Diagnostic Difficulties of Cogan Syndrome

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Abstract

Cogan’s syndrome (CS) is a very rare disorder of unknown origin characterised by inflammatory eye disease and vestibuloaditory symptoms. According to the International Chapel Hill Consensus Conference Nomenclature of Vasculitides, CS is defined as “variable vessel vasculitis”. We present the case of a 44-year old male, primarily diagnosed and treated for large/medium vessel vasculitis probably due to indeterminate colitis, who finally developed CS. Difficulties in the diagnosis of this rare disease are also discussed.

Keywords: Cogan syndrome; Exophtalmos; Inflammatory eye disease; Chronic diarrhea; Sudden hearing loss

Introduction

Cogan’s syndrome (CS) is a rare disorder characterised by inflammatory eye disease and vestibuloaditory symptoms. In about 30% of cases it can be associated with other systemic inflammatory manifestations such as fever, arthralgia, skin rash, gastrointestinal tract involvement and vasculitis [1]. Vasculitic manifestations include mainly arteritis affecting small, medium or large arteries and according to the International Chapel Hill Consensus Conference Nomenclature of Vasculitides, CS is defined as “variable vessel vasculitis” [1]. The onset of the disease is preceded in approximately 20% of cases by an infection, especially Chlamydia psittaci [2] and Chlamydia trachomatis [3]. Recent evidence strongly suggests that CS is an autoimmune disease that is mediated by a hypersensitive response to infectious agents associated with vasculitis [3-5]. We present the case of a 44-year old male, primarily diagnosed and treated for large/medium vessel vasculitis probably resulting from indeterminate colitis, who developed CS with inflammatory eye disease and vestibuloaditory symptoms. We discuss the diagnostic difficulties in this rare disease.

Case Report

A 44-year old male, a pigeon-fancier, was admitted to the hospital due to general weakness secondary to recurrent periods of fever (maximum 38.5°C), chronic watery diarrhea accompanied by severe headache and ophthalmopathy with decreased vision. All the symptoms occurred several months before hospitalization and gradually intensified. Physical examination revealed only bilateral exophtalmos. Laboratory tests had shown leukocytosis (white blood count 17.9*10^9/l), thrombocytosis (platelet count 600*10^9/l), mild anemia (hemoglobin level 11.6 g/dl), marked elevation of inflammatory markers (ESR 100 mm/h, CRP 10.9 mg/l) and an active urine sediment. Based on laboratory, serological and microbiological test, immunodeficiencies, Lyme disease, toxoplasmosis, the most common viral infections (hepatitis B and C, cytomegrovirus and HIV), atypical respiratory (Mycoplasma pneumonia and Chlamydia pneumonia) and urogenital (Ureaplasma urealyticum) infections were excluded. The blood, urine and stool cultures were also negative. Ophthalmological examination revealed changes suggestive of viral or autoimmune aetiology (Figure 1). Despite empiric antibiotic therapy (amoxicillin with clavulanic acid, ciprofloxacin) there was no clinical improvement and elevated leukocytosis, and inflammatory markers were still present (Table 1). Diagnostic Computed Tomography (CT) of the head, neck, thorax and abdomen, magnetic resonance imaging (MRI) of the orbits, echocardiography, carotid and thyroid Doppler ultrasound imaging were performed. Pathological findings included inflammatory infiltration

Figure 1: Right corneal lesions in the slit-lamp examination. Circular scars in the cornea (asterix), corneal infiltrates (best seen on the background of the pupil and around it), superficially and deeply ingrown vessels (arrow).

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anemia, marked elevation of inflammatory markers), imaging (thickening of the arterial walls) and immunological (lack of ANCA, the presence of antiendothelial cell antibodies), after exclusion of active infections, led to the most probable diagnosis of the large/medium vessel vasculitis in the course of indeterminate colitis. A total dose of 2.5 g (5 × 500 mg) of intravenous (iv.) methylprednisolone with subsequent oral steroid therapy (prednisone 1 mg per kg per day) in tapered doses and azathioprine (2 mg per kg per day) were administrated. Central ulceration of the left cornea was initially treated with antibiotics in drops (levofloxacin and azithromycin) and then a solution of 0.1% dexamethasone and 0.05% cyclosporine in eye drops was used to reduce extant symptoms in both eyes. Regression of the exophthalmos, relief of the diarrhea and fever, as well as general improvement were achieved. The inflammatory bowel disease (IBD) was finally excluded by gastroenterologists on the basis of magnetic resonance enterography and double-performed histopathological examination of the intestinal wall.

