Myoclonus-dystonia: classification, phenomenology, pathogenesis, and treatment

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Purpose of review
The present study will highlight recent advances in the field of myoclonus-dystonia with a focus on clinical aspects, pathogenesis, and treatment. We will also discuss genetics, classification issues, and diagnostic criteria.

Recent findings
Myoclonus-dystonia is a clinical syndrome corresponding to the phenotype linked to *SGCE*, the main causative gene. Childhood-onset myoclonus that predominates over dystonia with prominent upper body involvement, an absence of truncal dystonia, associated anxiety or compulsivity, and a positive family history are helpful diagnostic clues. Recent studies demonstrated that zonisamide is an interesting therapeutic option in myoclonus-dystonia, and that bilateral pallidal stimulation has major and lasting therapeutic effects. Accumulating evidence suggests that an alteration in cerebello-thalamic pathway function may play a prominent role and that this is possibly related to a GABAergic deficit reflecting Purkinje cell dysfunction. Impaired striatal plasticity and disturbed serotonin homeostasis may also be implicated. Newly available cellular and rodent models may further assist in investigating the pathogenesis of this disorder.

Summary
Comprehensive analysis of the phenotype and precise classification are important in patients with myoclonus and dystonia to identify homogeneous groups of patients. This is critical to guide tailored therapeutic strategies and promote effective research.

Keywords
cerebellum, dystonia, epsilon-sarcoglycan, imaging, myoclonus, physiology

INTRODUCTION

Myoclonus-dystonia is a clinical syndrome characterized by a particular combination of myoclonus and dystonia. *SGCE* is the main causative gene. Regarding the clinical phenotype, neurophysiological characteristics, and pathogenesis, patients with myoclonus-dystonia because of SGCE deficiency are paradigmatic of this syndrome. We will focus on this genetically homogeneous group of patients to highlight the recent refinements in the clinical spectrum, advances in treatment, and novel insights into the complex pathogenesis provided by basic research. We will also more broadly discuss other genes possibly involved in myoclonus-dystonia along with classification issues, and propose optimized diagnostic criteria based on the recent findings.

CLINICAL SPECTRUM AND COURSE OF THE DISEASE

A positive family history is common, and when present, dominant paternal transmission is the rule. The disorder occurs before age 10 in the vast majority of patients whereas onset after age 20 is very unusual [1,2▪,3,4]. In most cases, the presenting symptom is upper body myoclonus, which may be isolated or associated with dystonia. Isolated dystonia is the initial manifestation in the remaining 15–30% of cases [1,2▪,3].

Myoclonus is usually the main and most disabling feature. The typical phenotype is one of 'lightning-like' myoclonic jerks, which may be

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Curr Opin Neurol 2018, 31:484–490
DOI:10.1097/WCO.0000000000000577

KEY POINTS

- Myoclonus-dystonia is a unique syndrome typically characterized by childhood-onset subcortical myoclonus, isolated or predominating over dystonia, that mostly involves the upper body.
- Psychiatric manifestations often accompany the motor manifestations including anxiety-related disorders and obsessive compulsive disorder.
- Alcohol responsiveness of the motor symptoms and the risk of alcoholism are striking features of myoclonus-dystonia.
- Myoclonus-dystonia reflects a primary dysfunction of the cerebello-thalamic pathways.
- Pallidal deep brain stimulation is very effective for both myoclonus and dystonia and should be proposed in severe forms of myoclonus-dystonia.

either isolated or associated with mild to moderate dystonia. Myoclonus can virtually affect all body regions but generally predominates in the upper limbs and neck. It is often present but mild at rest, dramatically aggravated by action (postural and kinetic myoclonus), and is not stimulus-sensitive. Myoclonus usually predominates in the proximal segment of the limbs, although predominantly distal involvement can occasionally be observed. In contrast to other forms of action myoclonus, here it more often manifests as proximal limb or axial jerks with less direct involvement of the moving body part (e.g. the hand while writing). Patients can occasionally have speech-activated myoclonus that may mimic stuttering [5]. Importantly, myoclonus can be recorded outside of a dystonic burst and has specific neurophysiological characteristics which indicate a subcortical origin: mean duration of 100 ms, absence of giant somatosensory evoked potentials, no cortical correlate preceding the myoclonus on jerk-locked back-averaging, and no abnormal long-loop reflexes [1,6].

