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VIEWPOINT

Minipolymyoclonus: A Critical Appraisal

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INTRODUCTION

'Minipolymyoclonus' or 'polyminimyoclonus' is a hyperkinetic movement disorder phenomenology characterized by intermittent, low-amplitude, arrhythmic movements of the hands, commonly of several fingers, with "amplitudes just sufficient to produce visible and palpable movements of the joints."[1] It is mostly noticed while the individual is maintaining a posture (commonly outstretched hands) or during action (especially the initial phase of movement). The term "minipolymyoclonus" was first used by Dennis Giblin and then described by Alfred J. Spiro in the context of differentiating a neuropathic from a myopathic disorder in 1970.[1] The pathophysiology of this entity is confusing because its presence has been described in different neurological disorders such as anterior horn cell (AHC) disease and peripheral nerve hyperexcitability disorders as well as central neurodegenerative and epileptic disorders. In the field of movement disorders, the use of the term 'minipolymyoclonus' is currently a matter of debate. From this viewpoint, we have critically analyzed the term 'minipolymyoclonus' from a pathophysiological perspective.

PATHOPHYSIOLOGY OF MINIPOLYMYOCLONUS

Role of the cortex

The motor cortex plays a major role in the execution of fractionated muscle activation. It provides input to motor neurons innervating the forearm and intrinsic hand muscles via downstream corticoreticular projections to the brainstem and corticospinal projections to the spinal cord. As a result, myoclonic movements of cortical origin can manifest as fractionated movement of the fingers. Ikeda et al.[2] coined the term 'cortical tremor' for patients with "fine shivering-like twitchings" in outstretched hands, associated with brisk, irregular EMG discharges and cortical spikes in jerk-locked back averaging, suggesting a variant of 'cortical reflex myoclonus.' Trains of repetitive cortical bursts can occur rhythmically, as with 'cortical tremor' in familial cortical myoclonic tremor and epilepsy (FCMTE),[3] or arrhythmically, as with 'minipolymyoclonus.' Transcranial magnetic stimulation (TMS) studies of cortical myoclonus have shown enhanced cortical excitability. Such abnormal cortical excitability and motor cortex disinhibition in multiple system atrophy (MSA) and corticobasal degeneration (CBD) have been demonstrated in many studies.[4] However, it is debated whether the cortical hyperexcitability seen in these disorders is directly related to the generation of minipolymyoclonus.

Role of AHCs

Anatomically, AHCs are located at a critical juncture between the upper motor neurons (UMNs) and lower motor neurons (LMNs). The classic example of a disease involving AHCs is amyotrophic lateral sclerosis (ALS), where minipolymyoclonus has been described in the literature as a larger form of fasciculation. Although most of the literature suggests a distal origin of this fasciculation, some studies suggest a proximal source, and few studies suggest that the source shifts from proximal (the motor neuron pool of the spinal cord) to distal (individual motor neurons) with disease progression.[5] De Carvalho et al.[6] concluded that cortical TMS-evoked fasciculation potentials arise centrally, from hyperexcitable motor cells at the level of the spinal cord or more

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proximally in the motor cortex, and represent a marker of increased corticomotor excitability. Cortical hyperexcitability may actually precede LMN dysfunction in ALS. Hyperexcitability of the UMN pathway can promote hyperexcitability in the surviving AHCs among the LMNs and lead to fasciculation. In a physiological state, LMNs are well adapted to the level of incoming impulses from cortical motor neurons. If cortical hyperexcitability causes the burden of supraspinal input to an AHC to exceed the tolerance level of the lower motor neuron, it degenerates. In the early stage of ALS, such supraspinal excitability is the primary driver of simple fasciculations. However, in later stages with significant muscle atrophy, denervation-reinnervation with axonal sprouting and the formation of unstable motor units, ectopic activity of peripheral motor axonal generators is primarily responsible for complex fasciculation. Studies by Inoue et al.[7] and Bhat et al.[8] have both shown that fasciculation in motor neuron disease (MND) can give rise to small-amplitude, jerky "twitches" in the fingers (especially with the hands outstretched and fingers extended), a phenomenon known as 'minipolymyoclonus,' or it can present with large amplitude "shock-like" movements mimicking spinal myoclonus.[7]

Possible role of the brainstem

In MSA, the brainstem is commonly affected along with the reticular motor neurons. Hyperexcitability of the brainstem has been documented in MSA.[9] Clinically, it can manifest as facial action myoclonus and facial myokymia. Minipolymyoclonus in the parkinsonian variant of MSA (MSA-P) is commonly manifested as bilateral jerky postural tremor of the upper limbs, whereas unilateral focal onset of such movement has been described in CBD.[10,11] An exaggerated auditory startle response (ASR) has also been demonstrated in MSA, and ASR disinhibition was noted more often in MSA-P than in the cerebellar variant (MSA-C).[12] Therefore, brainstem hyperexcitability can also be a pathological factor generating bilateral minipolymyoclonus in MSA.

