

## COGAN'S SYNDROME

By  
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### CLINICAL CASE

Patient: A 28 year old man, Caucasian.

Chief complain 3/2000:

Redness and light sensitivity in both eyes.

Past ocular history:

Two year history of bilateral keratitis treated with topical steroids with initial improvement and subsequently become unresponsive.

Past medical history:

Idiopathic hearing loss since 1996, unresponsive to systemic cyclophosphamide and high doses of prednisone.

Review of systems:

- Headache: constant and in the frontal region, poorly responsive to conventional pain medications.
- Back pain and arthralgia.
- Subcutaneous nodules, rash on the volar part of the left arm.



Figure 1: skin nodules and rash

Previous work-up:

- Chest X-ray: possible left hilar adenopathy.
- Chest CT scan: normal.
- FTA-Abs, Lyme test, ACE, ESR: all normals.

Examination:

Visual acuity: OD=20/30 PH OS=20/20 PH

Slit-lamp: corneal neovascularization and abundant lipid deposition in the stroma in the superior half of both corneas.

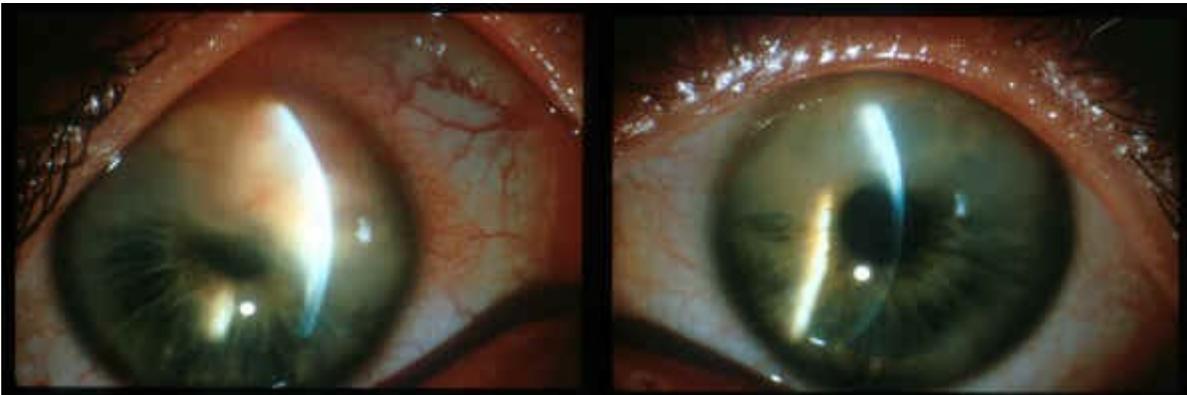


Figure 2: corneal neovascularization in OD(left) and in OS(right)

Corneal sensation: normal.

IOP: normal.

Ophthalmoscopy: unremarkable.

Assessment:

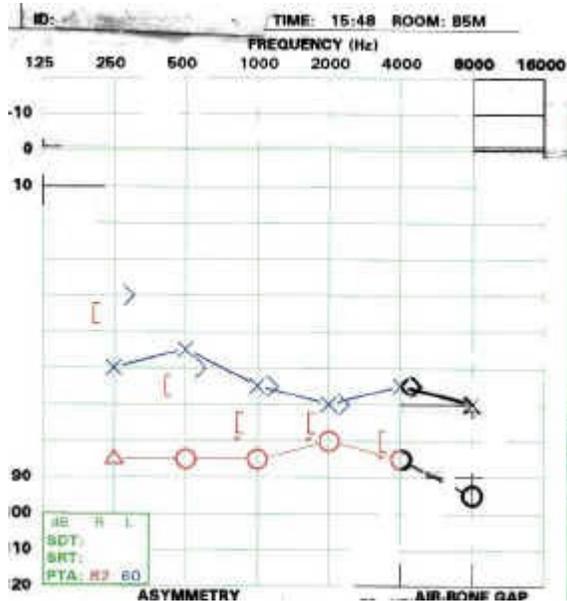
- Bilateral sectoral keratitis.
- Bilateral hearing loss.
- Systemic associated symptomatology.

