From James Parkinson to Friederich Lewy: leaving landmarks for further research journeys

It was in 1817 that James Parkinson first described in detail the features of the disease that was to take his name (first Paralysis agitans and subsequently Parkinson’s disease). It was not until 1912, however, that the most important pathological marker of this disease, a sort of neuronal inclusion body, was reported by Friederich H. Lewy in the dorsal motor nucleus of the vagus and in the nucleus basalis of Meynert, paving the way for new research strategies.

Lewy was a brilliant scientist and an excellent clinician and neuropathologist. He trained with outstanding teachers: Nissl, Alzheimer and Spielmeyer in neuropathology; Oppenheim and Cassierer in clinical neurology; Magnus in neurophysiological research; and Kraepelin in psychiatry.

In 1923 Lewy published his famous book about muscle tone and movement in which he described the pathological findings associated with Parkinson’s disease and tried to correlate them with the clinical features of the disorder. In this book he carefully detailed his original observation on the eosinophilic inclusion bodies and attempted to explain their development. He noted that axis cylinders become swollen and aggregated to produce compact basophilic cords. These swollen fibrils are then impregnated by eosinophilic cellular products and changed into elongated eosinophilic structures. Today, the Lewy body is again in the front line of research and it is emerging that this pathological entity indeed represents a structural manifestation of a cytoprotective cell response strategically designed to eliminate damaged cellular elements.

Seven years after the first report by Lewy it was the turn of a student presenting his thesis at the University of Paris. It was this very young investigator, Trétiakoff, who actually established the basic pathological substrate of Parkinson’s disease: rather severe neuronal loss in the substantia nigra and the presence of the neuronal inclusions previously reported by Lewy – in the meantime named Lewy bodies – in surviving neurons.

The description of the neuropathological basis of Parkinson’s disease was carefully completed by Greenfield and Bonsaquet (1953) and by Bethlem and Den Haltog Jager (1960), one and a half centuries after Parkinson’s original report.

The features that characterise Parkinson’s disease are: marked depigmentation of the substantia nigra and locus coeruleus, and abiotrophic degeneration with scattered Lewy bodies in several brainstem and diencephalon nuclei including the substantia nigra and locus coeruleus.

Indeed, Lewy bodies are also predominantly found in the hypothalamic nuclei, nucleus basalis of Meynert, dorsal raphe nucleus, superior central nucleus, dorsal vaginal nucleus and intermediolateral nucleus. In addition, intraneuritic Lewy bodies occur in the sympathetic ganglia and in the intramural autonomic ganglia of the digestive tract.

In the late 1970s, Kosaka and collaborators demonstrated Lewy bodies also in the cerebral cortex and basal ganglia, and in 1980 they proposed “Lewy body disease” as a distinct nosological entity.

Lewy body disease was defined, at that time, as a chronic progressive neuropsychiatric disease whose clinical features were mainly parkinsonian symptoms with or without dementia. Patients were usually classified as senile or presenile and the disease rarely appeared in the young.

Kosaka, when first proposing Lewy body disease, classified it in three types: a brainstem type, a transitional type and a diffuse type. While the brainstem type appears identical to Parkinson’s disease, Yoshimura (in 1983) proposed that the diffuse type, in which Lewy bodies are abundantly present in the cerebral cortex as well as in the basal ganglia, should be recognised as a distinct entity and termed diffuse Lewy body disease.

Further steps towards understanding this entity were made in the 1980s by R. H. Perry and collaborators in Newcastle upon Tyne, UK. In two seminal papers published in 1989 and 1990 these authors proposed a type of Lewy body disease which

‘Lewy body dementia has much to teach. Thorough investigation will improve dementia classification, provide insight into the neuropathologic basis of neuropsychiatric phenomena, and enhance understanding of the neurogenetics and neuropathology of dementia. This volume provides a comprehensive introduction to the issues and will allow investigators to begin unravelling the lesson of Lewy Body Disease’.

From the foreword by Jeffrey Cummings to Dementia with Lewy Bodies (R.H. Perry, I.G. McKeith, E.K. Perry, editors), Cambridge University Press, 1996.
they termed ‘senile dementia of Lewy body type’ (SDLT), now extensively recognised as dementia with Lewy bodies. These authors also reported SDLT as the second most common cause of dementia in the elderly after Alzheimer’s disease.

But is dementia with Lewy bodies clinically recognisable, and what its relationship with Parkinson’s disease and with Alzheimer’s disease?

The International Workshop on Dementia with Lewy Bodies, held in Newcastle in October 1995, generated the breeze that made it possible to navigate these uncharted waters. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies were discussed and modelled, under the leadership of I.G. McKeith, and subsequently published in Neurology, opening the way for better investigation of treatment issues. Dementia with Lewy bodies has since been recognised as a common form of dementia in the elderly, accounting for 15-25% of dementia presentations. Fluctuating cognitive impairment and attention deficits are usually accompanied by recurrent visual hallucinations and parkinsonism. Delusions, depressed mood, sleep disturbance, and auditory hallucinations are common neuropsychiatric features of Lewy body dementia. This large patient group poses a considerable therapeutic challenge since neuroleptic medication, the mainstay of the management of psychosis and behavioural problems in most other disorders, can provoke severe, irreversible, and often fatal sensitivity reactions in this type of dementia. A two- to threefold increased mortality rate associated with neuroleptic sensitivity reactions in dementia with Lewy bodies has been shown by necropsy studies to be at least in part mediated via acute blockade of postsynaptic dopamine D2 receptors in the striatum.