When present, dystonia is mild to moderate, and usually spares the face, the larynx, and trunk [2▪]. Cervical dystonia and writer's cramp are the most common dystonic manifestations. Lower limb dystonia interfering with walking and/or running is sometimes present and can be observed early in the disease course. It is noteworthy that patients with early-onset disease are more likely to develop lower limb dystonia [3].

Strikingly, most patients have a marked improvement in motor symptoms following alcohol ingestion with rebound worsening on alcohol withdrawal [7▪▪]. There is a risk of alcoholism in patients with myoclonus-dystonia, which may in part be because of self-treatment of motor symptoms but also is because of an underlying genetic predisposition [8,9▪▪]. Other psychiatric disorders, namely anxiety-related disorders (generalized anxiety disorders, panic disorder, social phobia, specific phobia) and obsessive compulsive disorder (compulsivity being the predominant component), are part of the myoclonus-dystonia phenotype [8,9▪▪]. Although it has not been definitely established, these psychiatric disorders more likely reflect an alteration of the *SGCE*-related brain function outside of the motor circuits rather than a pure secondary reaction to the motor disability.

Severity and the rate of progression are largely unpredictable, ranging from severe motor disability in adolescence to mild, nonprogressive symptoms lasting decades. Motor manifestations may significantly impair health-related quality of life by restricting daily life activities, increasing perceived stigmatization, and undermining self-esteem, the latter problems being further accentuated by the nonmotor behavioral manifestations. The clinical phenotype may evolve overtime in a given individual, particularly in childhood or adolescence, likely because of an interaction between the pathogenic mechanisms of the disease and brain maturation. In a proportion of affected children, limb dystonia can spontaneously improve and even completely remit before adulthood with concomitant worsening of myoclonus [1]. The motor manifestations usually remain fairly stable during adulthood and are compatible with an active life in most patients. In some cases, however, the disease may be progressive even during adulthood. It can then spread to previously unaffected body regions and/or worsen in severity in already affected body parts. In addition, psychological or physical stress can lead to a transient aggravation of the motor manifestations, as observed in most movement disorders.

PATHOGENESIS

Dysfunction of the cerebello-thalamic pathways is critical in the pathogenesis of myoclonus-dystonia. Neurophysiological studies have demonstrated abnormal saccade adaptation [10] and abnormal eye blink conditioning, which are mediated by olivopontocerebellar circuits [11]. Dysfunctional cerebellar-dependent associative motor learning is improved by alcohol administration, which transiently enhances GABAergic transmission [7▪▪], suggesting an underlying GABAergic deficit reflecting Purkinje cell dysfunction. Neuroimaging studies point to abnormalities in the parasagittal cerebellum, the posterior thalamus and inferior pons with

functional alteration / increased metabolic activity on [(18)F]-fluorodeoxyglucose PET scan [12] and structural abnormalities of the white matter in the upper brainstem on brain MRI [13].

In addition to a dysfunctional cerebellar network, basal ganglia and cortical pathogenic mechanisms are also implicated. Micro-recording studies performed at the time of deep brain stimulation (DBS) surgery have shown that patients with myoclonus-dystonia have abnormal neuronal activity in the internal globus pallidus (GPi) with faster and shorter bursts, and shorter pauses in comparison with what is observed in pure idiopathic or hereditary dystonia [14]. Increased coherence was observed between local field potentials of the GPi and activity of the affected muscles [15]. An impaired striatal plasticity (altered long-term depression of the cortico-striatal synapses) has been found in a genetic mouse model of SGCE deficiency, despite the absence of an obvious motor phenotype [16▪]. An adenosine A2 receptor ($A_{2A}R$) antagonist restored normal plasticity in this model, thereby opening new therapeutic avenues. Patients with myoclonus-dystonia have an increased propensity to develop cortical plasticity as observed in other dystonic disorders [11]. Intriguingly, active motor threshold is augmented, reflecting lower membrane excitability of the cortical neurons [11]. This differentiates myoclonus-dystonia from other dystonias [11]. Finally, the cortical activation process associated with sensorimotor integration may be altered [17] and the normal cortical drive to muscles in the beta band during sustained contraction may be lost in patients with myoclonus-dystonia [18].

