

COGAN'S SYNDROME

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Abstract

Objectives: The objective of our study was to review the current knowledge on Cogan's syndrome, including etiology, diagnosis and treatment.

Systematic review methodology: Relevant publications on Cogan's syndrome from 1945 to 2014 were studied.

Conclusions: Cogan's syndrome is a rare autoimmune vasculitis, with unknown pathogenesis. Infection was thought to have played a role in the pathogenesis of the disease, but now the autoimmunity hypothesis is considered more likely to be true.

Cogan's syndrome is characterized by ocular and audiovestibular symptoms similar to those of Meniere's syndrome. Approximately 70% of the patients have systemic disease, of which vasculitis is considered the pathological mechanism.

Corticosteroids are the first line of treatment; multiple immunosuppressive drugs were also used with varying degrees of success. The novelty in the treatment of the disease is tumor necrosis factor (TNF)-alpha-blockers, but more studies are necessary to establish their efficacy.

Keywords: Cogan's syndrome, autoimmune vasculitis, audiovestibular symptoms, Meniere's syndrome, intraocular inflammation

Introduction

Cogan's syndrome is a rare autoimmune systemic vasculitis characterized by intraocular inflammation and vestibulo-auditory dysfunction (usually neurosensory deafness, but also tinnitus and vertigo) [1].

The disease was first described in 1934 by Morgan and Baumgartner as a non syphilitic interstitial keratitis (IK) associated with vestibulo-auditory dysfunction, but it was defined as a clinical entity in 1945 by Dr. David Cogan, who reported 5 additional cases [2,3]. He described it as a “syndrome of non syphilitic

interstitial keratitis (IK) and vestibulo-auditory symptoms” that resembled Meniere's disease (sudden onset of tinnitus, nausea and vertigo, accompanied by gradual hearing loss) [2].

That disease probably existed long before being defined as a clinical syndrome, an example being the famous composer Ludwig von Beethoven [4].

In 1980, Haynes and co-authors [5] proposed the classification of Cogan's syndrome (CS) as “typical” CS (the one originally defined by Cogan) and “atypical” CS (chronic and recurrent conjunctivitis, scleritis, uveitis, optic disk edema and retinal vasculitis) [6].

The typical form of CS is characterized by: **1.** ocular involvement – non-syphilitic interstitial keratitis, sometimes associated with iritis, conjunctivitis or subconjunctival hemorrhage, **2.** audiovestibular involvement similar to Meniere's disease, progressive loss of hearing to the point of deafness within 1-2 months, **3.** an interval between the onset of ocular and audiovestibular manifestations of less than 2 years [7].

Cogan's syndrome is considered atypical if: **1.** another type of ocular involvement is present (significant inflammatory eye lesion in addition to or instead of interstitial keratitis: scleritis, episcleritis, retinal artery occlusion, choroiditis, retinal hemorrhages, papilloedema, exophthalmos); cases of conjunctivitis, iritis or subconjunctival hemorrhage without interstitial keratitis are also classified as atypical CS, **2.** typical ocular involvement is associated with audiovestibular symptoms that do not resemble Meniere's disease or arise more than 2 years before or after ocular symptoms [7,8].

Epidemiology

Cogan's syndrome is a rare disease, which primarily affects young adults; reports that establish the age of onset as ranging from 3 to 50 years have been published [9].

The average age of disease onset is 29 years. No gender predilection seems to exist in most of the literature series. In 25% of the 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 [9].

There are fewer than 250 reported cases in literature and it is mostly described in Caucasian patients of both sexes [10,11]. It is an extremely rare disease in Arabic and Middle Eastern countries; the first case in Jordan was reported in 2012 [11].

The actual number of people with Cogan's syndrome could be higher than reported. Many cases may be incorrectly diagnosed as idiopathic hearing loss/ deafness, autoimmune inner ear disease and idiopathic recurring keratitis [12].

Etiology and physiopathology

The exact cause of Cogan's syndrome remains unknown but in 20% of the cases, the

onset is preceded by an upper respiratory tract infection [7]. Several hypotheses have been suggested.

Initially it was thought to be caused by an infection. Chlamydia psittaci was isolated in a patient with Cogan's syndrome [13] and recent Chlamydia trachomatis infections were reported in 4 out of 13 patients, as well as significantly higher titres of antibodies to Chlamydia trachomatis in patients with Cogan's syndrome [5]. The responsibility of Chlamydia was not confirmed by Vollertsen et al. [14]. Other studies for an infectious agent responsible for the disease have remained negative and antibiotic therapy was not effective as a treatment [7].

