Autoimmunity Reviews 12 (2013) 396–400

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Cogan's syndrome: An autoimmune inner ear disease

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ARTICLE INFO

Article history:
Received 6 July 2012
Accepted 18 July 2012
Available online 28 July 2012

Keywords:
Cogan's syndrome
Autoimmune inner ear diseases
Vasculitis
Anti-neutrophil cytoplasmic auto-antibody
Autoimmunity
Aetiopathogenesis
Therapy

ABSTRACT

Objectives: The objective of our study was to review our current knowledge of the aetiopathogenesis of Cogan's syndrome, including viral infection and autoimmunity, and to discuss disease pathogenesis with relevance to pharmacotherapy.
Systematic review methodology: Relevant publications on the aetiopathogenesis and pharmacotherapy of Cogan's syndrome from 1945 to 2012 were analysed.
Results and conclusions: Cogan's syndrome is a rare autoimmune vasculitis, and its pathogenesis is unknown. Infection, but primarily autoimmunity, may play contributing roles in the pathogenesis of this disease. It is characterised by ocular and audiovestibular symptoms similar to those of Meniere's syndrome. Approximately 70% of patients have systemic disease, of which vasculitis is considered the pathological mechanism. The immunologic theory is based on the release of auto-antibodies against corneal, inner ear and endothelial antigens, and of anti-nuclear cytoplasmic auto-antibodies (ANCA).
Corticosteroids are the first line of treatment, and multiple immunosuppressive drugs have been tried with varying degrees of success. Tumour necrosis factor (TNF)-alpha blockers are a category of immunosuppressive agents representing a recent novel therapeutic option in Cogan's syndrome.

Contents

1. Introduction

Cogan's syndrome was first described in 1945 by an ophthalmologist, Dr David G. Cogan, who reported on a "syndrome of non-syphilitic interstitial keratitis (IK) and vestibuloauditory symptoms" that resembled Meniere's disease [1].

In addition to the ocular and audiovestibular involvement, numerous systemic manifestations were reported in 1960 by Cody and Williams in patients with Cogan's syndrome [2].

More than 100 cases of Cogan's syndrome have been reported in the literature, despite it being a rare condition that mostly affects Caucasian young adults [3]. The median age of onset is 25 years, and there is no gender-specific prevalence [4].

In 1980, Haynes et al. [5] proposed diagnostic criteria for typical and atypical Cogan's syndrome, which include a large spectrum of clinical manifestations.

Typical Cogan's syndrome is defined using Cogan's original criteria [1] with the following three conditions: (1) ocular symptoms, non-syphilitic

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1568-9972/$ – see front matter
http://dx.doi.org/10.1016/j.autrev.2012.07.012

IK; (2) audiovestibular symptoms similar to those of Meniere's syndrome (sudden onset of tinnitus and vertigo, accompanied by gradual hearing loss); and (3) an interval between the onset of ocular and audiovestibular manifestations of less than 2 years.

According to the criteria of Haynes et al. [5], patients with any of the following symptoms are classified as having atypical Cogan's syndrome: (1) inflammatory ocular manifestations, with or without IK; (2) typical ocular manifestations associated with audiovestibular symptoms different from Meniere-like episodes; or (3) a delay of more than 2 years between the onset of typical ocular and audiovestibular manifestations.

In addition to ocular and vestibuloauditory dysfunctions, approximately 70% of patients have underlying systemic disease for which vasculitis is considered the pathological mechanism [6].

Vasculitis has been reported; however, there are relatively few reports with a histological confirmation [7]. Although there is usually large and/or medium vessel vasculitis, any size vessel may be affected [8,9].

The most common symptoms are cardiovascular, neurological and gastrointestinal [4]. The most characteristic cardiovascular manifestation of Cogan's syndrome is aortitis with aortic insufficiency [10].

Neurological manifestations may include hemiparesis or hemiplegia due to a cerebral vascular accident and aphasia due to a transient ischaemic event [4,11,12]. Various gastrointestinal manifestations have been reported, including diarrhoea, melena and abdominal pain, sometimes related to mesenteric arteritis [13,14].

