Cochleovestibular Impairment in Pediatric Cogan’s Syndrome

Issa C. Ndiaye, MD*; Simon J. Rassi, MD*; and Sylvette R. Wiener-Vacher, MD*

ABSTRACT. Cogan’s syndrome is a rare, chronic inflammatory disorder that typically targets the eyes and vestibulolouditory apparatus, but it may also involve other organs. Three pediatric cases of Cogan’s syndrome (ages 5, 13, and 18 years) are reported with long-term follow-up and complete and regular cochleovestibular functional evaluation and ophthalmologic and neurologic examinations. One case was a typical form (characterized by an interstitial keratitis and cochleovestibular impairment), whereas the other 2 cases were atypical forms with uveitis and polyarthritis. In all 3 cases, the first clinical sign was nonspecific eye redness misdiagnosed as a banal conjunctivitis, initially or secondarily associated with bilateral endocochlear sensorineural hearing loss and complete bilateral peripheral vestibular deficit. During the acute phase, early steroid treatment (prednisolone, 1 mg/kg/day) was effective in treating the ocular lesions (3 of 3 cases) and improving hearing (2 of 3 cases) but less effective for the vestibular loss (2 of 3 cases). Adverse effects and dependence on the steroid occurred in 2 cases, and immunosuppressive drugs were necessary to avoid recurrences in 1 case. Over the long-term, the disease was controlled in 2 cases but continued to progress in the other. Cogan’s syndrome in childhood should be suspected in cases of conjunctivitis associated with inner-ear symptoms; a prompt steroid treatment can avoid progressive impairment of multiple sensorineural functions (vision, balance, hearing). Long-term management involves limiting disease recurrences by adaptive therapies, screening for complications (aortitis in particular), and planning rehabilitation for the sensorial deficits. Pediatrics 2002;109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e38; children, Cogan’s syndrome, sudden hearing loss, imbalance, vertigo, conjunctivitis.

ABBREVIATIONS. EVAR, earth vertical axis rotation; OVAR, off vertical axis rotation test; VOR, vestibulococular responses; SNHL, sensorineural hearing loss; NSAID, nonsteroidal antiinflammatory drugs; MRI, magnetic resonance imaging; EBV, Epstein-Barr virus.

Cogan’s syndrome is a relatively rare inflammatory disease characterized by nonsyphilitic ocular interstitial keratitis associated with sudden hearing loss and vestibular impairment. However, its early diagnosis and treatment with steroids can prevent loss of inner-ear sensorial function and limit ophthalmologic aftereffects. In 1934, Morgan and Baumgartner1 published the first case of the syndrome. In 1945, Cogan2 published the full description of the syndrome as an inner-ear disorder in its typical form. Several authors later reported atypical forms3,4 that differed from the typical presentation by the type of ocular lesions, which can include superficial keratitis, scleritis, episcleritis, iritis, or choroiditis, as well as variable hearing impairment and often systemic inflammation.5 Cogan’s syndrome is generally considered an autoimmune disease despite the frequent lack of direct immunologic evidence.6,7 The efficacy of steroid treatment in the acute phase provides a compelling argument for this hypothesis.

Diagnosis of Cogan’s syndrome is often missed or delayed because it is a rare disease and its clinical signs at onset are not specific (banal conjunctivitis). This is dangerous for the patients because steroid treatment should begin as early as possible to allow functional restoration of the inner ear and the eyes before irreversible lesions develop. Few pediatric cases have been reported in the literature, with no mention of long-term follow-up.5,8,9–14

We report 3 pediatric cases with long-term follow-up (4–9 years) and regular complete audiologic and vestibular testing to evaluate the sensorial deficits.

