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Authors' Affiliation:
[1]Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
[2]MEDIQ Clinic, Józefa Piłsudskiego 20, 05-120 Legionowo, Poland
[3]Foundation Health Dentistry in Warsaw, Wilhelma Roentgena 23, 02-781 Warsaw, Poland

[*]**Corresponding Author**
Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
Email: natalia_paduszynska@onet.eu

Contact List

Natalia Paduszyńska	natalia_paduszynska@onet.eu
Anna Dąbrowska	annaalicjadabrowska06@gmail.com
Adrian Kruszewski	adrkru7@gmail.com
Barbara Wawrzyńska	b.konerberger@gmail.com
Kacper Kwiliński	kacperkwilinski@wp.pl

ORCID List

Natalia Paduszyńska	0000-0001-9953-662X
Anna Dąbrowska	0009-0003-2289-5909
Adrian Kruszewski	0009-0003-6077-4948
Barbara Wawrzyńska	0009-0006-7504-304X
Kacper Kwiliński	0009-0001-6235-6155

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Deciphering Cogan's syndrome – unraveling the complexities of autoimmune ocular and vestibular inflammation

Natalia Paduszyńska[1*], Anna Dąbrowska[1], Adrian Kruszewski[1], Barbara Wawrzyńska[2], Kacper Kwiliński[3]

ABSTRACT

Cogan's syndrome is an uncommon disorder marked by an inflammatory process that affects the eyes, inner ears, and systemic vasculitis. The complications of the disease can be severe, in extreme cases leading to loss of vision or hearing. The disease may probably have an immunological basis, but the exact cause remains unidentified. The clinical appearance includes ocular, audiovestibular, and general symptoms. Detection could be demanding and delayed due to the rare occurrence of this condition and the analogy of symptoms of other diseases. Therefore, clinicians should exclude different abnormalities before making the final diagnosis. The treatment focuses on limiting the inflammatory process and preventing complications. However, glucocorticoids remain the first-line choice. The prognosis varies and depends on the detection time and appropriate therapy implementation. Some patients may achieve remission, but the other may develop chronic symptoms. Because Cogan syndrome is a sparse condition, knowledge about it may be limited. This article aims to change this state. In this paper, we provide an overview of the pathophysiology, clinical manifestations, and diagnostic options. Moreover, we highlight the differences between typical and atypical forms, analyze the utility of therapeutic strategies, and indicate possible research directions.

Keywords: Cogan's syndrome, vasculitis, etiology, diagnosis, treatment

1. INTRODUCTION

Cogan's syndrome (CS) was first identified by Morgan and Baumgartner in 1934 and later defined by an ophthalmologist David G. Cogan in 1945. The initial description of the condition involved non-syphilitic interstitial keratitis (IK) combined with vestibulocochlear symptoms that resemble those of Ménière's disease (MD) – tinnitus, vertigo and progressive hearing loss (Andres et al., 2021).

Considering the differences in clinical appearance and the time of symptoms onset, two forms of CS are distinguished (Iliescu et al., 2015). The typical form is consistent with this proposed by Cogan, and the time between ocular and audiovestibular symptoms development is less than two years. In turn, CS is atypical if different ocular abnormalities, including inflammatory lesions, occur alongside or instead of IK. Then, audiovestibular signs are not similar to MD, and the interval of symptoms onset is more than two years (Iliescu et al., 2015).

However, in addition to the clinical presentation mentioned above, general symptoms may also occur in CS, especially since vasculitis is present, which can affect any vessel. The etiology is still not fully understood. Nevertheless, the antibodies or rheumatoid factor in the patient's serum suggests an immunological background to this condition (Espinoza and Prost, 2015). There are still so many unknowns about Cogan's syndrome, so further research is necessary to understand better its processes underlying it, implement appropriate diagnostics, and apply therapy as early as possible to enhance the patient's quality of life and minimize potential complications. The article aims to offer a thorough review of the current understanding of pathophysiology, clinical manifestations, immunological aspects, and associated antibodies. Our objective is to discuss the effectiveness of various treatment methods, explore potential complications, and suggest future research directions to improve the management of patients with CS.

