Neurobiology of Non-Motor Symptoms in Parkinson Disease

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EDITORIAL

Parkinson disease (PD) is a multisystem disease clinically characterized by variegated motor and non-motor (NM) deficits. Many of these NM alterations antedate motor dysfunctions, representing a prediagnostic phase spanning 20 or even more years before the diagnosis of PD is established, and then worsen with disease progression. The clinical spectrum of NM symptoms in PD and atypical parkinsonism has been repeatedly reviewed [1-6]. Their causes of NM symptoms in PD are multifactorial and linked to widespread distribution of α-synuclein (αSyn), the basic pathological protein aggregated in neurons, neurites, presynaptic terminals and glia as hallmarks in PD and other synucleinopathies [7]. αSyn aggregation in presynaptic terminals that predates the formation of Lewy bodies (LB) and dystrophic neurites and does not necessarily correlate with LB pathology [8] is not restricted to specific dopaminergic brainstem nuclei, but involves multiple areas of the central, autonomic, and peripheral nervous system, the retina, sympathetic and parasympathetic ganglia, nerves, skin, salivary glands, and other organs [9,10]. The pathology of NM symptoms in PD has been reviewed recently [11], and its sequential part in the disease progression has been presented [12]. This is a brief update of the relations between αSyn deposition and the most frequent NM symptoms, and a discussion of animal models and their probable relevance for NM aspects of PD.

Non-motor features and staging of Lewy pathology

The essential NM symptoms of PD that until recently have received relatively little attention and often having been underrecognized, are currently assessed with the non-motor symptom questionnaire (NMSQ) [12]. The major NM manifestations of PD include olfactory, autonomic (gastrointestinal, urogenital, cardio-vascular, respiratory dysfunctions), sleep disturbances, pain and sensory symptoms, visual and neuropsychiatric (cognitive, impuls control, affective) dysfunctions (Table 1). Patients often report that nonmotor manifestations are more disabling and less amenable to treatment than some motor symptoms.

According to a neuroanatomically based staging scheme Lewy pathology begins in lower brainstem, the central and peripheral portions of the autonomic nervous system, and in the olfactory bulb. Involvement progresses in a caudal to rostral manner affecting the diencephalon, basal forebrain, medial temporal lobe structures and, finally, neocortical areas [13]. The validity of this staging scheme has gained in acceptance, but also has been the subject of vigorous debate [8,9,14]. Whether this staging scheme fits with the timing of NM features of PD is also a matter of discussion, as αSyn pathology has been described in the brain and the spinal and peripheral autonomic system in neurologically unimpaired elderly subjects [8,14]. Furthermore, some of the NM features (e.g. autonomic dysfunctions and psychiatric symptoms) may occur rather late in the disease [3,15].

Pathophysiology of NM features in PD

The anatomical basis of olfactory dysfunction present in early (preclinical) phases of PD includes αSyn pathology affecting

Table 1: Non-motor features in Parkinson disease.

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Olfactory</td>
<td>hyposmia / smell loss</td>
</tr>
<tr>
<td>Sleep</td>
<td>REM sleep behavior disorder, insomnia, daytime sleepiness, restless leg syndrome</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>dysphagia, constipation, swallowing difficulties, hypersalivation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>urgency, nocturia, increased frequency, impotence</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>orthostatic hypotension, syncope</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>seborrhoea, hypo-/hyperhidrosis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>dyspnea, stridor</td>
</tr>
<tr>
<td>Sensory</td>
<td>pain, abnormal sensations</td>
</tr>
<tr>
<td>Visual</td>
<td>diplopia, blurred vision, reading difficulties, dry eyes</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>anxiety, depression, behavioral disorder, dysexecutive syndrome, visuospatial deficit, psychosis, apathy, aggressiveness, disinhibition, hallucinations, cognitive impairment (dementia)</td>
</tr>
</tbody>
</table>
neurons and neurites in the olfactory bulb and related olfactory nuclei in the brain (amygdala, perirhinal cortex) with commonly negative biopsy studies of the olfactory epithelium suggesting that olfactory dysfunction in PD is related to involvement of the central olfactory pathways rather than from peripheral nerve fibers [16] (Table 2).

