J Mol Neurosci (2011) 45:336–342
DOI 10.1007/s12031-011-9616-1

Extrapyramidal Syndromes in Frontotemporal Degeneration

Andrew Kertesz · Paul McMonagle · Sarah Jesso

Received: 14 June 2011 / Accepted: 3 August 2011 / Published online: 2 September 2011

Abstract Descriptions of extrapyramidal (EP) involvement in Pick's disease (renamed recently as FTD) appeared 80 years ago. CBD pathology was confirmed as a common substrate for primary progressive aphasia (PPA). We suggested that CBD and PPA should be included with frontal lobe dementia as Pick complex. PSP was prototype for "subcortical dementia", and aphasia and apraxia, considered unusual for PSP, are now seen as a rule. The overlap of PSP and CBD is considerable. We recently reviewed our cohort with EPS in FTD and identified 22 patients with the movement disorder as a first syndrome and another larger group of 48 patients who developed EPS after an initial onset with a cognitive disorder: aphasic, behavioral or both. All cognitive onset CBD/PSP patients and all but two with motor onset developed aphasia during the course of their illness. General cognitive and behavioral measures are similar for each presentation, but language scores are worse in cognitive onset cases, reflecting the frequency of aphasic presentations. Anomic patients become non-fluent, logopenic, agrammatic and mute. Using the Frontal Behavioral Inventory (FBI), a questionnaire specifically designed for the spectrum of apathy and disinhibition displayed by patients with FTD, we have documented the behavior change in CBD/PSP with motor and cognitive onsets. The significant personality changes consisted of apathy, disinhibition, perseveration and inattention, some of the core symptoms of FTD. In 18 autopsied cases, 15 had tau pathology. The overlap of CBD/PSP with PPA and bvFTD suggests a spectrum of related entities and predicts tau-positive pathology. Cross-sectional studies without significant follow-up may not observe the subsequent development language or behavior deficit, or the evolution from PPA and/or FTD-bv to CBD/PSP.

Keywords Corticobasal degeneration · Progressive supranuclear palsy · Frontotemporal degeneration · Primary progressive aphasia · Extrapyramidal disorders · Dementia · Neuropathology · Neuropsychology

A. Kertesz (✉)
Department of Neurology, University of Western Ontario,
London, ON, Canada
e-mail: andrew.kertesz@sjhc.london.on.ca

P. McMonagle
Department of Neurology, University of Belfast,
Belfast, UK

S. Jesso
Cognitive Neurology, St Joseph's Hospital,
London, ON, Canada

Introduction

Descriptions of extrapyramidal (EP) involvement in Pick's disease (PiD) appeared early (von Braunmuhl 1930). There have been several case descriptions of PiD where the patients had prominent unilateral rigidity and parkinsonism, and the combination of aphasia and rigidity in clinical PiD was identified as Akelaitis' disease (Akelaitis 1944).

The syndrome of bradykinesia, axial rigidity, dystonia, falls, dysphagia and vertical gaze palsy with subcortical pathology was described as progressive supranuclear palsy (PSP) by Steele et al. (1964), and not much later, the clinical syndrome of unilateral rigidity, prominent apraxia, reflex myoclonus and alien hand syndrome as corticodentatonigral degeneration (Rebeiz et al. 1968) relabelled corticobasal degeneration (CBD) (Gibb et al. 1989). Rebeiz et al. (1968) recognized the resemblance of the pathology to PiD.

The cognitive impairment was initially underestimated in the CBD syndrome (CBDs), but later, it was recognized that the most common presenting symptom was "dementia" (Grimes et al. 1999). Apraxia and the "alien hand" were well-recognized cortical manifestations of CBD, but other cognitive features remained neglected as the disease was considered a primary movement disorder. Sporadic case reports appeared connecting aphasia with the movement disorder (Goulding et al. 1989; Lippa et al. 1991; Lang 1992; Kertesz et al. 1994), and eventually, a significant overlap was documented between CBDs and the syndromes of FTD/Pick complex in the majority of cases (Kertesz et al. 2000). A corollary to this overlap was that CBD pathology can produce focal cortical syndromes such as aphasia or disinhibited behavior *without* the movement disorder (Lippa et al. 1991; Mimura et al. 2001). CBD pathology was confirmed as a common substrate for primary progressive aphasia (PPA), and we suggested that CBD and PPA should be classified with frontal lobe dementia as Pick complex (Kertesz et al. 1994).

