

Cogan's syndrome: Organ-specific autoimmune disease or systemic vasculitis?

A report of two cases and review of the literature

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ABSTRACT

Cogan's syndrome is a rare disorder of unknown origin characterized by inflammatory eye disease and vestibuloauditory symptoms. Typically, young adults suffer from interstitial keratitis and sudden onset of tinnitus and hearing loss. Few cases (around 150) have been published and thus it is difficult to determine the percentage of patients with underlying systemic disorders such as systemic vasculitis. The variety of systemic manifestations is large and includes fever, splenomegaly, lymphadenopathy, and musculoskeletal complaints. Systemic vasculitis can be seen in around 10% of cases and may involve the large vessels, appearing as Takayasu-like vasculitis with affection of the aortic valve but also the coronary arteries and the small kidney vasculature. Evaluating the exact extension of the systemic features determines the choice of treatment. While corticosteroids have proved to be of short-term benefit, long-term treatment with immunosuppressive drugs is controversial. Auditory function in deaf patients has often been restored successfully with cochlear implants. To illustrate the nature of the syndrome, we present two patients with a wide clinical spectrum of symptoms from local disease restricted to the eyes and ears to a widespread vasculitis affecting arteries of the brain, kidney and the upper and lower extremities. We then review the typical aspects as well as the etiology of the disease.

Introduction

In 1934 Mogan and Baumgartner (1) were first to describe a patient with non-syphilitic interstitial keratitis and audiovestibular dysfunction. Eleven years later David Cogan (2), an ophthalmologist, reported four patients with the same symptoms and classified

this specific entity as "Cogan's syndrome". In 1960 Cody and Williams (3) emphasized the systemic manifestations of this syndrome. Most cases have since then been published in the otolaryngological literature. However, considering its systemic features, ophthalmologists and internists, especially cardiologists, nephrologists, and rheumatologists, may also encounter patients with Cogan's syndrome. An interdisciplinary approach might not only improve the diagnosis, but also shed light on the etiology and pathogenesis of this rare disorder.

Illustrative case reports

Patient 1

An 18-year-old man presented with sudden onset of hearing loss in the left ear accompanied by tinnitus and nausea. The patient also suffered from recurrent losses of balance and a tendency to fall to the left side. One week earlier he had experienced an episode of ophthalmologically diagnosed interstitial keratitis with photophobia and spontaneous remission after 24 hours. These symptoms then reappeared together with the hearing loss.

Audiometry showed bilateral sensorineural hearing loss (Fig. 1). Vestibular examination demonstrated a left beating nystagmus and bilateral absence of labyrinthine function by caloric testing on both sides. During a follow-up visit at an eye clinic, bilateral episcleritis in addition to typical non-syphilitic interstitial keratitis were found (Fig. 2). A complete physical examination revealed no other pathological findings (blood pressure 125/85 mm Hg, heart rate 63/min). Laboratory testing showed a slightly elevated ESR (18/44 mm/h) but no other abnormalities. Antinuclear antibodies, anti-DNA, anti-ds-DNA and rheumatoid factors were negative; serologic tests for sy-

