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*Cogan's syndrome: linking many medical specialties*

**N. C. Galanopoulos**

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## Cogan's syndrome: linking many medical specialties

Nikolaos C. Galanopoulos

Outpatient Department of University General Hospital Evros (Alexandroupoli), Thrace, Greece

### ABSTRACT

Cogan's syndrome is a chronic inflammatory disorder that most commonly affects young adults. Clinical hallmarks are interstitial keratitis and vestibule-auditory dysfunction in combination perhaps with systemic vasculitis, and aortitis. The predominant ocular manifestation of Cogan's syndrome is interstitial keratitis (which typically causes eye redness, pain, photophobia, and blurred vision). Inner ear manifestations are included Meniere-like attacks consisting of vertigo, ataxia, nausea, vomiting, tinnitus, and hearing loss and vestibular dysfunction which can cause oscillopsia. Systemic vasculitis with large- or medium- to small-sized vessel vasculitis or aortitis is also of great significance. Systemic manifestations have been reported in < 5% of patients. Therapeutic options for the treatment of Cogan's syndrome include the use of corticosteroids (topical agents or systemic administration) and in resistant cases, immunosuppressive therapy (cyclophosphamide, cyclosporine, methotrexate, leflunomide, mycophenolate mofetil). In cases with poor response to the aforementioned treatment, the administration of Anti-TNF $\alpha$  therapy (Infliximab) or Rituximab (a monoclonal antibody inducing depletion of B lymphocytes) offered successful and rapid improvement of the manifestations of the eye, the inner ear and the cardiovascular system.

#### Corresponding author:

Nikolaos Galanopoulos, MD, PhD  
Dragana, 681 00 Alexandroupolis,  
Evros, Greece  
Tel.: +30 2551352520  
E-mail: galanopoulos@axd.forthnet.gr

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**Keywords:** Cogan's syndrome, Progressive sensorineural hearing loss, hearing loss, vestibuloauditory dysfunction, aortitis, cyclosporine, methotrexate, leflunomide, mycophenolate mofetil, anti-TNF $\alpha$  therapy, infliximab, rituximab.

## INTRODUCTION

Cogan's syndrome is a chronic inflammatory condition that manifests by attacking the eyes (most commonly, interstitial keratitis) and inner ear (progressive severe attack on hearing and vestibular function), possibly combined with involvement of other systems; the most common being the cardiovascular.<sup>1-5</sup> Cogan's syndrome usually affects young people, preferentially those who are in their thirties. The mean age of attack at the start of the syndrome is estimated at 22 years (5 to 63 years).<sup>6-8</sup> Both genders are affected the same.

## ETIOPATHOGENESIS

Infectious triggers are a probable cause of the syndrome's appearance. In around 1/4-1/3 of patients, at the onset of the syndrome, there is a time period of outbreaks that seem like viral infections.<sup>2,9-11</sup> Immunological mechanisms play a very important role in the pathogenesis of Cogan's syndrome, since autoantibodies that damage inner ear epithelial tissue and endothelial cells have been found. Lunardi et al. 2002 used IgG from 8 patients with Cogan's syndrome to control autoantigens peptides associated with it. From the peptides identified, one was recognized by the sera of all patients. This peptide was similar to the autoantigen Ro/SSA and nuclear protein L1 of reovirus type III and to the DEP-1/CD148 protein (cell-density enhanced protein tyrosine phosphatase-1), expressed in the inner ear epithelial tissue and endothelial cells. The IgG autoantibodies against that peptide from the serum of patients recognized the DEP-1/CD148 protein associated with tissue from a human cochlea, and inhibited the proliferation of cells expressing the DEP-1/CD148 protein. These autoantibodies were also associated with connexin-26 mutations of the gene, which lead to congenital deafness via damage to the inner ear. The autoantibodies also had the ability to cause outbreaks of Cogan's syndrome in mice.<sup>9</sup> Smoking may also be a trigger cause.<sup>11</sup>

## CLINICAL MANIFESTATIONS

As mentioned, in around 1/4-1/3 of patients, at the onset of the syndrome, there is a time period of outbreaks that seem like viral infections.<sup>2,9-11</sup> Systemic manifestations, such as low fever, malaise, feeling easily fatigued and weight loss, as well as symptoms such as lymphadenopathy, hepatomegaly, splenomegaly, arthralgia or arthritis, myalgia and nettle rash were reported in less than 5% of patients.<sup>4,11-13</sup> Nevertheless, the symptoms of Cogan's syndrome leading to its diagnosis and determination of therapeutic approach primarily include symptoms coming from the eyes, the inner ear and the cardiovascular system.