2. METHODOLOGY

The paper analyzes the literature in PubMed, Google Scholar, and SCOPUS scientific databases for 1997-2024 using the phrases "Cogan's syndrome", "etiology", "pathogenesis", "diagnosis", "treatment", "biological drugs", "prognosis", "vasculitis", "interstitial keratitis", "autoimmune inner ear disease". The inclusion criteria were determined by the relevance to the topic and the presence of specific keywords. Publications that did not fall within the mentioned date range were rejected. We exclusively analyzed papers written in English. Finally, our publication contains 53 articles.

3. RESULTS AND DISCUSSION

Epidemiology

CS is an uncommon condition, with approximately 300 identified cases so far. However, clinicians should consider the possibility of underdiagnosis due to non-specific symptoms that complicate the diagnosis. The disease mainly impacts Caucasian young adults in their second and third decades, with an average age of about 30 years (Espinoza et al., 2020). However, different age onset is also possible, and the range may vary between 5 and 65 years (Grasland et al., 2004). The incidence is similar in both women and men, though some studies indicate that men are more likely to present with the atypical form and an earlier age of onset (Espinoza et al., 2020). Among smokers, the prevalence may be higher (Gluth et al., 2006).

Etiology

The disease's underlying cause remains unclear. However, researchers assume that an ongoing inflammatory process in the body may underlie CS. Severe cases have been described where a respiratory, gastrointestinal, or oral infection occurred before the syndrome (Haynes et al., 1980; Vollertsen, 1990). Experts have proposed several hypotheses about the disease's etiology. Initially, the cause of the syndrome was associated with Chlamydia infection. This assumption arose from studies of CS patients where researchers either isolated Chlamydia psittaci Darougar et al., (1978) or observed elevated levels of serum antibodies against Chlamydia trachomatis Hayneset al., (1980) or Chlamydia pneumoniae (Ljungström et al., 1997).

However, further studies did not confirm these suspicions (Vollertsen, 1990). The studies investigated the potential correlation of Borrelia species in the induction of CS, but they found no association (Van-Doornum et al., 2001). Moreover, the relationship between viruses and disease development was sought (Gluthet al., 2006; Grasland et al., 2004). Nevertheless, to date, no single infectious factor directly correlated to CS has been identified.

Pathogenesis

Currently, this syndrome is recognized as resulting from an autoimmune process. The identification of autoantibodies, clinical features indicative of collagen disease, the occurrence of vasculitis and polyarteritis nodosa during CS, and its similarities to autoimmune deafness all support this theory (Vinceneux, 2005). Autoantibodies detected in the patient's serum could target antigens in the cornea,

inner ear, or endothelium. A particularly significant antigen is the Cogan peptide, which has homologous fragments with cell-density enhanced protein tyrosine phosphatase-1 DEP1/CD148 and Connexin 26 (Lunardi et al., 2002). It is worth noting, that Connexin 26 mutations are responsible for congenital inner ear deafness. Research on animal models has demonstrated that these antibodies are critical for inducing autoimmunity, causing hearing loss, interstitial keratitis, and neurological symptoms in patients with CS, due to these antigens on nerve and glial cells (D'Aguanno et al., 2017).

An interesting phenomenon related to CS is the mechanism of molecular mimicry. Because of its structural similarity, the major core protein lambda of Reovirus III acts as an antigen that triggers a cross-reaction with self-peptides, leading to the activation of autoreactive cells (Salman and Tripathy, 2024). The Cogan peptide resembles several other autoantigens including SSA/Ro, laminin, and calcineurin (Kessel et al., 2014). The studies revealed that several factors could trigger the hypersensitive response that leads to autoimmunity against the ocular and inner ear structures, including infection, vaccination, injection of a foreign protein, exposure to toxic substances, pregnancy, and periodontal abscess (Tayer-Shifman et al., 2014).