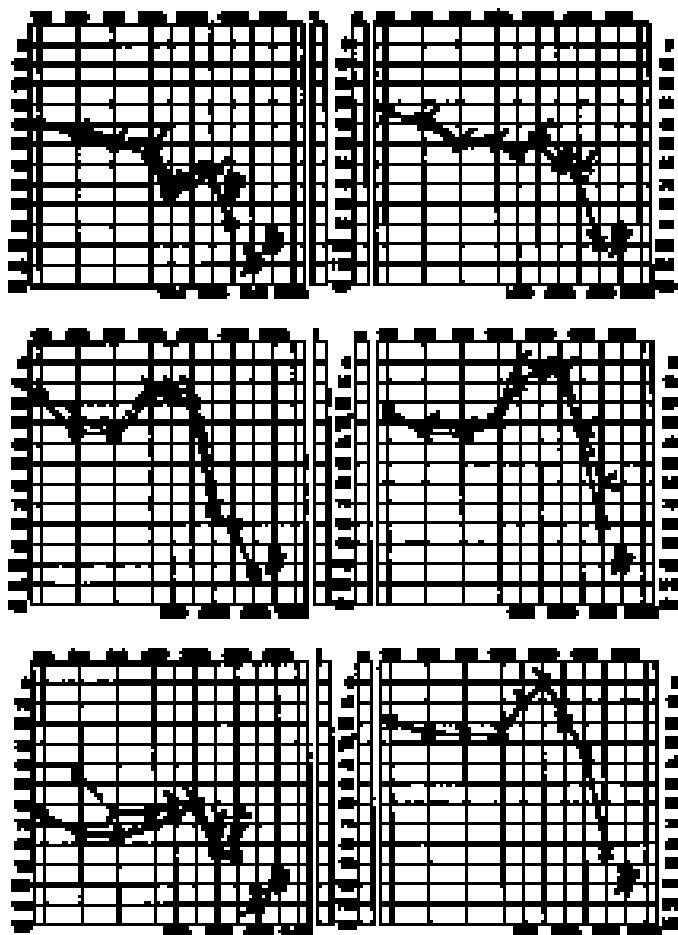


Fig. 1. Audiograms on admission (first line), and 2 months (second line) and 6 months (third line) later showing bilateral sensorineural hearing loss with partial remission under treatment.

philis, borreliosis and chlamydia infection were all within normal ranges, as were quantitative immunoglobulins and complement levels.

Initially the patient was treated with high doses of prednisolone (100 mg/d), azathioprine (100 mg/d) and dexamethasone eye drops. Under this regimen the audiometry results improved continuously and steroids were tapered

slowly. The patient was placed on long-term therapy consisting of fluocortolon (2.5 mg/d) and azathioprine and remained free of complaints except for ear involvement. During the 8 years of follow-up the patient experienced several episodes of sudden onset hearing loss of increasing severity. These were successfully treated each time with steroid pulse therapy, but moderate per-

manent hearing loss on the right side was sustained. Systemic symptoms were not observed.

Patient 2

A 36-year-old female teacher presented with a 12-month history of weakness and pain in her arms which appeared to be particularly pronounced when writing on the blackboard. Ten years earlier Cogan's syndrome had been diagnosed with recurrent episodes of keratitis, 7 months later accompanied by vertigo and progressive hearing loss. At the time, peripheral pulses had been normal and the blood pressure bilaterally was 140/80 mm Hg. Her ESR was elevated at 45 mm/h. Seven months after the onset of the first symptoms oral steroid treatment was started, resulting in the remission of keratitis and improvement of hearing. Despite several corticosteroid pulses and long-term azathioprine treatment, progressive hearing loss gradually developed.

When she became completely deaf 3 years ago, she received a cochlear implant with excellent results (Fig. 3). Physical examination now revealed the absence of radial pulses and no measurable blood pressure of the upper extremities. There was a new aortic valve murmur with continuation to her right carotid artery. Her ESR was 48 mm/h and CRP 7.4 mg/dl (n.v. < 0.5 mg/dl); routine laboratory values were otherwise normal. IgG was slightly elevated at 1640 mg/dl (n.v. < 1600 mg/dl); anti-nuclear antibodies, anti-DNA, rheumatoid factors, C and P-ANCA were negative, as were serologic tests for infections with chlamydia and borrelia. Ultrasound doppler examination documented a significant reduction in blood pressure in both the radial and ulnar arteries. Aortic angiography (Fig. 4) showed total occlusion of both subclavian and vertebral arteries with collateral supply to both arms, a distinct dilatation of the proximal part of the right carotid artery and a long narrow stenosis of the left carotid artery. The renal arteries showed a moderate asymmetric stenosis close to the aorta.

Oral cyclophosphamide, corticosteroid, and aspirin treatment resulted in a decline in the inflammatory markers.



Fig. 2. Left eye on admission, demonstrating typical signs of episcleritis.

