Point of view

A novel exaggerated "spino-bulbo-spinal like" reflex of lower brainstem origin

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ABSTRACT

Background: Many different oligosynaptic reflexes are known to originate in the lower brainstem which share phenomenological and neurophysiological similarities.
Objective: To evaluate and discuss the differences and aberrancies among these reflexes, which are hard to discern clinically using neurophysiological investigations with the help of a case report.
Methods: We describe the clinical and neurophysiological assessment of a young man who had a childhood history of opsoclonus-myoclonus syndrome with residual mild ataxia and myoclonic jerks in the distal extremities presenting with subacute onset total body jerks sensitive to sound and touch (in a limited dermatomal distribution), refractory to medications.
Results: Based on clinical characteristics and insights gained from neurophysiological testing we could identify a novel reflex of caudal brainstem origin.
Conclusions: The reflex described is likely an exaggerated normal reflex, likely triggered by a dolichoectatic vertebral arterial compression and shares characteristics of different reflexes known to originate in caudal brainstem, which subserve distinctive roles in human postural control.

Many different oligo-synaptic reflexes are known to originate from lower brainstem, such as the spino-bulbo-spinal reflex (SBS reflex), trigeminocervical reflex/head retraction reflex, and the startle reflex. They share many phenomenological similarities as they are clinically characterized by fairly symmetrical activation of the different muscles, originating most consistently in the muscles innervated by lower brainstem with a rostro-caudal propagation, making them clinically similar [1–5]. These reflexes also share many physiological similarities as they are all proposed to originate in the caudal brainstem reticular formation and are propagated up the brainstem and down the spinal cord by relatively slowly conducting efferent pathways; approximately 30 m/sec [1,4,6]. However, these reflexes are also different in terms of the afferent stimuli which induce them and their associations with certain neurological disorders. Differences are also noted in terms of the pattern of activation of different muscle groups (e.g. flexors vs extensors) and aberrancies in these patterns when they are abnormally exaggerated [4,7–10]. The differences and aberrancies among these

reflexes, though hard to discern clinically, can be identified using neurophysiological investigations which can provide useful pathophysiologic insights to guide treatment.

The best described of these reflexes in humans is the startle reflex, which is most extensively studied with auditory stimuli, though it can be elicited by visual, somatic or vestibular stimulation [1,7,11–13]. Exaggerated startle reflexes can be characterized by features such as excessive and more widespread muscle activation, excessive EMG bursts and amplitudes, lower thresholds for response and impaired habituation [1,7,14]. Both normal and exaggerated startle responses originate in the caudal pontine reticular nucleus and transmitted via efferent pathways which are similar to the other reflexes noted above [1,3,4]. SBS reflex is physiologically characterized by an early component that involves the local mono-synaptic reflex arc. The reflex further propagates along the spinal cord via two distinct pathways that have different conduction velocities. A slower conducting propriospinal pathway limited to and having reciprocal connections within the spinal

Table 1
Summary of comparative clinical and physiologic characteristics of jerk-like movements.

