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Brainstem pathology and non-motor symptoms in PD

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ABSTRACT

Parkinson's disease (PD) is considered a multisystem disorder involving dopaminergic, noradrenergic, serotoninergic, and cholinergic systems, characterized by motor and non-motor symptoms.
The causes of the non-motor symptoms in PD are multifactorial and unlikely to be explained by single lesions. However, several evidence link them to damage of specific brainstem nuclei. Numerous brainstem nuclei are engaged in fundamental homeostatic mechanisms, including gastrointestinal regulation, pain perception, mood control, and sleep–wake cycles. In addition, these nuclei are locally interconnected in a complex manner and are subject to supraspinal control. The objective of this review is to provide a better overview of the current knowledge about the consequences of the involvement of specific brainstem nuclei to the most prevalent non-motor symptoms occurring in PD. The multidisciplinary efforts of research directed to these non-nigral brainstem nuclei, in addition to the topographical and chronological spread of the disease — especially in the prodromal stages of PD, are discussed.

1. Introduction

Parkinson's disease (PD) has been classically considered a movement disorder, characterized by motor signs related to severe degeneration of the midbrain's substantia nigra (SN).

In the preceding few years, comprehensive clinical, laboratory, and neuropathological observations have led to PD being now considered a multisystem disorder involving dopaminergic, noradrenergic, serotoninergic, and cholinergic systems, characterized by motor and non-motor symptoms.

The non-motor manifestations of PD include a wide range of symptoms from constipation to depression (Table 1) [1–3].

Although these non-motor symptoms compromise the daily activities of patients in all stages of the disease, many of these are manifested before the onset of motor symptoms.

The causes of the non-motor symptoms in PD are multifactorial and, therefore, unlikely to be explained by single lesions. However, several evidence link them to damage of specific brainstem nuclei.

Lewy bodies (LBs) and Lewy neurites (LNs) are characteristic intracellular proteinaceous inclusions, mainly composed of alpha-synuclein, found in the soma and the processes of neurons. The characteristic distribution of LBs, LNs, and pale bodies is considered the neuropathological hallmark of PD. For the past 50 years, several studies have shown the presence of LBs and LNs in brainstem nuclei other than the substantia nigra (SN) [4,5]. In 2003, Braak et al. condensed and extended various previous studies to provide a stereotypic and chronological progression of LB appearance, beginning from the dorsal motor vagal nucleus located in the caudal medulla oblongata and progressing in an ascending course [6]. The SN is affected only in stage III, and the first motor symptoms are usually detected in stage IV, by which time most of the SN has already degenerated.

Recent clinicopathological studies show that at least 80% of cases follow the proposed scheme of Braak et al. and that LBs are detected in most of the vulnerable brainstem nuclei in more than 90% of the PD cases during the course of the disease.

The objective of this review is to provide an overview of the current knowledge about the consequences of the involvement of specific brainstem nuclei to the most prevalent non-motor symptoms occurring in PD. The multidisciplinary efforts of research directed to these non-nigral brainstem nuclei are highlighted, and the topographical and chronological spread of the disease, especially in the prodromal stages of PD, are discussed.

Abbreviations: dX, dorsal motor nucleus of the vagus; EDS, excessive daytime sleepiness; GI, gastrointestinal system; GCN, gigantocellular reticular nucleus; IRt, intermediate reticular zone; LBs, Lewy bodies; LC, locus coeruleus; LNs, Lewy neurites; NST, nucleus of the solitary tract; PD, Parkinson's disease; PPN, pedunculopontine nucleus; PPNd, pedunculopontine nucleus, pars dissipatus; RBD, REM-sleep behavior disorder; REM, rapid eye movement; SN, substantia nigra; SSRIs, selective serotonin reuptake inhibitors.

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Table 1
Non-motor symptoms of PD.

Neuropsychiatric symptoms
Depression
Hallucination
Dementia
Sleep disorders
REM-sleep behavior disorders
Excessive daytime somnolence
Autonomic dysfunction
Gastrointestinal symptoms
Constipation
Orthostatic hypertension
Pain
Sensory symptoms
Olfactory dysfunction

In single horizontal sections through the brainstem, most of the correspondent nuclei are inconspicuous, and it is frequently difficult to delineate them in conventional 10- to 20-μm-thick paraffin sections. Therefore, the topography, in addition to the size and extent of the nuclei under consideration, are illustrated using a 3D reconstruction of thick serial histological sections of the human brainstem [7,8].

