Chapter 8  Discussion and concluding remarks
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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 \textit{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.² 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 \textit{SGCE} gene (DYT11) observed in a proportion of cases.\textsuperscript{8–10} Within our cohort (\textit{SGCE} mutation positive \textit{n}= 19, \textit{SGCE} mutation negative \textit{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 \textit{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 (\textit{n}=16) and organic myoclonus (\textit{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 (\textit{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\textsuperscript{11,12}, and 3) further exploration of pain in functional movement disorders, already identified as an important symptom in functional (fixed) dystonia, is needed.\textsuperscript{13}

\section*{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%). 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.\textsuperscript{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.\textsuperscript{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 relying 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.\textsuperscript{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. 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, 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 \( \textit{GOSR2} \) gene, which likely has a founder effect in Friesland, located in the north of the Netherlands. 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. 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.\textsuperscript{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.
8.7 References


