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CASE REPORT

Lewy body dysphagia

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Abstract The presence of Lewy bodies (LB) in autonomic structures of the central and peripheral nervous system in Parkinson's disease (PD) is well known and could explain clinical signs of pure autonomic failure (PAF) or dysphagia, frequently associated with the disorder. There are many neuropathological reports in the literature with detailed descriptions of PAF, however, LB dysphagia has thus far only been reported once. In the present study, we describe two cases of isolated dysphagia without extrapyramidal syndrome, diagnosed clinically as progressive supranuclear palsy and amyotrophic lateral sclerosis, where detailed neuropathological examination identified LBs in the dorsal vagal motor nuclei in the medulla. These findings confirm the existence of isolated LB dysphagia and emphasize the importance of detailed neuropathological and immunohistochemical examination in cases of dysphagia.

Keywords Lewy body · Dysphagia · Neuropathology

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Introduction

Swallowing relies on complex voluntary and involuntary innervation of striated and smooth muscles via cranial nerves. Normal swallowing with simultaneous protection of the respiratory system needs the coordinated action of both autonomic and somatomotor systems, including cranial nerves (V, VII, IX, X, XI and XII) and large groups of striated and smooth muscles [20].

Dysfunction of swallowing may be due to cortical, bulbar, or cerebellar brain damage or to diseases of peripheral nerves and muscles. In elderly persons, dysphagia occurs frequently as pseudobulbar palsy in cerebrovascular disease, or as an accompanying sign of neurodegenerative disorders, i.e. Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration and amyotrophic lateral sclerosis (ALS) [20].

Swallowing abnormalities are common problems in these degenerative disorders. Usually, dysphagia appears earlier in the course of PSP and MSA than in PD [13]: the onset within the first year of disease is characteristic of atypical parkinsonian syndromes [13]. However, it is often seen in the earliest stages of PD [14, 15]. The reported incidence of swallowing dysfunction in PD ranges from 30 to 52% [15]. Symptoms correlate with disease severity and duration [4] and are associated with increased morbidity and mortality [12].

Although the presence of Lewy body (LB) pathology in the cranial nerve nuclei IX/X is well known in PD cases presenting swallowing dysfunction, there is only one neuropathological report in the literature concerning two cases with LB dysphagia [12]. Our paper describes two patients with isolated dysphagia, where neuropathological examination confirmed LB pathology at the medullary level.

Case report

Clinical summary

Case 1

This 89-year-old man developed dysphagia 4 years prior to death. He had multiple transient ischemic attacks (TIA) in a setting of auricular fibrillation with anticoagulation treatment. He suffered two novel TIAs 2 months before death, first with right hemiparesis; the second time 4 days later with paresis of the right arm and dysarthria. Neurological examination revealed a severe hypophonia and dysphagia, prompting a clinical suspicion of PSP with affection of cranial nerve X, but no further investigations were performed. The CT scan showed hypodensities in the left Sylvian and insular regions, possibly representing brain infarcts. He died of bronchopneumonia, confirmed by autopsy. Other autopsy findings were moderate atherosclerosis, pulmonary emphysema, and cardiac hypertrophy.

Case 2

An 86-year-old man was admitted to the hospital because of dyspnea, auricular fibrillation and suspicion of pulmonary abscess. In his anamnesis dysphagia was noted, beginning 2 years before death and progressing to aphagia. The performed oesophagogastroduodenoscopy did not yield any explication for dysphagia. The rest of his neurological status was normal. The clinical differential diagnosis included pseudobulbar palsy and amyotrophic lateral sclerosis (ALS). He died due to bronchopneumonia. The systemic autopsy revealed bilateral bronchopneumonia with empyema, pulmonary emphysema, mild atherosclerosis, cardiac hypertrophy, and a tubular adenoma of the colon.

Materials and methods

Brains obtained at autopsy were fixed in 15% formalin for 4 weeks and stored in 5% formalin. After macroscopic examination, both hemispheres were cut into 1-cm-thick coronal slices. For histological examination and immunohistochemistry, tissue blocks were taken from the frontal cortex (area 9), the middle temporal gyrus (area 21), the anterior cingulate cortex (area 24), the parietal cortex (area 40), the transentorhinal cortex, substantia nigra, pons at the level of locus coeruleus, and medulla at the level of inferior olive. Samples were embedded in paraffin and cut into 14-μm-thick sections. Serial sections were stained consecutively with haematoxylin–eosin, cresyl-violet and with the following antibodies: AT8 (mouse, monoclonal, Innogenetics, Gent, Belgium; 1:3,000), anti-ubiquitin (rabbit, polyclonal, Sigma; 1:100), anti-α-synuclein (mouse, monoclonal, Zymed, 1:3,000) and monoclonal antibody against core amyloid Aβ protein 4G8 (mouse, monoclonal, Signet Laboratories, Dedham, MA, USA; 1:2,000).

