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”. In 1963, Lance and Adams described negative myoclonus in patients with post-hypoxic myoclonus.

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. In patients presenting at the emergency room with movement disorders, 27.6% suffered from myoclonus, mostly provoked by a metabolic disturbance or drugs.

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. 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. Three forms of negative myoclonus have been described. 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. 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. 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.
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. Neuropathological studies however show broader involvement of other brain areas including the cerebellum, fronto-temporal cortex, hippocampus, and thalamus, among other areas. 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. 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.

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, somesthetic, or provoked by a verbal stimulus (reflex myoclonus). 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.
1.4.1.3 Electrophysiological testing
Video-polymyography in cortical myoclonus reveals short EMG bursts (usually 50-100 ms). 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).\textsuperscript{25,28,29} In case of myoclonic encephalopathy with a rapidly progressive dementia, a prion disease must be considered.\textsuperscript{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.\textsuperscript{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,\textsuperscript{30,32} and orthostatic myoclonus.\textsuperscript{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.\textsuperscript{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. 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. In rare cases hyperekplexia can have an acquired cause including brainstem encephalitis, or a lesion in the brainstem (e.g. Multiple Sclerosis, vascular lesion).

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. 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. Myoclonus-Dystonia is often accompanied by psychiatric co-morbidity including anxiety, panic attacks and obsessive-compulsive disorder.

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. 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.\textsuperscript{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.\textsuperscript{53} In most cases peripheral myoclonus is caused by damage to the peripheral nerve system (PNS), and the EMG shows varied burst duration.\textsuperscript{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\textsuperscript{54}, spinal root\textsuperscript{55}, the long thoracic nerve or after amputation ("jumping stump").\textsuperscript{53,56}

1.4.5 Functional myoclonic jerks
In approximately 10-20\% of functional movement disorders, patients suffer from functional (psychogenic) myoclonic jerks.\textsuperscript{57,58} In a study of 212 patients with myoclonus, 8.5\% were defined as functional.\textsuperscript{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.\textsuperscript{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 premovement 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.\textsuperscript{52,59}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Figure4.png}
\caption{Example of a Bereitschaftspotential (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.}
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### 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. 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. 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.

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

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<th>First choice of treatment</th>
<th>Alternative treatment</th>
<th>Other therapy</th>
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<td><strong>Cortical myoclonus</strong></td>
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<td>In general</td>
<td>Levetiracetam</td>
<td>Valproic acid, Clonazepam</td>
<td>Add on therapy with: Primidone, Phenobarbital</td>
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<td><strong>Myoclonus dystonia</strong></td>
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<td>Levodopa, L-5-HTTP*, Sodium oxybate</td>
<td>Deep brain stimulation</td>
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<td>Treatment of underlying syndrome: Rituximab, ACTH, iv immunoglobulin</td>
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<td>Carbamazepine, Tetrabenazine, Botulinum toxin</td>
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<td>Carbamazepine, Clonazepam</td>
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<td>Others</td>
<td>Botulinum toxin</td>
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* = 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. Treatment of functional jerks must be initiated soon after diagnosis, because a longer duration of the syndrome is related to poor outcome.
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. 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. 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 \textit{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 \textit{SGCE} mutation.

\textit{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.\textsuperscript{65} However, also organic movement disorders are frequently accompanied by psychopathology.\textsuperscript{46,66} Furthermore, quality of life seems to be equally impaired in functional as in organic movement disorders.\textsuperscript{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.

\textit{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.
1.8 References


Chapter 1


