supressing factors	posture	5	0	2	1	8
	alcohol	3	1	0	1	5
	suppressible	0	0	5	0	5
	distraction	1	0	3	0	4
	none	24	3	8	1	36
Stimulus sensitive	Yes	19	0	9	2	30
	No	14	4	11	1	30
Change of jerks with Distraction	Yes	1	0	16	1	18
	No	32	4	4	2	42

Classification of myoclonus is given as the final diagnosis following review at six months post-diagnosis.
CM: Cortical myoclonus, FJ: Functional jerks, MMS: Multiple myoclonus subtypes,
SCM: Subcortical myoclonus.

6.4.2 Clinical diagnosis of myoclonus pre-electrophysiological testing

Of the 72 individuals with myoclonus, these were subdivided into CM (n=25), SCM (n=7), SM (n=2), and FJ (n=15), with subtype diagnoses not possible in 23 patients (32%) owing to the complexity of the movement disorder.

6.4.3 Electrophysiological diagnoses

In six cases (8%), clinically diagnosed with distal multifocal CM, the myoclonic jerks were of such small amplitude that the polymyographic recordings were indeterminate and unable to be interpreted. Of the remaining 66 patients,

electrophysiological testing supported a diagnosis of myoclonus in 60 (91%), with these subdivided into CM (n=30), SCM (n=10), multiple myoclonus subtypes (MMS) (n=3), and FJ (n=17). A cortical origin was detected in 5/9 (60%) of the CM cases using back-averaging, and 16/20 (80%) using coherence analysis. SSEP analysis demonstrated giant potentials in 3/14 (21%) of CM cases, and a Bereitschaftspotential was identified in 5/12 (42%) of FJ cases.

A full summary of the electrophysiological characteristics of this cohort can be seen in Table 3.

Table 3 - Electrophysiological characteristics of each subtype based on the electrophysiological findings

Electrophysiological characteristics		CM	SCM	FJ	MMS	Total
Number		30	10	17	3	60
Type	positive	15	8	17	2	42
	negative	0	1	0	0	1
	both	15	1	0	1	17
Burst duration (ms)	30-50	2	0	0	1	3
	50-100	27	2	0	1	30
	50-200	0	5	1	1	7
	100-300	0	1	3	0	4
	> 300	0	0	2	0	2
	Variable	1	2	11	0	14
Distribution	focal	1	1	0	1	3
	multi focal	29	9	7	1	46
	segmental	0	0	0	1	1
	generalized	0	0	0	0	0
	Variable	0	0	10	0	10
Backaveraging	CS present	5	0	0	2	7
	BP present	0	0	5	0	5
	CS absent	4	3	0	0	7
	BP absent	0	1	7	0	8
	not performed	15	1	0	1	17
	not possible	6	5	5	0	16
Positive coherence	Present	16	0	0	0	16
	Absent	4	4	0	1	9
	Not performed	10	6	17	2	35
Giant SSEP	Present	3	0	0	0	3
	Absent	11	5	1	2	19
	Not performed	13	5	15	1	34
	Unable to interpret	3	0	1	0	4

BP: Bereitschaftspotential, CM: Cortical myoclonus, CS: Cortical Spike, FJ: Functional jerks,
MMS: Multiple myoclonus subtypes, SCM: Subcortical myoclonus, SSEP: Somatosensory Evoked Potential

6.4.4 Comparison of clinical and electrophysiological diagnoses

There was agreement between the clinical diagnosis and electrophysiological testing in a diagnosis of myoclonus for 91% (60/66) of the study cohort. Of these 60 cases there was agreement of its subtype in 28 (47%) cases (14 CM, 2 SCM, and 12 FJ), and disagreement in 15 cases (25%). Of the remaining 17 cases (28%) without a clinical sub-classification, electrophysiological testing proved helpful, subdividing these into 12 CM, 2 SCM, and 3 FJ (Table e-2).

Table e-2 - Initial clinical diagnosis versus electrophysiological diagnosis

Initial clinical diagnosis		Electrophysiological diagnosis					
		CM	SCM	SM	PM	FJ	MMS
CM	19	14	4	0	0	0	1
SCM	7	4	2	0	0	0	1
SM	2	0	0	0	0	2	0
PM	0	0	0	0	0	0	0
FJ	15	0	2	0	0	12	1
MwS	17	12	2	0	0	3	0
Total	60	30	10	0	0	17	3

CM: Cortical myoclonus, SCM: Subcortical myoclonus, SM: Spinal myoclonus, PM: peripheral myoclonus, FJ: Functional jerks, MMS: multiple myoclonus subtypes, MwS: Myoclonus without subtype

6.4.5 Clinical opinion of the movement disorder specialist

There was agreement between the electrophysiological testing and specialist movement disorder opinion in 66 cases, and agreement on its subtype in 52/60 (87%) cases, considered a 'substantial' agreement (κ=0.78). A summary of the eight cases where there was disagreement between expert clinical diagnosis and electrophysiological testing are summarised in Table 4, in each there was a lack of conclusive electrophysiological findings to facilitate a diagnosis of myoclonus subtype.

Table 4 - Details of cases in which the clinical diagnosis changed after evaluation by the MDS

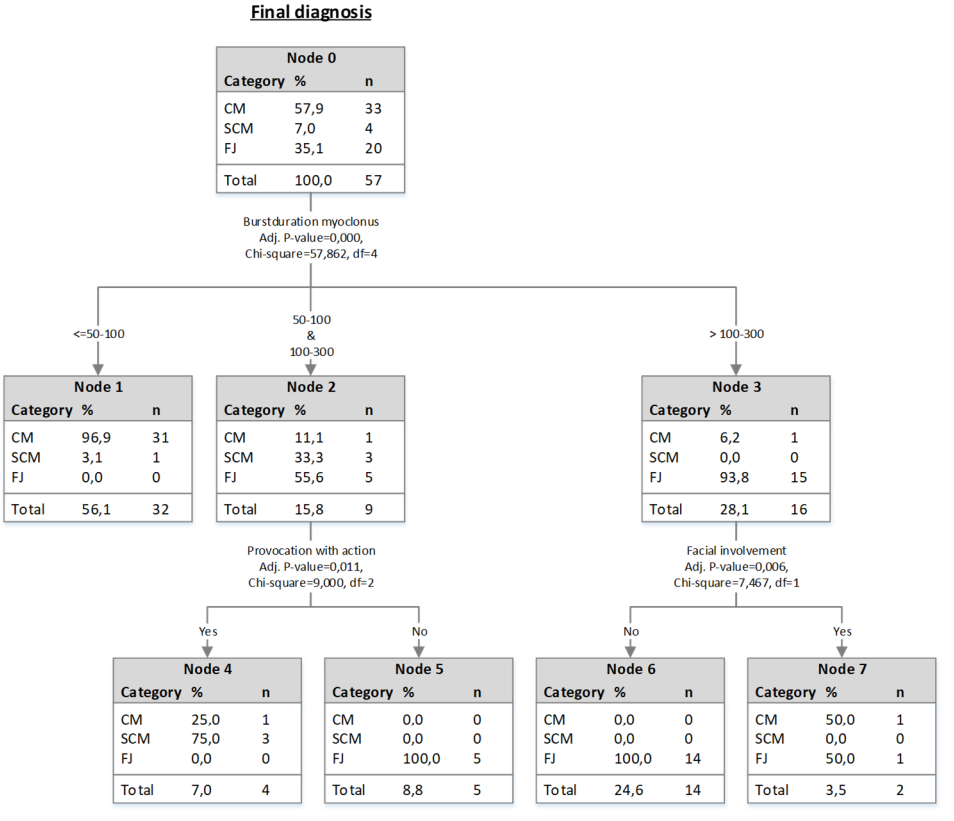
N	Age at onset (years)*	Age at examination (years)*	Clinical features	Electrophysiological findings	Electrophysiological diagnosis	Expert clinical diagnosis	Final clinical diagnosis	Reasons for revising the electrophysiological diagnosis
1	10	20	Distal limbs and face Provocation by action Stimulus sensitive	50-200 ms Back-averaging NP	SCM	CM	CM	Distal distribution Facial involvement Stimulus sensitivity No firm electrophysiological results

N	Age at onset (years)*	Age at examination (years)*	Clinical features	Electrophysiological findings	Electrophysiological diagnosis	Expert clinical diagnosis	Final clinical diagnosis	Reasons for revising the electrophysiological diagnosis
2	0	10	Distal > proximal limbs Face Provocation by action Stimulus sensitive	Positive and negative 50-100 ms Back-averaging NP	SCM	CM	CM	Distal distribution Facial involvement Stimulus sensitivity No firm electrophysiological results
3	69	69	Negative myoclonus Distal limbs Provocation by action Metabolic derangements	Negative 50-100 ms Back-averaging NP	SCM	CM	CM	Negative myoclonus Metabolic derangements No firm electrophysiological results
4	6	7	Distal limbs Provocation by action Stimulus sensitive Epilepsy	50-200 ms Negative back-averaging	SCM	CM	CM	Distal distribution Stimulus sensitivity Co-occurrence of epilepsy No firm electrophysiological results
5	16	17	Acute onset Distal upper limbs Entrainment Atypical sensory problems	50-200 ms Negative back-averaging	SCM	FJ	FJ	Acute onset Atypical sensory problems Entrainment No firm electrophysiological results
6	18	18	Acute onset Distal limbs Stimulus sensitive Change with distraction	Variable duration Multi focal Back-averaging NP	SCM	FJ	FJ	Acute onset Stimulus sensitive Change with distraction No firm electrophysiological results
7	20	20	Subacute onset Proximal and distal Provocation by rest Stimulus sensitive Change with distraction	50-200 ms Negative back-averaging	SCM	FJ	FJ	Provocation by rest Stimulus sensitive Change with distraction No firm electrophysiological results
8	14	20	Myoclonus, dystonia, tremor Cognitive difficulties Proximal and distal	Positive and negative 50-100 ms Back-averaging NP	CM	SCM	SCM	Combined myoclonus and dystonia No firm electrophysiological results

*Values are displayed as median.
CM: Cortical myoclonus, FJ: Functional jerks, SCM: Subcortical myoclonus

6.4.6 Final clinical diagnoses

Follow-up review after six months resulted in no changes to clinical diagnosis in all 60 cases, with the final sub-classification including 33 CM (55%), 4 SCM (7%), 3 MMS (5%), and 20 FJ (33%). The CHAID analysis demonstrated i) polymyographic measurement of the myoclonic burst duration, ii) exacerbation of the myoclonus with action, iii) facial involvement to be the most important criteria in determining myoclonic subtype (Figure e-2).



Observed	Classification Predicted CM	SCM	FJ	Percent Correct
CM	32	1	0	97,0
SCM	1	3	0	75,0
FJ	1	0	19	95,0
Overall	59,6%	7,0%	33,3%	94,7%

Growing Method: CHAID
Dependent Variable: Final Diagnosis

Figure e-2 - Decision tree of clinical and electrophysiological criteria in the diagnosis of the myoclonic subtypes

Decision tree based on a Chi-squared Automatic Interaction Detection (CHAID) (SPSS, parent nodes n<3, child nodes n>1). CM: Cortical myoclonus, FJ: Functional jerks, SCM: Subcortical myoclonus.

6.4.7 Severity of myoclonus

The median UMRS severity score was 27 (Rest 11/128 / Action 15/144) and GCI-S score 4/7. No significant statistical difference was observed between the subtypes of myoclonus (p=0.2). The inter-rater concordance was 'excellent' (ICC= 0.94 (95% CI: 0.9- 0.96) and 'good' (ICC= 0.72 (95% CI: 0.58- 0.82) for the UMRS and GCI-S respectively.

6.4.8 Underlying aetiology of the myoclonus

Of the 40 cases diagnosed with an organic movement disorder, an underlying aetiology was identified in 21 cases (53%). In 12 patients a causative genetic mutation was identified, and nine were found to have an acquired cause including metabolic disturbances (n=3), drug-induced myoclonus (n=1) and structural brain lesions (n=2). Of those with an underlying genetic etiology, the highest rate was amongst those with CM (n=10), with mutations in the *NKX2.1* (n=2) and *NPC1* (n=2) genes being most common. A single case with a contiguous gene deletion (578kb, 16p11.2) involving the *PRRT2* gene was identified with an extended phenotype including psychomotor retardation, hemiplegic migraine, epilepsy, myoclonus and dystonia. All patients with a myoclonic epilepsy syndrome had evidence of epileptiform discharges on EEG, with the CM in those with Juvenile Myoclonus Epilepsy and Lafora Disease demonstrating an epileptic origin. All four SCM had a clinical diagnosis of Myoclonus Dystonia, with a *RELN* variant identified in one case. Table 5 summarizes the etiological diagnoses and additional clinical characteristics.