PATIENTS AND METHODS

Three cases of Cogan’s syndrome in children aged 5, 13, and 18 years at the onset of disease are presented. They were recruited from 950 children with balance problems referred to the vestibular clinic over a 10-year period. Each patient underwent complete testing including: audiologic tests (pure tone audiometry, speech recognition test, impedanceometry, and evoked otoacoustic emissions), vestibular testing (clinical vestibular examination, caloric bithermal test, earth vertical axis rotation [EVAR] test, off vertical axis rotation [OVAR], subjective vertical measurement, and vestibular evoked otolithic myogenic potentials) and ophthalmologic examination. These tests were repeated over time to follow the evolution of the disease and evaluate the response to treatment.

The vestibular test battery evaluated both canal and otolith functions. The bithermal caloric test evaluated canal function by successive irrigation of each ear canal with 30°C and 44°C water, followed by a count of the quick phases of the vestibuloocular responses (VORs) through videovcopy from the 60th to 90th seconds after the beginning of the irrigation.

Recordings of the VORs were performed with the electrooculography technique. Measurements were made in complete darkness while patients kept their eyes open.

Recordings of canal and otolith VORs were made during EVAR and OVAR, respectively. Vertical and horizontal eye movements were recorded with lightweight adhesive electrooculographic electrodes. A computer-controlled rotating chair delivered the vestibular stimulation by applying at first a brief acceleration (of 40°/s²) achieving a constant velocity (60°/s) rotation about the
earth vertical axis, and then inclining (at a 13° tilt) the axis of rotation; this is the rotation-tilt paradigm, a method previously described in detail.\textsuperscript{13,16} Canal and otolith vestibular functions were quantitatively evaluated by measuring the parameters of the canal VORs (including time constant and maximal slow phase velocity) and from the parameters of the otolith VORs (modulation amplitude and bias for horizontal and vertical eye movement slow phases) of the baseline side.

The ophthalmologic examination included a measure of the visual refraction and a slit-lamp examination. This was performed initially to establish the diagnosis and then to follow the evolution of ocular lesions under treatment. Complementary tests were performed for each case and followed the diagnostic explorations.

Table 1 lists the 3 reported cases, and Table 2 summarizes the battery of tests performed and their results.

CASE REPORTS

Case 1

A 5-year-old boy suffered from bilateral conjunctivitis with moderate uveitis 1 week after a second intradermic desensitization treatment against mite antigens. Two months later, he experienced vertigo lasting 24 hours without vomiting or tinnitus. After 4 days, bilateral profound sensorineural hearing loss (SNHL) occurred suddenly and predominantly at high frequencies (Fig. 1). Evoked auditory brainstem responses confirmed the profound SNHL with no identifiable responses to 100-dB clicks. The stapedius reflexes were absent at all frequencies. The neurologic examination and ophthalmologic examination revealed uveitis secondary to probable viral conjunctivitis with after-effects of previous inflammatory episodes. Vestibular testing showed complete canal areflexia and some residual weak otohelic response to the OVAR test.

The diagnosis of atypical Cogan’s syndrome was suggested because of the association of conjunctivitis and inner-ear lesions. All immunologic investigations were negative (Table 2). Steroid therapy was prescribed intravenously (prednisolone, 1 mg/kg/ day). After 1 week, hearing thresholds improved by 25 dB at all frequencies on the left side. The uveitis remained without papillitis or keratitis. However, each attempt to decrease and eventually stop the steroid treatment was associated with recurrent uveitis and a decrease in the hearing thresholds. This dependence on the steroid was associated, 3 months after the beginning of the treatment, with ocular side effects—early-stage cataract (visual acuity of 2/10 in the right eye and 5/10 in the left eye) and acute glaucoma that required surgical treatment (trabeculectomy on both sides). Treatment with colchicine was attempted with relative success for the ophthalmologic status but not on hearing. Nine years after the onset of the disease, this child required no medical treatment but had bilateral profound deafness requiring special rehabilitation, vision that was stable and still compatible with scholastic activity, and complete bilateral vestibular deficit that was well-compensated for. Cochlear implantation was suggested but declined by the patient’s family for religious reasons.

