Clinical and functional studies in Myoclonus-Dystonia
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10 General Discussion
Discussion and summary

This chapter reviews the main findings of the clinical and pathophysiological studies on Myoclonus-Dystonia (M-D) described in the present thesis, places the results into a broader perspective of other performed research in this field, and gives suggestions for future research.

I. Introduction

Myoclonus-Dystonia (M-D) is a movement disorder characterized by myoclonic jerks and dystonic movements or postures, very often responsive to alcohol. The myoclonic jerks typical of M-D are brief lightning-like movements usually beginning and most affecting the neck, trunk and upper limbs. Approximately half of the M-D patients have focal or segmental dystonia usually presenting as cervical dystonia and/or writer’s cramp. Psychiatric symptoms are frequently associated to the motor symptoms. 1,2

Myoclonus-Dystonia is inherited in an autosomal dominant fashion with reduced penetrance and is caused by mutations in the $SGCE$ gene. In only one third of the investigated M-D patients, a mutation in the $SGCE$ gene has been detected suggesting genetic heterogeneity. 1,2 Reduced penetrance is explained by maternal imprinting of the $SGCE$ gene, implying that clinically affected individuals inherit the mutation from their father. 3

The pathophysiology of M-D is elusive. The lack of stimulus-sensitivity of the myoclonus, the absence of a giant somato-sensory evoked potentials (SSEP) and the combination with dystonia, known to result from basal ganglia dysfunction, supports the hypothesis that M-D is a disorder of the basal ganglia. 1

II. Clinical studies

During the phenotypical characterization of two Dutch M-D families (chapter 2–5) we recognized several unusual clinical features. This has led to the extension of the clinical spectrum of M-D and the modification of the original diagnostic criteria, i.e. epileptic seizures and EEG abnormalities are no longer exclusion criteria. Distal myoclonus in the arms appears to be rather frequent in contrast to the traditional description of mainly proximal symptoms, and age of onset is not always in the first or second decade. 1
II.1 Motor symptoms

Epilepsy

Epileptic seizures were observed in three out of five affected DYT11 mutation carriers (MC) from the Dutch M-D family described in chapter 2. The presence of seizures could not be explained by alcohol withdrawal or the use of epileptogenic medication as described by others. 4 We were the first to report the possible association of seizures with the M-D phenotype. 5 To date, another M-D family has been reported with at least two DYT11 mutation carriers with complex partial seizures. 6 However, due to the limited number of M-D families with epilepsy reported so far, we cannot exclude that the association of the M-D phenotype with epilepsy is a coincidence.

Distal myoclonus

The definition of M-D states that myoclonus is mainly affecting the neck, trunk and proximal upper limbs. 1 Characterization of the motor symptoms in the large Dutch M-D family in chapter 3 revealed that slight jerky movements of the fingers in six of the 20 DYT11 affected mutation carriers (MC) may be the only presentation of myoclonus in M-D. 7 One could argue that this finding is specific to the mutation found in this particular family. However, in six of the seven affected DYT11 mutation carriers (MC) identified at our centre with different SGCE mutations, distal upper limb myoclonus could be observed. 8 Moreover, in the literature, very often no distinction has been made between proximal and distal upper limb myoclonus in other DYT11 positive M-D families which may lead to an underestimation of the prevalence of this feature. 1

Late age of onset

Three of the 20 affected DYT11 mutation carriers (MC) from the Dutch M-D family described in chapter 3 had an age of onset in (late) adulthood: 43, 60 and 75 years. This implies that, although age of onset is usually before the age of 20 years, older age at onset does not rule out the possibility to find a SGCE mutation especially when family history is positive.

Possibly affected DYT11 mutation carriers

Fourteen of the 34 DYT11 mutation carriers (MC) of the Dutch M-D family described in chapter 3 inherited the mutation from their mother and were supposed to be asymptomatic DYT11 mutation carriers (MC) due to the mechanism of maternal imprinting. Remarkably, five DYT11 mutation carriers (MC) did not have complaints but showed subtle dystonia on neurologic examination. The detection of five ‘possibly affected’ mutation carriers (MC) inheriting the mutation from their mother is concordant with the reported 5-10% rate of maternally inherited SGCE mutations in literature 2,3,9,10 Escape from maternal
imprinting might explain the presence of motor symptoms in these individuals. However, the underlying mechanism for the loss of imprinting is unclear. Co-expression of the mutated and the wild-type allele was demonstrated by Müller et al. at the cDNA level in one affected DYT11 mutation carrier (MC) who inherited the mutation from her mother. However, the maternal allele was not expressed in peripheral blood leucocytes at the cDNA level in our patients and another patient reported in literature. Another possible explanation is a different level of imprinting in brain compared to peripheral blood leucocytes (PBL) (imprinting mosaicism) as has been previously suggested in mice. Future research focussing on the imprinting patterns of the SGCE gene in different tissues, including human brain tissue, may elucidate the escape of imprinting mechanism in DYT11 mutation carriers (MC) inheriting the mutation from their mother.