Table 5: Underlying etiological diagnoses and additional clinical characteristics

Myoclonus Subtype	Etiological diagnosis or syndrome	Additional Clinical Characteristics	n=
CM (n= 33)	Juvenile huntington (CAG repeat in *HTT* gene)	Cognitive impairment, severe epilepsy, spasticity	1
	Wilson disease (mutation *ATP7B* gene)	Parkinsonism, dystonia, ataxia, cognitive impairment	1
	Niemann pick type C (*NPC1* mutation)	Eye movement disorder, ataxie, dystonia (n=1)	2
	Lafora disease (mutation *NHLRC1* gene)	Severe epilepsy, mild cognitive impairment	1
	Juvenile myoclonus epilepsy (no genetic mutation identified)	Epilepsy	1
	Myoclonus epilepsy (no genetic mutation identified)	Epilepsy, mild cognitive impairment	1
	Ramsay Hunt syndrome (*GOSR* mutation)	Ataxia, areflexia, eye movement disorder	1
	Ramsay Hunt syndrome (no genetic mutation identified)	Ataxia, areflexia, eye movement disorder	1
	Benign hereditary chorea (mutation *NKX2.1* gene)	Chorea, dystonia, areflexia	2
	Paroxysmal Kinesigenic Dyskinesia (16p11.2 deletion (578 Kb), including the *PRRT2* gene)	Severe cognitive impairment, hemiplegic migraine, epilepsy, dystonia	1
	Myoclonus Dystonia (18p11.21 deletion (14.9 Mb))	Dystonia	1
	Mycolonus dystonia (no genetic mutation identified)	Dystonia, bradykinesia (n=1), eye movement disorder (n=1)	2
	Medication-induced	Cognitive impairment (n=1)	2
	Metabolic derangements due to liver or kidney disease	Cognitive impairment (n=2), polyneuropathy (n=1)	3
	Structural cerebral lesion	Mild cognitive impairment (n=1), vascular parkinsonism (n=1)	2
	Unknown		11
SCM (n= 4)	Myoclonus dystonia (*RELN* variant)	Dystonia	1
	Mycolonus dystonia (no genetic mutation identified)	Dystonia	3
	Unknown		0
MMS (n= 3)	Myoclonus dystonia (*RELN* variant)	Dystonia	1
	Creutzfeldt Jacob disease	Cognitive impairment, stiffness	1
	Lumbar radiculopathy and FJ	Functional gait problem	1
	Unknown		0

CM: Cortical myoclonus, MMS: Multiple myoclonus subtypes, SCM: Subcortical myoclonus

6.5 Discussion

This prospective study has sought to demonstrate the benefit of electrophysiological testing alongside clinical examination, in determining the diagnosis of myoclonus and its subtype in an unselected cohort. We have shown that this combined approach leads to changes in the initial diagnosis of myoclonus and its subtype in 53% of cases.

Overall, agreement of a diagnosis of myoclonus between the examining clinicians and the electrophysiological findings was 91% (n=60), decreasing to 47% (n=28) with anatomical subtype. These findings contrast with results from similar studies in tremor cohorts (n=210) where agreement between the two assessment forms was 87%, potentially reflecting greater clinical familiarity and larger patient cohorts.[18-20] We identified several clinical groups where there was some consistency in the change in diagnosis following electrophysiological testing. These included: those with multifocal myoclonus (principally distinguishing between CM and SCM), combined movement disorders (e.g. myoclonus in the presence of dystonia), and functional jerks. The findings from this study also reflect the difficulty in determining a conclusive clinical diagnosis with myoclonus, and lend weight to the importance of electrophysiological testing, particularly in non-specialist centres.

Higher-level electrophysiological techniques were used to determine whether the myoclonus was of cortical origin or a FJ. The yield of back-averaging and coherence analysis to confirm a cortical origin was 60% and 80% respectively. The additive value of these techniques was lower than the 100% seen in previous studies, potentially due to the heterogeneity of our cohort in contrast to smaller more selected study groups (n=20 / n=3).[13,24] A CHAID analysis demonstrated that a combination of polymyography (burst duration) and clinical phenomenology provided the greatest accuracy (95%) in determining myoclonus subtype.

This study is limited by the lack of a definitive diagnostic test or marker. We have sought to reduce this by ensuring a minimum six-month follow-up period to allow for any changes in clinical symptomatology. However, this lack of objective testing also serves to reinforce the potential gain of routine electrophysiological testing to both aid, and provide additional evidence of the diagnosis of myoclonus and its subtype. Our cohort also likely reflects a more

complex group of patients than might be expected in routine clinical practice, owing to the recruitment from a single specialist movement disorder center. We also acknowledge that while the electrophysiological tests discussed are readily available within our center, such access varies considerably between centers and internationally.

Electrophysiological testing is an important contributing diagnostic tool for the classification of myoclonus and its subtypes. While this clearly constitutes an important element of clinical work for neurologists with an interest in movement disorders, this algorithm of testing is also likely to be of use for those working in the fields of metabolic disorders, paediatrics and epilepsy. Further development of the electrophysiological criteria for myoclonus subtypes, and application of this work to larger, unselected patient cohorts is essential to improve its objectivity and diagnostic value.

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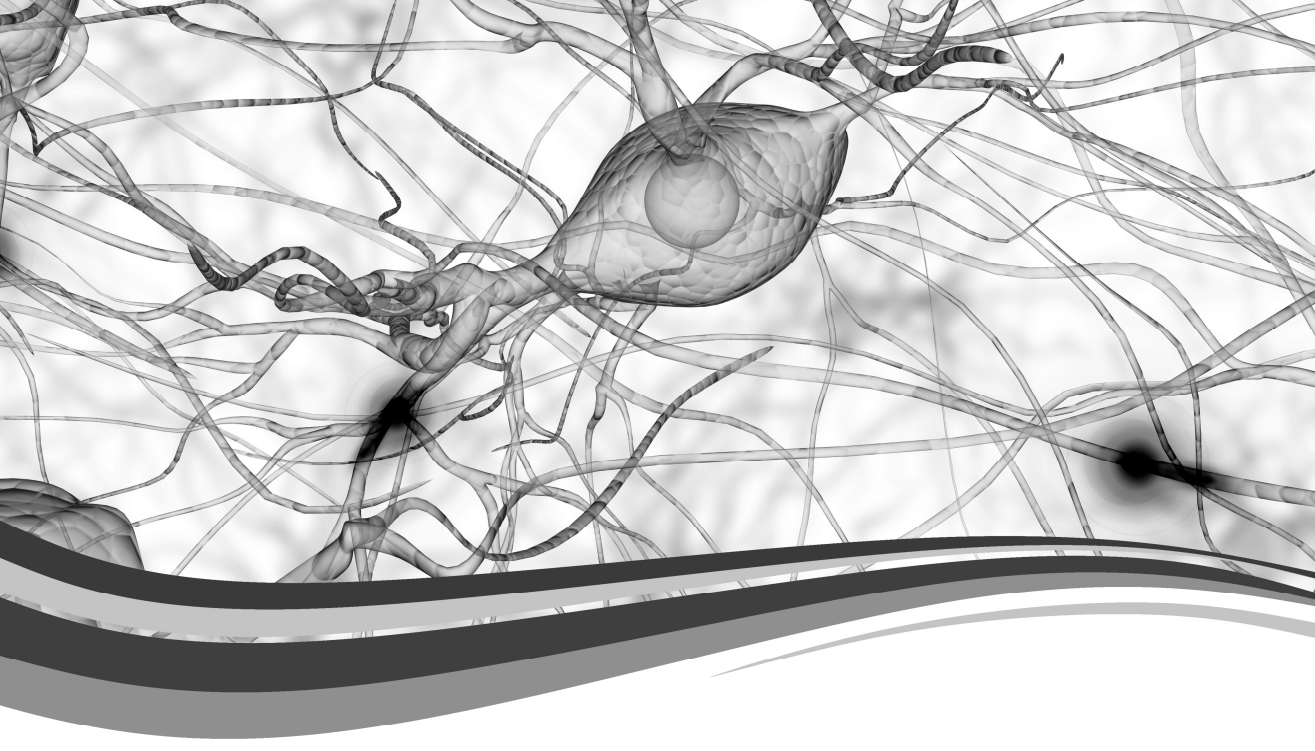

Chapter 7 Improving Neurophysiological Biomarkers for Functional Myoclonic Movements

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Submitted

7.1 Abstract

Background |Differentiating between functional jerks (FJ) and organic myoclonus can be challenging. At present, the only accepted diagnostic biomarker to support FJ is the Bereitschaftspotential (BP). However, its sensitivity is limited and its evaluation subjective. Recently, event related desynchronisation in the broad beta range (13-45 Hz) prior to functional generalised axial (propriospinal) myoclonus was reported as a possible complementary diagnostic marker for FJ.

Objective | To study the value of ERD together with a quantified BP in clinical practice.

Methods | Twenty-nine patients with FJ and 16 patients with cortical myoclonus (CM) were included. Jerk-locked back-averaging for determination of the 'classical' and quantified BP, and time-frequency decomposition for the event related desynchronisation (ERD) were performed. Diagnostic gain, sensitivity and specificity were obtained for individual and combined techniques.

Results | We detected a classical BP in 14/29, a quantitative BP in 15/29 and an ERD in 18/29 patients. At group level we demonstrate that ERD in the broad beta band preceding a jerk has significantly higher amplitude in FJ compared to CM (respectively -0.14 ± 0.13 and + 0.04 ± 0.09 ($p < 0.001$)). Adding ERD to the classical BP achieved an additional diagnostic gain of 53%. Furthermore, when combining ERD with quantified and classical BP, an additional diagnostic gain of 71% was achieved without loss of specificity.

Conclusion | Based on the current findings we propose to the use of combined beta ERD assessment and quantitative BP analyses in patients with a clinical suspicion for all types of FJ with a negative classical BP.

7.2 Introduction

Functional myoclonic jerks (FJ) can be difficult to distinguish from organic myoclonus in clinical practice.[1] This is of crucial importance given different aetiologies, treatment and prognosis.[2] Ideally, the diagnosis of FJ would be supported by sensitive and specific diagnostic tests, enabling a "laboratory supported" level of diagnostic certainty.[3] At present, the only routinely used test to support the diagnosis of FJ is the presence of a Bereitschaftspotential (BP) in the EEG prior to a jerky movement. However, the reported sensitivity of a positive BP in FJ is heterogeneous ranging from 25%[4] to more than 80% in selected cohorts.[5,6]

In clinical practice there are no standardised criteria that define the presence of a BP, although some have been proposed in the research setting.[6] Currently, the definition of a BP is "clear and slow negative electrical shift" over the central cortical areas, that increases over time 1-2 s before movement onset.[7] However, a quantitative method would seem to be highly desirable to standardize laboratory supported diagnosis of FJ.

Recently, a new EEG marker of functional axial jerks has been proposed: event related desynchronisation (ERD) in the broad beta band.[4] Reductions of beta and low gamma oscillations occur prior to cued and self-paced movement[8] and may reflect changes in self-directed attention, as recently highlighted in a new explanatory model for functional neurological symptoms.[9] A recent study also showed ERD in the beta range prior to (psychogenic) non-epileptic seizures, suggesting applicability to functional neurological symptoms more widely and supporting a unifying pathophysiological model.[10]

In the present study we aimed to (1) replicate the findings of the first study on ERD in FJ in a cohort with different FJ phenotypes beyond generalised axial (propriospinal) myoclonus, (2) determine the diagnostic gain, specificity and sensitivity of ERD with both classical (subjective) and objective evaluation of the BP (3) develop a new diagnostic approach by combining the results of ERD and BP.

7.3 Methods

7.3.1 Patients

Participants with a diagnosis of FJ who underwent a combined video-polymyography and EMG-EEG back-averaging as part of their diagnostic work-up between 2006 and 2016, were identified from the database of the neurology department of the University Medical Center in Groningen. Electrophysiological testing included a minimum recording time length of 30 minutes with the aim to register at least 40 myoclonic jerks. Patients with both a clinical *and* an electrophysiological diagnosis of FJ and CM were included in the study. All clinical diagnoses were made by a movement disorder specialist (MT). The local ethical committee of the University Medical Center in Groningen confirmed that the study could proceed without formal consent in light of the retrospective and anonymised nature of the data (M14.157933).

