Neurobiology of Disease 41 (2011) 377–384

Contents lists available at ScienceDirect

Neurobiology of Disease

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

Striatal Aβ peptide deposition mirrors dementia and differentiates DLB and PDD from other Parkinsonian syndromes

M.E. Kalaitzakis *, A.J. Walls, R.K.B. Pearce, S.M. Gentleman

Neuropathology Unit, Centre for Neuroscience, Division of Experimental Medicine, Department of Medicine, Imperial College London, Charing Cross Campus, St Dunstan's Road, London, UK, W6 8RP

ARTICLE INFO

Article history:
Received 24 March 2010
Revised 29 September 2010
Accepted 7 October 2010
Available online 14 October 2010

Keywords:
Parkinson's disease
Dementia
Striatum
Amyloid-β peptide
[^{11}C]PIB ligand
Dementia with Lewy bodies
Neuropathology
Lewy body disease

ABSTRACT

Recent neuropathological studies have described widespread amyloid-β peptide (Aβ) deposition in the striatum of patients with Lewy body disorders, particularly in Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB). However, positron emission tomography (PET) studies using the [^{11}C]PIB ligand, binding to Aβ deposits, detects significant striatal pathology only in DLB and not in PDD. Employing immunohistochemistry, we examined striatal Aβ deposition in the caudate nucleus and putamen of 52 PD, 41 PDD, 14 DLB, 7 multiple system atrophy (MSA) and 14 progressive supranuclear palsy (PSP) cases in relation to the presence of dementia. PD, MSA and PSP cases showed little or no Aβ pathology in the striatum. In contrast, both PDD and DLB cases demonstrated significantly greater Aβ deposition in the striatum when compared to PD, MSA and PSP groups. We conclude that striatal Aβ pathology is common in both PDD and DLB and may reflect the development of dementia in these conditions. More detailed examination of the morphology of the Aβ pathology suggests that it is the presence of cored amyloid plaques in DLB, but not PDD, that underlies the differences seen in PET imaging.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the gradual onset and progression of both motor and non-motor disturbances (Fearnley and Lees, 1991). The defining pathological features of the disease are the loss of dopaminergic projection neurones of the substantia nigra pars compacta and locus coeruleus, as well as the presence of α-synuclein (αSyn) positive inclusions in cell bodies and cell processes of brainstem neurones, called Lewy bodies (LB) and Lewy neurites (LN), respectively. However, the pathology in PD exceeds the classical boundaries of the substantia nigra and locus coeruleus with involvement of multiple extranigral sites in both the central and peripheral (autonomic) nervous system (Braak and Braak, 2000). Co-morbid pathology characteristic of Alzheimer's disease (AD) is also often seen in patients with PD (Jellinger, 2009; Jellinger et al., 2002).

Although PD is traditionally viewed as a movement disorder, non-motor complications, including dementia, are commonly seen in PD patients, with a prevalence of up to 50% (Emre, 2003; Emre et al., 2007). The risk for dementia in PD (PDD) increases with age and duration of disease (Emre, 2003) with other risk factors including age at onset, an akinetic-rigid syndrome, depression, early autonomic failure and a poor response to dopaminergic treatment (Aarsland et al., 1996; Emre et al., 2007; Hietanen and Teravainen, 1988; Reid et al., 1996).

Despite a high incidence of dementia in PD (PDD) the precise anatomico-pathological basis for this remains unclear. Cortical, subcortical and limbic αSyn pathology have been linked to dementia in PD (Aarsland et al., 2005; Hurtig et al., 2000; Mattila et al., 2000), although other authors have described advanced αSyn pathology without clinical dementia (Parkkinen et al., 2005). We, and other groups, have demonstrated the presence of amyloid-β peptide (Aβ) pathology in the striatum of PDD and dementia with Lewy bodies (DLB) patients (Duda et al., 2002; Jellinger and Attems, 2006; Kalaitzakis et al., 2008; Liang et al., 2006). A possible distinction between PD, PDD and DLB on the basis of differences in Aβ striatal pathology has also been suggested (Jellinger and Attems, 2006; Kalaitzakis et al., 2008). Imaging studies, however, using Pittsburgh compound B ([^{11}C]PIB) positron emission tomography (PET), as a marker of brain amyloid deposition, have demonstrated an increased Aβ load in the striatum of DLB but not PDD patients (Edison et al., 2008).

In this immunohistochemical study we set out to explore the significance of striatal pathology in Lewy body diseases by investigating the extent and nature of Aβ deposition in the striatum of PD (n = 52), PDD (n = 41), DLB (n = 14), multiple system atrophy (MSA) (n = 7) and progressive supranuclear palsy (PSP) (n = 14) cases in relation to the presence of dementia.

* Corresponding author.
E-mail address: michail.kalaitzakis03@imperial.ac.uk (M.E. Kalaitzakis).
Available online on ScienceDirect (www.sciencedirect.com).

0969-9961/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.nbd.2010.10.005

Materials and methods

Neuropathological assessment

Neuropathological diagnosis was based on αSyn, tau and Aβ immunohistochemistry of superior frontal gyrus, hippocampus, and midbrain. Confounding pathology was assessed on haematoxylin and eosin stained slides from 18 brain tissue blocks. Tissue was collected and processed according to an established protocol (Vonsattel et al., 1995). Neuropathological diagnosis was performed using international neuropathological consensus criteria for the definite diagnosis of PD (http://www.ICDNS.org). AD pathology of isocortical and/or entorhinal types was also assessed using the generic grading system posted at http://www.ICDNS.org and staged according to the scheme of Braak and Braak using AT8 immunohistochemistry (Braak et al., 2006). Cases with a co-morbid clinico-pathological diagnosis of AD were excluded from further analysis. All human tissue work was carried out under the ethical approval held by the UK Parkinson's Disease Society Tissue bank at Imperial College (REC Ref: 07/MRE09/72).

