Eponyms in medicine revisited

Cogan's syndrome: an oculo-audiovestibular disease

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Summary

Typical Cogan's syndrome is a rare disease of young adults consisting of flares of interstitial keratitis and sudden onset of Ménière-like attacks (nausea, vomiting, tinnitus, vertigo and hearing loss). Life-threatening aortic insufficiency develops in 10% of reported cases. Atypical Cogan's syndrome (audiovestibular dysfunction with other types of inflammatory eye disease) is associated with vasculitis in 20% of cases and has a less favourable prognosis than typical Cogan's syndrome.

Keywords: Cogan's syndrome; hearing loss; autoimmune disease

Accumulating evidence strongly suggests that Cogan's syndrome is an autoimmune disorder. Topical ocular corticosteroids usually control interstitial keratitis and systemic corticosteroids must be administered as early as possible to render the hearing loss reversible. Immunological tests can help to establish the diagnosis and the prognosis for the recovery of hearing. Audiovestibular dysfunction in association with nonsyphilitic interstitial keratitis (IK) was classified as a clinical entity by Cogan in 1945.¹ Sudden onset IK is accompanied by photophobia, lacrimation and eye pain, and usually responds to local atropine and corticosteroid therapy. The audiovestibular symptoms, tinnitus, sensorineural hearing loss and acute episodes of vertigo, are usually bilateral. Cogan's syndrome is a disorder of young adults, the average age of onset being 25 years. Hearing loss progresses for 1 to 3 months and deafness occurs in about 60% of patients.² Auditory symptoms can precede or follow eye disease, usually within a short period of time. Cogan's syndrome is uncommon and, thus, most reports deal with individual cases.

Clinical symptoms and signs

Cogan's syndrome is a disease of young adults characterised by acute IK with audiovestibular dysfunction, associated in close temporal proximity to flares of IK, clinically indistinguishable from episodes of Ménière's disease (acute onset of nausea, vomiting, tinnitus and vertigo, rapidly followed by bilateral loss of hearing). Atypical disease presents with a significant inflammatory eye lesion in addition to or instead of IK. Thus, patients who developed scleritis, episcleritis, retinal artery occlusion, choroiditis, retinal haemorrhages, papilloedema, exophthalmos or tenonitis with or without IK were classified as having atypical Cogan's syndrome by Haines *et al.*² Cases in which conjunctivitis, iritis or subconjunctival haemorrhage was present in the absence of IK were also classified as atypical disease.² If the audiovestibular symptoms were not similar to those of Ménière's disease, or occurred more than 2 years before or after the onset of eye symptoms, the patient was again considered to have atypical Cogan's syndrome.²

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Clinical manifestations of Cogan's syndrome

Eye

- interstitial keratitis (T)
- scleritis, episcleritis, retinal vascular disease, uveitis, iritis, conjunctivitis, papilloedema, exophthalmos, tenonitis (A)

Ear

- recurrent Ménière-like attacks (T)
- sudden hearing loss (A)

Systemic features (more frequent in A, except for aortic insufficiency)

- fever, headache, malaise, myalgias
- gastrointestinal signs and symptoms (abdominal discomfort, peptic and colonic ulceration with bleeding)
- musculoskeletal involvement (myalgias, arthritis or arthralgias)
- cutaneous lesions (skin rash, nodules)
- cardiac findings (aortic insufficiency, cardiomegaly, congestive heart failure)
- genitourinary involvement (mild abnormalities on urinalysis)
- splenomegaly, lymphadenopathy
- hypertension
- eosinophilia

T: typical disease; A: atypical disease

Differential diagnosis in Cogan's syndrome (modified from²)

Infections

- congenital and acquired syphilis
- Chlamydial infections
- viral infections
- tuberculosis with streptomycin therapy

Connective tissue diseases

- systemic necrotizing vasculitis, including polyarteritis nodosa
- rheumatoid arthritis
- relapsing polychondritis
- aortitis syndrome (Takayasu's disease)

