Case report

Off-label application of intravenous immunoglobulin (IVIG) for treatment of Cogan's syndrome during pregnancy

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Accepted 5 September 2019

To cite: Scherg F, Haag F, Krieger T. *BMJ Case Rep* 2019;**12**:e227917. doi:10.1136/bcr-2018-227917

SUMMARY

We report the case of a woman with Cogan's syndrome concomitant with the wish to have children. After three major flares of the disease that led to unilateral deafness, immunosuppressive therapy with prednisolone and azathioprine was started. Because of the severe side effects, an off-label therapy with intravenous immunoglobulin (IVIG) was initiated, under which our patient has since given birth to three healthy children. To our knowledge this is the first report to describe Cogan's syndrome with multiple successful pregnancies under IVIG treatment.

BACKGROUND

Cogan's syndrome (CS) was described in 1945 by Dr David G Cogan,[1] based on four patients who displayed 'interstitial keratitis associated with vertigo, tinnitus and usually profound deafness'. Similar symptoms had been reported previously by Morgan and Baumgartner in 1934 (reported in ref 1).[1 2] In 1980 Haynes *et al*[3] introduced a classification of CS based on clinical characteristics: typical Cogan's syndrome (tCS) features ocular symptoms (classically interstitial keratitis) and audiovestibular Menière-like symptoms, such as vertigo, tinnitus and hearing loss. In tCS no longer than 2 years elapse between the onset of audiovestibular and ocular symptoms.

If more than 2 years pass between the onset of audiovestibular and ocular symptoms, the syndrome is considered atypical Cogan's syndrome (aCS). In aCS other ocular inflammatory manifestations apart from interstitial keratitis can occur in combination with audiovestibular symptoms that may differ from Menière-like symptoms.[3 4] This very rare disease mainly occurs in young adults.[5] While interstitial keratitis mostly heals under immunosuppressive therapy, audiovestibular inflammation often leads to deafness within 1–3 months, resulting in bilateral deafness in approximately 50% of cases.[4 5] Apart from ocular and audiovestibular symptoms, several other organ systems can be affected: 70% of patients show features of systemic manifestation with varying symptoms: headache (40%), arthralgia (35%), fever (27%), arthritis (23%) and myalgia (22%). Some patients report gastrointestinal conditions such as diarrhoea, pain and rectal bleeding, among others. Skin lesions are also reported in rare cases. Neurological symptoms vary from headache and neuropathy, up to hemiplegia. Furthermore, cardiovascular symptoms such as aortic insufficiency are reported in more than 10% of cases. Vascular manifestations can lead to intermittent claudication, abdominal pain and other afflictions. Both patients with typical and atypical CS can show the reported range of symptoms.[2 4–6]

CS is considered an autoimmune disease. Consistent with this, immunosuppressive therapy usually improves the symptoms. High-dose corticosteroids are recommended for acute exacerbations, and other immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, ciclosporin or tumour necrosis factor blockers are used in cases of treatment failure.[2 4]

Here, we report the case of a 27-year-old woman with severe aCS complicated by her wish to have children.

CASE PRESENTATION

In 2007 a 27-year-old woman without pre-existing chronic illness suffered an attack of vertigo, tinnitus, hearing loss and severe ache of her left ear. Previously, she had noted recurring arthralgia of ankle, hand and elbow joints accompanied by frequent colds with tonsillitis, sinusitis and earache. Two years before she had experienced an acute laryngitis of unknown origin that responded well to prednisolone treatment.

Laboratory investigation showed increased C3 and C4 complement factors, while erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were not elevated. Tests for infectious diseases did not reveal an acute infection with Lyme disease, toxoplasmosis, mycoplasma, mumps, hepatitis B/C or HIV. IgG and IgA levels in the serum were slightly increased. Antinuclear antibodies (ANA) were observed at a low titre (1:160) and could not be specified to react with SSA/Ro52, SSA/Ro60, SSB/La, SmD, SmB, RNP, SCL70, JO1 or CENP-B. Antiparietal cell antibody (PCA) levels were also elevated (1:60). None of the following antibodies could be detected: rheumatoid factor, double-stranded DNA, antiphospholipid antibodies, antinuclear cytoplasmic antibodies (ANCA), antismooth muscle antibodies, antiskeletal muscle antibodies, anticitrullinated protein antibodies and antiribonucleoprotein antibodies (anti-RNP-70k, anti-RNP-A and anti-RNP-C). MRI of the head revealed inflammation of the left facial and vestibulocochlear

nerves. An eye examination did not show pathological results. Transthoracic echocardiogram revealed a slight aortic insufficiency. A gastroscopy revealed an inflammation compatible with chronic autoimmune gastritis, consistent with vitamin B_{12} deficiency and PCA observed in blood tests.

