Anti-Hsp70 Antibodies and Cogan's Syndrome

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The assumption that progressive sensorineural hearing loss is an autoimmune disorder in some patients was first raised by McCabe in 1979 [1], who reported on a pattern of bilateral autoimmune sensorineural hearing loss characterized by a rapid progression of hearing loss over days to months. This assumption was initially based on the findings of a positive lymphocyte mitogen inhibition assay to cochlear antigens, and of a significant amelioration in the hearing loss following steroid therapy in such patients. Additional support for this assumption was the development of inner ear damage in animal models after immunization with inner ear tissue extracts, and that this injury is transferable with sensitized T cells [2,3]. However, definite proof for an autoimmune etiology came later when specific autoantibodies were found in association with primary ASNHL and with related disorders such as Meniere's disease and Cogan's syndrome. Cogan's syndrome (both typical and atypical) has been characterized by many to be immune mediated or autoimmune in origin. Both types present as ocular symptoms, and in both types SNHL and audiovestibular symptoms are present. In this case, SNHL (both unilateral and bilateral) is described to be sudden, fluctuating, and/or progressive. Progression to complete hearing loss was detected in audiometric assay in almost 50% of patients during follow-up [4]. In addition to the lymphocyte transformation test and to the evidence for cellular immune responses, Western blot immunoassay was also one of the early methods contributing to the assessment of all types of ASNHL [5]. In 1993 Mayot et al. [6] reported an abnormality of the T cell subgroups in peripheral blood of 57 individuals with sudden deafness (n=17, group I) and progressive SNHL (n=4, group II). A reduced amount of CD4+ cells was observed in group I, whereas a marked decrease in CD8+ cells was recorded in both groups. Moreover, antinuclear and anti-thyroid antibodies were frequently detected in the sera of group II patients (75%), while anti-cochlear and anti-cartilage antibodies were present similarly in both groups (71%). At the same time, a study by Shin et al. [7] found that approximately 40% of patients with rapidly progressive SNHL have antibodies to 68 kDa (heat shock protein 70) inner ear antigens. Here, immunoblot testing provided 58% sensitivity and 98% specificity for hsp70. Later, Boulassel and co-authors [8] used two-dimensional gel electrophoresis and immunoblot analysis to determine, at the molecular level, that inner ear autoantigens are recognized specifically by autoantibodies in the sera of patients considered to have ASNHL. In this study, 44% of the patients' sera had antibodies reacting against inner ear proteins such as 30, 42, and 68 kDa proteins.

Using indirect immunofluorescence technique, immunoglobulin G and A antibodies against human cornea and IgG antibodies against human inner ear tissue were demonstrated in the serum of a patient with Cogan's syndrome. In contrast, sera of healthy individuals were free of such antibodies. This finding strengthened the assumption that autoimmune mechanisms are indeed responsible for the development of CS [9]. In another study at that time (1985) [10], antibodies against healthy inner ear tissue were found in the serum of 15 of 21 patients suffering from idiopathic progressive SNHL; 2 patients with CS were found to have serum antibodies against epithelial structures of the cornea. A decade later, aiming to establish the finding of autoantibodies, namely IgM and IgG, to inner ear antigens and corneal structures, the serum of CS patients was analyzed for its ability to bind fresh cryosections of rat labyrinth and cornea. The predominant pattern of anti-corneal IgM was staining of the superficial cell layer of the non-keratinizing squamous epithelium. IgM against cornea was found in three patients, all of whom had bilateral inflammatory eye signs at the onset of the disease. During the first episode of CS in one patient, anti-corneal IgM became detectable 1 week after the onset of interstitial keratitis and 3 weeks after the onset of audiovestibular symptoms [11]. When humoral immune responses to inner ear proteins were studied in patients with SNHL, antibodies to both Hsp70 and the protein 68 kDa extracted from bovine inner ear could identify subsets of autoimmune SNHL, including CS [12].

Further studies were later published aiming to establish the significance of autoantibodies in recognizing inner ear and endothelial autoantigens in CS. In one of these, pooled IgG immunoglobulins from eight patients with CS were used to screen reactivity with relevant autoantigen peptides. The authors identified an immunodominant peptide that showed similarity

ASNHL = autoimmune sensorineural hearing loss
SNHL = sensorineural hearing loss

Hsp70 = heat shock protein 70
IG = immunoglobulin

CS = Cogan's syndrome

with antigens such as SSA/Ro and with the reovirus III major core protein lambda 1. The peptide sequence showed similarity also with the cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), which is expressed on the sensory epithelia of the inner ear and on endothelial cells. IgG antibodies against the peptide, purified from patients' sera, recognized autoantigens and DEP-1/CD148 protein, bound human cochlea, and inhibited proliferation of cells expressing DEP-1/CD148. Furthermore, these antibodies were able to induce the features of Cogan disease in mice. These findings indicate that CS is indeed an autoimmune disease, characterized by the presence of these specific autoantibodies [13]. The abovementioned autoantibodies are thought to be highly specific for the diagnosis of CS (hence called anti-Cogan peptide antibodies). However, they were later found to exist also in children diagnosed with idiopathic SNHL. This study suggested that these antibodies serve as a marker for ASNHL – a subset amenable for immune modulation therapy rather than being specific for CS only [14].

In this issue of *IMAJ*, Bonaguri et al. [15] report their findings on the specificity and sensitivity of anti-Hsp70 antibodies in typical CS. They found anti-Hsp70 antibodies in 93% of patients with typical CS in contrast to 53% of patients with ASNHL, suggesting that this antibody is a highly sensitive and specific diagnostic marker for typical CS. In an earlier study these same authors found anti-Hsp70 antibodies to be of great value for the diagnosis of ASNHL; half of their patients were characterized as suffering from CS. In that study, anti-Hsp70 antibodies were defined as a marker for ASNHL rather than a specific one for CS or one of its subtypes [16].

According to all the published data of several years, it is well proven that the presence of anti-Hsp70 antibodies is a good marker for defining ASNHL and a perfect indicator for the early initiation of steroids. More data assessing large cohorts of CS patients are required to finally establish whether this antibody is an optimal marker for typical CS. One should also remember that the diagnosis of CS, particularly the diagnosis of a specific subtype, is entirely a clinical one and sometimes some features are missing and the differentiation between typical and atypical is not clear-cut. The timing of immunosuppressive therapy in CS is very important. The earlier we initiate such therapy the better the chance of achieving a beneficial outcome by ameliorating both hearing loss and ocular symptoms. Therefore, using well-established and proven diagnostic tools is crucial [17]. At present, the finding of anti-Hsp70 antibodies in patients with progressive hearing loss is highly suggestive of ASNHL and calls for prompt steroid and/or immunosuppressive drug therapy. However, further studies are required to determine whether anti-Hsp70 antibodies are indeed highly specific for typical CS in particular, or rather are a marker for progressive hearing loss and an indicator for the initiation of steroid therapy.

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"A pedestal is as much a prison as any small space"

Gloria Steinem (b. 1934), American feminist, journalist, and social and political activist who became nationally recognized as a leader of the women's liberation movement in the late 1960s and 1970s

"I don't mind that you think slowly but I do mind that you are publishing faster than you think"

Wolfgang Pauli (1900-1958), Austrian theoretical physicist and one of the pioneers of quantum physics. In 1945, after having been nominated by Albert Einstein, Pauli received the Nobel Prize in Physics for his "decisive contribution through his discovery of a new law of Nature, the exclusion principle or Pauli principle." The discovery involved spin theory, which is the basis of a theory of the structure of matter