Familiar Waldenstrom´s Macroglobulinemia in Northern part of Sweden

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Background: Waldenstroms´s Macroglobulinemia (WM) is a rare disease, with an overall incidence rate of 3-4 cases per million people per year. The incidence in Sweden based on data from Swedish lymphoma registry is approximately 10 per million persons per year and in the northern part of Sweden in the counties of Norrbotten and Västerbotten the incidence is approximately 17 per million people per year.
Currently, the causes of WM are mostly unknown; however, recent data support a role for both genetic and immune-related factors in the pathogenesis. Familial clustering in WM has been observed in several studies (Treon et al, Annals of Oncology, 2006 and Kristinsson et al, Blood 2008). Patients with a personal history of autoimmune diseases (Kristinsson et al, JNCI, 2010) or infections (Koshiol et al, Arch Intern Med) have a higher incidence of LPL/WM.

Recently, hyperphosphorylated paratarg-7, a protein with unknown function, was identified as the target of 11% of IgM paraproteins in patients with IgM MGUS and WM (Grass et al, Blood 2011). Family analysis showed that hyperphosphorylated paratag-7 is inherited in a dominant fashion (Grass et al, Lancet Oncol, 2009).

Methods and Results: Seven families with two or more relatives with WM or IgM MGUS and 2 families with WM and myeloma (MM) were identified through the Regional Lymphoma Registry for the Northern Part of Sweden and the Swedish Cancer Registry from this region. In 4/9 of the families siblings were affected, in 3/9: parent-child and 2/9: other relationships.
The index patients and their relatives were contacted for prior medical history, complete blood counts, LDH, beta-2-microglobuline, serum protein electrophoresis, immunofixation, free light chains in serum and research samples.
In 5/9 families there was a history of autoimmune disease and in 3/9
another hematological malignancy than WM and MM. In total, 44 blood samples from 8 families have up till now been analyzed with serum protein electrophoresis and immunofixation. 22/44 (50%) of all patients and 11/33 (33%) of the unaffected relatives had an abnormal serum protein electrophoresis. 16/44 (36%) had a monoclonal paraprotein (7 WM, 1MM, 5 IgM MGUS, 2 IgG MGUS, 1 light chains). 3 patients had polyclonal hypergammopathy (2 IgM and 1 IgA) and 4 patients subnormal levels of IgG. In 15% of the unaffected relatives an unknown paraprotein was detected. All patients with paraproteins in the same family had the same light chain. Abnormal FCL ratio was only seen in patients with WM.

Conclusions: In 2 counties of the northern part of Sweden with high incidence of WM, the relatives to patients with WM have a high frequency of serum immunoglobulin abnormalities (monoclonal gammopathy, polyclonal gammopathy and subnormal levels of IgG) and may indicate a higher risk for develop WM. Analyses of paratarg-7 are ongoing in collaboration with Prof. Michael Pfreundschuh and Dr Klaus-Dieter Preuss, Saarland University Medical School, and the results will be presented.