PSP, although initially also described as a movement disorder, became the prototype for "subcortical dementia", characterized by profound slowness of mentation, impaired memory retrieval and personality changes (mainly apathy with some outbursts of irritability) (Albert et al. 1974). Cognitive phenomena, such as aphasia and apraxia, initially considered unusual for PSP, even an exclusion, are now seen as a rule. The degree of cognitive slowing in PSP syndrome (PSPs) appears independent of motor slowing. Personality and behavior change can be occasionally quite florid in PSP and may appear before the characteristic oculomotor and movement disorder (Kertesz et al. 2007).

The clinical overlap of CBD with PSP has been increasingly recognized. Many CBD patients also have vertical gaze palsy, falls and axial rigidity, and some have symmetrical extrapyramidal syndrome. Both syndromes are associated with significant cognitive and language disturbance. Oculograms and neuroimaging are often inconclusive, although they do have features that are used to differentiate these syndromes. Some studies comparing the neuropsychological features of PSP and CBD found no significant difference between them except for apraxia, which was more severe in CBD in some studies (Pillon et al. 1995; Leiguarda 1994; Soliveri et al. 2005; Pharr et al. 2001). The pathological, biochemical and genetic features also overlap to a great extent (Feany et al. 1996; Di Maria et al. 2000; Houlden et al. 2001; Boeve et al. 2003; Sha et al. 2006). Pathologically, PSP is characterized by globose tangles, thorny astrocytes and a midbrain target and CBD by fronto-parietal-striatal, asymmetrical distribution, neuronal achromasia, tau-positive neuronal inclusions and glial plaques (Munoz 1998; Dickson 1999). Cases of PSP pathology mimicking the asymmetry of the corticobasal syndrome, and vice versa, are frequent. They are both considered to be predominantly four repeat tauopathies and have common tau haplotypes and mutations such as P301L, P301S, for example on Chromosome-17 in familial cases. Clinicians have struggled to define each syndrome painstakingly, but these definitions overlap when patients are followed longitudinally and symptoms from the other syndrome appear with time. Furthermore, when an autopsy is carried out, the underlying pathology often does not match the clinical label. This is at times interpreted as heterogeneity.

Some studies of FTD still exclude patients with EP syndromes (EPS) or treat them as separate entities. 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 abulia or depression. Cross-sectional studies without significant follow-up may not observe the subsequent development language or behavior deficit. Reports of aphasia in EPS tend to be cross-sectional rather than longitudinal, tend not to reflect the evolution from PPA and/or FTD-bv to CBD/PSP or compare between motor and cognitive presentations of CBD/PSP. Furthermore, cases of FTD or PPA, not followed long enough, may potentially develop EPS later.

The aim of this review is to present our updated experience on these topics and place this in the context of current opinion and a representative review of the literature.

Methods

We have reviewed our cohort of patients with EPS in FTD, 70/319 (22%) in a clinical population of cognitive neurology patients in 10 years. Patients were included if they had an adequate description of the clinical syndrome of CBDs or PSPs any time during the course. On the average, patients had 3.26 yearly follow-up (Kertesz et al. 2007). The statistical methods used in the tables for selected cognitive parameters are described in our paper, which is the basis for this review (Kertesz et al. 2007). Not all of the patients included in this update had quantitative examination, and some of the following comments such as oculomotor function are based on clinical observation and are noting the presence or absence of the symptom. Quantitation was mainly in language, praxis visuospatial function and behavior. Executive function, although tested in some patients, was not included in the tables, and the reason for this is explained in the discussion of this topic.

Results and discussion

We identified two types of presentation (Tables 1 and 2):

1. Patients with the movement disorder as a first syndrome: 22: 15 CBDs and 7 PSPs
2. Patients who developed EPS after an initial onset with a cognitive disorder (aphasic, behavioral or both; *N*=48).

