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Cogan's syndrome: Unsuccessful outcome with early combination therapy

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ABSTRACT

Interstitial keratitis and vestibulo-auditory symptoms (vertigo and hearing loss) are the typical signs of Cogan's syndrome, a rare inflammatory vascular disease. Signs of vasculitis in many organ systems may appear, among which neurologic problems are sometime predominant. The efficacy of glucocorticoids on the ocular and systemic symptoms is established, but their effect on hearing loss is unknown. We describe a case of Cogan's syndrome with neurological involvement in which early treatment with combination therapy (prednisolone and cyclosporin) failed to bring ear inflammation under control.

Introduction

Cogan's syndrome (CS) is a rare disease (about 100 cases described over the past 50 years) of unknown origin that occurs in young adults. A late onset of disease has been reported (1, 2). Patients present symptoms of eye and ear involvement, i.e., non-syphilitic interstitial keratitis (IK) associated with vestibulo-auditory dysfunction (3). Signs of systemic disease have also been reported (4-11) (Table I) and vasculitis in many tissues has been considered to be the underlying pathologic mechanism (5, 6). Cogan's syndrome can have a poor prognosis should eye, ear and cardiovascular complications appear. At present the deafness which occurs in 43% of patients (13) is often irreversible (10, 12). Blindness may develop in 8% of patients, aortitis evolving into aortic insufficiency requiring surgery (14-16) in 14%, and death in 9% (13).

Table I. Clinical features of patients with Cogan's syndrome.

EYE
Typical (Bilateral interstitial keratitis)
Atypical (scleritis or episcleritis, conjunctivitis, uveitis, choroiditis, retinal hemorrhages, in addition to or rather than interstitial keratitis)
EAR: Bilateral sensorineural hearing loss, vertigo, tinnitus
SYSTEMIC FEATURES
Non-specific
Clinical: fever, weakness, arthralgias, myalgias, weight loss
Biological: anaemia, elevated ESR, CRP, WBC and neutrophils
Specific (vasculitis): skin, kidneys, cardiovascular system, neurological system, gastrointestinal tract

Hearing loss is the most serious sign in patients with CS. Spontaneous improvement has been rarely reported (17). Untreated patients have moderate, severe or profound hearing loss at 5-year follow up (10), while early (i.e., within the first two weeks of onset) oral glucocorticosteroid (GC) administration can reduce the severity of ear damage to mild or moderate but does not prevent deafness (18, 19). Combined therapy (immunosuppressive drugs and GC) has been attempted in patients in whom GCs failed to control disease activity (i.e., associated vasculitis) or in whom vision-threatening inflammatory eye disease developed (20). Little or no effect (12, 21) on hearing loss has been observed using this therapeutic approach. Immunosuppressive therapy has also been tried for its steroid-sparing effect in patients with chronic disease characterised by frequent relapses. Fluctuations in hearing loss frequently occur, due either to cochlear hydrops (a condition that must be treated with diuretics) or to relapses when the oral GC dose is decreased. When the GC dosage must be raised, immunosuppressive therapy may allow one to limit the increase (22, 23).

The disappointing results thus far obtained in controlling hearing loss and preventing deafness in CS prompted us to try early, aggressive combination therapy, which has been shown to be useful in treating vasculitic syndrome. We describe the case of a 30-year-old woman whose CS failed to respond satisfactorily to treatment with glucocorticoids (GCs) and cyclosporin A (CsA).

Case report

A 30-year-old woman presented in December 1996 with a fever peaking at 38° C, weakness, arthromyalgias, low back pain, photophobia and bilateral conjunctival hyperaemia of 10 days' duration. A slit lamp ophthalmologic examination revealed bilateral IK with a circum-scle-

rocorneal junction stromal infiltrate. She had a history of recurrent keratoconjunctivitis with corneal ulcers beginning one year before her admission.

Five days later nausea, nystagmus, cranial neuropathy of the right VII nerve and meningeal syndrome suddenly developed with tinnitus, vertigo and bilateral hearing loss. A lumbar puncture showed a clear colourless cerebrospinal fluid (CSF); the white blood cell (WBC) count was increased to 20/mm^3 (normal range < 5/mm^3) with 100% lymphocytes; the protein level was 20 mg/dl (normal range < 40 mg/dl); the IgG, IgA and IgM indices were normal; and an IgG oligoclonal band was present. Cultures of the blood and CSF for bacteria, fungi and viruses were negative.