Examination of sera from patients suffering from CS allowed the isolation of anti-neutrophil cytoplasmatic autoantibodies – ANCA (myeloperoxidase-anti-neutrophil cytoplasmic auto-antibodies and anti-human leukocyte elastase-ANCA), anti-nuclear antibodies (ANA) rheumatoid factor – RF, and revealed reduced level of complement proteins. Researchers suspect that the presence of ANCA could be related to glomerulonephritis and the development of necrotizing vasculitis of small vessels in the course of Cogan's syndrome Greco et al., (2013), Lepse et al., (2011), especially because they also appear in other systemic vasculitides such as Wegener's granulomatosis, Churg-Strauss syndrome, or polyarteritis nodosa (Greco et al., 2013).

The conducted research also proved that antibodies against heat shock protein anti-Hsp70 are associated with autoimmune sensorineural hearing loss (ASNHL) and serve as markers of the typical form of CS (Bonaguri et al., 2014). Nevertheless, the levels of antibodies do not correlate with disease activity and their absence does not exclude CS (Iliescu et al., 2015). In addition to the immunological mechanisms involving the humoral response, researchers propose that the cell-mediated response also participates in the disease pathogenesis. The activation of lymphocytes after contact with specific antigens of the cornea and inner ear, combined with a deficiency in naive cytotoxic T cells in patients with hearing loss, provides evidence for this (Greco et al., 2013).

Clinical manifestation

Clinicians categorize the symptoms of Cogan's syndrome into three groups: ocular, audiovestibular, and systemic. The primary ocular characteristic of CS is interstitial keratitis, which results in eye redness, photophobia, or blurred vision, and very rarely may be asymptomatic. Usually, IK is a bilateral process, but its occurrence is unnecessary for diagnosis. The deterioration of visual acuity is temporary, but there are also cases of amaurosis or blindness. In atypical form, the inflammatory process affecting the other ocular structures is predominant, and it is possible to occur iridocyclitis, conjunctivitis, episcleritis, anterior or posterior uveitis, or retinal vasculitis. Among the less common disorders occur acute angle closure glaucoma, papillitis, central vein occlusion, vasculitic optic neuropathy, and papilledema (Tayer-Shifman et al., 2014; Vinceneux, 2005).

The typical presentation of inner ear involvement resembles Ménière's disease with vertigo, nausea, vomiting, tinnitus, and hearing loss. Most often, vestibular symptoms precede hearing deficit. Sensorineural hearing loss, which affects about half of patients, is detected with audiometry, which indicates dysfunction regarding low and high frequencies. In turn, the clinical examination reveals spontaneous nystagmus and ataxia. Typically, the auditory abnormalities impact both ears, progress rapidly, and can lead to complete deafness within hours or days. Complete reversal of these changes is rare, particularly without treatment (Murphy et al., 2009; Vinceneux, 2005). Analyzing the occurrence and timing of symptoms allows for the classification of the disease into the appropriate group according to current classification standards (Table 1).

Cogan's syndrome is a multi-organ condition. Depending on the systems and organs involved, the symptoms are diverse. Systemic manifestations resulting from underlying vasculitis occur in 15 to 21% of patients with CS. Abnormalities originating from the cardiovascular, neurological, and gastrointestinal systems concern even 70% of these patients (Espinoza and Liu, 2019). Among constitutional features are fever, fatigue, weight loss, or headache (Wang et al., 2023). The involvement of the cardiovascular system is the most common and results in aortitis, and aortic insufficiency, which could contribute to left ventricle hypertrophy, and sometimes it may be necessary valve replacement (Kaya et al., 2015). Vasculitis could contribute to aneurysm development (Saiin et al., 2022). Arrhythmias and even myocardial infarction can also occur (Beltagy et al., 2019).

