CASE REPORT

Cytokine profile of nasal and middle ear polyps in a patient with Woakes' syndrome and eosinophilic otitis media

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SUMMARY

Woakes' syndrome is characterised by severe recurrent nasal polyps in early childhood with broadening of the nose, nasal dyscrinia, frontal sinus aplasia and bronchiectasis. Eosinophilic otitis media (EOM) is an intractable condition that can cause gradual or sudden deterioration of hearing and is associated with comorbid asthma. For these reasons, both diseases must be recognised and treated appropriately. We present a case of a 20-year-old man with Woakes' syndrome complicated by EOM, with polyps in both middle ears; this condition has so far not been described as an entity of eosinophilic disease in the literature. We have, from reviewing the literature, learned that this is the first time that results of tissue examination on nasal polyposis with respect to tissue IgE, eosinophil-cationic protein, interleukin (IL)-17 and IL-5 in a patient with Woakes' syndrome and EOM, has been reported and discussed.

BACKGROUND

Chronic rhinosinusitis (CRS) is a prevalent disease affecting approximately 11–15% of the general population.^{1 2} It can be divided into two clinical entities: CRS with nasal polyps (CRSwNP) and without nasal polyps. CRSwNP is considered to represent the more severe condition and in 40% is associated with comorbid asthma, leading to substantial further impact on the patient's quality of life.³ In European adults, nasal polyps mostly represent an eosinophilic inflammation of the upper airways, characterised by poor impact of therapeutic interventions and frequent recurrences after surgery.⁴ Normally, sinus disease with polyps and comorbid asthma starts in the third to fifth decade of life; in the patient presented here, however, the disease started in his adolescence, with mucosal tissue pressure leading to hypertelorism in his growing face. In children, nasal polyps are normally associated with cystic fibrosis or primary ciliary dyskinesia, but rarely with asthma, aspirin sensitivity and Woakes' syndrome.⁵ Woakes' syndrome, or ethmoiditis, was first described by Woakes in 1885. He reported a case of extensive polyp growth in the paranasal sinuses leading to bone erosion of the sinus walls, causing facial disfigurement. In 1923, the syndrome was defined by the 'Société Française de Laryngologie' by the following four characteristics: bilateral nasal polyps in the middle meatus beginning during childhood, ethmoiditis, hypertrophic process with nasal pyramid deformation and

therapeutic failure, with constant and rapid recurrences.⁶ Since then, few cases have been published.

The patient also showed eosinophilic otitis media (EOM). EOM is characterised by a highly viscous effusion containing eosinophils. Diagnostic criteria for EOM were recently established by the EOM study group.⁷ One major criterion for diagnosis is otitis media with eosinophil-dominant effusion. The disease is often associated with bronchial asthma and nasal polyposis. Patients show gradual or sudden deterioration of hearing, nasal obstruction, pressure and loss of smell, as well as bronchial symptoms such as wheezing, cough and dyspnoea. Some patients show gradual deterioration of hearing and cases of deafness in EOM have been reported.⁸ Thus, a proper diagnose of EOM is important to start adequate treatment.⁵

While the clinical features of nasal polyposis and asthma are known to specialists and general practitioners and affect up to 4% of the population, the combination of Woakes' syndrome and EOM has not been described in the literature so far. As this disease may already develop in adolescence, paediatricians should also be aware of it. We also add the histopathological element of eosinophilic disease. The literature on Woakes' syndrome and EOM is discussed, with both conditions being relatively unknown by clinicians.

This study was approved by the Ethics Committees of Ghent University Hospital, Belgium and written informed consent was obtained from the patient before collecting personal data.

CASE PRESENTATION

A 20-year-old man presented to our department, with severe nasal obstruction and continuous nasal secretions. Additionally, broadening of the nasal pyramid and hypertelorism were present (figure 1). The initial symptom of nasal obstruction had occurred at the age of 13 years. The first CT scan of the paranasal sinuses had been taken at the age of 14 years. It showed a complete obstruction of all sinuses by bilateral nasal polyposis and expansive convex boundaries of the medial orbital wall on both sides with deformation of the orbit. It also showed hypertelorism and relatively little room for the bulbi oculi. Remodelling of the medial orbital wall was present, which tended to be progressive on later CT scans, even after repeated surgery (figure 2).