IgM antibodies against measles, Varicella Zoster virus (VZV), Parotitis, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Herpes simplex (HSV) and Morbillous were absent in both the CSF and the serum. IgG antibodies against CMS, HSV and Morbillous were present in both the CSF and serum. IgG antibodies against measles, VZV and Parotitis were present only in the serum, IgG antibodies against EBV were absent either in serum or in CSF. Serologic tests for syphilis (VDRL, TPHA, IFTA) were negative in both the CSF and blood. EEG, brain CT scan and MRI were negative.

Serum tests revealed increased ESR (114 mm/hr), α_2 globulin (15.4 g/dl), WBC (13,600/mm^3, neutrophils 75%, lymphocytes 15%, monocytes 10%) and CRP (5 mg/dl). Red blood cells (3.54 x 10^6/mm^3), Hgb (9.01 gr/dl), Hct (28%), MCV (78.9 fl), and MCH (25.4 pg) were decreased. Normal values were found for other routine laboratory analyses, including urinalysis, liver and renal function tests, serum complements C3 and C4 and immunoglobulin IgG, IgA and IgM levels. A urine culture was sterile, HIV serology was negative, circulating immunocomplexes (C1q binding assay) were absent, and serum electrophoresis and immunoelectrophoresis were normal.

None of the following were detected in the patient's serum: anti-nuclear (ANA), anti-mitochondrial (AMA), anti-smooth muscle (ASMA), anti-liver kidney microsome (anti-LKM), anti-double-stranded DNA (anti-ds DNA), anti-gastric parietal cell, and anti-neutrophil cytoplasmic (ANCA) antibodies or rheumatoid factor (RF). A chest radiograph and echocardiogram were normal. Vestibuloaudiometric tests showed bilateral sensorineural hearing loss which was more severe in the right ear.

A diagnosis of CS was made and combination therapy was begun 5 days after the onset of hearing loss: methylprednisolone bolus (1 gm i.v. per day for 3 consecutive days followed by 1 mg/Kg p.o. per day for 4 weeks) and CsA (3 mg/kg per day). The patient's fever, arthralgias, meningeal syndrome and IK disappeared, while her hearing acuity improved slightly (particularly in the left ear) within 48 hours of the treatment. Cranial neuropathy improved slowly. The ESR, CRP, and WBC count returned to normal values. One month later corticosteroid therapy was gradually tapered. A flare of the ear symptoms appeared at a daily dosage of 0.5 mg/kg per day. Diuretics were inefficacious. The steroid dosage was increased and an improvement in hearing acuity was registered. Tapering again resulted in a hearing loss, and CsA was replaced by cyclophosphamide (500 mg i.v./weekly). Relapses of hearing loss occurred each time a steroid dosage of 0.5 mg/kg per day was given. Bilateral and permanent deafness occurred eight months after the onset of the disease.

Discussion

In this report we describe a case of CS with dominant neurologic manifestations at the onset, which we treated with early aggressive therapy.

Cogan's syndrome is a primitive systemic vasculitis characterised by the association of oculo-vestibulo-auditory signs. Eye and ear symptoms may both be present at the onset but usually the disease begins with one symptom, the other developing within a year. Other symptoms that may be present at onset include diarrhoea, pleuritic chest pain, and headache; low back pain is seen in 5% of patients (10). Non-specific manifestations (fever, weakness, arthralgias and myalgias) and specific systemic features (vasculitis involving many organ systems) have been reported in 50% and 10% of patients (10, 11). The skin, kidneys, gastrointestinal tract, and cardiovascular and nervous systems may be affected (4, 5, 7, 10, 11, 24, 25).

Neurological signs have been reported with a variable frequency, ranging from 2-5% (26) to more than 50% of patients (24). The most common features were headache, neck pain, EEG and CSF abnormalities. Cranial nerve involvement is not frequent (24). Other reported nervous system manifestations were ataxia, seizures, cerebrovascular syndromes, peripheral neuropathy, organic mental syndrome (26), cerebellar involvement (26-28) and meningeal syndrome (29). Neurologic features may be isolated or predominant (24), and can sometimes be serious (24, 26). In our case meningitis was a dominant sign. The presence of eye and ear symptoms was determinant in the differential diagnosis.