Aphasia

All cognitive onset CBDs/PSPs patients and all but two with motor onset developed aphasia during the course of their illness. General cognitive and behavioral measures were similar for each presentation, but language scores were worse in cognitive onset cases, reflecting the frequency of aphasic presentations. Initially, these aphasic patients are significantly anomic, and comprehension is preserved. Over time, the picture changes with anomic patients becoming non-fluent, logopenic, agrammatic and mute. Our longitudinal follow-up showed that both behavioral and aphasic presentations are distinct from motor onset at first, but by the fourth year of illness, the motor onset group had also begun to develop significant aphasia paralleling the cognitive CBDs/PSPs group (Table 2).

Two of our patients had striking preservation of repetition consistent with transcortical sensory aphasia, while another two had relatively fluent aphasias classified as Wernicke's aphasia by the WAB, both uncommon findings in the CBDs literature. 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, conforming to semantic dementia. He subsequently showed apraxia and behavioral change, characterized by mental rigidity, irritability, aggression, gluttony, hoarding and utilization behavior. Extrapyramidal signs were late in these exceptional patients (McMonagle et al. 2006a).

As in CBD, language and speech disorders are a feature of PSP. In particular, progressive non-fluent aphasia due to PSP pathology is well recognized (Kertesz et al. 2005, Josephs et al. 2006a, b, Knibb et al. 2006). Logopenic aphasia also occurs with PSP (Esmonde et al. 1996) and refers to decreased speech output and impaired repetition, but otherwise grammatically correct and free of paraphasias. Language deficit may be unrecognized in PSPs because of dysarthria and bradyphrenia.

Apraxia of speech (AOS)

AOS is also called aphemia, verbal apraxia or anarthria. It is easily mistaken for dysarthria as it also has an articulatory difficulty component. It is a feature of PSP, CBD and other tau-positive diseases with or without Progressive Nonfluent Aphasia (PNFA). Adult onset stammering was among the initial symptoms in case 1 from Albert's PSP series (1974). AOS is considered as a disorder of motor planning and programming of speech with distorted sound production, stammering and abnormal prosody yet typically an intact ability to execute non-speech oral movements. AOS frequently accompanies PNFA, with or without dysarthria, but it has also been reported as the initial manifestation of degenerative neurologic disease such as CBD (Lang 1992) and PSP (Josephs et al. 2006a, b). Several studies, including ours, examining clinicopathologic correlates in AOS identified a strong relation between AOS, PNFA and the presence of tau-positive pathology such as CBD, PSP or PiD, with important potential implications for predicting the underlying pathology and a specific target for pharmacotherapy.

Apraxia

Apraxia is featured in all diagnostic criteria of CBDs, but determining the actual prevalence is difficult. Leiguarda et al. (1994) estimated the frequency at 70% in clinically

Table 1 Clinical features of the behavioral, aphasic, CBDs and PSP presentations

	FTD	PPA	CBDs	PSP	Total
Sample size (*N*)	18	30	15	7	70
Age of onset (mean/sd.)	61/6.8	63.4/8	62.5/8.1	64.6/9.9	62.8/7.9
Gender (M/F)	10/8	15/15	7/8	2/4	34/36
IM/ID apraxia	13/10	25/20	13/10	6/5	57/45
Alien hand	7	20	14	4	45
Gaze palsy	10	10	8	7	35
Motor side r/l l>r-r>l	10	4	0	3	17
	6-1	4-22	2-13	1-3	13-38
Average Duration	8.4	7.2	5.9	3.9	6.3
Tau+/−autopsy	5/3	8/3	6/2	2/0	21/8

Table 2 Cognitive test results in the motor and cognitive presentations

Cognitive tests	Max	Movement presentation X(SD)	Cognitive presentation X(SD)	*T*-test results Significance
MMSE	30	21.9 (5.1)	15.2 (9.8)	NS
MDRS	144	108.0 (20.6)	81.1 (45.2)	NS
WAB	100	88.6 (12.3)	68.6 (20.8)	$P<.02$
Naming	60	58.6 (1.2)	37.3 (20.5)	$P<.003$
Word fluency	20	10.8 (4.6)	5.2 (6.1)	$P<.04$
Apraxia	60	46.6 (6.9)	40.1 (12.2)	NS
RCPM	38	20.0 (8.9)	13.7 (11.1)	NS
FBI (> 29=bvFTD)	72	19.2 (8.4)	24.9 (17.6)	NS