Reflex Characteristics	Startle Reflex	Spino-Bulbo-Spinal	Vestibulospinal Reflex	Audiospinal Reflex	Electrical Blink Reflex	Trigeminocervical Reflex	Propriospinal Myoclonus	Reticular Myoclonus	Cortical Myoclonus
Phenomenology	Bilaterally synchronous flexor response to a startling stimulus	Total body jerk-like movements beginning at the level of cutaneous stimulation	Postural adjustments and sway to counteract changes in head and neck position/galvanic vestibular stimulation	Facilitation of ongoing motor activity and monosynaptic spinal reflexes in response to an auditory stimulus	Eye blink in response to electrical stimulation of supra-orbital branch of V1 division of trigeminal nerve	Neck withdrawal and adoption of a defensive posture upon noxious stimulation in the supra/infra orbital trigeminal nerve distribution	Arrhythmic, usually flexor, brief jerks involving the trunk, hips, knees in a fairly uniform pattern	Spontaneous jerks involving the entire body which can also be evoked by somatosensory stimuli to distal extremities	Spontaneous jerks more commonly involving the face and distal upper extremities
Reflex Physiology	Early eyelid blink followed most consistently by SCM with subsequent cranio-caudal propagation	Early component involving segmental reflex followed by late component mediated via cranio-caudal propagation originating in caudal brainstem	Short latency reflex response, followed by a medium latency sway response; medium latency/sway responses can be influenced by other sensory inputs	A conditioning auditory stimulus causes most consistently an initial facilitation followed by a period of inhibition of the spinal mono-synaptic reflex arc	Early oligosynaptic short latency R1 component ipsilaterally followed by polysynaptic R2 component causing bilateral blink	Early oligosynaptic component mainly characterized by drop in EMG activity in tonically active neck muscles (most consistently SCM), followed by late Splenius muscle activation mediated via polysynaptic pathways	Craniocaudal EMG discharge usually beginning at the level of the abdominal muscles; restricted to spinal cord propriospinal pathways	Craniocaudal EMG discharge beginning at the lower medulla	Cortical onset short lasting EMG bursts (simultaneous agonist-antagonist discharge) with a cortical EEG correlate on back averaging.
Afferent Stimulus	Auditory; can also be elicited by visual, somatic and vestibular stimulation	Cutaneous nerve stimulation	Postural changes; Vestibular stimulation	Auditory	Electrical stimulation of supra-orbital nerve	Noxious stimulation in trigeminal nerve distribution in the face	Spontaneous; but can be induced by tactile or auditory stimuli	Spontaneous; can be induced by somatosensory stimuli, touch or muscle stretch of distal extremities	Spontaneous; but can be triggered by tactile or other somatosensory stimuli more commonly to distal upper extremities.
Pattern of Muscle activation; Flexors vs Extensors	Mainly flexors (but extensors also noted to be activated)	Mainly flexors (but extensor activation noted; mainly based on animal studies)	Adaptive response to counteract the head and neck postural changes	Both flexors and extensors	Bilateral blink	Mainly neck extensors	Mainly flexors	Both flexors and extensors	Mainly involving distal upper extremities and face (which have a large cortical representation)
Site of origin	Caudal pontine reticular formation (nucleus reticularis pontis caudalis)	Medullary reticular formation	Lateral Vestibular Nucleus (medullary reticular formation)	Brainstem reticular formation	Trigeminal and facial nuclei in pons and descending tract of spinal trigeminal nucleus in medulla for R2 component	Descending tract of spinal trigeminal nucleus and spinal nucleus of accessory nerve	Limited to spinal cord (note that most cases are functional)	Medullary reticular formation (likely nucleus reticularis gigantocellularis)	Cerebral cortex
Velocity of conduction of bulbo-spinal efferent volley	~30 m/sec	~30 m/sec	~30 m/sec	~100 m/sec	NA	NA	5–15 m/s	> 50 m/sec	~100 m/sec
EMG burst duration	> 70 msec	> 70 msec	> 70 msec	> 70 msec	> 70 msec	> 70 msec	~150–450 msec (can be longer)	< 50 msec	< 50 msec

cord and another faster conducting afferent pathway having a relay center in cadual brainstem reticular formation that is the site of origin of efferent pathways giving rise to the late component of the SBS reflex, similar to startle reflex. The late reflex discharges of SBS reflex are more consistently noted with stimulation of purely cutaneous nerves compared to motor/mixed nerves, suggestive of a highly specialized function of this reflex pathway involved in postural reflexes. Most of our understanding about SBS reflex comes from animal studies and very little is known about the normal and exaggerated physiology of this distinctive reflex in humans [3,15]. Though startle and SBS reflex share certain clinical and physiological characteristics, they have distinguishing features which suggest they mediate different aspects of motor control. They are also distinct compared to those involved in the transmission of reticular and cortical myoclonus; which are common conditions in the clinical differential diagnosis [12,16,17]. A summary of the comparative clinical and physiological characteristics of some of the reflexes of caudal brainstem origin and myoclonic disorders is presented in Table 1 [3,12,17–20].

Here we present a case of a young man who had a childhood history of opsoclonus-myoclonus syndrome with residual mild ataxia and myoclonic jerks in the extremities. He presented to us with symptoms characterized by total body jerks sensitive to sound and touch, refractory to medications.

1. Case report

29-year-old, right-handed man with a childhood history of opsoclonus-myoclonus syndrome(OMS), attributed to viral encephalitis. He underwent treatment with immunosuppressive therapy with significant improvements. He was left with deficits in fine motor control, ataxia, tremors and myoclonic jerks (mainly involving his extremities), cognitive impairment and behavioral problems. However, over the last 2 years he started to develop total body jerks mainly triggered by loud noises, but also caused by touch in the back of his neck or a pat on his shoulders. The jerks were greatly disabling resulting in falls and requiring him to be accompanied by someone always for safety. He had mild spasticity, distal weakness with associated fine motor difficulties in the left upper extremity. He had left more than right dysmetria, dysdiadochokinesia, wide based gait with associated difficulties with tandem gait, and a hypoactive gag reflex. At rest his head was held tilted to the right side, slightly flexed and any sudden sound or touch in the restricted region of the back of his head/neck and between shoulder blades triggered total body jerks characterized by head retraction, backwards jerking of the right shoulder, followed by extensor posturing of the trunk which did not habituate even after multiple trials (Video 1). These jerky movements could also be elicited by passive head extension. Head retraction reflex with tapping in the mid-face was negative [5,21]. Additionally, he had mild postural tremors with associated myoclonic intrusions which were residual and stable since his childhood OMS. He was being treated with a combination of Levetiracetam, Valproic acid and Clonazepam with suboptimal benefit.