Other diseases

- Wegener's granulomatosis
- sarcoidosis
- Vogt-Koyanagi-Harada disease
- Ménière's disease with eye symptoms

Box 2

Diagnosis of Cogan's syndrome

Clinical picture

- immunological work-up
- erythrocyte sedimentation rate
- serum IgG, IgA, IgM
- complement system (C₃, C₄)
- autoantibodies: antinuclear antibodies, extractable nuclear antigen
- rheumatoid factor
- immunophenotype analysis of peripheral blood lymphocytes

Microbiology

- syphilis: VDRL, fluorescent treponemal antibody absorption
- Mycoplasma pneumoniae
- Epstein-Barr virus
- Herpes simplex virus
- Varicella-zoster virus
- cytomegalovirus
- respiratory syncytial virus
- influenza A, B, and parainfluenza 1, 2, 3
- adenovirus group
- mumps

MRI study

Box 3

Treatment of Cogan's syndrome

- eye inflammation: topical atropine and ocular corticosteroids
- audiovestibular dysfunction: systemic corticosteroids
- systemic vasculitis: prednisone with or without cytotoxic drugs
- aortic insufficiency: prednisone and surgical replacement of the aortic valve

Box 4

Certain entities may mimic the clinical picture of Cogan's syndrome. There is a clear association between upper respiratory tract infection and the onset of both typical and atypical Cogan's syndrome, and a number of viral infections have been associated with IK and deafness (mumps, herpes zoster, and rubella).

In atypical forms of the disease, inflammation can spread to other parts of the eye (scleritis, uveitis or conjunctivitis) and association with systemic vasculitis and related disorders occurs in 20% of cases.²⁻³

Diagnosis

The clinical diagnosis is based on the audiovestibular symptoms, the ocular inflammation and nonreactive serologic tests for syphilis. The diagnostic suspicion based on the clinical course must be completed with an immunological work-up. The existence of a population of deficient naive cytotoxic T cells could suggest *a priori* a poor response to steroid therapy. The decrease in this cell population might be implicated in a possible deficiency of the cytotoxic mechanisms in response to the antigen that triggers the process.⁴ This finding provides additional support for a cell-mediated type IV response.⁵

The observation of hyperintensity within the membranous labyrinth on precontrast T1-weighted magnetic resonance imaging (MRI) has been reported in a patient with Cogan's syndrome⁶ and probably represents haemorrhage and leakage through the abnormal labyrinthine membrane due to active disease (inflammation of the blood vessels of the stria vascularis).

Pathogenesis

Recent experiences strongly suggest that Cogan's syndrome is an autoimmune disease,⁷⁻¹⁰ mediated by means of a hypersensitivity 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 virus infection prompts an antibody response that develops a cross-immunity with similar proteins in the tissues of the audiovestibular system, eye, and occasionally other organs as well.²⁻¹¹ Temporal bone pathology includes endolymphatic hydrops, atrophy of the organ of Corti, plasma cell and lymphocytic infiltration of the spiral ligament, osteoneogenesis of the round window, spiral ganglion cell degeneration, cystic degeneration of the stria vascularis, middle ear effusion, demyelination of the eighth cranial nerve and vasculitis of the internal auditory artery.¹¹⁻¹³

Lymphocyte transformation has reportedly been detected when the patient's lymphocytes are exposed to corneal antigen, scleroprotein, and inner ear antigen, suggesting the presence of cell-mediated autoimmune reactivity.^{7-9,14}

Treatment

Therapy consists of high-dosage corticosteroids; the outcome varies from complete recovery of the hearing level, if treatment is given early during the course of illness, to no improvement whatsoever.¹⁵ When a limited vasculitis results in labyrinthine ischaemia, a beneficial response to treatment can be predicted. Over the long term, the organ of Corti can degenerate and fibrosis and osteoneogenesis can develop within the perilymphatic space; thus, significant improvement should not be expected with steroid treatment. Subepithelial keratitis usually responds to local atropine and corticosteroid therapy. 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.

