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AUTOIMMUNITY (T TARRANT, SECTION EDITOR)

Cogan's Syndrome: Clinical Presentations and Update on Treatment

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Abstract

Purpose of Review Cogan's syndrome (CS) is a rare systemic vasculitis that can severely affect vision and hearing, which may also have significant systemic effects. Early recognition of this autoimmune disorder and intervention can minimize disabling and irreversible damage.

Recent Findings This article will review the varying clinical presentations of CS and emerging information of systemic disease associated with CS. We will also review recently published promising treatment outcomes using immune modulating medications.

Summary As our framework for recognizing the markers of CS and the associated systemic disorders expands, more effective guidelines and treatment options may emerge.

Keywords Cogan's syndrome · Autoimmune disease · Hearing loss · Vasculitis · Infliximab

Introduction

Cogan's Syndrome (CS) is a rare clinical disease that has been classified as a primary variable vessel vasculitis with systemic involvement in up to 80% of patients. There are now just over 300 cases of CS reported in the literature, although this is likely an underrepresentation of the true impact of this disease as it can easily go undiagnosed. CS may be seen at any age, but most frequently affects young adults in their 3rd or 4th decade of life [1–3, 4••]. Prevalence appears to be similar in women and men, though some have found that atypical presentation and early onset CS may predominate in males [4••, 5••]. The pathogenesis and etiology of CS are not yet understood, although it has been widely accepted to be an autoimmune disease due to the discovery of autoantibodies to inner ear antigens and corneal structures, as well as the clinical response to immunosuppression.

Our aim is to familiarize physicians with the latest literature regarding clinical presentations and medical management of CS to help ensure that patients receive effective and timely care.

Clinical Presentations of Cogan's Syndrome

CS was initially described in the literature in 1934 by Morgan and Baumgartner as a patient with Meniere's syndrome and interstitial keratitis [6]. CS is the namesake of ophthalmologist Dr. David G. Cogan who presented a series of 4 patients in 1945 with vestibuloauditory symptoms and non-syphilitic interstitial keratitis [7]. CS has been categorized into two groups based on onset of symptoms: Typical CS is diagnosed when ocular and vestibuloauditory symptoms arise within 2 years of each other, and atypical CS is diagnosed when there is a delay of more than 2 years between ocular and vestibuloauditory symptoms [1]. There is no single test available to confirm the diagnosis of this chronic disease, so understanding the constellation of symptoms that indicate the presence of CS is critical in making the diagnosis. The most recent large review of CS included 62 cases and revealed that the median time from the onset of symptoms to diagnosis was 12 months, with 98% of patients experiencing vestibulo-auditory symptoms,

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92% experiencing ocular symptoms, and 68% showing systemic symptoms at the time of diagnosis [5••]. The presence of scleritis and systemic disease has been found to be more predominant in the atypical form, although my experience has been that patients that present as the typical CS may later develop the hallmarks of atypical CS over time.

Vestibuloauditory Symptoms

Patients typically present with sudden onset tinnitus and vertigo that cause nausea, vomiting, ataxia, and nystagmus. The acute onset of symptoms often resolve after a few days but is followed by progressive sensorineural hearing loss in one or both ears. CS is categorized as an autoimmune inner ear disease (AIED) based on the discoveries that treatment with immunosuppressive agents is effective and that autoantibodies against the inner ear and endothelial antigens have been discovered [8–10]. The histopathology of the inner ear in patients with CS has revealed that damage occurs to the auditory and vestibular neuroepithelium, with associated endolymphatic hydrops, fibrosis, and labyrinthitis ossificans [11]. Symptoms of endolymphatic hydrops may present as fullness or a pressure sensation in the ear in addition to tinnitus and decreased hearing. Jung et al. reported an acute case of typical CS that provided evidence of direct small vessel vasculitis in the cochlea and vestibular system as a mechanism for the damage caused by this disease [11].