Table 1 Classification of Cogan's syndrome

	Typical Cogan's syndrome	**Atypical Cogan's syndrome**
Ocular symptoms	Non-syphilitic interstitial keratitis	Other abnormalities (including ocular inflammatory lesions) besides or instead of interstitial keratitis
Audiovestibular symptoms	Mimic Meniere's disease	Not mimic Meniere's disease
The interval between ocular and audiovestibular symptoms onset	< two years	> two years

Inflammatory processes may affect the myocardium, pericardium, or aortic branches. This results in ischemic changes in distal organs and the limbs (Mohseni, 2022). Musculoskeletal involvement manifests as arthritis, synovitis, myositis, polyarthralgia, or myalgia. Gastrointestinal symptoms include diarrhea, melena or rectal bleeding, and abdominal pain. Sometimes, physical examination may reveal hepato- or splenomegaly (Vinceneux, 2005). Neurological signs are primarily caused by the impact on the central nervous system rather than the peripheral nervous system. Therefore, it is observed more often in hemiparesia, hemiplegia, cerebellar syndrome, aphasia, spinal cord disease, epilepsy, meningeal syndrome, or encephalitis. The evidence of peripheral system involvement includes reflexes abolition, paresthesis, trigeminal neuralgia, facial palsy, and polyneuritis (Antonios and Silliman, 2012).

Furthermore, non-specific symptoms may be present, such as headache, and also coma, psychosis, convulsions, and even ischemic stroke (Rolon et al., 2022). Mucocutaneous lesions appear mainly due to disease exacerbations, which are diagnosed as skin rashes, vitiligo, nodules, and ulcerations of limbs, genital organs, and oral cavity. Vascular purpura, auricular, or nasal chondritis also could occur. Pulmonary involvement includes symptoms like cough, dyspnea, hemoptysis, or interstitial pneumopathy (Vinceneux, 2005). The urinary symptoms encompass glomerulonephritis, proteinuria, microscopic hematuria, or renal artery stenosis.

Lymphadenopathy, hypo- or hyperthyroidism, and febrile parotiditis can also be detected in the course of CS (Vinceneux, 2005). Immunological disorders in CS patients and the effects of the treatment lead to a predisposition for developing additional autoimmune diseases. It concerns sarcoidosis, Takayasu's arteritis, polyarteritis nodosa, relapsing polychondritis and spondyloarthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), rheumatoid arthritis, renal amyloidosis with monoclonal gammopathy, inflammatory bowel disease (Crohn's disease), tubulointerstitial nephritis and uveitis (TINU syndrome) (Espinoza et al., 2020).

Diagnosis

Detection of CS is demanding due to gradual and progressive symptomatology and the absence of definitive laboratory tests or diagnostic consensus. Generally, the disease confirmation process consists of clinical evaluation regarding audiovestibular symptoms and ocular inflammation, but also negative syphilis serological tests, exclusion of alternative causes of inflammation and infection, histological vasculitis, and satisfactory response to glucocorticoid treatment (Ma et al., 2019; Zhou et al., 2021). Laboratory tests reveal abnormalities typical for acute phase response, especially during exacerbations, such as increased erythrocyte sedimentation rate (ESR), level of C-reactive protein (CRP), and interleukin-6 (Il-6).

Moreover, anemia, eosinophilia, leucocytosis, or thrombocytosis may occur (Rücklová et al., 2023). Protein electrophoresis presents increased gammaglobulins and alpha2-globulins. To verify the immunological disorders associated with CS, serum tests are conducted. These tests can detect various antibodies in some patients, including ANA, ANCA, RF, cryoglobulins, lupus anticoagulants, antibodies to smooth muscle, mitochondria, phospholipids, inner ear, or corneal antigen (Shamriz et al., 2018). To observe the symptoms that meet the disease classification criteria, an eye examination with a slit lamp and audiograms (sometimes with caloric tests) are obligatory.

However, to assess systemic involvement, it is obvious to conduct additional tests, including urinalysis, serum electrolytes, creatinine, and hepatic transaminases (Lee et al., 2019). Echocardiography allows for the assessment of valvular defects, while angiography is performed when suspected ischemic heart disease (Wang et al., 2023). Imaging studies usually do not deviate from the norm, but sometimes the use of MRI with gadolinium contrast may be effective in detecting the pathology of the cochlea and the vestibular labyrinth in the form of its obliteration by soft tissue or calcification (D'Aguanno et al., 2017). In turn, positron emission

tomography with 2-deoxy-2-[18F]fluoro-D-glucose (PET/CT) may be useful in the evaluation of large vessel vasculitis (Orsal et al., 2014).