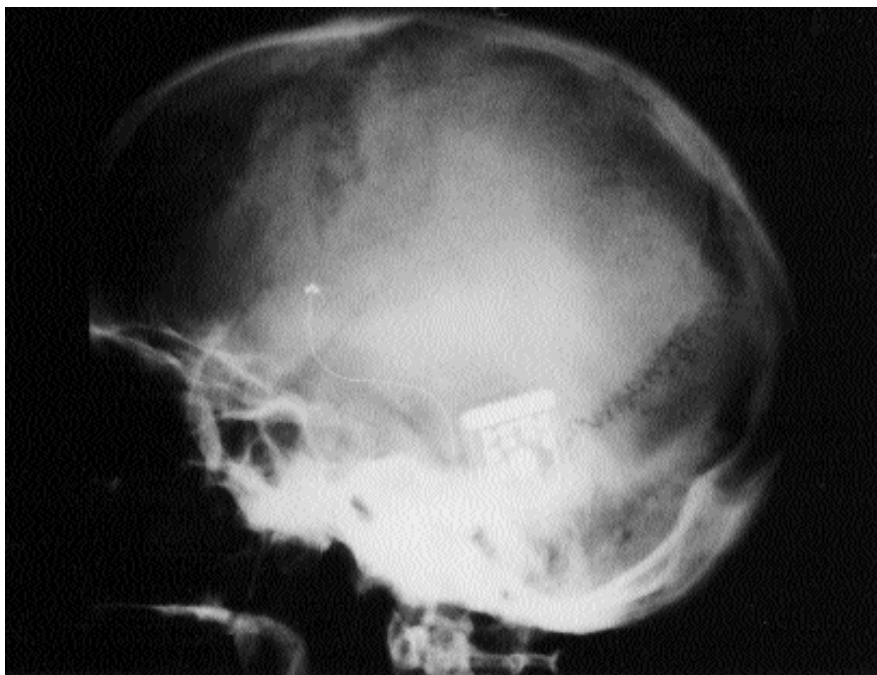


Fig. 3. Radiograph of the cranium showing implant and electrode to the cochlea.

An aortic angiogram 12 months later documented an unchanged status in the aortic arch and its branches, but a moderate stenosis of both femoral arteries. One year later the patient remains in good health with inflammatory parameters within the normal range and only slight lower extremity exertional claudication. Cyclophosphamide treatment was changed to cyclosporine A

(200 mg/d, then 150 mg/d with further tapering until it was finally discontinued) and daily alternating prednisolone doses of 7.5 and 10 mg.

Epidemiology

Cogan's syndrome is a rare disease occurring primarily in young adults. The overall number of published cases is close to 150; however, it is possible that

some cases may have been counted twice - as case reports as well as in reviews. The median age of onset was about 25 years in the two largest cohorts, and the sex distribution was even (4, 5). Some cases of Cogan's syndrome in children (4,6,7) and in persons more than sixty years of age (4) have been reported. The actual number of patients suffering from Cogan's syndrome could well be substantially higher because many cases are incompletely or wrongly diagnosed as idiopathic hearing loss/deafness, autoimmune inner ear disease, or idiopathic recurring keratitis. Since these disorders are frequently treated with corticosteroids, the typical or complete clinical picture of Cogan's syndrome may often be blurred.

Pathogenesis

Although the cause of Cogan's syndrome remains obscure, an immunologic etiology has been suggested by many authors. This opinion has been supported by laboratory and histopathological findings, as well as by the favorable response to immunosuppressive treatment in the majority of cases. Most authors found elevated erythrocyte sedimentation rates (4,8), which were particularly high in patients with large vessel vasculitis, and elevated white blood cell counts. Typical laboratory markers of systemic autoimmune disease (e.g., antinuclear antibodies, antineutrophil-cytoplasmic antibodies) could be detected in a very small number of patients (9, 10). Several patients tested for antibodies to corneal antigens were found to be positive (11, 12). A more specific characterization of the possible corneal autoantigen still needs to be carried out.

Chronic inflammation is the most consistent finding in histopathological studies in patients suffering from Cogan's syndrome. The arterial wall may show signs of acute and chronic inflammation with inflammatory cells (lymphocytes, plasma cells), fibrinoid necrosis, and intimal proliferation (5, 14).

Upper respiratory infections preceding the onset of Cogan's syndrome were found in a remarkable 32-65% in Haynes' and Vollertsen's reviews (4, 5).



Fig. 4. Aortic angiography with total occlusion of both subclavian arteries, collateral supply to both arms, distinct dilatation of the proximal part of the right carotid artery, and long distance filiform narrowing of the left carotid artery.

Table I. Systemic vasculitic involvement in patients with Cogan's syndrome.

Artery	Clinical symptoms	References
Aorta	Aortic valve regurgitation, stenosis of the ostium of coronary arteries, aneurysm	Vollertsen (4), Haynes (5), Cochrane (18), Tseng (19), Ho (20)
Coronary arteries	Exertional dyspnea, stenocardia	Allen (8), Livingston (22)
A. mesenterica	Mesenteric insufficiency	Allen (8), Thomas (21)
A. renalis	Reduced perfusion in renography	Vella (16)
A. subclavia	Upper extremity claudication	Allen (8), Raza (17)
A. carotis	None	Cochrane (18)
A. femoralis	Lower extremity claudication	Vollertsen (4), Allen (8)

Antibodies to chlamydia trachomatis were found in some (5,15), but not all patients (16,17). However, in most patients antibiotic regimens were not effective.

