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Voxel-based morphometry in autopsy proven PSP and CBD

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Abstract

The aim of this study was to compare the patterns of grey and white matter atrophy on MRI in autopsy confirmed progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), and to determine whether the patterns vary depending on the clinical syndrome. Voxel-based morphometry was used to compare patterns of atrophy in 13 PSP and 11 CBD subjects and 24 controls. PSP and CBD subjects were also subdivided into those with a dominant dementia or extrapyramidal syndrome. PSP subjects showed brainstem atrophy with involvement of the cortex and underlying white matter. Frontoparietal grey and subcortical grey matter atrophy occurred in CBD. When subdivided, PSP subjects with an extrapyramidal syndrome had more brainstem atrophy and less cortical atrophy than CBD subjects with an extrapyramidal syndrome. PSP subjects with a dementia syndrome had more subcortical white matter atrophy than CBD subjects with a dementia syndrome. These results show regional differences between PSP and CBD that are useful in predicting the underlying pathology, and help to shed light on the in vivo distribution of regional atrophy in PSP and CBD.

Keywords: Progressive supranuclear palsy; Corticobasal degeneration; Magnetic resonance imaging; Pathology; White matter; Grey matter; Dementia; Parkinsonism; Extrapyramidal

1. Introduction

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are neurodegenerative diseases that were both initially described as distinct clinicopathological entities [41,50]. The cardinal clinical features of PSP are a symmetric akinetic-rigid syndrome with vertical supranuclear gaze palsy and early falls [9,15,31,32], while in CBD the cardinal features are asymmetric apraxia, dystonia, cortical sensory loss, and Parkinsonism [4,30]. Both PSP and CBD were initially considered an extrapyramidal disorder.

Over the last decade however there have been numerous reports of "atypical" clinical presentations of pathologically confirmed PSP and CBD [5,24–26,34,44,52,53,57]. Both entities can present as a predominant motor or dementia disorder [2]. In one series dementia was the most common presentation of CBD [17]. Therefore, it is now recognized that PSP and CBD can present either as a predominant extrapyramidal/motor disorder, or as a predominant dementia disorder.

Clinical syndromes are defined by a set of relatively specific signs and symptoms which result from dysfunction or damage to specific anatomical structures. In neurodegenerative diseases, however, the relationship between specific clinical syndromes and pathological diagnoses remains unclear [26]. It is also unclear whether a specific clinical syndrome,

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e.g. a dementia syndrome, arising from either PSP or CBD has the same anatomic correlate.

Therefore, the aims of this study were: (1) to compare the patterns of grey and white matter atrophy on MRI using voxel-based morphometry (VBM) in a group of autopsy confirmed PSP subjects to a group of autopsy confirmed CBD subjects, (2) to determine whether the patterns of atrophy in a dementia syndrome arising from PSP is identical to those from a dementia syndrome arising from CBD, and (3) to determine whether the patterns of atrophy in an extrapyramidal syndrome arising from PSP is identical to those from a extrapyramidal syndrome arising from CBD.

2. Methods

From our pathological database located in Rochester, Minnesota, we identified all subjects with autopsy confirmed CBD ($N=21$) and PSP ($N=52$) between 1 January 1970 and 31 December 2005. Detailed clinical information on all of these 73 cases (except for three recent cases) was previously published [26]. The historical records were reviewed by a clinician versed in movement disorders and dementia (KAJ), blinded to pathological diagnosis, for the abstraction of data, including gender, education, age at onset, illness duration, short test of mental status (STMS) [29], Hoehn and Yahr scale score [23], Mattis Dementia Rating Scale score (DRS) [21], the Clinical Dementia Rating (CDR) [35] scores (sum of boxes and global scores) and the signs and symptoms recorded in the historical records by the treating physician at the time of MRI scan. We included only subjects that had been evaluated and treated by a neurodegenerative specialist. We excluded any subject who did not have a volumetric MRI scan. Of the 21 cases of CBD, 11 met our inclusion and exclusion criteria while 13 of the PSP subjects met criteria. All cases were followed as part of the Mayo Clinic Alzheimer's Disease Research Center (ADRC), or the Alzheimer's Disease Patient Registry (ADPR) and all diagnoses were made prospectively. Each case was age and gender matched to a normal control (total $N=24$). In addition, a fluid attenuated inversion recovery (FLAIR) sequence from each subject was assessed by an experienced neuroradiologist (CRJ) in order to evaluate the degree of white matter disease burden. The white matter disease burden was found to be negligible in all cases. The MRI scans of all the CBD subjects were visually inspected to determine asymmetry. Four CBD subjects had greater involvement of the left hemisphere, four had greater involvement of the right hemisphere, and three showed a symmetric pattern.

