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Mini Review

Treatment of Cogan's Syndrome during Pregnancy with Off-Label Application of Intravenous Immunoglobulins (IVIG)

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ABSTRACT

We report the case of a woman with Cogan's syndrome and the desire for pregnancy. After three major flares leading to unilateral deafness, immunosuppressive therapy with prednisolone and azathioprine was started. Because of severe side effects, an off-label therapy with Intravenous Immunoglobulins (IVIG) was initiated, under which the patient has 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.

Keywords: Cogan Syndrome; Immunoglobulins; Intravenous; Pregnancy

INTRODUCTION

Cogan's Syndrome (CS) was described in 1945 by Dr. David G. Cogan based on four cases of nonsyphilitic "interstitial keratitis associated with vertigo, tinnitus and usually profound deafness [1] "after similar symptoms had been reported before by Morgan and Baumgartner in 1934 [2]. In 1980 Haynes et al. introduced a classification of CS based on clinical characteristics: Typical Cogan's Syndrome (tCS) features ocular symptoms (classically interstitial keratitis) and audio vestibular Menière-like symptoms, such as vertigo, tinnitus and hearing loss [3]. In tCS no longer than two years elapse between the onset of audio vestibular and ocular symptoms.

If more than two years pass between the onset of audio vestibular 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 audio vestibular symptoms that may differ from Menière-like symptoms. This very rare disease mainly occurs in young adults. While interstitial keratitis mostly heals under immunosuppressive therapy, audio vestibular inflammation often leads to deafness within 1-3 months, resulting in bilateral deafness in approximately 50% of cases. Apart from ocular and audio vestibular 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 with diarrhea, pain, rectal bleedings and more. Skin lesions are also rarely reported. Neurological symptoms vary from headache and neuropathy up to hemiplegia. Furthermore, cardiovascular symptoms like aortic insufficiency are reported in more than 10% of cases. Vascular manifestations can lead to intermittent claudication of limbs, abdominal pain and other afflictions. Both, patients with typical and atypical Cogan's syndrome, can show the reported range of symptoms [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, cyclosporine or tumor necrosis factor-alpha blockers are used in cases of treatment failure.

Here, we report the case of a 27-year-old woman with severe atypical Cogan's syndrome complicated by her desire to have children. The patient gave her written consent for publication of this case report. The off-label treatment was managed in accordance with German laws.

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LITERATURE REVIEW

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.

Because laboratory investigation showed an elevated erythrocyte sedimentation rate, elevated CRP and increased C3 and C4 complement factors, further diagnostics regarding infection, inflammation and auto-immunity were performed.

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. Anti-Nuclear Antibodies (ANA) were observed at a low titer (1:160) and could not be specified to react with SSA/Ro52, SSA/Ro60, SSB/La, SmD, SmB, RNP, SCL70, JO1 or CENP-B. Anti-parietal cell antibody levels were also elevated (1:60). None of the following antibodies could be detected: Rheumatoid factor, dsDNA, anti-phospholipid antibodies, ANCA, anti-Smooth Muscle Antibodies (SMA), anti-Skeletal Muscle Antibodies (SKA), Anti-Citrullinated Protein Antibodies (ACPA), Anti-Ribonucleoprotein Antibodies (anti-RNP-70k, -RNP-A, and -RNP-C). Magnetic resonance imaging of the head revealed inflammation of the left facial and vestibulocochlear nerves. An eye examination did not show pathological results. Transthoracic echo revealed a slight aortic insufficiency. A gastroscopy revealed an inflammation compatible with chronic autoimmune gastritis, consistent with a vitamin B_{12} shortage and anti-parietal cell antibodies found in blood tests.

Although varicella zoster virus and herpes simplex virus IgM levels were not elevated the patient was treated with aciclovir. In spite of additional therapy with an antibiotic, prednisolone and piracetam, she lost hearing and sense of balance in her left ear completely.

In 2008 she experienced two major exacerbations with severe hearing impairment of her right ear concomitant with severe pain, vertigo, tinnitus, arthralgia and blurred vision. 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 atypical Cogan's syndrome was diagnosed based on her medical history. The long-term therapy with azathioprine and prednisolone led to cushingoid appearance, osteopenia, cataract and elevated liver enzymes, making a change in drug therapy imperative. Because the patient planned to become pregnant, a change of therapy to methotrexate or mycophenolate was not considered suitable.

Hence, a therapy with Intravenous Immunoglobulins (IVIG) was initiated. A starting dose of 2 g/kg body weight was followed by injections of 1 g/kg body weight every four weeks thenceforward. 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 cochlea implant was performed at the University Medical Center in Hannover, which restored hearing of her left ear. Between 2011 and 2016 the patient was pregnant three times and gave birth to three healthy children under ongoing IVIG therapy. During her second pregnancy an interstitial keratitis of her left eye occurred that was treated with prednisolone. No other complication during that period was reported.

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

Apart from that event, the patient reports only small recurring exacerbations during IVIG therapy with small inflammatory skin lesions on her lower limb, earache, aggravated tinnitus, vertigo and slight impairment of hearing of her right ear. These exacerbations were self-limiting and did not require additional therapy.

