Parkinsonism and Related Disorders 20S1 (2014) S57–S61

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Staged pathology in Parkinson's disease

Irina Alafuzoff [a,b,*], Laura Parkkinen [c]

[a] Department of Pathology and Cytology, Uppsala University Hospital, Uppsala, Sweden
[b] Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
[c] Nuffield Department of Clinical Neurosciences, Oxford Parkinson's Disease Centre, University of Oxford, United Kingdom

ARTICLE INFO

Keywords:
α-Synuclein
Neuropathology
Staging

SUMMARY

There has been a tremendous development since a regional progression of pathology in subjects with Lewy bodies (LB) was initially proposed 30 years ago. The entity of dementia with Lewy bodies has been acknowledged, the main protein constituent of LBs – aggregated α-synuclein (αS) – has been identified and a stepwise progression of the pathology has been reported. Implementation of the staging strategies published provides a common ground for handling a case with a suspected α-synucleinopathy. It is always important to state the staging strategy implemented while assessing a case, as the strategy applied might influence both the reported stage of LB pathology and, ultimately, the final diagnosis of the patient.

1. Introduction

Neuropathological diagnosis of neurodegenerative diseases is generally based on visualization of pathological alterations in the brain tissue. Regarding Parkinson's disease (PD), the hallmark lesion, Lewy body (LB) measuring 5 to 25 μm in diameter, was described already 100 years ago [1], followed by the description of a pale body measuring around 30 μm in diameter in 1930 [2]. Since then, clinicians have looked for these pathological lesions in selected neuroanatomical regions in the postmortem brain tissue of patients succumbing to a clinical diagnosis of PD.

In 1961 it was reported, and later confirmed by other studies, that neuronal cytoplasmic LBs are not only observed in the pigmented neurons in the subtentorial regions of the brain but are also seen in the cortex. Furthermore, it was noted that subjects with widely distributed LB pathology displayed clinical signs of dementia [3,4]. Thus, it became evident that LBs that had been investigated in PD cases should also be investigated in subjects with dementia, i.e., in subjects with the newly defined dementia with Lewy bodies (DLB) [4]. Previously, visualization of LBs was based on conventional histological stains such as hematoxylin–eosin stain (Fig. 1) and from the 1980s onwards ubiquitin immunohistochemistry (IHC) was applied that was considered sensitive and reliable. At the end of the 1980s, a protein, the presynaptic α-synuclein (αS), was described and towards the end of the 1990s it was clear that this protein was a significant component of LBs (Fig. 1) [5,6]. Soon after this, it was noted that the hallmark pathology, i.e. aggregation of αS, was not just confined to the neuronal cytoplasm and processes, but was also observed in the glial cells in cases defined as multiple system atrophy (MSA) [7]. Thus, the initially observed LB in a solitary disease entity, i.e., PD, had evolved into a complex syndrome including disease entities such as PD, DLB, and MSA all sharing the same protein alteration. Currently, it is still debated whether these diseases represent one and the same "disease" or different diseases displaying one shared alteration.

Several reports have indicated that the αS aggregation was not only observed within the brain but was rather universally widespread as it was seen in the neuronal compartment in the spinal cord, gastrointestinal tract, and in the endocrine organs [8–10]. Already in the 1970s, it was assumed that the pathological alterations in PD/DLB spread throughout the brain in a certain fashion. Thus, in the 1980s, the first report suggesting standardized assessment of LBs in subjects with Lewy body disease (LBD), based on regional distribution of pathology was published [11]. Based on these principles, the first consortium guidelines for neuropathological diagnosis of DLB were launched in 1996 [12] followed by a detailed staging strategy of LB-related pathology in PD in 2003 [13].

