Clinical Features and Outcome of Cogan Syndrome

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Objective To review the clinical features of Cogan syndrome, a rare vasculitis characterized by systemic, ocular, and audiovestibular symptoms.

Study design Clinical records of patients with Cogan syndrome followed at 2 pediatric rheumatology institutions and those from a database search were reviewed. Data included clinical features at onset and during the disease course, treatments, and outcomes.

Results Twenty-three children with Cogan syndrome (15 males; mean age, 11.4 years [range, 4-18 years]) were included in the analysis. Eleven patients (47.8%) exhibited systemic features at disease onset, including fever, arthralgias-arthritis or myalgias, headache, and weight loss. Twenty-one patients (91.3%) had ocular symptoms, due mainly to interstitial keratitis, uveitis, or conjunctivitis/episcleritis. Vestibular symptoms (39.1%) included vertigo, vomiting, and dizziness. Auditory involvement (65.2%) consisted of sensorineural hearing loss, tinnitus, and deafness. Four patients had cardiac valve involvement, and 3 had skin manifestations. After a median 2 years of follow-up, 30.4% of the patients were in clinical remission, but all others had irreversible complications (deafness, 21.7%; sensorineural hearing loss, 13.0%; vestibular dysfunction, 4.3%; ocular complications, 13.0%; cardiac valve damage, 17.4%).

Conclusion Audiovestibular and ocular involvement have a major impact on prognosis in children with Cogan syndrome. *(J Pediatr 2012;160:303-7)*.

Cogan syndrome is a rare vasculitis characterized by recurrent interstitial keratitis and audiovestibular symptoms including hearing loss, tinnitus, and vertigo.[1-5] Fever, fatigue, and weight loss may be present as well. Rarely, patients may exhibit enlarged lymph nodes, rash, chest or abdominal pain, night sweats, cardiac involvement, and shortness of breath.[6] Cogan syndrome usually occurs between the second and fourth decades of life, and only a few pediatric cases have been reported in the literature.

The actual incidence of Cogan syndrome is not known, because it may be overlooked and thus underdiagnosed. The majority of cases reported in the literature are Caucasians, and no sex predominance has been observed.[3,5] The etiology is also unknown, but an infectious trigger, such as an upper respiratory tract infection, is frequently reported. Studies have suggested an association with *Chlamydia* infection or vaccination for tuberculosis.[7,8]

Although the pathogenesis of the disease is not known, Cogan syndrome is generally considered an autoimmune disease.[5,9] This hypothesis is supported by the frequently successful remission of hearing loss after steroid administration, the positive transformation of the lymphoblastic test on cochlear antigen stimulation, the association with other autoimmune disorders such as rheumatoid arthritis, and the demonstration of antibodies against corneal and inner ear tissue.[5,6,10,11] The presence of antiphospholipid antibodies and antineutrophil cytoplasmic antibodies and an association with antigens of the human leukocyte antigen system, such as A9, Bw17, Bw35, and Cw4, also have been reported.[12-14]

Because the disease has been rarely described in the pediatric age group, here we report our own cases and review the literature on children with Cogan syndrome to analyze the clinical manifestations of the disease at onset and over its course, treatment approaches, and outcomes.

Methods

Since 1995, we have followed 3 patients with Cogan syndrome who had at least 1 year of follow-up. Two of these patients have been seen at the Pediatric Rheumatology Unit of Padua, and the other has been treated at the Pediatric Rheumatology Unit of the Meyer Children's Hospital in Florence. To investigate the clinical course and prognosis of the Cogan syndrome presenting in childhood, we conducted a MEDLINE search of all articles published in the English language during the last 30 years. The terms used

ENT	Ear, nose, and throat
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drugs
SNHL	Sensorineural hearing loss

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for the search were "Cogan syndrome in childhood" in combination with "interstitial keratitis," "vestibular dysfunction," and "vasculitis and hearing loss." Because there are no diagnostic criteria for children with Cogan syndrome, we based our selection on the authors' clinical diagnosis of Cogan syndrome. Articles with incomplete clinical data, short follow-up, or more than one description of the same case were excluded. Sixteen of 19 articles, reporting 20 patients with disease onset by 18 years of age, eventually fulfilled our selection criteria.[2,4,8,15-27] We extracted the same data from these case histories and from our 3 patients and constructed a customized database by entering demographic and clinical variables.

follow-up. The clinical features at disease onset and over the course of disease included systemic signs and/or symptoms (eg, fever, arthralgia, arthritis, myalgias, headache, weight loss, anorexia, thoracic or abdominal pain), ocular signs and symptoms (eg, ocular hyperemia, photophobia, vision loss, interstitial keratitis, uveitis, conjunctivitis, episcleritis), vestibular signs and symptoms (eg, vertigo, nausea or vomiting, dizziness), auditory signs and symptoms (eg, tinnitus, sensorineural hearing loss [SNHL], deafness), cardiovascular manifestations (eg, valvular insufficiency, vascular aneurysms), and cutaneous changes (eg, skin rash and urticarial vasculitis).