Clinical assessment and selection of cases

In the present study 128 cases collected from the UK Parkinson Disease Tissue Bank with PD and related neurodegenerative diseases were examined. This included 52 cases with PD (mean age at death 75.5 years), 41 cases with PDD (mean age at death 78.4 years), 14 cases with DLB (mean age at death 75.8 years), 7 cases with MSA (mean age at death 69.2 years) and 14 cases with PSP (mean age at death 77.9 years) (Table 1).

Clinical data of cases were compiled retrospectively from hospital records by a movement disorder neurologist (RKBP). Only subjects evaluated by a clinician within 2 years prior to death and with complete clinical histories were included in this study. The clinical diagnoses of PD, PDD and DLB were based on published criteria (Daniel and Lees, 1993; Hurtig et al., 2000; McKeith et al., 2005). PD was considered to be present if the patient had at least 2 of the 4 cardinal symptoms (rigidity, hypokinesia, resting tremor and postural instability) and exhibited a positive response to levodopa (Daniel and Lees, 1993). Patients with PD who developed late dementia (>2 years after motor symptoms) were classified as PD with dementia (PDD) (Hurtig et al., 2000). The diagnosis of DLB was made if dementia preceded extrapyramidal symptoms by 1 year or they developed together within a 12-month period (McKeith et al., 2005). The diagnosis of dementia satisfied DSM-IV and ICD-10 clinical criteria. Retrospective case–note analysis is a well accepted method of case ascertainment and has often been used in clinico-pathological studies involving both dementia and parkinsonism (Kalaitzakis et al., 2009; Litvan et al., 1998; Papapetropoulos et al., 2005).

Immunohistochemistry

Immunohistochemistry was performed using standard protocols (Parkkinen et al., 2005). The primary antibody used in this study was 4G8 for visualization of Aβ plaques (Signet at a dilution of 1:2000) as recommended by a recent study from the BrainNet Europe Consortium (Alafuzoff et al., 2008) and tyrosine hydroxylase for examination of nigrostriatal fibers (Vector, Peterborough, UK, at a dilution of 1:30).

Semi-quantitative assessment of Aβ pathology

For each case, a representative section from the caudate nucleus (CN) and putamen (Put) was assessed for Aβ immunoreactivity. Sections were screened in their entirety at 10× primary magnification for overall deposit burden. Assessment of pathology was carried out by examining the extent of deposits with semi-quantitative grading ranging from (0) 1 to 3 corresponding to (absent) sparse, moderate and frequent (Fig. 2) as previously described (Kalaitzakis et al., 2008). Sections were graded by two investigators blinded to diagnosis (MEK and AJW). Cohen's kappa statistic revealed an inter-rater reliability of 0.85 for Aβ lesions.

Statistical analysis

Statistical analysis was performed using the SPSS program version 15.0 for Windows XP and GraphPad Prism 4. The differences in Aβ burden as well as age at disease onset, age at death and duration of disease between the different diagnostic groups were analyzed with the non-parametric Mann–Whitney *U*-test. The association between Aβ burden and age at death, onset and duration of disease among the different diagnostic groups was assessed using Spearman's two-tailed correlation analysis (non-parametric). Cohen's kappa statistic was used to test inter-rater reliability for the Aβ semi-quantitative assessment between the two investigators. Intra-rater reliability was also examined by measuring the striatum of ten randomly selected subjects on six occasions at least a week apart. On each occasion, all operator-dependent processes (i.e. region of interest semi-quantitative assessment) were performed blinded to previous values. High intra-rater (and inter-rater) reliability was observed. P values <0.05 were considered significant.

Results

Clinical data

The clinical characteristics of the different diagnostic groups examined are shown in Table 1. Statistical analysis demonstrated a significant difference with respect to age at disease onset between PD and DLB cases with the latter showing a later disease onset (61.7 vs. 69.5 years, respectively; $p=0.01$). Cases with a diagnosis of MSA demonstrated a significantly earlier age at death than cases with a diagnosis of PDD (69.2 vs. 78.4 years, respectively; $p=0.04$). Compared to PD and PDD cases the duration of disease was significantly shorter in DLB ($p=0.001$, $p=0.003$, respectively), MSA ($p=0.008$, $p=0.004$, respectively) and PSP ($p=0.01$, $p=0.005$, respectively) cases (Table 1).

Tyrosine hydroxylase immunohistochemistry

Tyrosine hydroxylase (TH) immunohistochemistry was performed in all cases and global patterns of staining in the CN and Put were assessed. All cases showed severe dopaminergic terminal denervation as indicated by with scant or essentially absent TH positivity (Fig. 1).

Striatal Aβ pathology

Aβ pathology was detected in all diagnostic groups to a varying extent. Aβ deposition was observed in the caudate nucleus and putamen, but no Aβ pathology was detected in the internal capsule. The caudato-lenticular gray bridges were also involved. The extent of Aβ burden in the different diagnostic groups is shown in Fig. 2.

The morphology of Aβ deposits was similar to that we have described previously (Kalaitzakis et al., 2008) (Figs. 2 and 3). The most common form of Aβ striatal pathology was that of small, intensely stained 'diffuse' deposits that outnumbered large plaques by a factor of 3:1. Intensely stained diminutive (the size of a glial cell nucleus) and 'dot-like' aggregates were also present. Perhaps most significantly, all but one of the DLB cases demonstrated cored plaques (Fig. 3), with an average number of 20 cored plaques per section. By contrast none of the PDD, PD, MSA and PSP cases exhibited any cored plaques