defined CBDs, and though present in all of the early descriptions, there are cases of pathologically confirmed CBD without apraxia in retrospective case series, though the authors acknowledge that this is not routinely looked for by many neurologists. It is also seen in PSP, but to a lesser extent (Soliveri et al. 1999; Pharr et al. 2001). In our own experience, ideomotor apraxia, which is apraxia on command and imitation for iconic gestures and transitive movements, was the most common form and was equally frequent in motor and cognitive onset cases (Table 2). In many cases, ideational or object-use apraxia, where the conceptual system for action is disrupted, was also prominent. The definition of ideational apraxia is controversial, but object-use apraxia is a common way of testing and defining it (Spatt et al. 2002). Its occurrence without ideomotor apraxia is an unusual dissociation that we and others have observed mainly in degenerative disease, particularly CBDs (Zadikoff and Lang 2005).

The nosology of limb kinetic apraxia, where fine distal movements are impaired for all movements, remains controversial, with some authors regarding it as a mild corticospinal or elemental motor deficit. It was reported in CBDs initially as an uncommon finding, but later recognized as frequent and, in some cases, the dominant form (Leiguarda et al. 2003). Similar variability applies to reports of buccofacial apraxia in CBDs. Some report orofacial apraxia and articulatory difficulty (verbal apraxia) as a presenting feature of CBD with pathology centered on Broca's area (Lang 1992).

Executive function

Impaired working memory (digit span, reverse spelling, phonemic and category fluency), categorization (card sorting), divided attention (trail making, interference inhibition: Stroop test) and sequencing (Luria's motor sequence) were often impaired, when tested, but the number of testable individuals was small because of the language deficit and the progression of motor symptoms of the disease. Frontal lobe dysfunction was emphasized early in PSP (Albert et al. 1974; Grafman et al. 1990). Yet, there were patients in the early stages where executive function tests were relatively spared. Furthermore, since executive functions are affected in just about every kind of brain damage, they have the least specificity and contribute the least to diagnosis and severity measures.

Behavior

Behavior change in CBDs/PSP overlaps to a large extent with that seen in behavioral presentation of FTD (bvFTD) (Table 2). Using the Frontal Behavioral Inventory (FBI), a questionnaire specifically designed for the spectrum of apathy and disinhibition displayed by patients with FTD (Kertesz et al. 1997), we have previously described the behavior change in CBDs with motor and cognitive onsets (Kertesz et al. 2000). The significant personality changes consisted of apathy, disinhibition, perseveration and inattention, some of the core symptoms of FTD (Neary et al. 1998). Not all of these symptoms appeared in all patients, however. Using the Neuropsychiatric Inventory (Litvan et al. 1996), high levels of depression, apathy, irritability, anxiety and disinhibition in CBDs were found.

Visoconstructive deficit, constructional apraxia

Pronounced deficits on visuospatial and visuoconstructive components of standardized tasks, impairment in handwriting and visuoconstructive tasks such as drawing and copying (constructional apraxia) are frequent in CBDs/PSPs (Table 2). Visuoperceptual impairment in handwriting and visuoconstructive tasks such as drawing and copying (constructional apraxia) are also prominent in some studies, reflecting parietal involvement (Gibb et al. 1989; Bak et al. 2005; Sha et al. 2006). Overlapping cases of CBDs and Balint's syndrome (simultanagnosia, optic ataxia and oculomotor apraxia) and the confirmation of CBD pathology in posterior cortical atrophy have been seen also (Mendez 2000; Tang-Wai et al. 2003; Bak et al. 2005; McMonagle et al. 2006b). Visuoperceptual impairment as

assessed with the Visual Object and Space Perception Battery is documented in clinically diagnosed cases (McMonagle et al. 2006b).

