Lewy body-related α-synucleinopathy in the aged human brain

K. A. Jellinger

Institute of Clinical Neurobiology, Vienna, Austria

Summary. To clarify the significance of Lewy body (LB)-related α-synucleinopathy in aging and various neurodegenerative disorders, its incidence and topographic pattern were examined in 260 brains of elderly patients, including 116 autopsy-proven cases of Alzheimer disease (AD), 71 cases of clinically and autopsy-proven Parkinson disease (PD), 38 of dementia with Lewy bodies (DLB), 8 patients with progressive supranuclear palsy (PSP), one with senile tremor, and 26 age-matched controls without neuropsychiatric disorders. Using immunohistochemistry, α-synuclein (AS) positive lesions were assessed semiquantitatively. For technical reasons, the olfactory system was not systematically studied. All PD-brains showed AS-positive lesions in medullary, pontine and mesencephalic nuclei, with involvement of the nucleus basalis (90.1%), limbic cortex (58.9%), cingulate cortex (46%), amygdala, CA 2/3 hippocampal region (36.2%), neocortex (28.8%), and striatum (11%). 88% of clinical PD cases corresponded to LB pathology stages 4–6, 12% to stage 3 according to Braak et al. (2003). 84% of DLB brains were PD stage 5 or 6 and 17% stage 4, without significant differences between DLB with and without neuritic AD pathology, suggesting morphologic similarities between these disorders. 6/8 PSP and senile tremor cases, 49.1% of AD and 69% of aged controls were negative. AS-positive lesions in AD showed decreasing incidence from midbrain (24–28%), limbic cortex and amygdala (17–18%), nucleus basalis and medullary nuclei (13–17%), cingulate cortex (12%), CA 2/3 region (8%) to neocortex (2%), without gender differences or relationship to the severity of AD pathology (mean Braak stage 5.1). AD cases with AS positive lesions, particularly those with AS pathology in the amygdala, were older at death than negative ones (86.6 vs 83.3 yrs), but this difference was not statistically significant. 15 AD cases (seven of them with mild PD symptoms) and 3 aged controls without parkinsonian signs but LB pathology stages 3 (n = 5) and 4 (n = 13) were considered “incidental LB disease”. 16 AD brains without parkinsonian symptoms had AS positive lesions.

* In memory of Prof. Mel Yahr, M.D., the great pioneer of Parkinson research
in various areas without medullary involvement, suggesting deviation from the proposed stereotypic expansion pattern. Located AS-pathology in the midbrain and limbic cortex was seen in 31% of asymptomatic aged controls. These data 1. largely confirm Braak’s staging of LB-pathology in PD; 2. suggest morphologic and pathogenic relations between PD (brainstem type) and DLB with and without coexistent AD pathology; 3. the occurrence of LB-related α-synucleinopathy in about 50% of AD brains and about 30% of aged controls. However, the basic mechanisms of LB-related AS-pathology and their pathogenic and clinical relevance in aged brain and neurodegenerative disorders await further elucidation.

Keywords: α-Synuclein pathology, Parkinsonian syndromes, dementia with Lewy bodies, Alzheimer disease, immunohistochemistry, staging of Lewy body pathology.

Introduction

Lewy body (LB)-related α-synucleinopathy is one of the most important processes of posttranslationally modified protein accumulation in the aging brain. Alpha-synuclein (AS) immunoreactive inclusions (LBs and dystrophic neurites/LNs), are one of the morphological hallmarks of Parkinson disease (PD) or brainstem type of LB disease, the most common neurodegenerative movement disorder in the elderly, but also occur in dementia with LBs (DLB), a combination of cognitive impairment and parkinsonism (McKeith et al., 1996), and in a variety of neurodegenerative disorders including aging and Alzheimer’s disease (AD) (Alafuzoff and Parkkinen, 2003; Jellinger, 2003; Kotzbauer et al., 2001; Lippa, 2003; Parkkinen et al., 2003; Saito et al., 2003, 2004). Some of them may correspond to “incidental LB disease” (Del Tredici et al., 2002) or incipient synucleinopathy with no or only little clinical manifestation, suggesting that subclinical PD is present concurrently in some elderly subjects.

There is increasing evidence that PD is a multiple system disorder with progressive degeneration of the dopaminergic nigrostriatal systems and widespread extranigral pathology (Braak et al., 2002, 2003; Jellinger and Mizuno, 2003). The onset of LB-related AS-pathology in PD has been shown in the “gain setting nuclei” of the lower brainstem (dorsal motor vagal nuclei/dmX, adjoining areas of magnocellular reticular formation and raphe system) and the olfactory system (stage 1–2), with ascending progression to the coeruleus complex (LC), substantia nigra pars compacta (SNc), the magnocellular nuclei of the basal forebrain, subnuclei of thalamus and amygdala (stage 3), and inconsistent involvement of the neocortex (stages 5 and 6) (Braak et al., 2002, 2003; Jellinger, 2003). Stages 1 and 2 were considered presymptomatic; stage 3 being occasionally associated with PD symptoms, that usually occur in stage 4 (prosencephalic and limbic cortical lesions), and in the terminal stages 5 and 6 (involvement of sensory association and prefrontal areas, later of primary sensory and motor areas). These late stages may indicate a transition between PD and DLB (Jellinger, 2003; Saito et al., 2004).

AS pathology, both cortical and subcortical, has been observed in up to 14% of subjects over the age of 40 years, more frequently in demented individuals (Alafuzoff and Parkkinen, 2003; Parkkinen et al., 2003; Saito et al., 2003),