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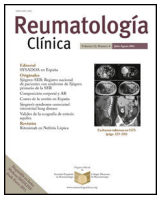

Brief Report

Cogan syndrome: Descriptive analysis and clinical experience of 7 cases diagnosed and treated in two third level hospitals☆

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ABSTRACT

Objective: Cogan's syndrome (CS) is an inflammatory disease classified as variable vessel vasculitis. It is a rare disease with few published series, and therefore we reviewed our experience in the last ten years in two centres.
Materials and methods: Description of 7 diagnosed cases of CS, according to the classification criteria (typical or atypical), their clinical manifestations, treatments used and their complications. A comparative analysis was performed with the series and cases described in the literature.
Results: 7 cases were included, three men and four women, with a mean age at diagnosis of 43 years, and an average disease duration of 47 months. Five patients met the typical characteristics according to the 1980 classical criteria, the rest being atypical cases, one due to the absence of interstitial keratitis and another due to a period between the onset of ocular and auditory-vestibular clinical symptoms greater than two years. All received immunosuppressants, methotrexate being the most commonly used, followed by azathioprine. In 5 cases, biological drugs were used, infliximab in 4 times and 2 tocilizumab. One patient died from bacterial endocarditis and septic shock.
Conclusion: The characteristics of the series presented are like those published to date, with clinical differences mainly in the involvement of large vessels. Given the low frequency, it seems necessary to create multicentre records to improve the evidence regarding the management of patients with Coganś Syndrome.

Síndrome de Cogan: análisis descriptivo y experiencia clínica de 7 casos diagnosticados y tratados en 2 hospitales de tercer nivel

Palabras clave:
Síndrome de Cogan
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RESUMEN

Objetivo: El síndrome de Cogan (SC) es una enfermedad inflamatoria clasificada como vasculitis de vaso variable. Se trata de una enfermedad rara con escasas series publicadas por lo que revisamos nuestra experiencia en dos centros en los últimos diez años.
Material y métodos: Descripción de 7 casos diagnosticados de SC, atendiendo a los criterios de clasificación (típico o atípico), sus manifestaciones clínicas, tratamientos utilizados y sus complicaciones. Se realizó un análisis comparativo con las series y casos descritos en la literatura.
Resultados: Se incluyeron 7 casos, tres varones y cuatro mujeres, con una edad media al diagnóstico de 43 años, y un tiempo de evolución medio de 47 meses. Cinco pacientes cumplían las características típicas según los criterios clásicos de 1980, siendo el resto casos atípicos, uno por ausencia de queratitis

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intersticial y otro por un periodo entre la aparición de clínica ocular y auditivo-vestibular mayor de dos años. Todos recibieron inmunosupresores, siendo el más utilizado el metotrexato, seguido de la azatioprina. En 5 casos se utilizaron fármacos biológicos: infliximab en 4 ocasiones y en 2 tocilizumab. Un paciente falleció por endocarditis bacteriana y shock séptico.

Conclusión: Las características de la serie presentada son similares a las publicadas hasta ahora, con diferencias clínicas fundamentalmente en la afectación de grandes vasos. Ante la escasa casuística, parece necesario la creación de registros multicéntricos para mejorar la evidencia en cuanto al manejo de pacientes con Síndrome de Cogan.

Introduction

Cogan syndrome (CS) is an inflammatory disease which was described for the first time in 1934 by Morgan and Baymgamer[1] and, later by David G. Cogan in 1945.[2] Classified as variable vessel vasculitis by Chapel-Hill in 2012,[3] it is characterized by ocular, vestibular-auditory and vasculitis symptoms, generally of the large vessels.[4] This is a rare disease which presents mainly in young Caucasian males,[2] and may also affect children.[4]

Two well differentiated, typical and atypical CS[3] phenotypes have been described within the disease spectrum. The first corresponds to those patients who present with non-syphilitic interstitial keratitis, associated, or not, with conjunctivitis or subconjuntival bleeding; vestibular symptoms similar to Ménière's syndrome with progressive hearing loss up to deafness in months, with an interval between ocular and auditory-vestibular symptoms of under 2 years. Atypical CS is characterised by ocular symptoms without interstitial keratitis or for an interval between auditory-vestibular and ocular symptoms above 2 years.[5]

The causes of this disease are not well known and there are few pathological or experimental references that lead to the creation of a pathogenic hypothesis.[3] CS is considered to be an immune mediated disease,[6] but there are no auto-antibodies or markers of clinical use. Due to the low frequency of CS, clinical and therapeutic management of this disease is based on the observations of the few published series.[7]

Material and methods

We carried out a review of the diagnostic codes in the hospital databases of 2 third level centres, which attended to a total population of approximately 800,000 inhabitants between both, to identify the diagnosed CS cases in the last 5 years (Table 1), creating a descriptive analysis of a retrospective nature.