Symptoms

Ophthalmologic findings

Pain, eye redness, photophobia, and blurred vision are typical complaints in the early stages of interstitial keratitis. Iritis and conjunctival hemorrhage may also develop. Originally, Cogan suggested that there might be two forms of the syndrome: a typical form characterized by these ocular symptoms, and an atypical form in which scleritis, episcleritis, retinal artery occlusion, chorioiditis, retinal hemorrhage, or exophthalmus are present.

Vestibuloauditory findings

Vestibuloauditory involvement begins with the sudden onset of vertigo, tinnitus, nausea, vomiting, and hearing loss. The clinical picture mimics that of Menière's disease and typically develops just prior to or soon after interstitial keratitis. Audiometry demonstrates sensorineural hearing loss affecting all frequencies. Hearing may be influenced by the natural course of the disease (exacerbations and remissions) and by treatment. However, a majority of the 50% of patients who develop deafness do so within the first three years after onset (4,5).

Systemic findings

According to the largest case series published, many patients have systemic complaints: these may be unspecific (e.g., fever, weight loss, fatigue, headache, arthralgias and myalgias), but

may also represent symptoms of vasculitic involvement of different sized vessels. Table I summarizes the vasculitic manifestations and typical symptoms of Cogan's syndrome involving the aorta, large vessels (particularly the aortic arch vessels), and medium sized arteries. The clinical picture may offer a variety of other findings such as pleuropericarditis, lymphadenopathy, abnormal urinalysis, cutaneous nodules, and rashes.

Diagnosis

Generally accepted diagnostic criteria have so far not been agreed upon. Today, the diagnosis of Cogan's syndrome requires the presence of inflammatory eye disease (interstitial keratitis or other inflammatory eye manifestations) **and** objective vestibuloauditory dysfunction with hearing loss and vertigo. Possible additional symptoms are unspecific systemic signs and symptoms of systemic vasculitis. The physical examination should focus on, but not be limited to, eye and ENT examinations. A general medical history and physical examination must look specifically for signs of systemic involvement, especially vasculitis. The interview should include questions regarding fever, weight loss, cutaneous abnormalities, neurological symptoms such as hypesthesia, motor weakness, pain as a symptom of abdominal angina, and claudication secondary to peripheral artery disease. During the physical examination one must consider lymphadenopathy, cutaneous efflorescences (e.g., vasculitic or necrotic), and heart and large vessel murmurs, as well as differences in pulses and blood pressure between the left and right sides.

Findings should be further evaluated by ultrasound-doppler and, if necessary, angiography.

Typically, the laboratory results in Cogan's syndrome are unspecific. Since there is no specific marker available, screening should include ESR, a complete blood count, and routine serum parameters. To narrow the differential diagnosis, screening for infectious pathogens including borreliosis and treponema should be performed. With regard to autoimmune disease, antinuclear antibodies and antineutrophil-cytoplasmic antibodies should be screened for. Radiologic imaging must include a standard chest x-ray and, if necessary, a cranial MRI which could show high signals in the cochlear and vestibular structures with enhancement on T1-weighted images, and eventually exclude retrocochlear lesions such as acoustic neurinomas, another possible cause of hearing loss or symptoms of dizziness (23,24). Angiographic procedures are indicated in cases of side differences in the peripheral pulses or blood pressure and abnormalities in the vascular ultrasound.

Treatment

The degree and intensity of treatment depend on the extension of the disease, especially the presence of systemic vasculitis. Interstitial keratitis may respond to the local administration of corticosteroids and atropine eye drops. However, the course of vestibuloauditory function depends on early treatment with systemic corticosteroids (2 mg/kg/d prednisolone), which therefore is recommended in most patients with suspected Cogan's syndrome (25-28). How rapidly this dose can be ta-

pered depends on the clinical response, especially with regard to audiometric improvement. Should the response be delayed or incomplete, an immunosuppressive agent should be added. Evidence from large studies is lacking, but in the small numbers of patients reported in the literature azathioprine (4,29), cyclosporine A (8) and methotrexate (19,30-32) have been found to be beneficial in some but not all patients. For patients developing deafness during the course of the disease, a cochlear implant is a well-established therapeutic option with convincing results (33,34). Systemic vasculitis with its sometimes widespread, life-threatening sequelae may require even more aggressive immunosuppression using cytotoxic agents. There is some experience with cyclophosphamide therapy, both pulse and daily, but this has not been proven to be successful in all severely ill patients (8,35,36). However, a combination therapy or a step down regimen starting with cyclophosphamide and then switching to methotrexate or cyclosporine A after having achieved at least a partial response might be a promising option for the future.