Case 2

During winter, a 13-year-old boy had fever (38°C–40°C) associated with myalgia, arthralgia, severe asthenia, headache, vomiting, and eye redness. At first, this suggested a viral infection, a reasonable diagnosis in the seasonal context. Treatment with amoxicillin and nonsteroidal antiinflammatory drugs (NSAIDs) was not effective.

The child was then hospitalized. His medical history revealed that 1 month earlier he had experienced a severe reaction to a second vaccination for tuberculosis (BCG) with a large necrotic ulceration site.

The physical examination found cutaneous inflammatory signs at the level of the painful articulations (hands, ankles, the right elbow, and knee). The ophthalmologic examination was normal, as were otohelicaryngologic, cardiovascular, and neurologic evaluations. The results of the biological tests showed a nonspecific inflammation (Table 2). This inflammatory syndrome associated with joint pain suggested a dermatomyositis, but muscle, as well as liver, enzyme levels were normal. Joint radiographs were normal. Juvenile arthritis with a systemic onset was diagnosed despite the absence of fever spikes, cutaneous rash, swollen lymph nodes, and hepatosplenomegaly. NSAIDs (aspirin and indomethacin) were again prescribed without clear improvement of symptoms. Slow intravenous injections of immunoglobulines (1 g/kg for 2 days) had no effect. One month after disease onset, the child reported, for the first time, tinnitus, hearing impairment, and a sensation of vertigo. These signs suggested an iatrogenic origin related to the NSAID treatment. The child was then referred to our otorhinolaryngology department for audiovestibular testing. Moderate to severe bilateral SNHL primarily in high frequencies was found with recruitment (characterized by stapedial reflex thresholds at 100 dB) (Fig. 1). The vestibular testing showed spontaneous nystagmus to the left, bilateral canal areflexia at the caloric test but normal otolithic responses to OVAR. Brain and inner-ear magnetic resonance imaging (MRI) with gadolinium injection showed a right-ear malformation (pes cavus) with limb jerk areflexia and familial malformations (pes cavus).

Ophthalmologic follow-up was requested because of persistent eye redness. A slit-lamp examination revealed interstitial keratitis.

This immediately suggested Cogan’s syndrome with systemic manifestation, and steroid therapy was instituted (prednisone, 1 mg/kg/day). This treatment was quickly effective against the fever and the arthralgia. Immuneologic tests were negative for the serodiagnosis of parvovirus B19 and the serodiagnosis of hepatitis B, despite the absence of vaccination (Table 2).

The ophthalmologic signs improved after 1 month of steroid treatment, and no evidence of eye disease was found 9 weeks after treatment initiation. Improvement of the hearing thresholds was slower and incomplete. Hearing remained severely impaired on the right side (loss of 70 dB) but moderately impaired on the right side (loss of 30–40 dB) but stable. Seven years after disease onset, no other problems have occurred. Auditory and vestibular function have remained unchanged.

Case 3

An 18-year-old boy complained of sudden right-ear hearing loss and tinnitus without vertigo. He was hospitalized and treated intravenously with steroids, mannitol, and vasodilators for 10 days. This treatment normalized the hearing thresholds. Three weeks later, he suffered from sudden left-ear hearing loss, bilateral tinnitus, headache, and ataxia without vertigo. He received the same treatment as before, but this time it was not effective. He continued to complain of left-ear hearing loss and ataxia especially in darkness. Three months later, he was referred to our department for vestibular evaluation.

The patient reported photophobia and eye redness before the first episode (right-ear hearing loss). His history revealed foot malformations (pes cavus) with limb jerk areflexia and familial malformations (pes cavus). Eight months later, he had received a second injection of vaccine for mumps (rubello, oreillons, rougeole). Two months before the first episode of sudden hearing loss, his brother had mumps. His serology for Epstein-Barr virus (EBV) infection was strongly positive, indicating a recent contact with the virus (Table 2).

The results of neurophysiologic explorations (evoked visual potentials, evoked somesthesic potentials of the upper and lower limbs, and electromyelogram) confirmed the diagnosis of hereditary polynuropathy (Charcot-Marie-Tooth, type 1).

