

## Staging of brain pathology related to sporadic Parkinson's disease

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### Abstract

Sporadic Parkinson's disease involves multiple neuronal systems and results from changes developing in a few susceptible types of nerve cells. Essential for neuropathological diagnosis are  $\alpha$ -synuclein-immunopositive Lewy neurites and Lewy bodies. The pathological process targets specific induction sites: lesions initially occur in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus. Thereafter, less vulnerable nuclear grays and cortical areas gradually become affected. The disease process in the brain stem pursues an ascending course with little interindividual variation. The pathology in the anterior olfactory nucleus makes fewer incursions into related areas than that developing in the brain stem. Cortical involvement ensues, beginning with the anteromedial temporal mesocortex. From there, the neocortex succumbs, commencing with high order sensory association and prefrontal areas. First order sensory association/premotor areas and primary sensory/motor fields then follow suit. This study traces the course of the pathology in incidental and symptomatic Parkinson cases proposing a staging procedure based upon the readily recognizable topographical extent of the lesions. © 2002 Published by Elsevier Science Inc.

**Keywords:** Parkinson's disease; Staging procedure;  $\alpha$ -synuclein; Lewy bodies; Lewy neurites; Limbic system; Motor system

### 1. Introduction

Sporadic Parkinson's disease (PD) is a progressive degenerative illness of the human nervous system that manifests itself clinically after the pathology already has reached an advanced stage [31,32,51]. A prerequisite for the post-mortem diagnosis of both the presymptomatic and symptomatic phases of the pathological process underlying PD is evidence of specific inclusion bodies, which develop as spindle- or thread-like Lewy neurites (LNs) in cellular processes, and in the form of globular Lewy bodies (LBs) in neuronal perikarya [33,53,54,60]. In sporadic PD, only a few specific types of nerve cells are prone to develop the lesions. A major component of LNs and LBs is an aggregated form of the normally presynaptic protein  $\alpha$ -synuclein. It is still unknown why this hydrophilic protein leaves its binding sites within synaptic boutons and, together with other components such as phosphorylated neurofilaments and ubiquitin, a heat shock protein required

for the non-lysosomal ATP-dependent breakdown of abnormal proteins, gradually transforms into virtually insoluble LNs or LBs [1,2,15,25,29,41,49,67,70].

Damage to specific subnuclei of the substantia nigra, pars compacta, with severe obliteration of their neuromelanin-laden projection neurons, frequently is considered to be the most important hallmark of PD [20,31,38,39,43]. The nigral damage, however, always is accompanied by extensive extranigral pathology, including that in the dorsal motor nucleus of the glossopharyngeal and vagal nerves (i.e. dorsal IX/X motor nucleus) and adjoining intermediate reticular zone, in some subnuclei of the reticular formation and the raphe system, the coeruleus–subcoeruleus complex, the magnocellular nuclei of the basal forebrain, and many subnuclei of the thalamus and amygdala. Cases with severe damage usually show lesions reaching the neocortex [10,13,22,23,50,53,63].

The question arises as to whether the pathology evolves simultaneously at all of these nigral and extranigral induction sites or whether the various sites differ in their susceptibilities to develop the disease-related alterations and, accordingly, follow a coherent sequence. The present study, therefore, intentionally includes a spectrum of cases exhibiting LNs and LBs in a specific subset of neuronal

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types and predilection sites, which are known to be involved in clinical PD cases. In doing so, we assume it to be correct that nonsymptomatic and symptomatic cases can be ordered in such a manner that cases exhibiting the mildest pathology represent the starting point and those most heavily involved the terminus of a disease spectrum, with a tendency toward increasing severity on the part of the overall pathology (Table 2). According to this assumption, the neuronal damage does not develop randomly but, rather, follows a predetermined sequence marked by characteristic changes in topographical extent. The present study is aimed at working out a neuropathological staging procedure based upon the topography of these changes. It is not our intent here to correlate the proposed neuropathological stages with clinical symptoms. Furthermore, we would like to emphasize that the study sample does not include cases clinically diagnosed as diffuse LB disease. Likewise, we did not detail study cases which were neuropathologically classified as fully-developed Alzheimer's disease (AD) with co-occurring LBs and LNs in prosencephalic areas. It remains to be seen whether deviations from the proposed staging scheme exist in cases of advanced AD with LBs or in cases of clinically assessed diffuse LB disease.

