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Neuropathology of cervical dystonia

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ABSTRACT

The aim of this study was to search for neuropathological changes in postmortem brain tissue of individuals with cervical dystonia (CD). Multiple regions of formalin-preserved brains were collected from patients with CD and controls and examined with an extensive battery of histopathological stains in a two-stage study design. In stage one, 4 CD brains underwent a broad screening neuropathological examination. In stage two, these 4 CD brains were combined with 2 additional CD brains, and the subjective findings were quantified and compared to 16 age-matched controls. The initial subjective neuropathological assessment revealed only two regions with relatively consistent changes. The substantia nigra had frequent ubiquitin-positive intranuclear inclusions known as Marinesco bodies. Additionally, the cerebellum showed patchy loss of Purkinje cells, areas of focal gliosis and torpedo bodies. Other brain regions showed minor or inconsistent changes. In the second stage of the analysis, quantitative studies failed to reveal significant differences in the numbers of Marinesco bodies in CD versus controls, but confirmed a significantly lower Purkinje cell density in CD. Molecular investigations revealed 4 of the CD cases and 2 controls to harbor sequence variants in non-coding regions of *THAP1*, and these cases had lower Purkinje cell densities regardless of whether they had CD. The findings suggest that subtle neuropathological changes such as lower Purkinje cell density may be found in primary CD when relevant brain regions are investigated with appropriate methods.

Introduction

Dystonia is a disorder characterized by sustained or intermittent involuntary muscle contractions leading to twisting movements and abnormal postures (Tarsy and Simon, 2006). The most frequent manifestation is regional involvement of isolated muscle groups, with the neck as the most commonly affected area (Defazio, 2010). People with cervical dystonia (CD, or torticollis) suffer from over-activity of neck muscles with involuntary turning, tilting, or twisting of the head. A cause is not identifiable in most cases, where the disorder is known as primary or isolated CD. In contrast, a cause is identifiable in secondary or acquired CD and may include medications, trauma, space-occupying lesions, and developmental or degenerative conditions. Although CD is the most common primary dystonia, conclusive evidence implicating specific regions of the nervous system is lacking (Hedreen et al., 1988; McGeer and McGeer, 1988; Standaert, 2011). A review of the literature disclosed only 15 reports, and no consistent neuropathological changes were noted (Table 1). The failure to detect overt changes has contributed to the belief that there are no neuropathological defects in primary CD.

On the other hand, imaging techniques consistently reveal abnormalities in primary CD (Neychev et al., 2011; Zoons et al., 2011). Positron emission tomography has revealed abnormal activity of the cerebral cortex, basal ganglia, cerebellum, and thalamus. Voxel-based morphometry has shown abnormal white and gray matter volumes in the cerebral cortex, basal ganglia, cerebellum and thalamus.

Abbreviations: ACC, nucleus accumbens; AD, Alzheimer's disease; BG, basal ganglia; BL, blepharospasm; BS, brainstem; CAUD, caudate; CD, cervical dystonia; COD, complication of the disorder; CNF, cuneiform nucleus; CN III, cranial nerve III; CN IV, cranial nerve IV; CRB, cerebellum; CTX, cerebral cortex; CVD, cerebrovascular disease; F, female; FD, facial dystonia; FHD, focal hand dystonia; GP, globus pallidus; HT, hand tremor; H&E, hematoxylin/eosin; HIP, hippocampus; IC2, anti-polyglutamine antibody; ID, identifier; INC, interstitial nucleus of Cajal; LC, locus ceruleus; M, male; MB, midbrain; MRI, magnetic resonance imaging; NA, not available; NFT, neurofibrillary tangles; NBM, nucleus basalis of Meynert; NR, not relevant; NT, neck tremor; PAG, periaqueductal gray; PMI, post-mortem interval; PPN, pedunculopontine nucleus; PUT, putamen; RF, reticular formation; RN, red nucleus; SC, spinal cord; SN, substantia nigra; STN, subthalamic nucleus; sv, sequence variant; TDP-43, TAR DNA binding protein 43; TG, tegmentum; THAL, thalamus; uINI, ubiquitinated intranuclear inclusions.

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Table 1
Postmortem studies of cases with cervical dystonia.

