

Cogan's syndrome

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Abstract

Typical Cogan's syndrome is defined by non-syphilitic interstitial keratitis associated with audiovestibular involvement similar to that of Ménière's disease with progressive hearing loss to complete deafness within 2 years. Cogan's syndrome becomes atypical when the eye and/or ear involvement is of a different type or when the interval separating their appearance exceeds 2 years. The syndrome affects primarily young adults, involves another organ in 2/3 cases and gives a clinical picture of systemic disease reminiscent of vasculitis in 1/3 patients. The most common symptoms are cardiovascular, musculoskeletal, neurological, gastrointestinal and mucocutaneous. Complementary examinations reveal an inflammatory syndrome and, sometimes, immunological abnormalities. No specific biological test is diagnostic of this pathology. The mechanism of lesion formation is unknown; the role of infectious and/or immunological phenomena is the most frequently evoked. The prognosis is dominated by the risk of definitive deafness and by cardiovascular complications, notably aortic insufficiency. Treatment consists mainly of corticosteroids. The ocular symptoms usually regress but deafness is only rarely reversible. Diverse immunosuppressive agents are prescribed in the case of corticoreistance or corticodependence.

Key words

typical Cogan's syndrome, atypical Cogan's syndrome, interstitial keratitis, deafness, Ménière's disease, vestibular syndrome, aortic insufficiency, joint involvement, arterial involvement, cerebral vasculitis, peripheral neuropathogenic involvement, vascular purpura, atrophic polychondritis, polyarteritis nodosa, immunological deafness, corticotherapy, immunosuppressant.

Name of the disease and its synonyms

Oculovestibulo-auditory syndrome

The association of non-syphilitic interstitial keratitis and audiovestibular involvement was first reported in 1934 by Mogan and Baumgartner, then Cogan described four additional cases in 1945. In 1980, Haynes et al. proposed retaining the diagnosis of

atypical Cogan's syndrome when different ocular and audiovestibular symptoms were observed. In many cases, the symptomatology is not restricted to the eyes and ears, and the involvement of other organs gives a clinical picture of systemic disease, often close to that of polyarteritis nodosa (PAN).

Diagnostic criteria/definition

Typical Cogan's syndrome

The 'typical' form of this syndrome is characterized by:

- ocular involvement that is primarily represented by interstitial keratitis, sometimes associated with conjunctivitis, subconjunctival hemorrhage or iritis;
- audiovestibular involvement giving a clinical picture similar to that of Ménière's disease accompanied with progressive loss of hearing, usually ending in deafness within 1-3 months. The interval separating ocular and audiovestibular symptoms is 1-6 months for Cogan but may be as long as 2 years according to Haynes *et al.*

Atypical Cogan's syndrome

The diagnosis of the atypical form can be retained when:

- another type of ocular involvement is present and associated or not with interstitial keratitis, subconjunctival hemorrhage or iritis;
- typical ocular involvement is associated with audiovestibular symptoms not characteristic of a pseudo-Ménière's disease or arising more than 2 years before or after ocular symptoms.

Differential diagnosis

When interstitial keratitis, vestibular syndrome and rapid onset of deafness are associated, the diagnosis of Cogan's syndrome is easily made, if one is aware of its existence. Several other diseases can, nonetheless, be evoked by the association of ocular and audiovestibular symptoms:

- congenital syphilis, which is an exclusion criterion for Cogan's syndrome;
- [Vogt-Koyanagi-Harada syndromes](#), which associate audiovestibular involvement with uveitis, alopecia, poliosis and vitiligo;
- the association of serous otitis and systemic vasculitis, sometimes with episcleritis, described by Sergent and Christian in 1994. This entity is distinguished from Cogan's syndrome by the absence of inner ear involvement;
- [Susac syndrome](#) (retinocochleocerebral vasculopathy), caused by lesions of the retinal, cochlear and cerebral arterioles, is manifested by crises associating, in variable ways, loss of visual acuity, deafness and central neurological disorders;
- finally, diverse systemic diseases, such as PAN, [sarcoidosis](#), [Wegener's granulomatosis](#), [Relapsing polychondritis](#), rheumatoid arthritis, systemic lupus erythematosus, [Behçet's disease](#), [Sjögren's syndrome](#) or [Horton's disease](#) (giant-cell arteritis) can be responsible for the audiovestibular involvement and ocular signs.