II.2 Psychiatric symptoms

In several M-D families the presence of psychiatric symptoms was noticed, already before the detection of the SGCE gene. Until now, only 3 studies, including ours (chapter 5), have systematically addressed the psychiatric comorbidity in DYT11 proven M-D families. The three studies do agree on the association of psychiatric symptoms to the motor symptoms, but the results with respect to the type of psychopathology are conflicting. OCD and alcohol dependence, but not depression nor anxiety were more prevalent in the affected DYT11 mutation carrier (MC) group from Hess and co-workers, whereas in our study depression and anxiety, including panic attacks, but no alcohol dependence nor OCD were more prevalent in the affected DYT11 mutation carrier (MC) group. The presence of depression and anxiety in our study correlated with the severity of motor symptoms which might suggest that these psychiatric symptoms are secondary to the motor symptoms and not part of the M-D phenotype. On the contrary, one can also argue that a more severe motor phenotype comes with a more severe psychiatric phenotype. Psychiatric comorbidity worsened after a dramatic improvement of the motor symptoms induced by bilateral GPi stimulation in three out of four DYT11 mutation carriers (chapter 9). When considering psychiatric symptoms being secondary to the motor symptoms, one would have expected at least an improvement of depressive and anxiety symptoms co-occurring with the dramatic improvement of myoclonus and dystonia. Psychiatric comorbidity is obvious in DYT11 mutation carriers (MC) but so far, it remains unclear whether psychiatric symptoms are part of the phenotypic spectrum of M-D or are secondary to the debilitating motor symptoms. Uniform standardized assessment of a larger number of symptomatic and asymptomatic DYT11 mutation carriers (MC) may give more conclusive insights.

II.3 Phenotype-genotype correlation

Mutations in the SGCE gene have been associated with familial M-D and to a lesser extent with sporadic M-D. However, a considerable amount of typical M-D patients do not carry mutations in the SGCE gene. Because mutational testing of the SGCE gene is
expensive and laborious, several studies, including the study described in chapter 4, have addressed the question whether distinct phenotypic features may predict the presence or absence of a **SGCE** mutation in M-D patients. \(^8,20-23\)

Seven of 31 patients with the M-D phenotype in our study carried a mutation in the **SGCE** gene. Study of phenotypic differences among the **SGCE** gene positive and negative M-D patients revealed that age of onset in the first two decades of life, onset with a combination of myoclonus and dystonia, positive family history and the presence of truncal myoclonus and/or axial dystonia were significantly associated with the presence of a **SGCE** mutation. Myoclonus of the upper part of the body and alcohol sensitivity seems of limited value in predicting the **SGCE** mutation carrier status.

Valente and coworkers found 6 **SGCE** mutations in a group of 58 patients of whom 29 had a M-D phenotype (21 M-D and 8 essential myoclonus). \(^23\) Five of the mutation positive patients had the M-D phenotype and one essential myoclonus. They concluded that young onset, predominant myoclonus of the upper body and alcohol sensitivity are helpful but not exclusive for the detection of **SGCE** positive M-D patients. However, statistical analysis has not been performed.

Tezenas du Montcel and coworkers studied 76 patients of whom 54 patients with the M-D phenotype (49 M-D and 5 essential myoclonus). Sixteen out of the 54 patients (11 M-D and 5 essential myoclonus) showed a mutation in the **SGCE** gene. \(^22\) In this study young onset, the presence of lower limb dystonia and alcohol sensitivity but not the pattern of myoclonus and dystonia predicted the presence of **SGCE** mutations.

The two described studies included also different types of myoclonic and dystonic syndromes to define the extent of the phenotypic spectrum of M-D: idiopathic generalized torsion dystonia, benign hereditary chorea and Ramsay-Hunt syndrome. No **SGCE** mutations were detected in those patients.