Hearing tests showed normal right tonal and vocal hearing thresholds with moderate left SNHL at lower frequencies (50 dB at 125, 250, 750, and 500 Hz; 35 dB at 1 kHz) and normal threshold for high frequencies (>2 kHz) (Fig. 1). Auditory brainstem-evoked responses were normal. Stapedial reflex thresholds were normal on the left side despite SNHL that indicated some recruitment and an endocochlear disorder.

Vestibular testing revealed no spontaneous nystagmus and no canal VORs during rotatory impulsions or caloric tests, whereas the otohelic VORs were very weak bilaterally, indicating a severe bilateral vestibular deficit.

Brainstem and inner-ear MRI showed no pathology of the cerebellum pontine angle but an increased signal on T1 of the left inner ear, indicating a labyrinthitis.

Ophthalmologic evaluation showed corneal dystrophy with loss of vision (right eye: 6/10; left eye: 8/10) and interstitial keratitis at the slit-lamp examination.

The diagnosis of a typical Cogan’s syndrome was then established, and intravenous steroid treatment (prednisone, 1 mg/kg/day) was started. After 5 days of steroids, vestibular testing showed a persistent complete bilateral vestibular deficit. Hearing
tests showed improvement of hearing thresholds for the frequencies 250, 500, and 1000 Hz (with normal thresholds for higher frequencies) on the left side. Steroids were continued orally with prednisolone (1 mg/kg/day).

Two months later, hearing thresholds were normal for both ears. In contrast, vestibular function remained altered. Instability improved with regular physical therapy but remained disabling in darkness, probably because of the lack of somesthesic and proprioceptive information related to the familial polyneuropathy. At a 4-year follow-up, hearing thresholds were normal, vestibular function was still impaired, and an ocular examination was normal. However, every attempt to decrease and stop the steroid treatment has been followed by fluctuating hearing loss and conjunctivitis. An immunosuppressive drug therapy (methotrexate) was started recently to improve the control of the disease with relatively good success, but after 5 months, attempts to decrease the dosage led to recurrence of eye and hearing impairments.

DISCUSSION

Cogan’s syndrome is a rare chronic inflammatory disease that can be successfully treated if it is recognized early in its course. Children may present with signs identical to those of adults with typical Cogan’s syndrome (as in case 3) such as associated nonsyphilitic interstitial keratitis and cochleovestibular deficits (including vertigo and SNHL); or pediatric cases may involve atypical forms (case 1 with uveitis and case 2 with polyarthritis). Vollertsen et al17 reported that adult cases consist of 70% typical forms and 30% atypical.

Published data emphasize that in atypical forms the inflammation can involve the cornea as well as other parts of the eye.3 Audiovestibular symptoms may appear before or after ocular involvement (with as much as a 2-year interval).9 Our 2 cases of atypical Cogan’s syndrome involved bilateral uveitis 15 days after conjunctivitis with no associated interstitial keratitis. In one case, a severe flu-like syndrome preceded by approximately 4 weeks the onset of ocular and cochleovestibular disorders.

Arguments Supporting an Autoimmune Origin for Cogan’s Syndrome

The exact cause of Cogan’s syndrome remains unknown although several hypotheses have been suggested. The most commonly accepted hypothesis—an autoimmune mechanism6,7,17,18—is supported by the frequently successful remission of hearing loss after steroid administration, the positive transformation of the lymphoblastic test regarding cochlear antigen in some cases,19,20 and the association of Cogan’s syndrome with other autoimmune diseases such as rheumatoid arthritis.21–23

Schuknecht and Nadol24 published a histologic study of the temporal bone from a patient who had suffered from Cogan’s syndrome and later died of another pathology. The lesions observed in this case were similar to those usually found in other autoimmune diseases: acute labyrinthitis with inner-ear tissue atrophy, endolymphatic hydrops, diffuse fibrosis, and neural degeneration. In case 3 of our series, MRI also revealed signs of labyrinthitis on 1 side (hypersignal on T1).18