Sleep disturbances that can appear decades before manifest PD, in addition to insomnia and daytime sleepiness, include REM sleep behavior disorder (RBD) [17]. Many patients with “idiopathic” RBD show early clinical manifestations of an evolving neurodegenerative disorder, and its combination with olfactory dysfunction is an indication for α-synucleinopathy [18]. RBD is related to damage to several brainstem nuclei that are involved in very early stages (LB stage I to III). Recent data suggest a complex dysfunction involving GABAergic, glutamergic and cholinergic systems due to impairment of brainstem structures in the laterodorsal pontine tegmental nuclei that modulate RMS sleep. It is related to the latero-dorsal pontine tegmental nuclei - pedunculopontine nucleus, lateral tegmental nucleus and locus (sub) cereuleus and their anatomical connections (e. g. amygdala, pallidum, neocortex) [19]. Nigrostriatal dopaminergic degeneration could be part of the pathogenesis of RBD, but appears not essential for it [20].

**Table 2:** Relation of α-synuclein pathology to non-motor features in PD.

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>α-Synuclein pathology</th>
<th>Break PD stage</th>
<th>Non-motor feature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomic nervous system:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic ganglia (paravertebral, celiac)</td>
<td>LN, LB</td>
<td>1-6</td>
<td>Autonomic Constipation</td>
</tr>
<tr>
<td>Gastroesophageal/enteric plexus</td>
<td>LN, LB</td>
<td>1-6</td>
<td>Nocturia, impotence, urgency</td>
</tr>
<tr>
<td>Pelvic plexus</td>
<td>LN, LB</td>
<td>1-6</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Cardiac sympathetic nerves</td>
<td>LN, LB</td>
<td>?</td>
<td>Fatigue, adynamia</td>
</tr>
<tr>
<td><strong>Skin:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal nerves</td>
<td>LN</td>
<td>2-6</td>
<td>Abnormal sensations, pain</td>
</tr>
<tr>
<td><strong>Olfactory bulb:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior olfactory nucleus (olfactory brain nuclei)</td>
<td>LN, LB</td>
<td>1</td>
<td>Hyposmia</td>
</tr>
<tr>
<td><strong>Medulla:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal motor n. vagus (parasympathetic)</td>
<td>LB, iLB</td>
<td>1</td>
<td>Dysautonomia (gastrointestinal tract, bladder)</td>
</tr>
<tr>
<td><strong>Pons:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locus ceruleus, raphe, lateral tegmental nuclei</td>
<td>LB, LN</td>
<td>2</td>
<td>Depression, sleep disorder, REM behavior disorder</td>
</tr>
<tr>
<td><strong>Midbrain:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>LB, LN</td>
<td>3</td>
<td>Extrapyramidal motor</td>
</tr>
<tr>
<td>Diencephalon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>LB, LN</td>
<td>3</td>
<td>Sleep disorders, weight changes</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Basal forebrain:</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus basalis Meynert Amygda, hippocampus</td>
<td>cLB, LN</td>
<td>4</td>
<td>Executive dysfunction, emotional, behavior problems</td>
</tr>
<tr>
<td><strong>Neocortex:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>cLB, LN</td>
<td>5</td>
<td>Agnosia, apraxia</td>
</tr>
<tr>
<td>Temporal parietal cortex</td>
<td>cLB, LN</td>
<td>6</td>
<td>Dementia, Psychosis</td>
</tr>
</tbody>
</table>

**Gastrointestinal disorders** that can be significant problems years before motor symptoms of PD are related to αSyn pathology involving the autonomic control areas (dorsal motor nucleus of vagus providing preganglionic parasympathetic innervation, sacral parasympathetic nuclei, intramural enteric nervous system, adrenal medulla, and sympathetic ganglia/intermediolateral nucleus of the thoracic spinal cord, etc.) [21,22]. All these areas are involved in early LB stages I and II. Analysis of the enteric nervous system by routine colonoscopy biopsies may be a useful tool for pre-mortem diagnosis of PD, and also provides insight into the progression of NM and motor symptoms [23].

Damage to the peripheral autonomic nervous system explains frequent genitourinary dysfunctions (urgency, nocturia, urinary retention, erectile dysfunction) in both presymptomatic PD and in up to 25% of healthy adults that have significant impact on quality of life [4,24].