Cogan's syndrome is currently believed to be an autoimmune disorder. The involvement of an immune mechanism was suggested by the detection of diverse autoantibodies, the clinical elements suggestive of collagen disease, the presence of vasculitis and polyarteritis nodosa and similarities with autoimmune deafness [7].

In 1999, Garcia Berrocal et al. [8] suggested that Cogan's syndrome was an autoimmune disease caused by a hypersensitivity response to one or more infectious agents associated with vasculitis. In their opinion, it was quite probable that a virus infection prompts an antibody response that develops a cross-immunity with proteins of the audiovestibular system, eye and other organs.

A decade ago, multiple groups detected antibodies against a corneal antigen or constituents of the inner ear [15]. Histopathological examination of corneal tissue and cochlea showed lymphocytic and plasma cell infiltration, suggesting a cell-mediated reaction. Vasculitis is considered the pathological mechanism [15]. The histopathologic manifestations appear to explain the audiovestibular dysfunction that has been reported in Cogan's syndrome, including bilateral fluctuating hearing loss, tinnitus, and severe vertigo [15,16].

Clinically, vasculitis has been reported to affect the skin, kidneys, distal coronary arteries, central nervous system, and muscles. Autopsies have revealed vasculitis in the dura, brain, gastrointestinal system, kidneys, spleen, aorta, and the coronary arteries (Crawford, 1957; Fisher and Hellstrom, 1961; Vollertsen, 1990). Pathologic examinations of the proximal portion of the aorta in patients with Cogan's syndrome

have shown generalized dilatation and narrowing of the coronary arteries in the region of the aortic valve [17].

In 2002, Lunardi et al. [18] published a study in which they used pooled Ig G immunoglobulins derived from 8 patients with Cogan's syndrome to identify disease relevant autoantigen peptides. A peptide (later named Cogan peptide) was recognized by all the patients' serum. This peptide was similar to autoantigens as SSA/ Ro and the reovirus III major core protein lambda 1. Also it showed similarities with the cell-density enhanced protein tyrosine phosphatase-1 (DEP-1/ CD 148) found in the sensory epithelia of the inner ear and on endothelial cells. The Ig G antibodies from the patient serum recognized this protein, bounded to human cochlea, inhibited proliferation of cells expressing DEP-1/ CD148 and bounded to connexin 26, which has been implicated in congenital deafness. The same study demonstrated the induction of clinical features of Cogan's disease in animals after passive transfer of peptide-specific antibodies or active immunization with autoantigen peptide. The results indicate that Cogan's syndrome is an autoimmune disease.

Bonaguri C et al. [19] published a study in 2007 that suggested anti-Hsp70 antibodies as a marker of the autoimmune origin of hearing loss. The anti-Hsp70 antibodies were present in 50% of the tested patients with Cogan's syndrome, with prevalence in patients with typical Cogan's syndrome, without a statistical confirmation.

Anti-neutrophil cytoplasmic auto-antibodies (ANCA) were recently identified in 5 patients with Cogan's syndrome, two of them also showing ANCA-related glomerulonephritis [20,21].

There are also studies that describe the presence of some antigens of the histocompatibility leukocyte antigen system in Cogan's syndrome: haplotypes A9, Bw17, Bw35 and Cw4 [22].

Rheumatoid factor, anti-nuclear antibodies and diminished complement levels were also detected in a minority of patients with Cogan's syndrome, suggesting that immune mechanisms are involved [14].

In 2014, Bonaguri C et al. published a new study [6] on 112 patients assigned in four groups: typical CS 914 patients, atypical CS (24

patients), ASNHL (idiopathic and/ or associated with systemic autoimmune disease other than CS - 55 patients) and controls (19 patients). The study confirmed a significant relationship between anti-Hsp70 antibodies and autoimmune sensorineural hearing disorders. Anti-Hsp70 antibodies were present in all but 1 patient with typical CS. The patient was the youngest in the study (8 years old). The absence of the antibodies could be explained by the uncompleted development of immunity competence.

The absence of antibodies in a patient does not exclude the diagnosis of Cogan's syndrome.

Clinical findings and diagnosis

The onset of the disease is preceded by an upper respiratory tract infection in approximately 27% of the cases, or, less common, by diarrhea, dental infection or immunization [23].

