Diagnosis and treatment of IgM related paraproteinaemic neuropathies

Dr MPT Lunn, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Paraproteins are associated with neuropathy far more frequently than can be explained by chance alone and IgM paraproteins account for about 50% of these. Most frequently the paraprotein is a monoclonal gammopathy of undetermined significance (MGUS) but pathogenic paraproteins also occur with Waldenström's macroglobulinaemia (WM) and other lymphomas and these can have identical neuropathy phenotypes. Importantly, although the MGUS may be entirely benign in its own right, or the WM appropriate to observe and monitor, the neuropathy may be progressive and disabling and determine the need for treatment. Not infrequently the neuropathy may be the presenting feature for the haematological diagnosis. If possible, partnership with a neurologist is both rewarding and mutually beneficial.

A number of neuropathy phenotypes are recognised including the sensory ataxic demyelinating anti-myelin associated glycoprotein associated neuropathy, painful patchy sensorimotor neuropathies due to amyloid, light chain deposition or vasculitis, and distal painful small fibre neuropathies. Unrelated phenotypes may be recognised and referred elsewhere. The recognition and distinction of these neuropathies determines appropriate investigation to exclude differential diagnoses and reach a correct paraprotein associated diagnosis which has implications for treatment selection.

The IgM paraproteinaemic neuropathy associated with antibodies to MAG is the commonest association. Classically, elderly males present with unsteadiness and a typical tremor with pronounced vibratory threshold sensory impairment out of proportion to small fibre involvement. The light chain is almost always kappa and the MGUS paraprotein level is frequently <3g/l. However the pathogenic titre of anti-MAG activity is extremely high. MAG is a transmembrane glycoprotein with roles in axon-Schwann cell growth and cell signalling. The paraprotein binds to a carbohydrate HNK-1 epitope and produces pathognomic myelin changes and collapse of the neurofilament axonal cytoskeleton. Some anti-MAG neuropathies remain benign and non-progressive and, although irritating, do not warrant treatment. Others are more severe and may respond to intervention. IVIG is effective in the short term, and single agent rituximab improves patient scores in two trials but was not effective in the primary end-points. Studies of the effect of regimens of rituximab and proteosome inhibitors with appropriate neurological outcomes are required as investigations of opportunity in haematological trials.

The neuropathies of amyloid or light chain deposition are dramatic and may be clinically devastating. Rapid laboratory supported diagnosis and nerve biopsy confirmation can precipitate timely treatment, help in guiding therapeutic choices and frequently lead to reversal of progression. Small fibre neuropathies are often more indolent and difficult to diagnose with any laboratory supported certainty. They may respond to reduction in the paraprotein with plasma exchange, but this is short lived. Pain and disability in both of these neuropathies may necessitate multi-agent therapy or occasionally autologous peripheral blood stem cell transplantation.