The prognosis for ocular symptoms is usually good with current therapy, while auditory deficiency rarely improves and more often further deteriorates, deafness being a possible sequel (10, 12, 13). Moderate eye involvement is generally treated with topical GC and atropine drops (10). Severe eye involvement, vestibulo-auditory symptoms and systemic features require high dose oral GC (1-2 mg/kg per day) (10, 30). Ocular and systemic symptoms usually respond within a few days to this therapy, while the cochlear pathology is rarely modified.

Partial improvement in hearing loss has been reported when GCs are given early, i.e. within the first 2 weeks of the onset of auditory deficit (18). However, even here optimism must be moderate as total deafness may eventually ensue (31) (Table II). Improvement in hearing loss is less likely to occur if treatment is initiated when the patient is already deaf (6). Prevention of deafness is not obtained with early oral GC treatment: at follow-up, only 7% of treated patients had normal hearing (10). Combined treatment with GCs and immunosuppressives has been suggested for patients in whom vision loss and vascular manifestations fail to respond to steroids (20). Combined treatment has also been suggested to obtain a steroid-sparing effect in patients with a chronic course of the disease (22, 32, 33). Azathioprine (11, 12, 28), cyclophosphamide (4, 11, 20),

Table II. Clinical characteristics, treatment and outcome of hearing loss in patients with Cogan's syndrome.

Eye involvement*	Vasculitis	Therapy§	Lag from ear symptoms#	Outcome of auditory disease	Ref.
Mixed	Absent	GCs	Early	Improvement	18
Typical	Absent	GCs	Early	Total deafness	31
Typical	Absent	GCs	N. A.	Deafness unchanged	29
Typical	Absent	GCs	N. A.	Deafness unchanged	2
Typical	Absent	GCs + MTX	Late	Improvement	22
Typical	Absent	GCs + MTX	N. A.	Improvement	32
Typical	Absent	GCs + MTX	N. A.	Improvement	33
Mixed	Present	GCs + CsA	N. A.	Deafness unchanged	20
Typical	Present	GCs + CsA	N. A.	Stabilisation	20
Mixed	Present	GCs + CsA	N. A.	Worsening	20
Mixed	Absent	GCs + CsA	N. A.	Stabilisation	20
Atypical	Present	GCs + CsA	N. A.	Deafness unchanged	21
Typical	Present	GCs + CsA	N. A.	Deafness unchanged	16
Atypical	Present	GCs + CYC	Early	Improvement	23
Atypical	Absent	GCs + CYC	Early	Total deafness	34
Typical	Absent	GCs + AZA	N. A.	Stabilisation	28

* Mixed = both typical and atypical

§ Glucocorticoids (GCs), Methotrexate (MTX), Cyclosporin A (CsA), Cyclophosphamide (CYC), Azathioprine (AZA)

Early: 2 weeks after the onset; late: more than two weeks after the onset and/or during relapses of hearing loss; N.A.: not available.

cyclosporin A (16, 20, 21) and methotrexate (12, 22, 32, 33) have been used. This therapeutic approach was beneficial for severe ocular disease and vasculitis (10, 20). Concerning ear involvement results were partial (12, 20) or absent (20, 21, 34). Good results have been obtained with MTX in patients without vasculitis (22, 32, 33) (Table II). Prevention of hearing loss was not obtained in any of the cases. The poor efficacy of immunosuppressive agents against ear disease could perhaps be explained by the late introduction of these drugs, after GC therapy had failed or during relapses of disease (20). Its early use could be more effective in controlling ear disease and preventing hearing loss.