Age at onset	Age at death	Sex	Body region affected	Brain regions investigated	Pathological findings	Probability of primary CD	Source
23	24	M	Neck	BG, MB/BS, CRB	Loss of neurons, gliosis, multiple small and bilateral lacunes in PUT, substantia innonimata; perivascular lymphocytic infiltration suggestive of vasculitis	Low	(Foerster, 1933)
21	25	F	Neck	CTX, THAL, CAUD, PUT, GP, SN, CRB	Cell loss in CTX; cell loss in the molecular and Purkinje cell layers in CRB; diffuse perivascular lymphocytic infiltration and meningeal thickening consistent with chronic encephalitis	Low	(Grinker and Walker, 1933)
43	90	M	Neck, tongue, forearm, hand, fingers	CTX, GP, CAUD, PUT, THAL, SN, RN	Atrophy of CAUD and PUT; cell shrinkage in CAUD, PUT and GP bilaterally, with vacuolization, pyknotic nuclei, neuronophagia, gliosis, and presence of lipoid pigment; cell loss in GP	Low	(Alpers and Drayer, 1937)
59	65	F	Neck	CTX, THAL, GP, CAUD, PUT, CRB (vermis, hemispheres and peduncles), MB, NBM, RN, SN, INC, pons, medulla, SC	Normal	High	(Tarlov, 1970)
NA	NA	NA	Neck	Upper pons	Normal	Indeterminate	(Tarlov, 1970)
56	62	F	Neck, upper and lower face	BG, SC, BS, CRB, cerebrum	Normal	High	(Garcia-Albea et al., 1981)
NA	50	F	Neck	NA	Normal	Indeterminate	(Zweig et al., 1986)
61	68	F	Upper face, larynx, neck	CTX, HIP, CAUD, PUT, GP, hypothalamus, THAL, MB, pons, medulla, CRB	Normal	High	(Jankovic et al., 1987)
47	50	F	Neck	HIP, amygdala, GP, CAUD, PUT, basal forebrain, THAL, STN, BS, CRB	Normal	High	(Zweig et al., 1988)
<33	68	M	Upper and lower face, neck	HIP, amygdala, CAUD, PUT, ACC, GP, THAL, STN, CRB, SN, LC, NBM, raphe, PPN, medulla, CN III, CN IV	Depigmentation in SN, LC; NFT in NBM; neuronal loss in SN, raphe, PPN, LC; astrocytosis in SN	Low	(Zweig et al., 1988)
59	68	F	Neck, lower face	CTX, CAUD, PUT, GP, NBM, THAL, STN, RN, SN, LC, raphe, inferior olive, SC (cervical and thoracic)	Normal	High	(Gibb et al., 1988)
54	72	F	Neck, face	PAG, PPN, RF, CNF, GP, CAUD, PUT, HIP, CTX (anterior frontal, parietal, temporal)	Diffuse gliosis in GP; patchy gliosis in CAUD, PUT; signs of AD, Lewy bodies in BS	Moderate	(Holton et al., 2008)
46	79	F	Neck, lower face, hand	Same as above	Cystic infarct in CAUD; diffuse gliosis in GP; patchy gliosis in CAUD, PUT; small vessel disease in BG	Low	(Holton et al., 2008)
47	65	M	Axial, larynx	Same as above	Diffuse gliosis in GP; patchy gliosis in CAUD, PUT; mild small vessel disease	Moderate	(Holton et al., 2008)
73	80	F	Neck	Same as above	Diffuse gliosis in GP; patchy gliosis in CAUD, PUT	High	(Holton et al., 2008)

This table includes only cases originally described or typically cited as examples of primary or idiopathic dystonia. Segmental and multifocal dystonia cases were included if dystonia of the neck also was a prominent feature of the disorder. Probability of primary cervical dystonia is classified as low, moderate and high according to current clinical and pathological criteria. Cases were classified with high probability if the clinical description was consistent with current clinical criteria. Cases with one atypical feature were considered with moderate probability, whereas cases with two or more atypical features were classified with a low probability of primary CD. The limited information available for some cases did not allow proper classification and, thus, they were listed as indeterminate. ACC, nucleus accumbens; AD, Alzheimer's disease; BG, basal ganglia; BS, brainstem; CAUD, caudate; CD, cervical dystonia; CNF, cuneiform nucleus; CN III, cranial nerve III; CN IV, cranial nerve IV; CRB, cerebellum, CTX, cerebral cortex; GP, globus pallidus; HIP, hippocampus; ID, identifier; INC, interstitial nucleus of Cajal; MB, midbrain; NA, not available; NFT, neurofibrillary tangles; NBM, nucleus basalis of Meynert; PAG, periaqueductal gray; PPN, pedunculopontine nucleus; PUT, putamen; RF, reticular formation; RN, red nucleus; SC, spinal cord; STN, subthalamic nucleus; THAL, thalamus.