Usually, the first symptom affects either the eye (41%) or the ear (43%) alone. The interval between the involvement of the two organs varies from 1 month to 11 years (in atypical Cogan's syndrome); rarely the two organs are affected at the same time (16%) [7].

The clinical spectrum of patients with Cogan's syndrome includes ocular manifestations, vestibulo-auditory symptoms and systemic features often similar to those of polyarteritis nodosa (PAN) [7,9].

Ophthalmologic findings

The ocular involvement in Cogan's syndrome is variable; the most common is interstitial keratitis, but it can present itself in other ways too: scleritis, episcleritis, retinal vascular disease, uveitis, iritis, conjunctivitis, papilloedema, exophthalmos, tendonitis [8].

Rarely the interstitial keratitis is asymptomatic and it is discovered at an ophthalmological examination of a patient with audiovestibular symptoms [7]. The most common clinical findings are ocular redness (74%), photophobia with tearing (50%), ocular pain (50%) and transitory diminution of visual acuity (42%) [7].

Examination reveals ciliary injection with mild iritis and discrete opacities in the deep portion of the corneal stroma [15], an irregular, granular corneal infiltration, particularly in the posterior part of the cornea, near the limbus [23]. The earliest corneal findings are bilateral faint white subepithelial infiltrates similar to those found in viral keratoconjunctivitis, but located in the peripheral cornea measuring 0.5 to 1 mm in diameter [26]. Subepithelial scars or epithelial erosions may appear after the resolution of the corneal inflammation. Repetitive examinations are necessary because the episodes of inflammation are alternating with remission periods [9]. Secondary neovascularization is frequently seen. In most cases both eyes are affected, but the symptoms vary from one eye to the other and from day to day [23]. In some cases, patients presented with amaurosis or blindness [23].

Audiovestibular findings

The vestibular system is the first one affected in Cogan's syndrome. The cochlear system follows by an interval of days or weeks [24]; as a general rule, the vestibular syndrome regresses when the auditory deficit appears [7].

The audiovestibular manifestations are very similar to those of recurrent Meniere's disease: abrupt onset including vertigo, nausea, instability, vomiting and tinnitus; the vestibular manifestations are secondarily associated with progressive hearing loss, leading to deafness in a period of 1- to 3-months [15,23]. Hearing loss is sensory in nature and it is often bilateral from the onset of the disease; in some patients, it can be unilateral in the beginning and become bilateral later on [23]. The loss of hearing is severe and usually definitive [7].

Physical examination can show a degree of ataxia and spontaneous nystagmus [7].

Audiometry demonstrates sensorineural hearing loss affecting all frequencies [12]; the hearing loss is more pronounced at the extreme frequencies, with relatively sparing of the mid range [9].

Auditory evoked potentials are also reduced or absent and suggestive of sensorineural deafness and the caloric test is also absent in 70% of patients [9].

Puretone thresholds may remain stable from one examination to the next but word recognition ability may show deterioration or improvement; an initial evaluation shows sensory hearing loss with abnormal electronystagmography [25]. Cranial, mastoid and auditory canal radiographs are normal; CT and MRI with injected gadolinium can show obstruction or calcification of the semicircular canals, the vestibule or the cochlea [7].

Systemic findings

Grasland et al. [23] published a study that concluded the disease remains restricted to the ear and eye in 17/ 52 (33%) patients with typical CS and 7/ 59 (12%) patients with atypical CS.

The presence of associated symptoms is not rare: at least one more organ is involved in 2 out of 3 cases and systemic disease is observed in 1/ 3 of the patients [7].

Other studies have shown that up to 70% (63% of the cases of Yamanishi [20]) of the patients with Cogan's syndrome have underlying systemic disease in addition to ocular and audiovestibular dysfunctions. The pathological mechanism is considered to be vasculitis affecting the large and medium vessels, although few reports have a histological confirmation [2,14]. In some cases, systemic manifestations can be the only manifestation of Cogan's syndrome for a long period of time, delaying the diagnosis [23].

General symptoms can appear such as fever (up to 39°C) and weight loss (up to 10 kg) [7].

The most common symptoms are cardiovascular, neurological and gastrointestinal.

Frequent cardiac involvement in CS is aortic insufficiency, present in 15% of the cases; almost half of them require valve replacement to prevent the development of left ventricle insufficiency that can be fatal [7]. Histological examination shows that the entire aortic wall is affected, sometimes accompanied by a localized aneurismal dilation and involvement of the coronary ostia; giant and epithelioid cells and fibrinoid necrotic foci can be seen. The aortic valve's cusps can be normal or can present alteration comparable to those of the aortic wall [7]. Other cardiac lesions observed in patients with Cogan's syndrome are: coronaritis,

coronary stenosis, pericarditis, arrhythmia, mitral insufficiency, myocardial necrosis and myocarditis [7,24].