The effect of early combination therapy with GC and immunosuppressive agents in vasculitis (35, 36) is well known: a higher survival rate in patients with severe vasculitis supports the use of these drugs as a first-line therapy. Continuous oral GC and CYC has been widely employed (37, 38); unfortunately severe toxicity is a problem in the long term (39). The dosage and route of administration of GCs and CYC have been modified to reduce the side effects. Prednisolone pulse therapy followed by low maintenance doses (40) and intermittent CYC boluses [0.50 - 0.75 gr/m^2 monthly (41) or 500 mg/weekly (42)] is as effective as oral CYC and may have the advantage of fewer side effects and lower mortality in the long term (43), although this remains to be confirmed. Hoffman (44) pointed out that the side effects and mortality were quite high in the patient series reported by Guillevin (43). Furthermore, recently this therapeutic regimen has been associated with the risk of cancer as a long-term side effect (45).

To reduce the risks of long-term CYC treatment, other less aggressive immunosuppressive strategies have been proposed (46, 47). Among these CsA, a cyclic lypophilic undecapeptide, has been suggested because of its non-cytotoxic immunosuppressive effect (inhibition of IL-2, IL-3 and IFNγ production) and low toxicity (44, 48-50). A CsA dosage of up to 5 mg/kg per day was efficacious, while relapses were observed with tapering to 1 - 2 mg/kg per day in the treatment of patients with Wegener's granulomatosis (51). Low doses of CsA (initial dosage 2.5 - 3.5 mg/kg per day, never exceeding 5 mg/Kg per day) have been used to reduce nephrotoxicity, the major side effect of this drug (52). We therefore decided to use a 3 mg/kg/day dosage in our patient to preserve renal function.

Different studies have reported that combined treatment with GCs + CsA was successful in controlling vasculitis and eye disease in CS (16, 20, 21). Results on hearing loss were generally unsatisfactory, with worsening reported in one case, but it must be kept in mind that treatment was started when hearing loss or deafness were already present (16, 20, 21). The absence of deafness at the onset of treatment (6) and prompt treatment (10) are prerequisites for preventing hearing loss. Recently the importance of early treatment was confirmed in a report on ear involvement in a patient with Behçet's disease: in the treatment of sudden cochlear hearing loss prednisone plus CsA was ineffective, probably because it was initiated late (53).

It seems to us that a rational therapeutic approach to prevent deafness in Cogan's syndrome could be early (within the first 2 weeks of onset) aggressive therapy with GC (i.v. pulses of methylprednisolone, followed by 1 mg/kg per day) and immunosuppressive agents. In our patient the presence of: (1) non-specific clinical and biological signs of a systemic inflammatory disease; (2) neurological signs (meningitis, right VII cranial nerve involvement); (3) interstitial keratitis; and (4) vestibuloauditory signs and symptoms, led to the diagnosis of severe Cogan's syndrome with systemic involvement, and boluses of methylprednisolone plus CsA were administered. This combination treatment was started early (5 days after the acute onset of ear symptoms) as a first-line therapy, unlike previous cases where aggressive therapy was used as a second-line approach (4, 11, 12, 16, 20-22 28, 33, 34). Despite this treatment, permanent deafness developed in our patient, while the eye disease, systemic and neurologic signs resolved completely.

In conclusion, this combined therapeutic approach was neither successful for ear involvement nor steroid-sparing in the long term. The failure could have been due to the low CsA dose used (no

more than 3 mg/kg per day in order to preserve kidney function) or to the inefficacy of CsA. An alternative approach at this point might be the early use of boluses of GCs and CYC, as suggested by a recent report of an amelioration in hearing loss obtained with the early use of boluses of CYC and methylprednisolone in a patient with CS (23), in contrast to a previous report where hearing loss was unresponsiveness to boluses of CYC and methylprednisolone (34). The different protocols used (15 mg/kg i.v. every 3 weeks for five times vs 600 mg i.v. per month) could explain the conflicting results. Hearing loss and other symptoms resolved 4 months after the onset of therapy (23). The length of the follow up was not reported, but it is possible that no recurrence of symptoms was subsequently observed when remission was maintained with low dose oral MTX (23). This result makes it possible to retain that early aggressive therapy with GCs and CYC could represent an effective short-term therapy to prevent deafness and avoid the side effects of long-term CYC.

Prevention of deafness is a difficult result to obtain in CS. However, this ear complication can be treated by surgery. Good results have been obtained with cochlear implants in CS patients with permanent bilateral deafness (14, 54, 55). The case described here underlines the poor prognosis for auditory symptoms in Cogan's syndrome despite aggressive early therapy with a combination of drugs.

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