The presence of abnormal antibodies in Cogan’s syndrome is an argument for its immunologic origin; however, this is not consistently found. In a recent study, Casoli and Tumiati25 found elevated antibody
immunoglobulin G and immunoglobulin M antiphospholipid at 53.5 U/mL (normal value: 10 U/mL) and 41.5 U/mL (normal value: 6 U/mL), respectively, in a patient with Gougerot-Sjögren syndrome, who presented with Cogan’s syndrome 6 years later. These authors suggest a correlation between the presence of the anticardiolipid antibody and Cogan’s syndrome. Yamanishi et al described a case with atypical Cogan’s syndrome associated with antineutrophil cytoplasmic antibody. In our case 3, assays for this antibody were negative. In published papers, some antigens of the histocompatibility leukocyte antigen system are also described in Cogan’s syndrome: haplotypes A9, Bw17, Bw35, and Cw4. We found haplotype Cw4 in our case 1. Some authors consider vaccinations and infections to be triggering factors for Cogan’s syndrome. In our study, the serology of parvovirus B19 was increased in case 2, and the serology of EBV in case 3 indicated recent infection with EBV. In cases 2 and 3, a second vaccination (for tuberculosis and mumps, respectively) could be related to the onset of Cogan’s syndrome. In case 1, the second injection of desensitization against mite antigens was followed 15 days after the onset of Cogan’s syndrome.

TABLE 2. Biological Tests Results for the 3 Reported Cases of Cogan’s Syndrome

<table>
<thead>
<tr>
<th>Blood Tests Results</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood count</td>
<td>Hypereosinophilia</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Erythrocyte sedimentation test</td>
<td>25 mm/h</td>
<td>125 mm/h</td>
<td>205 mg/L</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>EBV serology</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Mumps serology</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV serology</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Coxsakies A-B serology</td>
<td>Negative</td>
<td>Positive immunoglobulin G and immunoglobulin M</td>
<td>Positive virus B</td>
</tr>
<tr>
<td>Parvovirus B19 serology</td>
<td>Negative</td>
<td>Positive virus B</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis serology</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Antithymus antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Rhumatoid factors</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Proteins electrophoresis</td>
<td>A2B, A29, B5, B35, Cw4, Bw4, Bw6</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Histocompatibility leukocyte antigens</td>
<td>A2B, A29, B5, B35, Cw4, Bw4, Bw6</td>
<td>A2, B51, B8</td>
<td>Normal</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Ophthalmological slip</td>
<td>Uveitis</td>
<td>Interstitial keratitis</td>
<td>Interstitial keratitis</td>
</tr>
<tr>
<td>Cardiac echography</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Abdominal echography</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

- Air conduction thresholds: ○ right ear, × left ear, absence of response ↓ right ear, ↑ left ear
- Bone conduction thresholds: [ ] right ear, ] left ear
- Stapedius reflex thresholds: C+ sound in the left ear, right stapedius reflex recorded

Fig 1. Hearing thresholds at onset of Cogan’s syndrome for the 3 reported cases. In cases 2 and 3 the SNHL is associated with recruitment (gap between the thresholds of the stapedial reflexes [C+] and the air conduction hearing thresholds is clearly inferior to 70 dB).
later by conjunctivitis and uveitis, whereas hearing and vestibular loss appeared 2 months later. These events in our 3 cases could correspond to an over-stimulation of a fragile immune system triggering the onset of Cogan’s syndrome. This evidence argues for extreme prudence in managing immunizations in potentially vulnerable patients.