The finding of LBs in dopaminergic neurons that had been grafted into PD patients [14] together with pathological observations of anatomical "spread" endorsed the hypothesis that αS pathology could be propagated from region to region in a prion-like fashion. Although there is now accumulating evidence from cell cultures and animal models demonstrating that exogenously applied αS infiltrate surrounding cells and initiate PD-like pathological response, we do not know whether this occurs in a human setting. Other mechanisms such as oxidative stress could explain the appearance of αS in the grafted dopaminergic neurons as these cells show

* Corresponding author. Prof. Irina Alafuzoff, M.D., Ph.D., Uppsala University/Uppsala University Hospital, Department of Immunology, Genetics and Pathology, Rudbeck Laboratory, Dag Hammarskjölds väg 20, 751 85 Uppsala, Sweden.
E-mail address: irina.alafuzoff@igp.uu.se (I. Alafuzoff).

1353-8020/$ – see front matter

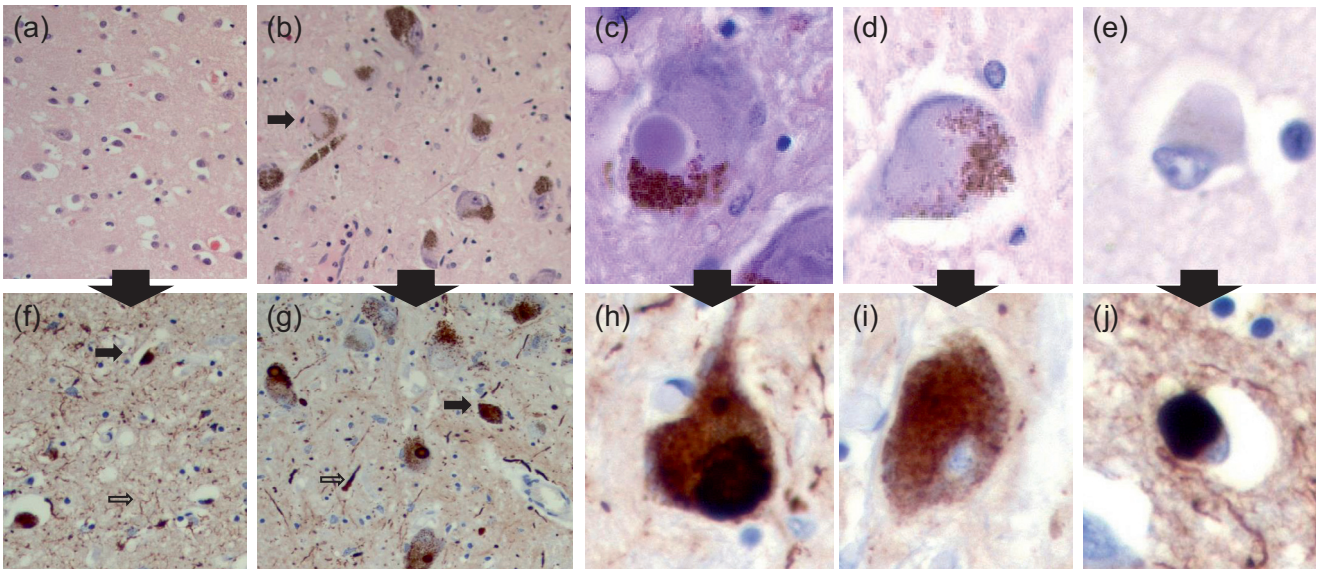

Fig. 1. Visualization of the difference in demonstrating Lewy bodies while applying histological (hematoxylin–eosin [HE]) and immunohistochemical (IHC) stains (brown chromogen α-synuclein [αS]). Note numerous labeled neurites (open arrows) and neuronal inclusions (black arrows) in panel (f) (IHC/αS) when compared with panel (a), both taken from the frontal cortex of the same subject with dementia with Lewy bodies. Note a Lewy body in HE in panel (b) from the substantia nigra of a subject with Parkinson's disease when compared with neurites and inclusions seen in panel (g) with IHC/αS in the same region. In panel (c) a Lewy body, in (d) a pale body in substantia nigra, and in (e) a cortical Lewy body in the frontal cortex in HE stain when compared with the same lesions in the same regions in IHC/αS stain in (h)–(j). (The color version of this figure is available in the online publication.)