During the following twenty months there were periods of exacerbations and improvement in ophthalmic changes (exophthalmia, conjunctival chemosis) as well as in inflammatory markers in laboratory tests (but these were not so high as before the immunosuppressive treatment). The patient was treated with prednisone (the average dose 20 mg, daily) and cyclosporine (150 mg twice a day) orally, and both 0.1% dexamethasone and 0.05% cyclosporine topically in eye drops. Two twenty two months after the onset of the initial symptoms, even though continuous immunosuppression has been provided, the patient suffered sudden left sensorineural hearing loss with vertigo, paralytic right-beating horizontal-rotatory nystagmus (Figure 2a) and tinnitus with accompanying nausea and fever. In Romberg's test he fell to the left, indicating the free phase of nystagmus. Otolaryngological examination revealed no abnormalities. Pure tone audiometry (PTA) showed left-sided sensorineural hearing loss (Figure 2b). Videonystagmography (VNG) revealed left canal paralysis. In addition to immunosuppressive therapy, lidocaine, hydrocortisone, pentoxifylline and vitamins (B1 and B6) were applied but with no hearing improvement. Despite treatment, after two weeks the patient developed right-sided sensorineural hearing loss and the left-sided hearing loss was intensified. There was no hearing improvement after systemic steroids either (Figure 2c). Brainstem auditory evoked potentials (BAEPs) (Figure 2d) revealed no retrocochlear type of hearing deterioration. The result of a tympanometric examination was normal (Figure 2e and 2f). The patient reported persistent tinnitus localised in both ears, which was slightly reduced after the use of a hearing-aid in the right ear. In the meantime fluid in the right sub-Tenon's space and the rotary horizontal nystagmus to the right were observed. In laboratory tests inflammatory markers (ESR 79 mm/h, CRP 266 mg/l) and leukocytosis (WBC 27.1 10^9/l) were elevated, but ANCA remained negative (Table 1). During the following week the same symptoms appeared in association with the other ear. A series of treatments in a hyperbaric chamber was prescribed as additional therapy but with no improvement. Blurred vision with aggravated corneal lesions, in this circumstance recognized as interstitial keratitis (IK), also reappeared. Based on clinical presentation, the symptoms of inflammatory eye disease with vestibuloauditory involvement as well as large/medium vasculitis recognized 2 years earlier led us to identify vasculitis in CS. Methylprednisolone infusion and cyclophosphamide (CYC) treatment was then administrated. A total dose of 7.0 g of CYC was given in 1.0 g i.v. pulses every three weeks. In view of the patient's long-term contact with pigeons,

suspecting infectious background of the exacerbations, the antibodies against Chlamydophila psittaci were checked, and IgA antibodies were present. Taking into account described in the literature the relationship between Chlamydophila psittaci infection and CS it was decided to antibiotics. Macrolide antibiotic treatment was administrated for three months (Azithromycinum 500 mg, daily three days in a week) in conjunction with immunosuppressive therapy.

After six months of treatment partial remission was achieved. Ultrasound of the eye showed more severe bilateral thickening of the back wall of the eyeball in the right eye. Moreover, the wall of the right eyeball was irregular and a "T-sign" was present (Figure 3). Spectral Domain Optical Coherence Tomography showed the actual position of corneal scars and confirmed ectasia of the cornea (Figure 4). For the time being, the patient remains under the rheumatologic and ophthalmologic care. Immunosuppressive treatment is still ongoing at the time of the writing (prednisone 30 mg, daily and azathioprine 100 mg, daily orally, as well as 0.05% cyclosporine twice a day and 0.1% dexamethasone once a day in eye drops).

Discussion

In 1980 Haynes et al. proposed diagnostic criteria for typical and atypical Cogan's syndrome (CS) according to the type of its ocular manifestations (Table 2) [3,6]. Presence of IK implies classification as typical CS. In atypical CS many other ocular lesions have been reported,
either in isolation or in association with IK. These include episcleritis or scleritis, retinitis, optical neuritis, glaucoma, papillary oedema, cataracts, ocular motor palsy, exophthalmia, central retinal artery occlusion, xerophthalmia, ptosis and tendonitis [3,6]. Exophthalmos was one of the initial symptoms in the presented case. Thyroid eye disease, the main cause of exophthalmos [7], was excluded in our patient. Improvement after immunosuppressive therapy was evidence of the autoimmune background of the disease [8-12]. Episcleritis is often linked to autoimmune diseases and it may also occur in CS [3,6]. In this case it was accompanied by unilateral posterior scleritis [3,9,13] appeared during ultrasonography of the eyeballs as the presence of fluid under the right sub-Tenon’s space and thickening of the back wall of the eyeballs. We conclude that those changes were the dominant cause of

Table 1: Laboratory test results.