Plan:

- Otolaryngologist consult because of the association of ear and ocular manifestations.
- Additional serology to exclude any type of vasculitis (mainly PAN and Wegener's) because of the peripheral location of the keratitis (PUK like) and also to assess the systemic involvement through markers of immune system activity and systemic inflammation.
- Neurologic consult because of the persistent headache in order to exclude possibility of CNS involvement.

Results of investigations:

- Audiogram: sensorineural deafness, cochlear pathology pattern.



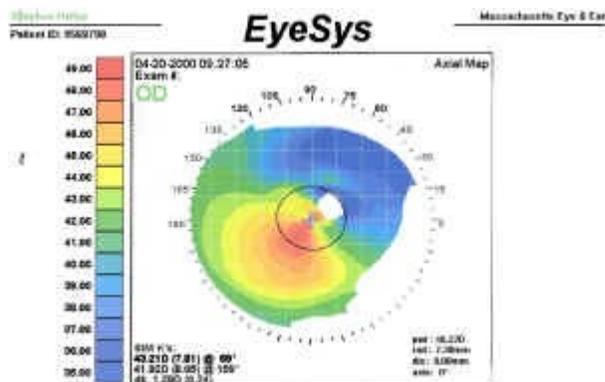
- Antibodies against inner ear (HSP 70) detected with Western blot.
- Elevated serological parameters: ESR, CRP, alpha-1 acid glycoprotein, eosinophil count.
- MRI of the brain: normal.

Diagnosis:

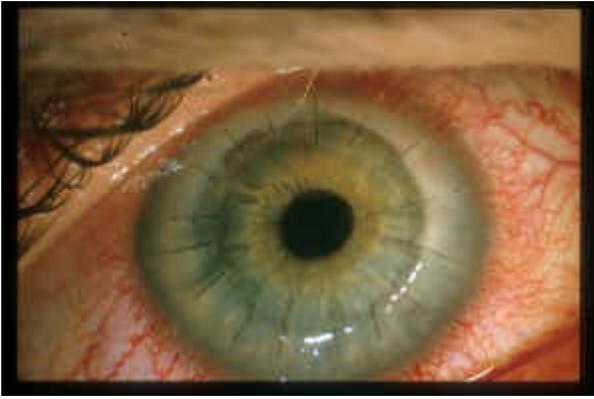
Definite diagnosis of Cogan's syndrome was made.

Follow up 4/2000:

- Decreased vision and increased astigmatism in OD: VA OD=20/400



- Penetrating keratoplasty performed on 6/2000.



- Visual acuity at one month follow-up: VA OD=20/40
- Audiogram stable with daily dose of 40 mg prednisone.

Teaching points of the case:

- Atypical case of Cogan's syndrome because of the extreme delay (3 years) between ear and ocular manifestations and the lack of interstitial keratitis at the time of ear involvement.
- Unusual corneal neovascularization in both eyes resulting in visual impairment and requiring penetrating keratoplasty.
- Presence of serological markers indicative of systemic involvement: patient need to be carefully monitored for presence of complications secondary to systemic vasculitis.

#### COGAN'S SYNDROME

David Cogan first described in 1945 a syndrome characterized by non syphilitic interstitial keratitis associated with vertigo, tinnitus and profound deafness.

Since then, approximately 150 cases with ocular inflammation and vestibuloauditory symptoms have been described in the literature.

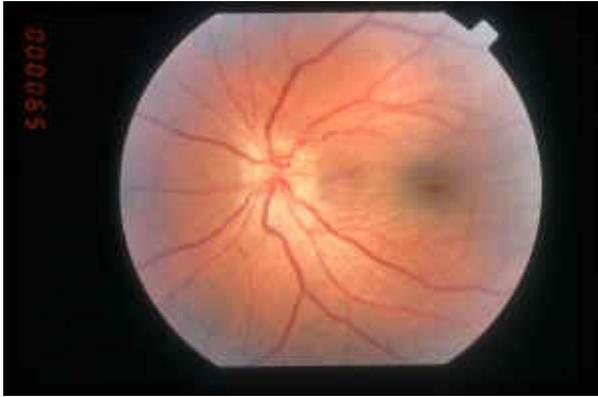
#### Epidemiology

Cogan's syndrome is a rare disease, and affects predominantly young adults. The average age of disease onset is 29 years (range 3 to 50 years). In most of the literature series there seems to be no sexual predilection. In 25% of patients the eye and the ear can be affected simultaneously and in another 10% of the cases systemic vasculitis can complicate the course of the disease. The clinical spectrum of patients with Cogan's syndrome includes ocular manifestations, vestibuloauditory symptoms and systemic features.