Incidence

The incidence of Cogan's syndrome is not known. Our retrospective inquiry, which interrogated all the internal medicine departments in France, identified 30 cases over a 15-year period. When the broader definition proposed by Haynes is applied, approximately 200 cases have been reported in the literature. It can be thought that the real frequency of this disease, which is poorly known, is underestimated.

Clinical description

Affected population

Cogan's syndrome predominantly affects young adults, with its onset occurring 1 out of 2 times between 20 and 30 years of age, and 8 out of 10 times between 10 and 40 years, at a mean age of 30 years, and an age range of 3.5 months to 81 years. The majority of reported cases were in Caucasians, but no sexual predominance was observed (52% males and 48% females).

Analyses of the HLA groups of affected patients are rare. The abnormal frequency of the B14 locus observed in the first studies was not confirmed subsequently. The 10 patients investigated by Kaiser-Kupfer carried HLA loci A9, Bw35 and Cw4 more often than 489 control subjects.

Mode of onset

The etiology of Cogan's syndrome is unknown, but the onset of the disease is preceded in approximately 20% of the cases by an upper respiratory tract infection.

For most patients, the first symptom affects either the eye (41%) or ear (43%) alone. The mean interval between the involvement of the two organs is 3 months for the typical forms, but can be as long as 11 years for atypical Cogan's syndrome; more rarely, the two symptoms appear at the same time (16%). Finally, sometimes the first clinical manifestation is merely weight loss or a clinical picture of systemic involvement.

Clinical signs

Ocular signs

The most striking clinical symptomatology associates, in variable ways, ocular redness (74%), photophobia (50%) with tearing, ocular pain (50%) and usually transitory diminution of visual acuity (42%). Very rarely, interstitial keratitis is asymptomatic and is discovered by an ophthalmological examination ordered for the evaluation of a patient with an audiovestibular syndrome. Interstitial keratitis is manifested by a granular and irregular corneal infiltrate that preferentially affects the posterior part of the cornea, which can secondarily be the site of neovascularization. The involvement is usually bilateral during the course of the disease; however,

the lesion can sometimes be strictly unilateral. The loss of visual acuity is usually moderate and often regresses, but the occurrence of amaurosis or blindness has been described.

In some cases, interstitial keratitis is associated with or arises after diverse ocular lesions: conjunctivitis (26%), uveitis (26%), episcleritis or scleritis (25%), more rarely scleromalacia sometimes with perforation that can lead to loss of the eye, or superficial keratitis with corneal ulceration (11%). Diverse other punctual types of ocular involvement have been reported.

Audiovestibular signs

Audiovestibular symptoms usually start with an isolated vestibular syndrome or are associated, immediately or later on, with often profound deafness. The clinical picture resembles that of Ménière's disease, starting suddenly with severe dizziness and instability, accompanied in half the cases with nausea, vomiting and tinnitus; physical examination can show spontaneous nystagmus and a certain degree of ataxia. Progression oscillates or is intermittent for several days or months. As a general rule, the vestibular syndrome regresses when the auditory deficit appears. The latter is often bilateral from the start, but can be unilateral at the beginning and become bilateral later, usually within several weeks or sometimes later, after several months or years. The auditory involvement is severe and frequently progresses within several hours or days to total deafness; this loss of hearing is usually definitive and the complete disappearance of auditory disorders has only been observed in several isolated cases. Almost all patients experience this hearing loss during the first 3 years of progression. The complementary examinations show that it is sensorineural deafness and vestibular test results are abnormal to different degrees, sometimes markedly. Cranial, mastoid and auditory canal radiographs are normal but the computed tomography (CT) scans and magnetic resonance imaging (MRI), with injected gadolinium-enhancement reconstructions of the images in 3-dimensions, sometimes show obstruction or calcification of the semicircular canals, the vestibule and/or the cochlea.

Table 1. Frequencies of the main manifestations of Cogan's syndrome other than ocular and audiovestibular signs based on 160 cases reported in the literature.