DISCUSSION

Taking her total medical history into account, the patient showed classic symptoms of CS, such as hearing loss, vertigo, tinnitus and Interstitial Keratitis (IK). Since IK occurred more than two years after her first audio vestibular symptoms, the Cogan's syndrome is considered atypical. Some patients with CS also show elevated levels of Anti-Nuclear Cytoplasmic Antibodies (ANCA) or Antinuclear Antibodies (ANA). Consistent with that, our patient exhibited low titers of ANA. Lunardi et al. described antibodies against the so-called Cogan's peptide in the serum of patients with CS. This peptide resembles known auto-antigens like SSA/Ro and receptor-type tyrosine-protein phosphatase eta (CD148), the latter of which can be found on endothelial cells of the inner ear. Furthermore, these antibodies were able to induce CS-like symptoms in mice [7]. Unfortunately, however, this peptide is not commercially available for diagnostic testing. Interestingly, in 2014 Bonaguri et al., discovered that over 90% of patients with tCS display elevated levels of anti-Hsp70 antibodies, while only about 15% of patients with aCS do so [8]. These autoantibodies are related to autoimmune sensineural hearing loss [9]. Anti-Hsp70 antibodies were not tested in our case, since these were not yet discovered in 2007.

In addition to the ocular and audio vestibular symptoms the patient showed a wide range of systemic afflictions, such as headache, arthralgia and paresthesia that fit to published reports. The reported aortic insufficiency could be the result of an undetected aortitis, which is the most frequent cardiovascular

manifestation in CS. In general vasculitis is considered to be the cause of systemic manifestations. Consistent with the observation that 20% of CS cases are preceded by upper respiratory tract infections, the patient reported recurring colds and tonsillitis preceding her first exacerbation.

The patient reported severe earache in combination with other symptoms in every exacerbation, although earache is not a classic symptom of CS. In addition, the patient showed several other autoimmune phenomena not typically associated with CS, such as skin lesions compatible with erythema nodosum and autoimmune gastritis characterized by gastric inflammation accompanied by anti-parietal cell antibodies and vitamin B_{12} shortage. Major exacerbations could be effectively controlled with prednisolone. Because the patient developed three major exacerbations within the first year of disease, a long-term therapy with daily 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 the patient's desire for pregnancy.

The physician in charge decided to initiate a therapy with Intravenous Immunoglobulins (IVIG). Following a starting dose of 2 g/kg IVIG therapy was maintained at a dose of 1 g/kg body weight every four weeks. Although the doses of azathioprine and prednisolone were reduced gradually until IVIG was the only remaining therapy, no major exacerbations occurred between 2010 and 2016. Under this regimen the patient gave birth to three healthy children following uncomplicated full-term pregnancies between 2012 and 2016. The only exacerbation in this period was an isolated episode of IK during her second pregnancy that was controlled well by application of systemic prednisolone.

A search of the literature turned up only three other reports of pregnancy in combination with Cogan's syndrome. Apart from one case of uncomplicated interstitial keratitis similar to the case reported here, all three pregnancies were uneventful [10]. Only one of the three women received a long-term therapy (with hydrochloroquine) during pregnancy. One patient even reported subjective improvement of her symptoms without continuous therapy during pregnancy. 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 treatment of immune deficiencies and several immune-mediated diseases like Guillan-Barré syndrome, Kawasaki syndrome and chronic inflammatory demyelinating poly radiculo neuropathy. IVIG were developed primarily for the treatment of immune deficiencies, 75% of the administered IVIG in the United States are given to patients with autoimmune or inflammatory conditions.

It is known that high-dose IVIG application leads to a diminished production of pro inflammatory cytokines, down regulation of adhesion molecules and reduced chemokine expression. Yet, the mechanisms of action responsible for its immunosuppressive effects are not completely clear. Most evidence points to the Fc (crystallizable fragment) region of Immunoglobulin G (IgG) as the mediator of anti-inflammatory effects. Mechanisms discussed include the blockade of activating Fc-Receptors (FcR) or shortening the serum half-life of autoantibodies by blocking the neonatal FcR. Recent work has demonstrated that administration of IVIG leads to increased expression of inhibitory FcgRIIB and that the anti-inflammatory effects are dependent on the glycosylation pattern (sialylation) of the Fc fragment.

The high therapy costs of IVIG are their biggest disadvantage. However, this might change due to the ongoing development of synthetic or correctly glycosylated Fc proteins. Although IVIG therapy is expensive, it should be contemplated in CS patients with a wish for pregnancy. IVIG has been applied during pregnancy for treatment of unexplained infertility and recurrent pregnancy loss or abortion, improving overall pregnancy and live birth rates compared to a placebo cohort. 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.

CONCLUSION

To our knowledge, only one case of IVIG treatment for CS has been reported so far together with 31 other cases. Apart from audio vestibular 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 or side effects of the therapy were not reported in detail.

All in all, IVIG are 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 and the wish for a child.

CONFLICT OF INTEREST

None.

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