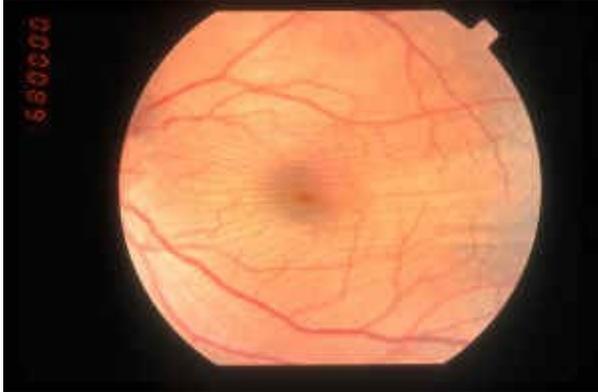
#### Ocular features

Patients with typical Cogan's syndrome present with interstitial keratitis (72%) and Ménière's-like audiovestibulatory dysfunction with acute onset of nausea, vomiting, tinnitus and vertigo, rapidly followed by bilateral hearing loss. Conversely, atypical manifestations of Cogan's syndrome include scleritis (anterior and posterior), episcleritis (20%), iritis (32%), conjunctivitis, vitritis, pars planitis, retinal vasculitis, retinal hemorrhages, choroiditis, papillitis, orbital pseudotumor, and tenonitis. The audiovestibulatory symptoms can precede or follow the ocular manifestations, but usually the length of time between the ear and ocular involvement ranges from 2 to 52 weeks; when the audiovestibulatory dysfunction is different from the Ménière's disease or occurs more than two years after ocular abnormalities, the patient is considered to have atypical Cogan's disease.

The interstitial keratitis was originally described by Cogan's as a granular type of corneal infiltrate, with patchy distribution, situated predominantly in the posterior half of the cornea. The most common early corneal findings are faint peripheral, anterior stromal subepithelial infiltrates measuring approximately 0.5 to 1 mm in diameter, mimicking adenovirus and chlamydial keratitis and disappearing promptly with institution of topical corticosteroids. Faint subepithelial scars or epithelial erosions may overlie the stromal infiltrates after resolution of the corneal inflammation. Since the disease can have a capricious course characterized by intermittent episodes of ocular inflammation alternated by periods of quiescence, and the ocular findings can be evanescent, repetitive examinations may be necessary to demonstrate evidence of ocular inflammation, particularly interstitial keratitis.



Papillitis in a case of atypical Cogan's



Chorioretinal folds in atypical Cogan's

Progression to late corneal neovascularization causing visual impairment and requiring penetrating keratoplasty is rare and occurs in less than 5% of patients.

|  |
|--|
| TYPICAL COGAN'S DISEASE                |
| Interstitial keratitis                 |
| Meniere's symptoms                     |
| Interval between eye and ear < 2 years |

|   |
|---|
| ATYPICAL COGAN'S DISEASE  |
| Scleritis, episcleritis, conjunctivitis                         |
| Iridocyclitis   |
| Vitritis  |
| Retinal vasculitis, hemorrhages, cotton-wool spots, choroiditis |
| Orbital pseudotumor, exophthalmos, tenonitis                    |

**Ear findings**

Patients frequently present with sudden onset of Meniere's like symptoms such as nausea, vomiting, tinnitus, fluctuations of hearing and severe vertigo.

The auditory involvement may be unilateral initially, but bilateral hearing loss usually follows. Vestibular system dysfunction can also produce severe nystagmus, oscilloscopia and ataxia. In the majority of patients (92%) Meniere's symptoms are associated with hearing loss. Untreated, deafness become complete in weeks to months, while vestibular symptoms usually improve and disappear after a few years from disease onset.

The audiogram test is abnormal in 95% of patients with Cogan's syndrome; the hearing loss is more pronounced at the extreme frequencies, with relatively sparing of the mid range, with a pattern usually seen in patients with Meniere's syndrome indicating cochlear pathology.