The patient was diagnosed with acute labyrinthitis with otovestibular failure of unknown origin, and a treatment with prednisolone and piracetam in combination with an antibiotic and acyclovir was initiated, although varicella zoster virus and herpes simplex virus IgM levels were not elevated. Despite this therapy she lost hearing and sense of balance in her left ear completely.

In 2008 she experienced two further major exacerbations with severe hearing impairment of her right ear concomitant with severe pain, vertigo, tinnitus, arthralgia and blurred vision. Inflammation parameters such as ESR and CRP were in the normal range. A treatment with high doses of prednisolone led to an improvement of hearing, while tinnitus remained. Subsequently a daily therapy with azathioprine in combination with prednisolone was initiated to prevent further events.

In 2010 her condition was diagnosed as aCS based on the medical history. The long-term therapy with azathioprine and prednisolone resulted in a cushingoid appearance, osteopaenia, cataract and elevated liver enzymes, making a change in drug therapy imperative. Because our patient planned to become pregnant, methotrexate or mycophenolate was not considered to be suitable alternatives. Hence, an intravenous immunoglobulin (IVIG) therapy was initiated with a starting dose of 2 g/kg body weight followed by injections of 1 g/kg body weight every 4 weeks. Simultaneously, the therapy with azathioprine and prednisolone was reduced gradually until IVIG was the only continuous treatment. Apart from single episodes of headache and nausea at the beginning of the therapy, no other side effects were observed.

In 2011 a cochlear implant was performed at the University Medical Center in Hannover, which restored hearing of her left ear.

Between 2011 and 2016 our patient was pregnant three times and gave birth to three healthy full-term neonates by vaginal delivery under ongoing IVIG therapy: (1) female, birth weight: 3520 g, Apgar: 9/10/10; (2) female, birth weight: 3690 g, Apgar: 10/10/10; and (3) male, birth weight: 4150 g, Apgar: 9/10/10. Since CS is not considered to be a monogenetic inheritable disease, prepregnancy cytogenetic analysis was not deemed necessary. All three pregnancies were closely monitored in accord with the German 'motherhood guidelines' (Mutterschaftsrichtlinie) issued by the German Federal Joint Committee of physicians, dentists, hospitals and health insurance funds. These include but are not limited to screenings for gestational diabetes, pre-eclampsia, anaemia and maternal infections. Three ultrasound examinations were performed to look for possible fetal abnormalities. None of the examinations showed pathological results.

During her second pregnancy, an interstitial keratitis of her left eye occurred, which was treated with prednisolone. Apart from this, no treatment other than IVIG therapy was performed during the pregnancies. No other complication during this period was reported. Notably, she did not suffer from signs of pre-eclampsia, such as hypertension, proteinuria or oedema, during her pregnancies.

OUTCOME AND FOLLOW-UP

In 2016 our patient developed recurring migraine-like symptoms that ceased after the IVIG dose was reduced from 70 mg to 60 mg every 4 weeks. About 1 year later she experienced a major exacerbation with blurred vision, severe vertigo, unsteady gait and paresthesia of her right foot. She also reported a chronic inflammation of the fifth digit of her right foot since 2016. CT imaging, eye examination, neurography and radiography of her right foot did not reveal any pathological results. The symptoms were relieved by treatment with high-dose prednisolone in addition to the ongoing IVIG therapy.

Apart from this latter major event, our patient has reported only minor recurring exacerbations, such as small inflammatory skin lesions on her lower limb, earache, aggravated tinnitus, vertigo and slight impairment of hearing of her right ear during IVIG therapy. These were self-limiting and did not require additional therapy. ESR and CRP also remained in the normal range during IVIG therapy.

DISCUSSION

Considering her complete medical history, our patient showed classical symptoms of CS, such as hearing loss, vertigo, tinnitus and interstitial keratitis. Since interstitial keratitis occurred more than 2 years after her first audiovestibular symptoms, her CS is considered atypical.[3] Some patients with CS also show elevated levels of ANCA or ANA.[2 5] Consistent with this observation, our patient exhibited low titres of ANA. Lunardi *et al*[7] described antibodies against the so-called Cogan's peptide in the serum of patients with CS.