Disruption of serotonin and dopamine homeostasis may also play a role in the pathogenesis. A low level of the serotonin metabolites in the cerebrospinal fluid was found in patients with myoclonus-dystonia. As blood serotonin levels were normal, this abnormality is likely to pertain to the central nervous system [19]. Increased endogenous dopamine at striatal level with reduced dopamineD2 receptor expression in *SGCE* knock out mice [20,21] or reduced dopamine D2 receptor availability in patients with myoclonus-dystonia has also been described [22].

Within the emergent conceptual model of dystonia [23▪▪] which involves interactions of the basal ganglia-cortical networks and the cerebello-thamo-cortical network, myoclonus-dystonia stands apart from other dystonias, as a unique entity. It is a paradigm of prominent dysfunction of the cerebellar 'node' with few 'additional hits'.

Details of the main experimental findings on pathogenesis are shown in Table 1 [7▪▪,10–15,16▪, 17–22,24▪]

TREATMENT

There is no cause-specific treatment for myoclonus-dystonia. Symptomatic oral medications usually have an incomplete and/or transient effect and their use is often restricted by poor tolerability. A recent controlled study provided class 1 evidence that zonisamide improves myoclonus and its associated disability [25▪]. Where approved and available, this treatment may thus be the first line option early in the disease course, at a later stage in mild to moderate forms, or for patients with severe forms that are not eligible for DBS. Other drugs that should be considered include benzodiazepines and anticholinergics. These drugs can also be used in combination. Many other drugs have been proposed with anecdotal reports of positive effects including various antiepileptics, dopaminergic and serotonin agents, zolpidem, sodium oxybate, amantadine, and more recently tetrabenazine [26]. The balance between potential benefits and risks of trying these latter drugs remain to be determined. Pallidal DBS is well tolerated and effective, and should be considered in patients with severe forms of myoclonus-dystonia. Although not yet formally evaluated, its benefits seem to be at least equivalent to those seen in patients with other primary dystonias, with an improvement usually exceeding 60% [27]. Interestingly, this treatment is effective on both the myoclonus and dystonia with a sustained benefit observed over years [28]. The behavioral features variably respond to GPi DBS and, in some, these remain the major source of disability despite motor improvement. Other possible treatments that might also be helpful in managing the disease and its associated burden include botulinum toxin injection for focal dystonic manifestations (particularly cervical dystonia), physical therapy, and psychotherapy.

GENETICS, NOSOLOGICAL ISSUES, AND REAPPRAISAL OF THE DIAGNOSTIC CRITERIA

SGCE is the sole gene that is unequivocally linked to myoclonus-dystonia syndrome but mutation or intragenic deletion of this gene is only found in about half of all patients with the typical phenotype, reflecting genetic heterogeneity [29]. SGCE is a ubiquitous membrane protein that is part of the dystrophin-associated glycoprotein complex in brain [30] and is widely expressed in central nervous system neurons, especially in the cerebellum [24▪]. The exact function of SGCE within the brain is largely unknown. A promising model of induced pluripotent stem cell derived neurons, which recapitulates most of the molecular aspects of the disease [31▪▪] and a new mouse model with suppression of major

Table 1. Pathogenesis: main abnormalities in mouse models and patients with myoclonus-dystonia