Based on the results of the genotype-phenotype correlation studies, we may conclude that the phenotype associated with mutations in the **SGCE** gene is rather narrow and we propose to confine the **SGCE** screening to patients with the “classic” M-D phenotype, i.e. myoclonus consisting of brief, lightning-like movements and not myoclonus which is restricted to a body part affected by dystonia, i.e. jerky movements superimposed to the dystonia. In contrast to what has been previously suggested, we advise to perform mutational screening in patients with the “classic” phenotype, also with late age of onset, especially when family history is positive.

The detection of new genes will probably elucidate the large number of **SGCE** negative ‘classic’ M-D patients.
III. Pathophysiological studies

Functional studies have been used to study the involvement of different brain structures in dystonia and myoclonus. Coherence analysis is a useful tool to gain insight into the oscillatory coupling between brain and muscle and between muscles and gives insight in the time domain, while functional magnetic resonance imaging (fMRI) is a technique to study differences in brain activation patterns between patients and healthy controls and gives insight in the spatial domain.

III.1 EEG-EMG and EMG-EMG coherence analysis

A cortical drive to muscles in the 15-30 Hz frequency band is observed in healthy controls during weak isometric contraction. This 'physiological' drive was absent in 20 studied DYT11 mutation carriers (MC) and suggests that the cortical drive to muscles in DYT11 mutation carriers (MC) is deranged. With EMG-EMG coherence analysis, we investigated the presence of a 'pathological' (probably basal ganglia driven) drive to the muscles of DYT11 mutation carriers (MC).

No significant intermuscular coherence could be detected in the group analysis of the 20 DYT11 mutation carriers (MC). However, when analysing the individual data, we found an abnormal low frequency (3-10 Hz) drive in DYT11 mutation carriers (MC) with pronounced mobile dystonia, i.e. dystonic movements superimposed on the dystonic posturing. A similar low frequency drive has been described in cervical dystonia and DYT1 positive dystonia patients. These findings suggest that the detection of the low frequency drive is not specifically related to a phenotypic subtype of DYT11 mutation carriers (MC) but more likely to reflect a pathological drive to muscles affected by (mobile) dystonia.

The technique of coherence analysis requires two stationary signals and is therefore not an appropriate neurophysiological technique to study the action induced brief myoclonic jerks in DYT11 mutation carriers (MC). This may explain that the detection of an abnormal low frequency drive was restricted to DYT11 mutation carriers (MC) with predominant (mobile) dystonia.

III.2 GPi LFP-EMG coherence analysis

Increased coherence in the 3 to 15 Hz frequency band between internal Globus Pallidus (GPi) local field potential (LFP) activity and dystonic muscles in two DYT11 mutation carriers who underwent deep brain stimulation was detected. Taking the results of the intermuscular coherence study into account, it is likely that the increased GPi synchrony is associated with muscles exhibiting (mobile) dystonia and not with muscles affected by myoclonus. This is supported by similar significant coherence (range 3-7 Hz) between GPi LFP activity and dystonic muscles in patients with idiopathic dystonia.
Functioning of the basal ganglia circuitry is characterized by synchronization of oscillations across different populations of neurons. Event related synchronization and desynchronization studies investigate the increase or decrease of this oscillatory brain activity in relation to different motor tasks. Desynchronization in the beta band, i.e. a decrease in the synchronized oscillatory activity of basal ganglia structures in the beta band, is thought to be a physiological mechanism that facilitates movement. Due to an increase of beta band synchrony in Parkinson’s disease in the resting state, the beta band desynchronization observed before movement cannot ‘break through’ and results in hypokinetic movements. The observation of synchronization of GPi neuronal activity in the 3-15 Hz frequency band before movement in the two studied DYT11 mutation carriers (MC) may be interpreted in the same perspective: abnormal muscle activity is generated due to the increase in low frequency GPi oscillatory synchrony.

It would be interesting to study temporal relationships between subcortical structures and muscles affected by myoclonus with a neurophysiological tool equivalent to the EEG back averaging technique. In this light, magneto-encephalography (MEG), which has a larger spatial resolution compared to EEG may be a good option.