Arterial involvement in Cogan's syndrome was also studied. The lesions can be asymptomatic or they can cause abolition of the pulse, intermittent claudication of the upper or lower limbs, abdominal pain, ischemic necrosis of the hands and feet, embolic events or Raynaud's phenomenon. Arteriography can show stenosis, thrombosis or more lesions that are diffuse like an aneurismal dilation affecting the aortic root [7].

Gastrointestinal symptoms are present in about ¼ of patients. The patient can present with diarrhea, rectal bleeding or melena, abdominal pain sometimes associated with mesenteric arteritis, peptic or colonic ulcerations [7,8]. Hepatomegaly, splenomegaly and liver steatosis have been observed in some cases [7,23].

Neurologic manifestations are not specific and can vary from headaches to coma [24]. Hemiparesis or hemiplegia due to a cerebral vascular accident or aphasia do to a transient ischemic event are the most common [2]. Other rare manifestations are: cerebellar syndrome, pyramidal syndrome, epilepsy, spinal cord disease, meningeal syndrome, encephalitis, facial palsy, peripheral neuropathy [7,23].

Musculoskeletal manifestation can occur: myalgias, arthritis, arthralgias, synovitis and possibly articular effusion. Sometimes the muscle biopsies are abnormal: muscle necrosis, atrophy, morphological aspect resembling myositis [7,24].

Other systemic manifestations are rare, like cutaneous signs (erythematous or urticarial rash, vascular purpura, nodules, ulcerations), pulmonary involvement (thoracic pain, dyspnea, hemoptysis, pleurisy, cough, discrete and transient anomalies on radiological images), lymphadenopathies, mild abnormalities on urinalysis [7,8,23,24].

The possibility of systemic vasculitis must be considered and investigated at any stage of Cogan's disease. Similarities with polyarteritis nodosa have been noted in the histopathologic features of the affected vessels: prominent infiltration of large veins and muscular artery walls with lymphocytes and neutrophils; focal degeneration and fibrosis in the vessel walls have also been described [9].

Laboratory findings

There is not a specific marker for Cogan's syndrome, but some parameters can be abnormal.

Leukocytosis and elevated erythrocyte sedimentation rate (ESR), accompanied by anemia and thrombocytosis are the usual findings in patients with Cogan's syndrome. During attacks, hyperfibrinemia is often present and an elevation in the level of C reactive protein (CRP) can be observed [7,11].

Surveying for infections is usually negative, although evidence of Chlamydia infection was reported in some cases [23].

Urinary abnormalities can be present, such as hematuria and proteinuria. Test for hepatic function are usually normal. In some cases, rheumatoid factor and antinuclear antibodies were detected, as well as: cryoglobulins, antibodies to smooth muscle or lupus anticoagulant [7,23].

Antibodies directed against a corneal antigen or constituents of the inner ear have been detected in some patients [23].

None of the laboratory findings can either deny or confirm the diagnosis of Cogan's syndrome.

Differential diagnosis

There are several diseases that can be evoked as a differential diagnosis for Cogan's syndrome because of the association of ocular and audiovestibular symptoms: congenital syphilis (an exclusion criterion for Cogan's syndrome), Susac syndrome (retinocochleocerebral vasculopathy), Vogt-Koyanagi-Harada syndrome, the association of serous otitis and systemic vasculitis with episcleritis described by Sergent and Christian in 1994 (there is no inner ear involvement) and diverse systemic diseases (Wegener's granulomatosis, polyarteritis nodosa, Takayasu's arteritis temporalis) [7,12].

Vogt-Koyanagi-Harada syndrome associates audiovestibular involvement with uveitis, alopecia, poliosis and vitiligo [7]. It is an uveoencephalitis with meningitis signs, decreased visual acuity with possible blindness, sensorineural hearing loss and discoloration of hairs (poliosis) or alopecia. Meningism is

sometimes present in patients with Cogan's syndrome, but poliosis and alopecia do not occur [24].

Susac syndrome is caused by lesions of the retinal, cochlear and cerebral arterioles. It manifests as loss of visual acuity, deafness and central neurological disorders [7].