Cochleovestibular Lesions: Labyrinthitis

In the literature, the vestibular system in Cogan’s syndrome is affected before the cochlear system is by an interval of days or weeks.\(^7,28\) Most often vestibular damage is detected by clinical examination only, and instrumental vestibular testing is seldom realized, particularly in children. Cochlear damage is usually better documented.\(^30\)

In Cogan’s syndrome the hearing loss may have a sudden onset, as was the case with 2 patients in our series (cases 1 and 3). Fluctuating hearing loss may occur during the course of the disease,\(^29,31\) like in case 2. Without steroid treatment, it can rapidly progress to complete and definitive SNHL. In 2 cases (2 and 3) the gap between thresholds of hearing (air conduction) and the thresholds of the stapedial reflex (Fig. 1) was smaller than found in normal subjects. This indicates recruitment and an endocochlear mechanism of the SNHL supporting the hypothesis of labyrinthitis in these 2 cases.

In our study, we evaluated vestibular and cochlear function over the course of several years of follow-up. In case 2, vestibular function fluctuated as did cochlear function. In this case the vestibular damage affected only semicircular canals but otolithic function was spared. In the other 2 cases vestibular function was more severely impaired, suggesting a lesion of the whole sensorial vestibular apparatus.

In cases 1 and 2, the complete bilateral vestibular deficit was not disabling because of possible proprioceptive and visual compensation. But in case 3 the instability was disabling (particularly in darkness), likely because of the lack of proprioceptive and somesthetic information attributable to the degenerative polyneuropathy.

Radiologic investigations were often done in the cases reported in the literature. Computed tomographic scans are typically normal, whereas MRI with gadolinium may reveal lesions consistent with labyrinthitis, such as in case 3. This sign, although only rarely found, may depend on the stage of the inflammation at the level of the inner ear and could be a very temporary sign. In case 3, which involved 2 successive sudden hearing loss episodes at a 3-week interval (the first one on the right side and the second on the left), the MRI showed increased signal on T1 in the left ear (the side of sudden hearing loss at that time) but the MRI was normal for the other side. Although many authors propose repeated MRI to better evaluate the progression of the disease,\(^32-34\) this costly strategy may be less informative and effective than cochleovestibular functional evaluations.

Ophthalmologic Abnormalities

Initially, clinical ocular signs—including conjunctivitis, photophobia, and eye redness—are apparently benign. However, these symptoms must alert the ophthalmologist, especially if there is no obvious history of allergy. Intertitial keratitis represents the most typical lesion of ocular disease in Cogan’s syndrome; however, a slit-lamp examination is required to confirm the diagnosis. Inflammation may involve other tissues in the atypical forms, whether or not associated with interstitial keratitis.\(^3\) Uveitis associated with SNHL may be confused with Vogt-Koyanagi-Harada syndrome. The latter is an uveoencephalitis characterized by meningitis signs, a decrease of visual acuity with possible retinal separation and blindness, SNHL, and discoloration of hairs (poliosis) or alopecia. Poliosis and alopecia do not occur in Cogan’s syndrome, even if meningism is sometimes present.\(^32,33\) Iritis, scleritis,\(^4\) episcleritis, and chorioretinitis are rarely found in Cogan’s syndrome.

Systemic Manifestations

Cogan’s syndrome is an inflammatory disease not always restricted to the eyes and the inner ear. Systemic manifestations occurred in 63% of the cases of Yamanishi\(^26\) and 72% for Cheson.\(^35\) In 37% and 28% (respectively 26, 35), the disease is only localized to the eyes and inner ear, as in our cases 1 and 3. The systemic manifestations can occur from 2 months to 7 years\(^32,33,36\) after the first signs of Cogan’s syndrome. This illustrates the interest of long-term follow-up and the difficulties in the detection of these delayed lesions. Symptoms such as fever, arthralgia, myalgia, and weight loss are reported.\(^32,33\)

Systemic manifestation may be the first and only manifestation of Cogan’s syndrome for a long period, and this may delay diagnosis. This was the case in our second patient, whose fever, myalgia, and arthralgia occurred 1 month before the onset of audiveistibular loss.

