Autoantibody markers identified in glaucoma

Stefanie Petrou Binder MD
in Berlin

**ANTI-BO-DO!** profiles of patients with primary open-angle glaucoma and normal tension glaucoma lend support to the idea of an autoimmune role in glaucoma pathogenesis, German researchers report.

"Glaucoma is characterised by a progressive loss of retinal ganglion cells that results in a characteristic optic neuropathy associated with visual field loss. At the time of detection, the minimal loss in RGC is frequently as high as 50%. Intraocular pressure can be elevated or normal at this time. By the time glaucoma is detected in the clinic, most patients will have suffered from it for over 10 years. The pathogenesis of this disease remains unclear. We have strong evidence that this disease may have to do with autoimmune mechanisms," said Franz Grus MD.

"At the time of detection, the minimal loss in RGC is frequently as high as 50%. Intraocular pressure can be elevated or normal at this time. By the time glaucoma is detected in the clinic, most patients will have suffered from it for over 10 years"

Dr Grus conducted a study that included US and German study groups, to allow for direct comparison between the consistency of antibody profiles. The study included 40 patients with primary open-angle glaucoma, 40 with normal tension glaucoma and 40 healthy volunteers. The investigators used Western blot assays against bovine optic nerve antigens present in patient serum. The retinal and optic nerve antigens involved are heat shock proteins (HSP27, HSP90) and alpha crystalline. They analysed complex antibody profiles with the use of multivariate statistical techniques. They also assessed immunoreactivity against recombinant alpha-fodrin with ELISA.

**Similar antibody profiles**

The investigators could demonstrate a strong similarity between all antibody profiles in primary open-angle glaucoma and normal tension glaucoma patients compared to controls, in particular HSP and alpha crystalline. This occurred in both US and German study populations with regard to the number and frequency of up- and down-regulation of antibody reactivity. Complex IgG autoantibody repertoires were present in glaucoma and healthy subjects from both the German and US study populations.

Dr Grus reported that certain antibody reactions were elevated in glaucoma patients, while other antibody reactions were decreased in these groups compared to controls. He explained that this evidence validated the conclusion drawn from earlier trials on the subject that not only autoimmune (auto-aggressive) mechanisms were involved in glaucoma, but in addition also changes in natural immunity, which may indicate lowered protection and regulatory functions in glaucoma patients.

The multivariate analysis detected a significant difference between the glaucoma groups and healthy subjects against optic nerve antigens. The normal tension glaucoma group revealed the highest variance from controls (P<0.01), as previous studies on the subject corroborate, Dr Grus said.

**New marker identified**

He further identified a highly significant newly described antibody biomarker in both study populations, known as alpha-fodrin. The high alpha-fodrin autoantibody activity in glaucoma patients was confirmed by ELISA tests with recombinant human alpha-fodrin.

Alpha-fodrin is a cytoskeleton protein. It is cleaved by caspase and may therefore result from an autoimmune process in the eye, making it a good marker for apoptosis, Dr Grus noted. He pointed out that the antigen is commonly found in other neurodegenerative diseases, such as Alzheimer's disease.

Ophthalmologists who attended Dr Grus' lecture were curious as to why antigens to alpha-fodrin were present in healthy subjects, claiming that if that were the case, the specificity of this compound in detecting glaucoma would in fact be low.

Dr Grus explained that antigenic reactivity to alpha-fodrin is present in 40-50% of healthy people and 80-90% of normal tension glaucoma patients. He explained, however, that it is not the presence alone of antigen, but the intensity of reactivity that set the reactions apart. Furthermore, sensitivity and specificity reactions are not elicited from alpha-fodrin alone, he said. Antigenic reactions are complex, being elicited through 10 or 20 complex reactions.

**Possible autoimmune changes**

Dr Grus said that previous studies have also shown changes in serum antibody profiles of glaucoma patients, suggesting a role for autoimmune involvement in the pathogenesis of glaucoma in some patients. HSP antibodies were among the first to be recognised in glaucoma patients.

Researchers are still not sure if the autoantibodies seen in glaucoma are an epiphenomenon, ie develop during the disease as a consequence of the disease, or are causative in glaucoma. However, they have proven that glaucoma patients have characteristic differences of serum autoantibody repertoires from control patients, providing further proof for changes in the natural autoimmunity of glaucoma patients.

Dr Grus is certain that a blood test for these and other antigens will be a strong modality with which to detect glaucoma in the future. Even if detection relies on the presence of very few antibodies or if the presence of antibodies turns out to be an epiphenomenon of glaucoma, it would represent a viable means of early detection, before the appearance of any clinical signs.

Günter K Krieglstein MD who moderated the session found it interesting that the antibody profiles of both the US and German study cohorts were so similar, in terms of which antibody reactions were heightened and which were lowered in healthy and glaucoma patients.

Dr Grus agreed that it was quite surprising to find such high consistency between the two groups. He explained that healthy subjects have autoimmune profiles that are stable for life, the so-called immunologic homunculus. The immunologic homunculus changes, however, in individuals suffering from immunologic disease, he said. It was not clear, however, to which extent these autoimmune profiles change or whether they can be used as longitudinal markers, as no studies on that subject exist, Dr Grus said.

FGEGRUS.de