PROGRESS IN NEUROLOGY 2017-2018

AHV SCHAPIRA

The last few years have seen accelerated progress in the field of neurology, encompassing both an understanding of disease and novel forms of treatment. The translation of discovery to therapy is a focus of all disciplines, but neurology has been a particularly fertile area for the application of this priority. The molecular basis for many, albeit still a minority, of neurological diseases has been identified over the last 30 years in particular. Modern techniques for the manipulation of genes and gene expression are now being developed and tested for the treatment of diseases such as Huntington and Duchene muscular dystrophy, and available for specific types of spinal muscular atrophy. Against this exciting background, the practice of neurology faces the daily challenge of managing common problems such as stroke, headache, epilepsy and neurodegenerative diseases. This annual review highlights some areas of interest for the practising clinical neurologist from articles published in the European Journal of Neurology during 2017.

Stroke remains the most common problem for neurologists to diagnose and treat (1-56). Preventative measures such as control of hypertension, reduction in smoking and treatment of hyperlipidaemia have made a significant contribution to preventing and delaying stroke onset. Other environmental factors play important roles in modifying stroke risk. For instance, a Taiwanese study showed that those that undertook >30 minutes physical activity three times per week or more had fewer complication and better outcomes following stroke (11). This could be a consequence of a parallel association with less obesity, hypertension, diabetes, smoking etc. It is of interest that chronic renal disease, with proteinuria and reduced estimated glomerular filtration rate pre-stroke are associated with poor outcome after stroke in those treated with thrombolysis (15,16). Thus incidence, severity and outcome of stroke is influenced by several factors amenable to appropriate management including preventative medicine.

Thrombolysis remains the mainstay of the treatment of acute stroke but the potential for increasing use of thrombectomy for large vessel occlusion is attracting more attention, although the practical difficulties of identifying the most appropriate patients and delivery of treatment remain a significant challenge (18,19). Thrombolysis improves outcome in both lacunar and non-lacunar stroke according to a study from Austria (26). Guidelines on the treatment of acute cerebral venous sinus thrombosis recommend low molecular weight heparin and decompressive surgery for the prevention of death due to brain swelling and herniation (32). However, there remains a lack of evidence base yet on the utilisation of the duration of anti-coagulation after the acute phase, or the use of thrombolysis/thombectomy.

The management and outcome of multiple sclerosis has been transformed by the use of immunomodulation therapies (57-83). Outcome measures as judged by patient reported outcomes, remains an important area for development and is relevant for care delivery design (68,70). The use of biomarkers that reflect natural history and response to treatment are invaluable and the use of cerebrospinal fluid neurofilament light protein and tau to correlate with brain atrophy is helpful (71,75,77). A provisional retrospective analysis has suggested that immunomodulatory therapy may not need to be continued indefinitely, but this needs to be the subject of further study (78).

The world-wide prevalence of Parkinson disease (PD) is rising steadily as the global population ages, and significant advances are being made in the understanding of pathogenesis and treatment (84-108). It is of interest that in Portugal, where there is a high prevalence of LRRK2 G2019S mutation in PD, a recent study found PD prevalence to be

0.24% of those aged>50 years, with a total of 180/100,000 population, rather lower than might be expected, although this is probably explained by methodological issues (87). This mutation may be associated with specific inflammatory markers that appear to be associated with the severity of motor and non-motor dysfunction and these could provide a useful biomarker for stratification (93). A similar suggestion is that the presence of rapid eye movement sleep behaviour disorder may also be associated with specific patterns of motor function and striatal dopamine transporter uptake (94). Non-motor problems in PD remain a major challenge for effective therapy. A meta-analysis of bilateral sub-thalamic nucleus deep brain stimulation found a significant improvement in gait and freezing of gait for more than four years; this effect was best predicted by pre-operative levodopa response (96). Fludrocortisone 0.2mg/day has been shown to improve orthostatic hypotension in patients with PD (101)

Dystonia is a manifestation of a wide range of underlying pathologies and irrespective of the aetiology, its effective management is limited (109-116) The use of both pallidal (111) and transcranial stimulation (115) have recently been explored (116). Other movement disorders (117-122) are benefitting from increased attention with new imaging modalities.

Neurodegenerative diseases in general and the dementias and Alzheimer disease (AD) specifically, are one of the commonest problems facing clinicians (123-132). It is of interest to note that some have suggested the incidence of dementia is in decline as a result of improved treatment of vascular risk factors, although this observation remains in debate. Hypertension has been shown to be associated with worse cognitive function, behavioural symptoms and hippocampal glucose hypometabolism, but not with increased amyloid or tau pathology (126). Mortality from AD is increasing in the European Union (132). The genetic basis of amyotrophic lateral sclerosis (ALS) has seen several important recent advances over the last few years although treatment remains limited (133-142). The role of the environment in the evolution of ALS is considered important (133,141). Epilepsy is another example of a neurological disorder that has seen significant insights into causation, particularly at the genetic level. The management of epilepsy remains a challenge, despite the development of additional anti-convulsants (143-154). There has been a steady decline in mortality of newly diagnosed patients with epilepsy over the last 30 years, attributable to better diagnosis and management (148). There is an increasing awareness of the need to manage epilepsy and its co-morbidities and anti-convulsant side effects in a multidisciplinary manner (145,147,149,152).

Neuromuscular disorders encompassing both primary myopathies, neuropathies and diseases of the neuromuscular junction are together a group of diseases that are often challenging to disentangle diagnostically (155-173). Many of these have a genetic basis and novel causative mutations continue to be identified (162,163,165,173) and the clinical phenotype of existing mutations more clearly defined (156,161,169). Treatment modalities are limited, with the exception of the immune mediated diseases and those with a defined biochemical cause that lends itself to specific therapy such as Pompe disease (166). Immune-mediated diseases of the central nervous system (CNS) (174-184) are a heterogenous group of disorders characterised by specific antibodies to CNS proteins such as the autoimmune encephalitides and neuromyelitis optica. Significant progress has been made in the diagnosis and treatment of these (174,175,179,181). Infectious encephalitis remains a global concern, particularly in the light of limited therapeutic options.

Of all of the clinical presentation to the neurologist, headache is the most common (185-191). New strategies to improve service provision with accelerated diagnosis and treatment are being employed, through for instance telemedicine (187), a model that appears

successful. Neurological involvement in medicine remains active across a large spectrum of presentations (192-210). Novel mutations in adult-onset leukoencephalopathy (192) and the spinocerebellar ataxias (201) and the search for biomarkers in neurological disease (198,206,208) are some examples of the involvement of neurology research across this spectrum.

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Stroke Pathophysiology

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Multiple Sclerosis-General

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