Oculomotor deficit

The hallmark of PSP is of course the supranuclear palsy of eye movements, particularly in vertical gaze (Steele et al. 1964). Less often recognized is the prevalence abnormal eye movements in CBD, such as delayed and interrupted incomplete saccades and at times impaired or saccadic following movements (square-wave pursuit) (Vidailhet et al. 1994). Many of the oculomotor studies are cross-sectional, but longitudinal case studies suggest the evolution of these symptoms in progression, rather than distinctive, unchanging abnormalities. It remains to be seen if the time-consuming quantitation of these abnormalities to distinguish the varieties in this spectrum of EPS will be useful for clinical and therapeutic studies

Pathology

We had 67 autopsied cases of clinically diagnosed and followed FTD/Pick complex (Kertesz et al. 2007). In 18 of these cases, which were considered clinically CBDs or PSPs some time during the course of their illness, autopsy showed features of CBD (ten), PSP (two) and Pick body disease (three). One stained for TDP-43, one had Creutzfeldt–Jakob's disease, and one had Alzheimer`s Disease (AD). The tau-negative cases occurred with the cognitive presentation (Table 1). We also had two cases of CBD pathology without any movement disorder recorded in their lifetime. A different view is obtained from the point of view of an autopsy PSP series from the same center, but with different investigators. In a retrospective review of 32 cases with PSP pathology in 17 years (Keith-Rokosh and Ang 2008), eight had FTD/PPA, 12 had no specified cognitive deficit, and 12 had insufficient clinical data. Coexisting CBD was found in 32%, AD in 19% and Lewy Body Dementia (LBD) in 12% of the cases.

In a larger pathological series (179 PSP and 29 CBD), 42 % of CBD and 54% PSP autopsies had clinical PSP syndrome, renamed as "Richardson's syndrome" (Ling et al. 2010). In contrast, in a clinical series of 545 dementia cases, 45 had CBD, and only seven had PSP pathology (Yu et al. 2010). The results from the Mayo clinic PSP bank with both CBD PSP pathologies indicate that the commonest underlying pathology of CBDs is PSP. In variants of PSP presenting with focal cortical syndromes, such as frontotemporal dementia, corticobasal syndrome and apraxia of speech, there is greater cortical pathology than in typical PSP. In variants of PSP presenting with levodopa-responsive parkinsonism, as well as pure akinesia and gait failure, there is less cortical pathology and more severe degeneration in the globus pallidus, subthalamic nucleus and substantia nigra (Dickson et al. 2010).

Progranulin (PRGN) mutation and TDP-43 pathology have been described in CBS/PSP with increasing frequency (Paviour et al. 2004; Masellis et al. 2006; Spina et al. 2007; Kovacs et al 2009; Yokota et al. 2010; Yu et al. 2010). LBD and LRRK mutations are also seen with CBDs/PSPs (Ross et al. 2006; Wider et al. 2010), and these findings, including genetics, indicate further overlap of these conditions and have been reviewed by Wszolek in this volume

Conclusions

The clinical overlap of PSP and CBD is considerable. In the past, the emphasis on movement disorders overlooked the extent in which these conditions are related to FTD and PPA. The continuing controversy about the differentiation or overlap of PSP and CBD is partly related to the clinical–pathological discrepancies in brain bank experience. The true clinical and pathological incidence and prevalence of these syndromes are not yet known. Cross-sectional studies without significant follow-up may not observe the subsequent development of language or behavior deficit, or the evolution from PPA and/or FTD-bv to CBDs/PSPs.

Although the cohesion of the clinical syndrome is beginning to be accepted, the underlying pathology is still regarded as heterogeneous, even unrelated, by many. The evidence for the clinical and pathological overlap of CBD and PSP is sufficient in that they may be considered together as an extrapyramidal component of the "Pick complex" along the language and behavioral components designated as primary progressive aphasia (PPA) and frontotemporal degeneration (FTD). The underlying pathology in CBD/PSP is predominantly a tauopathy, differentiated as CBD, PSP or Pick body disease, but there are TDP-43 positive and AD pathologies found especially in CBDs, which warrant caution in predicting specific pathology.

References

Akelaitis AJ (1944) Atrophy of the basal ganglia in Pick's disease. Arch Neurol Psychiatry 51:27–34

Albert ML, Feldman RG, Willis AL (1974) The "subcortical dementia" of progressive supranuclear palsy. J Neurol, Neurosurg Psychiatry 37:121–130

Bak TH, Crawford LM, Hearn VC et al (2005) Subcortical dementia revisited: similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). Neurocase 11:268–273

Boeve BF, Lang AE, Litvan I (2003) Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol 54(S5):15–19

Di Maria E, Tabaton M, Vigo T et al (2000) Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. Ann Neurol 47:374–377

Dickson DW (1999) Neuropathological differentiation of progressive supranuclear palsy and corticobasal degeneration. J Neurol 246: S6–S15

Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA (2010) Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol 23:394–400

Esmonde T, Giles E, Xuereb J, Hodges J (1996) Progressive supranuclear palsy presenting with dynamic aphasia. J Neurol Neurosurg Psychiatry 60:403–410

Feany MB, Mattiace LA, Dickson DW (1996) Neuropathologic overlap of progressive supranuclear palsy, Pick's disease and corticobasal degeneration. J Neuropathol Exp Neurol 55:53–67

Gibb WR, Luthert PJ, Marsden CD (1989) Corticobasal degeneration. Brain 112:1171–1192

Goulding PJ, Northen B, Snowden JS et al (1989) Progressive aphasia with right-sided extrapyramidal signs: another manifestation of localized cerebral atrophy. J Neurol Neurosurg Psychiatry 52:128–130

Grafman J, Litvan I, Gomez C, Chase TN (1990) Frontal lobe function in progressive supranuclear palsy. Arch Neurol 47:553–558

Grimes DA, Lang AE, Bergeron CB (1999) Dementia as the most common presentation of cortical-basal degeneration. Neurology 53:1969–1974

Houlden H, Baker M, Morris HR et al (2001) Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. Neurology 56:1702–1706

Josephs KA, Petersen RC, Knopman DS et al (2006a) Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 66:41–48

Josephs KA, Duffy JR, Strand EA et al (2006b) Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain 129:1385–1398

Keith-Rokosh J, Ang LC (2008) Progressive supranuclear palsy: a review of co-existing neurodegeneration. Can J Neurol Sci 35 (5):602–608

Kertesz A, Hudson L, Mackenzie IRA, Munoz DG (1994) The pathology and nosology of primary progressive aphasia. Neurology 44:2065–2072

Kertesz A, Davidson W, Fox H (1997) Frontal behavioral inventory. Diagnostic criteria for frontal lobe dementia. Can J Neurol Sci 24:29–36

Kertesz A, Martinez-Lage P, Davidson W, Munoz DG (2000) The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology 55:1368–1375

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG (2005) The evolution and pathology of frontotemporal dementia. Brain 128:1996–2005

Kertesz A, Blair M, McMonagle P, Munoz D (2007) The diagnosis and course of frontotemporal dementia. Alzheimer Dis Assoc Disord 21:155–163

Knibb JA, Xuereb JH, Patterson K, Hodges JR (2006) Clinical and pathological characterization of progressive aphasia. Ann Neurol 59:156–165

Kovacs GG, Murrell JR, Horvath S et al. (2009) TARDBP variation associated with frontotemporal dementia, supranuclear gaze palsy, and chorea. Mov Disord 24(12):1843–1847.

Lang AE (1992) Cortico-basal ganglionic degeneration presenting with "progressive loss of speech output and orofacial dyspraxia. J Neurol Neurosurg Psychiatry 55:1101

Leiguarda R, Lees AJ, Merello M, Starkstein S, Marsden CD (1994) The nature of apraxia in corticobasal degeneration. J Neurol Neurosurg Psychiatry 57:455–459

Leiguarda RC, Merello M, Nouzeilles MI et al (2003) Limb-kinetic apraxia in corticobasal degeneration: clinical and kinematic features. Mov Disord 18:49–59

Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, Paviour DC, Lees AJ (2010) Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain 133(Pt 7):2045–2057

Lippa CF, Cohen R, Smith TW, Drachman DA (1991) Primary progressive aphasia with focal neuronal achromasia. Neurology 41:882–886

Litvan I, Mega MS, Cummings JL, Fairbanks L (1996) Neuropsychiatric aspects of progressive supranuclear palsy. Neurology 47:1184–1189

Masellis M, Momeni P, Meschino W, Heffner R Jr, Elder J, Sato C, Liang Y, St George-Hyslop P, Hardy J, Bilbao J, Black S, Rogaeva E (2006) Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. Brain 129(Pt 11):3115–3123, Epub 2006 Oct 9

McMonagle P, Blair M, Kertesz A (2006a) Corticobasal degeneration and progressive aphasia. Neurology 67:1444–1451

McMonagle P, Deering F, Berliner Y, Kertesz A (2006b) The cognitive profile of posterior cortical atrophy. Neurology 66:331–338