## 2. Materials and methods

Three groups of cases were studied. The first group consisted of brains obtained at autopsy from 41 individuals with clinical diagnoses of PD (19 females, 22 males, aged  $75.7 \pm 7.2$  years, Table 2). The clinical protocols of these cases noted the predominance of either tremor or rigidity combined with hypokinesia and postural instability. The brain tissue exhibited nigral LBs and severe loss of nigral neuromelanin-laden neurons [16,30,37,62] (Fig. 2).

The second group included autopsy brains from 69 individuals. In most of these cases, the clinical records made no reference to PD-associated symptoms. A few cases with severe pathology were misdiagnosed or did not receive a clinical diagnosis (Table 2). All 69 cases showed the presence of LNs and/or LBs in a subset of neuronal types at the aforementioned predilection sites (35 females, 34 males, aged  $76.1 \pm 7.9$  years). Cases with comparably mild alterations are referred to here as incidental cases. They were detected by screening 413 autopsy cases sent to the Institute from several general hospitals. Cases from specialized clinics for neurological or psychiatric diseases were excluded from the screening procedure [59]. None of the incidental cases found in the material was secondarily excluded.

The third group, which included 58 age- and gender-matched cases (25 females, 33 males, aged  $75.9 \pm 8.2$  years, data from individual cases not shown), was used for comparison. The previous medical histories of these cases did not include a record of neurological or psychiatric disease. None of these cases contained LB/LNs in the dorsal IX/X motor nucleus. The same sets of tissue blocks were taken

and the same staining procedures performed as those applied to the incidental cases, chiefly to exclude the possibility that cases develop the first LNs/LBs at induction sites other than those described in this study.

The severity of co-occurring AD-related pathology was classified according to a procedure permitting differentiation of stages I–VI in the development of neurofibrillary changes and stages A–C in the evolution of  $\beta$ -amyloid deposits (Table 2) [6,48].

The brains were fixed by immersion in a 4% aqueous solution of formaldehyde. The 33 cases (Table 2, indicated by “4” under “mat”) were processed in the following manner: the brain stems were severed at the border between the pontine tegmentum and mesencephalic tegmentum. The hemispheres then were divided midsagittally, and one hemisphere from each case was embedded in polyethylene glycol (PEG 1000) [7] and sectioned perpendicular to the intercommissural (Forel's) axis into uninterrupted series of 100  $\mu\text{m}$  thick free-floating sections. The brain stems were similarly processed but cut perpendicular to the brain stem (Meynert's) axis.

The incidental cases with LNs and LBs were processed differently. The brain stems of some were severed from the hemispheres at the latitude of the mamillary bodies, thus including the substantia nigra in its entirety. These brain stems were processed as described earlier, and additional blocks of brain tissue were dissected from one of the hemispheres, usually cut in the frontal plane. In each case, the blocks included (1) a portion of the magnocellular nuclei of the basal forebrain (usually part of nucleus of the diagonal band) as well as adjoining portions of the amygdala, (2) uncus portions of the hippocampal formation, the entorhinal region, the anteromedial temporal mesocortex together with the adjoining neocortex usually extending up to the first temporal convolution, (3) the hippocampal formation at the level of the lateral geniculate body, (4) an expanse of tissue from the agranular to granular insular cortex, (5) the anterior cingulate proneocortex and adjoining frontal neocortex, and (6) the olfactory bulb, tract, and/or anterior olfactory nucleus.

The brain stems of all of the other cases (marked by “1” under “mat” in Table 2) were cut into slices of about 3 mm thickness. Selected sections from a subset of these slices included (1) the dorsal IX/X motor nucleus and adjoining intermediate reticular zone, (2) the gigantocellular reticular nucleus and nucleus raphes magnus, (3) the coeruleus–subcoeruleus complex, and (4) the posterior subnuclei of the substantia nigra. These brain stem blocks were supplemented by the full number of the above-listed prosencephalic blocks, which were removed from one of the hemispheres. The free-floating 100  $\mu\text{m}$  thick sections were processed using various staining methods.

For topographical orientation, sections were stained for lipofuscin pigment (aldehyde-fuchsin) as well as for Nissl material (Darrow red). Aldehyde-fuchsin staining was employed because pigmentation properties can be utilized to

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