## I. Ocular symptoms

The foremost ophthalmic manifestation is interstitial keratitis, followed by peripheral, anterior stromal sub-epithelial keratitis.<sup>14</sup> This manifests clinically with pain, photosensitivity, redness in the eyes and blurred vision. During slit-lamp examination, a granular cornea infiltration will be seen locally and in its deepest layers. The histological examination of corneas of patients with interstitial keratitis detected infiltrations with lymphocytes and plasma cells that were located in the deepest layers.<sup>15</sup> Patients that do not receive effective treatment of the ocular infection of the syndrome may develop neovascularization and corneal clouding, affecting sight.<sup>11,16</sup> The eyes of patients with Cogan's syndrome also present conjunctivitis, episcleritis, anterior or posterior scleritis, iridocyclitis and severe retinal vasculitis.<sup>3,6,11,12,17</sup> In cases of severe posterior scleritis and/or retinal vasculitis, there is a risk of severe visual disturbances.

## II. Symptoms of attack on the inner ear

Clinically, this attack shows symptoms of vertigo, ataxia, nausea or vomiting in combination with possible reduction of hearing.<sup>13</sup> In an attack of vestibular function, oscillopsia may be observed (a sense that objects in space move forwards or backwards when the patients quickly turn their head to the side). The absence of vestibular function is often observed during caloric testing. Recurrent episodes of this attack can lead to progressive hearing loss. This reduction, which is shown in about two-thirds of patients, is likely to lead to deafness.<sup>2,3</sup> Gluth et al. report that in 60 patients with such manifestations, 73 of the 120 ears had reached deafness.<sup>11</sup> Also, this might also lead to hydrops screw with increasing endocochlear pressure to attack hearing as well.<sup>18</sup>

Temporal bone biopsies revealed infiltration by lymphocytes and plasma cells of the spiral link, degenerative changes of the organ of Corti, intralymphatic hydrops, severe bone formation in the area of the inner ear and demyelination of the cochlear and vestibular nerve, which are branches of the auditory nerve.<sup>19-21</sup>

Audiometric tests reveal sensorineural attacks, primarily relating to hearing low and high frequencies, in conjunction with poor speech discrimination. At least 30% of patients observed a  $\geq 60$  dB hearing threshold, corresponding to moderately severe hearing loss.<sup>4</sup>

At this point it should be mentioned that regarding progressive sensorineural hearing loss and vestibular dysfunction, Cogan's syndrome by some investigators is considered an autoimmune disease within the group of autoimmune diseases of the inner ear (Autoimmune Inner Ear Diseases [AIEDs]).<sup>22-26</sup> In this group are diseases that cause systemic manifestations such as rheumatoid arthritis, systemic lupus erythematosus, etc.,

diseases that attack the eyes, such as interstitial keratitis and Cogan's syndrome, and diseases with only progressive sensorineural hearing loss. About 25%-50% of patients observed vertigo and feeling of ear fullness, while 50% had symptoms of vestibular dysfunction.<sup>23</sup> Also, 15%-30% of patients reported coexistence of symptoms with autoimmune disease.<sup>23,24</sup>

### III. Symptoms from the attack of the cardiovascular system

Regarding the heart, the heart valves and coronary arteries were attacked, whilst the vessels attacked are often the largest sized, and less frequently of medium- and small-size vessels.<sup>27-39</sup> Regarding heart valves, the aortic valve is primarily affected leading to severe insufficiency of the aortic and mitral valve with the development of progressive congestive heart failure.<sup>40</sup> The histological examination of affected aortic valves found infiltration by lymphocytes, myxomatous degeneration and fibrinoid necrosis with fattening or thinning, shrinking or perforation of the aortic cusps.<sup>27-31</sup> Breach of the aorta was reported in 10% of patients, weeks or even years after the onset of the syndrome's events.<sup>2,3,13</sup> The dilatation of the proximal part, aortic valve insufficiency and the attack on the orifice of coronary arteries may lead to the development of stable angina.<sup>41</sup> The creation of aneurysms of the thoracic and abdominal aorta were also reported.<sup>27,28,33-35</sup> Samples from the aneurysmal wall of the ascending aorta revealed intense disruption with lysis of collagen and elastic fibers and strong expression of metalloproteinases-1, 2 and 9 in conjunction with granulocyte macrophage colony stimulating factor (GM-CSF).<sup>42</sup>