2. General aspects of the brainstem nuclei involved in PD

The brainstem is considered an intermediate regulatory system that links the spinal cord with the superordinate prosencephalon. It is divided rostrocaudally into mesencephalon, metenchephalon (pons), and medulla oblongata. The brainstem encloses the sensory and motor nuclei of 10 cranial nerves. It serves as a pathway for the long ascending and descending fiber tracts from the prosencephalon to the spinal cord. Two prominent association centers are found on its dorsal or posterior part — the tectum and the highly evolved cerebellum. The latter gives rise to the exponential evolution of the pons and the inferior olive. The core of the brainstem is occupied by the reticular formation, an extensive network that is considered to end rostrally in the basal telencephalic nuclear complex. Monoaminergic cell groups are embedded within the reticular formation [9]. The reticular formation is targeted by spinal, telencephalic, and diencephalic efferents [9]. On the basis of the works of Dahlstrom and Fuxe [10], these monoaminergic cell groups are named using letters (A = catecholaminergic, B = serotoninergic, C = adrenergic) and numbers, beginning from the medulla oblongata . Finally, some cholinergic cell groups (Ch5 and Ch6, based on the nomenclature of Mesulam et al. [11]) are also found in the brainstem.

All serotoninergic nuclei, select cholinergic, noradrenergic, some precerebellar and cranial nerve nuclei, in addition to the reticular formation, are vulnerable to PD. Nevertheless, it does not automatically imply that these aminergic nuclei and the sensory or motor brainstem nuclei are simultaneously and uniformly affected. The non-vulnerable neurons conserve their morphological and functional integrity even when they are located directly contiguous to diseased neurons. This implies that neuronal damage in the brain during PD is not arbitrary and follows a typical distribution pattern [6,12]. The reason for the selective vulnerability of some neuronal types is yet to be understood.

There are evidence that the vulnerable neurons share some features. For instance, independently of the neurotransmitter system, the vulnerable neurons are projection neurons with disproportionately long axons. In addition, these neurons are poorly myelinated [13], and most of them are rich in pigments, including neuromelanin, lipofuscin, or both (Fig. 1) dorsal motor vagal nucleus. In addition, these neurons are poorly myelinated [13], and most of them are rich in pigments, including neuromelanin, lipofuscin, or both (Fig. 1).

3. Main brainstem nuclei involved in early stages of PD

a) Dorsal motor nucleus of the vagus

The dorsal motor vagal nucleus (dX) is the largest parasympathetic nucleus of the brainstem. It acts as a general visceral efferent that controls the postganglionic parasympathetic nerve cells of the enteric system (esophagus, stomach, liver, pancreas, spleen, small intestine, and proximal large intestine) and heart [14]. The dX emits both excitatory and inhibitory pathways, all of them using acetylcholine as their primary neurotransmitter [15].

The dX is located in the dorsomedial medulla oblongata and extends from the level of the pontomedullary junction to the pyramidal decussation, neighboring the nucleus of the solitary tract and intercalate nucleus [14]. Its neuronal population is heterogeneous, and a few medially located pigmented neurons constitute the areas A2 and C2.

In PD, a loss of cholinergic dX neurons and A2 neurons is observed [16,17]. LBs and LNs are found spread out all over this nucleus from the very early stages [18–20].

b) Intermediate reticular zone

The intermediate reticular zone (IRt) of the medulla oblongata was first delineated in the rat in the 1980s [21]. Soon afterward, many studies corroborated this finding [22–25]. The IRt is intercalated between the gigantocellular and the parvocellular reticular nuclei. It extends rostrally from the pontomedullary junction to the level of the

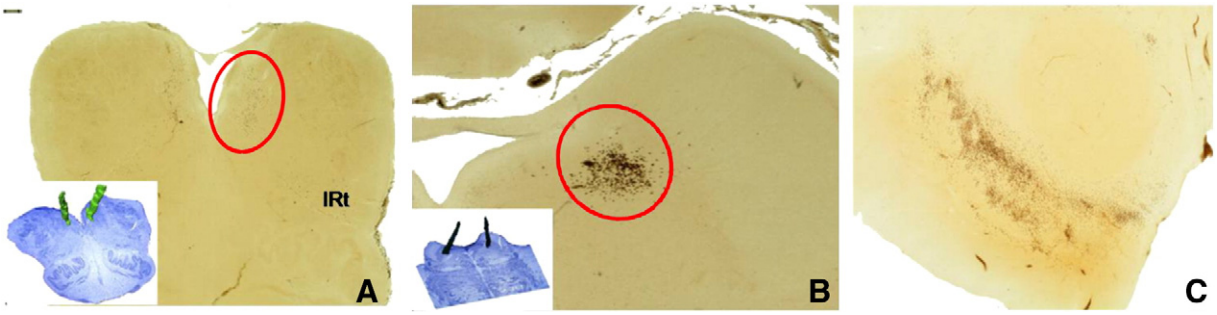

Fig. 1. Depicts unstained sections at the level of the medulla oblongata (A) from the locus coeruleus (B), and SN (C), important nuclei affected in PD. Note the pigment-rich neurons (circle in red on A and B) of the dorsal motor vagal nucleus and intermediate reticular zone (A), locus coeruleus (B) and substantia nigra (C). The 3D reconstructed dorsal motor vagal nucleus and the locus coeruleus are shown on the detail. IRt: intermediate reticular zone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)