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Review

Cogan syndrome — Pathogenesis, clinical variants and treatment approaches

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ABSTRACT

Non-syphilitic keratitis, coexisting with vestiboloauditory symptoms namely hearing loss and dizziness was first reported by Morgan and Baumgartner back in 1934. It was then ten years later when D.G. Cogan, an ophthalmologist (1908–1993) described 4 patients having the same symptoms but in addition, attacks of vertigo, tinnitus, hearing loss and ocular symptoms. This was published in Archives of Ophthalmology in 1945 and later named Cogan's syndrome (CS). Almost 20 years later on, bilateral recurrent episcleritis associated with vestiboloauditory symptoms were defined to be the atypical form of CS occurring in association with rheumatoid arthritis (RA). During the coming two decades the division of CS into typical (classical) and atypical variants, based mainly on the clinical presentation of this syndrome was accepted. Typical CS manifests primarily with interstitial keratitis and hearing loss, whereas atypical CS is usually presented with scleritis, chroiditis and more frequently with systemic inflammation. Approximately, 70% of these patients have systemic manifestations, of which vasculitis is considered the pathogenic mechanism and therefore carries a less favorable prognosis than typical CS. Since then, CS was considered by many to be autoimmune or immune mediated in origin, supported mainly by the beneficial response to corticosteroids. It was only later, using well developed assays such as western blotting and immunofluorescence (IF) when antibodies to inner ear antigens, anti neutrophil cytoplasmic antibodies (ANCA) and anti-endothelial antibodies were found and described to be associated with CS.

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Contents

1. Introduction

The autoimmune theory in CS was finally confirmed in the 80s by the frequent finding of many autoantibodies against corneal, inner ear and endothelial antigens part of which are considered specific and of diagnostic value [1–4]. Later, other autoantibodies such as ANCA, rheumatoid factor (RF) and others were also found to be present in association with CS though of less specificity, but further pointing to the autoimmune origin of CS. In acceptance with this is the early report on the histopathological nature of Cogan's. In this report the examination of corneal tissue and cochlea from patients with CS showed lymphocytic and plasma cell infiltration, strengthening the assumption that this disorder is of immune-mediated character [5].

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1.1. CS and autoantibodies to inner ear antigens

Using the indirect IF technique, IgG and IgA 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 was the beginning of suggesting autoimmune mechanisms to be responsible for the development of CS [6]. In another study back then, antibodies against healthy inner ear tissue were found in the serum of 15 out of 21 patients suffering from idiopathic progressive sensorineural hearing loss. In 2 cases of CS, in addition to the above finding, it was also possible to demonstrate serum antibodies against epithelial structures of the cornea [7]. A decade later, aiming to establish the finding of autoantibodies to inner ear antigens and corneal structures, the serum of CS patients, namely IgM and IgG 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 3 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 one week after the onset of interstitial keratitis and 3 weeks after the onset of audiovestibular symptoms [8]. When humoral immune responses to inner ear proteins were studied in patients with sensorineural hearing loss (SNHL), antibodies to both heat shock protein 70 and the protein 68kDa extracted from bovine inner ear were found to identify subsets of autoimmune SNHL among which was also CS [9].

Further studies were later published aiming to establish the significance of autoantibodies to inner ear and endothelial autoantigens in CS. In one of these, pooled IgG immunoglobulins derived from 8 patients with CS was used in order to screen reactivity with relevant autoantigen peptides. Here, the authors identified an immunodominant peptide that showed similarity 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 patient's 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 [10]. The above mentioned autoantibodies thought to be highly specific for the diagnosis of CS (therefore called anti-Cogan peptide antibodies). However, they were found later also to be existing in children diagnosed as having idiopathic SNHL. This study suggested these antibodies to become a marker for autoimmune SNHL a subset amenable for immune modulation therapy rather than being specific solely for CS [11].

The finding of other non-specific autoantibodies in patients with CS was also reported in many studies. Among these ANCA was reported in many cases of both typical and atypical CS. In some of these, it was in association with ANCA-related glomerulonephritis. Rheumatoid factor, anti-nuclear and anti-endothelial antibodies have also been reported in some patients with CS, suggesting again that autoimmunity is involved and therefore suggested that CS should be treated with steroids and cytotoxic therapies [12,13].

2. Clinical variants of Cogan syndrome

Cogan syndrome has been reported in many case studies to be presented by typical oratypical clinical manifestations. In most of these, CS developed in young Caucasian adults, mostly during their first three decades of age, and with no gender-specific prevalence [14–16].

2.1. Typical Cogan's syndrome

Is defined by the following characteristic three conditions: (i) ocular symptoms, classically presented as non-syphilitic interstitial keratitis (IK); (ii) audiovestibular symptoms similar to those of Meniere's syndrome (sudden onset of tinnitus and vertigo, accompanied by hearing loss); and (iii) an interval between the onset of ocular and audiovestibular manifestations of less than 2 years.

2.2. Atypical Cogan's syndrome

Is characterized by (i) different inflammatory ocular manifestations, with or without IK; (ii) In association with audiovestibular symptoms but mostly different from Meniere-like symptoms; and mostly (iii) a delay of more than 2 years between the onset of ocular and audiovestibular manifestations. In many cases it is difficult to differentiate between the two types of Cogan's syndrome (typical or atypical), because some patients do not present interstitial keratitis at the onset of disease or alternatively they develop this condition during the following years. Timing and the association between manifestations of Cogan's syndrome are extremely variable. Finally, systemic manifestations are much more frequent in atypical Cogan's and can be used in the differentiation between the two types.

2.3. Audiovestibular manifestations

Of these, the most common symptoms are hearing loss, vertigo, tinnitus, ataxia and oscillopsia. These symptoms were noted at any time during the course of the disease. Hearing loss (both uni or bilateral) is mostly similar to the course of sensorineural hearing loss. On physical examination, at least 20% of patients have spontaneous or gaze-induced nystagmus. In one case study, abnormal results of formal vestibular function testing were noticed in 90% of patients. In this study, specific abnormal vestibular responses included; a bilateral absence of vestibular responses to caloric testing, bilateral weak vestibular responses to caloric testing and unilateral weak or absent responses to caloric testing were noticed in 20–40% of all patients. Only few patients experienced clinical symptoms of vestibulopathy that lasted for days or weeks from the time of onset without resolution that frequently resulted in hospitalization and/or rehabilitation. Hearing loss was sudden, usually bilateral, fluctuating, and\or progressive. Progression to complete bilateral hearing loss was detected in audiometric assay in almost 50% of patients during the follow-up period, whereas permanent hearing loss in one ear was observed in 20% of patients. Normal hearing in both ears remained so in only few patients when evaluated at last visit [17].

2.4. Ocular manifestations

The most frequent symptom and one of the hallmarks of typical Cogan's syndrome is interstitial keratitis which appears in 80% of cases, and is mostly bilateral. In some cases IK developed later during the course of disease and was missed at the initial examination. The other ocular worth mentioning manifestations mainly in patients with atypical CS, are acute closure angle glaucoma, cases of retinal vasculitis, papillitis, central vein occlusion, vasculitic optic neuropathy, and papilledema. Most of the patients maintained normal or near-normal vision at the last visit of follow-up and only few developed some degree of visual loss directly attributable to inflammatory eye disease [17].

2.5. Systemic manifestations

In addition to the typical ocular and vestibuloauditory presentation, approximately 30%–50% of patients have features of systemic manifestations, the mechanism of which in most cases is considered to be vasculitis involving all vessel sizes [14,18]. Among the most common systemic symptoms that were reported in a survey which included 60

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