The involvement of large-size vessels is reminiscent of the Takayasu disease's attack, with obstructive areas causing intermittent claudication of the upper and lower sides and/or breach of the renal arteries.<sup>2,19,27-31</sup> Histologically, chronic and acute inflammatory findings were detected in the wall of the affected blood vessels.<sup>2,19,27-31</sup> The involvement of the peripheral vessels in patients with Cogan's syndrome may be asymptomatic: it is necessary to be suspected and detected.<sup>43</sup> Weyn et al. 2009 mentioned the case of a 30-year old woman with Cogan's syndrome with occlusion of the left primary branch of the coronary artery in conjunction with severe impairment of the mitral valve and reduction of the function of the left ventricle of the heart, leading to heart failure. The right vertebral, left subclavian and carotid arteries of both arteries were also attacked.<sup>44</sup> Also, Branislava et al. 2011 described a 32-year old woman with severe stenosis (75%) of the stem and the orifice of the circumflex branch of the left coronary artery combined with significant stenosis (90%) of the right femoral artery.<sup>39</sup>

A study of all 60 patients with diagnosed Cogan's syndrome at Mayo Clinic in Rochester, Minnesota during the period of 1940-2002 by Gluth et al. 2006 reported that the most common initial event was sudden hearing loss and vestibular dysfunction, whilst the most common ocular manifestation was interstitial keratitis. Arthralgia was reported in 35%, fever in 27%, headache in 40% and attack on the aorta in 12%. The rate of complete hearing loss was estimated to 52%.<sup>45</sup>

### IV. Rarer clinical manifestations

Other symptoms were reported rarely, such as of the nervous system.<sup>46,47</sup> Riku et al. 2011 reported the case of a man with headache, bilateral facial nerve palsy, episcleritis of the right eye and bilateral sensorineural hearing loss. Magnetic head scans revealed sinusitis. Testing for syphilis or vasculitis associated with ANCA antibodies was negative (by serological tests and search for ANCA antibodies, respectively). Computed tomography with injection of a contrast agent revealed the presence of thickening and narrowing of the aorta using fluorodeoxyglucose positron emission tomography. Mucosal biopsy from the sinuses of the head showed vasculitis of capillaries, arterioles and venules. Daily IV administration of 500 mg methylprednisolone for 3 consecutive days and then oral prednisone led to a decline in symptoms outside of the attack on hearing, but relapsed during the effort of reducing prednisolone dosage. Afterwards, the administration of methotrexate and prednisolone resulted in remission of symptoms.<sup>47</sup>

### COEXISTENCE OF COGAN'S SYNDROME WITH OTHER DISEASES

Cases of coexistence with inflammatory enteropathy have been reported.<sup>48-50</sup> Scharl et al. 2011 report 4 patients with inflammatory enteropathies (3 with ulcerative colitis and 1 with Crohn's disease) in immunosuppressive therapy, who developed Cogan's syndrome symptoms, such as sudden hearing loss, vertigo and inflammation of the eyes (the 3 patients, despite immunosuppressive therapy, completely lost their hearing in a few years).<sup>50</sup> A patient with Cogan's syndrome developing ANCA-associated renal vasculitis was also reported.<sup>51</sup>