The clinical diagnosis is based on audiovestibular symptoms, ocular inflammation and nonreactive serologic tests for syphilis in the presence of histologically proven vasculitis [15]. Due to the variable onset of symptoms and the lack of specific laboratory tests, the diagnosis of Cogan's syndrome is a challenge and is often based upon a good response to corticosteroid treatment [16,17].

Radiographic studies, such as cranial computed tomography (CT) and magnetic resonance imaging (MRI), are often normal [18], though some authors have reported the presence of labyrinthine aspecific radiological abnormalities. MRI scans (gadolinium) show calcification or narrowing and soft tissue obliteration of the vestibular labyrinth and the cochlea [16].

Differential diagnoses to consider are Takayasu's arteritis, polyarteritis nodosa, Wegener's granulomatosis, giant cell arteritis, and rheumatic arthritis [4]. It is particularly difficult to distinguish between Takayasu's arteritis and the vasculitis of Cogan's syndrome in the sense that they both involve large vessel vasculitis. However, unlike Cogan's syndrome, Takayasu's arteritis does not routinely involve the eyes and ears [19].

Histopathological examination of corneal tissue and cochlea from patients with Cogan's disease also showed lymphocytic and plasma cell infiltration, suggesting a cell-mediated reaction [20].

2. Aetiology

The aetiology and pathogenesis of Cogan's syndrome are unknown. Initially, the disease was thought to be caused by an infection; however, Cogan's syndrome is currently believed to be an autoimmune disorder [4,5].

3. Infectious hypothesis

Chlamydia psittaci has been isolated from a patient with Cogan's syndrome [21], and serological evidence of a recent Chlamydia trachomatis infection was reported in 4 of 13 patients [5].

The genus *Chlamydia* is comprised 2 species, *Chlamydia trachomatis* and *Chlamydia psittaci*. *Chlamydia trachomatis* is responsible for a variety of ocular and genital infections in humans [22–25]. *Chlamydia psittaci*, which is generally associated with animals, may occasionally cause ocular infections in humans also [26,27]. A research group at the National Institute of Health found that patients with Cogan's syndrome had significantly higher titres of antibodies to *Chlamydia trachomatis* [5]. Ljungstrom et al. reported a patient with Cogan's syndrome who had a fourfold increase in their serum IgG antibody titre to *Chlamydia pneumoniae* [28].

Furthermore, it has been reported that *Chlamydia* infections are related to vascular injury, such as arteriosclerosis and vasculitis. A relationship between a previous *Chlamydia* infection and coronary artery disease is supported by seroepidemiological studies. It has been suggested that the bacteria adhere to endothelial cells because *Chlamydia pneumoniae* are detected in atherosclerotic plaques by both polymerase chain reaction and culture [29]. Infectious causes have also been suggested for *Borrelia* species, but not proven [15].

4. Immunologic theory

Other study results indicate an autoimmune pathogenesis for Cogan's syndrome. A decade ago, antibodies directed against a corneal antigen or constituents of the inner ear were detected by multiple groups [30–33].

Lymphocyte activation has reportedly been demonstrated when the patient's lymphocytes are exposed to corneal and inner ear antigens, suggesting the presence of cell-mediated autoimmune reactivity [34–36].

The presence of auto-antibodies against endothelial antigens found in some patients with Cogan's syndrome adds further evidence for the autoimmune nature of this disease [37].

Antibodies against a peptide antigen (Cogan peptide) have been found in sera from patients with Cogan's syndrome. This peptide antigen shares sequence homology with CD148 and connexin 26, which are expressed on endothelial cells and in the inner ear [37]. Antibodies directed against the Cogan peptide showing similarity with auto-antigens, including CD148, were identified. The same antibodies also are bound to connexin 26, which has been implicated in congenital deafness. It is noteworthy that these antibodies are able to transfer the disease to animals. After passive transfer of antibodies directed against the Cogan peptide into Balb/c mice, antibodies are localised within the cochlea of the tested animals, whereas antibodies against an irrelevant peptide did not bind to cochlear cells (Figs. 1 and 2). Also a rabbit immunised with a different peptide derived from CD 148 developed hearing loss and interstitial keratitis. The induction of clinical features of Cogan's disease in animals after either passive transfer of peptide-specific autoantibodies or active immunisation with autoantigen peptides, indicates that Cogan's syndrome is an autoimmune disease [37].