Computed tomography (CT) scans and magnetic resonance imaging (MRI) may be normal but can pick up labyrinthitis, inflammation, or calcification of the semicircular canals, the vestibule, or the cochlea (Fig. 1a). The vestibular symptoms will usually regress as the hearing loss appears. Durtette et al. found that at the time of CS diagnosis, 21% of patients already had unilateral deafness and 31% of patients had bilateral deafness [5••]. The progression to severe sensorineural hearing loss in CS can occur in approximately 50–90% of patients with or without treatment [1–3, 12, 13]. Testing for sensorineural hearing loss includes audiometric assays that will typically affect both low and high range frequencies (Fig. 1b).

Ocular Symptoms

The most common ophthalmic finding is interstitial keratitis. This can present with eye redness, light sensitivity, eye discomfort, and blurred vision. Slit lamp examination must be performed to confirm the presence of the corneal infiltrate. The most common causes for interstitial keratitis are infectious and include syphilis, herpes, chlamydia, tuberculosis, rubeola, mumps, Lyme disease, and parasitic entities. These etiologies would be ruled out based on the history and directed laboratory testing, and they typically will not cause the vestibular symptoms experienced in CS. Other periocular findings have been reported including conjunctivitis, tearing, ciliary flush, uveitis, episcleritis, scleritis, optic neuritis, papilledema, glaucoma, choroiditis, orbital inflammation,

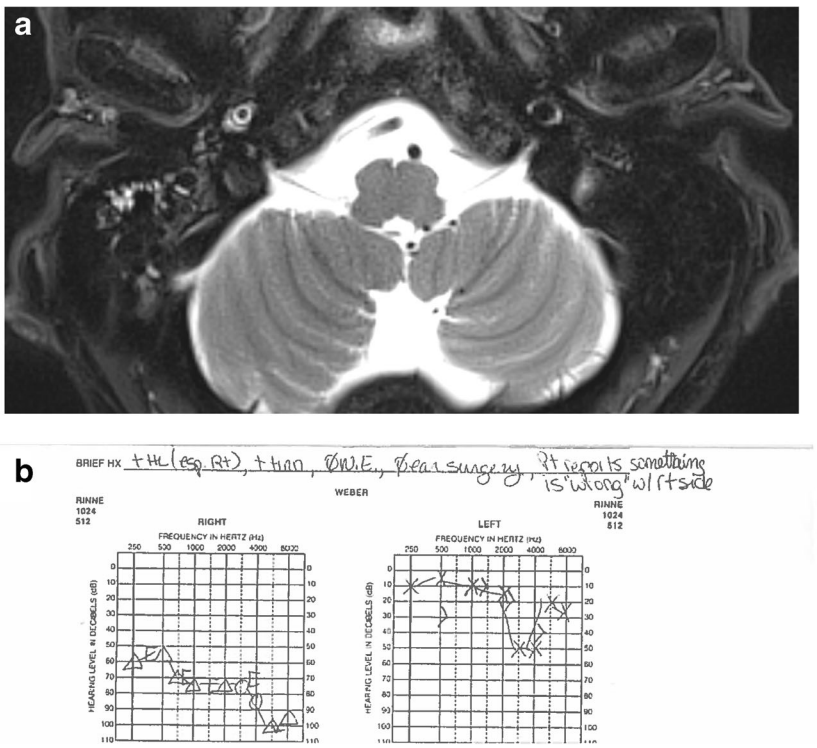

Fig. 1 **a** MRI scan axial fat-saturated T2 weighted image showing acute mastoiditis and labrynthitis in a patient with typical Cogan's syndrome. **b** Audiometric hearing test in the same patient showing moderately severe to profound sensorineural hearing loss on the right side more than the left

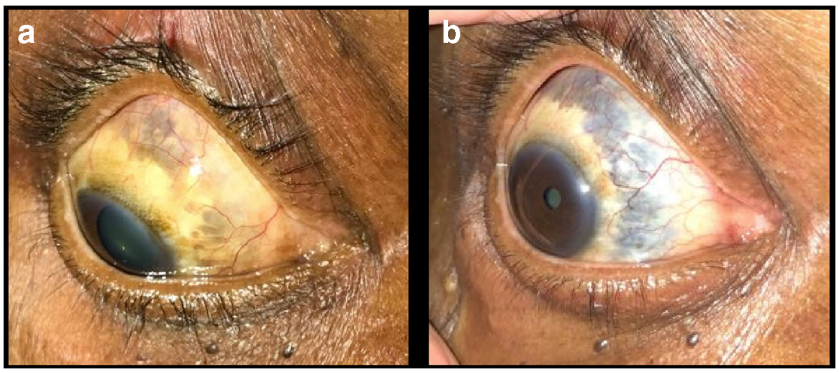

Fig. 2 **a** Scleral thinning 4 years after initial typical CS diagnosis from intermittent bouts of scleritis. **b** Scleral thinning progression 6 years after initial typical CS diagnosis despite ongoing immunosuppressive therapy