Age at diagnosis and duration of disease was recorded, together with the main clinical, therapeutic and evaluative aspects, in accordance with the classification criteria.

Auto-antibody profiles found in the patients were described and the data of involvement of large vessels studied through the use of positron emission tomography to computerised tomography (PET/CT) in all patients. The association, described in the literature, with inflammatory bowel disease, [8] and joint involvement were recorded to a lesser extent in the published series.[9]

We then performed a description of treatment used, including steroids, immunosuppressant and biologic treatments, recording the frequency of each of them and the complications associated with them, as well as the most relevant data on evolution and outcomes.

Results and discussion

Seven diagnosed cases of CS (Table 1) were described, 5 of them with the typical phenotype and 2 atypical, due, in one case, to the absence of interstitial keratitis and in the second to a period of over 2 years before the appearance of the ocular and auditory-vestibular symptoms.

Mean age at diagnosis was 42 years (32-63) with a mean follow-up from diagnosis of 47 months (7-132). The predominant ocular manifestation was the interstitial keratitis, present in 5 of the 7 cases, and with the additional presence of anterior uveitis in 5 cases (3 of them bilateral), as well as scleritis/epiescleritis in 2 patients, with no conjunctivitis in any case. In previously published series symptoms have been described in the before-mentioned ocular regions, although with a lower proportion of uveitis, and the rest of the symptom percentages being similar to those in our series.[7,8]

All the patients presented with auditory symptoms (deafness or hearing loss), which is in keeping with the published series.[2] In this respect, there was a non response to treatment, with no improvement in the audiometric controls after treatment. The presence of vestibular symptoms (a typical trait of this disease)[2,7,10,11] were constant, except in one case, where the course of the disease was not as prolonged (7 months from diagnosis), classified as atypical CS.

All patients were studied using PET/CT, with observation of large vessel symptoms in 3 cases, a higher proportion than that descried in the literature[3,6,10] probably related to the systematic search for vascular involvement in our series. Imaging tests for diagnosis or follow-up was not clearly established. In our patients no subsequent complications, such as occlusive phenomena or the development of aneurisms, were recorded.

Three patients presented with joint symptoms, 2 with ankle arthritis, one with sacroiliac joints and another affecting the small joints in the hands. These symptoms presented to a similar extent to that published up until now, where arthromyalgias were described in approximately 15%–35% of cases, depending on the series.[7,8]

One of the patients presented with an intestinal symptom compatible with inflammatory bowel disease (IBD), which was diagnosed through biopsy. The relationship between CS and the presence of IBD has already been reported in previous publications and may be part of the clinical spectrum of CS symptoms,[8,9] albeit uncommon.

Experimental data exist which describe the presence of class IgG and IgA auto-antibodies aimed against inner ear tissues and corneal tissues in patients with CS,[6,11] which present similarities with the SSA/Ro and CD148 auto-antigens.[6,12] These auto-anti-bodies are not normally used in clinical practice. In some patients with CS, anti-neutrophil cytoplasmic anti-bodies ANCA)[12] have also been described (in our series one of the patients presented with antinuclear anti-bodies by virtue of 1/40, another patient presented with positive anti-To antibodies, and one patient presented with positive anti-PR3 antibodies, with no other clinical symptoms or associated diseases.

Regarding treatments used most frequently in the published series, corticoid therapy is the baseline initial treatment, with frequent use of corticoid pulses.[13,14] in our series corticoid pulses were used in all cases. In addition to corticotheapy methotrexate was the

Table 1
Description of cases diagnosed with Cogan syndrome in 2 third level hospitals.