| Laboratory test | Normal range | Results in the time of diagnosis of vasculitis | Results at the onset of vestibulocochlear symptoms |
|-----------------|--------------|-----------------------------------------------|--------------------------------------------------|
| WBC (10^9/l)    | 4.0-10.0     | 17.9                                          | 27.1                                             |
| Hgb (g/dl)      | 12.0-15.0    | 11.6                                          | 13.2                                             |
| PLT (10^9/l)    | 150-410      | 600                                           | 203                                              |
| ESR (mm/h)      | 2-30         | 100                                           | 79                                               |
| CRP (mg/l)      | 0.0-5.0      | 10.9                                          | 266.4                                            |
| Procalcitonin   | <0.1 ng/ml   | <0.1                                          | <0.1                                             |
| AIAT (UI)       | <55          | 23                                            | 26                                               |
| AspAT (UI)      | 5-34         | 14                                            | 12                                               |
| GGTP (UI)       | 9-36         | 262                                           | 35                                               |
| Urine specific gravity | 1.018-1.030 | 1.025                                         | 1.025                                            |
| urine pH        | 5.0-8.0      | 5.5                                           | 5.0                                              |
| RBCs in urine (HPF) | <3          | 4-10                                          | 4-10                                             |
| WBCs in urine (HPF) | 1-5         | 8-10                                          | 1-5                                              |
| protein in urine | negative     | trace                                         | trace                                            |
| TSH (IU/ml)     | 0.27-4.20    | 1.09                                          | 0.76                                             |
| Ferrum (µg/dl)  | 59-158       | 24                                            | 25                                               |
| Ferritin (ng/ml) | 30-400       | 947                                           | 384                                              |
| C3 (g/l)        | 0.9-1.8      | 2.0                                           | np                                               |
| C4 (g/l)        | 0.1-0.4      | 0.4                                           | np                                               |
| IgG (g/l)       | 7.0-16.0     | 18.03                                         | np                                               |
| IgM (g/l)       | 0.4-2.3      | 1.1                                           | np                                               |
| IgA (g/l)       | 0.7-4.0      | 3.02                                          | np                                               |
| ANA HEp2        | 1:100        | 1:100                                         | np                                               |
| anti-CCP (RU/ml)| 0.0-5.0      | 2.7                                           | np                                               |
| ANCA-anti-neutrophil cytoplasmic antibodies | <1:40 | negative | negative |
| ANCA-PR3 (RU/ml)| <20          | 2.0                                           | np                                               |
| ANCA-MPO (RU/ml)| <20          | 2.0                                           | np                                               |
| ANCA-profile (anti-PR3, anti-LF-E, anti-MPO, anti-CAT, anti-BPI) | <1.0 | <0.1 | np |
| Immunological complexes C1q (RU/ml) | <20 | 68.2 | 11.9 |
| C3d (µg/ml) | <40 | 77.3 | 0.03 |
| Anti-TSH (TRAB) (IU/l) | <1.0 | 0.51 | <20 |
| ASCA (Anti-saccharomyces cerevisiae antibodies) (IU/ml) | IgA <10 | 34.15 | 0.74 |
| AECA (antiendothelial cell antibodies) | <1:10 | 1:10 | 1:20 |

Figure 3: Ultrasound image of the right eyeball - HAX projection. (A) Thickening and irregular shape of the eyeball’s back wall - “T-sign”. (B) “T-sign” marked with red line.

Figure 4: Spectral domain optical coherence tomography images of corneas. Scars located in the corneal stroma (reddish area). Concomitant tissue contraction (ectasia). Right eye (OD) on the left and left eye (OS) on the right side.
and mouth ulcerations, skin changes, patergy reaction, alopecia and antibodies, RA was excluded in our patient. An absence of orogenital Vogt-Koyanagi-Harada syndrome, sarcoidosis and giant-cell arteritis polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), conditions that cause similar ocular and audiovestibular manifestations, the eyes changes were the initial symptom of CS in this case. Involving the inner ear, enabled CS to be identified. We believe, that picture suggested vasculitis secondary to inflammatory bowel disease presented here followed a different course, greatly hindering proper onset of the disease. Both ophthalmological and vestibuloauditory a prodrome very similar to a viral infection a few weeks preceding the are extremely variable. As reported in the literature, there is frequently a delay of more than 2 years between the onset of typical ocular and vestibuloauditory manifestations.

| Atypical Cogan's syndrome |
|---------------------------|
| 1. inflammatory ocular manifestations, with or without IK |
| 2. typical ocular manifestations associated with audiovestibular symptoms different from Meniere-like episodes |
| 3. a delay of more than 2 years between the onset of typical ocular and audiovestibular manifestations |

Table 2: Diagnostic criteria for typical and atypical Cogan's syndrome.