Differential diagnosis

Before making a final diagnosis, it is necessary to exclude also other diseases, apart from syphilis, whose clinical appearance includes the coincidence of ocular structures and inner ear inflammation, such as Menière disease, Lyme disease, sarcoidosis, tuberculosis, polyarteritis nodosa, granulomatosis with polyangiitis and Takayasu arteritis. In addition, the differentiation process may also contain rheumatoid arthritis, systemic lupus erythematosus, Behçet's disease, Sjögren syndrome, Behçet disease, Vogt-Koyanagi-Harada syndrome, Susac syndrome (Vinceneux, 2005).

Treatment

Cogan's syndrome therapy is sophisticated because specialists have not yet developed a transparent treatment protocol. The first-line drugs in CS remain systemic glucocorticoids. Their impact on ocular, visceral symptoms, and vasculitis is relatively high, while auditory symptoms respond less effectively to these drugs, especially once to these drugs, especially once deafness has already developed (Vinceneux, 2005). For mild ocular involvement of the disease, doctors recommend using topical corticoids along with atropine as a cycloplegic (Lou et al., 2023). In cases with more severe eye involvement, systemic issues, or hearing loss, doctors implement systemic treatment. The typical dosage is 1-1,5 mg/kg/day of prednisone, and the improvement in symptoms is noticeable within 2-3 weeks. The most excellent chance of successfully combating hearing loss occurs when the therapy begins within two weeks of the onset of the abnormality (Espinoza et al., 2020).

However, studies have shown that the most optimal duration of GCS monotherapy is three weeks. Beyond this limit, the risk of adverse effects increases, and the ability to control disease with low maintenance doses decreases (Mora et al., 2017). When the patient is steroid non-responsive or steroid-dependent, and when contraindications for steroids occur, then second-line treatment is chosen, which contains immunosuppressive agents such as methotrexate, cyclophosphamide, azathioprine, or cyclosporin A, which belong to conventional disease-modifying antirheumatic drugs (DMARD). And the other available option is a biologic drug – infliximab. Methotrexate, cyclophosphamide, and cyclosporine reveal effectiveness in medium and large-vessel vasculitis (Bhandari et al., 2019). Infliximab, a promising biological agent for first-line therapy in severe cases, is a monoclonal antibody targeting tumor necrosis factor-alpha (TNFα) due to the reported increase in this cytokine in CS.

This drug is indicated especially in advanced CS stages with bilateral hearing loss, inflammation of ocular structures, and systemic involvement (Shamriz et al., 2018). According to the research, infliximab revealed even greater efficiency in the context of audiovestibular response than steroids and DMARD (Durtette et al., 2017). It is also worth mentioning supportive therapies consisting of hearing aids and implants. Surgical intervention in the form of cochlear implantation is a hopeful method for patients who do not respond to treatment, with poor prognosis and considerably advanced disease (Bacciu et al., 2015). The evaluation of speech reception threshold and maximum intelligibility among patients with implanted devices revealed significant improvement (Boumghit et al., 2023). Below is a summary of the therapeutics used in CS patients (Table 2).

Table 2 Drugs implemented in Cogan's syndrome therapy

First-line treatment	Glucocorticoids (prednisone)
	Infliximab (sometimes as first-line)
Second-line treatment	Methotrexate
	Cyclophosphamide
	Azathioprine
	Cyclosporin A

Future perspectives

Biological drugs are promising approaches for patients and constitute an element of targeted therapy (Table 3). These agents target specific molecules participating in immunological processes or cytokines involved in inflammation (Padoan et al., 2019).

