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Movement Disorders

Clinical Vignette

**CORTICAL LIMB MYOCLONUS IN PATHOLOGICALLY PROVEN PROGRESSIVE
SUPRANUCLEAR PALSY**

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Running title: Cortical limb myoclonus in pathologically proven PSP

Clinical vignette

Progressive supranuclear palsy (PSP) is a sporadic tauopathy with insidious onset and a progressive course, first described in 1964 as parkinsonism, postural instability, axial rigidity, supranuclear gaze palsy, pseudobulbar palsy and cognitive changes.[1] However a much broader clinical spectrum is now recognised in association with PSP.[2] PSP may present as corticobasal syndrome (CBS) with asymmetric rigidity, apraxia, dystonia and variable cortical and basal ganglionic features.[3, 4] CBS was first reported in association with the pathological entity of corticobasal degeneration (CBD),[5] but is now recognised to develop secondary to PSP pathology as well as Alzheimer's disease, frontotemporal dementia, and other less common causes.[6] This overlap contributes to difficulties with accurate ante-mortem diagnosis of both PSP and CBD. It has been suggested that myoclonus favours the likely pathological diagnosis of CBD rather than PSP,[7, 8] although very few pathologically proven cases of PSP have documented myoclonus.[9, 10] We report the clinical and neurophysiological features of cortical myoclonus in a patient with pathologically proven PSP, in order to highlight the clinical features that are helpful in distinguishing CBS arising from PSP compared with CBD pathology.

Clinical history and examination

A 72 year old man presented with a 5 year history of progressive impairment of dexterity predominantly affecting his left hand. He described turning screws the wrong way and being unable to position his hand at the correct angle to shave himself suggesting his primary problem was one of praxis rather than akinesia. He reported hyperaesthesia in his left hand, feeling insecure on steps and occasional dribbling. There was no family history of neurological disorder. On examination there was a marked stare with slurred speech and generalised bradykinesia. Gait was slow with reduced arm swing especially on the left and impaired postural reflexes. Finger

taps could not be performed on the left and were markedly impaired on the right, with no grasp reflex. Both vertical and horizontal saccades were slow and hypometric. There was no tremor and muscle power and reflexes was normal. Sensation was normal.

Five months later, he reported severe difficulty with reading. Neuropsychological assessment showed impaired non-verbal reasoning, visuospatial conceptualisation, visuoconstructive abilities and milder impairment of verbal memory and executive function, interpreted as indicating predominant right hemisphere dysfunction. Neurological examination revealed head thrusts to initiate saccades, moderate rigidity of the upper limbs with cogwheeling, and occasional flurries of polyminimyoclonus in the left arm and fingers.

Twenty months after presentation he reported occasionally getting tangled in his bed sheets and being unable to release his grip on objects in his left hand. His right hand was affected to the point where he was unable to hold a pen. His slurred speech was worse and he reported difficulty in orobuccal tasks such as sucking through a straw. There was rigidity in both upper limbs, more severe on the left, intermittent grasp reflex in the left hand, and a fine irregular tremor in his left hand with bursts of myoclonus superimposed.

Thirty four months after presentation, his speech was almost unintelligible though attention and comprehension were maintained. He could only walk with assistance. There was marked rigidity of both upper limbs. His left hand was clenched in a fist and immobile except for low amplitude myoclonic jerks. He was unable to move his right hand but could slowly move his right shoulder and elbow. There were virtually no vertical eye movements to command and horizontal movements were severely restricted. He died of pneumonia 3½ years after presentation.

Investigations

Surface EMG (Figure 1A-C) showed irregular, highly synchronous, moderate amplitude (to 1 mV peak-peak) bursts in both intrinsic hand and forearm muscles. Following stimulation of the left median nerve at the wrist at twitch threshold, a C reflex was present at a latency of ~40 ms (forearm) and ~45 ms (hand). These findings are typical of CBS.[4, 11] MRI showed patchy widening of cortical sulci and non-specific periventricular and subcortical hyperintensities predominantly in frontal and parietal regions. Genetic testing did not reveal any known or novel mutations in the *MAPT* gene for tau protein. Apolipoprotein E genotype was 3/3. Neuropathological features were consistent with a neuropathological diagnosis of PSP (see supplementary figure).