The clinical diagnosis of FJ was based on positive criteria including an acute onset, inconsistent distribution, and reduction with distraction.[11] Electrophysiological criteria for FJ included a long and / or variable burst duration, variable muscle recruitment, distractibility, and the presence of a BP on back-averaging.[7,12] In this cohort, the classical BP was only present in 14/29 (47%) of the FJ cases.

Sixteen patients with the clinical and electrophysiological diagnosis of CM were included as a control group. The diagnosis of CM was based on clinical and electrophysiological features. Clinically, patients suffered from myoclonus with a facial and distal (multi-) focal distribution.[11] Electrophysiological criteria for CM included burst duration of less than 100 ms, presence of negative myoclonus, and a positive pre-myoclonic cortical spike on back-averaging.[7]

7.3.2 BP analysis

In order to compare different methods for estimating BP, the BP was determined using two different approaches. For both approaches the onsets of jerks were obtained using an automated ‘level trigger’ and visually inspected for artefacts plus subsequent rejection if necessary. The first approach was the classical visual inspection approach (‘classical’ BP) and was performed using EEG jerk-locked back-averages that were calculated across events (Brain Vision Analyzer 2.1, Brain Products GmbH, München, Germany). This approach was performed prior to the present study as ‘care as usual’ by treating physicians.

7.3.3 Objective BP analysis

Beyond 'care as usual', an objective approach (objective BP), obtaining the amplitude of the deflection prior to the myoclonic jerk, was performed. In line with the literature on the time-course of the BP EEG data was epoched from -1500ms relative to movement onset.[13] All quantitative and statistical analyses were performed with custom written scripts using Matlab R2015a (The Mathworks, Natick, MA, USA). With a view to clinical applicability, the approach was kept as simple as possible and overlapping epochs (i.e. jerks with less than 1500ms duration in between jerks) were not rejected. However, to minimise this effect, the amplitude of the BP was obtained from the last, and steepest, phase of the BP, called the negativity slope which ranges from -500ms to movement on-set.[14] So by not including the slowly rising negativity between -1500ms and -500ms before FJ, the risk of overlapping intervals was reduced. Given the heterogeneous localization of the myoclonic jerks (unilateral, axial, and/or bilateral) within and between patients with FJ, the central (Cz) electrode with T5 and T6 as reference were used for obtaining the objective BP. In healthy volunteers, the amplitude of the BP is largest at this electrode, which roughly detects neural activity from the supplementary motor area.[15]

7.3.4 ERD Analysis

For the analyses of the ERD, the same time-courses as for the objective BP were used. Power spectral density (PSD) was obtained using a fast Fourier transform using a 200 ms spectrogram with a 100ms sliding window. For the ERD analyses the interval -1500ms prior to jerk onset was used which covers the timing of the main deflection in the previous report on ERD.[4]

Since this ERD occurs earlier than the negativity slope in the BP (-500ms), the whole interval of -1500ms to jerk onset was used for further analyses. For the quantification in the 'broad beta band' a range from 13-45 Hz consisting of the beta band (13-30 Hz) and the low gamma (30-45 Hz) was used in line with the literature on ERD in the beta range prior to voluntary movements and the findings of the previous report on ERD.[4] Baseline normalisation was performed to the value of the 200ms window -1500ms prior to jerk onset. ERD was expressed as a fraction of the 200ms window around - 1500ms and therefore the ERD represents the power in the window of analysis divided by the baseline power.

7.3.5 Statistical analyses

Descriptive statistics of the patient characteristics are reported using medians and (interquartile) ranges. For the neurophysiological data, data were checked for normality using Koglomorov-Smirnov tests and expressed in means and standard deviations. For the comparison of the objective BP and ERD between patients with CM and FJ with or with without a subjectively defined BP, two-sample t-tests were used. Multiple comparisons were corrected by applying the false discovery rate.[16] The correlation between the objective BP and ERD was performed using Pearson's correlation coefficient. Receiver operating characteristics (ROC) were expressed as area under the curve and mutually compared.[17] To combine the objective BP and ERD in the ROC, a rank between 1 and 45 was assigned to every patient for both the objective BP and the ERD. For each subject, the two ranks were added and divided by two. This resulted in an average rank on the combined diagnostic tests.

Finally, the three different approaches, classical (subjective) and quantitative (objective) BP and ERD, plus their combination were compared. This was done by statistically comparing the sensitivities of the different approaches and their combinations at a specificity level of 100%. When one method was superior to another the difference in sensitivity was expressed in a percentage and named 'diagnostic gain'. Cutoff values for BP and ERD were obtained from the maximum values seen in the CM group. Different approaches, or their combinations were mutually compared using the Wilcoxon ranksum test.

7.4 Results

7.4.1 Patients

Forty-seven patients with either FJ or CM were identified, of which two were excluded due to the coexistence of both cortical and subcortical myoclonus subtypes. Forty-five patients were included in the study; 29 patients with FJ (48% female, median age at examination 51 years) and 16 with CM (56% female, median age at examination 28 years). The median number of jerks available for back-averaging was 47 (IQR; 36) in the FJ group and 106 (IQR; 323) in the CM group. The clinical and electrophysiological features of both groups are shown in Table 1.

Table 1 - Clinical and electrophysiological characteristics

Clinical characteristics		CM (n=16)	FJ (n=29)
Gender	male/female	7 / 9	15 / 14
Age at examination		27,5 (6-73)	51 (15-77)
Age at onset of myoclonus		22 (4-73)	43 (13-75)
Rate of onset	acute/subacute	5/0	8/11
	gradually	11	5
	missing	0	5
Preceding	yes	2	14
contributary	no	14	9
event	missing	0	6
Provoking factors	rest	3	13
	action	4	1
	supine position	0	10
Distribution	face	6	2
	proximal	3	28
	distal	11	1
	both	2	0
Change of jerks	yes	1	21
with Distraction	no	15	8
Electrophysiological characteristics			
Type of jerks	positive	12	29
	negative	0	0
	both	4	0
Burst duration	30-50	1	0
(ms)	50-100	14	0
	100-300	0	9
	> 300	0	6
	variable	1	14
Distribution	focal	3	0
	multi focal	12	8
	segmental	1	1
	generalized	0	0
	variable	0	20
Backaveraging	number of jerks	106 (34-1769)	47 (15-120)
	CS present	7	0
	CS absent	9	0
	BP present	0	14
	BP absent	0	15

7.4.2 Bereitschaftspotential

Using the subjective approach, a BP was present in 14/29 of the FJ patients and in none of the CM patients (sensitivity 47%; specificity 100%, Fig. 1). 15/29 had an objective BP that was lower than the lowest value of the CM group (i.e. -2.18 V). This objective approach ('BP obj') had a sensitivity of 51% with a specificity of 100%. When comparing the average BP deflection of the subjective BP negative (n=15, -1.91 ± 2.05 uV) and BP positive (n=14, mean -4.75 ± 2.59 uV) FJ group with the CM group, differences in amplitude were statistically different (Average BP deflection (uV) respectively 6.2 ($p<-0.001$) and average BP deflection (uV) =2.6 ($p=0.003$), Fig 2B.). Finally, when comparing the subjective BP negative with the BP positive group a significant difference was present within the FJ group as well ($T=5.1$, $p<0.001$).

7.4.3 Event Related Desynchronisation

FJ patients with or without a subjective BP both showed significantly more ERD in the broad beta band relative to CM (Fig 2B, p=respectively <0.001 and 0.001) and did not significantly differ from each other ($p=0.06$). 18/29 FJ patients had an ERD that was lower than the lowest value of the CM group cut-off (i.e. 10% decrease in broad beta power). When using this 10% decrease as a differentiating criterion, a sensitivity of 62% was achieved with 100% specificity (Fig 1). This did not significantly differ from using the objective BP approach ($p=0.62$). No significant correlation was present between the amount of jerks and ERD amplitude in either the CM or FJ group.

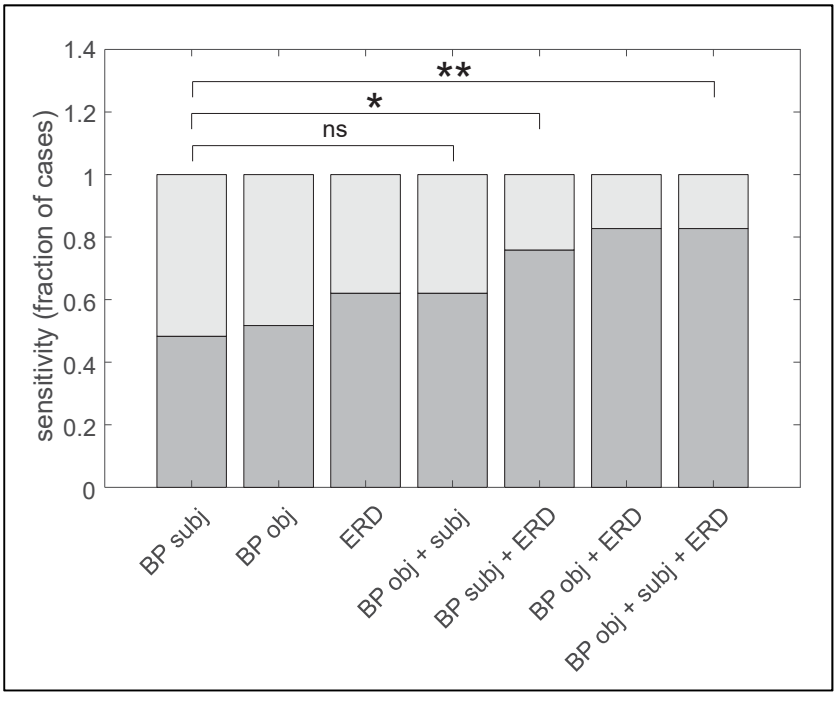
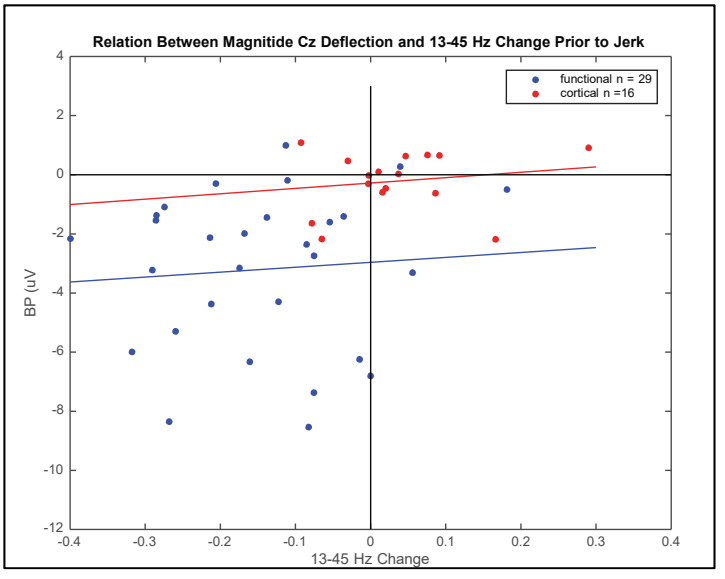


Figure 1 - Comparison between the senisitivity of the visually determined Bereitschaftspotential (BP), quantitatively determined BP, event-related desynchronisation (ERD), and their combinations

Comparison between the sensitivity of the visually determined BP (BP subj; subjective), the quanti-tatively determined BP (BP obj; objective) and event-related desynchronisation (ERD) and their combinations in ascending order. The sensitivity is depicted by the dark-grey bars which depict the fraction of patients in which neurophysiological evidence for a functional genesis of the myoclonic jerks is present, and vice versa. *=p<0.05, **=p<0.01, ns=non-significant.

7.4.4 Relationship between ERD and Objective BP

The amplitude of the objective BP and the ERD did not correlate significantly in the FJ (cc=0.08, p=0.67) or in the CM (cc 0.16, p=0.53) group (Suppl Fig 1). An example of the temporal relation between the objective BP and ERD derived from two patients with FJ is provided in Figure 3. In this figure it is visible that the BP and ERD can occur simultaneously (Fig 3 A) or sequentially (Fig 3 B).



