



Chlamydia pneumoniae infection as a trigger for a Cogan's syndrome

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Summary Cogan's syndrome is often preceded by upper respiratory tract symptoms. The only reported specific agent possibly involved in pathogenesis of the Cogan's syndrome was *Chlamydia pneumoniae*. Positive IgA, IgM and IgG antibodies against *C. pneumoniae* in our patient suggest possibility of *Chlamydia's* role as a trigger for the vasculitis.

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Introduction

Cogan's syndrome is a rare autoimmune multi-system disease, characterized by the presence of autoantibodies able to induce tissue damage by binding on cell surface molecules present on the inner ear sensory epithelia and endothelial cells.¹ The main clinical features of typical Cogan's syndrome are vestibuloauditory dysfunction and interstitial keratitis that cause eye pain, photophobia and blurred vision.¹ Audiovestibular dysfunction and other types of inflammatory eye disease characterize atypical Cogan's syndrome.

Cogan's syndrome is often (up to 50%) preceded by upper respiratory tract symptoms.² This observation suggests respiratory infections as a possible

trigger for the vasculitis. The only reported specific agents possibly involved in pathogenesis of the Cogan's syndrome were *Chlamydias*.^{1,3,4} However, a direct link between *Chlamydia* species and Cogan's syndrome has not been proven.⁵

Case report

A 43-year-old male was admitted to the otolaryngology ward of another hospital in February 2003 because of sudden hearing loss, vertigo, nausea, vomiting, tinnitus, nystagmus and conjunctivitis with decreased visual accuracy. His auricles were erythematous, painful and swollen. A diagnosis of Meniere's syndrome was made. He was treated symptomatically for several days. After few days,

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vertigo, nystagmus, ataxia, nausea and vomiting abated but he became deaf. Because of fever, headache and deafness the patient was transferred to our hospital for suspected meningitis.

The careful medical history taking revealed that his symptoms started 6 months ago with abrupt onset of vertigo, nausea, vomiting and tinnitus that spontaneously abated for a week. After interval of 3 months his eyes became red with swollen conjunctiva and blurred vision but without discharge. The patient visited an ophthalmologist who prescribed sulphonamide eye solution but without any beneficial effect.

One month prior to admission to the hospital he became febrile with myalgias in his legs and pain in mandible and teeth. One week later, he noted enlarged and painful lymph nodes on his neck and under his jaw that resolved during next few days without any treatment.

The patient was otherwise healthy. There was no history of behavioral disturbances, oral or genital ulcers, arthritis, arthralgias, rash, motor or sensory deficits, neck stiffness, chest or abdominal pain, melena, cough, exposure to tuberculosis, herpes labialis, head injury or other illnesses in recent months.

His temperature was 37.3 °C, pulse 75 and respiration 14. Blood pressure was 130/85 mmHg.

On physical examination the patient had bilateral blepharoconjunctivitis with marked conjunctival oedema. There was no preauricular lymphadenitis, herpetic vesicles or any kind of discharges found. Also, there was no lymphadenopathy. His auricles were erythematous, swollen and painful.

On neurologic examination the patient was alert and oriented with intact and loud speech. There was discrete horizontal nystagmus to the right side. Deep-tendon reflexes were facilitated and symmetric. Plantar responses were flexor. His gait was wide-based and patient appeared to be incapable of walking with a tandem gait. The result of Romberg's test was positive—he felt to the backward and left side. He reported deafness and tinnitus in the both ears.

Erythrocyte sedimentation rate was 90/h. C-reactive protein was 44 mg/l. Fibrinogen was 7.22 g/l. Complete blood count and urine were normal. The patient's immunoglobulin profile was normal.

A lumbar puncture yielded clear, colourless cerebrospinal fluid that contained 12 mononuclear cells per cubic millimetre, the total protein level was 0.480 g/l and glucose level was 2.5 mmol/l.

Chest radiography, brain CT scan, MRI and MR-angiography showed no abnormalities. An electroencephalogram taken on admission showed normal

8-9 Hz alpha rhythm. Tonal audiogram showed complete sensoryneural hearing loss in the both ears.

Test for human immunodeficiency virus 1 and 2 antibodies was negative. *Treponema pallidum* haemagglutination test (TPHA) was negative.

Autoimmune workup revealed elevated C3 and C4 component of the complement (2.2 g/l and 0.54 g/l, respectively) and positive IgG and IgM anti-cardiolipin antibodies but within normal range. Rheumatoid factor, anti-nuclear factor, dsDNA antibodies, cytoplasmic anti-neutrophil antibodies, circulated immunocomplexes and lupus anticoagulant was negative. Total serum complement and angiotensin-converting enzyme levels were normal. All culture samples were sterile and negative, respectively, (blood, spinal fluid and throat swab). Tests for antibodies (blood and cerebrospinal fluid samples) against herpes simplex virus 1 and 2, varicella-zoster virus, parvovirus-B19, human herpesvirus type 6, Epstein-Barr virus, cytomegalovirus, parainfluenza viruses 1, 2 and 3, adenoviruses, tick-borne encephalitis virus, *Mycoplasma pneumoniae* and *Borrelia burgdorferi* were negative. Serology was also negative for *Listeria monocytogenes* and *Leptospire*s. Species-specific IgA, IgG and IgM antibodies to *Chlamydia pneumoniae* using immunofluorescence technique (IFA) were positive, clearly demonstrated acute infection. Titre of IgA was 128, IgG 512 and finally IgM titre was 160.

