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Behavior and cognition in corticobasal degeneration and progressive supranuclear palsy

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ABSTRACT

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), previously described as Parkinsonian syndromes are also cognitive disorders, and biologically related to the frontotemporal dementia or Pick's disease. PSP and CBD overlap clinically, pathologically and genetically, sharing tau haplotypes and mutations. In our series of CBD/PSP patients with cognitive presentation ($n=36$), primary progressive aphasia (PPA) was particularly common, but behavioral onset occurred also. CBD or PSP as motor presentations developed significant language disorder in 17/19. The underlying pathology is predictably tau positive in these clinical combinations, regardless of the presentation. Other cognitive features of CBDS include apraxia, alien hand and apathy, but often frontal lobe dementia with disinhibition develops also. CBDS also has visuospatial deficit, because of the parietal involvement. PSP was considered the prototype of subcortical dementia, with bradyphrenia, poor recall and executive deficit, but cortical features were recognized to be important also. Language testing and a behavioral inventory should be part of neuropsychological tests to facilitate diagnosis and to quantify the deficit. The clinical, genetic and pathological relationship is strong between CBD /PSP and the aphasic and behavioral components of the Pick complex.

1. Introduction

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) were considered primarily as motor disorders or "Parkinson Plus" syndromes with atypical parkinsonism. When PSP was described first as a syndrome of axial dystonia, bradykinesia, falls, dysphagia, and vertical gaze palsy, the mental changes were not emphasized but were evident in all of the cases [1]. Subsequently PSP became the starting point and the most representative example of "subcortical dementia", characterized by 'bradyphrenia' or slow responses, better recognition than recall, preservation of visuospatial and language function (which later turned out to be inaccurate) [2].

Corticobasal degeneration (CBD), originally coricodentatonigral degeneration [3] has core features of asymmetric rigidity (basal ganglionic) and apraxia (cortical) with other features such as cortical sensory loss, alien limb behavior, myoclonus, dystonia, gaze palsy and atypical tremor. The original authors recognized the pathologic similarity of CBD to Pick's disease, but felt that "mental faculties were relatively preserved" in their cases. However, with close reading of the case descriptions, personality and language disorders were evident. Following this report it took 20 years to rediscover CBD [4]. The emphasis in categorizing CBD as a movement disorder remained with the belief that higher cognitive function was "relatively preserved" [5]. Reflecting this perspective the first diagnostic criteria for CBD included "early dementia" as an exclusion [6]. Soon afterwards the same authors described cognitive presentations of CBD pathology [7] and later found that dementia was in fact the most common presentation in their pathologic series of CBD [8].

Cortical involvement was recognized to be also significant pathologically. CBD is characterized by lobar atrophy, which is mainly superior parietal and frontal with relative sparing of the occipital and temporal lobes [9]. PSP pathology is more subcortical in distribution, and it is also characterized by the abnormal accumulation of tau protein accompanied by neuronal loss and gliosis. Tau containing globose neurofibrillary tangles are frequent in subcortical structures particularly basal ganglia and oculomotor nuclei but in PSP extension of tangles to the cortex is well documented.

The overlap of PSP with CBD has been increasingly recognized lately. Many CBD patients also have vertical gaze palsy; some have falls, and PSP patents at times have asymmetrical extrapyramidal syndrome. The pathological biochemical and genetic evidence also support the relationship. They are both considered to be predominantly 4 repeat tauopathies. They have common tau haplotypes [10] and pathogenic tau mutations such as P301L, P301S, and R406W cause either phenotype. There is continuing controversy to what extent PSP and CBD can be differentiated and pathological criteria for each have been validated recently [11]. The evidence is very much in favour however that CBD/PSP are closely related conditions. Furthermore CBD and PSP may be the pathology underlying other conditions in the FTD/Pick complex without the extrapyramidal component (for

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example progressive aphasia and behavioral variant FTD), so the clinical syndromes of CBD and PSP are therefore designated as CBDS (at times CBS) and PSP-S (or PSPS) to distinguish from the prototypic pathologic entities.

A significant overlap between CBDS and the syndromes of FTD/Pick complex was demonstrated in a large series [12]. All of our 35 patients with the clinical syndrome of CBD (CBDS) either had a language disorder or a behavioral and personality change characteristic of FTD (FTD-bv). At times the movement disorder and the progressive aphasia or behavioral disorder developed simultaneously, but in the majority of the cases the cognitive disorder came first ($n=20$). Similarly, in all the cases presenting as the typical CBDS movement disorder ($n=15$), aphasic or behavioral change developed sooner or later indicating that CBDS should be considered part of the Pick complex. Eleven of our 35 cases came to autopsy, six had CBD pathology (one considered having overlapping features of PSP), three cases had Pick's disease (PiD), one had MND-type (motor neuron disease) inclusions, and one DLDH (dementia lacking distinctive histology). The conclusion was that CBD/PSP should be considered part of FTD/Pick complex.