2.1. Pathological analysis

All 24 cases had died after 1991 and neuropathological examinations were performed according to the recommendations of the Consortium to Establish a Registry for Alzheimer's disease [33]. After removal of the brain, one hemisphere was fixed in 10% buffered formaldehyde for 7–10 days followed by the taking of 7 μ sections. Routinely sampled areas were the middle frontal gyrus (Brodmann area, BA, 9), inferior parietal lobule (BA 17), anterior temporal gyrus (BA 24), hippocampus at the level of the lateral geniculate, amygdala, transentorhinal and entorhinal cortices at the level of the mamillary bodies, nucleus basalis, cerebellum, dorsomedial thalamus with subthalamic nucleus, midbrain with substantia nigra, pons, and medulla. All samples were processed in paraffin and had been stained with hematoxylin and eosin, glial fibrillary acid protein and modified Bielschowsky or Bodian silver. Immunohistochemical analysis was also performed with a battery of antibodies: glial fibrillary acid protein (clone GA5, 1:1000; BioGenex, San Ramon, CA) and either CD68 (clone PG-M1, 1:1000; DAKO, Carpenteria, CA) or HLA-DR (LN-3, 1:5; ICN, Costa Mesa, CA) for microglia. Neuronal pathology was studied with antibodies to neurofilament protein (NF-L: clone 2F11, 1:75; DAKO, Carpenteria, CA; NF-H: clone SMI-31, 1:2000; Sternberger Monoclonals, Lutherville, MD); ubiquitin (clone Ubi-1 (MAB1510), 1:250; Chemicon, Temecula, CA); alpha-synuclein LB509, 1:200; Zymed, South San Francisco, CA or NACP98, polyclonal antibody, 1:2000; Mayo Clinic Jacksonville), phospho-tau (CP13: gift from Dr. Peter Davis, Albert Einstein College of Medicine, Bronx, NY or clone AT8, 1:1000; Innogenetics, Alpharetta, GA).

All brain tissue slides had been reviewed independently by two neuropathologists with expertise in degenerative diseases (DWD and JEP) to confirm that the pathological diagnosis met recent published pathological criteria for PSP and CBD [13,20]. PSP was diagnosed if there were neurofibrillary tangles, coiled bodies, neuronal and glial threads, and tufted astrocytes in cardinal nuclei [20], while CBD was diagnosed if there were corticobasal bodies, balloon neurons, coiled bodies, an abundance of neuronal and glial threads and astrocytic plaques in cardinal nuclei [13].

2.2. Subgroup classification

Within each pathological subtype subjects were subgrouped according to whether extrapyramidal signs, or cognitive impairment, dominated the clinical syndrome at the time of MRI scan. The presence or absence of a list of six core features of cognitive impairment, and six core features of motor dysfunction was confirmed for each subject, and a score was given from 0 to 6 for both dementia and extrapyramidal features. The six features of dementia included impairment in orientation, memory, visuospatial skills, attention, language, and learning. The features of motor impairment included akinesia, rigidity, tremor, postural instability, praxis, and dystonia. The subjects were then placed in a specific subgroup based on whether the number of dementia features present, or the number extrapyramidal features present, yielded the higher score. In the event of a tie, the severity of the signs present was then entered into the model to place them into a subgroup. This was possible because each subject had a stan-