central vein occlusion, and retinal vasculitis [1–3, 12, 14, 15].

Uveitis, episcleritis, and scleritis will often present similarly to interstitial keratitis with eye pain, redness, light sensitivity, and blurred vision. Vision loss is more pronounced in cases with posterior inflammation such as optic neuritis and vasculitis, but the second most common presentation of ocular inflammation in CS is scleritis/episcleritis. Chronic scleritis can occur despite treatment and will notably cause thinning of the sclera, which causes a bluish hue to the eye (Fig. 2).

Systemic Symptoms

Systemic disease affects approximately 80% of patients. Durtette et al. reported a 68% presence of systemic symptoms at time of CS diagnosis with the majority of patients exhibiting constitutional symptoms of fever or weight loss and half of the patients experiencing arthromyalgias [5••]. Other commonly reported symptoms include fatigue, arthritis, abdominal pain, headaches, and skin rash, though reporting bias limits our understanding of the prevalence of these symptoms [12]. Aortitis is the most common systemic vasculitis that presents in approximately 10% of CS patients. Aortitis can produce the nonspecific constitutional symptoms noted above but may additionally cause angina due to aortic insufficiency or aortic dissection [16••].

Associated autoimmune diseases have been found to be present in 8–10% of CS patients and include sarcoidosis, Takayasu arteritis, polyarteritis nodosa, relapsing polychondritis and spondylarthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), rheumatoid arthritis, renal amyloidosis associated with monoclonal gammopathy, and tubulointerstitial nephritis and uveitis (TINU syndrome)

Table 1 Autoimmune diseases associated with Cogan's Syndrome (CS)

Manifestations independent of CS	Vestibuloauditory findings	Ocular findings
Sarcoidosis	Neurosarcoidosis leading to sensorineural hearing loss	Granulomatous uveitis, retinal vasculitis, optic neuropathy
Takayasu's arteritis	Inner ear vasculitis with sensorineural hearing loss	Decreased vision, retinopathy, ocular ischemic syndrome
Polyarteritis nodosa	Mixed hearing loss due to middle ear effusions and inner ear vasculitis	Scleritis, keratitis, retinal vasculitis, nongranulomatous uveitis, orbital inflammation
Relapsing polychondritis and spondylarthritis	Mixed hearing loss due to cartilaginous inflammation and Inner ear vasculitis	Conjunctivitis, scleritis, iritis
Granulomatosis with polyangiitis (Wegener's granulomatosis)	Sensorineural hearing loss, conductive hearing loss	Conjunctivitis, keratitis, episcleritis/scleritis, intermediate uveitis, optic neuropathy, ophthalmoplegia, periorbital inflammation
Rheumatoid arthritis	Sensorineural hearing loss	Keratoconjunctivitis sicca, marginal keratitis, peripheral ulcerative keratopathy, scleritis, retinal vasculitis
Renal amyloidosis associated with monoclonal gammopathy	Rare deposition of amyloid causing sensorineural hearing loss	Rare keratopathy or maculopathy
Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	Autoimmune inner ear disease with sensorineural hearing loss	Common: Episcleritis, scleritis, conjunctivitis; Uncommon: Uveitis; Rare: keratitis, orbital inflammation, retinal vasculitis, optic neuritis
Tubulointerstitial nephritis and uveitis (TINU syndrome)		Uveitis

[3, 5••, 12, 17]. Vavricka et al. have reported on a growing series of cases showing a strong connection between CS and inflammatory bowel disease (IBD) [18, 19]. It is important to note that CS can arise de novo in patients who are already on immunosuppressive therapies and be vigilant and proactive at the first sign of vestibuloauditory or ocular symptoms (Table 1).

