SHORT REPORT

Association between Cogan's syndrome and inflammatory bowel disease: A case series

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Abstract

\textbf{Background and Aims:} Cogan's syndrome (CS) is a rare autoimmune disease with less than 250 cases reported. It mainly affects the audiovestibular system and the eyes frequently resulting in deafness. Inflammatory bowel disease (IBD) consists of two subtypes, Crohn's disease (CD) and ulcerative colitis (UC), and represents a common form of chronic intestinal inflammation. Here, we report an association between CS and IBD in four patients.

\textbf{Methods:} Patient data were collected using a questionnaire that was sent to one of our outpatients and three of the 13 members of the German CS self-help group.

\textbf{Results:} In all Cogan patients with IBD (3 female with UC, 1 male with CD), intestinal disease was diagnosed years before the onset of CS. After suffering from a complicated IBD disease course, they suddenly developed CS-related symptoms, such as hearing loss, tinnitus or eye inflammation. Three of them went deaf within a few years after diagnosis. Although all of them had been on immunosuppressive IBD therapy, these treatment regimens did not prevent the onset of CS.

\textbf{Conclusions:} Our data suggest a strong association of IBD and CS. Since CS rapidly leads to bilateral deafness, it seems to be a rare, but nevertheless important disease that can occur in association with IBD. However, neither an early diagnosis nor an immunosuppressive therapy seems to efficaciously prevent disease progression.

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\textit{Abbreviations:} CS, Cogan's syndrome; CD, Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; IK, interstitial keratitis; TNF, tumor necrosis factor; UC, ulcerative colitis.

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1. Introduction

Cogan’s syndrome (CS) represents a rare form of an autoimmune disease with about 250 cases reported in the literature. The classic form of CS consists of the following triad: 1) bilateral audiovestibular involvement, resembling the symptoms of Meniere’s disease, 2) progressive hearing loss, frequently resulting in deafness within several months and 3) bilateral ocular involvement mostly presenting as a non-syphilitic interstitial keratitis (IK). Usually, ocular and audiovestibular symptoms occur within a time frame of less than two years. Thus, a patient might be diagnosed with CS due to specific audiovestibular symptoms, despite lacking eye involvement. In addition to the classic CS, Haynes et al. defined an atypical CS, featuring ocular symptoms other than IK or audiovestibular symptoms other than Meniere-like appearances. Additional symptoms of CS are headache (40% of the patients), arthralgia (35%), fever (27%), arthritis (23%) and myalgia (22%). Interestingly, unspecific abdominal pain occurs only in about 13% of CS patients.

Inflammatory bowel disease (IBD) represents a group of chronic inflammatory conditions of the gastrointestinal (GI) tract. IBD patients frequently suffer from extra-intestinal manifestations (EIM), affecting skin, joints, eyes and other organs. Similar symptoms can also be seen in CS patients with systemic disease (3). To date, an association of CS and IBD has been described only in a few patients (an overview is presented in Table 1).

Here, we report a case series of four patients suffering from IBD and CS in the later course of the disease. Given the low overall number of reported cases for CS in literature, our four cases represent a significant contribution to this disease association between IBD and CS. This observation may help to establish a correct diagnosis for IBD patients suffering from audiovestibular and/or ocular symptoms in order to initiate an appropriate therapy strategy as early as possible.

2. Materials and methods

One of the reported patients was diagnosed and treated in our IBD outpatient clinic at the University Hospital Zurich.

Table 1: Patients characteristics of the previously described patients. Abbreviations: ulcerative colitis, UC; Crohn’s disease, CD; interstitial keratitis, IK; u.k. means unknown.

<table>
<thead>
<tr>
<th>Pat.</th>
<th>Authors</th>
<th>Gender</th>
<th>IBD-type</th>
<th>Patient age</th>
<th>Medication</th>
<th>IBD before CS</th>
<th>CS symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Haynes et al.</td>
<td>Female</td>
<td>CD</td>
<td>22</td>
<td>Corticosteroids</td>
<td>No</td>
<td>Bilateral deafness, IK</td>
</tr>
<tr>
<td>2</td>
<td>Gluth et al.</td>
<td>u.k.</td>
<td>UC</td>
<td>u.k.</td>
<td>u.k.</td>
<td>Yes</td>
<td>u.k.</td>
</tr>
<tr>
<td>3</td>
<td>Gluth et al.</td>
<td>u.k.</td>
<td>UC</td>
<td>u.k.</td>
<td>u.k.</td>
<td>Yes</td>
<td>u.k.</td>
</tr>
<tr>
<td>4</td>
<td>Froehlich et al.</td>
<td>Female</td>
<td>CD</td>
<td>27</td>
<td>Corticosteroids</td>
<td>No</td>
<td>Bilateral deafness</td>
</tr>
<tr>
<td>5</td>
<td>Buge et al.</td>
<td>Female</td>
<td>CD</td>
<td>20</td>
<td>Corticosteroids</td>
<td>No</td>
<td>Bilateral deafness</td>
</tr>
<tr>
<td>6</td>
<td>Peeters et al.</td>
<td>Female</td>
<td>CD</td>
<td>22</td>
<td>Corticosteroids</td>
<td>No</td>
<td>Partial bilateral hearing loss, sclerokeratitis</td>
</tr>
<tr>
<td>7</td>
<td>Karvonen et al.</td>
<td>Male</td>
<td>CD</td>
<td>18</td>
<td>Corticosteroids</td>
<td>Yes</td>
<td>Partial bilateral hearing loss</td>
</tr>
<tr>
<td>8</td>
<td>Bachmeyer et al.</td>
<td>Male</td>
<td>CD</td>
<td>20</td>
<td>Corticosteroids, sulphasalazine</td>
<td>Yes</td>
<td>Partial bilateral hearing loss</td>
</tr>
<tr>
<td>9</td>
<td>Fair et al.</td>
<td>Male</td>
<td>CD</td>
<td>24</td>
<td>None described</td>
<td>No</td>
<td>Partial bilateral hearing loss, IK</td>
</tr>
</tbody>
</table>

