Clinical and functional studies in Myoclonus-Dystonia

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Summary
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Myoclonus-Dystonia (M-D) is an autosomal dominant movement disorder characterized by myoclonic jerks and dystonic movements or postures. Genetic analysis revealed the SGCE gene (DYT11) as the major gene for M-D. Identification of SGCE mutations in Dutch familial and sporadic M-D patients enabled us to study the phenotypic heterogeneity in M-D. Furthermore, we performed different types of functional studies to unravel the pathophysiology of this movement disorder. Because dystonia is a heterogenous disease with varying etiology, previous functional studies in dystonia have been hampered by heterogenous groups of dystonic patients. DYT11 positive M-D patients are a homogenous patient group and this has given us the opportunity to study dystonia in a well-defined ‘dystonia-plus’ syndrome. The myoclonus in M-D is considered to be of subcortical origin and may serve as a human model for subcortical myoclonus in future studies, especially since other types of subcortical myoclonus are rare.

In chapter 2 and 3 we describe the clinical characteristics of two Dutch DYT11 positive M-D families. This has led to the extension of the phenotypic spectrum of M-D. The presence of epileptic seizures in three out of five affected DYT11 mutation carriers of the Dutch family described in chapter 2 has changed the original diagnostic criteria, i.e. epileptic seizures and EEG abnormalities are no longer exclusion criteria for the clinical diagnosis of M-D.

All 20 affected DYT11 mutation carriers of the large Dutch family studied in chapter 3 displayed distal myoclonus in contrast to the ‘classical’ proximal upper limb myoclonus and late age of onset was observed in three affected DYT11 mutation carriers. This has strengthened the need to pay attention to the presence of subtle myoclonic jerks of the fingers in patients presenting with myoclonus and dystonia and may subsequently lead to the detection of a larger amount of DYT11 mutation carriers. Moreover, patients presenting with the “classic” M-D phenotype at older age should be tested for the DYT11 mutation especially when family history is positive.

The detection of five ‘possibly’ affected DYT11 MC in the large Dutch M-D family implies an escape of maternal imprinting and is concordant with the reported 5-10% rate of maternally inherited SGCE mutations in literature.

However, the underlying mechanism for the loss of imprinting is unclear. Co-expression of the mutated and the wild-type allele may be a possible explanation. A different level of imprinting in brain compared to peripheral blood leucocytes (PBL) (imprinting mosaicism) as has been previously suggested in mice should also be considered. Future research should focus on the imprinting patterns of the SGCE gene in different tissues, including human brain tissue.
Mutations in the \textit{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 \textit{SGCE} gene. In \textbf{chapter 4}, we addressed the question whether distinct phenotypic features may predict the presence or absence of a \textit{SGCE} mutation. It is of particular interest as mutational testing is expensive and laborious.

Study of the phenotypic differences among the 7 \textit{SGCE} gene positive and 24 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 \textit{SGCE} mutation. Myoclonus of the upper part of the body and alcohol sensitivity seems of limited value in predicting the \textit{SGCE} mutation carrier status. Taking the results of our study combined with two additional studies performed in this field, we conclude that the phenotypic spectrum of M-D is more narrow than previously thought and consists of myoclonus characterized by brief, lightning-like movements and not myoclonus which is restricted to a body part affected by dystonia, i.e. jerky movements superimposed on the dystonia.

In \textbf{chapter 5}, we studied whether psychiatric symptoms are more prevalent in DYT11 mutation carriers of the large Dutch M-D family described in chapter 3. Depression and anxiety but not OCD were more prevalent among the 26 DYT11 mutation carriers and might be considered part of the phenotypic spectrum of M-D. However, the presence of depression and anxiety correlated with the severity of motor symptoms in M-D patients suggesting that psychiatric symptoms are secondary to the chronic debilitating motor symptoms and not part of the M-D phenotype. Because of the limited sample size and the small number of other studies addressing this clinically important issue, definite conclusions cannot be drawn as to yet. Future studies should include larger numbers of DYT11 positive M-D patients and assess them with a uniform set of psychiatric tests.

\textbf{Chapter 6, 7 and 8} provides the results of the functional studies we performed in DYT11 mutation carriers in order to gain more insight into the pathophysiology of this hyperkinetic movement disorder.

Coherence analysis of EEG-EMG and EMG-EMG is a technique to study the oscillatory coupling between brain activity and muscles in the time domain. (chapter 6). Deep brain stimulation of the basal ganglia is an effective therapy for different types of medication-refractory movement disorders. This neurosurgical therapy enables us to study the oscillatory coupling between basal ganglia activity and muscles. (chapter 7) Functional magnetic resonance (fMRI) is a technique to measure brain activity in the spatial domain. Typically, brain activity in relation to a motor or cognitive task is compared between patients and healthy controls. (chapter 8)
In chapter 6, we observed that the physiological 15-30 Hz cortical drive to isometrically contracting muscles in the 20 studied DYT11 mutation carriers (MC) is absent. Intermuscular coherence analysis showed an abnormal low frequency drive in the 3 to 10(15) Hz frequency band in the DYT11 mutation carriers. This abnormal drive was only observed between the affected muscles in the four DYT11 mutation carriers with pronounced mobile dystonia, i.e. dystonic movements superimposed on the dystonic posturing. It was not observed in DYT11 mutation carriers with predominant myoclonus. 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. On the other hand, we may conclude that coherence analysis, which requires two stationary signals, is not the appropriate technique to study the action induced brief myoclonic jerks in DYT11 mutation carriers.

In Chapter 7 similar significant coherence (range 3-7 Hz) between GPi LFP activity and dystonic muscles was detected in two DYT11 mutation carriers who underwent deep brain stimulation because of medication-refractory motor symptoms. We also observed an increase of synchronization in the 3 to 15 Hz frequency band before movement. Similar to the increase of beta band (15-30 Hz) synchrony in the subthalamic nucleus in Parkinson’s disease, which is believed to result in hypokinetic movements, we hypothesize that the increase in low frequency GPi oscillatory synchrony generates abnormal, i.e. dystonic muscle activity.

Chapter 8 reports the results of a functional magnetic resonance imaging study that investigated the brain activity in 17 DYT11 mutation carriers compared to 11 controls. We showed hyperactivity of the ipsilateral more than the contralateral pre-motor and motor cortex during the performance of three motor tasks in the affected DYT11 mutation carriers which may reflect hyperactivity of the cortical motor planning areas and “overflow” of activity. During the performance of the serial reaction time task, an implicit learning task, hyperactivity of the dorsolateral prefrontal cortex was observed which points to effortful learning instead of implicit learning. However, it remains unclear whether the observed hyperactivity in different brain regions reflects normal, compensatory or pathological brain activity. Further studies using EMG in fMRI are required to study hyperkinetic movements in M-D.

In chapter 9 the results of bilateral internal globus pallidus stimulation are reported. Four patients with medication-refractory M-D symptoms improved dramatically with respect to the motor symptoms, but unfortunately psychiatric symptoms did not improve or even deteriorated. These results stress the importance to take the psychiatric co-morbidity into
account when considering DYT11 mutation carriers suitable candidates for deep brain stimulation.

In chapter 10 the main findings of this thesis are discussed and related to recent important literature in this field. Suggestions for future research are also provided. We conclude that the clinical studies performed in the two Dutch M-D families have led to the extension of the phenotypic spectrum of DYT11 mutation carriers. Furthermore, the results of the functional studies have given more insight into the pathophysiology of (myoclonus)-dystonia. However, we are convinced that future research needs to focus on more appropriate techniques to study the subcortical myoclonus in M-D.