Manifestations	%
Fever	39
Cardiovascular	28
Vasculitis (large and/or small vessels)	27
Gastrointestinal	26
Neurological	26

Weight loss	26
Skin-mucosal	19
Urogenital	16
Adenopathies	8

Other symptoms (Table 1)

Ocular and audiovestibular signs are part of the definition of Cogan's syndrome, and are essential for its diagnosis, but the presence of associated symptoms is not rare: at least another organ is involved in 2 out of 3 cases and a clinical picture of systemic disease is observed in 1/3.

General signs

General symptoms are not rare during the course of Cogan's syndrome and usually accompany multivisceral involvement. Fever, which can reach or exceed 39°C, was present in 39% of the case reports, and 26% of the patients reported in the literature lost weight, sometimes more than 10 kg.

Cardiovascular signs

Cardiac involvement

Cardiac involvement during the course of Cogan's syndrome is, above all, aortic insufficiency, present in 15% of the patients. It is a severe complication which, in almost half the patients, requires valve replacement, without which left ventricle insufficiency develops and can be fatal. Histological examination shows that the entire aortic wall is affected and can be accompanied by a localized aneurysmal dilation and also involve the coronary ostia. The microscopic lesions are non-specific, sometimes with fibrinoid necrotic foci, and giant and epithelioid cells, which can lead to consideration of the diagnosis of Horton's and/or Takayasu's (pulseless) disease. The cusps of the aortic valve (semilunar valvulae) can be normal or present alterations comparable to those of the aortic wall, sometimes with thickening and myxoid degeneration, deformation, prolapse or even valve perforation. Mitral insufficiency is reported more rarely. Myocardial dysfunction linked to coronaritis has been reported several times and is attributed to a specific arteritis with stenosis and sometimes aneurysmal dilation or patent stenosis. Myocardial necrosis sometimes occurs. The development of myocarditis or regressive pericarditis under treatment has been reported and can be responsible for the formation of adhesions, cardiac symphysis, or first or second degree atrioventricular block (two cases described).

Arterial involvement

Specific involvement of the walls of the large vessels has been described several times, notably during the last few years. These lesions can be asymptomatic or be responsible for a heart murmur, abolition of the pulse, abdominal pain, intermittent claudication of the upper and lower limbs, and even ischemic necrosis of the hands and feet.

Arteriography shows stenoses or thromboses and sometimes more diffuse lesions responsible for the tortuosity and irregularity of the arterial tree, or a genuine aneurysmal dilation, affecting, in particular, the aortic root. These abnormalities can be responsible for a true aortic arch syndrome, cerebral or multivisceral embolic events, Raynaud's phenomenon or renal artery stenosis with arterial hypertension.

Musculoskeletal symptoms

Joint involvement usually takes the form of polyarthralgias, but sometimes monoarthritis, oligoarthritis or true polyarthritis with synovitis and possibly articular effusion. Myalgias, sometimes intense, can exist alone or in association with joint symptoms, and sometimes with abnormal muscle biopsies: arterial involvement, muscle necrosis and atrophy or a morphological aspect resembling myositis.

Neurological signs

Neurological signs are present in about 1/4 patients, usually central type involvement, giving rise to various clinical pictures: hemiparesia or hemiplegia, aphasia, cerebellar syndrome, pyramidal syndrome, spinal cord disease, epilepsy, meningeal syndrome or vigilance disorders sometimes with characteristics of encephalitis. At least, diffuse and isolated electroencephalogram anomalies can exist. Images suggestive of localized cerebral ischemia with infarction are sometimes seen on CT scans but cerebral MRI can also detect multiple lesions of the white matter compatible with cerebral vasculitis. Anatomical verification, carried out in 4 patients, showed meningoencephalitis due to cerebral angitis, subarachnoid hemorrhage or cerebral vasculitis. Peripheral neuropathogenic involvement has been observed more rarely, giving rise to different clinical pictures: abolition of reflexes, hand and/or foot paresthesias, localized hypoesthesia, trigeminal neuralgia, or motor deficit involving pairs of cranial nerves, the phrenic nerve or several nerve trunks as in polyneuritis. In cerebrospinal fluid obtained by lumbar puncture, the white blood cell count can be high and/or the protein concentration can be moderately elevated.