Supplementary Figure 1

Correlation between the change in relative central (Cz) EEG 13-45 Hz power spectral density (13-45 Hz Change) prior to myoclonus jerks and the magnitude of the Bereitschaftspotential (BP) in cortical myoclonus (cortical, red dots) and functional jerks (functional, blue dots). The red line indi-cates the linear regression line for the cortical myoclonus group and the blue line the linear regres-sion line for the functional myoclonus.

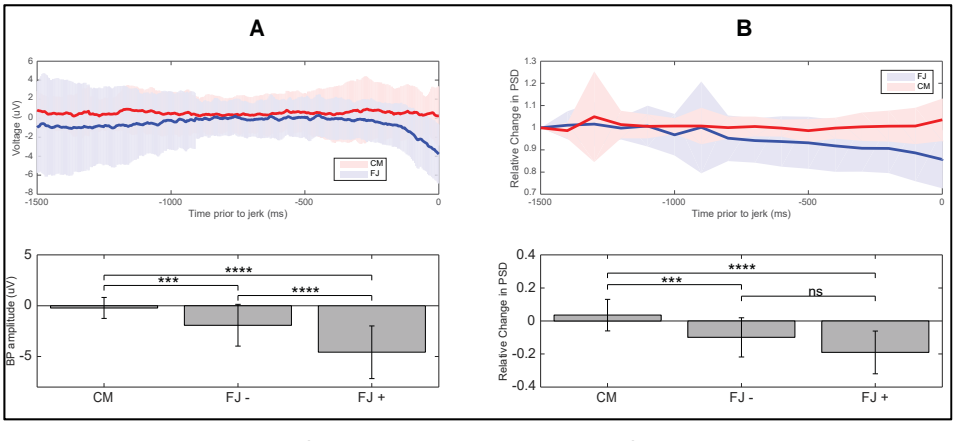


Figure 2 - Time courses of central EEG amplitude deflection and normalised central EEG 13-45 Hz power spectral density prior to myoclonic jerks

A: (upper panel) Time courses of central (Cz) EEG amplitude deflection prior to myoclonic jerks in the patient group with cortical myoclonus (CM) and functional jerks (FJ) and their standard devia-tions ranging from -1500 ms prior to jerk to jerk onset. (lower panel) Average amplitude of central (Cz) EEG deflection prior to myoclonic jerks from -500 prior to jerk to jerk onset in cortical myo-clonus (CM), functional jerks with absent (FJ -) or present (FJ +) visually rated bereitschaftspotenti-al.

B: (upper panel) Time courses of normalised central (Cz) EEG 13-45 Hz power spectral density (PSD) prior to myoclonus jerks (i.e. event related desynchronisation) in cortical myoclonus (CM) and functional jerks (FJ)

and their standard deviations ranging from -1500ms prior to jerk to jerk onset. (lower panel) Average amplitude of normalised central (Cz) EEG 13-45 Hz power spectral density prior to myoclonic jerk from -1500 prior to jerk to jerk onset in cortical myoclonus (CM), functional jerks with absent (FJ -) or present (FJ +) visually rated bereitschaftspotential.

µV = mi-crovolt, ms = millisecond, *** = p < 0.005, **** = p < 0.001, ns = non-significant.

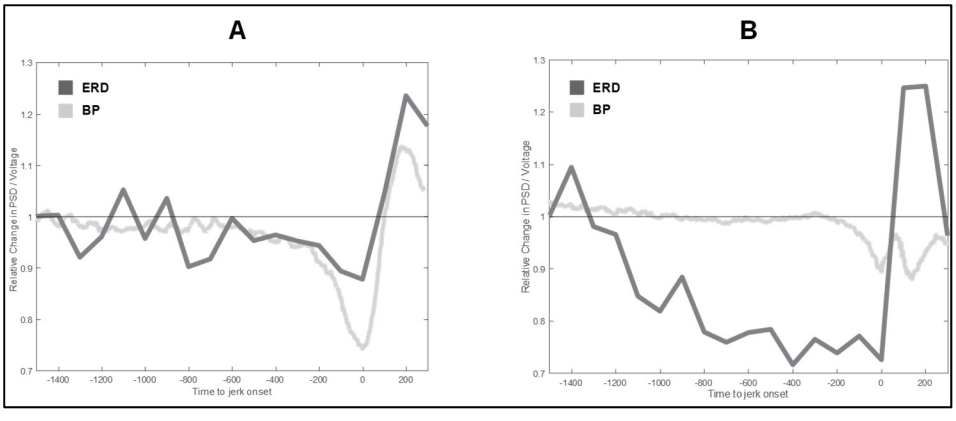


Figure 3 - Examples of time courses of the Bereitschaftspotential (BP) and central (Cz) EEG 13-45 Hz Event Related Desynchronisation (ERD) prior to myoclonic jerks in two patients with functional jerks

Examples of time courses of the Bereitschaftspotential (BP) and central (Cz) EEG 13-45 Hz Event Related Desynchronisation (ERD) prior to myoclonic jerks in two patients with functional jerks. A: simultaneous time-course of ERD and BP. B sequential time-course in which ERD starts earlier than BP that only consists of a late 'negativity slope' (see M & M).

7.4.5 Receiver Operating Characteristics

Both the objective BP and the ERD approach showed a 'good' (i.e. AUC between 0.8-0.9) ROC AUC (Fig. 4). When combining the two methods, an 'excellent' (i.e. AUC between 0.9-1.0) ROC AUC was obtained. There was no statistically significant difference between objective BP and ERD analysis (p=0.66). This was also the case when comparing the objective BP and ERD separately with their combination (i.e. obj BP + ERD, p respectively, 0.52 and 0.29). In supplementary Figure 2 the relations between sensitivity and specificity at different voltage / relative power changes are presented.

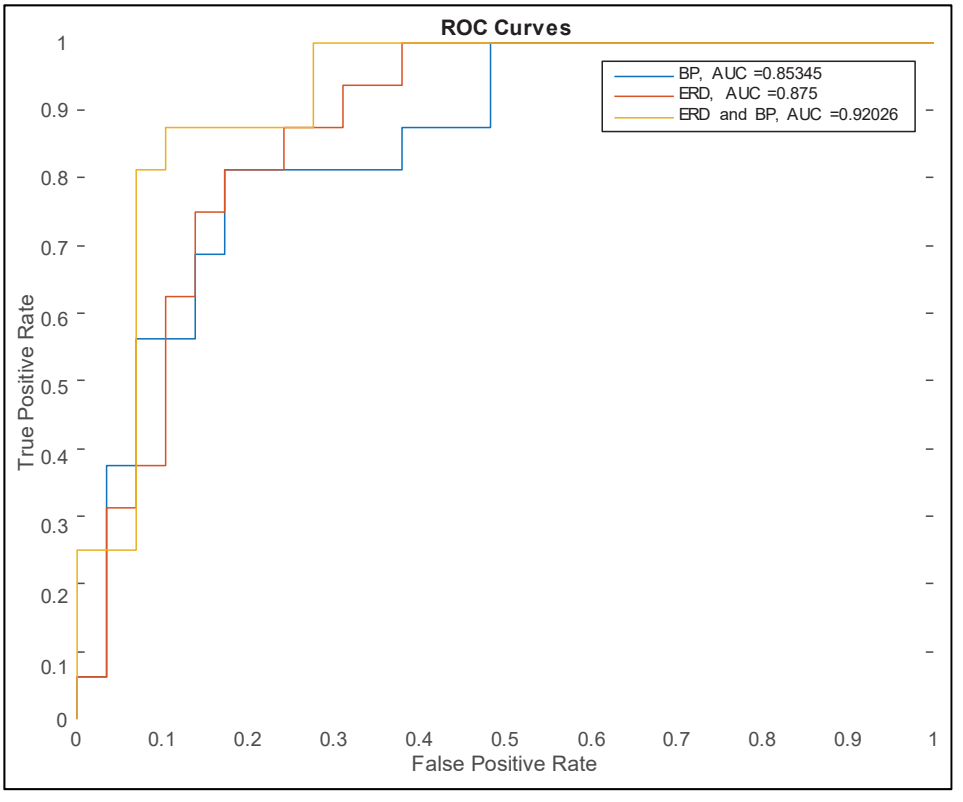
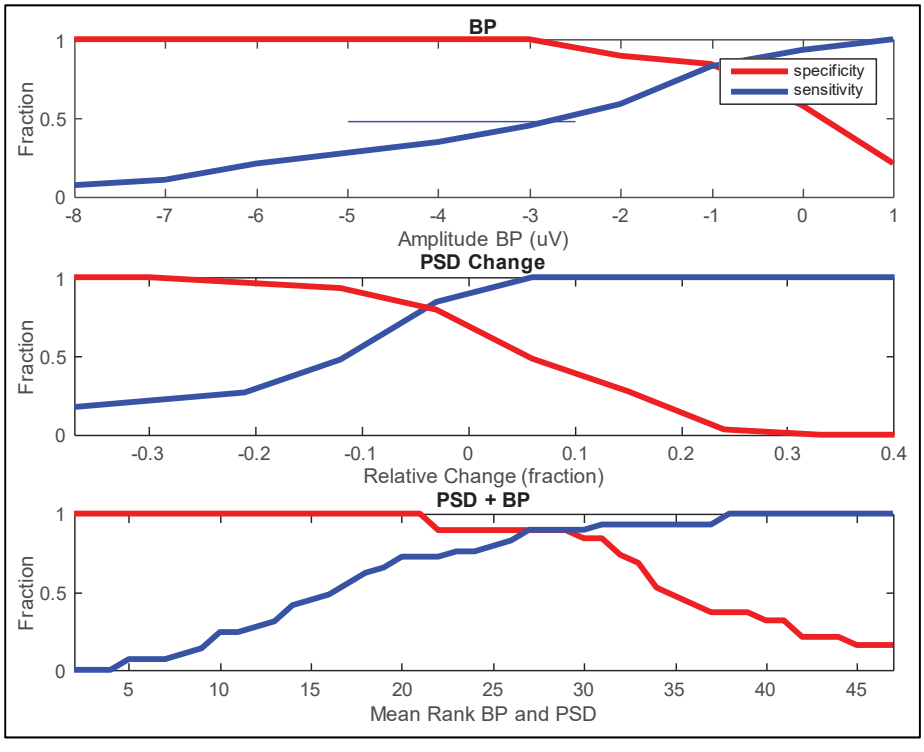


Figure 4 - Receiver Operating Characteristics (ROC) for the use of the quantified Bereitschaftspotential (BP), Event Related Desynchronisation (ERD) and the combination of the two (ERD and BP) and their Areas Under the Curve

Receiver Operating Characteristics (ROC) for the use of the quantified Bereitschaftspotential (BP), Event Related Desynchronisation (ERD) and the combination of the two (ERD and BP) and their Areas Under the Curve (AUC, range 0 - 1). None of the AUC's differed significantly.



Supplementary Figure 2

Upper panel: The relation between the amplitude of the quantified Bereitschaftspotential (BP) and its specificity (red) and sensitivity (blue, both in fractions) for discriminating functional jerks from cortical myoclonus. The horizontal bar indicate the values used in clinical practice for determining whether a BP is present which ranges from -5 µV to -2.5 µV. Middle panel: The relation between the change in relative central (Cz) EEG 13-45 Hz Power Spectral Density (PSD) prior to myoclonic jerks and its specificity and sensitivity for discriminating functional jerks from cortical myoclonus. Lower panel: The relation between the rank-based combination of BP and change in PSD and its specificity and sensitivity for discriminating functional jerks from cortical myoclonus. n.b. the rank is based on the average rank of BP and PSD in a cohort of 45 patients.

7.4.6 Diagnostic Gain

When using the ERD prior to the myoclonic jerk, eight of 15 with a FJ, that had a negative subjective BP, could be distinguished from CM without losing specificity (Fig. 1). This resulted in a diagnostic gain of 53% compared to subjective BP alone that had a sensitivity of 14/29 (47%). This difference was significant ($p = 0.03$), whereas when adding the objective BP to the subjective BP no significant increase in diagnostic gain was obtained (29%, $p=0.29$). Finally, when both adding the objective BP and the ERD, the highest increase in diagnostic gain was obtained (71%, $p<0.01$).

7.5 Discussion

In this study we were able to replicate the recent finding of the presence of event-related desynchronisation (ERD) in the broad (13-45 Hz) beta band preceding functional jerks (FJ) beyond the propriospinal myoclonus phenotype (e.g. focal, multi-focal and segmental FJ). In addition, we showed that its sensitivity for detecting a functional origin of myoclonus jerks is higher compared to the classical subjective BP. Furthermore, we showed that when the ERD method is added in BP negative patients a significant additional diagnostic gain of 53% is achieved. Finally, when adding a quantified, 'objective' BP analysis this gain increases to 71%. This meant that sensitivity (at 100% specificity) increased from 47% to 80%.