Wegener's granulomatosis frequently affects the eye and ear. Hemorrhagic lesions of the throat and nose, vasculitic changes of small vessels, glomerulonephritis, pulmonary infiltrates and the presence of ANCA are usually observed in patients suffering from Wegener's granulomatosis. Patients with Cogan's syndrome do not fulfill the diagnostic criteria for Wegener. The diagnosis is difficult in the early stages of the disease [12].

Patients who suffer from microscopic polyangiitis often have inflammatory eye involvement. The difference between CS and this disease is the presence of ANCA in 80% of the cases and the vasculitis restricted to small vessels [12].

Takayasu's arteritis is a vasculitis of unknown origin that affects young women. Visual involvement has been described, but keratitis and scleritis are very unusual symptoms [12].

Diagnosis

The diagnosis is based on the audiovestibular symptoms, the ocular inflammation and nonreactive serological tests for syphilis, combined with laboratory findings, after eliminating the differential diagnosis [8].

The physical exam should focus on the eye and ENT examinations. It should also search for adenopathies, heart or vessels murmurs, differences in pulse or blood pressure between the right and left sides. Signs of systemic involvement should be searched for in a general medical history, as well as questions regarding weight loss, fever, cutaneous anomalies, hyperesthesia, motor weakness, pain or claudication [12].

There is no specific marker to diagnose Cogan's syndrome, but screening should include ESR, a complete blood count, infectious agents and antibodies. A chest X-ray may not show abnormalities, but an MRI could show high signals in the cochlear and vestibular structures

and exclude the presence of an acoustic neurinoma [12].

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 emphasizes the need for communication between ophthalmologist, otolaryngologist and internist [9].

Treatment and outcome

Treatment depends on the extension of the disease, especially the presence of systemic vasculitis, but no treatment has proven to be spectacularly effective [7].

Interstitial keratitis may respond well to corticosteroid eye drops or local atropine, but the course of audiovestibular involvement depends on early treatment with systemic corticosteroids (1-2 mg/kg/day prednisolone) [12]. The corticoid therapy is rapidly discontinued if there is no improvement in 2 weeks; if an improvement is seen, corticosteroids have to be gradually tapered over 2-6 months [23].

No treatment has been proven to have clear-cut efficacy when the audiovestibular involvement is corticosteroid resistant [12].

If the response to therapy is incomplete, an immunosuppressive agent is added. The most used drugs are azathioprine, cyclosporine A and methotrexate, which were found to be beneficial for some patients. A cochlear implant is a good therapeutic option for patients developing deafness [12].

If the vasculitis is widespread, the treatment should be more aggressive: cytotoxic agents. A combined therapy or a step down regimen starting with cyclophosphamide and then switching to methotrexate or cyclosporine A after achieving a partial response may be a promising option [12].

A recent therapeutic option for Cogan's syndromes are the TNF-alpha blockers [2,27]. Etanercept is not effective in improving hearing loss, but it does improve word recognition [2,28]. Infliximab seems to be effective in inducing and maintaining remission in patients

with therapy resistant Cogan's syndrome [2,27]. Rituximab may help in avoiding deafness or cochlear implants in severe cases and may reduce the number of medications necessary to control the systemic manifestations of the disease, but it is not recommended as a first line therapy [2,29].

There is a rapid growing interest in a possible stem-cell based therapy for autoimmune diseases, but further studies are required to establish the efficacy and long-term safety [2,30].

The evolution of Cogan's syndrome is unpredictable. Patients with ear and eye involvement alone have a good prognosis and an average life expectancy [15]. The corneal disease may improve even without therapy, while prognosis for hearing is usually poor on the long-term, deafness being often irreversible [15,24].

Patients with serious vasculitis have a diminished life expectancy due to complications; therefore, early assessment and treatment are needed [15].

Conclusion

Cogan's syndrome is a rare presumed autoimmune disorder characterized by non-syphilitic interstitial keratitis and audiovestibular symptoms that resemble Meniere's syndrome, sometimes associated with systemic manifestations, especially cardiac complications.

The diagnosis should be suspected whenever there are ocular abnormalities closely followed or preceded by audiovestibular symptoms.

No serological marker for the disease has been found, so the diagnosis is an exclusion one.

Corticosteroids are the first line of treatment and can aid in the recovery of hearing if they are administered early in the disease course. In some cases, immunosuppressive drugs have proven to be effective. The most recent therapeutic options are TNF-alpha blockers.

Patients without systemic involvement have a good prognosis with average life expectancy, while patients with serous vasculitis have an increased risk of death due to complications.

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