Diagnostic workup included normal routine EEG, somatosensory evoked potentials without any giant waves for the early components and normal clinical blink reflex study. Brain MRI showed dolichoectatic vertebral arterial compression at cervical-medullary junction without any evidence of myelomalacia or aneurysmal dilatation per CT angiogram (Fig. 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.10.007.

Poly EMG recordings were performed to assess the pattern and latency of propagation of the discharge with surface EMG recordings. The signal was amplified using Nihon Kohden amplifier, bandpass filter was set at 10–1000 Hz. Responses were studied to acoustic stimuli of 50 ms duration, 120 dB intensity given through headphones and to tactile stimuli to the back of the head/neck region by tapping over a surface electrode to mark the stimulus for assessment of onset latency. EMG

data were reviewed, traces with artifacts rejected, and the signal was rectified and averaged from the acoustic/tactile stimuli. Data were analyzed offline using Spike software (Cambridge Electronic Designs). For the blink reflex recovery cycle, surface EMG was recorded over both orbicularis oculi muscles with electrical stimulation applied to the supraorbital nerve in the supraorbital notch with a bipolar stimulating electrode. Single and double electrical pulses were given with the following interstimulus intervals (ISI): 200 ms, 300 ms, 500 ms, 1000 ms, 3000 ms. Data were rectified and area under the curve was obtained from the R2 responses. The recovery cycle was calculated as the ratio between conditioned and unconditioned R2 for each ISI.

With the auditory stimulus, there was a consistent and reproducible pattern of activation beginning with the SCM, closely followed by the cervical paraspinals and the masseter with an average latency of 78 ms that propagated rostrally to the orbicularis oculi and caudally to the thoracic paraspinals and limb muscles (Fig. 2a). Onset latencies and velocity of propagation were consistent with that of a startle reflex [11,12] with no habituation, suggestive of an exaggerated startle reflex [7,13]. However, the early EMG component in orbicularis oculi, sometimes referred to as the auditory blink was not seen, and there was a predominant extensor muscle group activation(Fig. 2a) [12]. The body region for tactile induced jerks was limited to a restricted distribution involving the back of the neck and nape region. Using tactile stimuli, a similar pattern of EMG activation was noted with the most consistent onset noted in cervical paraspinal muscles with an average onset latency of 64 ms with subsequent rostro-caudal propagation similar to the auditory stimulus induced reflex. However, with tactile induced jerks there was an early small EMG component noted in SCM with an average latency around 30 ms followed by another small component with an average latency of 73 ms. Additionally, there was another major late EMG component noted in head and trunk flexors that followed the paraspinal muscles (head and trunk extensors); this SCM EMG component was noted to have an average latency of 150 ms that was followed by rectus abdominus EMG component with an average latency of 170 ms (Fig. 2b). The blink reflex recovery cycle showed about 50% suppression of R2 at 200 ms suggestive of some brainstem hyper-excitability.