In accord with published reports,[2 5] our patient showed a wide range of systemic manifestations, such as headache, arthralgia and paresthesia, in addition to her ocular and audiovestibular symptoms. Systemic manifestations of CS are mostly attributed to vasculitis.[2 4] Thus, the reported aortic insufficiency could be the result of an undetected aortitis, which is the most frequent cardiovascular manifestation in CS.[4] Our patient also reported recurring colds and tonsillitis preceding her first exacerbation. This is in line with the observation that in 20% of CS cases the onset of symptoms is preceded by upper respiratory tract infections.[5]

In every flare our patient reported severe earache in combination with other symptoms, although earache is not a classic symptom of CS. In addition, she showed several other autoimmune phenomena not typically associated with CS, such as erythema nodosum and autoimmune gastritis.

Major exacerbations could be effectively controlled with prednisolone. Because our patient developed three major flares within the first year of the disease, a long-term therapy with daily doses of prednisolone and azathioprine was started. Although this effectively slowed disease progression until 2010, the severe side effects made a change of therapy mandatory. The choice of a suitable therapeutic alternative was further complicated by our patient's wish to have children.

An IVIG therapy was initiated. Although azathioprine and prednisolone were gradually phased out until IVIG remained as the sole therapeutic agent, no major flares occurred between 2010 and 2016. Blood tests did not show elevated indicators of inflammation during this time period. Under this therapeutic regimen, our patient gave birth to three healthy children, resulting from uncomplicated full-term pregnancies between 2012 and 2016. The only flare in this period was an isolated episode of interstitial keratitis during the second pregnancy, which was well controlled by systemic prednisolone.

Although our patient did not show signs of pre-eclampsia, it is important to note that symptoms of pre-eclampsia and eclampsia could be confused with an exacerbation of CS. While

typical symptoms of pre-eclampsia such as hypertension and proteinuria are not typical for CS,[4] headache occurs in approximately two-thirds of patients with pre-eclampsia or eclampsia and in about 40% of patients with CS.[4 8] Since pre-eclampsia and eclampsia are still the leading cause of maternal morbidity and mortality, early diagnosis of pre-eclampsia is crucial.[9] Recent studies show promising new markers in maternal blood that might facilitate the early detection of pre-eclampsia in the future.[10 11]

A search of the literature revealed only three other reports of pregnancy in combination with CS to date.[12–14] Apart from one case of uncomplicated interstitial keratitis similar to the case reported here, all three pregnancies were uneventful. Only one of the three women received a long-term therapy (with hydroxychloroquine) during pregnancy.[14] One patient reported subjective improvement of her symptoms during pregnancy even without continuous therapy.[12] To our knowledge, our case report is the first to show multiple pregnancies in a patient with CS.

Immunoglobulins pooled from healthy blood donors are approved for the treatment of immunodeficiencies and several immune-mediated diseases, such as Guillain-Barré syndrome, Kawasaki syndrome and chronic inflammatory demyelinating polyradiculoneuropathy.[15] Although IVIG was developed primarily for the treatment of immunodeficiencies, 75% of the administered IVIGs in the USA are given to patients with autoimmune or inflammatory conditions.[15]

The biggest disadvantage of IVIG is its high cost. However, this might change due to the ongoing development of synthetic or correctly glycosylated Fc proteins.[16 17] Although IVIG therapy is expensive, it should be contemplated in patients with CS with the wish to have children. IVIG has been applied during pregnancy for treatment of unexplained infertility and recurrent miscarriage, improving overall pregnancy and live birth rates compared with a placebo cohort.[18 19] Thus, the application of IVIG during pregnancy can not only be considered safe but may even improve pregnancy outcome. Reported side effects are rather mild and include headache, flushing, fever, fatigue and nausea, while severe side effects such as thromboembolic complications or acute renal failure are very rare.[20]

To our knowledge, only one case of IVIG treatment for CS has been reported so far.[21] Apart from audiovestibular and ocular symptoms, this patient also suffered from aortitis concomitant with carotid and subclavian arteritis. Despite treatment with a combination of cyclophosphamide and IVIG, the disease led to complete deafness. Unfortunately, dosage, efficacy and side effects of the therapy were not reported in detail.[21]

Learning points

- Cogan's syndrome can be effectively treated with intravenous immunoglobulin (IVIG).
- IVIG can be regarded as safe for administration during pregnancy.
- IVIG should be considered as a treatment option in female patients who wish to become pregnant.

In summary, IVIG constitutes an effective immunosuppressive therapy that is tolerated well by patients with a wide range of autoimmune diseases. In addition, IVIG can safely be applied during pregnancy and should therefore be considered in patients with CS who wish to become pregnant. Nevertheless, off-label use during pregnancy has to be evaluated carefully based on national law and guidelines.

Contributors FS: drafting the manuscript, acquisition of data, patient consent. FH: drafting the manuscript, revising the manuscript. TK: treating the patient, acquisition of data, revising the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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