peculiarly large amounts of neuromelanin for "10-year old neurons". In addition, most of the PD patients are already in later stages and therefore we do not know how and if the spreading of αS pathology has occurred. Also, many have reported cases where LB pathology is not observed in all predilection sites as expected [15,16]. Thus, there is not enough evidence to rule out different patterns of spreading (if it exists) and the possibility of multifocal initiation of αS pathology. Other unanswered questions include which αS species (i.e. oligomeric, fibrillar) could spread and why this transmission would be only through specific neural connections when experimental evidence has shown that αS can also be taken up by non-neuronal cells [17].

Neuropathological assessment has been primarily carried out to confirm a clinical presumption that the neurological symptoms observed were based on LB pathology. Incidental pathology, i.e., pathological alteration seen in non-impaired subjects, was seldom reported routinely. When we examined LB pathology by using αS IHC in a large autopsy cohort (n = 1720) irrespective of clinical status, we found overall prevalence to be around 15% but this varied between selected subcohorts [15]. Moreover, we found that ~50% of cases with widespread αS pathology (Braak's PD stages 5–6) lacked clinical signs of dementia and/or parkinsonism [15]. Later on, these findings have been supported by the fact that neither the distribution nor the actual densities of LBs in the brainstem or cortex correlate with nigral cell loss [18,19] contradicting their primary pathological role. These studies on human brains have provided strong support for the recent biomolecular studies proposing that LBs may represent failed cytoprotective efforts of protein quality control machineries in response to accumulating toxic intermediate αS species. However, until we understand more about these pathogenetic cellular mechanisms it remains crucial to assess patients with similar pathology together, so that they are comparable to one another.

Thus, in summary, starting with identifying a "hallmark" lesion some 100 years ago, the neuroscience community has evolved identifying a certain protein constituent that can be visualized by means of IHC, broadening the view regarding the regional distribution of the lesion of interest, and launching guidelines regarding assessment strategies, i.e., staging of αS pathology. Moreover, in recent years it has been suggested that αS aggregation can spread throughout the brain in a predictable stepwise fashion and that this process could start outside of the central nervous system. Each of the issues above is influenced by many often unpredictable factors that are discussed below.

2. Visualization of lesions

Since the 1980s, the neuropathology community has implemented IHC techniques in diagnostics, in addition to the conventional histological stains, thereby visualizing protein constituents in the lesions observed. There are a huge number of proteins to be visualized, proteins that are structurally altered, or physiological proteins that are increased or decreased in the tissue/cells due to a pathological process. One should be aware that the obtained IHC staining results are influenced by the technique applied, the antibody used, and the characteristics of the tissue assessed.

In the field of neurodegenerative disorders, when studying humans, the brain tissue available is obtained postmortem. The brains are sampled primarily for diagnostic purposes from subjects suffering from a disorder causing neurological symptoms. There are several "brain banks" that sample postmortem brains for research (http://www.brainnet-europe.org). The cases included are often subjects enrolled in prospective studies of a disorder of interest. The postmortem brain is subjected to many events that alter the tissue and should be acknowledged. One such event is agonal state. Many of the epitopes to be targeted by antibodies via IHC might be significantly altered by premortem ischemia. Pneumonia and circulatory failure are both common final causes of death in the aged population with neurodegenerative disease. Another factor to be aware of is the postmortem delay that can range from a few hours to weeks. In one center, including 2,270 postmortem cases, the mean for postmortem delay was 3.4 days, in another including 505 cases the mean was 4.5 days (personal experience). Postmortem delay in brain banks for research is usually shorter, but the material is generally highly selected. Furthermore, some of the deceased are stored in refrigerated facilities during most of this time