Neuropathology

Case 1

The brain weight was 1380 g. With exception of a severe atherosclerosis, the brain did not show any macroscopic lesions. No brain infarct was present, but the white matter showed moderate demyelination. In the substantia nigra a LB was observed in one neuron accompanied by some Lewy neurites (LN), without appreciable neuron loss (Fig. 1a, c, d). Both dorsal vagal motor nuclei—without significant neuronal loss—(Fig. 1g, h), the obscure raphe nucleus (Fig. 1i), the intermediate reticular zone, the nucleus ambiguus and the locus coeruleus (Fig. 1j) also contained some LBs and LNs. The hypoglossal nuclei were free of inclusions. In other regions of the brainstem and cortical areas α-synuclein containing inclusions were absent. Amyloid deposits were absent and only the hippocampus and entorhinal cortex showed some neurofibrillary tangles.

Case 2

The brain weighed 1350 g. Macroscopic examination revealed only the following lesions: a mild frontal atrophy, a 2 mm diameter lacune in the left putamen and an old 4 cm diameter infarct in the right occipital lobe around the calcarine fissure.

The substantia nigra did not show any neuronal loss or α-synuclein-inclusions (Fig. 1b), however, the locus coeruleus contained a few LBs and LNs (Fig. 1e, f). Histological examination also showed the presence of α-synuclein-positive inclusions in the absence of neuronal loss in the dorsal vagus motor nuclei and in the intermediate reticular zone. LBs and LNs were absent in the nucleus ambiguus or other structures at the medullary level. Neurofibrillary tangles were scarce and restricted to the entorhinal cortex and the CA1 field of hippocampus. Mild amyloid deposition was noted only in the parietal neocortex.

Discussion

Above, we present two cases of isolated dysphagia with a suspected clinical diagnosis of PSP and ALS diagnosed neuropathologically as LB dysphagia.

Lewy bodies (LB) were described as the pathological hallmarks of idiopathic Parkinson's disease (PD) [18]. Recently, it was recognised that they are present in other