Auditory evoked potentials are also reduced or absent and suggestive of sensorineural deafness and the caloric test is also absent in 70% of patients.

**Systemic features**

In association with the eye and the ear involvement non specific systemic symptoms can occur such as fever, fatigue, headache, arthralgia, myalgia and weight of loss.

Some of the systemic symptoms may be secondary to systemic necrotizing vasculitis, which is present in 10 to 50% of patients with Cogan's syndrome.

The vasculitis affects large- vessels (Takayasu-like) and medium-vessels (polyarteritis nodosa-like). Systemic necrotizing vasculitis has been in described in different vessels such as coronary, gastrointestinal tract, subclavian, femoral, renal, skin, testicle and muscle.

The most serious manifestation of the vasculitis is cardiovascular involvement and patients often have silent coronary artery disease. Inflammatory aortitis leading to aortic insufficiency is one of the most frequent problems, affecting about 10 % of cases. Patients can be asymptomatic or have associated cardiac abnormalities ranging from valvular defects, coronary disease, aneurysm, myocardial infarction, coronary arteritis, pericarditis, and arrhythmias.

The aortitis may develop within weeks to years after the onset of Cogan's syndrome.

Other symptoms indicative of systemic vasculitis include abdominal pain, lower extremity claudication, symptoms of mesenteric insufficiency, proteinuria or microscopic hematuria due to renal involvement. The diagnosis of systemic necrotizing vasculitis is made with angiography or biopsy.

Ten percent of patients have fatal or nearly fatal complications secondary to systemic vasculitis, especially patients who are asymptomatic. Echocardiographic and doppler abnormalities have been described in patients with asymptomatic aortic insufficiency.

The possibility of systemic vasculitis with prompt recognition of signs and symptoms of organ involvement and further appropriate investigations must be considered at any stage of Cogan's disease, and institution of systemic immunosuppression is mandatory in such cases.

Similarities with polyarteritis nodosa have been noted in the histopathologic features of the affected vessels consisting of prominent infiltration of large veins and muscular artery walls with lymphocytes and neutrophils; focal degeneration and varying degrees of fibrosis in the vessel walls have also been described.

**Systemic symptoms in Cogan's syndrome**

|                   |  |
|-------------------|--|
| Organ involvement | Symptoms and signs   |
| Nervous system    | Headache, meningismus, encephalitis, psychosis, cerebral infarction, cavernous sinus thrombosis, psychosis, peripheral nerve involvement |
| Musculoskeletal   | Arthralgia, arthritis, myalgia   |
| Gastrointestinal  | Abdominal pain, gastric hemorrhage   |
| Cardiac           | Aortic insufficiency, arrhythmias, ventricular hypertrophy, valvular defects   |
| Skin              | Nodules, non-specific rash, palpable purpura,  |
| Genitourinary     | Abnormal urinalysis, hematuria, proteinuria, testicular pain   |
| Pulmonary         | Pleuritis, pulmonary nodules,  |

|                 |   |
|-----------------|---|
|                 |   |
| Lymphoreticular | Lymphadenopathy, splenomegaly, hepatomegaly |

#### Diagnosis

The diagnosis of Cogan's syndrome is established by the clinical observation of ocular and audiovestibular abnormalities. When the symptoms are not present concomitantly or when the patient presents with atypical ocular findings, the diagnosis as well as prompt institution of corticosteroid treatment may be delayed, causing severe and irreversible hearing loss.

Antibodies against the inner ear and cornea may support the clinical suspicion, but they are not specific for Cogan's syndrome because they present also in other idiopathic bilateral vestibulopathies.

Laboratory abnormalities usually associated with the syndrome are eosinophilia, anemia, thrombocytosis, elevated erythrocyte sedimentation rate. Low titers of rheumatoid factor, antinuclear antibodies and cryoglobulins are observed in 15% of patients.

An increased frequency of HLA-B17 and HLA-A9 has been reported, but the significance of these studies is not clear.

Cerebrospinal fluid abnormalities including leukocytosis, elevated protein and increased gamma globulin fraction are seen in 25% of patients.

The clinical diagnostic tests in patients with Cogan's syndrome should include: audiogram, caloric test, echocardiography, doppler test, and angiography when systemic vasculitis is suspected. The multisystemic aspect of the syndrome emphasize for the need for coordination between ophthalmologist, otolaryngologist and internist.