### LABORATORY CHECK

There are no observed laboratory findings to contribute to the diagnosis and monitoring of Cogan's syndrome. The study of peripheral blood smears may show leukocytosis, and measurement of inflammatory markers may show increased ESR and C-reactive protein. Tests for the detection of rheumatoid factors, antinuclear antibodies, antibody C or P ANCA (antibodies against polymorphonuclear leukocyte granules) or other auto-antibodies prove negative.<sup>52-54</sup> Testing for viral or oth-

er infections such as tuberculosis, congenital syphilis, chlamydia, herpes, Epstein-Barr virus, etc. prove negative in the majority of cases. In a retrospective study by Bonaguri et al. 2007, during the four-year period from 2001-2004, 88 patients with autoimmune sensorineural hearing loss in the ENT Department of the University of Parma in Italy compared with 21 healthy controls indicated the presence of antibodies against heat-shock proteins (anti-hsp70) in 52% of the patient group, compared to 4% in the control group ( $P < 0.001$ ). In the subgroup of patients with Cogan's syndrome, it was found in 50%.<sup>54</sup> Possibly in the future, detection of these antibodies can offer to the diagnosis of Cogan's syndrome. The use of imaging techniques such as computed tomography and magnetic resonance contributes to the exclusion of other conditions with similar manifestations of the syndrome, primarily from the head as stroke or tumor or multiple sclerosis.<sup>45</sup> High-resolution MRI can differentiate between active and non-active attacks on the inner ear.<sup>55</sup> Angiography offers the distinction of breach of vessels and assesses its extent and severity.

#### DIFFERENTIAL DIAGNOSIS

Cogan's syndrome symptoms of the eyes, inner ear, cardiovascular and systemic symptoms must be differentiated from a large number of states with similar clinical manifestations.

- Regarding ocular attacks, differentiation from infection by chlamydia or herpes (plain or shingles), tuberculosis, sarcoidosis and Lyme disease.
- Regarding attack on the inner ear, differentiation from viral infections, toxic effects of drugs, multiple sclerosis, stroke, tumors and primarily from Meniere's disease.
- Regarding attack to the eyes and the inner ear, in combination or not combined with severe cardiovascular attack, differentiation from large number of diseases such as sarcoidosis, Crohn's disease, Takayasu's disease, Whipple's disease, Sjögren's syndrome, Adamantiades-Behcet's disease, ANCA-related vasculitis, rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, relapsing polychondritis, etc.

There is also a need to differentiate from subacute encephalopathy syndrome from obstructive non-vasculitic vascular disease that affects young people and occurs with sensorineural hearing attack, occlusive vascular retinal and neuropsychiatric events. On its differentiation from Meniere's disease, it must be mentioned that the vestibular attack in Cogan's syndrome is more severe and lasts longer, with a course characterized by exacerbations and remissions, and possibly, without complete remission. Also, bilateral vestibular attack in Cogan's syndrome can result in disorder and/or oscillopsia.<sup>45</sup>

#### TREATMENT

Treatment depends on the organ(s) or system(s) affected, and the severity of the infection.

#### OCULAR ATTACK

In interstitial keratitis and anterior uveitis, topical application of ophthalmic corticosteroid drops (such as acetyl prednisolone 1%) and mydriatic agents for the treatment of symptoms (pain, redness, photosensitivity) and prevention of further growth is used.<sup>18,56</sup> Improvement is expected in 3-7 days.<sup>3</sup> If there is no improvement, the possibility of infection should be investigated; the most common being chlamydia, which will require daily oral administration of doxycycline 200 mg for 2-3 weeks. It should be noted that application of topical ophthalmic corticosteroid (CS) drops is not contraindicated, because it does not lead to exacerbation of ocular attack.<sup>18,56,57</sup> If topical treatment is ineffective, after excluding the possibility of infection, oral systemic administration of CS will be required, in dosage of about 0,5 mg/kg of body weight of prednisone.<sup>58</sup> Conjunctivitis, scleritis and episcleritis are treated topically applying CS and mydriatic agents. Scleritis and episcleritis are also improved by the administration of nonsteroidal anti-inflammatory medicine.<sup>56</sup> Failure of response in scleritis will require systematic CS administration.<sup>56</sup> Posterior uveitis will require systemic administration of CS in dosage of about 1 mg / kg body weight of prednisone orally, with gradual dose reduction after positive therapeutic response. In unsatisfactory response or recurrence of ocular infection in the effort to reduce the dosage of CS, the administration of immunosuppressants would be required; such as methotrexate (15-25 mg / week orally), cyclophosphamide (2-3 mg / kg per day orally) or cyclosporine (5 mg / kg per day orally).<sup>24,56,59</sup> During remission of ocular infection for 6-9 months, we can gradually stop administration of CS and other immunosuppressive drugs in 3-4 months.<sup>59</sup> Semeraro et al. 2011 described a patient's case with Cogan's syndrome and progressive reduction of visual acuity, conjunctivitis, pain and sensitivity to light in which the slit-lamp examination revealed interstitial keratitis. The study of fundus fluorescein angiography and indocyanine showed the presence of cystoid macular edema, swelling of the optic disc and angiomatous peripheral retinal damage. Intravitreal injection of bevacizumab did not improve visual acuity or macular edema. However, the oral administration of CS led to improvement of both. Cryotherapy was successfully applied in treating angiomatous retinal damage and preventing its exudative detachment.<sup>60</sup> Inflammation of the orbit was also determined with prolapse, ecchymosis and injection of the right eye, which was successfully treated with the administration of azathioprine and CS (originally methylprednisolone IV and then 60