Immunoassay for circulating antibodies against inner ear structures and cornea were negative.

Treatment with corticosteroids (64 mg methylprednisolone per day) was started immediately after admission. Beside corticosteroids, patient also received azithromycine (500 mg for 3 days) because of positive serology for *C. pneumoniae*.

Treatment resulted in partial recovery from the ocular, systemic and neurological symptoms of disease. Unfortunately, the hearing loss was unrecuperable. Because of delayed initiation of corticosteroid treatment, the clinical course of the disease was unfavorable with permanent hearing loss. Dose tapering of methylprednisolone was unsuccessful because of symptoms recurrences. The patient was discharged from hospital and the outpatient treatment was continued with combination of methylprednisolone and cyclophosphamide.

Discussion

Vestibuloauditory dysfunction in Cogan's syndrome starts abruptly with Meniere-like attacks of vertigo,

ataxia, tinnitus, nausea, vomiting and sudden hearing loss. Fever and weight loss are associated with active vasculitis which can involve aorta or medium and small vessels.⁶ Systemic vasculitis can lead to numerous organ system abnormalities such as cerebellar involvement, meningeal syndrome and peripheral neuropathy.¹ Permanent hearing loss and cardiovascular disease are main causes of morbidity in this syndrome. Aortic insufficiency was the most severe cardiac lesion.

Clinical diagnosis is sometimes difficult without careful medical history taking. Also, the fact that eye and ear symptoms can develop at the same time or even 1-2 years apart should be kept in mind.¹ The median duration between onset of eye and ear involvement was 1 month.² In every Meniere-like attack, physician must actively pursue signs of inflammatory eye disease in recent past. The only chance to prevent hearing loss in these patients is urgent and high-dose corticosteroid therapy.

Elevated erythrocyte sedimentation rate, anemia, leukocytosis with neutrophilia, elevated C-reactive protein level, thrombocytosis and elevated fibrinogen are common but non-specific laboratory abnormalities. Rheumatoid factor and cytoplasmic autoantibodies against neutrophils are present in some patients.^{1,7}

Erythrocyte sedimentation rate and C-reactive protein level are useful markers for disease activity in these patients but not in all.⁸ Disease activity can also be estimated by high resolution MRI.⁹ In the acute stage the best treatment is topical ocular and high-dose systemic corticotherapy. In the chronic stage cyclophosphamide or cyclosporine A is preferred.

If medical treatment with corticosteroids fails and no benefit could be obtained with hearing aids at patient's end stage, all patients should receive a cochlear implant. The results are excellent.¹⁰

Careful medical history taking in our patient revealed vestibuloauditory dysfunction, inflammatory eye disorder with decreased vision, myalgias, lymphadenopathy, mandibular nerve neuralgia and finally hearing loss. These symptoms together with laboratory findings and fever suggested systemic immune-mediated disorder. Sensorineural hearing loss may be caused by Wegener's granulomatosis, lupus erythematosus, Behcet disease, polyarteritis nodosa, giant-cell arteritis and Cogan's syndrome.

Behcet's disease and Vogt-Koyanagi-Harada syndrome were ruled out because there were no orogenital ulcerations, alopecia, vitiligo or poliosis nor exudative uveitis or retinal detachment. All above mentioned symptoms accompanied with laboratory abnormalities were sufficient for conclusion that our patient met diagnostic criteria for

Cogan's syndrome. Because signs of interstitial keratitis were absent we concluded that atypical Cogan's syndrome was correct diagnosis. The clinical diagnosis in this patient was not confirmed by test for circulating antibodies against inner ear structures and cornea. However, this is not necessary because negative result does not rule out clinical diagnosis.¹¹ On the other hand, obvious benefit from corticosteroid treatment also confirmed clinical diagnosis.

Typical clinical presentation of Cogan's syndrome in our patient was accompanied with swollen, red and painful auricles, mimicking bilateral auricular perichondritis.

To our knowledge, this is the first report of such symptom in Cogan's syndrome. Titres of IgG, IgM and IgA antibodies to *C. pneumoniae* clearly demonstrated actual infection that correlated with aggravation of symptoms and sudden hearing loss. Unfortunately, at a time of admission there was no lymphadenopathy. Thus, we were unable to take bioptic lymph node specimen.

We are prone to believe that *C. pneumoniae* possesses ability to trigger vasculitis or at least to induce a significant deterioration of already established disease. Therefore, we suggest that in every case or suspicion of Cogan's syndrome serology for *C. pneumoniae* should be taken, especially if disease is preceded by upper respiratory tract symptoms.^{2,4} If there is evidence of acute infection or reinfection with *C. pneumoniae* we suggest treatment with azithromycine or doxycycline because influence of *C. pneumoniae* infection to disease course could be harmful.

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