CASE REPORT

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Cogan's syndrome – A case series

Cogan-ov sindrom – serija slučajeva

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Abstract

Introduction. Cogan's syndrome is a rare variable vessel vasculitis. It can be typical and atypical. Basis of the treatment comprises glucocorticoids, and in patients with systemic manifestations, immunosuppressive drugs. **Case report.** We wanted to present the experience of the Clinic for Rheumatology and Clinical Immunology of the Military Medical Academy, Belgrade, in diagnosing and treating patients suffering from Cogan's syndrome. The analysis included 7 patients. Patients' demographic characteristics, disease manifestations, course of the disease, applied treatment and treatment outcome were analysed. Five of the patients were women and 2 were men, with the average age of 39 ± 13 (25–65) years. The typical form of the disease manifested in 1 patient. In 6 patients, the first manifestation was the audiovestibular dysfunction. In 1 patient, systemic manifestations were the first to appear. In the cases where the disease manifested atypically, 3 patients developed conjunctivitis, 2 episcleritis, and 1 uveitis. They all had systemic manifestations. One female patient was diagnosed with aortitis and aortic insufficiency. They all tested positive for inflammatory biohumoral syndrome. Four patients had positive antinuclear antibodies, 3 anticytoplasmic antibodies, and 1 positive rheumatoid factor. They were all treated with glucocorticoid and immunosuppressive drugs. Methotrexate was administered to all the patients in doses up to 20 mg per week. Pulses of cyclophosphamide were administered to 2 female patients. All patients went successfully into remission. The female patient with the typical form of the disease experienced permanent bilateral hearing loss. **Conclusion.** Patients with a rapidly developed audiovestibular dysfunction should be viewed as suffering from Cogan's syndrome from the viewpoint of differential diagnosis. A timely treatment with glucocorticoids can prevent hearing loss and the development of systemic manifestations of the disease. Precedence should be given to methotrexate when selecting an immunosuppressive drug.

Key words:
cogan syndrome; vasculitis; vestibular diseases; keratitis; adrenal cortex hormones; immunosuppressive agents.

Apstrakt

Uvod. Cogan-ov sindrom je zajedno sa Behcet-ovim sindromom prema najnovijoj klasifikaciji svrstan u grupu posebnih vaskulitisnih sindroma. Može biti tipičan i atipičan. Osnov lečenja čine glukokortikoidi, a kod bolesnika sa sistemskim manifestacijama i imunosupresivi. **Prikaz slučaja.** Prikazali smo iskustvo Klinike za reumatologiju i kliničku imunologiju Vojnomedicinske akademije, Beograd, u dijagnostici i lečenju bolesnika sa Cogan-ovim sindromom. Analizom je obuhvaćeno sedam bolesnika dijagnostikovanih i lečenih u periodu od 2004. do 2016. godine. Analizirane su demografske karakteristike obolelih, manifestacije i tok bolesti do dijagnoze, primenjena terapija i ishod lečenja. Od ukupno sedam bolesnika pet su bile žene i dva muškarca, prosečne životne dobi od 39 ± 13 (25–65) godina. Tipičnu formu bolesti imao je jedan, a atipičnu 6 bolesnika. Kod šest bolesnika prva manifestacija bolesti bile su vrtoglavica i naglo slabljenje sluha. Samo kod jednog bolesnika prvo su se ispoljile sistemske manifestacije. U slučajevima atipičnog Cogan-ovog sindroma tri bolesnika su imala konjuktivitis, dva episkleritis i jedan uveitis. Svi bolesnici imali su sistemske manifestacije. Kod jedne bolesnice dijagnostikovan je aortitis sa posledičnom insuficijencijom aortne valvule. Svi bolesnici imali su pozitivan zapaljenski biohumoralni sindrom. Tri bolesnika imala su pozitivna antinuklearna antitela a dva perinuklearna anticitoplazmatska antitela. Svi su lečeni glukokortikoidima i imunosupresivnim lekovima. Metotreksat je primenjen kod šest bolesnika u dozi do 20 mg nedeljno. Pulsne doze ciklofosfamida primenjene su kod dve bolesnice. Kod svih bolesnika postignuta je remisija bolesti. Kod bolesnice sa tipičnom formom bolesti gubitak sluha bio je obostran i trajan. **Zaključak.** Bolesnike sa naglo nastalom audiovestibularnom disfunkcijom uvek treba dife-

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rencijalno dijagnostički posmatrati kao Cogan-ov sindrom. Na vreme započeta terapija glukokortikoidima može sprečiti gubitak sluha i razvoj sistemskih manifestacija bolesti. Među imunosupresivnim lekovima prednost treba dati metotreksatu.