Patient	Sex	Age	Age at diagnosis (years)	Disease duration (months)	Phenotype (reasons for atypical type)	AA	Auditory symptoms	Vestibular symptoms	Ocular symptoms	Joint symptoms	Aorta/large vessel symptoms	Association with IBD type	Corticoid bolus on diagnosis	Systemic treatments received	Complications	Death (cause)
1	Man	54	49	62	Typical	No	Sensorineural deafness with cochlear involvement	Peripheral Vertigo	Interstitial keratitis	No	Aortitis. Left carotid	No	Yes	1st line : CFM + PDN 2nd line : MTX + PDN 3rd line: AZA + PDN 4th line: IFX + AZA + PDN	Chronic HBV carrier. Ischaemic heart failure. Aortic and mitral valvulopathy. Sensitive-motor polyneuropathy	No
2	Woman	63	63	7	Atypical (> 5 years between regions)	Anti-Ro+	Sudden deafness	No	LE anterior Uveitis. interstitial keratitis	No	No	No	Yes	1st line: AZA + PDN 2nd line: MTX + PDN	Uncontrolled HBP	No
3	Male	48	46	25	Atypical (no interstitial keratitis	No	Bilateral Cofosis. Neurosensory deafness in left ear	Peripheral vertigo	Bilateral anterior uveitis. Bilateral scleritis	Sacroileitis Arthritis in right ankle	Aortitis (abdominal aorta). Iliac arteries Common carotids, bifurcation and external carotids	No		1st line: CFM + PDN 2nd line: MTX + PDN 3rd line: TCZ + MTX + PDN	Left facial paralysis. Mild leuconeutropenia Steroid Diabetes	Yes (endocarditis bacteriana)
4	Woman	48	42	73	Typical	ANA+ 1/40	Sensorineural deafness	Peripheral vertigo	Bilateral nodular Epiescleritis. Instertitial keratitis. LE anterior uveitis	Bilateral ankle arthritis	Aortitis	No	No	1st line: AZA + DZC	Carpal tunnel syndrome. Mild hypertransaminasemia. Episodic lymphopenia	No
5	Male	35	34	15	Typical	No	Left sensorineural deafness	Peripheral vertigo	Interstitial keratitis. Bilateral anterior unveils	No	No	Ileitis terminal Crohn like foot-and-mouth disease	Yes	1st line: MTX + PDN 2nd line: IFX + MTX + PDN	Mild hypertransaminasemia	No

Table 1 (*Continued*)

Patient	Sex	Age	Age at diagnosis (years)	Disease duration (months)	Phenotype (reasons for atypical type)	AA	Auditory symptoms	Vestibular symptoms	Ocular symptoms	Joint symptoms	Aorta/large vessel symptoms	Association with IBD type	Corticoid bolus on diagnosis	Systemic treatments received	Complications	Death (cause)
6	Woman	33	32	18	Typical	No	Bilateral tinnitus. Severe RE deafness	Peripheral vertigo	Interstitial keratitis. In RE. Anterior uveitis in LE	No	No	No	Yes	1st line: MTX + PDN 2nd line: IFX + PDN	No	No
7	Woman	44	33	132	Typical	p-ANCA+ /anti -PR3	Bilateral hearing impair-ment	Right vestibu-lar paresis	Interstitial keratitis. Bilateral intersti-tial keratitis	Small joint arthritis	No	No	Yes	1st line: PDN + MTX, 2nd line: MMF 3rd line: IFX, TCZ	Recurrent neutrophilic dermatitis. Sensorineural deafness	No

AA: auto-antibodies; ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; AZA: azatioprine; CFM: ciclophosphamide; DZC: deflazacort; IBD: inflammatory bowel disease: IFX: infliximab; LE: left eye; MMF: micophenolate mofetil; MTX: methotrexate; PDN: prednisone; RE: right eye; TCZ: tocilizumab.

most used immunosuppressant (6 cases), followed by azatioprine (3 cases), in a similar proportion to previously described cases.

Biologic therapies have been in use since 2000 to treat both ocular and auditory symptoms, particularly in refractory patients, with the most used agents being the anti-TNF, mostly infliximab (IFX),[14,15] used in 4 of the 7 patients. Tocilizumab was used in 2 patients.

Finally, the evolution of patients in our series during the study period was diverse. The area with the best prognosis was ophthalmologic, with recovery or improvement in all cases. The auditory–vestibular area in contrast presented with torpid evolution, despite treatments administrated (corticoids, standard immunosuppressant's or biologic therapies).

In our patients only one serious complication was recorded, a death from septic shock by bacterial endocarditis, in the patient who had received tocilizumab, after having previously been in fist line treatment with cyclophosphamide and second line treatment with methotrexate, together with a high corticoid dose.

Conclusions

As far as we know, this is the most numerous patient series with CS to be described on a national level, and shows general similar characteristics to published series. Joint symptoms and particularly large vessel symptoms could be more frequent in this disease than described, and based on our observation, their systematic search could bring to light silent cases.

In the absence of quality evidence, therapeutic guidelines are unallied, highlighting the need for multicentre records for this type of low incidence diseases.

Conflict of interests

The authors have no conflict of interests to declare.

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