The work was conducted with the approval of the local ethics committee.

3. Results

Here, we report the results of the questionnaire that was sent to four to date not previously described patients with IBD and CS. Patient and disease characteristics are summarized in Table 2.

3.1. Case 1

A currently 48-year old Caucasian female suffered for the first time from bloody diarrhea at age 17. UC was diagnosed by clinical symptoms, colonoscopy and pathohistologic appearance of biopsy specimen. Extra-intestinal manifestations included frequent and recurrent arthralgia and vitiligo-like dermatological symptoms. During the following years, UC remained mainly in remission while the patient was on azathioprine, E. coli strain Nissle 1917 capsules and Lactobacillus acidophilus capsules.

She did not report any cardiovascular, pulmonary or endocrinologic diseases and no tumour history. Her family history was negative for both, IBD and CS and the patient never smoked or had alcohol consumption.

At age 32 an IK was diagnosed accompanied by nausea, abdominal pain and the feeling of intermittent hardness of hearing. During the following years, the patient developed episodes with increasing intensity of IK, strabismus, fever,
fatigue and tinnitus. These symptoms were commonly accompanied by nausea, vomiting and flatulence as well as bloody diarrhea, the latter likely indicating acute flares of UC. At age 39 she lost her bilateral cochlea function resulting in deafness and loss of equilibrium sense. At this time, diagnosis of CS was finally confirmed and the patient underwent a bilateral cochlea implantation.

### 3.2. Case 2

A currently 46-year old Caucasian female patient suffered from bloody diarrhea, nausea, vomiting, rectal tenesmus and abdominal cramping at age 36. By clinical appearance, colonoscopy, pathohistologic assessment of intestinal biopsies and radiological investigations, diagnosis of UC was established. She then suffered from a complicated disease course with recurring perianal abscesses and arthralgia/arthritis of the large joints, mainly knees and elbows. Her current UC-associated GI symptoms are frequent bowel movements (three to eight times per day), intermittent nausea, vomiting, rectal tenesmus and abdominal cramping. Neither her immunosuppressive therapy regimen including azathioprine, prednisone, budesonide, methotrexate, mesalazine nor certain intermittent corticoid therapy regimen (including prednisone and budesonide) induced a stable remission to date.

She reported neither cardiovascular, pulmonary or endocrinologic complications nor tumours and had a negative family history for IBD and CS. She smoked until diagnosed for UC and CS, but quit at age 43.

At age 40, she suffered from severe tinnitus, a progressive loss of equilibrium sense, loss of equilibrium sense, ongoing tinnitus and a progressive worsening of the visual sense.

### 3.3. Case 3

A currently 52-year old Caucasian female suffered from intermittent diarrhea since age 40 and was diagnosed with UC at age 44 by clinical appearance, colonoscopy and histology of intestinal biopsies. At age 44, she developed a primary sclerosing cholangitis (PSC). Additional extra-intestinal manifestations were oligo-arthritis of several finger joints and the knees as well as recurring, not further specified skin lesions. Though she was also suffering from a symptomatic iron deficiency anemia, vitamin B12-deficiency and folic acid deficiency, she did not report any relevant stenosis, abscesses or fistulae. Her UC-associated medication included prednisone, azathioprine, mesalazine and *E. coli* strain *Nissle 1917*. Currently, she is reporting two to three solid bowel movements per day.

Her history was negative for cardiovascular, pulmonary or endocrinologic complications as well as for tumours. Her sister suffers from celiac disease. She smoked until age 22, but has no or low alcohol consumption.

At age 51, she recognized acute, progressive hearing loss, tinnitus and dizziness. Though the bilateral audiovestibular symptoms are still ongoing and accompanied by fatigue, she did not report any ocular involvement so far. Due to clinical symptoms and to the results of audiometry, visual-evoked motor potentials, nystagmus testing as well as assessment of the equilibrium sense, CS had been diagnosed. However, she did not yet receive cochlear implants.