Possible role of the cerebellum

In a physiological state, cerebellar cortical Purkinje cells are the dominant source of negative control (GABAergic) over the deep cerebellar dentate nucleus and thus inhibit overexcitation of the excitatory dentato-rubro-thalamo-cortical loop [cerebellar motor cortex inhibition (CBI)]. In cerebellar pathology, the loss of Purkinje cells disinhibits this excitatory loop and thus disinhibits the cortex. In MSA, striatonigral degeneration (SND) and olivopontocerebellar atrophy occur in various combinations in the MSA-P and MSA-C variants. The cerebellum can be involved in both variants, preferentially affecting different anatomical and functional zones. Altered connectivity in the cerebellocortical loop has been identified by functional MRI studies in MSA-P, in addition to involvement of the striato-pallido-thalamo-cortical loop.[13] Furthermore, cerebellar low-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to correct abnormal cortical excitability in MSA-C.[14] Recent studies have further highlighted the role of the cerebellum and the cerebello-thalamo-cortical loop in sustaining the spectrum of cortical myoclonus.[3,15]

The cerebellum appears to have a role to play here, but some other modulators impact the final clinical manifestation as minipolymyoclonus, frank cortical myoclonus or both. The intrinsic cortical inhibitory circuitry and the basal ganglia can these additional modulatory roles. GABAergic interneurons such as parvalbumin-positive (PV+) chandelier, fast-spiking basket and somatostatin-positive (SST+) Martinotti cells are integral parts of this intrinsic inhibitory circuitry that inhibits pyramidal cortical neurons.[16] From a therapeutic perspective, drugs such as valproate and clonazepam enhance the GABAergic inhibitory tone of these circuits to suppress cortical myoclonus. Therefore, it is possible to assume that this inhibition is lost to different degrees, determining whether the clinical manifestation will be minipolymyoclonus (with mild loss of inhibition) or higher-amplitude cortical myoclonus (with major loss of inhibition).

Possible role of the basal ganglia

The role of the basal ganglia, especially the striatum and the fronto-striato-thalamic circuitry, cannot be ignored, especially because minipolymyoclonus is common in the MSA-P or SND, which features striking striatal involvement. The striatum is connected to the cortex via the excitatory direct pathway and the inhibitory indirect pathway. In rodent models, striatal injection of picrotoxin (a GABA antagonist) can trigger myoclonus in the opposite front limb.[17] Striato-frontal deafferentation has been demonstrated in MSA-P by an FDG-PET study.[18] Bejjani et al.[19] have shown the development of myoclonus and irregular jerky tremor in the upper limb in response to low-frequency stimulation of the contralateral thalamus. Fronto-striato-thalamic circuitry can be evaluated further by means of newer imaging techniques, such as tractography, in the pathogenesis of minipolymyoclonus.

PERIPHERAL AND CENTRAL VARIANTS

In the literature, minipolymyoclonus has been described in disorders with AHC involvement, such as spinal muscular atrophy (SMA),[1,20] brachial monomelic amyotrophy,[21,22] bulbospinal muscular atrophy,[8] and syringomyelia (secondary AHC involvement),[23] as well as in congenital nemaline myopathy.[24] Quivering or rippling movements of the intrinsic hand muscles resembling polyminimyoclonus have also been described in disorders of peripheral nerve hyperexcitability, such as anti-CASPR2-asso-

ciated paraneoplastic Morvan syndrome.[25] On the other hand, it has been well documented in central neurodegenerative disorders such as multisystem atrophy parkinsonian type (MSA-P),[26-28] Alzheimer's disease[29,30] and Parkinson's disease.[31,32] Wilkins et al.[30] described minipolymyoclonus in epileptic disorders such as Lennox-Gastaut syndrome, progressive myoclonic epilepsy, absence seizure, Down's syndrome and cerebral palsy. Quinn highlighted this jerky postural tremor as a 'red-flag sign' in parkinsonism that favors the diagnosis of MSA,[33] which has been further emphasized in recent studies.[34] A small-amplitude unilateral-onset 'jerky tremor' has also been described in CBD, even prior to the development of more classic clinical signs.[11]

Clinically, minipolymyoclonus of peripheral and central origin can be differentiated by examining 'the company they keep', such as peripheral denervation for the peripheral variant and atypical or typical parkinsonism and epilepsy for the central variant.[35] However, electrophysiological data on minipolymyoclonus are limited in the literature compared to myoclonus. In some of these studies, cortical[28,30,31] or subcortical[29] correlates of this entity have been described by jerk-locked back averaging or EEG-EMG coherence analysis, while no such correlates were found in other studies.[27] Wilkins et al.,[30] in their description of minipolymyoclonus, noted a slow negative bi-frontocentral cortical wave preceding the onset of minipolymyoclonus by 40−60 ms. However, Ikeda et al.[2] demonstrated a cortical correlate spike in the contralateral sensorimotor cortex, preceding myoclonic movement by a shorter duration (15.4−20.8 ms). In Alzheimer's disease, Hallett and Wilkins[29] suspected that the activity of 'subcortical generator' was responsible for 'bifrontal negativity in the EEG that precedes the myoclonic jerk,' the electrophysiological correlate of minipolymyoclonus. In MSA-P, Salazar et al.[27] noted synchronous bursts and silent periods of EMG discharges from the forearm and hand muscles, varying in duration and amplitude but lasting less than 100 ms. Fast Fourier transform spectrum analysis of the accelerometric recording did not show any predominant frequency (in contrast to tremor). Enhanced long-latency EMG responses were noted in response to cutaneous stimulation at 50−63 ms (similar to reflex myoclonus), but they were accompanied by normal somatosensory evoked potentials and EEG, without any back-averaged cortical correlates. Thus, Salazar et al.[27] were uncertain of the origin of minipolymyoclonus in MSA. Grippe et al.[36] have described minipolymyoclonus as "an irregular 1−20 Hz activity with muscle synchronous bursts of 25−50 ms in duration" that can arise from a peripheral or central generator. However, peripherally originating minipolymyoclonus from degenerating motor neurons generally has an EMG burst duration of < 20 ms, similar to a typical motor unit potential.[8,37] In contrast, centrally originating minipolymyoclonus typically has a burst duration of < 100 ms (typically 20−50 ms).[30] In an EEG-EMG correlation study, cortically originating minipolymyoclonus should have time-locked cortical potential that is absent in the case of peripheral origin.