Table 3 Biological drugs with possible therapeutic potential in Cogan's syndrome

Name of the molecule	Target
Etanercept	TNFα
Certolizumab pegol	TNFα
Tocilizumab	Il-6
Tofacitinib	JAK1 and JAK3
Rituximab	CD20

Etanercept is a fusion protein and antagonist of TNFα. An open-label prospective pilot study assessed the effectiveness of etanercept in treating 23 patients with immune-mediated cochleovestibular disorders (IMCVDs). Hearing improved in 7 cases, remained the same in 13, and worsened in 3 (Matteson et al., 2005). Certilizumab pegol is a TNFα inhibitor with an anti-inflammatory effect. A case study Venhoff et al., (2020) positively evaluated its effectiveness among pregnant women. Tocilizumab is a monoclonal antibody that targets the interleukin-6 receptor. Some case reports indicate that administering tocilizumab has been effective in alleviating symptoms and inflammation, especially in cases of large vessel vasculitis (Hara et al., 2022; Higashida-Konishi et al., 2023; Shibuya et al., 2013). Tofacitinib is a selective kinase JAK 1 and JAK3 inhibitor.

The mechanism of that molecule combats the inflammatory process in vasculitis by blocking memory cells and cellular angiogenic pathways. A pilot study indicated that tofacitinib is effective in ANCA-associated vasculitis (Liu et al., 2021). Rituximab is a monoclonal antibody targeted to cluster of differentiation CD20 antigens present on B cells, which contribute to depletion of these cells and reduced antibody production. Improvement in hearing function was noticed in 5 among 7 patients in a pilot study of rituximab in immune-mediated inner ear disease (IMED) (Cohen et al., 2011). A case report showed similar results, where rituximab improved auditory parameters and enabled a reduction of the immunosuppressive treatment (Orsoni et al., 2010). The support for the effectiveness of biological therapy derives from limited scientific evidence, highlighting the need for more research and randomized trials to develop targeted treatments and improve patient care and quality of life.

Prognosis

The disease usually progresses with periods of exacerbations and remissions. Referring to the course of the disease, Gluth et al., (2006) revealed that multiple relapses occurred in 62% of patients, a single relapse occurred in 13% of patients, in 22% no recurrences were reported, and in 3% there was no remission. The prognosis primarily depends on permanent hearing loss and the occurrence of systemic problems. The estimated mortality rate among patients with CS is 10% and is a result of the cardiovascular consequences and vasculitis. The inflammatory process can impact various vessels and becomes particularly dangerous when it involves medium and large vessels that supply vital organs. This condition, in addition to deafness and blindness, may also result in myocardial infarction or ruptures of aneurysms. The other, less common complications include renal issues, gastrointestinal bleeding, cerebrovascular accidents, and subarachnoid hemorrhage (Hedin et al., 2016; Sevgi et al., 2016).

4. CONCLUSIONS

Cogan syndrome remains a challenging condition due to its variable onset, lack of specific diagnostic tests, and broad spectrum of clinical manifestations. Despite being rare, this autoimmune vasculitis can lead to significant morbidity, primarily through its impact on ocular and auditory functions. Timely identification and swift treatment are vital to avoid permanent damage, such as irreversible hearing loss and severe ocular complications. The current management standard includes using corticosteroids, particularly during the acute phase, but their long-term use is limited due to potential toxicity. For patients unresponsive to steroids or those with contraindications, alternative treatments like infliximab and other immunosuppressive agents have shown promise. Emerging therapies, such as tofacitinib, offer potential benefits and warrant further investigation. There is a clear need for more robust clinical trials to establish standardized treatment protocols and improve outcomes.

Author's Contribution

Natalia Paduszyńska: Conceptualization, writing- rough preparation, methodology, investigation

Anna Dąbrowska: Conceptualization, methodology, data curation, supervision
Adrian Kruszewski: Formal analysis, supervision, writing-review and editing
Barbara Wawrzyńska: Writing-rough preparation, investigation, data curation, visualization
Kacper Kwiliński: Formal analysis, writing-review and editing, methodology

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Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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