#### Differential

#### Diagnosis

When interstitial keratitis is present other causes for corneal inflammation such syphilis, sarcoidosis, tuberculosis, viral conditions (HSV, VZV), Lyme disease and leprosy must be excluded.

A wide spectrum of infectious and rheumatologic conditions which cause ocular inflammation associated with audiovestibulatory symptoms and hearing loss may also be considered in the differential diagnosis.

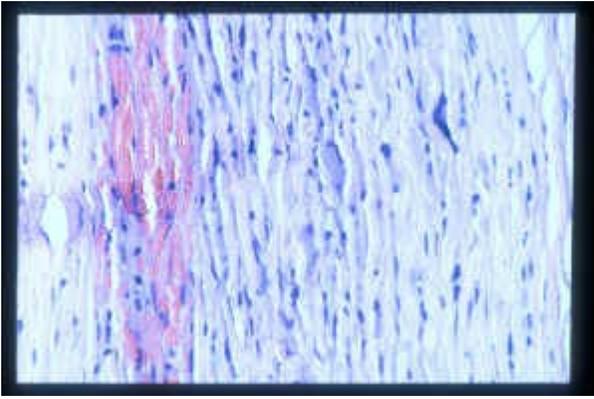
Causes of eye and ear involvement.

|                   |   |
|-------------------|---|
| <b>Infectious</b> | Syphilis (congenital > acquired), Lyme, Viral, Chlamydia, Tuberculosis with streptomycin  |
| Autoimmune        | Polyarteritis nodosa, Wegener's granulomatosis, giant cell arteritis, Takayasu arteritis, relapsing polychondritis, rheumatoid arthritis, Behçet's, Vogt-Koyanagy-Harada, sarcoidosis, Meniere with ocular inflammation |
| Others            | Cobalt, desferioxamine  |

#### Pathogenesis

The pathogenesis of Cogan's syndrome is unknown; an autoimmune mechanism has long been postulated but it has remained unclear whether this process is mediated by cellular or humoral immunity.

Some pathological and immunological findings such as lymphocytes, and plasma cell infiltration in the cochlea and in the cornea, presence of antibodies (IgG) against inner ear and cornea, as well as the beneficial effect of corticosteroids and immunosuppressants all support an autoimmune pathogenesis. Moreover, most of the patients exhibit variable, multiple organ involvement reminiscent of polyarteritis nodosa and other collagen diseases with presumed autoimmune etiology.



Histopathologic section of the cornea

The evidence of immediately preceding upper respiratory tract infection in 40% of patients and elevated antibody titers against chlamydia has led some authors to hypothesize that Cogan's syndrome is an autoimmune disease mediated by hypersensitivity response to one or more infectious agents.

#### Pathogenesis of deafness

Temporal bone pathology has shown different findings responsible for deafness including endolymphatic hydrops, atrophy of the organ of Corti, plasma cell and lymphocytic infiltration of the spiral ligament, osteogenesis of the round window, spiral ganglion cell degeneration, degeneration of the stria vascularis, demyelination of the eighth cranial nerve and vasculitis of the internal auditory artery.

#### Treatment

Therapy of Cogan's syndrome, when ear involvement is detected, consists of high doses systemic corticosteroids (1-2 mg/ Kg/day) which are subsequently slowly tapered based upon the responses on the audiogram test. When systemic corticosteroids are given early during the course of the disease, the outcome varies from partial recovery of the hearing loss to absence of response and profound deafness.

Some reports indicate that the hearing loss may be reversible if the diagnosis is made within the first two weeks and high doses of corticosteroids therapy is initiated promptly.

Systemic immunosuppression is mandatory in patients with necrotizing vasculitis; cyclophosphamide is the drug of choice, but azathioprine, methotrexate and cyclosporin have also been reported to be effective.

In cases of hearing loss unresponsive to corticosteroid treatment, immunosuppressant agents may be used and better responses are usually obtained when a chronic low dose of steroid is maintained.

The ocular manifestations typically respond to topical steroids and systemic treatment is reserved to patients with posterior involvement (retinal vasculitis, posterior uveitis).