Our patient's hearing did not improve. This lack of response may be directly related to the intensity of the hearing loss, similar to cases of idiopathic sudden deafness,¹⁶ and correlates with the MRI findings; a good correlation between labyrinthine enhancement and loss of cochlear and/or vestibular function will only be seen in patients with severe loss of function.¹⁶⁻¹⁸ Moreover, the decrease in naive cytotoxic T cells has been related to a worse prognosis for the recovery of the hearing loss.⁴

Although Cogan's syndrome is the prototype of 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. On the other hand, the application of a study protocol including MRI and a series of immunological tests might facilitate the establishment of the prognosis for the auditory injury, opening new lines of research focusing on the pathophysiological mechanisms of the disease.

Prognostic factors for permanent hearing loss

- profound bilateral sensorineural hearing loss
- hyperintensity within the membranous labyrinth on precontrast T1-weighted MRI
- deficiency of CD8+CD45RA cells (naïve T cytotoxic cells)

Box 5

Case report

A 20-year-old man presented burning sensation in his eyes, photophobia, blepharospasm and bilateral lacrimation. He had presented with an upper respiratory tract infection and was diagnosed as having adenovirus-induced subepithelial keratitis.

Ophthalmologic examination revealed whitish, bilateral, peripheral, round subepithelial infiltrates, one of which presented a mild epithelial defect that stained with fluorescein. Three weeks later, he complained of an acute episode of vertigo, nausea and vomiting, tinnitus and bilateral hearing loss. Otologic examination showed a bilateral profound sensorineural hearing loss. Pure tone audiogram demonstrated no sound perception bilaterally. Stapedial reflex was absent. Brainstem auditory evoked potentials detected no waves. Caloric testing elicited no nystagmus in left ear and a reduced response on the right side. Immunologic work-up disclosed normal erythrocyte sedimentation rate, serum immunoglobulins and complement factors C3-C4. Antinuclear antibodies, rheumatoid factors, cryoglobulins and antineutrophil cytoplasmic antibodies were negative.

Microbiological studies and tuberculin skin test were negative. Immunophenotype study of peripheral blood T lymphocytes showed a normal population of CD4+ cells (helper T lymphocytes, 43.9%), decreased CD8+ cells (cytotoxic T lymphocytes, 13.6%), high CD4/CD8 ratio (3.22) and decreased naïve T cells (CD8 CD45RA+ cells, 17.6%), compared with control subjects.⁴ Immunohistochemical study revealed the presence of T-lymphocyte markers (CD3) and occasional B lymphocytes (CD20).

Chest X-ray was normal. An enhanced MRI revealed such a marked hyperintensity within the membranous labyrinth in precontrast T1-weighted images that it was difficult to assess the enhancement in contrast-enhanced T1 images (figure 1). A biopsy of conjunctiva demonstrated mild lymphocytic infiltration of the chorion. Lymphocytes accumulated in the perivascular space (figure 2).

A diagnosis of an immune-mediated disorder, atypical Cogan's syndrome was established and the patient was admitted to the hospital and placed on bed rest. Low molecular heparin (7500 units) was administered subcutaneously every 24 h. 100% Oxygen was inhaled continuously (3 l/min). Nimodipine (30 ml/8 h iv) and 6-methylprednisolone (80 mg daily iv) were administered for 10 days. Given a lack of response, three pulses of methylprednisolone (0.5 g/24 h) were administered. Hearing loss remained unchanged. Oral prednisone was started at 60 mg daily and subsequently tapered.

Figure 1 Axial MRI of the inner ear showing hyperintensity within the membranous labyrinth on precontrast T1-weighted images when compared to the eighth cranial nerves

Figure 2 Photomicrography of the conjunctiva section showing mild lymphocytic infiltration of the chorion

Box 6

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