At preschool age, the patient had been diagnosed with bronchial hyper-reactivity. As a child, he had suffered multiple upper airway infections with the

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Figure 1 A 20-year-old man with severe recurrent growth of nasal polyposis causing broadening of the nasal pyramid and hypertelorism.

need for antibiotics. After a period of improvement, there was an increased shortness of breath at the age of 11 years and the diagnosis of asthma was made. The patient was diagnosed with suspected bronchiectasis for the first time at the age of 13 years, which was confirmed by new imaging at the age of 15 years. The patient had been taking aspirin and other non-steroidal anti-inflammatory drugs, without any problems. At the age of 20 years, the eosinophilic peripheral blood count was 2360 eosinophils/ μ L (normal value 28–273/ μ L) and the serum IgE level was 306, 4 ku/L (0–100 ku/L). Skin prick tests for inhalant allergens were positive for house dust mite and *Aspergillus fumigatus*. No other family members suffered from nasal polyposis.

Additionally, the patient had symptoms of reduced hearing bilaterally at the age of 15 years. Initially, otomicroscopy had shown otitis media with effusion on both sides. This had been treated conservatively. During the following years, the patient developed chronic otorrhoea with mucous and purulent discharge from both ears. At the age of 16 years, the first polypoid changes of the middle ear mucosa were identified. When we saw this young man at the age of 20 years, otomicroscopy showed perforated eardrums, with polyps bulging through them from both middle ears (figures 3 and 4). Underneath the polyps and the eardrums, we could aspirate sticky mucus, containing eosinophils. Pure tone audiometry showed a bilateral mixed hearing loss, slightly more pronounced on the left than the right

Figure 2 CT of the paranasal sinuses at the age of 17 years, showing bilateral recurrent massive nasal polyposis, hypertelorism and remodelling of the medial orbital wall. The situation after 2× 'full house' functional endoscopic sinus surgery, 3 years before revision of all sinuses and Draf III surgery.

Figure 3 Microscopic image of the left ear.

ear (figure 5). Biopsy of the polyps showed an eosinophilic inflammation with granulation tissue.

INVESTIGATIONS

Pathological examination of the nasal polyps showed a large amount of eosinophils. Additional measurements of cytokines and mediators in the homogenates of polyp tissue demonstrated a high eosinophil-cationic protein (ECP) concentration of 25 520 μ g/L (normal values 27–696 μ g/L), an increased tissue IgE of 726 ku/L (normal values 9–75 ku/L), as well as an interleukin (IL)-17 concentration of 53.2 pg/mL (detection limit: 0.34 pg/mL) and a strongly increased IL-5 concentration of 796.8 pg/mL (detection limit: 0.21 pg/mL). Biopsies of the middle ear polyps also revealed an eosinophilic inflammation with highly increased ECP (26 334 μ g/L), tissue IgE (1016 ku/L), IL-5 (242 pg/mL) and IL-17 (358 pg/mL). Postoperatively, the eosinophilic peripheral blood count was decreased to 1430 eosinophils/ μ L (normal value 28–273/ μ L).

DIFFERENTIAL DIAGNOSIS

Woakes' syndrome

A sweat test had ruled out cystic fibrosis at the age of 7 months and was repeated negatively at the age of 15 years.

A ciliary biopsy was taken and did not show primary ciliary dyskinesia.

Figure 4 Microscopic image of the right ear.

Figure 5 Pure tone audiometry showing a bilateral mixed hearing loss, slightly more pronounced on the left than the right ear.

Blood tests were negative for antineutrophil cytoplasmic antibody-related vasculitis such as Wegener's granulomatosis and Churg-Strauss syndrome.

Clinically and proven through blood tests, there was evidence for neither an immune disorder, nor diabetes mellitus, nor thyroid disease.

Eosinophilic otitis media

Biopsy of the middle ear polyps showed an eosinophilic inflammation with granulation tissue. Malignancy, vasculitis and granulomatous inflammation were not present.

TREATMENT

At the age of 15 years, the patient had, for the first time, undergone functional endoscopic sinus surgery bilaterally. Postoperative therapy with local and peroral steroids, antibiotics and rinsing of the nose with physiological solution had been unable to prevent recurrence. Second and third sinus surgeries had been performed at the ages of 17 and 19 years, respectively. Fast recurrence of nasal polyposis had, in each case, been seen postoperatively. At the age of 20 years, we did revision surgery. A total sphenoidectomy with Draf III frontal sinusotomy, as previously described,⁹ was performed. A pedicled septal mucosal flap, based on the anterior ethmoidal artery, was made to prevent restenosis and to reconstruct frontal recess mucosa at the level of exposed bone. During the procedure, we could aspirate tough, sticky, mucopurulent secretions, especially from the maxillary and sphenoid sinuses. This phenomenon, also known as dyscrinia, had also been a finding during previous surgeries. Currently, the most reliable treatment for EOM is systemic and topical administration of corticosteroids,¹⁰ which were administered in our patient with partial regression of polyps and relief of subjective symptoms.