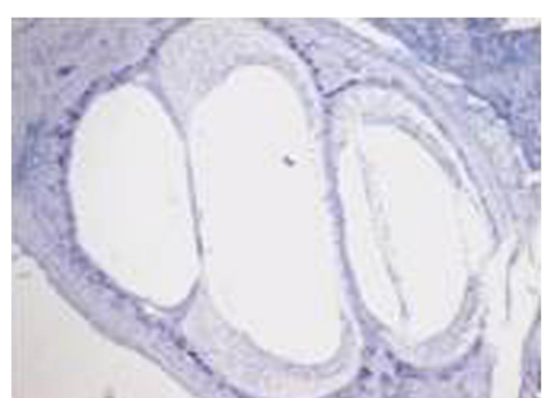

Fig. 1. Pathogenicity of antibodies against the Cogan peptide: murine cochlea of Balb/c mice exposed to antibodies directed against an irrelevant peptide (negative control). Taken from Lancet 2002; 360: 915–21.

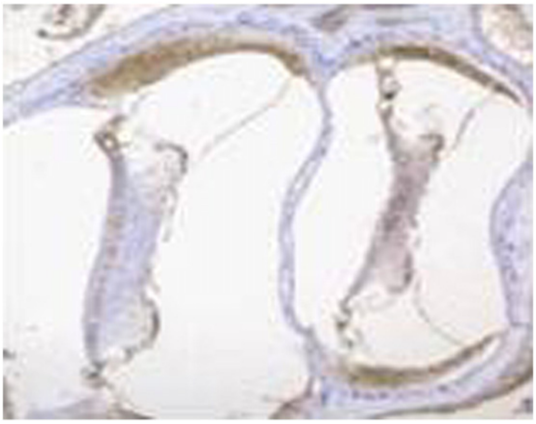

Fig. 2. Pathogenicity of antibodies against the Cogan peptide: murine cochlea of Balb/c mice exposed to antibodies directed against the Cogan peptide.
Taken from Lancet 2002; 360: 915–21.

Recent evidence strongly suggests that Cogan's syndrome is an autoimmune disease [34,38] that is mediated by a hypersensitive response to one or more infectious agents associated with vasculitis. Several authors have noted an immediately preceding upper respiratory tract infection. Thus, it is quite probable that a viral infection prompts an antibody response that develops a cross-immunity with similar proteins present in the audiovestibular system, eye, and occasionally, other organs as well [39].

The relationship between Cogan's syndrome and the manifestations of autoimmune sensorineural hearing loss described by McCabe in 1979 [40] also remain unclear. Anti-Hsp70 antibodies have been suggested as a marker of the autoimmune origin of hearing loss [41].

Anti-neutrophil cytoplasmic auto-antibodies (ANCA) have recently been identified in patients with some forms of systemic vasculitis, such as Wegener's granulomatosis, Churg–Strauss syndrome and polyarteritis nodosa [42]. After the discovery of ANCA, myeloperoxidase (MPO) and proteinase 3 (PR3) were identified as the two major antigens [43]. Normally, MPO and PR3 are localised intracellularly; however, when neutrophils are pre-activated by pro-inflammatory cytokines, these enzymes become expressed on the cell surface and are accessible to circulating ANCA. These antibodies may be involved in the immune pathogenesis of vasculitis by activation of primed neutrophils, leading to the release of lytic enzymes [44].

Tervaert et al. [45] reported one case of Cogan's syndrome that was also positive for myeloperoxidase-anti-neutrophil cytoplasmic auto-antibodies (ANCA) and anti-human leukocyte elastase-ANCA. Yamanishi et al. [46] also described a case of atypical Cogan's syndrome associated with anti-neutrophil cytoplasmic auto-antibodies (ANCA). To date, five cases of Cogan's syndrome associated with ANCA have been reported [46,47], and two of them also showed ANCA-related glomerulonephritis.