2. Discussion

The case highlights the importance and utility of objective neurophysiological techniques in identification, localization of the site of origin and providing insights into the potential pathophysiologic processes implicated in movement disorders. Considering the childhood history of OMS, the likely etiology for the total body jerks was initially thought to be reticular myoclonus, based on similar site of pathology implicated for both these disorders, namely the caudal pontine nucleus [16,22,23]. On clinical examination, there were findings noted to be localizing to the medullary region (hypoactive gag reflex), which were new. Additionally, the phenomenology of the new movement disorder which was characterized by non-habituating sensitivity to sound and touch mainly in the back of the neck and nape region along with the absence of head retraction reflex was suggestive of an exaggerated startle reflex [5,7,9,24,25]. A brainstem vascular compression from a dolichoectatic vertebral artery was noted at the level of the cervical medullary junction (Fig. 1) which would explain the localizing signs; however, the site of compression was further distal to the caudal pontine region implicated in the pathogenesis of reticular myoclonus and startle reflex. Neurophysiological testing revealed non-habituating reflex similar to startle based on relatively low velocity of transmission and burst duration compared to reticular myoclonus, with the implicated site of origin being in the lower brainstem considering the first muscle being activated with subsequent cranio-caudal propagation. Another clinical finding noted in this case was the new head position which the patient adopted (holding his head titled to the right and slightly flexed) and triggering of the head jerks by passive head
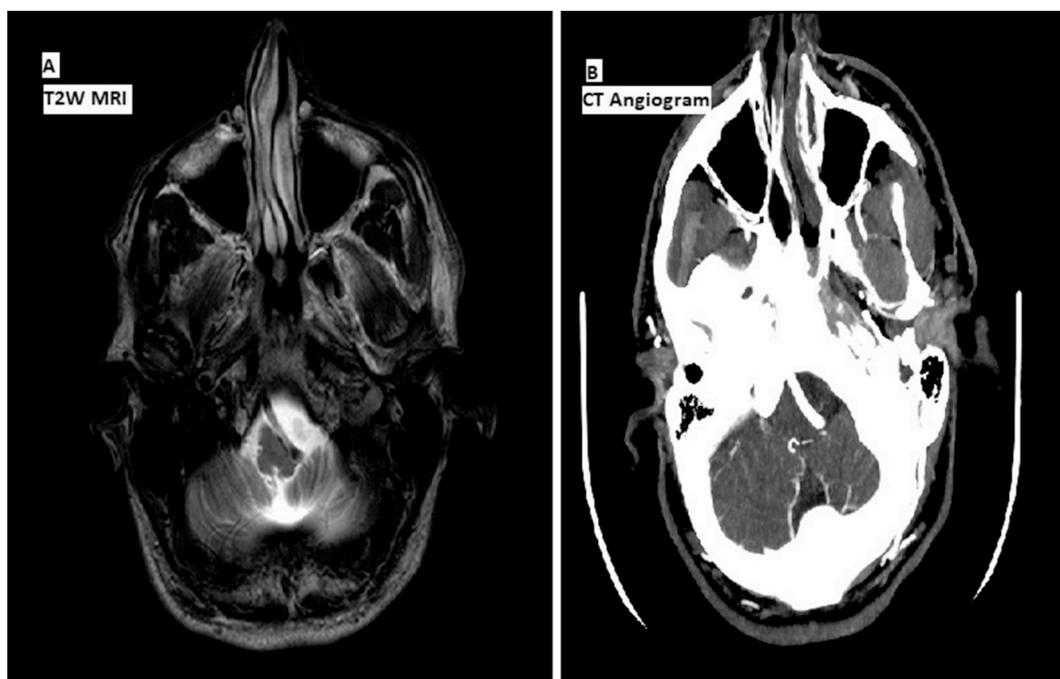
Fig. 1. A) T2 weighted MRI axial view showing compression of the medulla (compressing the medullary pyramids and olives predominantly on the left side) by a dolichoectatic vertebral artery without any evidence of myelomalacia. B) CT angiogram showing brainstem vascular compression without any evidence of aneurysmal dilatation.
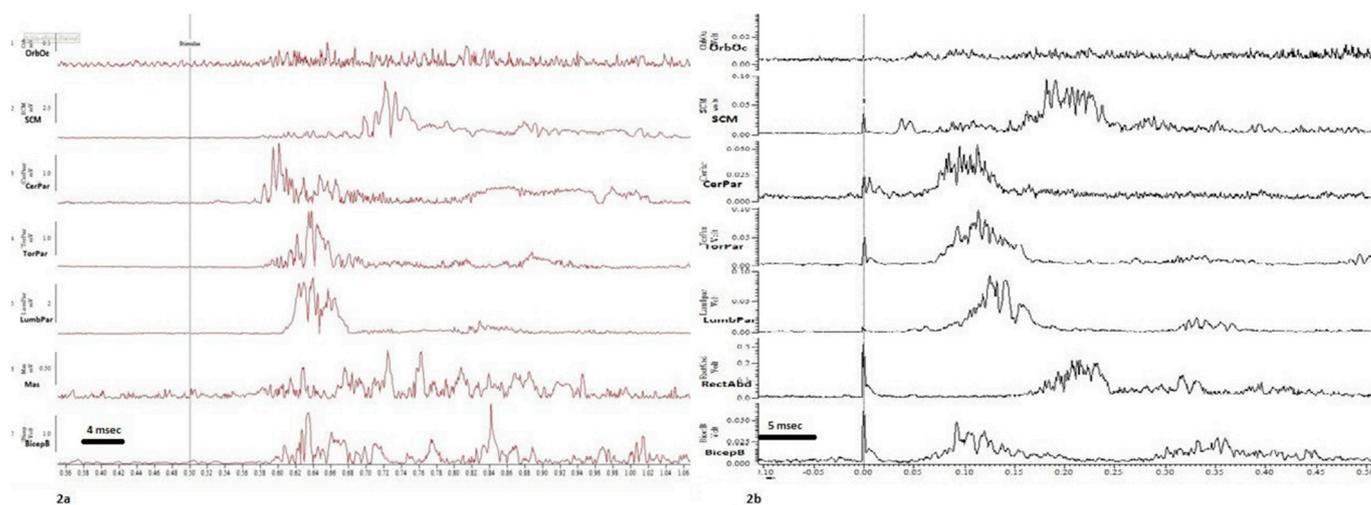