Mice models	**Striatal plasticity deficit (synaptic level)** **Abnormal striatal dopaminergic function** **Region-specific abnormalities in the cerebellum**	**Phenotype**
Scge$^{+/-}$ mice (deletion of exon 5 in *Sgce*) Maltese *et al.*, 2017	Physiology (cortico-striatal slices) **Molecular characteristics of the mice** Marked decrease in SGCE expression in paternal heterozygote due to nonsense mediated mRNA decay **Striatal plasticity deficit** impaired striatal plasticity with altered LTD Adenosine A2 receptor antagonist restore normal plasticity	No mention of a particular motor phenotype
Sgce $^{m+/pGt}$ mice Disrupted *Sgce* terminal exons (3′ to exon 9) Xiao *et al.*, 2017	Molecular biology / biochemistry / behavioral experiments **Molecular characteristics of the mice** Reduced level of brain-specific Sgce (-60–70% of long isoforms) in homozygotes and paternal heterozygotes Expression of short isoforms was preserved and may compensate for deficiency of major and brain-specific isoforms **Region specific expression** The major and brain-specific isoforms are required for normal motor and cognitive functioning in mice Sgce enriched in the cerebellum In the cerebellum, dysregulated genes associated with SGCE deficiency were involved in cell cycle and development	Reduced body weight, altered gait dynamics, and reduced open-field activity, anxiety-like behavior
Sgce$^{+/KO}$ mice (deletion of exon 4 in *Sgce*) Yokoi *et al.*, 2006; Zhang *et al.*, 2012	Molecular biology / biochemistry / behavioral experiments **Molecular characteristics of the mice** Absence of SGCE expression in paternal heterozygote due to nonsense mediated mRNA decay **Abnormal striatal dopaminergic function in Sgce KO mice** Increased levels of dopamine and its metabolites in the striatum Decreased of the striatal D2 receptor Increase of dopamine release after amphetamine injection	Myoclonus, various mild motor impairments, anxiety- and depression-like behaviors
Clinical research in patients with myoclonus-dystonia	**Dysfunction of the cerebello-thalamic pathways** **Abnormal neuronal activity in the pallidum** **Altered cortical properties** **Abnormal monoamine metabolism**	**Experimental samples**
Beukers *et al.*, 2009	Neuroimaging (IBZM-SPECT) **Reduced dopamine D2 receptor availability in patients with myoclonus-dystonia**	11 patients with myoclonus-dystonia and 4 asymptomatic *SGCE* mutation carriers/ 15 controls
Beukers *et al.*, 2010	Neuroimaging (fMRI) **Abnormal activation pattern in the networks involved in sensorimotor integration during a motor task** (increased bold signal in the contralateral inferior parietal cortical areas, ipsilateral premotor and primary somatosensory cortex, and ipsilateral cerebellum)	13 patients with myoclonus-dystonia / 11 controls
Carbon *et al.*, 2013	Neuroimaging (measurement of brain metabolism using [(18)F]-fluorodeoxyglucose PET) **Genotype-specific metabolic abnormalities: increase brain metabolism in the inferior pons and posterior thalamus**, reduction in ventromedial prefrontal cortex **Phenotype-specific metabolic abnormalities: increase brain metabolism in the cerebellum** (parasagittal lobule 5) Shared abnormalities in myoclonus-dystonia and other forms of dystonia: Increased metabolic activity: superior parietal lobule (cortex) Reduced metabolic activity: ventromedial prefrontal cortex	6 patients with myoclonus-dystonia and 6 asymptomatic *SGCE* mutation carriers / 24 controls
Van der Meer *et al.*, 2012	Neuroimaging (voxel-based morphometry and diffusion tensor imaging) **Altered white matter in the cerebello-thalamic pathways**	16 patients with myoclonus-dystonia / 18 controls
	Neurophysiology **Dysfunction of the cerebello-thalamic pathways**	
Hubsch *et al.*, 2011	Abnormal saccadic adaptation (oculomotor paradigm involving the cerebellum)	14 patients with myoclonus-dystonia / 14 controls
Weissbach *et al.*, 2017	Defective cerebellar-dependent associative learning (conditioned eyeblink responses), restored by alcohol intake	17 patients with myoclonus-dystonia / 21 controls
Popa *et al.*, 2014	Failure of cerebellar-dependent extinction of a conditioned response (conditioned eyeblink responses) **Altered striato-pallido-thalamo-cortical circuits with abnormal neuronal activity in the pallidum**	12 patients with myoclonus-dystonia / 12 controls
Foncke *et al.*, 2007	Increased coherence in the 3–15 Hz frequency band between the local field potential of the internal pallidum and affected muscles	2 patients with myoclonus-dystonia
Welter *et al.*, 2015	Micro recording studies of the internal pallidum: higher burst frequency, lower mean burst, and pause durations in myoclonus-dystonia compared with isolated dystonia **Altered cortical properties**	6 myoclonus-dystonia / 6 idiopathic or hereditary dystonia
Popa *et al.*, 2014	Enhanced motor threshold reflecting lower membrane excitability of the corticocortical axons Abnormal plasticity of the motor cortex	12 patients with myoclonus-dystonia / 12 controls
Foncke *et al.*, 2007	Loss of the normal cortical drive to muscles in the beta band during sustained contraction	15 patients with myoclonus-dystonia and 5 asymptomatic *SGCE* mutation carriers/ 13 controls
Peall *et al.*, 2017	CSF analysis Low 5-hydroxyindoleacetic level suggesting a possible alteration serotonin metabolism	4 patients with myoclonus-dystonia

