

Cognitive Profiles of Parkinsonian Syndromes

What the MMSE won't tell you and why

In the early 1970's a group of psychiatrists devised the Mini Mental State Examination (MMSE)¹ "for the serial testing of the cognitive mental state in patients on a neurogeriatric ward". The original sample of 69 patients included, apart from patients with affective illness, schizophrenia and neurosis, 29 patients with "dementia syndromes due to a variety of brain diseases", reflecting the concept of dementia as "a global deterioration of intellect". Thanks mainly to its brevity MMSE became the most widely used cognitive screening test, applied to a variety of neurological conditions for which it was not originally designed, among them Parkinson's Disease (PD) and related disorders.

There are two serious problems connected with the use of MMSE in this patient group. Firstly, MMSE has been demonstrated to be particularly insensitive to frontal-executive dysfunction, which, as will be shown below, constitutes the most common cognitive deficit in basal ganglia diseases. Secondly, based on the unitary concept of dementia, it does not examine different cognitive domains but confines itself to one global 'dementia score'. It is, therefore, unable to determine qualitative differences between diseases. Seen in historical perspective, these shortcomings of the MMSE are not surprising: frontal dysfunction and selective cognitive deficits in different types of dementia became the focus of scientific research many years after its publication. A test designed at the time in which the routine imaging procedure was pneumoencephalography can hardly be expected to be state-of-the-art 30 years later.

This does not mean, however, that cognitive assessment has to be long and laborious. The aim of this review is to demonstrate that brief and simple tests, which can be easily performed at the bedside, can distinguish the cognitive profiles of the individual diseases and detect deficits that would go unnoticed by the MMSE.

Motor and cognitive features of parkinsonian syndromes: two sides of the same coin?

Although a large number of diseases can present with 'parkinsonian features', such as tremor, rigidity or bradykinesia, we confine ourselves in this review to five diagnostic entities: PD, Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), Corticobasal Degeneration (CBD) and Dementia with Lewy Bodies (DLB). PSP, CBD and MSA (and to a much lesser degree DLB) share some common features which distinguish them from the classical PD and lead to their designation as Atypical Parkinsonian Syndromes (APS).² The borderline between PD and DLB is somewhat arbitrary: according to the current diagnostic criteria a patient presenting with parkinsonism followed by dementia is diagnosed as PD, if dementia precedes the parkinsonism the diagnosis is DLB.³

While all five diseases are associated with typical (or even pathognomonic) features (Table 1), none of them can be diagnosed on the basis of one single symptom. This applies in the same degree to motor as to the cognitive symptoms. Prominent tremor, for instance, is most often encountered in PD, apraxia in CBD, but both can also occur, albeit usually less pronounced, in other conditions, such as PSP. Interpreted in this way, the cognitive symptoms can be as useful in diagnosing the disease as their motor counterparts. In fact, with growing understanding of fronto-striatal connections it seems likely that at least some cognitive and motor symptoms are different manifestations of the same underlying pathology.⁴

The spectrum of cognitive symptoms in parkinsonian syndromes

In 1974, around the time of the publication of MMSE, Albert et al⁵ described characteristic cognitive and behavioural changes in 5 PSP patients (Table 2). They noted that the symptoms were different from those encountered in Alzheimer's disease (AD), but similar to those



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Table 1: Typical features of different parkinsonian syndromes:

PD	asymmetrical parkinsonism, including tremor, good L-Dopa response
PSP	vertical supranuclear gaze palsy, imbalance with falls backwards
MSA	dysautonomia, cerebellar dysfunction, imbalance with falls
CBD	apraxia, alien hand syndrome, cortical sensory dysfunction
DLB	fluctuating course with periods of disorientation, visual hallucinations

Table 2: The key symptoms of the Albert syndrome:

• slowing of thought processes
• impaired ability to manipulate knowledge
• forgetfulness
• behavioural and personality changes