Abnormal αSyn pathology in periadrenal tissues and in the adrenal gland, observed in 26.4% in an autopsy sample of elderly patients and in 11.1% of PD cases beginning in LB stage 0-I and increasing in frequency with LB stage, has been associated with orthostatic hypotension in LB disease [25].

The cardiovascular autonomic system is affected due to cardiac sympathetic denervation early and progressive in PD [26,27]. Recent studies showed diminished tyrosine hydroxylase (TH) immunoreactivity in the cardiac system and myocardium in PD [28]. αSyn aggregates in epicardial nerve fascicles were significantly different between incidental Lewy body disease (iLBD), PD, multiple system atrophy (MSA), and controls [27], although degeneration of cardiac sympathetic nerves can occur in MSA [27,29]. Parasympathetic denervation of the heart is seen in late stages of PD.

While a wide spectrum of pain manifestations often present as a NM symptom in PD [30] is related to early involvement of the pain-control system in the brainstem [31] and, later, to dysfunction of dopaminergic systems in basal ganglia [32], frequent sensory deficits are related to cutaneous denervation by αSyn pathology [33]. LB pathology in abdominal cutaneous nerves has been observed in 23-71% of cases with Lewy stages II and III, corresponding to preclinical and early stages of PD. Skin biopsy for assessment of autonomic denervation in PD has been recommended. The sweat glands and blood vessels were most affected, although these findings did not correlate with complaints of hyperhydrosis or orthostatic hypotension [34].

Visual symptoms are common in PD, ranging from reading difficulties, perceptual disturbances and complex visual hallucinations that are a considerable cause of morbidity in PD. They occur at several levels of the visual pathway. Altered intraretinal dopaminergic synaptic activity, in addition to disorders of higher (cortical) visual processing may contribute to visual symptoms experienced PD patients [35].

Neuropsychiatric symptoms, such as affective, cognitive changes, apathy, psychosis, dementia, and their neuropsychological and pathophysiological backgrounds have been reviewed repeatedly [15,36-38] and, therefore, will not be discussed.
Animal models of NM symptoms in PD

There are several animal models of NM symptoms in PD. Alterations of dopaminergic markers in the gastrointestinal tract have been observed in rodent models of PD [39]; In 6-OHDA-treated rats, the protein levels of TH and dopamine transporter (DAT) in the GI tract were significantly increased while the mRNA levels of both substances were decreased. Increased dopamine levels in the gut might cause the down-regulation of TH and DAT mRNA, which might explain their decrease in 6-OHDA-treated rats. By contrast, in MPTP-treated mice, the protein level of TH was significantly decreased, associated with atrophy of gastric epithelial cells, although the protein level of DAT was not significantly changed. MPTP causes a loss of enteric neurons in mice and non-human primates [40,41]. GI dysfunctions were also observed transgenic mice overexpressing wild-type αSyn driven by the Thy-1 promoter, but histopathologic data from the ENS are not available. Enteric nervous system abnormalities preceding central nervous system changes have been reported in mice transgenic for artificial chromosomes containing PD-associated αSyn gene mutation (A53T or A30P of the human SNCA gene). Both show robust ENS dysfunctions and αSyn immunoreactive aggregates in ENS ganglia. The A53T line also has abnormal motor behavior but cardiac autonomic abnormalities, olfactory dysfunctions, dopaminergic neurotransmitter deficits, LB inclusions or neurodegeneration [42].

Chronic administration of rotenone, a potent mitochondrial complex I inhibitor that hinders ATP production and promotes reactive oxygen species production, induced several GI dysfunction in rats without loss of ENS neurons [43]. Chronic exposure of rotenone reproduces PD GI neuropathology in rats, with increase of αSyn positive protein aggregates that are reminiscent of enteric LBs and causing moderate loss of small intestine myenteric neurons associated with moderate slowing of GI motility [44]. Oral (intragastric) administration of rotenone that did not reduce complex I activity in muscle or brain, i.e. not crossing the hepatoporal system and acting solely on the ENS, caused reduction of αSyn inclusions in the enteric nervous system [45].

