ANTIGENIC DETERMINANTS IN IgM RELATED NEUROPATHIES

Eduardo Nobile-Orazio, MD, PhD, 2nd Neurology, Department of Translational Medicine, Milan University, IRCCS Humanitas Clinical Institute, Via Manzoni 56, 20089, Rozzano, Milan, ITALY

The association of neuropathy with monoclonal gammopathy has been known for several years, but only in the last 25 years the clinical and pathogenetic relevance of this association has been partly clarified. In particular the high prevalence of neuropathy in patients with IgM monoclonal gammopathy (30% to 50%), reinforces the hypothesis that, at least in this condition, the M-protein plays a pathogenetic role in the neuropathy. Different forms of neuropathies have been associated with IgM monoclonal gammopathy, possibly reflecting the different mechanisms involved in their pathogenesis: cranial nerve palsies, mononeuropathies or mononeuritis multiplex have been mainly associated with Waldenström's macroglobulinemia (WM) and other malignant IgM gammopathies being related to lymphoplasmacytic infiltration of nerves, amyloid deposition, cryoglobulinemic vasculitis or microangiopathy of endoneurial vessels. The vast majority of patients however and particularly those with IgM MGUS or indolent WM, has a chronic progressive, symmetric and predominantly distal neuropathy which was occasionally related to endoneurial accumulation of the M-protein, or diffuse microangiopathy but most frequently to a reac¬tivity of the M-protein with a number of neural antigens. Several data support in particular the pathogenetic role of IgM M-proteins reacting with the Myelin-associated glycoprotein (MAG) in the neuropathy including its frequent association with a clinically homogeneous demyelinating neuropathy, the presence of deposits of IgM M-protein and complement on nerve myelin and the clinical improvement observed concomitantly to the reduction of anti-MAG IgM. Even if several immune therapies have been reported to be effective in these patients, their impact on the long-term outcome of the neuropathy remains to be established. Recently treatment with Rituximab was found to durably improve the neuropathy in two-third of the patients, particularly in those with moderately increased anti-MAG titres, which may be more easily reduced by this treatment. Several other monoclonal IgM reactivities with nerve antigens have been reported, though less frequently, in these patients including cytoskeletal proteins, chondroitin sulfate C, several gangliosides and sulfatide even if, with the only exceptions of anti-sulfatide and anti-GQ1b ganglioside IgM reactivities their possible pathogenetic and clinical relevance remain to be established.