Ključne reči:
coganov sindrom; vaskulitis; vestibularni aparat, bolesti; keratitis; kortikosteroidni hormoni; imunosupresivi.

Introduction

In 1945, David Cogan [1], an ophthalmologist, was the first who identified and described the clinical entity in which the major manifestations include interstitial keratitis (IK) and audiovestibular dysfunction that is similar to that of Ménière's disease. In 1980, Haynes et al. [2] defined the diagnostic criteria for the typical and atypical Cogan's syndrome. With the development of medical knowledge, Cogan's and Behcet's syndrome were classified into a special category of systemic vasculitides [3]. Cogan's syndrome is a rare disease. Over 250 cases have been described in literature so far [4–6]. Patients with IK have red eyes, photophobia and pain [2, 4, 6]. In most of the patients both eyes are affected. In the atypical forms, other structures of the eye are affected, in isolation or in conjunction with IK. Episcleritis or scleritis, retinitis, optic neuritis, glaucoma, papilloedema, central retinal artery occlusion, ptosis, exophthalmus and other manifestations may occur [6]. Audiovestibular manifestations in Cogan's syndrome are similar to those of Ménière's syndrome [1, 2, 4]. Hearing loss is progressive. According to literature, bilateral hearing loss occurred in up to 43% of such patients [4, 6]. Approximately, two thirds of the patients had systemic manifestations (febrility, headache, arthritis, large vessel vasculitis, etc.). Cogan's syndrome can occur in people of all ages, but usually it affects young adults. It equally affects both sexes. The etiology of the disease is unknown. Infections and autoimmune disorders are cited as being the predisposing factors of the disease. In favour of the immunological theory there are findings of antibodies in cornea, anticochlear antibodies (anti-HSP70), antiendothelial antibodies, antinuclear antibodies (ANA), rheumatoid factor (RF) and antineutrophil cytoplasmic antibodies (ANCA) [7–10]. The basis of the treatment comprise glucocorticoids (GCs) [11, 12]. In patents with systemic vasculitis, it is necessary to administer immunosuppressive drugs alongside GCs [13, 14].

The aim of our work is to present our experience in diagnosing and treating 7 patients suffering from Cogan's syndrome.

Case report

A retrospective analysis included 7 patients diagnosed and treated at the Clinic for Rheumatology and Clinical Immunology of the Military Medical Academy, Belgrade, Serbia, between 2004 and 2016. The patients' demographic characteristics, audiovestibular, ophthalmological and systemic manifestations of the disease, the effects of the applied therapy and course of the disease were analysed. The Cogan's and Hayne's original criteria were used for the classification of Cogan's syndrome into typical and atypical [1, 2]. The typical form of the disease is characterised by: interstitial keratitis, audiovestibular symptoms akin to those of Ménière's disease including hearing loss and the interval between the onset of eye disease and audiovestibular manifestations shorter than 2 years. The atypical form of Cogan's syndrome is characterised by: absence of IK, the absence of audiovestibular manifestations akin to those of Ménière's syndrome in patients with IK and the interval between the onset of eye disease and ear disease longer than 2 years.

Out of 7 patients, 5 were women and 2 men, with the average age at the onset of the disease being 39 ± 13 (25–65) years. One patient had the typical form of the disease (Table 1). From the onset of the first symptoms until the diagnosis of the disease passed on average 4.3 years (2 months to 15 years). The first manifestation of the disease in 6 patients was the audiovestibular dysfunction similar to that of Ménière's syndrome. Only in 1 female patient the audiovestibular dysfunctions and eye disease were preceded by systemic manifestations. Only the female patient with the typical form of the disease had interstitial keratitis. Three patients had scleritis (Figures 1 and 2), 2 conjunctivitis and 1 patient had uveitis.

