Changing panoramas and new horizons in Parkinson's disease

In last month's edition of *BJHM*, Sauerbier and Chaudhuri (2014) described a variety of symptoms in Parkinson's disease. Traditionally, Parkinson's disease has been thought of as a movement (motor) disorder, but these non-motor symptoms are additional to motor symptoms, and so widen the spectrum of the phenotypes of the illness.

The recognition of non-motor symptoms dates back, as they describe, to the earliest description of parkinsonism, but it was not until relatively recently that an integrated approach has been suggested, to provide a more holistic view of Parkinson's disease, using validated measures (Chaudhuri et al, 2007). These concepts do not in any way counteract the importance of the traditional motor symptoms of Parkinson's disease, and further there can be instances of overlap. For example, drooling of saliva can be secondary to impaired pharyngeal muscular activity, and nocturnal sleep can be disturbed by nocturnal akinesia as medication for motor symptoms wears off. However, such a holistic view not only offers advantages to patients' management but also opens new insights into ways of conceptualizing Parkinson's disease, its pathology and its future research. Hence, the article shows that multiple panoramas of Parkinson's disease are changing.

Holistic treatment

From a clinical therapeutic perspective, the authors point out that where non-motor symptoms are recognized, they can be assessed (sometimes by the application of other specific scales) and therapies are available, as they describe. The therapies themselves can help one symptom but unfortunately in some instances worsen another. This highlights two important notions. First, that the non-motor symptoms can have different aetiologies (e.g. a neurodegeneration effect, or a medication effect, or both combined). Second, that a balance may need to be reached to provide a patient with holistic, but individualized, care.

In a 'multi-morbid' illness such as Parkinson's disease, the recognition of an increase in the spectrum of symptoms reported by patients is a step away from management that is aimed at 'fixing' a symptom, but rather management that is aimed at selecting treatment options that are best able to address patient priorities across the panorama of symptoms, with the appreciation that 'perfection' in any one may not be holistically optimal.

Such applications of 'personalized' medicine have been recognized previously (Acquadro et al, 2003) and it is becoming increasingly clear that this is required in Parkinson's disease, because the disease is complex and its treatments can be complex. This applies to both standard oral and transdermal therapies and equally when one increases the available treatment options to include the invasive therapies of continuous subcutaneous apomorphine infusion, deep brain stimulation or intrajejunal levodopa infusion (NHS Commissioning Board, 2013; Volkmann et al, 2013). Some of these invasive therapeutic options can have an influence on both motor and non-motor symptoms of Parkinson's disease (Fasano et al, 2012), while others are under investigation.

Understanding the pathology

The panorama of Parkinson's disease pathology is also changing. The classical notion of the illness arising as a consequence of dopaminergic cell loss in the substantia nigra, with resultant striatal denervation, is incomplete. Traditional therapy, that of boosting dopaminergic function with either levodopa preparations or dopamine agonists, is based on this notion and is clearly effective for some of the motor symptoms. The recognition that non-motor symptoms can have different aetiologies, however, adds to the weight of evidence, as reviewed by Sauerbier and Chaudhuri (2014), that there is a need to develop non-dopaminergic strategies for management of some of these symptoms. New developments of pharmacological options, targeting non-dopaminergic pathways, are awaited.

It should also be remembered that individual nuclei within the brain are interconnected and that clinical expression of a disordered state may not simply arise from a single abnormal nucleus, but from how that nucleus influences (and is influenced by) others in a circuit of pathophysiology. The concept of pathological circuits (DeLong and Wichmann, 2007), as opposed to pathological nuclei, may underpin the combinations of symptoms in Parkinson's disease. The abnormal non-motor circuits of Parkinson's disease could therefore be potentially amenable to therapeutic intervention at multiple points in a circuit by medical or invasive treatment options. This requires future research. An analogy could be seen in the case for treatment of the motor symptoms of Parkinson's disease by deep brain stimulation at different target nuclei within a pathological motor circuit (Weaver et al, 2012).

Clinical phenotype

Finally, the panorama of the clinical phenotype is becoming more varied. A variability of motor expression of the disease has been recognized (Jankovic et al, 1990), with some patients showing mainly tremor-dominant disease while others have bradykinetic/gait disease. By analogy, there may come a need to consider other phenotypes, more based on non-motor symptoms. As Sauerbier and Chaudhuri (2014) point out, a 'pre-clinical' state, 'pre-motor' state, a combined motor and non-motor state may need to be considered as subdivisions. There may also be a need to consider a 'pure motor' state. If it can be shown that such states justify formal classification, based on stringent but different diagnostic criteria and pathological findings, then this would not only

have clinical significance but also research significance, for it could determine which phenotypes are entered into clinical trials, as well as allowing stratification of trial results to focus specific treatments on specific research questions in subgroups of Parkinson's disease.

Conclusions

Recognition of the multi-morbid nature of Parkinson's disease currently has clinical relevance, and is likely to have significant future relevance to defining pathological and research questions in Parkinson's disease. BJHM

KEY POINTS

- Parkinson's disease can have motor and non-motor symptoms.
- Recognition of these allows for consideration of their treatment.
- Identification could influence Parkinson's disease classification and future research.

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