Discussion

We have described two cases of Cogan's syndrome representing the wide clinical spectrum of this rare disorder. Patient 1 had first been seen by our otolaryngology department with the typical vestibuloauditory symptoms of Cogan's syndrome such as hearing loss, tinnitus and nausea. The ocular involvement was less marked, with recurring temporary keratitis accompanying other symptoms. At no time did the patient have systemic complaints and his only laboratory abnormality was a slightly elevated ESR. Treatment with steroids and azathioprine improved the hearing symptoms, although moderate hearing loss did develop over the 8 years of observation, with intermittent flares responding well to steroid pulse therapy.

This first patient fulfilled the main criteria required for the diagnosis of Cogan's syndrome, i.e. simultaneous involvement of the eyes and ears. As in the majority of patients, neither symp-

toms of systemic vasculitis nor systemic complaints such as fever or malaise, both of which can be found in patients without systemic vasculitis, developed. Early diagnosis and aggressive treatment may have prevented the development of systemic disease, and it surely preserved sufficient hearing for daily life.

Patient 2 presented a dramatic course of Cogan's syndrome with severe organ damage despite attempts to halt its course with several treatment regimes. Initial symptoms were restricted to the eye and when – 6 months later – dizziness, nausea and hearing loss appeared, corticosteroid treatment was started within weeks. Over the years the patient's hearing inexorably deteriorated, however, ending in deafness and the need for a cochlear implant. Cochlear implantation dramatically improved her hearing, enabling her to resume her job as a teacher.

If her symptoms had been limited to these, one could have called her case a typical course of Cogan's syndrome with eye and ear involvement. Interestingly, however, 11 years after the first ocular symptoms the patient developed signs of systemic vasculitis for the first time. This is especially surprising considering that she had received immunosuppressive treatment throughout that period. Retrospectively, however, it appears that the drug selection and dosage may not have been sufficient to normalize the laboratory parameters of inflammation. The precise starting-point of the vascular changes in this patient, in particular the stenosis of the subclavian arteries, remains speculative. Being common in aortic arch syndromes of a wholly different etiology, it took around 12 months starting from the onset of the first complaints to perform an angiogram and thus to diagnose the widespread vasculitic changes.

The vasculitic involvement in this patient is the most extensive thus far published in the literature on patients with Cogan's syndrome. Our patient had angiographically proven vasculitic obstruction or stenosis in the carotid, vertebral, subclavian, renal, and femoral arteries, as well as in the abdominal aorta. In one prior case, published by

Allen (8), a stenotic lesion of the left subclavian artery, the brachiocephalic trunk, and the renal arteries was described. This patient was initially treated with cyclophosphamide, and then switched to cyclosporine A with a good response. Aggressive immunosuppressive treatment, including cyclophosphamide therapy, failed to totally normalize the inflammatory parameters in our patient, although a significant reduction could be observed. This may explain the lack of any dramatic events such as cerebral ischemia, or peripheral or central ischemic necrosis.

Taking into consideration these highly different manifestations of Cogan's syndrome, we conclude that:

- All patients with inflammatory eye disease should be interviewed for symptoms of vestibuloauditory dysfunction and vice versa.
 - This recommendation should especially be made to ophthalmologists and otolaryngologists, to whom these patients typically present first.
 - In patients with involvement of both organ systems justifying a strong suspicion of Cogan's syndrome, a thorough physical examination must follow, including auscultation of the heart and large arteries of the chest and abdomen, together with bilateral blood pressure measurements of both the upper and lower extremities. In cases of abnormalities ultrasound doppler and, if necessary, intra-arterial angiography should be performed.
 - Treatment should be aimed at ensuring a sufficient suppression of inflammation, which can be monitored by laboratory parameters as well as subjective complaints. Systemic symptoms require constant monitoring with periodic examination in order to diagnose the early signs of systemic vasculitis.
- However, these two case studies with their significant differences raise the question as to whether they merely represent different variations of Cogan's syndrome or actually constitute totally different entities. Both patients presented the typical combination of eye and ear involvement which rarely complicate other systemic conditions. In the differential diagnosis Wegener's granulomatosis, polyarteritis nodosa, micro-

scopic angiitis, Takayasu's arteritis temporalis and the rarer manifestations of systemic connective tissue diseases (e.g., systemic lupus erythematosus) should be included. In our cases there were none of the typical symptoms of any of these diseases.