The patients were treated with corticosteroids (eg, oral prednisone, deflazacort), pulsed intravenous methyprednisolone, immunosuppressive drugs (eg, cyclosphosphamide, methotrexate/leflunomide, mycophenolate mofetil), and topical ocular drops.

Outcome was defined as complete clinical remission in the absence of signs and symptoms of active disease or irreversible complications, and as severe clinical course in the presence of signs and symptoms of active disease and/or complications, such as irreversible SNHL, deafness, vestibular dysfunction, and irreversible ocular or cardiovascular complications, at the last follow-up visit.

Statistical Analysis

Demographic variables and clinical features were analyzed using descriptive statistics. The χ^2 test and Fisher exact test were used, as appropriate, to compare the categorical variables between 2 groups: good outcome and poor outcome. McNemar's test was used to compare frequencies in paired observations (at onset and over the follow-up). Finally, a logistic regression model (backward stepwise method) was applied to determine which of a set of explanatory variables (ie, sex, age at onset, delay of treatment, or clinical features at onset) was predictive of the final outcome.

All statistical tests were 2-sided, and a P value $<.05$ was considered significant. Statistical analyses were performed using SPSS version 14.0 for Windows (SPSS Inc, Chicago, Illinois).

Case Histories

Case 1 is a previously healthy 4-year-old Caucasian boy who developed bulbar conjunctivitis, intermittent fever (up to 39-40°C), and arthralgia 10 days after a mild upper respiratory tract infection. He was admitted to a community hospital, where he developed abdominal pain, transient macular rash, and arthritis of the right knee. He was diagnosed with Kawasaki disease and treated with intravenous gammaglobulins, without benefit. Two weeks after disease onset, he was referred to the Pediatric Rheumatology Center of Padua. Physical examination showed an irritable boy with a weight loss of 2 kg, conjunctivitis, photophobia, high-grade fever, and arthritis of the right knee and ankle. Because the boy complained of transient vertigo and hearing problems, an ear, nose, and throat (ENT) evaluation was performed that revealed moderate to severe bilateral SNHL with depressed speech discrimination. Bilateral interstitial keratitis and aortic and mitral valve insufficiency were also identified.

Laboratory tests revealed anemia (hemoglobin, 7.5 g/L), leukocytosis (white blood cell count, 16 600/mmc), a high platelet count (797 000/mm^3), an erythocyte sedimentation rate of 129 mm/hour, and a C-reactive protein level of 115 mg/L. Levels of anitnuclear antibodies, extractable nuclear antigens antibodies, rheumatoid factor, complement fractions, antineutrophil cytoplasmic antibodies, and antineutrophil perinuclear antibodies and the general biochemical profile were normal or negative. Culture for bacteria and viruses from blood, throat, and urine were all negative, and syphilis was excluded.

The patient was diagnosed with Cogan syndrome, and treatment with oral prednisone (1.5 mg/kg/day) was started. Fever rapidly disappeared, aortic and mitral valve function improved in 3 weeks, and ocular involvement normalized. Hearing loss improved, and after 6 weeks of treatment, his audiogram was completely normal.

The patient has been followed closely, with rheumatologic, ophthalmologic, ENT, and cardiologic evaluations every 6 months. Corticosteroid treatment was stopped after 9 months. At the most recent follow-up, at age 20 years, he was asymptomatic except for persistent slight mitral insufficiency.

Case 2 is a previously healthy 9-year-old girl who, at 1 week after febrile gastroenteritis, developed abdominal and back pain, headache, and vertigo. She was admitted to a community hospital, where she developed arthritis of the left hip, tinnitus, and bilateral hearing loss. Her neurologic evaluation was negative, as were brain computed tomography and magnetic resonance imaging (MRI) scans. Gadolinium-enhanced MRI of the inner ear revealed bilateral labyrinthitis. ENT evaluation documented a severe bilateral SNHL. Treatment with antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and intravenous gammaglobulins was started but was ineffective, with all signs and symptoms persisting. Two months later, while on NSAID treatment, she developed bilateral photophobia, ocular pain, and redness, at which point she was referred to the Pediatric Rheumatology Center of Padua. Ophthalmologic examination revealed bilateral interstitial keratitis, and ENT evaluation confirmed the presence of severe bilateral SNHL. Laboratory tests showed microcytic anemia (hemoglobin, 8.8 g/L), leukocytosis (white blood cell count, 17 940/mmc), high platelet count (553 000/mmc), and erythrocyte sedimentation rate and