### 3.4. Case 4

A currently 29-year old Asian male patient suffered from abdominal pain and bloody diarrhea at age 26. Since then the patient frequently suffered from oral lesions (aphthae and cheilitis granulomatosa), generalized acne, multiple perianal abscesses that twice had to be surgically drained and
spondylarthritides, mainly in the knees and the spine. By clinical appearance, colonoscopy and histology, the diagnosis CD was established in the same year. He did not respond to azathioprine. At age 27 and under immunosuppressive therapy with certolizumab pegol, he developed a bilateral progressive hearing loss, a sudden loss of the equilibrium sense, frequent headaches, tinnitus and eye manifestations, such as scleritis and episcleritis, leading to the diagnosis of CS. Since then he rapidly developed a bilateral deafness, bilateral cochlear implants were performed at age 28. After the onset of CS, but before the cochlea implants, he also received two different TNF-blockers for the treatment of CD, infliximab and certolizumab pegol, which both did neither improve CS nor CD. Infliximab was switched to certolizumab pegol 1 month prior to first cochlea implant due to non-response, and certolizumab pegol was stopped 6 months after the second cochlea implant due to non-response and after two infectious complications (twice perianal abscesses under certolizumab pegol). One year after the cochlea implants, the patients received a third anti-TNF antibody, adalimumab, which was stopped after 3 months due to non-response of CD symptoms. Infliximab was used again, but had to be stopped after 3 injections due to a rise in serum transaminases and suspected infliximab-associated hepatitis. Taken together, none of the TNF-blockers improved either CS symptoms or CD symptoms. Infliximab had to be stopped due to intolerance. Currently he is still suffering from hearing loss and recurring tinnitus, however intestinal CD activity is controlled by methotrexate which was started one and a half year after the cochlea implants. According to the Vienna classification, the CD has been classified as A1, L3, and B3.

He never had any cardiovascular, pulmonary or endocrinologic complications. His patient history is negative for tumours and none of his family members was suffering on IBD or CS. Additionally, he never smoked or drank alcohol.

4. Discussion

CS is a rare autoimmune disease leading to deafness as the most important complication. To date, about 250 patient cases have been reported in the literature and less than ten have been additionally diagnosed with IBD. Gluth et al. described in 2 out of 60 patients a positive diagnosis for both CS and IBD in a long-term observational study. Here we report four new cases, including one CS patient treated at the University Hospital Zurich and three CS patients out of the German CS self-help group consisting of 13 people. This suggests a by far stronger association between IBD and CS (3 out of 13 patients in the German patient group) than previously considered. Nevertheless, since we obtained our data by contacting a self-help group, one must admit that the reported association might be somewhat over-called due to the ascertainment bias.

Autoimmune-related disorders are a common complication of CS, detectable in 15% to 30% of CS patients. Auto-antibodies reacting with the inner ear proteins CD148 and connexin 26 as well as with cornea antigens have been associated with CS. Though certain auto-antibodies are also associated with IBD, neither UC nor CD are regarded as a classical autoimmune disease. Evidence suggests that genetically determined predispositions cause a dysfunctional immune response of the innate as well as the acquired immune system to commensal flora that drives the development of chronic intestinal inflammation. To date no common susceptibility risk genes, auto-antibodies or environmental risk factors for the onset of CS and IBD have been identified. Therefore, since no common pathogenetic mechanism has been demonstrated, it might be that the association between CS and IBD simply reflects an incidentally occurring cluster of disorders featuring a dys-regulated immune system in these patients.

CS symptoms sometimes respond to immunosuppressive treatments. Though corticosteroid treatment alone is often insufficient, the combination with immunomodulators such as cyclosporine or methotrexate seems to have beneficial effects on disease course. Recent reports suggest anti-TNF therapy as a promising treatment option for CS patients. Infliximab has been described as alternative therapy for CS, especially in cases not responding to corticosteroids or other immunosuppressants. However, the efficacy of infliximab seems to be limited, since full remission of CS-related symptoms could only be reached in one of five reported cases. In three patients, at least a partial remission could be achieved, while in one patient, anti-TNF treatment did not have any beneficial effect. The latter case is in accordance with our own observations, since our patient (case 4) developed progressive hearing loss resulting in deafness, despite the fact that he received various TNF-blockers after the onset of CS symptoms.

Immunosuppressive therapy is also crucial in the treatment of IBD patients. IBD was diagnosed in all of the four patients before the onset of CS-related symptoms, while in the cases reported in literature, the onset of CS often precedes IBD manifestation. Nevertheless, the described patients developed a progressive hearing loss leading to complete bilateral deafness in three of four patients, despite the immunosuppressive IBD therapy. This outcome is consistent with the literature, since CS leads to complete deafness in over 50% of patients. Although the available data suggest that only an early and aggressive therapy opens the chance to maintain at least a partial hearing function, the efficacy of these therapy regimen seem to vary from individual to individual.

In summary, our case series suggests a strong association between CS and IBD. Since CS rapidly leads to complete deafness, one must carefully consider the diagnosis of CS in every IBD patient reporting symptoms such as dizziness, hearing loss, tinnitus or visual problems. However, even an early diagnosis of CS accompanying the IBD symptoms and an appropriate immunosuppressive therapy regimen already at early stage disease seem to have only a limited effect in preventing disease progression.

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References