Wegener's granulomatosis (WG) is the form of vasculitis in which eye and ear involvement is most frequently seen; WG is characterized by hemorrhagic lesions of the throat and nose, pulmonary infiltrates, vasculitic changes of the small vessels, glomerulonephritis, and the frequent detection of anti-neutrophil-anticytoplasmatic antibodies (ANCA). Our patients did not fulfill the diagnostic criteria for Wegener's granulomatosis (37). However, in the early stages of both diseases, especially when presenting with an incomplete clinical picture, the differentiation might be difficult or impossible. These patients should be monitored regularly, with particular regard to the development of ANCA, pulmonary infiltrates or glomerulonephritis.

Another systemic vasculitis associated with glomerulonephritis is microscopic polyangiitis. Patients suffering from microscopic polyangiitis often show inflammatory eye involvement; the detection of ANCA (in up to 80% of patients) may help to differentiate this entity from Cogan's syndrome. In contrast to Cogan's syndrome and Wegener's granulomatosis, microscopic polyangiitis is restricted to the small vessels such as arterioles and usually does not involve the medium sized arteries (38).

Patient 2 was characterized by widespread vasculitic involvement of the large and medium sized arteries of the upper and lower body halves; such extensive involvement has been frequently reported in patients with Takayasu's arteritis, a vasculitis of unknown, probably autoimmune, origin affecting particularly young women (39). In this disorder visual impairment has been described in a noteworthy percentage of patients; however, keratitis and scleritis are not regarded as typical manifestations of Takayasu's arteritis (40). Other vasculitic disorders involve arteries of smaller size and can therefore be

excluded.

These considerations make Cogan's syndrome the most likely diagnosis in our patients. It remains speculative whether Cogan's syndrome can appear in an extended version with systemic vasculitic changes, in addition to its typical form with eye and ear involvement, (41). Arguably, the development of extended disease might be related to a delayed start or to insufficient immunosuppressive treatment, giving the vasculitic process the chance to spread from the eye and ear to other vessels.

Histopathological sections did not demonstrate vasculitic changes (13,42); several reasons, however, argue for a vasculitic pathogenesis of the eye and ear manifestations in Cogan's syndrome. The coincidence of systemic vasculitis is close to 10% and is unlikely to be caused merely by chance. Only a few patients, all on quite different therapy regimens, have undergone histopathological analysis of corneal and cochlear material. These may not reflect the typical or early picture of the disease. Stone in his review "Immune-mediated inner ear disease" (43) underlines the difficulties of obtaining relevant tissue specimens from untreated patients. The mechanisms of autoimmune diseases of the ear and eye are still obscure; quite possibly, the autoimmune processes in these organs are temporary and do not even produce a systemic autoimmune response that can be detected in specimens such as blood samples. Hughes (44) demonstrated that an inner ear membrane extract inhibited lymphocyte migration in a patient with Cogan's syndrome, while Peeters (45) describes lymphocyte stimulation by eye-specific proteins (S antigen, outer rod segment, cornea protein or scleroprotein). Recent studies recommend screening for antiendothelial autoantibodies [positive in 8 of 15 patients with sudden hearing loss in Ottaviani's study (46)] and to combine a Western blot for heat shock protein (hsp) 70 with ESR, which were the most predictive tests for a good response to steroid treatment in Hirose's group (47). Finally, the good response to the early institution of corticosteroid therapy which was observed with very

few exceptions (36) – as well as the beneficial effects of several other immunosuppressive regimens (8, 29-32) – support the hypothesis of an autoimmune process underlying Cogan's disease.

Considering all of these observations, evidence seems to suggest an immunologic etiology for Cogan's syndrome, one producing a typical vasculitis in some patients and inflammatory manifestations of the cornea and inner ear which are not yet clearly understood in other patients.

Conclusion

Cogan's syndrome is a rare, but perhaps underestimated disorder consisting of interstitial keratitis and vestibuloauditory involvement with nausea, tinnitus and hearing loss often progressing to deafness. Since the clinical course is extremely variable, one must be aware of potential systemic features and an interdisciplinary approach appears to be essential for early diagnosis and treatment. Therapy consists of corticosteroids; additional immunosuppressive agents, if necessary, should be used to normalize the inflammatory markers and prevent an organ-threatening progress of the disease. Although there is some evidence for an autoimmune process initiating systemic vasculitis in a minority of patients, the exact pathogenesis leading to corneal and inner ear damage remains to be investigated.

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