OUTCOME AND FOLLOW-UP

After his last surgery, the patient experienced a broad nasal passage and there was no recurrence of the nasal polyps 1 year postoperatively. Moreover, the patient indicated a subjective improvement in pulmonary function and sense of smell since the surgery.

DISCUSSION

Woakes' syndrome or ethmoiditis was first described by Woakes in 1885. In 1923, the syndrome was further defined by the 'Société Française de Laryngology' by the following four characteristics: bilateral nasal polyps in the middle meatus beginning during childhood, ethmoiditis, hypertrophic process with nasal pyramid deformation and therapeutic failure, with constant and rapid recurrences.³ The clinical picture of our patient matches with all the criteria of the syndrome. In 1979, Kellerhals and De Uthemann reported four cases of severe recurrent infantile nasal polyposis with broadening of the nose, frontal sinus aplasia, bronchiectasis and nasal dyscrinia, which they called Woakes' syndrome.¹¹ According to their definition, our patient met 3 of the 4 criteria for the diagnosis: severe recurrent nasal polyps in early childhood with broadening of the nose, nasal dyscrinia and bronchiectasis. However, in agreement with Abbud-Neme *et al*,¹¹ there was no frontal sinus aplasia in our patient. The aplasia described by Kellerhals and De Uthemann may be found in early childhood, whereas our patient was a teenager at the time of diagnosis. As we know that frontal sinuses usually develop at 7 years, it is appropriate that our patient had already shown development of the frontal sinuses before his first symptoms and time of diagnosis.¹¹

The tissue examination of the middle ear polyps and middle ear effusion showed eosinophilic inflammation. According to the EOM study group, the diagnosis of EOM can be made, since our patient also had nasal polyposis and bronchial asthma.⁵ Pure tone audiometry showed mixed hearing impairment with a mild bone conduction hearing loss, bilateral at 2–4 kHz. Conductive hearing impairment is observed at the initial stage and tends to lead to mixed hearing impairment with deterioration of bone conduction hearing level during the course of EOM development.⁸ This latter finding may be due to eosinophilic and bacterial inflammatory products invading the inner ear via the round window, causing inner ear damage.¹²

According to the previous literature, elevated concentrations of the above cytokines in CRS with nasal polyps are related to a profile with predominant T helper cells type 2, with eosinophilic inflammation and consecutive local IgE formation.¹³ Patients with this endotype of inflammation in the sinuses have

frequent comorbid asthma¹⁴ and a high risk of recurrence of nasal polyps after surgery.⁶ This case of massive nasal polyposis and asthma establishes this comorbidity and extends it to the ears, since the polyps in both middle ears and the nose showed, very similarly, highly increased concentrations of type 2 cytokines. The extension from the nose to the ears most probably occurred through the eustachian tubes,⁵ with bacteria and antigenic material being directed up to the ears when blowing the nose. Typically, the patient's serum IgE concentration of 306 kU/L was lower than the mucosal concentrations in the sinus (726 kU/L) and middle ear (1016 kU/L) tissues, in line with a prominent local polyclonal immune response.

In future, further research is needed to determine if disease recurrence and the association with EOM and asthma is inherent in patients with Woakes' syndrome.

Learning points

- ▶ The symptoms of eosinophilic otitis media with nasal polyps, such as gradual or sudden deterioration of hearing, nasal obstruction, pressure and loss of smell, as well as bronchial symptoms of asthma such as wheezing, cough and dyspnoea, are frequent single symptoms often confronting the general medical disciplines, but in this case presenting all together as a chronic disease manifestation. The combination of organs involved also brings to mind the 'common airways' paradigm.
- ▶ In such patients, the different organ systems possibly involved—including the ears—need to be investigated during the physical check and serum samples as well as an eosinophil count is indicative for the inflammatory pattern.
- ▶ In a severe multiorgan disease case, as in this patient, which was finally diagnosed as Woakes' syndrome with middle ear manifestation, biologics targeting IgE or type 2 cytokines may be used.^{5 13}

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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