Mendez MF (2000) Corticobasal ganglionic degeneration with Balint's syndrome. J Neuropsychiatry Clin Neurosci 12:273–275

Mimura M, Oda T, Tsuchiya K et al (2001) Corticobasal degeneration presenting with nonfluent primary progressive aphasia: a clinicopathological study. J Neurol Sci 183:19–26

Munoz D (1998) The pathology of Pick complex. In: Kertesz A, Munoz D (eds) Pick's disease and pick complex. Wiley-Liss, New York, pp 211–243

Neary D, Snowden JS, Gustafson L et al (1998) Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. Neurology 51:1546–1554

Paviour DC, Lees AJ, Josephs KA et al. (2004) Frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes: broadening the clinical picture to include progressive supranuclear palsy. Brain 127(11)2441–2451.

Pharr V, Uttl B, Stark M, Litvan I, Fantie B, Grafman J (2001) Comparison of apraxia in corticobasal degeneration and progressive supranuclear palsy. Neurology 56:957–963

Pillon B, Blin J, Vidailhet M et al (1995) The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. Neurology 45:1477–1483

Rebeiz JJ, Kolodny EH, Richardson EP Jr (1968) Corticodentatonigral degeneration with neuronal achromasia. Arch Neurol 18:20–33

Ross OA, Whittle AJ, Cobb SA et al. (2006) Lrrk2 R1441 substitution and progressive supranuclear palsy. Neuropathol Appl Neurobiol 32(1):23–25.

Sha S, Hou C, Viskontas IV, Miller BL (2006) Are frontotemporal lobar degeneration, progressive supranuclear palsy and corticobasal degeneration distinct diseases? Nat Clin Pract Neurol 2 (12):658–665

Soliveri P, Piacentini S, Girotti F (2005) Limb apraxia in corticobasal degeneration and progressive supranuclear palsy. Neurology 64:448–453

Spatt J, Bak T, Bozeat S, Patterson K, Hodges JR (2002) Apraxia, mechanical problem solving and semantic knowledge: contributions to object usage in corticobasal degeneration. J Neurol 249:601–608

Spina S, Murell JR, Huey ED et al. (2007) Corticobasal syndrome associated with the A9D Progranulin mutation. J Neuropathol Exp Neurol 66(10):892–900.

Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy. Arch Neurol 10:333–359.

Tang-Wai DF, Josephs KA, Boeve BF, Dickson DW, Parisi JE, Petersen RC (2003) Pathologically confirmed corticobasal degeneration presenting with visuospatial dysfunction. Neurology 61:1134–1137

Vidailhet M, Rivaud S, Guider-Khouja N, Pillon B, Bonner A-M, Gaymard B, Agid Y, Pierrot-Deseilligny C (1994) Eye movements in parkinsonian syndromes. Ann Neurol 35:420–426

Von Braunmuhl A (1930) Ueber Stammganglienveranderungen bei Pickscher Krankheit. Ztschr fd ges Neurol u Psychiat 124:214

Wider C, Dickson DW, Wszolek ZK (2010) Leucine-rich repeat kinase 2 gene-associated disease: redefining genotype-phenotype correlation. Neurodegener Dis 7(1–3)175–179.

Yokota O, Davidson Y, Bigio EH, Ishizu H, Terada S, Arai T, Hasegawa M, Akiyama H, Sikkink S, Pickering-Brown S, Mann DM (2010) Phosphorylated TDP-43 pathology and hippocampal sclerosis in progressive supranuclear palsy. Acta Neuropathol 120(1):55–66, Epub 2010 May 30

Yu CE, Bird TD, Bekris LM, Montine TJ, Leverenz JB, Steinbart E, Galloway NM, Feldman H, Woltjer R, Miller CA, Wood EM, Grossman M, McCluskey L, Clark CM, Neumann M, Danek A, Galasko DR, Arnold SE, Chen-Plotkin A, Karydas A, Miller BL, Trojanowski JQ, Lee VM, Schellenberg GD, Van Deerlin VM (2010) The spectrum of mutations in progranulin: a collaborative study screening 545 cases of neurodegeneration. Arch Neurol 67 (2):161–170

Zadikoff C, Lang AE (2005) Apraxia in movement disorders. Brain 128:1480–1497