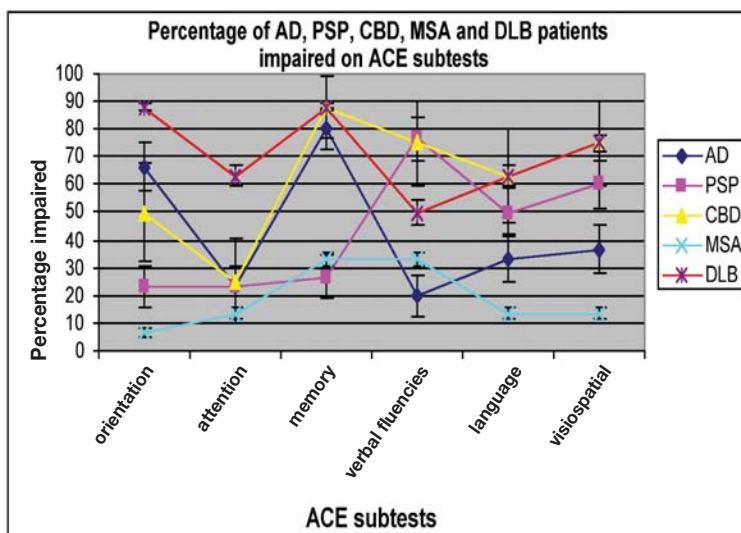


Figure 1: Cognitive profiles of AD, PSP, CBD, MSA, DLB and on the ACE.

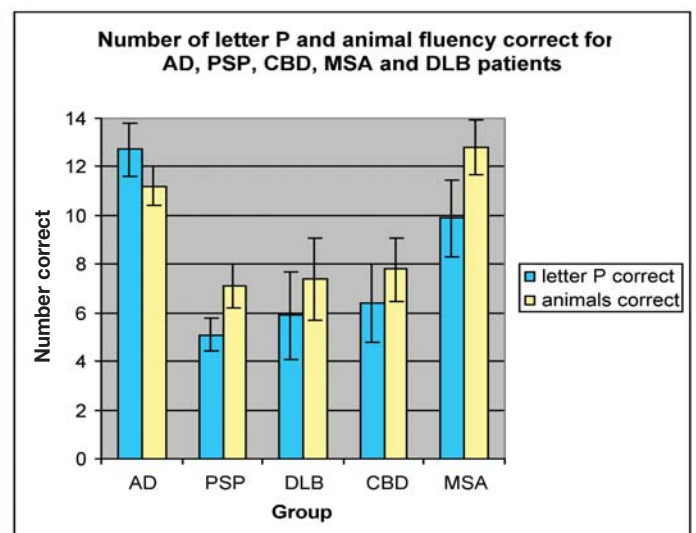


Figure 2: Letter and category fluency in AD, PSP, CBD, MSA and DLB.

described in frontal lobe disorders. They called the clinical picture 'subcortical dementia', assuming that the deficits were caused by a disruption to fronto-striatal pathways. A similar pattern was later described in other basal ganglia diseases, including PD.⁶ However, the critics of the notion of 'subcortical dementia' stressed the anatomical inaccuracy of the term, as the advances in neuroscience called into question the neat distinction between 'subcortical' and 'cortical' pathology.⁷ We propose, therefore, to refer to this constellation of symptoms as 'Albert syndrome', stressing the descriptive accuracy of a clinical, rather than anatomical, entity. This term is also more precise than the broad notion of 'frontal-dysexecutive syndrome', since frontal lobes are extraordinarily complex in terms of their functional anatomy and the term 'frontal dysfunction' can be applied to very different clinical pictures.

The diseases which represent the 'Albert syndrome' in its purest form, are MSA and PSP. The difference between them is a more quantitative than qualitative nature. The cognitive dysfunction in MSA is often so mild that the patients are classified as unimpaired on most cognitive screening tests,² the only abnormality being a slight reduction in verbal fluency and free recall (Figure 1).⁷ We have seen only one patient with a clinical diagnosis of MSA and pronounced dementia; interestingly, his post-mortem showed a combination of alpha-synuclein and tau pathology. The cognitive dysfunction in PSP, although more pronounced, is similar in pattern, with a particular reduction in letter fluency (Figure 2).^{2,7}

In contrast, CBD and DLB have the widest range of cognitive abnormalities, extending well beyond the frontal-dysexecutive syndrome and in keeping with the widespread cortical involvement, as suggested by neuroimaging and neuropathology. Deficits in orientation, attention, memory and visuospatial function in DLB are well recognised, and have contributed to the designation of this disease as a 'dementia'.³ CBD was initially regarded as a purely motor syndrome, but recent studies documented a severe impairment in visuo-spatial functions⁸ and language,⁹ at times amounting to a full-blown non-fluent aphasia.¹⁰