Fig. 2. (**a**). Rectified surface EMG traces of 7 muscles to the acoustic stimulus. 1.OrbOc: Orbicularis Oculi; 2.SCM: Sternocleidomastoid; 3.CerPar: Cervical Paraspinal; 4.TorPar:Thoracic paraspinal; 5.LumbPar: Lumbar Paraspinal; 6.Mas: Masseter; 7.BicepB: Biceps brachi.(**b**). Average rectified surface EMG traces of 7 muscles with tactile stimulus. 1.OrbOc: Orbicularis Oculi; 2.SCM: Sternocleidomastoid; 3.CerPar: Cervical Paraspinal; 4.TorPar:Thoracic paraspinal; 5.LumbPar: Lumbar Paraspinal; 6.RectAbd: Rectus abdominus; 7.BicepB: Biceps brachi.

extension which suggested a potential dynamic vascular compression [26,27]. We did not perform poly EMG recordings with passive head extension since the jerks noted clinically were limited to the neck paraspinal musculature and did not propagate, additionally artifacts were introduced to the recordings by passive head manipulation.

Neurophysiological and clinical characteristics of the reflex noted in the current patient shares features of some of the reflexes noted above. Clinically it is characterized by non-habituating jerks to auditory and tactile stimuli (in a limited dermatomal distribution) which are similar to exaggerated startle reflex; however, predominant extensor muscle activation and the absence of the early EMG component in orbicularis oculi associated with the auditory blink are notable differences [7,12]. Additionally the dermatomal specificity of the tactile induced jerks suggest irritability in a local reflex arc leading to an exaggerated reflex

upon stimulation only at that level, which also happens to be the site of dolichoectatic vascular compresson. The latencies and pattern of activation involving the early reflexive component at the same level of tactile stimulation followed by cranio-cadual propagation involving mainly the head and trunk extensors followed by late flexor EMG activation (likely stretch/propriospinal reflex mediated) is more compatible with a SBS reflex. Although the SBS reflex also involves predominant flexor activation in quadrupedal animals, it is poorly studied in humans, and extensor motor neuron activation has also been described in SBS reflex [3,6,28]. Considering the latencies of onset and activation pattern, the source of this aberrant reflex in our patient is in the lower medulla, likely triggered by dynamic vascular compression, distinguishing it from a startle reflex.

Exaggerated startle reflex has been previously reported as part of

OMS syndrome [29]. Vascular compression has also been implicated to cause exaggerated startle reflex [26,27]. To the best of our knowledge, this is the first report of a novel exaggerated 'SBS-like' reflex in humans, likely triggered by dynamic vascular compression, which also happens to be at the level in caudal brainstem where SBS reflex has been proposed to originate, based on animal studies. The current case highlights the importance of astute clinical examination combined with detailed neurophysiological testing in the identification of movement disorders and their pathophysiologic mechanisms, which have a bearing on treatment. Further exploration of the distinguishing characteristics, functions and aberrancies of the different postural reflexes originating in the cadual brainstem reticular formation is needed to gain more insights into human postural control. The vascular compression identified in this case may be further contributing towards the aberrant brainstem hyper excitability from baseline OMS, leading to poor response to pharmacological treatment. The vascular compression noted may be potentially amenable to decompression surgery, if symptoms become more disabling [26].

Author roles

SM: Research project: Conception, Organization, Execution; Manuscript: Writing of the first draft, Review and Critique FV: Research project: Organization, Execution; Manuscript: Review and Critique.

GL: Research project: Organization, Execution; Manuscript: Review and Critique SF: Research project: Conception, Execution; Manuscript: Review and Critique.

SPL: Research project: Conception, Execution; Manuscript: Review and Critique.

MH: Research project: Conception, Execution; Manuscript: Review and Critique.

Relevant financial disclosures and conflict of interest

None (for all co-authors).

Acknowledgements

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