In the previous study on ERD in FJ, only patients with propriospinal FJ were included.[4] The current data show that beta ERD occurs in all kinds of FJ phenotypes (Table 1). In addition, beta ERD was recently reported to occur prior to psychogenic non-epileptic seizures.[10] This suggest that beta ERD might be a useful diagnostic marker for a wider range of paroxysmal functional neurological disorders.

At present the BP is often defined as a negative deflection prior to movement, exceeding 5 uV.[7] Our data suggest, however, that a less stringent definition of the BP (< -2.5 uV) is justified, as 100% specificity persists for distinguishing FJ from CM. In earlier reports, 'borderline' BP's with an amplitude of lower than -2.5 uV were interpreted blinded from the clinical case by experienced neurophysiologists.[6] Based on amplitude, shape, artifact and signal to noise ratio it was decided whether the BP was present or not in the study by van der Salm et al. In the study from van der Salm et al, as well as in our study, this resulted in an increase of the presence of BP's in FJ.[6]

Interestingly, we found that the amplitude of ERD and BP were not correlated at the within subject level. Pathophysiologically, this might imply a different basis of these biomarkers. A previous study showed additional topographic segregation between BP and ERD, the latter being more widely distributed across temporal, parietal and higher-order motor area.[18] This is consistent with the idea that modulation of beta oscillations is related to attention.[19] Changes within attentional networks, reflected by ERD, are also predicted by the attention based model of functional neurological disorders.[9] The BP is mainly present in (pre)motor areas and might be a more direct reflection of the

planned movement, although explanations are still speculative.[20] Both processes, i.e. altered attention and changes in planning of movement, are hypothesised to be disturbed in FJ.

7.5.1 Limitations

Our results might have been more pronounced in a selection of patients with identical jerks in the same body area.[5] However, the presence of ERD in our heterogeneous cohort demonstrates its potential applicability as a neurophysiological biomarker in a broader range of functional neurological disorders. Furthermore, the amount of patients with FJ and a positive BP is higher in earlier studies.[6] However, these studies had a prospective design and we cannot rule out that in our cohort neurophysiology was omitted in patients with sufficient clinical evidence for a functional origin of the jerks. Furthermore, we only compared FJ with CM and not with other forms of organic myoclonus, e.g. subcortical myoclonus. For this reason we can't directly extrapolate our findings to all organic forms of myoclonus. The 'excellent' (AUC 0.9-10) ROC characteristics that were achieved by combining ERD and BP in a single cohort. We cannot prove with this study generalizability of our results, nevertheless this is the second cohort in which these ERD changes have been found.[4]

In conclusion, ERD appears to be a promising neurophysiological biomarker to support the clinical diagnosis of FJ, especially in combination with objective BP. The reduction in beta oscillations prior to FJ found in our cohort strengthens the hypothesis of the role of changes within attentional networks in the pathogenesis of functional disorders. These findings stimulate further research regarding the applicability of ERD in clinical practice, pathophysiology of functional movement disorders, and exploration of therapeutic options influencing the beta power in FJ. Based on the current findings we propose adding ERD and objective BP analyses to the diagnostic algorithm for patients with a clinical suspicion of FJ with a negative subjective BP.

7.6 References

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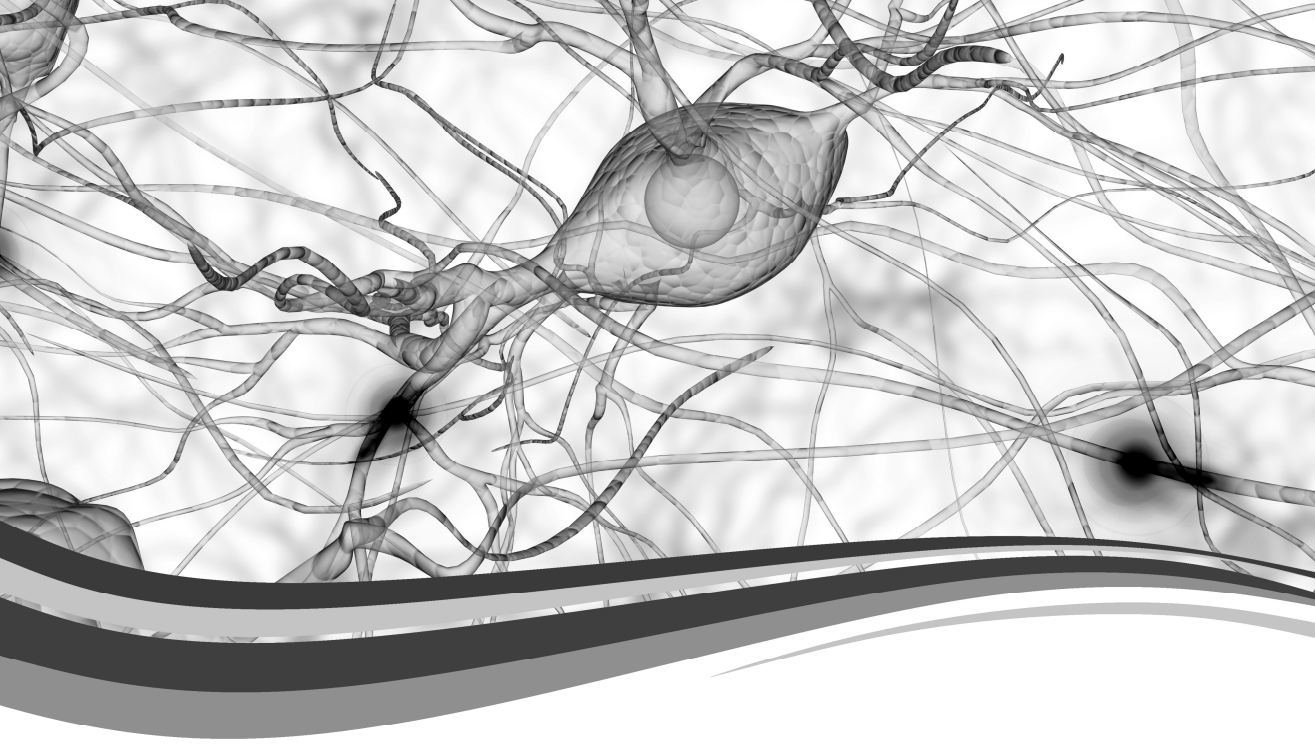

Chapter 8 Discussion and concluding remarks

Discussion and concluding remarks

Myoclonus is a frequently encountered hyperkinetic movement disorder characterized by involuntary jerks, or short interruptions of muscle tone.[1] Myoclonus can be anatomically classified into cortical, subcortical, spinal, and peripheral myoclonus[2], as well as forming a component of functional movement disorders.[3,4] Myoclonus can be present in a large number of both acquired and genetically determined disorders. Accurate diagnosis and classification of its anatomical subtype is important in determining an aetiological differential diagnosis, and guiding therapeutic management. However, clinical diagnosis of myoclonus remains challenging due to its manifestation in a large number of clinical phenotypes, and the number of causative disease causing genes increasing year on year. These challenges and opportunities reinforce the need for a novel and systematic approach to those patients presenting with myoclonus.

This thesis aims to provide a cohesive and logical discussion of the means of diagnosing myoclonus, and utilising clinical skills and investigative techniques to maximise accuracy of diagnosis and symptomatic management. The first section outlines a novel diagnostic algorithm for patients with myoclonus, incorporating the expanding repertoire of Next Generation Sequencing (NGS) techniques for the first time, and highlighting its potential application in an atypical case of Progressive Myoclonic Epilepsy (Chapter 2). Although NGS is of particular aid in determining genetic diagnoses, clinical phenotyping remains central in reaching a diagnosis. In Chapter 3, we describe the motor characteristics observed in Myoclonus-Dystonia (subcortical myoclonus), and explore whether these features enable distinction of patients with and without a mutation in the *SGCE* gene. Given their increased recognition and symptomatic importance, Chapter 4 focuses on the discriminative value of non-motor characteristics (depression, anxiety) and quality of life in distinct subtypes of myoclonus.

The latter portion of this thesis focuses on the use of electrophysiological testing in the identification and anatomical classification of myoclonus. In spite of being used frequently in clinical practice, the sensitivity and specificity of these electrophysiological techniques remains largely unknown. Chapters 5 and 6 therefore examine the value of existing electrophysiological techniques, both when used independently, and in conjunction with clinical phenotyping, in determining an accurate diagnosis. Finally, in Chapter 7, we explore the

contribution of a novel electrophysiological biomarker, 'event-related EEG desynchronization' (ERD) to improve electrophysiological diagnosis of functional myoclonic jerks, and its potential implication for use in future studies.

8.1 Development of a novel diagnostic algorithm for patients with myoclonus

As well as providing a comprehensive overview of the acquired and genetic causes of myoclonus, this algorithm aims to guide clinicians in the accurate identification of myoclonus, determination of its anatomical substrate, and ultimately diagnosis of the underlying disorder (**Chapter 2**). In our eight-step algorithm, we initially rule out acquired causes, mitochondrial disorders and late-onset neurodegenerative disorders, identifying the subgroup of patients in whom NGS diagnostics are highly recommended for the simultaneous analysis of potential myoclonus-associated genes. In the coming years, the systematic use of NGS diagnostics in neurology clinics will likely lead to a higher diagnostic yield, aiding identification of novel disease causing genes and atypical myoclonic phenotypes.

In spite of providing enormous diagnostic potential, the use of NGS also raises other challenges, such as data filtering and determination of novel variant pathogenicity, factors likely to augment further with the increased use of whole-genome sequencing. Diagnostic panels also require constant update and validation with the identification of novel disease-causing genes.[5] It is also important to appreciate the limitations of NGS, with mitochondrial disorders often going undetected, and current techniques unable to detect repeat expansions, large structural rearrangements, and mutations in noncoding regions.[1,6,7] Managing these challenges and providing accurate diagnostic information to patients will require the ongoing close working and collaboration of clinicians, molecular biologists and biostatisticians.

8.2 The importance of clinical phenotyping in diagnosis and classification of myoclonus

In **Chapter 3**, we investigated whether clinical motor characteristics might predict *SGCE* mutation status in patients with Myoclonus-Dystonia. Myoclonus-Dystonia is a young onset movement disorder with myoclonic and dystonic components predominantly affecting the upper body.[8,9] Myoclonus-Dystonia is

inherited in autosomal dominant fashion with causative mutations in the *SGCE* gene (DYT11) observed in a proportion of cases.[8-10] Within our cohort (*SGCE* mutation positive n= 19, *SGCE* mutation negative n=20), truncal dystonia and co-existence of myoclonus and dystonia in the same body region with action, were identified as being of predictive value in determining the absence of an *SGCE* mutation. This chapter serves to highlight that in spite of novel diagnostic techniques, a systematic and robust clinical examination, with accurate phenotyping, remains central to determining the differential diagnosis of myoclonic disorders.

In addition to the motor component, there is accumulating evidence that non-motor symptoms form an integral part of movement disorder phenotypes. In order to further explore an element of this in **Chapter 4** we investigated whether the presence of depression and anxiety and perceived health related quality of life could discriminate between functional myoclonic jerks (n=16) and organic myoclonus (n=23). Interestingly, pain provided the only significant marker of differentiation between the groups, being higher in those with functional myoclonic jerks (median RAND-36 scores FJ: 49, CM: 80 ($p< 0.05$). In contrast, rates of depression, anxiety and health related quality of life were similar between the two groups. These findings suggest a number of important implications; 1) co-morbid psychiatric pathology may not be helpful in identifying functional disorders, 2) as has been demonstrated in certain subgroups, further work needs to be undertaken to determine whether psychiatric symptoms form part of the disorder phenotype in distinct myoclonic disorders[11,12], and 3) further exploration of pain in functional movement disorders, already identified as an important symptom in functional (fixed) dystonia, is needed.[13]

8.3 The role of electrophysiological testing to aid diagnosis and sub-classification of myoclonus

In the Netherlands, video-polymyography is a widely used electrophysiological technique to aid diagnosis in hyperkinetic movement disorders. The more advanced electrophysiological tests, including back-averaging and coherence analysis, are readily accessible in most specialist movement disorder centers. However, access and use of these techniques varies significantly between countries, with very little routine use of electrophysiological techniques in some regions. **Chapter 5** explores the relationship between clinical

phenotyping and the results of electrophysiological testing. We initially undertook a retrospective study of 119 patients referred for video-polymyography due to a clinical diagnosis of myoclonus. While the clinical diagnosis was confirmed in the majority (88/119 (74%)), there was greater disagreement when it came to anatomical sub-classification (agreement in only 49 cases (56%)), with distinction between propriospinal myoclonus and functional jerks being most challenging to clinicians. In addition, a number of clinical characteristics were identified to aid distinction of cortical and functional myoclonic jerks, including age and rate of onset, provocation of the jerks with action or being in a supine position, and history of a preceding contributory event. In line with previous literature, the most common organic myoclonus subtype identified in this cohort was cortical myoclonus, while interestingly nearly half were diagnosed as having functional myoclonic jerks (47%).[14] This potentially highlights the difficulties associated with diagnosing functional myoclonic jerks, and a likely higher tendency to refer these cases to specialist centres.