III.3 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) may give insight in brain activity during (in) voluntary movements. We performed a motor task which induces involuntary movements in movement disorders in an on/off fashion (blockdesign) and correlated this with brain activity in 17 DYT11 mutation carriers (MC) and 11 controls. In addition, we performed the serial reaction time task, an implicit learning task known to result in activation of striatal structures during fMRI. We detected hyperactivity of the pre-motor (Brodmann Area 6) and motor cortex during the three motor tasks which may reflect hyperexcitability of the cortical motor planning areas. Remarkably, the hyperactivity was predominantly ipsi-and not contralateral suggesting ‘overflow’ of activity. Increased activity of basal ganglia structures could not be detected during the motor tasks, which is probably due to the choice of a non-complex motor task. Interestingly, we detected similar but less pronounced hyperactivity in all eight asymptomatic DYT11 mutation carriers (MC). The hyperactivity in asymptomatic DYT11 mutation carriers (MC) is suggesting that an escape of maternal imprinting may be not only expressed in the clinical presentation but may be restricted to subclinical functional changes in brain activity.

During the implicit learning task (SRT), hyperactivity in the dorsolateral prefrontal cortex (Brodmann Area 10) and the putamen was observed. The dorsolateral prefrontal cortex is associated with ‘higher order’ cognitive processing and points to explicit, effortful learning instead of implicit learning. However, when performing different tasks in patients with M-D, the myoclonic and dystonic movements are not recorded and therefore, it may be difficult to make a
distinction between normal, compensatory and pathological brain activity. Recently, simultaneously recording of EMG activity during fMRI has become available which allows to measure the involuntary movement itself and to directly correlate this abnormal movement with brain activity. The comparison of this new fMRI technique in DYT11 mutation carriers (MC) with the fMRI study we performed will confirm our findings or will lead to the conclusion that the observed hyperactivity in different brain regions is not related to myoclonus nor dystonia but only reflects differences in task performance between DYT11 mutation carriers (MC) and healthy controls.

IV. Therapy: Deep brain stimulation in medication-refractory M-D patients

The natural course of M-D is usually benign. However, some patients are seriously impaired by the symptoms of myoclonus and dystonia leading to restrictions in the activities of daily living. Since medical treatment, including botulinum toxin, has proven to be very often ineffective, those M-D patients may benefit from deep brain stimulation. Good improvement of the motor symptoms has been reported after stimulation of the GPi and the thalamus, but the effect on the psychiatric comorbidity has not been addressed. We studied the effect of bilateral GPi stimulation in four DYT11 mutation carriers with medication-refractory motor symptoms and associated psychopathology. (chapter 9) Despite a dramatic improvement of the motor symptoms, patients were not able to take part in normal social life due to psychiatric deterioration. This stresses the need for elaborate psychiatric support pre-and postoperatively.

V. Suggestions for future research

V.1 Genotypic and phenotypic heterogeneity of SGCE mutation carriers
Mutations in the SGCE gene are detected in only a minority (30%) of ‘typical’ M-D cases. A challenge for future studies lies in the identification of ‘prognostic factors’ that will increase the sensitivity of detecting SGCE mutations. The detection of specific patterns of ‘brain dysfunction’ in functional studies could lead to the fine tuning of the presently available clinical prognostic factors. The identification of new genes related to the M-D phenotype is another challenge. This is of importance to improve genetic counseling.

V.2 Functional studies
The functional studies we performed in the present thesis, have given more insight into the pathophysiology of myoclonus-dystonia (M-D). However, we came across several
methodological limitations. Future research should focus on the development of an appropriate technique to study the myoclonus in DYT11 mutation carriers (MC) which in turn may lead to the availability of a human model to study myoclonus of subcortical origin.

In functional MRI studies, simultaneously recording of EMG activity has become recently available which allows to measure the involuntary movement itself (myoclonus and dystonia) and to directly correlate this abnormal movement with brain activity. Magneto-encephalography (MEG) has a larger spatial resolution compared to EEG. However, functional changes in subcortical structures can only be estimated by studying the cortical activities that might be influenced by the functional abnormalities of these subcortical structures, i.e. basal ganglia structures. A challenge for future research is the integration of the high spatial resolution fMRI and the high temporal resolution MEG with the goal to come to a multimodal neuroimaging tool with the capacity to study functional changes in M-D and other movement disorders.

V.3 Deep brain stimulation in M-D

Psychiatric deterioration after bilateral (posteroventrolateral) GPi stimulation in medication-refractory M-D patients was observed in the present thesis. Based on the positive results of more anterior (than ‘classic’) GPi stimulation and thalamic stimulation in other movement disorders with psychiatric comorbidity, it is of interest to study these other basal ganglia targets and to reconsider the (posteroventrolateral) GPi being the target of first choice.
References


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