Gastrointestinal symptoms

Present in about a quarter of the patients, gastrointestinal symptoms are usually seen in the context of diffuse systemic involvement; they can be diarrhea, rectal bleeding or melena, abdominal pain, sometimes associated with mesenteric arteritis. Hepatomegaly and splenomegaly have been observed in several patients.

Mucocutaneous signs

During attacks, various mucocutaneous signs can appear, consisting of non-specific erythematous or urticarial rash, vascular purpura, nodules or ulcerations of the limbs, genital organs and/or oral cavity. Histological slides show signs of non-specific or leukocytoclastic vasculitis. The development of auricular or nasal chondritis, sometimes with cartilage destruction, raises the problem of the nosological boundaries among Cogan's syndrome, chronic atrophic polychondritis and Wegener's granulomatosis.

Other symptoms

- Pulmonary involvement is sometimes present, represented by a cough, dyspnea, discrete and transitory anomalies on radiological images, but also hemoptysis and/or pleural involvement, sometimes associated with pericarditis or elements resembling interstitial pneumopathy.
- Peripheral or mesenteric adenopathies can appear during attacks.
- Also reported are: testicular pain, associated in one patient with Peyronie's disease, with vasculitis of the corpus cavernosum and impotence; thyroid goiter; hyper- or hypothyroidism; endocrinopathy associating obesity, testicular hypoplasia and mild feminization; and febrile parotiditis.

Evolution/prognosis

The profile of Cogan's syndrome progression varies. Usually, the initial acute episode is followed by a chronic, pauci-symptomatic phase. In other cases, ocular and/or vestibular attacks are repeated at variable intervals, between which apparently complete remission is observed. When deafness appears, it is often definitive, even if several rare exceptions have been reported, under treatment or sometimes even spontaneously. In contrast, ocular symptoms recur periodically but respond favorably to treatment. Review of the literature shows that, during evolution of the disease, almost 90% of the patients suffer severe hearing loss or total bilateral deafness, while ocular sequelae are rare. Systemic involvement is frequent and the possibility of severe deterioration appearing several years later justifies prolonged monitoring. Several deaths have been reported, usually patients with cardiac failure or congestive heart failure after disease progression for several months or years, but also myocardial necrosis, cerebral infarction, subarachnoid hemorrhages or internal hemorrhages resulting from rupture of a renal artery. Vollertsen et al. attempted to identify the prognostic factors of Cogan's syndrome based on the analysis of 78 patients described in the literature for whom a mean follow-up of 22 months (maximum: 36 years) was available. That study showed that, clinically, weight loss, cardiac and abdominal symptoms, and, biologically, elevated erythrocyte sedimentation rate (ESR), anemia, elevated white blood cell count and

thrombocytosis are significantly associated with a poor outcome. The presence of these symptoms could justify close monitoring of these patients.

Anatomical pathology

Anatomical pathology studies of the eye and ear are rare during the course of Cogan's syndrome; most of them were conducted during autopsies, long after the episodes of local progression, which limits their contribution to our understanding of this disease. Ocular lesions associate an inflammatory lymphoplasmocytic infiltrate and neovascularization of the cornea, particularly evident at the periphery and in the deep layers, more rarely (one reported case) in focal zones of necrosis.

Ear lesions are found in the cochlea and vestibule, with major degenerative lesions of Corti's organ and the semicircular canals, destruction of ciliated cells and lymphoplasmacytic infiltrations or atrophy of the spiral ligament. In addition, one can see cochlear and semicircular canal edema, with congestion of the endolymphatic spaces (hydrops), and fibrosis of the cochlea and/or vestibule, sometimes accompanied by localized ossification or even zones of bone resorption.

This aspect, resembling lesions seen during the course of chronic atrophic polychondritis or PAN, might correspond to late sequelae of ischemic lesions, possibly associated with vasculitis.

Histological anomalies of other organs reported during the course of Cogan's syndrome are very diverse and can affect numerous tissues with a predilection for vascular tissue. Other than the involvement of the walls of the aorta and large conduit vessels, vasculitis can also be detected in some patients, with involvement of intermediate-sized vessels and/or necrotizing vasculitis closely resembling PAN.

