Clinical and functional studies in Myoclonus-Dystonia
Foncke, E.M.J.

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1 General Introduction
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Background

Myoclonus-Dystonia (M-D) is a movement disorder characterized by myoclonic jerks and dystonic movements or postures. Abnormal movements most often affect the neck, trunk and the upper limbs. Alcohol alleviates the symptoms in most cases. Age of onset is usually in childhood or adolescence. Psychiatric symptoms are often associated to the motor symptoms. 1,2

M-D has already been described by Friedrich in 1881 as ‘paramyoclonus multiplex’ 3 but since then a large variety of terms has been used to describe the movement disorder: ‘hereditary essential myoclonus’ 4,5, ‘essential familial myoclonus’ 6, ‘familial essential myoclonus’ 7, ‘dominantly inherited myoclonic dystonia with dramatic response to alcohol’ 8, hereditary myoclonic dystonia 9, myoclonus-dystonia 10 and inherited myoclonus-dystonia syndrome 11. The hyphenated combination of the two terms ‘myoclonus’ and ‘dystonia’ with the specific order of presentation is now considered to be the appropriate term for M-D. M-D may occur sporadically or may be inherited autosomal dominantly with reduced penetrance. 2 Although M-D is a predominantly myoclonic syndrome associated with often mild dystonia, M-D is classified as DYT11 among the hereditary forms of dystonia since the detection of the ε-sarcoglycan (SGCE) gene in several M-D families. 2

Phenotypical characteristics

Phenotypic heterogeneity within and between families has been frequently observed. Differences in the affected body sites, the age of onset, the predominance of myoclonus or dystonia are often reported. 1 Unusual features have been described in selected families, including several forms of tremor 7,13 and mental retardation 14. The mechanism responsible for this heterogeneity remains to be elucidated. Psychiatric symptoms such as depression, anxiety, panic attacks, obsessive compulsive behavior and alcohol dependence are often accompanying the symptoms of myoclonus and dystonia. 1,15-17 It is unclear whether these psychiatric symptoms are co-segregating with the M-D genotype.

Genotypical characteristics

The SGCE gene on chromosome 7q

Linkage to chromosome 7q was observed in several M-D families in the late nineties. 18 In 2001, the SGCE gene encoding the epsilon sarcoglycan protein was identified on chromosome 7q. 2 Subsequently, SGCE gene mutations have been identified in many individuals with familial M-D and occasionally in sporadic M-D cases. 1 However, in only one third of the total number of genetically investigated M-D, a SGCE mutation can be demonstrated. This suggests genetic heterogeneity in M-D. 19 Mutations in two other genes have been associated with M-D, i.e. a missense mutation in the dopamine receptor 2 gene in a single family 20 and an 18-bp deletion in the DYT1 gene 21, usually associated with
early onset primary torsion dystonia, in another single family. In both families, however, an additional mutation in the \textit{SGCE} gene was subsequently identified.\textsuperscript{22} A large Canadian M-D family shows linkage to chromosome 18p (DYT15), but the contribution of this locus to the genetic heterogeneity of M-D remains unclear until the gene is identified.\textsuperscript{23} Recently, exonic deletions, not detected with direct sequence analysis, have been identified in several M-D families, indicating that \textit{SGCE} mutations may account for a larger amount of the genetic cases of M-D than was previously thought.\textsuperscript{24-26}

\textit{Reduced penetrance due to maternal imprinting}  

The reduced penetrance in DYT11 positive M-D patients is due to the mechanism of maternal imprinting.\textsuperscript{27,28} This implies that when inheriting the mutation from your mother the mutated maternal allele is silenced and the wild-type paternal allele is expressed leading to clinically unaffected mutation carriers (MC). Silencing of the mutated maternal allele is probably due to differential methylation of CpG nucleotides which have been demonstrated in the \textit{SGCE} gene.\textsuperscript{27} In the M-D families described up to date, about 90\% of the affected family members inherited the mutation from their father whereas unaffected family members inherited the mutation from their mother.\textsuperscript{1} Apparently, in a small proportion of family members inheriting the mutation from their mother an escape from maternal imprinting is responsible for the presence of symptoms. The underlying mechanism for the loss of imprinting is unclear.