Previously, Cheson et al. reviewed 53 cases of Cogan's syndrome [6]; 10/18 vessel or muscle biopsy specimens showed inflammatory vascular changes, of which four were considered to be diagnostic of polyarteritis in large and medium sized arteries. A common pathological feature of ANCA-associated vasculitis is necrotising vasculitis of small vessels [48]; therefore, arteries of all sizes may be affected in Cogan's syndrome.

The existence of a population of deficient naive cytotoxic T cells may be implicated in a possible deficiency of the cytotoxic mechanisms necessary for the antigen response that triggers this process [49]. This finding provides additional support for a cell-mediated type IV response [50].

Rheumatoid factor, anti-nuclear antibodies and diminished complement levels have also been detected in a minority of patients with Cogan's syndrome, suggesting that immune mechanisms are involved [7].

5. Therapeutic considerations

Treatment of Cogan's syndrome is difficult, and the only information we find in the literature is based upon clinical case reports, as no organised series of treatments have been published [51].

Medical treatment of Cogan's syndrome depends on how extensive the disease is at the time of diagnosis. In cases with only mild eye involvement, the treatment of choice is the application of topical glucocorticoids. When there is evidence of an inner ear pathology, a severe infection of the eye or systemic vasculitis, immunosuppressive therapy is used.

The first choice in immunosuppressive therapy is glucocorticoids (ex. prednisolone 1 mg/kg). Hearing improves significantly after treatment with intravenous methylprednisolone [15].

When a limited vasculitis results in labyrinthine ischaemia, a beneficial response to steroid treatment can be predicted. Over the long-term, the organ of Corti can degenerate, and fibrosis and osteoneogenesis can develop within the perilymphatic space; in such cases, significant improvement should not be expected.

Systemic vasculitis complicates Cogan's syndrome and should be treated initially with prednisone and occasionally, cytotoxic agents. Aortic insufficiency can be controlled with the administration of prednisone and surgical replacement of the aortic valve [52].

Nevertheless, corticosteroids have proven to be of short-term benefit; however, they can also be associated with side effects. Some authors have noted that hearing could be stabilised with corticosteroid treatment, but total bilateral vestibuloauditory dysfunctions may occur and deafness could not be prevented [53,54]. In cases of treatment failure or corticosteroid-sparing therapy, other immunosuppressive drugs can be used, such as cyclophosphamide [55], azathioprine, methotrexate [56], cyclosporine and tumour necrosis factor-alpha blockers [57,58].

The TNF-alpha blockers are a category of immunosuppressive agents that represent a recent novel therapeutic option for Cogan's syndrome [59].

Etanercept is a synthetic protein that binds TNF-alpha and inhibits its activity. It is not effective in preserving or improving hearing loss, however, it does improve word identification and recognition [60].

Infliximab is a chimeric monoclonal antibody directed against TNF-alpha and appears to be effective in inducing and maintaining remission in patients with therapy-resistant Cogan's syndrome [59]. Infliximab may be used as an alternative therapy for Cogan's syndrome, especially in cases of corticosteroid and immunosuppressive therapy failure. However, treatment may be more effective when initiated at an early stage of the disease, primarily for inner ear disease, when the lesions are still reversible [51].

The use of Rituximab in systemic vasculitis and autoimmune diseases with an antibody-mediated aetiology has a strong rationale and is increasingly reported in the literature [61,62]. Rituximab is a chimeric human–mouse monoclonal antibody against the lymphocyte CD20 surface antigen, and treatment induces depletion of B lymphocytes by various mechanisms. These antibodies are thought to act in vivo primarily through the activation of antibody-dependent cell-mediated cytotoxicity, in addition to complement-dependent cytotoxicity; although direct growth inhibition and/or induction of apoptosis may also play a role [63].

Therefore, the effect of Rituximab on B cells may help to avoid deafness and the need for cochlear implants in severe cases. It may also significantly reduce the number of medications necessary to control the multiple manifestations of this syndrome. We recommend a four week division of the overall drug dosing cycle, as it appears to be particularly safe, even though we do not recommend the use of this drug as a first line therapy [64].