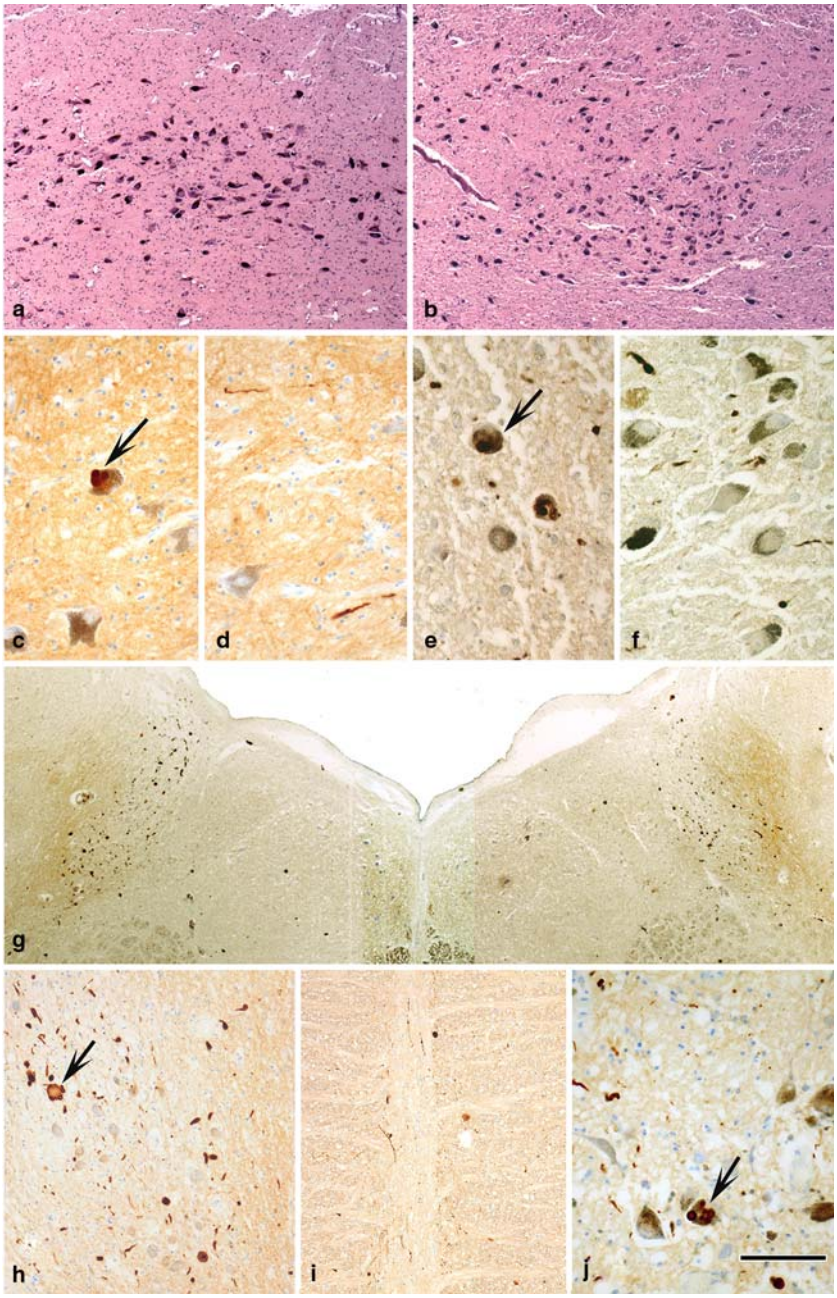

Fig. 1 Absence of neuronal loss in the substantia nigra in both cases **a** case 1, **b** case 2. A unique LB (*arrow*) and some LNs in the substantia nigra of case 1 (**c**, **d**) and in the locus coeruleus of case 2 (**e**, **f**). LBs (*arrow*) and LNs in the dorsal vagal motor nucleus bilaterally (**g**, **h**), the obscure raphe nucleus (**i**) and the locus coeruleus (**j**) of case 1. Haematoxylin–eosin (**a**, **b**) immunohistochemistry anti-α-synuclein (**c**–**j**). *Scale bar*: **a**, **b** 400 μm; **c**–**f**, **h**–**j**: 100 μm; **g** 700 μm

degenerative disorders; however, they are most often associated with PD. Idiopathic PD, LB dementia, autonomic failure and LB dysphagia [6] form the spectrum of the LB disorders—also called LB disease [9]. The clinical manifestations of LB pathology depend on the severity and anatomical distribution of LB involvement in the central and peripheral nervous system [8]. The clinical signs of an extrapyramidal syndrome, dysphagia or autonomic failure could be explained by the presence of LBs in the substantia nigra, dorsal vagal motor nuclei or sympathetic ganglia respectively [5, 7].

In the topographical evolution of LB pathology in stage 1 LBs and LNs are seen in the medulla, in the nuclei of cranial nerves IX and X and/or in the intermediate reticular zone; in stage 2 additional α-synuclein-positive inclusions appear in the pontine tegmentum, in the caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus–subcoeruleus complex [2]. A recent study described α-synuclein-immunoreactive inclusions in the spinal cord lamina I neurons preceding stage 1 in the evolution [3].

The neuroanatomical basis of dysphagia in PD—mainly observed in the advanced stages of the disease—is complex. The mechanism of swallowing dysfunction may be explained in part by bradykinesia and rigidity in the oral phase of swallowing [15]. In the pharyngeal and esophageal phases, autonomic cranial nerves and the

oesophageal myenteric plexus play a key role [19]. Cranial nerve motor neurons (nucleus ambiguus and vagal dorsal nucleus) innervating muscles of deglutition are serially activated by the central pattern generator [11]. The nucleus ambiguus innervates pharyngeal striated muscles; the dorsal vagal motor nucleus muscles of both lower pharynx and oesophagus [10], therefore the degeneration of the dorsal vagal nucleus may be responsible for both pharyngeal and oesophageal dysphagia.

Cases with incidental α-synuclein-pathology are described in the literature and their clinical importance is not yet clarified. In the olfactory system, where α-synuclein-positive lesions are present in the olfactory bulb early in the course of PD, causing impaired smell sensation or anosmia prior to the apparition of movement problems [1], a recent study found a correlation between olfactory dysfunction and incidental LB disease in the brainstem [16]. The affection of lamina I neurons in the spinal cord, having extended connections with sympathetic relay centers, could explain painful sensation not infrequently observed in PD [3].

However, dysphagia and olfactory dysfunction may not be clinically apparent, making retrospective neuropathological studies impossible.

Although the presence of LBs in the dorsal vagal motor nucleus is well known during the progression of PD, there are only two cases reported of isolated LB dysphagia, described by Jackson and colleagues in 1995 [7], corresponding to low Braak stages of LB pathology.

The recognition of Braak stages 1 and 2, corresponding to asymptomatic cases concerning extrapyramidal signs, may escape clinical diagnosis, and after neuropathological examination, could be diagnosed as incidental findings. Great importance should be given to the examination of the medulla in all cases with dysphagia to obtain the real frequency of the disorder. Furthermore, dysphagia may be an early hallmark of PD, similar to dysfunction of the olfactory system.

Our cases were different with regard to medullary pathology. Case 1 showed α-synuclein inclusions in both dorsal vagal motor nucleus and the nucleus ambiguus implying that both the pharyngeal and oesophageal phases of swallowing were disturbed. In case 2, the restriction of LBs to the dorsal vagal motor nucleus suggest affection of the late oesophageal phase [17]. The fact that the presented patients never developed parkinsonian signs during the several years (4 and 2 years) with dysphagia, supports that LB dysphagia can be an entity and not only an accompanying sign of PD and therefore underlines the importance of careful neuropathological examination.

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