\textit{Function of the SGCE protein}  

\textit{SGCE} is a member of the sarcoglycan family, transmembrane proteins that are part of the dystrophin-associated glycoprotein complex.\textsuperscript{29} This complex links the cytoskeleton to the extracellular matrix in skeletal and cardiac muscle. \(\alpha\)-, \(\beta\)-, \(\gamma\)- and \(\delta\)-sarcoglycan are only expressed in muscles and mutations in \(\alpha\)-, \(\beta\)-, \(\gamma\)- and \(\delta\)-sarcoglycan cause different forms of autosomal recessive limb girdle muscular dystrophies. However, \(\varepsilon\)-sarcoglycan is widely expressed in the membrane of different tissues including the brain. \textit{SGCE} is found in neurons of the cerebral cortex, basal ganglia, cerebellum, hippocampus and the olfactory bulb but the molecular function of the protein in neurons is still elusive.\textsuperscript{2,29}

Mutations in the \textit{SGCE} gene are thought to result in loss of function of the \textit{SGCE} protein. This loss of function may be either due to the mechanism of nonsense mediated decay which is a mRNA surveillance mechanism that detects premature stopcodons on mutant mRNA and prevents expression of a truncated protein. Lack of expression of the \textit{SGCE} protein is then believed to be the disease causing mechanism.\textsuperscript{1} Recently, torsin A, mutated in DYT1 dystonia, has been implicated in promoting degradation of intracellular mutant \textit{SGCE} by the proteasome, suggesting a different disease causing mechanism.\textsuperscript{30}
Pathophysiology
To date, it is unclear how changes in SGCE protein function cause the M-D phenotype. The myoclonus in M-D is considered to be from subcortical origin due to the lack of stimulus-sensitivity of the myoclonus and the absence of giant somato-sensory evoked potentials. It has been shown that basal ganglia (subcortical) dysfunction leading to disorganized cortical sensory-motor integration is responsible for different types of dystonia. M-D patients with a mutation in the SGCE gene form a very homogenous group of patients with clinical symptoms of both myoclonus and dystonia and may be used as a human model to study the pathophysiology of a broader spectrum of myoclonic and dystonic disorders.

Therapy
Pharmacological therapy such as benzodiazepines, antiepileptic drugs and anticholinergics is often ineffective. Alcohol often induces a dramatic relief of the symptoms of myoclonus and dystonia but due to the risk of addiction to alcohol, this appears an unacceptable “treatment” option. Trihexiphenydyl may improve the dystonia whereas clonazepam is sometimes effective to treat the myoclonus in M-D. Motor symptoms in some patients are severe and may lead to considerable disability. In selected patients deep brain stimulation of the internal globus pallidus or the ventral intermediate thalamic nucleus has shown to substantially improve the motor symptoms. The effect of deep brain stimulation on the frequently associated psychiatric symptoms is unknown.

Aims and outline of this thesis
The aims of this thesis were three-fold:
To study the phenotypic spectrum (motor and psychiatric symptoms) and phenotype-genotype correlation in M-D.
To investigate the pathophysiological mechanisms of DYT11 positive M-D patients with functional studies.
To study the effect of deep brain stimulation on the motor and psychiatric symptoms in medication-refractory DYT11 positive M-D patients.

Outline of this thesis:
Two Dutch M-D pedigrees with unusual clinical characteristics expanding the phenotypic spectrum of M-D are described in chapter 2 and 3. In chapter 4, we studied thirty-one unrelated patients with a typical M-D phenotype to identify clinical factors differentiating M-D patients with and without a mutation in the SGCE gene. In chapter 5, the results of a psychopathological study of the M-D family described in chapter 3 are presented.
To investigate the pathophysiological mechanism of M-D three functional studies were performed in DYT11 MC. In chapter 6 and 7, we describe the results of coherence analysis of simultaneously recorded electroencephalogram (EEG) and electromyogram (EMG), EMG-EMG coherence analysis and coherence analysis of local field potential (LFP) activity of the internal globus pallidus (GPI) and EMG activity. The results of a functional magnetic resonance imaging (fMRI) study are presented in chapter 8. Chapter 9 describes the effect of bilateral internal globus pallidus stimulation on the motor and psychiatric symptoms in four medication-refractory DYT11 mutation carriers. The results of the different studies are discussed in chapter 10 and suggestions for future research are proposed.
References