mg / day of prednisone orally, degressively).<sup>61</sup> Corneal clouding may require corneal transplantation. Cataract development will require surgery.<sup>16,56</sup>

### DAMAGE TO THE INNER EAR

Due to the threat of severe attack on hearing, immunosuppressive therapy with CS (prednisolone 1-2 mg / kg body weight per day orally) will be needed.<sup>3,4,56,62,63</sup> After improvement of hearing, expected in 2-3 weeks, we move to a progressive reduction of dosage while the patient is in regular audiometric testing. During worsening of hearing by reducing the dosage of CS, the patient should return to their last dose where stabilization of hearing improvement was observed. Deterioration after discontinuation of CS requires re-administering a dosage of 0,5-2 mg / kg body weight of prednisolone per day, depending on its severity. It may require long-term administration in order to maintain remission of hearing loss.<sup>18</sup> Intratympanic CS injection has also been used, with non-favorable results.<sup>64</sup> On the suspicion that hearing loss is not due to inflammation, administering diuretics may help (such as furosemide 10-20 mg / day or hydrochlorothiazide 25 mg / day orally) intending to handle cochlear hydrops.<sup>18</sup> After no response in 4-7 days, systemic administration of CS will be required.<sup>18</sup>

In poor response to systemic administration of CS or relapses during reduction of the dose or severe side effects, administration of immunosuppressants can help, such as methotrexate (15-25 mg weekly), oral cyclophosphamide (2-3 mg / kg body weight per day) and cyclosporine (5 mg / kg body weight per day) or leflunomide (20 mg) or azathioprine (1,5-2,5 mg).<sup>10,18,56,65-69</sup> Plasmapheresis may also be helpful.<sup>70</sup> Finally, in patients with severe hearing loss, unresponsive to conservative therapy, cochlear implants will be tested.<sup>11,71,72</sup>

### ATTACK ON VESTIBULAR FUNCTION

Acute attacks on vestibular function are improved by antihistamines such as meclizine hydrochloride (20-25 mg every four hours orally) or benzodiazepines such as diazepam (2-10 mg 4 times a day orally). During recurrent attack, systemic CS administration will be required as described above. In a child with Cogan's syndrome, in which remission of attacks on the eyes and vestibule / cochlea required high CS dosage (1 mg / kg body weight prednisolone orally), the administration of mycophenolate mofetil (MMF) led to maintaining the remission and discontinuation of CS.<sup>74</sup> During chronic attack of vestibular function, as in the acute attack, possibly in combination with vestibular therapy (vestibular therapy), exercise activities aimed at maximizing central nervous system compensation for vestibular dysfunction are indicated.<sup>2,10,11,74</sup>