Nosology

Since the first description, the boundaries of clear-cut Cogan's syndrome have been discussed repeatedly. The recent description by Haynes et al. of 'atypical' Cogan's syndrome raises the problem of the uniqueness, or not, of the two forms of this syndrome. The comparison of the symptoms observed in the patients reported in the literature showed comparable frequencies for most of them, which pleads in favor of the uniqueness of the syndrome in its two clinical forms. One can, nonetheless, note that the presence of fever, musculoskeletal involvement, mucocutaneous signs and adenopathies are more frequently observed during the course of atypical Cogan's syndrome.

In some patients, Cogan's syndrome is associated with a systemic disease: sarcoidosis, rheumatoid arthritis, juvenile rheumatoid arthritis, Sjögren's syndrome, Basedow's disease, [Crohn's disease](#) or [ulcerative colitis](#). An attack of ear and/or nose chondritis clearly raises the question of the

association or differential diagnosis with chronic [relapsing polychondritis](#). In addition, the possibility of multivisceral involvement and vasculitis during the course of the disease has led some authors to consider Cogan's syndrome to be a localized form of PAN, as it can mimic the latter's clinical and histological symptoms. Furthermore, it is known that eye involvement with scleritis or episcleritis and ear involvement with deafness or a vestibular syndrome can complicate the progressive course of PAN.

The relationships between Cogan's syndrome and elements characterizing the immunological deafness described by McCabe in 1979 remain poorly elucidated. The audiovestibular symptoms of the latter are very similar to those of Cogan's syndrome, during which ear involvement can be the first isolated sign of the disease. It is thus possible that, in certain cases, immunological deafness might be the first sign of Cogan's syndrome which will subsequently be joined by others, but the frequency of this progressive sequence of events is unknown.

Management/treatment

No treatment has proven spectacularly effective against Cogan's syndrome. Corticosteroids, the most frequently prescribed, often act favorably on ocular, vascular and visceral signs, but the effect on hearing is much more random, especially once stable deafness is present. When visceral symptoms or severe ocular involvement are present, an initial dose of prednisone (1 mg/kg/day) is usually recommended and can be tapered subsequently to a low maintenance dose.

Treatment of audiovestibular symptoms remains controversial. A beneficial effect of corticotherapy was reported for about one-third of the cases, sometimes with pulse administration of massive doses. Analysis of the literature showed that administration of high doses of corticosteroids led to hearing improvement during the first week in half the patients when deafness was not yet permanent, and almost never when deafness was already total at the onset of therapy. These results plead in favor of high-dose corticotherapy (1-1.5 mg/kg/day of prednisone), possibly preceded by intravenous pulses for 1-3 consecutive days as soon as audiovestibular symptoms appear. This treatment should be stopped rapidly (after 2 weeks) when no improvement is obtained. When deafness regresses, corticotherapy should be gradually tapered, attempting withdrawal within 2-6 months. In the case of failure or insufficient efficacy of corticotherapy, other therapeutic options are very poorly codified. Ocular symptoms might respond to local atropine eye drops or especially corticosteroid eye drops. No treatment has been proven to have clear-cut efficacy when the auditory involvement is corticosteroid resistant. The most frequently

prescribed alternative consists of immunosuppressants and some improvement has been obtained with azathioprine, cyclophosphamide, cyclosporin A or, especially, methotrexate. Finally, plasma exchanges have been unsuccessfully used twice.

In several patients, deafness could be attenuated with a hearing aid or cochlear implants. Finally, when cardiovascular complications are present, medical treatment with prostacyclin or thrombolysis, or vavuloplasty, bypass or angioplasty of coronary, mesenteric or limb arteries, or repair of an aortic aneurysm with a graft has been successful.

