David Marsden (1938-1998): contributions to cognitive neurology

Abstract
Professor C. David Marsden (1938-1998) made major advances in the understanding of movement disorders during his illustrious career prior to his untimely death 25 years ago. In addition to this body of work, he also made contributions to the understanding of cognitive functions in these disorders, necessarily so in view of the neuropsychological overlap of cognition and movement. This article briefly summarises Professor Marsden's clinical contributions to cognitive neurology, some of which still inform clinical practice today.

For neurologists of a certain age, it may come as something of a surprise, if not a shock, to realise that 2023 will mark a quarter of a century since the untimely death of Professor CD Marsden. This surprise may, in part, be related to the fact that publications bearing the Marsden imprimatur continued to appear long after his death, culminating in the eponymous *Marsden's Book of Movement Disorders* [1] which, though contemplated many years earlier, did not make its first appearance until late 2011/early 2012.

David Marsden is rightly known for his influential contributions, clinical, neuroscientific and administrative, to the field of movement disorders (one of his obituaries described him as "Master of Movement"), but his interests were not limited by this specialisation. As a consequence of his numerous collaborations, he was an author on many papers pertaining to cognitive function and its disorders, either directly or indirectly. A brief review of some of these is given here, restricted to clinical reports, in part to commemorate but also to illustrate the breadth of Marsden's contributions. It should be emphasised that this review does not claim to be exhaustive, and is given from the perspective of an outsider, not someone who ever worked in any capacity for Professor Marsden. An account from those who knew and worked with him is published [2], which briefly alludes to his studies of cognitive deficits in parkinsonian disorders (p.212).

1. Dementia

"Presenile" dementia

One of Marsden's earliest publications, dating from 1972, was based on work undertaken as, according to the paper in the *BMJ*, Senior Registrar at Queen Square, on the subject of (so called) "presenile" dementia [3]. Working with Michael Harrison (d. 2019), a retrospective study of more than 100 patients was presented, in whom intellectual impairment was confirmed in 84 and a "final" diagnosis established in 36. Aside from "cerebral atrophy of unknown cause" (n = 48), many presumed to have Alzheimer's disease or Pick's disease, intracranial space-occupying mass lesion and arteriosclerotic dementia were the next most common diagnoses (both n = 8).

Of the 22 patients classified with no or uncertain dementia, depression was the most common diagnosis. This study predated the availability of CT brain scanning; lumbar air encephalography was the most sophisticated neuroimaging investigation available. Moreover, the initial paper gave neither a definition of "presenile" nor details of the age of the patients investigated; the latter information emerged in a subsequent letter (age range 34-78, mean 61 years) [4].

"Senile" dementia

Patients with "senile" dementia, meaning onset over 65 years of age, formed one group, along with Parkinson's disease and "cerebral arteriosclerosis," in a 1974 study examining clinical features and response to levodopa. Evidently, the dementia patients were in the severe stage of disease, frequently unable to walk or stand; half of them reportedly had "whole body akinesia". Predictably, they did not respond to levodopa, and indeed as a group they showed deterioration in rigidity when treated [5].

Cortical versus subcortical dementia

Distinction between dementia ascribed respectively to cortical or subcortical pathology enjoyed something of a vogue in the 1980s and 1990s. So called cortical dementia was typified by the classical syndromes of amnesia, aphasia, and agnosia, whereas so called subcortical dementia, a terminology first used in the context of progressive supranuclear palsy, was typified by cognitive slowing, sometimes with apathy and depression. Brown and Marsden's review of these concepts, in the context of Alzheimer's disease, Parkinson's disease and Huntington's disease, found more overlap than separation in deficits between the patient groups, hence casting doubt on the functional independence of these two broad diagnostic categories [6].

Alzheimer's disease

Alzheimer's disease (AD) was not an area of particular clinical interest for Marsden but was encountered from time to time in the context of concurrent movement disorder. He was one of the authors on papers describing the alien hand sign [7] and frontal gait impairment [8] in patients found to have underlying Alzheimer's disease pathology. In the first of these reports, the patient had a clinical diagnosis of corticobasal degeneration prior to the availability of neuropathological findings [7] (hence what might now be termed corticobasal syndrome). In the second paper, the one patient in whom neuropathology was available had histological features of corticobasal degeneration as well as AD pathology, the latter most evident in the occipital cortex with relative sparing of the hippocampus [8]. Alzheimer-type changes were also observed along with cerebrovascular pathology in a patient presenting with a late onset generalised chorea [9].