### ATTACK ON THE CARDIOVASCULAR SYSTEM

The treatment of cardiovascular attacks depends on the severity of the infection. For vasculitis of small- and medium-sized vessels, the systematic administration of CS is required (prednisolone 1-2 mg / kg body weight per day orally), and, in unsatisfactory response or flares during reducing the dosage, administration of cyclophosphamide is required (2-3 mg / kg body weight per day orally).<sup>18,22,56</sup> In large-vessel vasculitis, systemic CS administration was tested, and in unsatisfactory response to cyclosporin administration (4 mg / kg body weight per day orally), methotrexate (15-25 mg weekly oral) or cyclophosphamide (2-3 mg / kg body weight per day orally) was tested. Severe attacks of the aortic valve and damage to the aorta wall, such as the development of aneurysms, are likely to require surgical intervention particularly when vascular attack activity has been tested by administering the appropriate pharmaceutical therapies.<sup>18,56</sup> Branislava et al. 2011 reported a case of a 32-year old female with severe (75%) stenosis of the stem and the orifice of the circumflex branch of the left coronary artery, in whom the administration of strong immunosuppressive therapy with CS and cyclophosphamide resulted in improvement, wherein one year later an aorto-coronary transplant was required.<sup>39</sup>

### TREATMENT OF SEVERE REFRACTORY EVENTS THERAPY

In patients with severe symptoms of Cogan's syndrome refractory to conventional disease modifying drugs, the administration of biological therapy with monoclonal antibodies against tumor necrosis factor-alpha (TNF- $\alpha$ ) has been tested in order to improve hearing (in conjunction with improved control audiometry) and vestibular function, decline in vertigo and tinnitus in the ears and ocular manifestations such as interstitial keratitis. The granting of this treatment allowed the discontinuation of CS administration, maintaining long-term symptom remission.<sup>75-77</sup>

- Fricker et al. 2007 report two patients with Cogan's syndrome with hearing loss and ocular attacks, that were resistant to the administration of high doses of prednisone (1 mg / kg body weight orally) and cyclophosphamide (IV in the first and 2 mg / kg body weight orally in the second) that responded well to IV administration of infliximab infusions (300 mg per month to the first patient and 300 mg in first injection, 400 mg every 8 weeks thereafter in the second). This treatment resulted in maintenance of remission, and granted reduction of dosage, and eventually cease of prednisone.<sup>75</sup>
- Ghadban et al. 2008 reported a woman's case with Cogan's syndrome with bilateral hearing loss along with dizziness and ear tinnitus. For 6 months, 750 mg cyclophosphamide IV was administered for 6 months in conjunction with methylprednisolone IV 250 mg / day for

the first 5 days. After the second cyclophosphamide IV, hearing improved. After the sixth cyclophosphamide IV, administration of azathioprine 150 mg / day orally began. However, despite this treatment, and whilst the patient was receiving dosage of 20 mg / day of prednisone orally, progressive hearing loss reappeared. Infliximab 3 mg / kg body weight (200 mg) was administered every 3 weeks, with significant improvement of hearing, after the second infusion was accompanied by an audiometric test improvement. Infusion of infliximab every 8 weeks was continued. The dosage of prednisolone was reduced to 5 mg daily. Hearing loss completely receded, whilst the audiogram remained the same.<sup>76</sup>

- Beccastrini et al. 2010 presented 3 patients with Cogan's syndrome and symptoms (auditory, vestibular function and ocular) that were resistant to administration of high-dose CS and immunosuppressive drugs (such as cyclophosphamide and methotrexate), in which the administration of infliximab infusions resulted in full remission.<sup>77</sup>

Also, the administration of Rituximab (a monoclonal antibody that binds to the molecule on the B cell surface leading to the transient applicators) has been mentioned. Orsoni et al. 2010 report the case of a female with severe bilateral sensorineural hearing loss in combination with vertigo and nausea, a year after the first acute conjunctivitis episode, interstitial keratitis and vertigo which, after the exclusion of situations implicated in interstitial keratitis, was diagnosed with Cogan's syndrome (the diagnosis was enhanced by the detection of anti-hsp70 antibodies). An IV regimen of cyclophosphamide was administered (400 mg monthly for 6 consecutive months) EM methotrexate (10 mg / m<sup>2</sup> per week), cyclosporine orally (2,5 mg / kg lean body weight daily) and prednisone (40 mg weekly), with remission of interstitial keratitis, improvement of vertigo and nausea, but no improvement in hearing loss. Adalimumab (anti-TNF therapy) was administered subcutaneously, 40 mg weekly with methotrexate and prednisone for 6 months. Hearing deteriorated, so 500 mg per week of Rituximab was administered for 4 consecutive weeks, with repetition of that scheme after 6 months, whilst administration of prednisone 10 mg every day orally continued. Improvement of hearing was observed on day 28 after the first infusion of the drug. In the twelve-month follow-up maintenance of remission of hearing loss was accompanied by the stabilization of the results of the audiometric tests.<sup>78</sup>