Paradoxically, the situation is probably most complicated in the case of the classical PD. The traditional view, since the late 1970s, was that of a subcortical dementia.⁶ However, recent studies

Table 3: The FAB, DRS and ACE subtests in comparison:

FAB	DRS	ACE
Letter fluency	Initiation/Perseveration (inc. category fluency)	Orientation
Similarity judgement		Attention
Motor sequencing:	Conceptualisation	Letter & category fluency
- Luria 3-step examination	Construction (drawing)	Memory
- 'go-no go'	Attention	Language
- conflicting instructions	Memory	Visuospatial functions

documented significant memory impairment, related in severity to the degree of medial temporal atrophy,¹¹ while molecular studies linked together the pathologies of AD and PD.¹² It seems likely that a substantial number of PD patients present with a combination of Albert syndrome with mnemonic and semantic deficits characteristic of AD. Moreover, PD is increasingly recognised as a heterogeneous disorder, with subgroups showing different cognitive profiles.¹³

Practical considerations

Since the MMSE is likely to continue dominating the clinical cognitive assessment in the foreseeable future, the most realistic way to improve the evaluation of parkinsonian patients is to combine it with other tests. The first step would be to add tests sensitive to frontal dysfunction (or, more precisely, the 'Albert syndrome'), the second to evaluate other cognitive domains.

Probably the easiest, fastest (less than 5 minutes) and yet clinically meaningful test of frontal function is verbal fluency. It is believed to reflect one of the most central features of parkinsonian syndromes: the profound difficulty in generation of actions (verbal as well as motor). A reduction in verbal fluency has been documented in all five diseases,^{7,14} but is usually most pronounced in PSP, where it occurs as one of the earliest symptoms, often preceding the occurrence of motor abnormalities.⁷ Out of the ca. 30 pathologically confirmed PSP patients we have followed up over the last ten years in Cambridge all but one had reduced verbal fluency already at the initial exam. Verbal fluency is part of many cognitive batteries, such as Frontal Assessment Battery (FAB),¹⁵ Dementia Rating Scale (DRS)¹⁶ and Addenbrooke's Cognitive Examination (ACE)¹⁷ (Table 3) and became a kind of a 'cognitive equivalent of Erythrocyte Sedimentation Rate (ESR)': not specific, but useful to screen for abnormali-

ties, which will necessitate further investigation.

Two types of verbal fluency are widely used: letter/phonemic (e.g. words starting with the letters F, A, S or P) and category/semantic (eg animals or supermarket items) fluency. The first one is believed to relate more to frontal, the second to temporal dysfunction. Accordingly, one would expect a more pronounced reduction in letter fluency in parkinsonian, and in category fluency in AD patients. Indeed, such dissociation has been documented between APS and AD (Figure 2).⁷ However, a meta-analysis of 68 verbal fluency studies suggest that in PD patients semantic fluency might be even more impaired than phonemic, although the difference is less pronounced than in AD:¹⁴ a result in keeping with the interpretation of PD as consisting of a combination of features of Albert syndrome and AD.

While verbal fluency (and FAB) can be very useful in adding a 'frontal dimension' to the MMSE, determining a cognitive profile of a disease requires assessment of other cognitive domains such as language or visuo-spatial functions. One way of doing it is to select appropriate tests for each domain. This approach has the advantage of flexibility, but requires a good knowledge of different testing instruments. An alternative approach, much easier to implement in the clinical setting, is to use one of the standardised testing batteries, such as the DRS or ACE. The DRS¹⁶ is widely used in research, but has not enjoyed the same popularity in bedside assessment, due to its length (25-30 minutes) and the necessity for special testing materials (stimulus cards etc.). The ACE¹⁷ is shorter (15-20 minutes), does not require additional materials and incorporates the MMSE. It has been validated in PSP, CBD and MSA^{2,7} (Figure 1) and is currently being evaluated in PD and DLB. It can be obtained free from eneida.mioshi@mrc-cbu.cam.ac.uk.

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