In **Chapter 6** we sought to take the findings from Chapter 5 and apply them to a prospectively recruited cohort. Here, we recruited 72 patients with a clinical diagnosis of myoclonus, and accounted for a number of features in a stepwise approach in order to optimise accurate diagnoses. These included, an initial clinical diagnosis and anatomical sub-classification, electrophysiological testing, expert clinical review, and follow-up for a minimum of six months. While agreement over the core diagnosis (myoclonus) was higher than that seen in the retrospective study (60/72 (91%)), agreement over anatomical sub-classification was similarly low (47%), increasing to 87% following expert review. These factors become increasingly important with the selection and instigation of therapy, with treatment being started in 62% (n=37) overall, and in 29 of these cases only once electrophysiological test results were available. Treatment was effective in 68% (n=25), with levetiracetam being of greatest benefit in cortical myoclonus (67%) in our selected group, and comprehensive explanation of the disorder and specialised physiotherapy programme for those with functional myoclonic jerks (67%).

The results of both the retrospective and prospective studies emphasize the clinical challenge, not only of diagnosing myoclonus, but also in determining the anatomical subtype and the significant utility that electrophysiological testing provides in aiding this process. Interestingly, no patients in the

prospective study were diagnosed with spinal myoclonus, likely due to the changing clinical view that these individuals are now thought to have jerks more consistent with a functional disorder.[15,16] The relatively high proportion of functional myoclonic jerks in these cohorts likely reflects some of the referral patterns to a tertiary centre however, the rate of response to treatment intervention in the prospective cohort demonstrates the importance of early and prompt intervention in this patient group.[17,18]

8.4 The contribution of novel electrophysiological techniques to diagnostic testing

Given the considerable number of patients with functional myoclonic jerks identified in the prospective study (Chapter 6), our interests turned to the potential role of electrophysiological testing in distinguishing these cases from other forms of myoclonus. In **Chapter 7** we evaluated whether the presence of desynchronization in the broad (13-45 Hz) beta band, and quantification of the bereitschaftspotential (BP) preceding the myoclonic jerks, could aid in the diagnosis of functional myoclonic jerks. Within this study cohort (functional myoclonic jerks = 29, cortical myoclonus = 16) event related desynchronization (ERD) and BP amplitude were significantly higher in those with functional myoclonic jerks compared to those with cortical myoclonus. The ERD component also demonstrated further utility when applied to cases reported as not being typical of a functional disorder when replying solely on the BP. Here an additional eight cases (53%) considered to be consistent with the ERD pattern of functional myoclonic jerks were identified. Previous studies have demonstrated a role for ERD in the diagnosis of functional propriospinal myoclonus and psychogenic non-epileptic seizures (PNES), while this work (Chapter 7) provides some preliminary evidence for its wider application across functional disorders.[19,20]

8.5 Future perspectives

8.5.1 Novel diagnostic approaches for patients with myoclonus

It is very likely that the large-scale implementation of the new diagnostic algorithm in combination with NGS diagnostics will increase the diagnostic yield in patients with myoclonus. It will be interesting to future evaluate this approach not only in terms of rates of diagnosis, but also the time taken to reach these diagnoses, and whether this impacts healthcare related costs. NGS

is generally perceived to be a costly investigative tool however, data is beginning to emerge that this approach to diagnostic genetic testing may provide longer term cost savings.[21] In addition, more widespread use of NGS will result not only in the broadening of recognised clinical phenotypes, but also potentially facilitate the identification of novel disease causing genes for myoclonus. It is here that robust clinical examination and phenotyping skills will be of vital importance, in identifying patient groups, and determining the potential pathogenicity of novel genetic variants. Future study of genetically homogenous cohorts will also aid in determining underlying disease-causing pathways, for example, the detection of a large number of myoclonus associated ion channel genes would further strengthen the pathophysiological hypothesis of changes in cortical excitability and could guide development of therapeutics.

8.5.2 Clinical phenotyping

Accurate and detailed clinical phenotyping remains the cornerstone of the clinical approach to patients with myoclonus. Future studies are needed to investigate in detail the clinical and electrophysiological features of specific myoclonic syndromes. For instance, Progressive Myoclonus Epilepsy (PME) syndromes have been studied extensively[22-24], but very little attention has been given to Progressive Myoclonus Ataxia disorders (PMA), despite the large overlap in clinical symptomatology. In the UMCG we have a particular interest in a PMA subtype caused by mutations in *GOSR2* gene, which likely has a founder effect in Friesland, located in the north of the Netherlands.[25] There is a lack of a clear demarcation of PMA syndromes, making their recognition and differentiation from other syndromes difficult, and frequently resulting in delays to diagnosis.

In addition, clinical phenotyping should not be restricted to motor characteristics, with our group and others having demonstrated the importance and prevalence of non-motor symptoms in myoclonic disorders.[11,26-29] Given the importance of the non-motor symptoms on HQoL and their need for treatment in clinical practice, this work should be expanded to larger myoclonus disease cohorts and must include child as well as adult case recruitment. Improved clinical and genetic characterisation of this group would be hoped to facilitate better understanding of mechanistic pathophysiology, and development of more tailored therapy.

8.5.3 Electrophysiological testing

In this thesis we have emphasized the importance of electrophysiological testing in the diagnosis and anatomical sub-classification of myoclonus. Video-polymyography is a useful, and for the most part, easily accessible, tool that enables distinction between myoclonus and other very similar hyperkinetic movement disorders (e.g. tremor). More advanced electrophysiological testing including back-averaging and coherence analysis can be applied to improve the diagnostic sub-classification of myoclonus. However, further development of the electrophysiological criteria for myoclonus subtypes, in particular for subcortical myoclonus, is essential for broader clinical application.

Work in this thesis has also demonstrated that a combined electrophysiological approach using ERD and BP as biomarkers can further improve the accuracy of electrophysiological testing in functional myoclonic jerks. This work has significant implication given the increasing recognition and diagnosis of functional movement disorders, as well as accumulating evidence that prompt diagnosis and intervention significantly improves outcome in this patient group. It is also of relevance in improving the pathophysiological understanding of these disorders, lending some support to the suggestion of changes within neuronal networks involved with regulating attention.[30,31] However, future studies are required to determine the exact cut-off values for these biomarkers, and whether variations in these values might be expected under circumstances such as symptom fluctuation. Moreover, the applicability of ERD needs to be investigated in 'non-jerky' functional movement disorders, such as functional dystonia and tremor. The development of dedicated software packages will also enhance the large-scale introduction of these parameters in clinical practice.

8.6 Conclusion

This thesis provides a new diagnostic approach for patients who present with myoclonus. We describe the challenges and importance of accurate clinical phenotyping, classification of the anatomical myoclonus subtype, and recognition of the frequently accompanying non-motor characteristics. Electrophysiological testing including video-polymyography and advanced techniques (e.g. back-averaging and coherence analysis) proved to play an important contributing role in determining an accurate diagnosis. These, together with the development and wider application of ERD may also

demonstrate future applicability in the diagnosis of highly complex hyperkinetic movement disorders, and in particular functional movement disorders.

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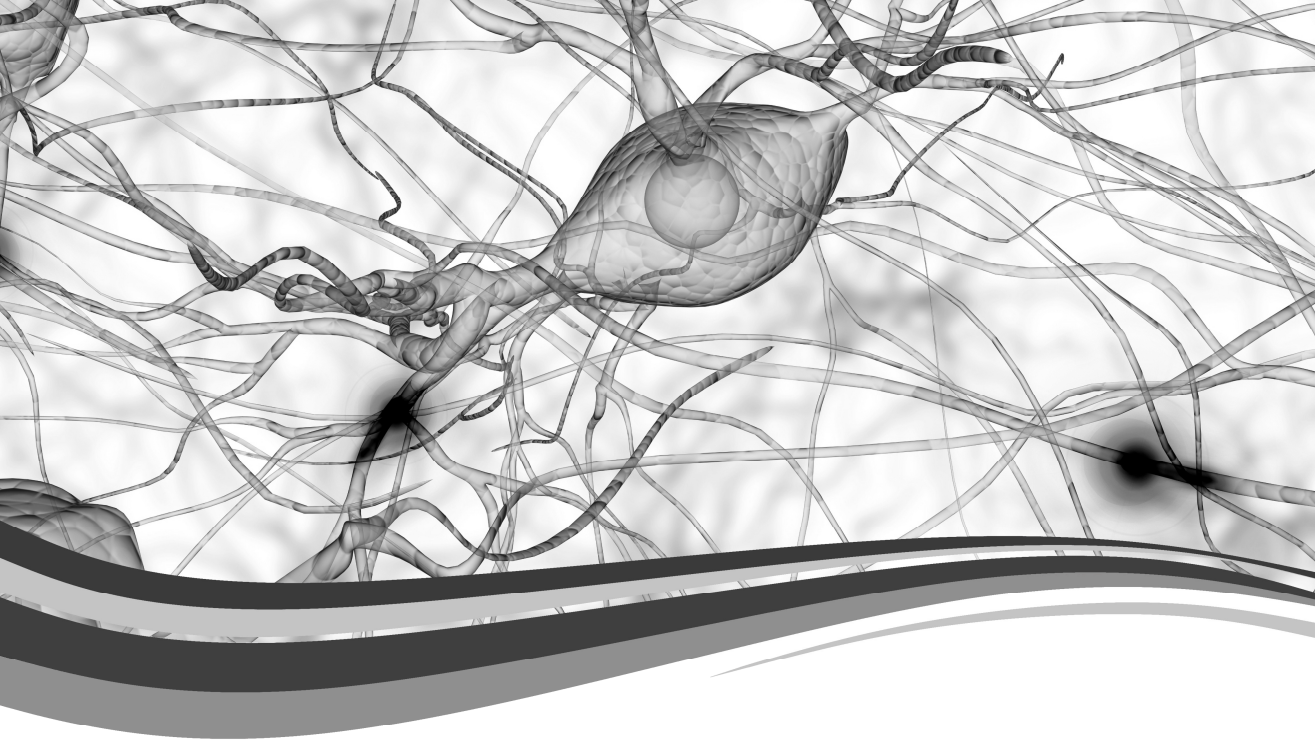


Chapter 9 Nederlandse samenvatting

Nederlandse samenvatting

Myoclonus is een frequent voorkomende hyperkinetische bewegingsstoornis die wordt gekenmerkt door spierschokken (*positieve myoclonus*) en / of het kortdurend wegvallen van de spiertonus (*negatieve myoclonus*). De klinische presentatie van myoclonus is heel divers. De schokken kunnen in één of meerdere lichaamsdelen optreden of gegeneraliseerd zijn. Myoclonus kan optreden in het gelaat, de nek, romp en de ledematen. Het kan in rust of juist bij actie optreden en wel of niet stimulusgevoelig zijn. Over het algemeen belemmert myoclonus patiënten ernstig in hun dagelijks functioneren, zoals bij eten / drinken, schrijven en lopen.