IS IT TIME TO REPLACE THE TERM 'MINIPOLYMYOCLONUS'?

The term 'minipolymyoclonus' or 'polyminimyoclonus' is confusing from diagnostic and pathophysiological perspectives. As this phenomenon is commonly seen in posture/action, such as keeping the hands outstretched, terms such as 'contraction fasciculation' or 'contraction pseudotremor of chronic denervation'[38] were coined for this entity of peripheral origin. 'Peripheral myoclonus' can be an alternative term for the peripheral variant of minipolymyoclonus. However, this term is nonspecific, and peripheral myoclonus can originate from plexuses, nerve root, AHCs and peripheral nerves.[39] In MND such as ALS, the term 'minipolyfasciculation' somewhat downplays the role of central hyperexcitability. However, in MND with predominant LMN involvement, such as SMA, the term 'minipolyfasciculation' fits perfectly.

Recently, Bhat et al.[8] proposed the term 'minipolyfasciculation' for peripheral origin while keeping the term 'minipolymyoclonus' exclusively for central origin. Latorre et al.[3] have described the spectrum of cortical myoclonus, encompassing sensory input−driven cortical reflex myoclonus, action-induced 'cortical action myoclonus,' focal spontaneous cortical abnormal activity-driven cortical myoclonus (arrhythmic) or cortical tremor (rhythmic), and widespread spontaneous cortical abnormal activity-driven epilepsia partialis continua (EPC) or myoclonic epilepsy. Can we also include a 'central variant of minipolymyoclonus' in this spectrum? Okuma and Mizuno[40] used the term 'cortical reflex myoclonic tremor' for this central variant. However, as Hallett and Wilkins[29] have mentioned, the central variant of minipolymyoclonus can be of 'subcortical origin', in which case it does not fit into the spectrum of 'cortical myoclonus'. Salazar et al.[27] were also unable to find 'a definite proof for the cortical origin' of these movements in MSA-P. Thus, can we further classify minipolymyoclonus of central origin into cortical and subcortical subtypes? More electrophysiological studies are needed to address this question.

Therefore, there may not currently be enough evidence to retire the term 'minipolymyoclonus' and rename the peripheral variant 'minipolyfasciculation' and the central variant 'cortical/subcortical action myoclonus.' By doing so, would we merely be replacing one confusing term with another? For now, it would be sensible to retain the term 'minipolymyoclonus' unless and until we find a better alternative.

SUMMARY

Minipolymyoclonus is an intriguing clinical phenomenology that is seen in central neurodegenerative and epileptic disorders as well as in AHC disease (primary or secondary) and peripheral nerve hyperexcitability disorders. Our review highlights the knowledge gaps and controversies regarding this interesting phenomenon and highlights the unmet need for more extensive clinical, electrophysiological and radiological correlation studies on the topic. Some unsolved issues regarding the pathophysiology remain open to further debate. It is necessary to consider the clinical setting in which it occurs, the presence of other clinical signs, and the results of electrophysiological studies to navigate through this gray zone of overlap.

Conflicts of Interest

Dr. Jog receives speaker's fees and research funding from Allergan, Abbvie, Merz Pharmaceuticals, Boston Scientific, Valeo Pharma, Sunovion and Paladin Labs. Dr. Jog also receives grants from Parkinson society Canada, CIHR, NSERC, MITACS, Research Council of Norway, Parkinson Society of Southwestern Ontario, Dystonia Medical Research Foundation and Academic Medical Organization of Southwestern Ontario. Dr. Ganguly receives fellowship funding from the Academic Medical Organization of Southwestern Ontario (AMOSO). Dr. Chai does not declare any conflict of interest.

Ethics Statement

The authors confirm that Institutional Review Board approval/patient consent was not required for this work. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Author Contributions

Conceptualization: Jacky Ganguly, Mandar Jog. Supervision: Mandar Jog. Writing—original draft: Jacky Ganguly, Jia Ren Chai. Writing—review & editing: Mandar Jog.

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