The diagnosis of typical CS is made on the basis of non-syphilitic IK, acute-onset sensorineural hearing loss, tinnitus, and vertigo. Recurrent episodes of inner ear disease frequently result in profound hearing loss, and the subject of the present case became completely deaf in about six weeks. In a retrospective series of 60 patients from one centre hearing loss was typically sudden, bilateral, fluctuating, and progressive, resulting in complete hearing loss in most cases [14]. Typically, audiometry testing demonstrates a sensorineural hearing loss, preferentially involving the low and high range frequencies. Hearing loss is often bilateral from the onset, but in some patients it may be unilateral initially, becoming bilateral later. In a review by Vollertsen et al. bilateral deafness affected 43.5% of patients and occurred on average three months after the onset of the initial symptoms [4].

The differential diagnosis of CS is made on the basis of various conditions that cause similar ocular and audiovestibular manifestations, polymyositis nodosa (PAN), granulomatosis with polyangiitis (GPA), relapsing polychondritis, rheumatoid arthritis (RA), Susac’s syndrome, Vogt-Koyanagi-Harada syndrome, sarcoidosis and giant-cell arteritis (GCA). In view of the absence of joint problems and lack of aCCP antibodies, RA was excluded in our patient. An absence of orogenital and mouth ulcerations, skin changes, patergy reaction, alopecia and vitiligo enabled us also to exclude Behçet's and Vogt-Koyanagi-Harada syndromes. Similarly, lack of changes in MRI of the brain allowed us to rule out Susac’s syndrome. ANCA negativity and no symptoms of small vessel involvement led us to exclude ANCA-associated vasculitis. Similarly the fact that there was no typical presentation of upper and lower respiratory tract involvement led us also to exclude GPA. Ocular manifestations of giant cell arteritis have a different form than in CS.

There was still a suspicion of IBD as a cause of symptoms in our patient. It has been reported that there is an association between CS and IBD [15], and the high level of ASCA along with gastrointestinal symptoms made the diagnosis of IBD likely. Many studies have reported the simultaneous presence of ASCA IgA and IgG to be highly specific for Crohn’s disease (CD). However, the absence of any typical changes in the microscopic bowel examination and in MRI ruled this disease out. In our opinion the gastrointestinal symptoms presented in our patient were the first sign of disease. Graslund et al. in their group of 32 patients with CS diagnosed 10 patients with gastrointestinal problems including abdominal pain, splenomegaly, hepatitis, oesophagitis and liver steatosis [6]. Various gastrointestinal manifestations, including diarrhea, melena and abdominal pain, sometimes related to mesenteric arteritis, have also been reported in the literature [4].

One of the factors potentially responsible for the development of the disease is chlamydial infection. There is some data in the literature concerning a link between CS and chronic chlamydial infection [2]. Long-term contact with pigeons, along with positive serology against Chlamydia psittaci, suggests chronic infection as a trigger for a CS in this case. Therefore, despite the presence of only IgA antibodies, it was decided to antibiotic therapy. Because of the absence of appropriate guidelines, the duration of treatment was based analogously to the treatment of chlamydial reactive arthritis.

The treatment of CS depends on the extent of the disease. If a mild eye involvement is the only manifestation, topical glucocorticoids are the treatment of choice. In cases of systemic vasculitis or hearing loss, however, systemic immunosuppressive therapy is required. Glucocorticoids (prednisolone 1 mg/kg) are the first-choice agents. If the response is incomplete, the addition of another immunosuppressive agent (methotrexate, cyclophosphamide, azathioprine, cyclosporine) should be considered [8]. Observations have also been made on the positive effect of rituximab [16], and anti-TNF blockers [17] in the treatment of patients with CS.

The prognosis for the maintenance of vision and the resolution of inflammatory eye lesions is generally good, but deafness generally remains permanent despite immunosuppressive treatment. An allogeneic corneal transplantation was considered to improve visual acuity [11]. Corneal transplantation may perhaps be possible in the future after stabilisation of the ocular lesions and the patient’s general condition. Similarly, with respect to the deafness, cochlear implants are planned, as these are believed to be effective in patients with deafness in the course of CS.

One should also be aware of the potentially life-threatening complication of CS – vasculitis. Aortitis, which may develop within weeks to years of disease onset, has been described in approximately 10 percent of patients [3,8]. It may cause proximal aorta dilation, aortic valvular regurgitation, ostial coronary artery disease, and thoracoabdominal aortic aneurysms.

Conclusions

Cogan’s syndrome is a rare autoimmune vasculitis with ocular and audiovestibular involvement. Atypical initial ophthalmologic symptoms
with predominant symptoms of gastrointestinal tract involvement may imitate IBD. The occurrence of audiovestibular symptoms associated with ophthalmological changes indicates a correct diagnosis. Early assessment and treatment of the systemic inflammation are needed to prevent a complete loss of sight and hearing, and life-threatening complications, in particular, vasculitis such as aortitis.

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