#### Prognosis

The ocular prognosis in patients with interstitial keratitis is usually very good and only rare cases have visual acuity impairment secondary to corneal opacity. More severe complications can occur in patients with atypical disease and chronic inflammation of the posterior pole.

Differently from the eye involvement, the ear prognosis is poor. Total and bilateral deafness is the predominant outcome in Cogan's syndrome, occurring in 25 to 50% of patients, even when corticosteroids are promptly administered; 95% of patients have moderate to profound hearing loss at five-years follow up. Vestibular symptoms and signs improve with time, but persistent ataxia and oscilloscopia have been reported in 15% of cases.

Systemic involvement is associated with 10% of fatal complications secondary mainly to aortic, coronary, mesenteric and renal vasculitis.

#### Conclusions

Cogan's syndrome is a systemic disease that typically presents with interstitial keratitis and audiovestibulatory symptoms. The presence of systemic vasculitis and potential fatal complications give reason for considering this disorder not only an "eye and ear problem". In some cases the atypical ocular manifestation and the lack of associated ear findings make the diagnosis more difficult and cause delay in institution of adequate treatment resulting in profound bilateral deafness.

#### References

1. Cogan DG. Syndrome of non syphilitic interstitial keratitis and vestibuloauditory symptoms. Arch Ophthalmol 1945; 33: 144-49.
2. Vollertsen RS et al. Cogan's syndrome: 18 cases and a review of the literature. Mayo Clin Proc 1986; 61: 344-61.

3. Morgan GJ et al. Cogan's syndrome: acute vestibular and auditory dysfunction with interstitial keratitis. *Am J Otolaryngol* 1984; 5: 258-61.
4. Garcia Berrocal JR et al. Cogan's syndrome: an oculo-audiovestibular disease. *Postgrad Med* 1999; 75: 262-64.
5. Vollertsen RS et al. Cogan's syndrome: audiovestibular involvement and prognosis in 18 patients. *Laryngoscope* 1985; 95: 650-54.
6. Schuknecht HF et al. Temporal bone pathology in a case of Cogan's syndrome. *Laryngoscope* 1994; 104: 1135-42.
7. Allen NB et al. Use of immunosuppressive agents in the treatment of severe ocular and vascular manifestations of Cogan's syndrome. *Am J Med* 1990; 88: 296-301.
8. Ho AC et al. Cogan's syndrome with refractory abdominal aortitis and mesenteric vasculitis. *J Rheumatol* 1999; 26: 1404-07.
9. Helmchen C et al. Cogan's syndrome: clinical significance of antibodies against the inner ear and cornea. *Acta Otolaryngol* 1999; 119: 528-36.
10. Heinemann MH et al. Cogan's syndrome. *Ann Ophthalmol* 1980; june: 667-74.
11. Cogan DG et al. Late corneal opacities in the syndrome of interstitial keratitis and vestibulo-auditory symptoms. *Acta Ophthalmol* 1989; 67: 182-87.
12. Cheson BD et al. Cogan's syndrome: a systemic vasculitis. *Am J Med* 1976; 60: 549-55.
13. Majoor MHJM et al. Corneal autoimmunity in Cogan's syndrome? Report of two cases. *Ann Otol Laryngol* 1992; 101: 679-84.
14. Del Carpio J et al. Cogan's syndrome and HLA-BW17. Letter to the editor. *N Engl J Med* 1976; 25: 1262-63.
15. Hughes GB et al. Autoimmune reactivity in Cogan's syndrome: a preliminary report. *Otol Head and Neck Surg* 1983; 91: 24-32.
16. Eisenstein B et al. Non syphilitic interstitial keratitis and bilateral deafness (Cogan's syndrome) associated with cardiovascular disease. *N Engl J Med* 1958; 258 (22): 1074-79.
17. Cogan DG et al. Nonsyphilitic interstitial keratitis with vestibuloauditory symptoms: a case with fatal aortitis. *Arch Ophthalmol* 1964; 71: 172-75.
18. Cobo LM et al. Early corneal findings in Cogan's syndrome. *Ophthalmology* 1984; 91: 903-07.
19. Gilbert WS et al. Cogan's syndrome: signs of periarteritis nodosa and cerebral venous sinus thrombosis. *Arch Ophthalmol* 1969; 82: 633-36.