Table 1

Patients' characteristics

Patient No	Type of disease	Age (yrs)*	Sex	First manifestation	Changes to the eye	Interval** (month)	Until diagnosed
1	Typical	39	F	Vertigo, bilateral hearing loss	Interstitial keratitis	1	2 months
2	Atypical	24	F	Vertigo, unilateral hearing loss	Uveitis	12	15 years
3	Atypical	26	F	Systemic manifestations, unilateral mild hearing loss	Scleritis	24	6 years
4	Atypical	43	M	Vertigo, bilateral hearing loss	Scleritis	2	6 months
5	Atypical	35	F	Vertigo, unilateral mild hearing loss	Scleritis	3	4 months
6	Atypical	22	M	Vertigo, unilateral mild hearing loss	Conjunctivitis	10	4 years
7	Atypical	65	F	Vertigo, unilateral hearing loss	Conjunctivitis	5	1 years

***At the onset of disease; **The period between vestibular dysfunction and eye disease.**

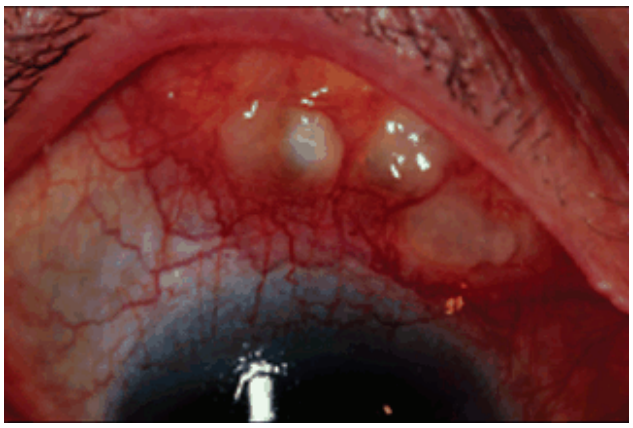

Fig. 1 – Scleritis in one of the patients with Cogan's syndrome.

All 7 patients had systemic manifestations (Table 2). They all had polyarthritis, 4 had headaches, 3 had fever, 1 had lymphadenopathy and splenomegaly and 1 patient had auricular chondritis. The female patient with the typical form of the disease developed aortitis with consequent aortic insufficiency and malignant arrhythmia (Figure 3). Six patients had an accelerated erythrocyte sedimentation rate during the active phase of the disease, (Table 3). The average rate was equal to 69 ± 39 mm/h (8–129). Two patients had anaemia. ANA were detected in 4 patients, ANCA in 3 patients, and rheumatoid factor RF in 1 patient.

All patients were treated with GCs locally and systemically before being diagnosed (Table 4). The treatment would be stopped after the symptoms and signs of ear and eye disease subsided. In the female patient with the typical form of the disease who developed bilateral hearing loss systemic administration of glucocorticoids was commenced one month after the onset of audiovestibular symptomatology. From the moment the patients were diagnosed with Cogan's syndrome, they were all treated with GCs at an initial dose of 0.5–1 mg/kg body weight (BW) of prednisone per day.

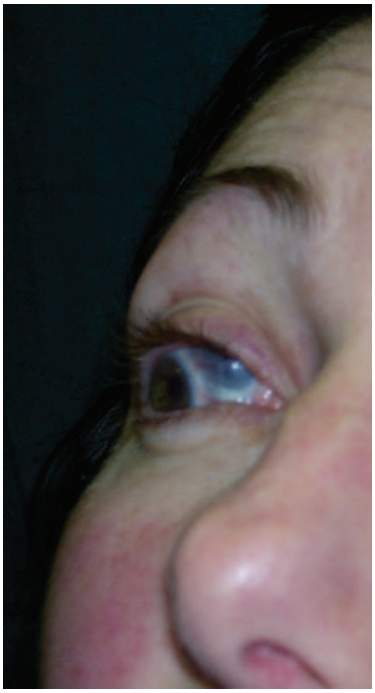

Fig. 2 – The consequence of scleritis.