There are also concerns that the therapeutic use of anti-TNF alpha agents may be associated with the development of cancer and lymphomas [65]. In recent years, a rapid growing interest in a possible stem cell-based cellular therapy for autoimmune diseases has emerged. Further studies are required to elucidate the efficacy and long-term safety prior to translation of this approach from in vitro experiments into clinical usage [66].

6. Conclusions

Cogan's syndrome is a rare autoimmune vasculitis. Although it is the prototype immune-mediated inner ear disease, the variability of ocular and audiovestibular clinical manifestations complicates its diagnosis, which should be suspected whenever there is a close temporal association between ocular abnormalities and cochleovestibular symptoms.

However, the application of a study protocol including MRI and a series of immunological tests may facilitate the prognosis of the auditory injury; thereby, opening new lines of research focusing on the patho-physiological mechanisms of the disease.

Corticosteroids are the first line of treatment, and it is argued that they can aid in the recovery of hearing if given early in the disease course. Immunosupressive drugs, such as methotrexate, azathioprine, cyclosporine and cyclophosphamide, have all been used with varying degrees of success. However, in the absence of controlled trials, there are no definitive therapeutic recommendations.

Patients without systemic disease generally have a good prognosis and an average life expectancy. Patients who develop serious vasculitis, such as aortitis, have an increased risk of death due to complications. Therefore, early assessment and treatment for systemic inflammation are needed to prevent life threatening complications.

Take-home messages

- Cogan's syndrome is a rare autoimmune vasculitis characterised by ocular and vestibuloauditory dysfunctions, and often by systemic disease as well. Its aetiology includes infection and autoimmunity. Vasculitis is considered the pathological mechanism. Histopathological examination of corneal tissue and cochlea shows lymphocytic and plasma cell infiltration, suggesting a cell-mediated reaction.
- Due to the possible autoimmune pathogenesis of this disease, the first choice in immunosuppressive therapy is glucocorticoids. In case of corticosteroid treatment failure, other immunosuppressive drugs can be used as cyclophosphamide, azathioprine, methotrexate and cyclosporine.
- Tumour necrosis factor (TNF)-alpha blockers like etanercept, infliximab and rituximab are a category of immunosuppressive agents representing a novel therapeutic option in Cogan's syndrome. In recent years, a rapid growing interest in a possible stem cell-based cellular therapy for autoimmune diseases has emerged. Further studies are required to elucidate the efficacy and long-term safety prior to translation of this approach from in vitro experiments into clinical usage.

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Switching multiple sclerosis patients with breakthrough disease to second-line therapy.

Multiple sclerosis (MS) patients with breakthrough disease on immunomodulatory drugs are frequently offered to switch to natalizumab or immunosuppressants. The effect of natalizumab monotherapy in patients with breakthrough disease is unknown. **Castillo-Trivino T, et al. (PLoS One 2011;6:16664)** performed an open-label retrospective cohort study of 993 patients seen at least four times at the University of California San Francisco MS Center, 95 had breakthrough disease on first-line therapy (60 patients switched to natalizumab, 22 to immunosuppressants and 13 declined the switch [non-switchers]). Poisson regression was used to adjust for potential confounders and to compare the relapse rate within and across groups before and after the switch. In the within-group analyses, the relapse rate decreased by 70% (95% CI 50,82%; $p<0.001$) in switchers to natalizumab and by 77% (95% CI 59,87%; $p<0.001$) in switchers to immunosuppressants; relapse rate in non-switchers did not decrease (6%, $p=0.87$). Relative to the reduction among non-switchers, the relapse rate was reduced by 68% among natalizumab switchers (95% CI 19,87%; $p=0.017$) and by 76% among the immunosuppressant switchers (95% CI 36,91%; $p=0.004$). Switching to natalizumab or immunosuppressants in patients with breakthrough disease was effective in reducing clinical activity of relapsing MS. However, authors suggest that the magnitude of the effect and the risk-benefit ratio should be evaluated in randomized clinical trials and prospective cohort studies.