2. Aphasia and language cognition

Descriptions of extrapyramidal involvement in Pick's disease appeared [13] and the combination of aphasia and rigidity in clinical PiD was identified by [14], subsequently called Akelaitis' disease. The overlap of aphasic and asymmetric extrapyramidal syndromes continued to be published in case reports. The Manchester group described a case of progressive aphasia with a right-sided extrapyramidal syndrome combined with limb apraxia, upgaze palsy, primitive reflexes and prominent left temporo-parietal atrophy on CT [15]. CBD pathology was confirmed as a substrate for primary progressive aphasia (PPA) by [16], who described a 69 year old man with a three year history of PPA defined as a transcortical motor aphasia who went on to develop rigidity and posturing of the right arm after the first year. Additional cases of PPA with CBD pathology followed, most [17–22], but not all [23] showing signs of extrapyramidal involvement at some stage before death. Kertesz et al. [19] described cases with PPA, overlapping extrapyramidal signs and behavioral disturbance that had Pick pathology and CBD at autopsy, suggesting that both CBD and PPA should be included with frontal lobe dementia under the rubric of Pick complex (Pick's disease has been reserved mainly by pathologists for Pick body pathology only, although many of us would prefer to restore this historically correct term for the overall clinical syndrome).

Mild anomia or aphasia may be overlooked in the face of motor presentations, and at times attributed to the dysarthria of the extrapyramidal disease or to generalized dementia. Cross-sectional studies without significant follow-up may not notice the subsequent development of the language loss. There is also a reluctance to label progressive loss of language as “aphasia” because this term is traditionally used for focal lesions. Nevertheless, the language loss, when examined formally, has the features of aphasia due to other causes. Despite the now recognized overlap between CBDS and primary progressive aphasia (PPA) there has been little direct comparison of language performance in both. Except for a few studies [19,23–25], reports of aphasia in CBDS tend to be cross-sectional rather than longitudinal, tend not to reflect the evolution from PPA and/or FTD-bv to CBDS or compare between motor and cognitive presentations of CBDS.

We recently reviewed our cohort with CBDS [26] and identified 19 patients with the movement disorder of CBDS as a first syndrome and another larger group of 36 patients who developed CBDS after an initial onset with a cognitive disorder; aphasic, behavioral or both. All cognitive onset CBDS patients and all but two with motor onset CBDS developed aphasia during the course of their illness. Previously we have shown that general cognitive and behavioral measures are similar for each presentation but language scores are lower in cognitive onset cases [12] reflecting the frequency of aphasic presentations. The change in language for cognitive CBDS patients was identical to our other patients with PPA based on the Western Aphasia Battery [27] save for a trend towards worse repetition in CBDS. Initially these patients are significantly anomic but with time they develop problems with expressive language while receptive language and single word comprehension are relatively preserved, corresponding to deficits in progressive non-fluent aphasia [28]. Over time, the picture changes with anomic patients becoming non-fluent, developing Broca's and global aphasias. Our longitudinal follow-up showed that both cognitive CBDS and PPA are distinct from motor CBDS at first but by the fourth year of illness the motor onset group had also begun to develop significant aphasia paralleling the cognitive CBDS group. Apraxia of speech with or without PNFA is a feature of CBD and other tau-positive diseases such as PSP [29].

Although non-fluent aphasia was the predominant pattern, two of our patients had striking preservation of repetition consistent with transcortical sensory aphasia while another two had relatively fluent receptive aphasias classified as Wernicke's by the WAB, both uncommon findings in the CBDS literature [21,30]. One patient in particular with CBD pathology confirmed at autopsy began with word finding difficulty, progressing to prominent deficits in object recognition, comprehension and naming with fluent but markedly circumlocutory speech containing frequent semantic paraphasias. He subsequently showed apraxia and behavioral change characterized by mental rigidity, irritability, aggression, gluttony, hoarding and utilization behavior. Extrapyramidal signs were late and atypical for CBDS because of bilateral rigidity and he died in a psychiatric hospital ten years after onset. Imaging with CT and SPECT scans revealed predominant left-sided frontotemporal atrophy and thinning of the left perisylvian, parietal and anterior temporal regions. This patient resembles semantic dementia [31,32] and it is of particular interest as this variant of FTD has so far been associated with the tau-negative pathology of FTD with motor neuron disease type inclusions and on occasion the tau-positive pathology of PiD but not corticobasal degeneration [33].

Emotional prosody, mediated by both the right hemisphere [34,35] and the basal ganglia [36], has not been systematically studied in CBDS though flat aprosodic speech is mentioned in some case reports of aphasic patients with CBD pathology before the emergence of rigidity [18,24]. It is not known whether this distinguishes CBD pathology from other causes of PPA but limited assessments to date suggest that in typical cases of PPA expressive emotional prosody is preserved [37].

It is generally assumed in CBDS that left hemisphere involvement and right-sided motor disturbance accompanies the aphasia [38]. We found no measurable difference in WAB scores for patients with right versus left-sided motor onset or for left versus right hemisphere atrophy. Another study [39] has used the WAB to examine language function in a cross-sectional study of patients with CBDS. Although the authors did not set out to analyze performance according to the motor side, this can be calculated from their paper and also shows no difference in WAB scores. Nonetheless, that the vast majority (3:1) in our cohort had right-sided motor change and left hemisphere atrophy does suggest a predisposition to aphasia in such patients though once present the severity of aphasia is the same regardless of the laterality. Among motor onset CBDS patients 32% had left-sided akinesia while the proportion in cognitive onset CBDS was smaller at 19%. In early reviews the experience from movement disorders clinics suggested an over-representation of left-sided symptoms in CBDS [6] while our study suggests the opposite. It may be that patients with right-sided motor disturbances are more likely to present to cognitive disorders clinics because of predominant left hemisphere involvement while those with left-sided akinesia present to movement disorders clinics since the “less eloquent” right hemisphere is involved.