Relapsing symptoms of CS can necessitate chronic immunosuppressant therapy, and CS-associated systemic vascular disease has been known to develop years after the onset of CS despite chronic immunosuppression [20–24]. The recent 2017 review by Durtette et al. found that the 5-year cumulative incidence of relapse was 13% and the 10-year cumulative incidence of relapse was 31%, while a decade ago Gluth et al. reported a general 75% relapse rate of Cogan's syndrome patients suffered disease relapses, 22% had no relapses, and 3% had no remission [3, 5••]. This may represent an improvement in recognition of this syndrome as well as improved treatment options, although a direct comparison cannot be made between the two cohorts.

Treatment and Outcome

Management of CS is directed to the severity of the disease and the organ system involved. While corticosteroids remain the standard of care, our information is based on retrospective evidence. The aim of treatment should be to prevent irreversible sensorineural hearing loss, deafness, vestibular dysfunction, ocular complications, or systemic complications from vasculitis.

Ocular manifestations of CS tend to respond well to treatment, with 84% responding to steroids alone, 90% responding to disease-modifying anti-rheumatic drugs (DMARDs), and 100% responding to biologic agents in the French study of 62 cases [5••]. Topical corticosteroids may be used for mild ocular symptoms, though the combination of ocular inflammation and steroid use may lead to premature formation of cataracts. Visual prognosis remains excellent in the majority of CS patients with only 3% showing long-term ocular symptoms [5••].

The use of DMARDs and biologic agents has been more widely utilized for the purpose of treating the systemic and vestibuloauditory manifestations of CS. The data is compelling that high-dose steroids (IV glucocorticoid or oral prednisone of at least 1 mg/kg/day) improve the odds of recovering hearing loss when given within 2 weeks of initial auditory symptoms [1, 12]. When a patient does not respond to steroids, is intolerant of steroids, or has a contraindication to steroid use, other immunosuppressive therapies are advisable to reduce the long-term morbidity of CS. Intratympanic steroid injections have been tried in various autoimmune inner ear diseases and could be considered as an adjunct therapy [25••]. DMARD therapies that have been used with varying success include cyclophosphamide, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine [25••, 26••]. Infliximab is rising as a potential 1st line therapy in conjunction with corticosteroids [5••, 26••]. Durtette et al. found an 80% response rate to infliximab of vestibuloauditory symptoms in patients who had failed multiple combinations of corticosteroid and DMARD therapy. This correlates well with an 89% cumulative success rate of infliximab in previous case reports [5••, 26••].

In an open-label prospective pilot study, etanercept was used in 3 CS patients with modest improvement in 2 of the 3 patients, though hearing loss was not prevented [27]. Tocilizumab was used successfully to improve inflammation and quality of life in a single case report of a 69-year-old man with sensorineural hearing loss and iritis diagnosed with atypical Cogan's syndrome [28]. He had achieved initial remission with high dose prednisolone, but relapse was resistant to various immunosuppressive drugs, including methotrexate, cyclosporine, azathioprine, and adalimumab. Rituximab has limited reported use in CS and AIED, but has shown some improvement in hearing loss symptoms [25••, 26••]. Other patients who progress to deafness may be referred for cochlear implant surgery to treat sensorineural healing loss [25••].

Aortitis and valvular dysfunction may require cardiovascular intervention. PET tomography is useful in the detection of increased aortic wall metabolism in a pattern that affects the root of the aorta to the middle portion of the aortic arch [16••]. Higher morbidity and mortality have been related to atypical CS when systemic vasculitis and aortic insufficiency secondary to aortitis are involved [29].

Conclusions

Cogan's syndrome continues to be a challenging diagnosis to make due to the variability in presentation and difficulty in initiating prospective research into this rare entity. The distinction between typical and atypical presentations has become less important when faced with a chronic disease that has relapsing symptoms that can evolve over years with significant morbidity of deafness or vasculitic complications in either group. The most promising data to date is the 80% response rate at 6 months of vestibuloauditory symptoms to infliximab.

Further understanding of the autoimmunological underpinnings of this disorder may lead to a more targeted treatment regimen in the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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