Table 2

Systemic manifestations of the disease

Patient No	Type of disease	Systemic manifestations
1	Typical	Fever, headache, arthritis, aortitis
2	Atypical	Arthritis
3	Atypical	Fever, headache, arthritis, lymphadenopathy, splenomegaly, chondritis
4	Atypical	Arthritis
5	Atypical	Fever, headache, arthritis
6	Atypical	Arthritis
7	Atypical	Arthritis, headache

Table 3

The results of laboratory tests

Patient No	Type of disease	Erythrocyte sedimentation rate (ESR) mm/h	Anaemia	Autoantibodies
1	Typical	92	+	RF, ANA, ANCA
2	Atypical	8	-	-
3	Atypical	80	+	ANA, ANCA
4	Atypical	87	-	ANCA
5	Atypical	48	-	-
6	Atypical	45	-	ANA
7	Atypical	129	-	ANA

RF – rheumatoid factor; ANA – antinuclear antibodies; ANCA – antineutrophil cytoplasmic antibodies.

Table 4

Treatment

Patient No	Type of disease	Treatment	Outcome	Follow-up (year)
1	Typical	GCs, CyP, AZA, CyA, MTX	Remission after introduction of MTX Permanent bilateral hearing loss	12
2	Atypical	GCs, MTX	Remission Hearing improvement	1
3	Atypical	GCs, MTX, CyP	Remission after introduction of CyP Hearing improvement	3
4	Atypical	GCs, MTX	Remission Hearing improvement	2
5	Atypical	GCs, MTX	Remission Hearing improvement	3
6	Atypical	GCs, MTX	Remission Hearing improvement	4
7	Atypical	GCs, MTX	Remission Hearing improvement	2

GCs – glucocorticoids; MTX – methotrexate; CyP – cyclophosphamide; CyA – cyclosporine A; AZA – azathioprine.

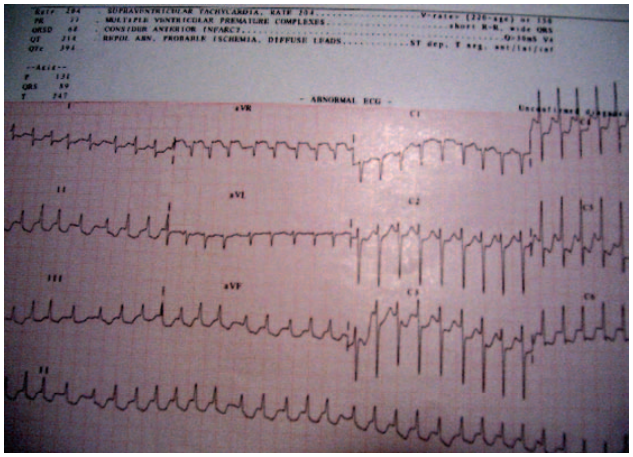

Fig. 3 – Paroxysmal supraventricular tachycardia in the patient who developed aortitis, aortic insufficiency and malignant arhythmia.

The female patient with the typical form of Cogan's syndrome was administered 3 pulse doses of methylprednisolone when signs of aortitis manifested. The maintenance dose was between 5–10 mg of prednisone *per* day. Methotrexate alongside GCs were administered to all patients. The maximum administered dose was 20 mg once *per* week. In 1 female patient, cyclophosphamide was introduced after methotrexate due to a lack of drug effect and was administered in pulse doses. This treatment resulted in remission. In the female patient with the typical form of the disease the treatment was started with GCs and pulse doses of cyclophosphamide. Due to a lack of drug effect cyclophosphamide was replaced with cyclosporine A. After the absence of effect of cyclosporine A, achieving remission was attempted with azathioprine. Remission was achieved only with methotrexate at a dose of 20 mg *per* week. In the female patient with the typical form of Cogan's syndrome bilateral hearing loss was permanent. Regarding the implantation of cochlear implant, recurrence of the disease occurred. In the remaining 6 patients, the treatment led to improvement of hearing.