NM symptoms of PD were revealed in a mouse model with reduced monoamine storage capacity [46]: Mice with a 95% genetic reduction of vesicular monoamine transporter expression (VMAT2-deficient, VMAT2-LO) display progressive loss of striatal dopamine, L-DOPA motor deficits, αSyn accumulation, and nigral cell loss. They demonstrate progressive deficits in olfactory discrimination, delayed gastric emptying, altered sleep latency, anxiety-like and depressive behavior. These animal models recapitulate the early GI and other NM abnormalities seen in human PD and could be used for targeting αSyn toxicity in its earliest stages, e.g. by restoring monoamine function that may be of benefit in treating the disease. By contrast, none of the currently available transgenic mouse models of MSA displayed any definite NM symptoms [47].

CONCLUSIONS

The currently available data on NM symptoms in PD can be summarized as follows:

(1) Variegated NM deficits and neurological symptoms, covering impaired olfaction, sleep disorders, gastrointestinal and genitourinary, cardiovascular, respiratory dysfunction, sensory, visual disorders, pain, neuropsychiatric and other symptoms may antedate motor dysfunction and frequently occur in pre-clinical stages of PD.

(2) A relationship between most of these signs and symptoms and αSyn and/or Lewy pathology exists that is characterized by widespread involvement of distinct neuronal populations and networks in the central (cerebrospinal), autonomic and peripheral nervous system and various visceral organs. The widespread distribution of these lesions, not restricted to the dopaminergic striatonigral system that is usually related with classical motor symptoms of PD, characterizes PD as a multisystem neurodegenerative disease.

(3) However, it is not clear whether the severity and distribution pattern of LB pathology, which, according to the Braak staging shows very early involvement of the olfactory and enteric nervous system, is associated with neuronal loss and axonal damage in these regions. Attempts at quantifying enteric neuron loss in PD have been limited and gave contradictory results. In one study, a majority of PD patients showed reduced dopamine neurons in the colon myenteric and submucosal plexuses [48], while another group failed to find overt neuronal loss in these plexuses in colonic biopsies [23]. Detailed post-mortem studies of ENS innervation throughout the GI tract are lacking.

(4) Another caveat concerns the relation between characteristic PD symptoms and the loss of dopaminergic nigral neurons. The previous concept that PD motor motor signs first appear when more than 50% of dopaminergic nigral neurons and 70-80% of striatal or putaminal dopamine are lost [49] has recently been changed by the suggestion that at the time of first diagnosis of PD only about 30% of dopaminergic nigral neurons but 50-60% of their axon terminals have been lost [50]. Thus, the early involvement of axons in PD has not been adequately emphasized as a rationale of for functional deficits in neurodegeneration. Studies concerning these facts are warranted to get deeper insight into the impact of non-dopaminergic and autonomous nervous system lesions for clinical phenomena.

(5) The relationship between clinical deficits and neuropathology was recently discussed: While the duration and severity of motor function, the corresponding decrease of dopamine, TH, DAT and VMAT-2 immunoreactivity in striatum are negatively correlated with total substantia nigra αSyn burden and neuronal loss [49-51], the latter shows no correlation with LB formation, and no relationship between morphologic LB staging and both clinical severity of PD (Hoehn & Yahr score) and age at death were found [52].

(6) LB and/or αSyn pathology in the central and peripheral autonomic nervous system in neurologically unremarkable elderly persons is a not infrequent finding, ranging from 10 to 31% [8,14,53], which was detected only in comprehensive studies of the whole nervous system. Comparison of such studies should account on case selection and the methods used for detecting LBs and αSyn [14].
Lack of correlation between α Syn pathology and impaired function is dramatically represented in relation with cognitive and mental function. Retrospective clinico-pathological studies have shown divergent results concerning the impact of LB/αSyn and Alzheimer-related pathologies on mental impairment in PD [8,9,36,54-56].

In conclusion, although there is increasing evidence that αSyn pathology beyond the nigrostriatal dopaminergic system is critically involved in both the presymptomatic and late-developing NM features of PD, much clinico-pathologic work remains to be done to refine correlations between motor and non-motor manifestations and their relation with morphological and functional pathophysiological lesions in the nervous system.

REFERENCES