Discussion

We report a patient who presented with asymmetric apraxia of the upper limb, bradykinesia and sensory symptoms and went on to develop dysarthria, oculomotor signs, severe rigidity and myoclonus. The presentation was consistent with CBS, with the presence of myoclonus favouring the likelihood of CBD rather than PSP as the pathological diagnosis.[7][12] A recent review of 404 cases of pathologically proven CBD reported that the occurrence of myoclonus in CBS was over 50%.[14] While comparison across autopsy-proven CBD presenting as CBS (CBD-CBS) with Richardson syndrome (typical presentation of PSP, CBD-RS) as well as PSP-RS show that myoclonus is present in 64% of CBD-CBS but absent in both CBD-RS and PSP-RS,[8] our data show that PSP pathology can underlie this clinical feature. In the present case, the abnormal vertical saccades raised the alternative possibility of pathological PSP, although this feature is also observed in a proportion of pathologically proven CBD cases (ref).

CBS myoclonus due to PSP has been documented in only two or three? other cases,[9, 10][13] however, to our knowledge, this is the first case of neurophysiologically documented cortical limb myoclonus in PSP. The true prevalence of myoclonus in pathological PSP is unknown as there are limited cases of pathologically proven PSP with neurophysiological data,[9, 10] and most case series do not specifically refer to the presence or absence of myoclonus as a clinical sign. The electrophysiological characteristics of the myoclonus in this case was typical of that described for CBS, as opposed to “classical” cortical myoclonus, as there was an absence of giant somatosensory evoked potentials, a lack of cortical activity preceding the myoclonic jerks and a latency of ~40 ms.[11] Other clinical features predictive of CBD pathology were the progressive asymmetric rigidity and apraxia, alien limb phenomena, and cortical sensory loss.[6, 7] Our data suggest that although the presence of cortical myoclonus may favour the pathological diagnosis of CBD in CBS,[7] it does not preclude the possibility of pathological PSP. This finding adds to the difficulties in making the clinical distinction between the differing pathological causes of CBS.

FIGURE LEGEND:**Figure 1:**

EMG recordings of spontaneous myoclonic jerks: **(A)** 2s sweep; **(B)** 100ms detail of (A) demonstrating a 5ms proximal-to-distal delay in muscle recruitment. Vertical calibration (μV) of each muscle in (B) indicated by vertical marker in (A). **(C)** Superimposed single trials demonstrating high amplitude C-reflexes.

Figure 2 (Supplementary data):

(A) Photograph of the superior surface of the brain (15% buffered formalin at room temperature for 3 weeks), demonstrating atrophy (arrow) of the precentral gyrus.

(B) Photograph of a coronal slice (3 mm in agar) through the area affected. The cortical ribbon is notably thin (curved arrow), and the underlying corpus callosum atrophic (arrowhead).

(C,D) Photomicrographs of haematoxylin and eosin stained sections through the substantia nigra

(C) showing depigmentation and gliosis in association with a relatively low density of neurons and a typical cerebellar folia (D) showing gliosis in the Purkinje layer, but with no neuron loss.

(E,F) Photomicrographs of tau-positive (T5530, Sigma, St Louis, Mo. USA, diluted 1:10,000, peroxidase visualisation) glia in the precentral gyrus, stained using immunohistochemistry to tau-II.

(G,H) Photomicrographs of tau-positive globose tangle in the subthalamus (G) and inferior olive (H).

(I,J) Photomicrographs of the substantia nigra showing pigmented neurons containing tau-positive (arrow, I) and silver (modified Bielschowsky) stained (arrow, J) globose tangles.

Normal appearing nigral neurons are indicated (arrowheads, I,J). The neuromelanin pigment has a dark-brown to black appearance, while the abnormal neurofibrillary tangles appear brown. No astrocytic plaques or other ubiquitin (Z0458, Dako, Glostrup, Denmark, diluted 1:200) or α -synuclein (18-0215, Zymed Laboratories Inc., San Francisco, Ca, USA, diluted 1:200)

immunopositive pathologies were found. Scales for E-G are equivalent to that in H. Scale for I is equivalent to that in J.

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Author roles

SK: manuscript writing of first draft; manuscript review and final draft.

AH: collection of clinical and pathological data; manuscript writing of first draft.

GH: collection of clinical and pathological data; manuscript writing of first draft.

NM: **EMG figure?**, manuscript review and critique.

VF: research project conception, organization and execution; collection of clinical data; manuscript review and final draft.

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