Discussion

Cogan's syndrome is a rare variable vessel vasculitis. The typical form is characterised by IK and audiovestibular dysfunction similar to that of Ménière's disease [1, 2, 4]. A whole range of systemic manifestations has been described in patients with Cogan's syndrome [6]. The most common cardiovascular manifestation, described in approximately 10% of the cases, is aortitis with aortic insufficiency [15–17]. It is difficult to differentiate aortitis in Cogan's syndrome from Takayasu's arteritis [18]. Large blood vessels are particularly affected. One should keep in mind that arteritis can develop many years after the onset of the disease.

The most common manifestation that will make a patient visit a rheumatologist is arthritis. All our patients were diagnosed after they had been referred to a rheumatologist for a check-up due to arthritis. Individual cases of Cogan's syndrome are described in patients with rheumatoid arthritis, juvenile idiopathic arthritis and ankylosing spondylitis [19]. The central nervous system involvement is presented with hemiparesis or hemiplegia, aphasia, cerebellar symptomatology, myelopathy, meningitis or encephalitis. The peripheral nervous system involvement can manifest as paraesthesia, trigeminal neuralgia, mononeuritis multiplex. All our patients had headaches which are, according to relavant literature data, manifested in approximately 40% of the patients [5, 6, 11, 12]. Manifestations in the gastrointestinal tract such as pain, diarrhoea, and melena are usually the result of arteritis of mesenteric arteries. One should keep in mind the fact that Cogan's syndrome can occur in patients suffering from inflammatory bowel diseases [20]. Hepatomegaly and splenomegaly have been described in separate cases so far. In our group of patients, one female patient had splenomegaly. Extremely rare manifestations in patients with Cogan's syndrome include sinusitis or chondritis. In our group of patients, one female patient had auricular chondritis and it occurred before she was diagnosed and the treatment was started. No laboratory test is specific for Cogan's syndrome. The erythrocyte sedimentation rate is usually accelerated. If any systemic manifestations are pre-

sent, a certain degree of anaemia is usually present as well. Hypocomplementemia and cryoglobulinemia are rarely detected and it is difficult to determine their relevance. The presence of rheumatoid factor (RF), antinuclear antibodies (ANA), and antineutrophil cytoplasmic antibodies (ANCA) point to the possible autoimmune nature of the disease. However, the pathogenic significance of these antibodies is not clear [9, 12, 21]. We established the presence of RF in 1 patient, ANCA in 3, and ANA in 4. In literature, an even greater importance is attached to the antibodies to the corneal antigens and the structures of the inner ear such as anti-Hsp70 [7, 8, 10, 22]. We could not determine these antibodies. It is still not clear whether anti-Hsp70 are pathogenic or they are indicative of progressive hearing loss.

The course of Cogan's syndrome varies. The most serious complication of ear disease is hearing loss that is quite often bilateral. In 6 of our patients ear and eye disease flares occurred at different time intervals but they all had systemic manifestations in between the flares. In the female patient with the typical form of the disease that started acutely and simultaneously to spread to the eye and ear, hearing loss promptly occurred and systemic manifestations were quite severe.

Glucocorticoids are efficient at disease management. When complete hearing loss ensues, it is usually irreversible. All our patients were treated with GCs and 6/7 of them experienced improved hearing. The female patient with permanent bilateral hearing loss was embedded a cochlear implant after achieving remission [23, 24]. Immediately after the surgical intervention a mild recurrence of the disease ensued. In literature, bone trauma is cited as the possible disease trigger [25]. To all our patients immunosuppressive therapy alongside GCs was administered. In all patients, a stable remission of disease is managed with methotrexate that was administered at a maximum dose of 20 mg once per week. Only in one female patient the absence of methotrexate effect was registered. Our experience with metotrexate administration is in conformity with the data found in literature [26, 27]. Other immunosuppressive drugs could be administered as well. Based on our experience, a precedence should be given to cyclophosphamide over azathioprine and cyclosporine A.

Conclusion

The diversity of the Cogan's syndrome manifestations makes diagnosing more difficult. The correlation between ocular and audiovestibular manifestations need to attract attention to this disease. Diagnosing Cogan's syndrome provides a challenge and it calls for a multidisciplinary approach. There are no clear treatment guidelines. Early administration of glucocorticoids can prevent permanent hearing loss and the occurrence of severe complications. In addition to glucocorticoids in patients with systemic manifestations immunosuppressive drug should be administered. Priority should be given to methotrexate.

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