A group of patients with "probable dementia of Alzheimer type" was investigated with tests of visual memory and tests sensitive to frontal lobe dysfunction as a comparator group for patients with Huntington's disease (vide infra) matched for "level of dementia," as defined by Mini-Mental State Examination (MMSE) score. The AD patients were found to be more impaired on tests of recall but superior on the tests sensitive to frontal lobe dysfunction than the Huntington's disease patients [10].

2. Cognitive features of movement disorders

It is perhaps easy to forget from our vantage point that the differentiation of Parkinson's disease from other parkinsonian disorders, sometimes labelled as "atypical parkinsonism" or "Parkinson's plus," was not so clear-cut in the late 1970s/early 1980s, when Marsden and his colleagues began publishing on the subject, than is now the case.
Certainly one of the debts we owe to them relates to the empirical studies which clarified this differential, including cognitive features.

Parkinson's disease

Whilst Charcot, unlike James Parkinson, had recognised that cognitive impairment could be a feature of the disorder upon which he had bestowed the eponymous label of Parkinson's disease (PD), relatively little attention was paid to this aspect of PD until the 1970s and 1980s. Marsden's engagement with the cognitive consequences of PD was evident in a *Lancet* review co-authored with Richard Brown

published in 1984 examining dementia in PD [11]. A downward revision of the frequency of dementia in PD from 1 in 3 to a more conservative 1 in 5 was suggested, in part due to diagnostic errors in distinguishing PD from other akinetic-rigid syndromes. This conclusion was based on the data then available, whereas subsequent studies have suggested a much higher cumulative frequency of cognitive impairment in PD.

As for the specific cognitive features encountered in PD, Marsden was involved in a number of studies examining these, dating back to the early 1970s [5]. Many years later, the cognitive deficits in PD were characterised in comparison to other parkinsonian syndromes, finding slowing in initial thinking time (bradyphrenia) and impairments on tests of frontal lobe function [12].

Progressive supranuclear palsy

In the study comparing various parkinsonian syndromes, patients with progressive supranuclear palsy (PSP) were shown to have cognitive deficits on tests of frontal lobe function, like PD patients, but the greatest deficit in attentional set shifting was found in PSP patients [12].

Multiple system atrophy

Multiple system atrophy (MSA) was generally thought to be free from cognitive dysfunction prior to a report on a "distinctive pattern" of cognitive deficits in MSA of striato-nigral predominance (MSA-P) by Marsden and his colleagues. This showed a prominent frontal-lobe-like component [13], later confirmed in a larger study [12].

Corticobasal degeneration

Marsden and his colleagues were some of the first to undertake systematic studies of patients with corticobasal degeneration (CBD). Understandably this was largely from the perspective of the movement disorders rather than the cognitive features, for example they reported that "Cognitive changes are unusual early in the disease, the intellect being preserved" [14]. Although noting the emergence of aphasia in some patients, there was no apparent awareness of non-fluent aphasic presentations of CBD with subsequent emergence of the typical motor features of CBD, as noted by later authors.

Huntington's disease

The cognitive features of Huntington's disease (HD) were compared to those in AD patients and shown to be distinct, with poorer performance on tests examining frontal lobe function, suggestive of a frontostriatal pattern of dysfunction [10].

3. Other contributions

Apraxia

The nature of apraxia, and the possible role(s) of the basal ganglia in its pathogenesis, was one of Marsden's enduring interests [15]. Apraxia was examined in various parkinsonian patient groups. In CBD severe ideomotor and ideational apraxia was found to correlate with global cognitive impairment [16]. Apraxia was also observed in PSP (three-quarters of patients) and PD (about one quarter of patients) but was not seen in MSA and neuroleptic-induced parkinsonism. Ideomotor apraxia in PSP correlated with cognitive deficit (MMSE scores) and in PD with deficits in frontal lobe related tasks [17].

Amnesia

Early in his clinical career (1974), Marsden was one of the authors on a classic paper showing that posterior cerebral artery occlusion may be a cause of acute onset of amnesia, so called "amnesic stroke," in association with unilateral or bilateral visual field defects. Although diagnosis of these patients was based on clinical evaluation alone [18], the inferences were amply confirmed by later neuroimaging studies. Occasional cases of amnesic stroke are still reported, some with a phenotype apparently indistinguishable from transient global amnesia.

Discussion

Like one of his illustrious predecessors at Queen Square, William Gowers (1845-1915) [19], David Marsden made contributions in the field of cognitive disorders, incidental to his major clinical interests. Since disorders of cognition occur not only in isolation but also as components of more widespread diseases of the nervous system, they may be encountered by clinicians with interests in areas other than cognitive function. The specific pattern of cognitive deficits may be helpful in differential diagnosis. The groundwork of David Marsden and his colleagues facilitated this clinical understanding.

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