and brain-specific isoforms [24▪], are now available and hold promise for future studies aimed at further investigating gene function and disease pathogenic mechanisms. Patients have a *SGCE* loss-of function owing to a defective expression of the protein at the cell surface. In families with mutations or intragenic deletion of *SGCE*, inheritance is autosomal dominant with reduced penetrance, due to imprinting and subsequent silencing of the maternal allele by methylation of CpG dinucleotides within the promoter region of the gene. The transmission is thus paternal in this setting. Sporadic *SGCE* mutated cases can be explained by *de novo* mutations or by a hidden family history when the mutated allele is maternally transmitted over successive generations.

Myoclonus-dystonia because of *SGCE* deficiency can occasionally be part of a more complex phenotype ('myoclonus-dystonia plus' syndrome) in patients with rare genetic abnormalities, including maternal disomy of chromosome 7 with bi-allelic *SGCE* silencing [32], or large interstitial deletions encompassing the entire *SGCE* along with adjacent genes on chromosome 7 [29]. Patients with myoclonus-dystonia because of maternal disomy of chromosome 7 are likely to have associated Silver–Russell syndrome. This syndrome is characterized by intrauterine and postnatal growth deficiency with proportionate short stature, normal head circumference but a particular facial appearance (frontal bossing, triangular face, and micrognathia). In patients with contiguous gene syndrome because of a deletion encompassing *SGCE*, manifestations accompanying myoclonus-dystonia frequently include mental retardation, microcephaly, facial dysmorphism, and intrauterine and postnatal growth deficiency.

Finally, the syndrome of myoclonus-dystonia is genetically heterogeneous and patients without *SGCE* deficiency can display a very similar phenotype. So far, the cause in many of these patients remains undetermined. Myoclonus-dystonia has also been reported to be associated with mutations in other genes including *ADCY5* [33], *KCTD17* [34], *CACNA1B* [35], *RELN* [36], and various genes encoding enzymes of the dopaminergic synthesis pathway [37], but these findings require further confirmation in additional families. Importantly, a large proportion of the reported patients with mutations in other genes have been referred to as patients with 'myoclonus-dystonia', despite their clinical phenotype differing from patients with *SGCE* mutations. For example, the *KCTD17* and *ADCY5* patients tended to have dystonia that predominated over myoclonus, with a significant laryngeal or facial involvement, which is unusual in patients with *SGCE* mutations [33,34].