However, systemic manifestations are basically attributable to systemic vasculitis of small, medium, and large vessels.\(^37\) The histologic characteristics of these lesions help rule out other causes of vasculitis, such as polyarteritis nodosa, Wegener’s granulomatosis, Takayasu’s disease, and Behçet’s disease.\(^5,37\)

Vascular lesions with thrombosis, stenosis, and bleeding can affect all organs. Cardiovascular manifestations are the most serious and represent 10% of cases of Cogan’s syndrome.\(^17,35\) Aortic insufficiency, coronary stenosis,\(^34,38\) pericarditis, and arrhythmia are the most common cardiac lesions. According to Haynes et al,\(^3\) aortic insufficiency is most common in typical Cogan’s syndrome, whereas systemic vasculitis occurs in the atypical form. This would suggest that typical Cogan’s syndrome should not be considered as a disorder strictly limited to the eyes and inner ear and that in a long-term follow-up a regular cardiac examination should be performed to promptly detect such complications for appropriate treatment.\(^35\)

Respiratory symptoms—including thoracic pain,
dyspnea, and hemoptysis or pleurisy—may occur. None of our patients had cardiovascular or respiratory problems.

Abdominal lesions such as gastrointestinal bleeding have been reported, and 1 case of Cogan’s syndrome was associated with Crohn’s disease. Neurologic manifestations are not specific, varying from headache to coma. Le Coz described 1 case of Cogan’s syndrome revealed by meningeal signs. Renal artery stenosis and cutaneous lesions (urticaria) have also been reported.

Treatment and Prognosis

Early diagnosis of Cogan’s syndrome is important because prompt treatment may prevent permanent profound hearing loss.

The most effective treatment is oral steroids. Promptly prescribed steroids can permit recovery of hearing. The inefficacy of delayed treatment is controversial. In our cases prednisone was administered at 1 mg/kg/day, the dose given in previously published cases of Cogan’s syndrome. However, some authors suggest that a higher dose of steroids (up to 2 mg/kg/day) during the 2 first weeks after onset of the disease would be more effective. Intravenous administration during the first week is recognized as preferable. However, such a high dose of steroids increases the risk of side effects.

In case of resistance to or dependence on steroids, some authors reported partial remissions when treatment was switched to or associated with methotrexate or cyclophosphamide. However, these drugs have adverse effects, which limit their prescription in children, and their efficacy is controversial in Cogan’s syndrome. For these reasons these agents should never be prescribed as a first treatment in children. In case 1, colchicine had been used because of steroid dependence and intolerance, but without success. In case 3 the serious dependence on steroids required a change in treatment to immunosuppressive drug therapy (methotrexate), but this treatment did not prevent recurrences.

The evolution of Cogan’s syndrome is unpredictable. The prognosis for hearing is usually poor over the long-term. Vollertsen et al reported 78 observations of Cogan’s syndrome in the literature, with poor prognosis in 63% of cases, including 43% with profound hearing loss or anacusis, 8% with total visual deficit, 14% with aortic insufficiency, and 9% who died. Cochlear implantation may be suggested in profound hearing loss, especially when it is associated with visual loss because the development of blindness can impede the acquisition of sign language communication.

CONCLUSION

Cogan’s syndrome is a systemic disease probably of autoimmune origin targeting preferentially the eyes and cochleovestibular apparatus. It can affect multiple organs other than the eyes or inner ears, and cardiac complications are not exceptional (10%). This syndrome must be familiar to otolaryngologists, ophthalmologists, pediatricians, and family physicians because delayed diagnosis can be deleterious to inner ear and visual sensoory organs attributable to delayed steroid treatment. The choice of therapy is difficult in the long-term because of the frequent side effects of the steroids and the risks of immunosuppressive drugs in children. In our experience Cogan’s syndrome appears to have been triggered by overstimulation of the immune system, which argues for caution regarding immunization, especially booster injections.

Prognosis of Cogan’s syndrome is difficult to evaluate in pediatric cases, and long-term follow-up is required to detect delayed complications, especially cardiovascular lesions, and to avoid their deleterious consequences. It is important to plan for the management of auditory and visual sensorial deficits, frequent after-effects of the disease.

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