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Defining neurodegenerative diseases

Disorders will be named after responsible rogue proteins and their solutions

Defining neurodegenerative diseases is like defining the continent of Europe: part history, part science, part politics, and to cap it, both could have an effect on health and prosperity.

A big advantage of the term is that it is a concept that patients can relate to from parallels in everyday life. Wearing out in time of certain components—sometimes replaceable, sometimes not—encompasses principles of selective neuronal death as a primary event with age as a major risk factor and good remedies patchy.

Paradoxes abound. Neurodegeneration is a major element and is often the cause of the disability in many diseases not usually classified as degenerative—for example, multiple sclerosis, epilepsy, some inborn errors of metabolism, schizophrenia, and even tumours. Conversely, inflammatory processes are activated and vascular compromise occurs in some degenerative diseases. A Napoleonic view could encompass most brain diseases under the rubric of neurodegenerative, but this would lack focus.

Few health authorities run services for neurodegenerative disease as a whole because they can cut across several subspecialties. Core members are the dementias, Parkinson's disease, motor neurone disease, cerebellar degenerations, Huntington's disease, and prion diseases. Subclassification is clearly of importance for research, management, and ultimately for more targeted treatment.

Problems exist with terminology. For example, patients whose diagnostic label changes midcourse may feel that they have been misled. Thus a patient initially labelled as having Parkinson's disease may have the diagnosis changed to a rarer label (Lewy body dementia, corticobasal degeneration, progressive supranuclear palsy, or multisystem atrophy) as additional features like dementia or a gaze palsy or autonomic failure become apparent. The case with Alzheimer's disease is similar—fronto-temporal, multi-infarct, and dysphasic versions of dementia.

When carving out bewildering classifications neurology has been slow to allow patients a vote. Practitioners may also have preferred a common stem of Parkinsonism or dementia, for example, with a subvariety—which was underplayed until the diagnosis was definite or a change needed because the treatment or prognosis altered significantly. Time could then be concentrated on more important errors—for example, missing Wilson's disease, mistaking essential tremor for Parkinson's disease, overlooking drug induced dementia or Parkinsonism, or mistaking conditions which respond to drug treatment, such as myasthenia or motor neuropathy, for motor neurone disease. In all these conditions, missing depression is easy enough unless it is specifically sought.

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Contributions from basic science

Genes and proteins involved with these conditions are being rapidly elucidated, and naming the condition after the protein is an option.[1–5] This already happens for Creutzfeld Jakob disease—CJD/prion disease. However, until we are able to make a molecular diagnosis in life and offer specific treatment it is probably premature to use this strategy in clinical settings, even for those conditions where the molecular defect has been identified. Classifications that need postmortem data have caused enough problems in the past. Asking the diagnostician to predict the presence of a Lewy inclusion body or neuropathological changes of Alzheimer's disease when no test is available is to ask for a lot. Nevertheless we need to be aware of evolving terminology: alpha synuclein, parkin, and Parkinson's disease; amyloid and Alzheimer's; tau and frontotemporal dementia and progressive supranuclear palsy; SODI (superoxide dismutase 1) and motor neurone disease; glutamine repeats and Huntington's disease; and the new neuroserpinopathies.[6]

Though causative mutations have been described in some families, both genetic and environmental risk factors play a part in the aetiology of these conditions. The ratio varies—the genetic contribution is higher in Huntington's disease, Alzheimer's disease, and cerebellar degenerations and lower in Parkinson's disease, motor neurone disease, and prion diseases. The expectation is that we will find the genes that interact with environmental factors, which may be dietary, chemical, or biological agents. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a good though rare example of an environmental agent that caused an epidemic of Parkinsonism among drug misusers.[7] MPTP is a simple chemical, and a viable hypothesis is that autointoxication by similar molecules may cause sporadic diseases.[8] Another example is the epidemic of a variety of degenerative diseases on Guam, where the environmental agent has not been discovered.[9]

A common feature of these conditions is a long run-in period until sufficient protein accumulates, followed by a cascade of symptoms over 2-20 years, with increasing disability leading to death. This provides a wide therapeutic window, especially as groups at risk are identified earlier and preclinical diagnosis becomes feasible. The increasing incidence

with age can be seen as a threat (given population projections) or as an opportunity—a delay in the onset of these conditions by, say, 5-10 years would dramatically reduce their incidence and therefore costs. Individuals have realised that if they are lucky enough to side step or survive cancer and vascular disease the next threat is neurodegeneration in its various guises. But have governments realised this? Secondary postponement of disability is possible[10] and it is impressive and fast moving in Parkinson's disease and modest in Alzheimer's and motor neurone disease.[11]

The key characteristics of these conditions are that progressive degeneration occurs as a primary event long before symptoms develop and that it is selective, at least initially, for a particular neuronal pool. Other groups of neurones could join—for example, sensory end organ failure—and there is overlap with what we arbitrarily accept as ageing. In the future these diseases will be increasingly defined by the proteins involved. Improved diagnostics will hopefully change terminology and reduce the need to second guess pathology, thus increasing the accuracy of classification from the start. Eventually the mechanisms through which particular proteins cause toxicity would be elucidated, as will genetic and environmental risk factors. Primary preventive strategies could then emerge and ultimately (as in the case of polio and vaccination) these diseases will be defined by their solutions.

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Treating neurodegenerative diseases

What patients want is not what doctors focus on

Parkinson's disease is an excellent example of the challenges of caring posed by people with neurodegenerative disorders. It is insidious in onset, inexorably progressive, of unknown cause, incurable, yet amenable to management with pharmacological and other interventions. With the ageing of the population the prevalence of Parkinson's disease and other such disorders is projected to increase in the years ahead.[1] Thus all doctors must be prepared to provide diagnostic and management strategies for this growing population of patients. Medical practitioners must understand the expectations of patients and their families and introduce these perspectives within the framework of scientific understanding and evidence based practice. Conventional medical education has set a tradition of practice based on science, basic and clinical, cemented by a period of postgraduate training in the conventional apprenticeship mode. This has ensured that practices are generally competent and safe and grounded in the best available information. But is this approach consistent with the mission of professionals to build partnerships with patients by means of strategies for care consistent with the knowledge, attitudes, and values of a public most of which is educated.

Do most people believe, for example, that the quality of life of patients with neurodegenerative disorders depends primarily on the severity of disease and the effectiveness of pharmacological interventions? Without a detailed examination of evidence or a familiarity with the risks associated with treatment, patients may have an outlook that differs from that of professionals with respect to health related factors conducive to a better quality of life. Moreover, protocols for the care of patients are likely to derive more from the research interests and focus of investigators than the daily burdens of the people who have the illness.

There is a growing consensus that a lack of congruence exists between what patients and doctors value in terms of the impact of disease on quality of life and what should be done about it. In Parkinson's disease, there is robust evidence in favour of this divergence of perspective which may represent a potential barrier to the effectiveness of protocols for care, guidelines for management, and the most effective and efficient use of health resources.[2] When face to face interviews with more than 1000 patients with Parkinson's disease and carers were carried out in six countries only 17.3% of the variation in perceptions of health related quality of life could be explained by the severity of disease and the effectiveness of drug treatment. Such evidence necessarily represents a wake-up call for those health providers who believe that these factors are most important for prognosis and require a large share of professional effort.[3]

During these interviews, patients were also given the opportunity to complete specially developed questionnaires and validated instruments to identify other domains of care of equal or greater importance which affect the quality of their life. These domains had been identified in pilot studies by the investigators. The salient responses that accounted for approximately 60% of health related quality of life were respondents' mood, satisfaction with the explanation at the time of

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