Etiology/pathogenesis

The etiology and mechanism of Cogan's syndrome remain unknown. Exposure to a toxic substance preceded symptom onset in several patients but it was primarily the possible triggering role of an infection, present in 30% of the cases in the weeks preceding ocular or audiovestibular symptomatology, that is evoked. The arguments supporting this latter hypothesis are, however, weak, based for the most part on serological studies, and they remain open to discussion. The responsibility of *Chlamydia trachomatis* was not confirmed by Vollertsen et al. Other serological studies and the search for an infectious agent have remained negative. In addition, antibiotic therapy was never shown to be effective, and some authors have even considered it responsible for triggering the ocular, audiovestibular and visceral symptoms. The detection during the course of Cogan's syndrome of diverse autoantibodies, the clinical elements sometimes suggestive of collagen disease, the presence of vasculitis and several cases of PAN, in addition to the similarities with the auditory involvement of off autoimmune deafness, have suggested the role of an immune mechanism. Results of experimental studies plead in favor of a cellular immune reaction directed against the constituents of the cornea and inner ear. However, antibodies directed against the mesenchymal structures of the inner ear and epithelial cells of the cornea have been detected punctually in the sera of two patients. Such observations suggest the participation of humoral immunity in the development of eye and ear lesions during the course of Cogan's syndrome. Recently, Lunardi *et al.* used pooled IgG immunoglobulins derived from eight patients with Cogan's syndrome to screen a random peptide library to identify disease relevant autoantigen peptides. Among the identified peptides, one was recognised by all the patients' sera. They identified an immunodominant peptide that shows similarity with autoantigens such as SSA/Ro and with the reovirus III major core protein lambda 1. The peptide sequence shows similarity also with the cell-density enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), which is expressed

on the sensory epithelia of the inner ear and on endothelial cells. IgG antibodies against the peptide, purified from the patients' sera, recognised autoantigens and DEP-1/CD148 protein, bound human cochlea, and inhibited proliferation of cells expressing DEP-1/CD148. This data if confirmed could help better comprehension of Cogan syndrome and its biological diagnosis.

Complementary examinations/biological diagnosis

Some parameters can be abnormal during the course of Cogan's syndrome, particularly during attacks, but none of them constitute a specific marker of the disease.

Leukocytosis, sometimes marked, is present in 2/3 of the patients and can be accompanied by anemia and thrombocytosis. During attacks, the ESR is usually elevated, sometimes exceeding 100 mm/1st h. The ESR and the differential white blood count are even more modified when vasculitis is associated. During attacks, hyperfibrinemia is often present, as are non-specific anomalies of protein electrophoresis (more gammaglobulins and alpha2-globulins, less albumin).

Urinary sediment abnormalities, essentially hematuria and/or proteinuria, are found in a small number of patients.

Hepatic function tests are usually normal, even though angiitis, hepatitis, hepatic infarction or fibrosis with hepatocyte regeneration can be detected histologically.

An immunological work-up provides no determinant information. Diverse anomalies have been punctually observed: rheumatoid factor; antinuclear antibodies; cryoglobulins; antibodies to smooth muscle, mitochondria, perinuclear constituents, phospholipids, factor VII or neutrophil cytoplasm; or lupus anticoagulant. Low concentrations of total complement or its C3 and C4 fractions have sometimes been reported during attacks.

Immune anomalies specific to the eye or ear have been sought in a small number of patients. The following were seen: inhibition of lymphocyte migration in the presence of corneal or inner ear antigen; detection of circulating antibodies directed against a corneal antigen or inner ear constituent using an immunofluorescence assay. These abnormalities, found in small series of patients, have not been reproduced by other authors and none of them can be used, at present, to support the diagnosis of Cogan's syndrome. If the work of Lunardi et al. is confirmed this could help to develop more efficient diagnosis test.

Almost all investigations based on working hypotheses of an infectious etiology have been negative. The results of serological studies suggested the role of *Chlamydia trachomatis* but they, too, have not been confirmed by subsequent investigations.

Unresolved questions

The nosology of Cogan's syndrome remains poorly defined. The boundaries between this disease and immunological deafness or systemic diseases affecting the eye and ear remain to be established.

The etiology and mechanisms of Cogan's syndrome are unknown: the role of triggering factors - perhaps infectious - has been evoked, as have immunological reactions directed against constituents of the eye and/or inner ear.

No biological test is available at present to affirm the diagnosis of the disease.

Treatment is poorly codified: the modalities of corticotherapy and recourse to other therapeutic agents (notably immunosuppressants) in the case of corticoresistance or corticodependence merit new studies.

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