Myoclonus heeft vele oorzaken, zowel verworven als genetisch. Voor het vaststellen van de onderliggende oorzaak en het bepalen van de juiste behandeling is het belangrijk myoclonus te herkennen en te onderscheiden van andere bewegingsstoornissen zoals bijvoorbeeld tremor en chorea. Na het herkennen kan myoclonus op basis van een anatomische classificatie worden ingedeeld in subtypes, i.e. naar de plaats in het zenuwstelsel waar de schokken ontstaan. Dit zijn corticale (hersenschors), subcorticale (diepe hersenkernen / hersenstam), spinale (ruggenmerg) en perifere (zenuwen / spieren) myoclonus. Daarnaast kunnen schokken ook een uiting zijn van een functionele (psychogene) stoornis. Door myoclonus op basis van de anatomische classificatie te groeperen kan diagnostiek gericht ingezet worden. In eerste instantie worden de verworven oorzaken uitgesloten. Daarna kan erfelijkheidsonderzoek plaatsvinden naar het snelgroeiend aantal genetische oorzaken dat met myoclonus geassocieerd is (>100). Gelukkig zijn de mogelijkheden in het diagnostisch onderzoek naar een genetische oorzaak de laatste jaren sterk toegenomen. Zo kunnen nu, met behulp van nieuwe technieken zoals het zogenaamde ‘next generation sequencing’ (NGS) alle potentiele genetische oorzaken in één keer worden getest. Het vaststellen van de onderliggende aandoening is belangrijk voor het inschatten van de behandeling, de prognose en, bij een erfelijke aandoening, voor genetische counseling voor de patiënt en zijn of haar familie.

Het doel van dit proefschrift is om verschillende facetten van het diagnostisch proces bij patiënten met myoclonus te onderzoeken en te optimaliseren. In hoofdstuk 2 wordt een nieuw diagnostisch algoritme beschreven voor patiënten met myoclonus, waarbij na een goede klinische beoordeling (het fenotyperen), wordt toegewerkt naar NGS als belangrijke laatste diagnostische

stap. Hoofdstuk 3 focust op de motorische verschijnselen van een speciale vorm van subcorticale myoclonus, Myoclonus-Dystonie, in patiënten met en zonder de veelvoorkomende mutatie in het *SGCE* gen. Naast het motor fenotype, is er de laatste jaren steeds meer belangstelling voor niet-motorische verschijnselen bij patiënten met bewegingsstoornissen. In hoofdstuk 4 wordt onderzocht wat het onderscheidend vermogen is van de niet-motorische symptomen angst, depressie en de kwaliteit van leven tussen functionele spierschokken en corticale myoclonus.

In het tweede deel van het proefschrift wordt de waarde van het klinisch neurofysiologisch (KNF) onderzoek onderzocht in het diagnosticeren en classificeren van myoclonus en het anatomisch subtype. Ondanks het feit dat de KNF-technieken al vele jaren worden toegepast in de klinische praktijk is er weinig bekend over de sensitiviteit en specificiteit van de verschillende neurofysiologische testen. In hoofdstuk 5 en 6 wordt de waarde van de bestaande KNF-technieken onderzocht. In hoofdstuk 7 wordt het proefschrift afgesloten met de evaluatie van een nieuwe neurofysiologische techniek genaamd 'Event-related EEG desynchronization' (ERD), in het diagnosticeren van functionele spierschokken.

9.1 Klinische diagnostiek myoclonus

Hoofdstuk 2 beschrijft een nieuw diagnostisch algoritme dat bestaat uit een acht-stappenplan, waarbij eerst een nauwkeurige fenotypering van myoclonus wordt uitgevoerd. Daarna wordt de focus gericht op het vaststellen van de oorzaak. Eerst wordt gekeken of er sprake is van een verworven en vaak behandelbare oorzaak voor myoclonus. Indien na deze stappen geen diagnose is gesteld, wordt NGS ingezet in de zoektocht naar een genetische oorzaak.

Het is belangrijk voor clinici om zich te realiseren dat niet alle erfelijke aandoeningen met routine NGS kunnen worden geïdentificeerd. Mutaties in het mitochondrieel DNA (mtDNA) bij mitochondriële ziekten, structurele DNA-veranderingen en mutaties in niet coderende delen van genen (intronen) worden gemist en onderzoek naar dit soort mutaties vereist andere diagnostische testen.

Het is de verwachting dat, door het systematisch toepassen van het nieuwe algoritme in combinatie met de mogelijkheden van NGS, de diagnostische opbrengst in patiënten met myoclonus zal stijgen. NGS heeft namelijk zijn

meerwaarde voor de klinische praktijk al reeds bewezen in andere heterogene neurologische aandoeningen zoals epilepsie en dystonie.

In **hoofdstuk 2A** wordt de toepassing van NGS geïllustreerd aan de hand van een atypische presentatie van een patiënt met een Progressieve Myoclonus Epilepsie waarbij de genetische diagnose 'Ziekte van Lafora' is vastgesteld.

In **hoofdstuk 3** wordt onderzocht of op grond van nauwkeurig fenotyperen van de motorische symptomen patiënten met Myoclonus-Dystonie met en zonder een *SGCE* mutatie kunnen worden onderscheiden. Myoclonus-Dystonie is een autosomaal-dominant overervend (subcorticaal) myoclonus syndroom dat wordt gekenmerkt door het ontstaan van myoclonus en dystonie op jonge leeftijd. Bij ongeveer de helft van de patiënten met dit klinisch syndroom wordt een mutatie in het *SGCE* gen gevonden. In het onderzochte Myoclonus-Dystonie cohort (19 patiënten met een mutatie in het *SGCE* gen en 20 patiënten zonder mutatie) bleek dat de aanwezigheid van dystonie van de romp en het samen voorkomen van dystonie en myoclonus in hetzelfde lichaamsdeel voorspellend is voor de afwezigheid van een mutatie in het *SGCE* gen. Het onderzoek laat zien dat het nauwkeurig klinisch fenotyperen richting kan geven aan het inzetten van het genetisch onderzoek.

Naast het adequaat diagnosticeren van de motorische verschijnselen vormen niet-motorische-verschijnselen, zoals angst, depressie, pijn, slaap en vermoeidheid, een steeds belangrijker onderdeel van het bewegingsstoornissen fenotype. In dit kader is in **hoofdstuk 4** onderzocht of de aanwezigheid van de niet-motorische symptomen angst / depressie en / of de kwaliteit van leven gebruikt kan worden om onderscheid te maken tussen functionele spierschokken (n=16) en organische corticale myoclonus (CM=23). Psychiatrische klachten worden vaak meer verwacht in functionele bewegingsstoornissen, echter in dit onderzoek, was het aantal patiënten met klachten van depressie en angst hoog in beide groepen zonder dat er sprake was van een significant verschil. Ook was de beperking in kwaliteit van leven niet verschillend tussen beide groepen. Een andere interessante uitkomst van deze studie is dat pijn de enige onderscheidende factor was tussen beide groepen en significant vaker voorkwam in patiënten met functionele spierschokken.

9.2 Neurofysiologische diagnostiek myoclonus

In Nederland wordt in de klinische praktijk veel gebruik gemaakt van een video-polymyografie voor het vaststellen van hyperkinetische bewegingsstoornissen. Geavanceerde KNF-technieken, zoals back-averaging en coherentie analyse, zijn beschikbaar in de meeste gespecialiseerde bewegingsstoornissen centra. De sensitiviteit en specificiteit van deze KNF-onderzoeken in het detecteren en classificeren van myoclonus zijn grotendeels onbekend. In **hoofdstuk 5** wordt de correlatie onderzocht tussen het klinisch fenotyperen en de resultaten van KNF-onderzoeken in een retrospectief onderzoek bestaande uit 119 patiënten die werden verwezen met de klinische diagnose 'myoclonus' voor een video-polymyografie. In het merendeel van de patiënten werd de klinische diagnose 'myoclonus' met KNF bevestigd (88/119 (74%)), daarentegen was er slechts in 49 patiënten (56%) bevestiging van het anatomisch myoclonus subtype. In de totale groep kwam in overeenstemming met de literatuur corticale myoclonus frequent voor, maar zeer opvallend was dat er bij vrijwel de helft van de patiënten (47%) sprake was van functionele spierschokken. Corticale myoclonus werd klinisch gekenmerkt door het ontstaan van spierschokken op jonge leeftijd, betrokkenheid van het gelaat en verergering van myoclonus tijdens actie. Functionele spierschokken karakteriseerden zich door een acuut begin, verergering van spierschokken in een liggende houding en de aanwezigheid van een uitlokkende gebeurtenis (o.a. ongeval, sterfte familielid, optreden van pijn) voorafgaand aan het ontstaan van de spierschokken.

In **hoofdstuk 6** is de waarde van KNF-onderzoeken in het diagnosticeren van myoclonus en het anatomische subtype getoetst in een prospectief studie-cohort. In totaal zijn 72 patiënten met een initieel klinische diagnose 'myoclonus' geïncludeerd. In vergelijking met de retrospectieve studie was er een nog grotere overeenstemming in de diagnose van myoclonus (60/72 (91%)) tussen clinici en KNF-resultaten. In het vaststellen van het anatomische subtype kwamen de resultaten overeen met de retrospectieve studie (47% overeenstemming). KNF-onderzoek had de grootste toegevoegde waarde bij 1) het onderscheiden van corticale en subcorticale myoclonus in patiënten met multifocale myoclonus. 2) het vaststellen van het myoclonus subtype bij patiënten met meerdere bewegingsstoornissen (o.a. dystonie), en 3) het diagnosticeren van functionele spierschokken.

De resultaten van zowel de retrospectieve als de prospectieve studie benadrukken de waarde van de KNF-onderzoeken in patiënten met myoclonus. Vooral het vaststellen van het anatomische myoclonus subtype wordt in ongeveer de helft van de gevallen verricht op basis van de uitslagen van de KNF.

In **hoofdstuk 7** wordt een nieuwe neurofysiologische marker voor functionele spierschokken onderzocht: de aanwezigheid van desynchronisatie in de brede (13-45 Hz) bèta band. Recente studies laten zien dat dit een potentiele elektrofysiologische marker is voor functionele propriospinale myoclonus en psychogene non-epileptische aanvallen (PNES). In de studie werd onderzocht of de aanwezigheid van deze 'Event related desynchronization' (ERD) in combinatie met een gekwantificeerde Bereitschaftspotentiaal (BP) ingezet kan worden ter verbetering van het diagnostisch proces voor patiënten met functionele spierschokken.

In deze studie (functionele spierschokken n=29, corticale myoclonus n=16) was de ERD op groepslevel significant groter in patiënten met functionele spierschokken in vergelijking met corticale myoclonus ($p < 0.001$). In acht extra patiënten (53%) kon op basis van het ERD-patroon elektrofysiologisch de diagnose functionele spierschokken worden vastgesteld. De combinatie van ERD en een gekwantificeerde BP verhoogt de KNF-sensitiviteit van 47% naar 80% met behoud van een 100% specificiteit in patiënten met functionele spierschokken.

Deze resultaten ondersteunen de bruikbaarheid van ERD als nieuwe neurofysiologische marker in de klinische praktijk en impliceren dat de KNF-techniek niet alleen kan worden ingezet in de twee specifiek onderzochte functionele stoornissen maar toepasbaar is in allerlei verschijningsvormen van functionele spierschokken.