In addition, clinicopathological correlative studies in Lewy body dementia have also shown extensive deficits in cholinergic neurotransmission. Neocortical cholinergic activity (assessed by choline acetyltransferase) is more severely depleted in dementia with Lewy bodies than in Alzheimer’s disease, a deficit correlated with the presence of visual hallucinations and global severity of cognitive impairment. Postsynaptic muscarinic receptors are better preserved and more functionally intact in Lewy body-type dementia than in Alzheimer’s disease, partly because of the absence of neocortical neurofibrillary tangle deposition. Therefore, drugs enhancing central cholinergic function offer, at the present time, a rational therapeutic approach for Lewy body dementia, cognitive and hallucinatory symptoms being the anticipated targets. Interestingly, in the late 1990s preliminary findings from open studies with cholinesterase inhibitors lent support to this approach, as did reports of patients diagnosed clinically with Alzheimer’s disease, but responding well to cholinesterase inhibitor treatments, only to be diagnosed with Lewy body dementia at necropsy.

On these bases rivastigmine, a cholinesterase inhibitor, was tested in a group of patients presenting the clinical characteristics of Lewy body dementia. The results were reported in a paper published in Lancet in 2000. Patients taking rivastigmine were significantly less apathetic and anxious, and had fewer delusions and hallucinations while on treatment than controls. Almost twice as many patients on rivastigmine (37, 63%), as opposed to placebo (18, 30%), showed at an at least 30% improvement from baseline. In the computerised cognitive assessment and the neuropsychological tests, patients performed significantly faster and better than those on placebo, particularly on tasks with a substantial attentional component. Both predefined primary efficacy measures differed significantly between rivastigmine and placebo.

McKeith and colleagues’ study was the first double-blind placebo-controlled trial of the use of this class of drug in non-Alzheimer patients. Other disorders with cholinergic abnormalities include Parkinson’s disease and patients with mixed Alzheimer’s and cerebrovascular disease, and these groups may also respond to cholinesterase inhibitors.

This, then, was the ‘Newcastle adventure’, whose sophisticated tone allows it to be likened to an overture at the breeze that made it possible to navigate these uncharted waters. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies were discussed and modelled, under the leadership of I.G. McKeith, and subsequently published in Neurology, opening the way for better investigation of treatment issues. Dementia with Lewy bodies has since been recognised as a common form of dementia in the elderly, accounting for 15-25% of dementia presentations. Fluctuating cognitive impairment and attention deficits are usually accompanied by recurrent visual hallucinations and parkinsonism. Delusions, depressed mood, sleep disturbance, and auditory hallucinations are common neuropsychiatric features of Lewy body dementia. This large patient group poses a considerable therapeutic challenge since neuroleptic medication, the mainstay of the management of psychosis and behavioural problems in most other disorders, can provoke severe, irreversible, and often fatal sensitivity reactions in this type of dementia. A two- to threefold increased mortality rate associated with neuroleptic sensitivity reactions in dementia with Lewy bodies has been shown by necropsy studies to be at least in part mediated via acute blockade of postsynaptic dopamine D2 receptors in the striatum.

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This, then, was the ‘Newcastle adventure’, whose sophisticated tone allows it to be likened to an overture at the dawn of the third millennium. Now the curtain is up and the performance is under way. To achieve greater aetiological and pathogenic understanding, to arrive at clinical diagnosis with the aid of biological markers and brain imaging, and to develop novel disease-targeted treatments for dementia with Lewy bodies are becoming the research priorities of an increasing number of basic and clinical investigators.

In summary, dementia with Lewy bodies burst onto the scientific scene as a major concern for clinicians and pathologists little more than a decade ago. The Lewy body, previously considered a common, if enigmatic, marker of idiopathic Parkinson’s disease, suddenly became a focus of interest as ubiquitin stains revealed that up to 30 per cent of patients diagnosed clinically and pathologically with Alzheimer’s disease have Lewy bodies in substantial numbers of cortical neurons. Is this a newly recognised dementing illness or a variant of Alzheimer’s disease?: what does the Lewy body tell us about a deranged intracellular metabolism?: do cortical Lewy bodies cause a dementia syndrome and, if so, how abundant must they be to produce clinically recognisable impairment in dementia with Lewy bodies?: what is the relationship between dementia with Lewy bodies and Parkinson’s disease?: does dementia with Lewy bodies have a different treatment response profile from Alzheimer’s disease?: What are the risk factors, both genetic and environmental?: what is the molecular pathogenesis?: These are the questions that an energetic and enthusiastic student community is now striving to answer, or at least to get into focus, so as to set the stage for future investigations.

The Editors