#### IN SUMMARY

- Cogan's syndrome is a chronic inflammatory condition that manifests itself by attacking the eyes (the most common interstitial keratitis) and inner ear (progressive insult hearing and vestibular function), combined possibly with involvement of other systems (cardiovascular being the most common).

- It affects both genders; usually young people in their thirties.
- Regarding etiopathogenesis, infectious trigger is a probable cause of the occurrence. In animal tests, viruses such as reovirus type III, the molecular mechanism imitation triggers the immune response in inner ear tissue. Patients reported response against antigenic epitopes expressed in the inner ear tissue and share homologous amino acid sequences with autoantigens Ro / SSA and nuclear protein L1 of reovirus type III.

#### CLINICAL MANIFESTATIONS

- **Systemic manifestations** such as low fever, malaise, feeling easily fatigued and weight loss in <5% of patients.
- **Ocular manifestations.** The prime ocular manifestation is interstitial keratitis. Also, conjunctivitis, episcleritis, anterior or posterior scleritis, iridocyclitis and severe retinal vasculitis have been reported.
- **Manifestations of attacks on the inner ear.** Vertigo, ataxia, nausea, retching or vomiting, combined possibly with hearing loss. Oscillopsia (a sense that the objects spatial moved forward or backward at the sudden turn of the head to the side) may be observed in breach of vestibular function. Audiometric tests will reveal attacks on sensorineural hearing in low and high frequencies in conjunction with poor speech discrimination.
- **Manifestations of attacks on the cardiovascular system.** The heart valves (primarily aortic), the coronary arteries and the vessels, often of large size (reminiscent of Takayasu disease attack, with obstructive areas causing intermittent claudication of upper and lower sides and/or breach of the renal arteries), and less often, medium and small vessels are attacked.
- Cases of coexistence with inflammatory bowel syndromes have been reported.

#### Laboratory check:

- No characteristic laboratory findings that offer to the diagnosis and monitoring of evolution of Cogan's syndrome have been observed.
- There is usually an increase of ESR and C-reactive protein.
- Testing for autoantibodies and infections are most commonly negative.

#### Differential diagnosis:

- Regarding ocular attacks from infection by chlamydia or herpes (plain or shingles), tuberculosis, sarcoidosis and Lyme disease.
- Regarding inner ear attacks from viral infections, toxic effects of drugs, multiple sclerosis, stroke, tumors and primarily from Meniere's disease.

- Regarding ocular and inner ear attacks, in conjunction or not in conjunction with severe cardiovascular attacks by a large number of diseases such as sarcoidosis, Crohn's disease, Takayasu's disease, Whipple's disease, Sjögren's syndrome, Adamiadis-Behcet's disease, ANCA-related vasculitis, rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, relapsing polychondritis, etc.

**Treatment:** Treatment depends on the organ(s) or system(s) affected and the severity of the infection.

- Use of corticosteroids topically or systemically. In unsatisfactory response or relapses during efforts to reduce dosage, administration of immunosuppressants such as methotrexate, cyclosporine, cyclophosphamide, leflunomide, or mycophenolate mofetil.
- In patients with severe attack of hearing and unresponsive to conservative treatment, placement of cochlear implants will be tested.
- In patients with severe manifestations of Cogan's syndrome who cannot take the aforementioned immunosuppressants, or where symptoms do not go away with the above immunosuppressive therapy, the administration of biological therapy with monoclonal antibodies against tumor necrosis factor-alpha (TNF-alpha) has been tested with very quick and satisfactory improvements in hearing loss (in combination with improved audiometric tests), vestibular function, vertigo and tinnitus in the ears and ocular manifestations such as interstitial keratitis. This allowed discontinuation of CS administration, whilst maintaining long-term remission of symptoms.
- Satisfactory results with the administration of Rituximab have also been reported.

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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