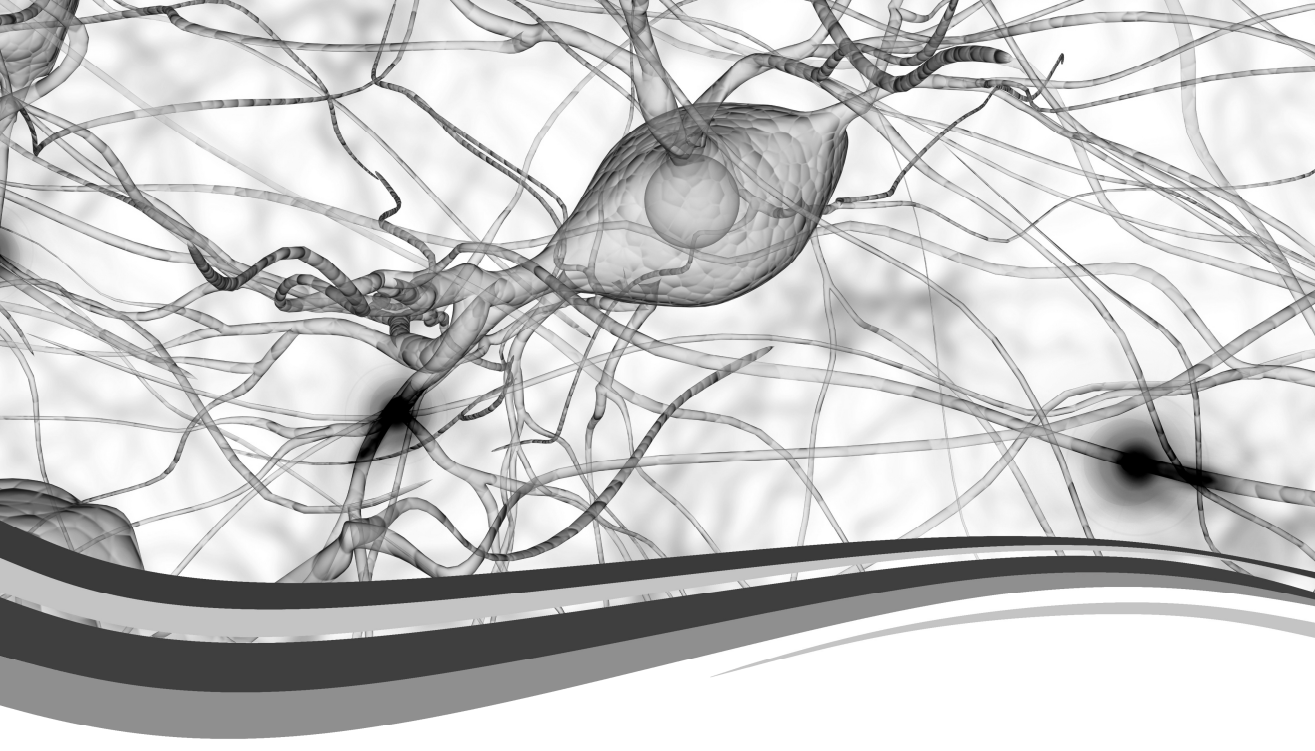
9.3 Toekomstperspectieven

Het gebruik van NGS zal leiden tot een groei van nieuwe ziektegenen geassocieerd met myoclonus. Daarnaast presenteren bekende genetische myoclonus syndromen zich met nieuwe klinische fenotypen. De toename van de met myoclonus geassocieerde genen zal meer inzicht geven in de onderliggende pathofysiologie en mogelijk leiden tot gerichtere behandelmogelijkheden.

Naast de enorme potenties leidt het gebruik van NGS ook tot nieuwe uitdagingen. De uitkomsten van NGS moeten adequaat worden gefilterd en de pathogeniciteit van een gevonden variant moet worden beoordeeld. Vooral varianten in genen die als “unknown or uncertain significance” geduid worden zullen bij een toename van het gebruik van NGS steeds vaker de conclusie van het diagnostisch onderzoek zijn. Het is hierbij de taak van de clinicus om het klinisch fenotype in deze patiënten, zowel motorisch als niet-motorisch, zorgvuldig in kaart te brengen zodat in de toekomst wel een uitspraak gedaan kan worden over het causale verband tussen de gevonden variant en de ziekte. Daarnaast blijft het zorgvuldig klinisch fenotyperen essentieel voor het creëren van homogene patiëntengroepen om het onderzoek naar nieuwe ziektegenen te faciliteren.

Video-polymyografie en de geavanceerde KNF-onderzoeken (back-averaging en coherentie analyse) hebben hun waarde getoond bij het diagnosticeren van myoclonus en het vaststellen van het anatomische subtype. Echter, op dit moment is het niet mogelijk in alle casus met zekerheid het subtype elektrofysiologisch vast te stellen en daarom is het belangrijk de KNF-technieken en elektrofysiologische criteria voor de verschillende myoclonus subtypen te blijven ontwikkelen. Naar verwachting kan de techniek van ERD op korte termijn worden geïmplementeerd in de klinische praktijk. Vereenvoudiging van de beschikbare softwarepakketten kan er voor zorgen dat de geavanceerde KNF-technieken breder toepasbaar worden voor de klinische praktijk.

Samenvattend biedt dit proefschrift een nieuw diagnostische aanpak voor patiënten met myoclonus. Het beschrijft de uitdagingen en het belang van het nauwkeurig klinisch fenotyperen van zowel motorische als niet-motorische symptomen en de classificatie van het anatomisch myoclonus subtype. Het klinisch neurofysiologisch onderzoek heeft een belangrijke toegevoegde waarde naast de klinische beoordeling in de (sub)classificatie van myoclonus.



Chapter 10 Dankwoord

Acknowledgements

Dankwoord | Acknowledgements

Beste lezer, bedankt voor de interesse in mijn proefschrift. Het afronden van mijn promotie is een belangrijke mijlpaal in mijn leven. Mijn vader heeft me geleerd dat geen enkel doel onmogelijk is; een Elfstedentocht, Honderd Cols Tocht, of het bereiken van een wetenschappelijke carrière, zolang je er met overgave voor gaat en niet opgeeft. Al toen ik erg klein was wilde ik in alles de beste zijn en heb ik weleens de opmerking gekregen een Olympisch leven te leiden. Zonder deze gedrevenheid was ik nu nog niet klaar geweest en om deze reden gebruik ik de Olympische Spelen als analogie voor mijn dankwoord.

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De Olympische Spelen bestaan uit team- en individuele sportonderdelen. In mijn favoriete sport, het wielrennen, behaalt één sporter een gouden medaille maar zonder een ultieme teamprestatie is zelfs de beste wielrenner kansloos. Mijn naam prijkt op het proefschrift, echter zonder de steun van mijn teamgenoten had ik hier nu niet gestaan.

Dr. K.J. Peall, dear Kathryn, one of our first meetings was in the weekend I had organized for the residents with the disastrous mountain bike trip where you had injured your leg badly. The subsequent visit to the emergency room was the beginning of our close friendship. You advise me when I get stuck in research or the English language, and know when it is time for physical exertion or relaxation.

Dr. M. Smit, lieve Marenka, je bent voor mij een dierbare collega in zowel het onderzoek als de klinische werkzaamheden. Super trots stond ik naast je als paranimf toen jij je proefschrift verdedigde en ik vind het een eer dat jij nu naast mij staat.

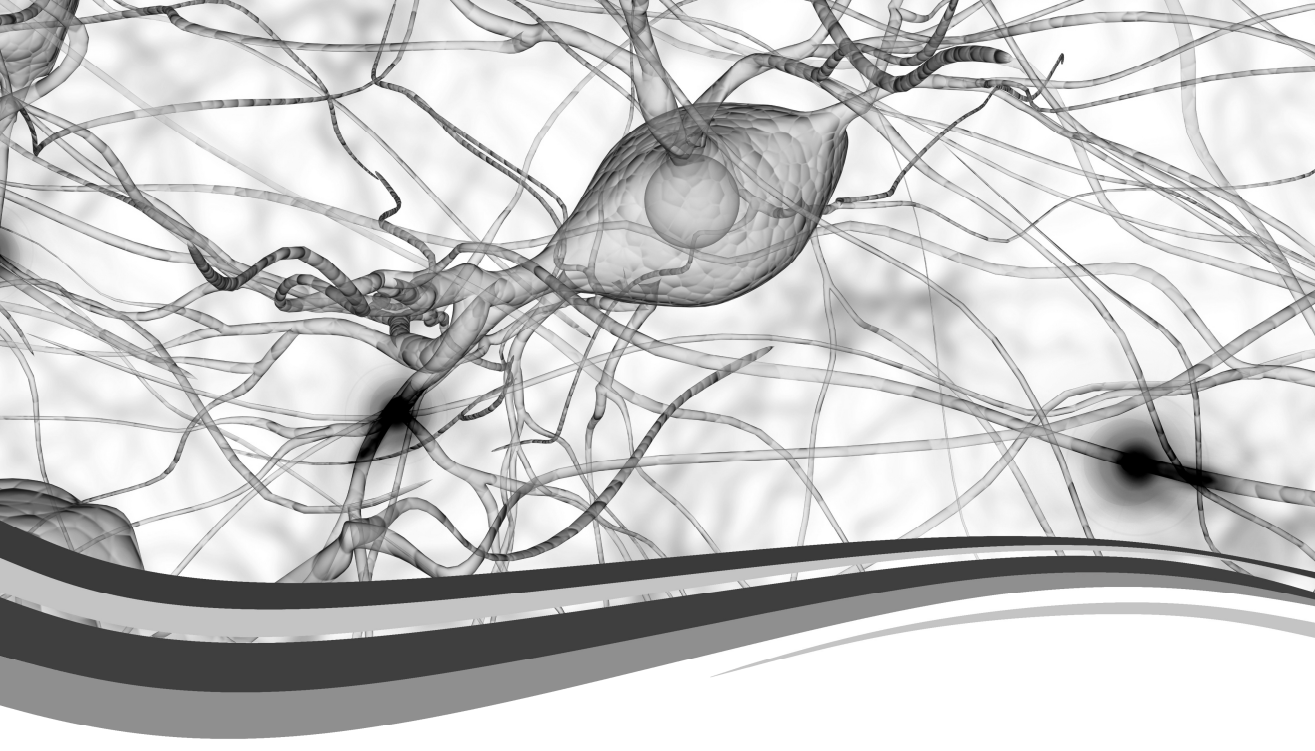
Collega-promovendi en (oud) AIOS neurologie, bedankt voor jullie hechte vriendschap. Ik heb me geen dag alleen gevoeld in het verre Groningen. Op de werkvloer is er een goede collegialiteit waarbij het altijd mogelijk is om elkaar advies te vragen op alle vlakken. Er wordt hard gewerkt, maar daarnaast wordt er veel gelachen. Ook wordt tijd gemaakt om samen activiteiten te ondernemen en te sporten. Bij de gedachte aan het martelblad waar de mannen wekelijks op hun fiets naar toe schakelden, schiet de kramp direct in mijn kuiten.

Met mijn olympisch leven wilde ik ook altijd de beste echtgenoot aan mijn zijde. Lieve Jeroen, jij hebt je bewezen door al die jaren meerdere rollen met verve te vervullen. Als soigneur zorg je dat de dagelijkse gang van zaken thuis vlot verloopt, zodat we in de weekenden tijd hebben voor ontspanning. Als mecanicien los je mijn computerproblemen op en dat zijn er nogal wat…

Nog een laatste bijzondere wetenschap over de Olympische Spelen in Amsterdam is dat deze niet financieel gesteund werd door de tweede kamer (geen respect voor de zondagsrust), echter het Olympisch Stadion is gebouwd

door steun van het eigen volk. In mijn promotie ben ik ook ontzettend gesteund op allerlei vlakken door mijn vrienden en familie.

Ik zal deze periode altijd blijven koesteren. De manier van samenwerken waarbij we het beste bij elkaar naar boven hebben weten te halen, blijft mijn inspiratie voor mijn toekomstige carrière. De hamvraag is of ik doorga tot de volgende Olympische Spelen….



Chapter 11 Curriculum Vitae

Curriculum Vitae

The author of this thesis, Rodi Zutt was born on February first, 1984 in Warmenhuizen, The Netherlands. After completing secondary school at the 'Murmellius Gymnasium' in Alkmaar, she started her medical education at the University of Amsterdam. During medical school, she developed enthusiasm about the field of Neurology and did a research project on neuromuscular disorders at the department of Neurology of the AMC (Dr. A.J. van der Kooi and Professor M. de Visser). During this period she developed a diagnostic algorithm for patients with recurrent episodes of rhabdomyolysis.

In December 2008, she obtained her medical degree (MD) and subsequently worked as a medical resident at the department of Neurology and Neurosurgery of the Medical Center in Alkmaar and Internal Medicine of the Kennemer Gasthuis in Haarlem for two years. In January 2011 she started her formal training as a neurological resident at the department of Neurology of the University Medical Center Groningen (Professor H.P.H. Kremer). Since 2014 she has combined her clinical work with research on myoclonus. Fascinated by movement disorders, she performed a one-year fellowship in movement disorders at the UMCG (Professor M.A.J. de Koning-Tijssen and Professor T. van Laar).

During her fellowship, Rodi was awarded the annual prize of the Dutch Movement Disorder Society for the best scientific paper in 2015-2016 'A novel diagnostic approach to patients with myoclonus' published in *Nature Review Neurology*. Furthermore, she was involved in organising several (inter) national congresses including the 'Dystonia training school' in 2015 (European COST platform), the International Parkinson and Movement Disorder Society Congress 'Myoclonus and other jerky movements' in 2016, the 'Functional Movement Disorders For Physiotherapists Symposium' and 'National Information Day For Patients With Movement Disorders' in Groningen in 2017.

In august 2017, she started as neurologist at the Haga Teaching Hospital in The Hague.

Rodi is married to Jeroen Steenbergen and mother of Rosalie Julia.