This raises nosological issues for both clinical practice and research. We advocate that the use of the term myoclonus-dystonia should be limited to patients with a *SGCE*-like phenotype. This will allow for the definition of a homogeneous group of patients to facilitate investigatory work-up and treatment in routine care, and advances in basic science research, such as the identification of new causative genes. Myoclonus-dystonia should be distinguished from what is better termed 'myoclonic dystonia' comprising primarily dystonic disorders manifesting as fast dystonic jerks that can be confused with myoclonus but are typically associated with muscle contractions longer than 300 ms (sometimes intermixed with shorter jerks), occurring in body parts affected by dystonia, usually intermingled with more obvious dystonic contractions; and other clinical pictures, in which the combination of dystonia and myoclonus has a different pattern or includes additional neurologic disorders. In ambiguous cases, neurophysiological examination is a useful tool. In particular, It can help to easily differentiate the typical brief subcortical myoclonus observed in myoclonus-dystonia syndrome from longer jerks seen in myoclonic dystonia or brief myoclonus of cortical origin that are associated with other signs of cortical hyperexcitability.

Table 2. Diagnostic criteria for the syndrome of myoclonus-dystonia

Major criteria
Myoclonus isolated or predominating over dystonia
Prominence of the motor manifestations in the upper body
Absence of truncal dystonia
Positive family history
Onset before age 18 years
Minor criteria
Obsessive compulsive disorder, anxiety related disorder or alcohol dependence
Spontaneous remission of limb dystonia during childhood or adolescence
Alcohol responsiveness
Exclusionary criteria
Other neurologic manifestation in addition to myoclonus and/or dystonia
Abnormal brain MRI
Neurophysiological findings that do not support the diagnosis (see text)

Myoclonus-dystonia is definite when patients have five major criteria + no exclusionary criterion, or four major criteria + two minor criteria + no exclusionary criterion.
Myclonus-dystonia is probable when patients have four major criteria + no exclusionary criterion or three major criteria + two minor criteria + no exclusionary criterion.

Several attempts have been made over the last few years to clarify the myoclonus-dystonia phenotype and to refine the clinical features predicting the presence of a genetic abnormality in *SGCE*. In particular, truncal dystonia or the coexistence of myoclonus and dystonia in the same body part appeared to be less frequent in patients with *SGCE* than in non-*SGCE* patients; whereas younger age at onset (particularly childhood-onset) and the presence of an associated psychiatric disorder in adults were strong predictors of *SGCE* mutation [2▪,3,4]. Response of the motor manifestations to alcohol may also be an interesting supportive criterion [7▪▪]. Taking the terminological clarification and the refinement of the phenotypic description into account we propose modified diagnostic criteria for myoclonus-dystonia (Table 2).

CONCLUSION

Comprehensive analysis of the phenotype is critical in patients with myoclonus and dystonia to identify homogeneous groups of patients. Neurophysiological examination can be very helpful in ambiguous cases. Clarification of the nosology and refinement of the diagnostic criteria will guide tailored therapeutic strategies and promote effective research. Because this disorder is a model of dystonia resulting from cerebello-thalamic dysfunction, deciphering myoclonus dystonia may be a valuable step towards a better understanding of more complex dystonias.

Acknowledgements

E. Roze is receiving support from Fondation Desmarest and AMADYS for his work on dystonia. M. Vidailhet is receiving unrestricted research support from Mrs. Anca Davis. We thank Eavan McGovern for helpful comments on the manuscript.

Financial support and sponsorship

None.

Conflicts of interest

E.R. received research support from Merz-Pharma, Orkyn, Aguettant, Elivie, Ipsen, Ultragenix; has served on scientific advisory boards for Orkyn, Aguettant, Merz-Pharma; has received honoraria for speeches from Orkyn, Aguettant, Merz-Pharma.

A.E.L. has served as an advisor for Abbvie, Acorda, Biogen, Bristol Myers Squibb, Janssen, Sun Pharma, Kallyope, Merck and Corticobasal Degeneration Solutions; received honoraria from Sun Pharma, Medichem, Medtronic, AbbVie and Sunovion; received grants from Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, and W. Garfield Weston Foundation; received publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press.

M.V. received unrestricted research support from Merz-Pharma and support from the MDS, EAN, DMRF.

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- ▪ of special interest
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