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Allergen immunotherapy in children with otitis media with effusion: a preliminary experience

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To the Editor,

Otitis media with effusion (OME) is characterized by the fluid present in the middle ear, behind an intact tympanic membrane, and without signs and symptoms of an acute infection (1). OME is very common because it has been reported that about 90% of children suffer from OME before school age (2). Physiologically, the middle ear is aerated 3-4 times /min from the Eustachian tube (ET) during swallowing. If ET function is compromised, a relative negative pressure develops in the middle ear, promoting fluid accumulation (3). In children, ET dysfunction mainly depends on post-infective or allergic inflammation and/or adenoid hypertrophy. Symptoms include hearing loss and feeling of ear fullness accentuated at night in the supine position. OME diagnosis is made through micro-otoscopy and tympanometry (1).
The efficacy of pharmacologic treatment is controversial (1). In persistent OME, myringotomy with tympanic paracentesis and trans-tympanic drainage positioning is an option. As a result, a careful workup is necessary to correctly manage OME, including the video-fiber-otoscopy of the nasal cavities and nasopharynx, analysis of oral functions allergy testing. The fundamental pathogenic role of allergy in OME is still debated in the literature (4, 5). There is mechanistic evidence that supports the role of allergic inflammation in ET dysfunction and fluid accumulation (6, 7). On the other hand, a direct demonstration of a causal mechanism exerted by allergy is still lacking. However, the prevalence of allergic disorders in OME patients may also be impressive, such as up to 80-90% (8, 9). In this regard, only one study has investigated the use of allergen immunotherapy (AIT) in OME patients (10). AIT lasted 2-8 years and was administered to 21 patients who refused the standard therapy. This study evidenced that AIT provided a completed resolution of effusion or drainage in 85% of cases. This study's relevance depended on the demonstration that AIT was able to improve OME acting on immune mechanisms. This outcome rekindled the interest in the role of allergic mechanisms in OME.
In this background, the current experience aimed to investigate whether AIT could improve OME in children with associated allergic rhinitis. In this open study, 20 children (mean age 9.4 years, range 6-12, 12 males) with OME and persistent allergic rhinitis (AR) due to *Dermatophagoides* were treated with a 2-year course of AIT for mites (Staloral 300, Stallergenes, Milan, Italy). Another

group of 20 children (mean age 8.9 years, range 6-12, 11 males) with OME and persistent AR was treated only with medications. The inclusion criteria were: age between 6 and 12 years, tympanometry type "B" in both ears, severe persistent AR, monosensitization to mites. Exclusion criteria were: recurrent respiratory infections, adenoid hypertrophy (grade 3-4), non-allergic rhinitis, mechanical obstruction of ET, septal deviation, oral breathing.
The Review Board approved the procedure of Azienda Sanitaria Provinciale of Catania. The parents signed informed consent.
The AIT schedule was five drops/3-time-week per sublingual route. All children were also treated with medications (oral antihistamines and/or intranasal corticosteroids) on demand.
The primary outcome was the change of tympanometry findings. We scored tympanometry considering the type of curve: type A (normal) = 0; type C = 1; type C1 (pressure < 200 mm-H_2O) = 2; type B = 3.
Children were examined at baseline (T_0) and every 6 months (T_{1-4}). The statistical analysis was performed using a t-test for independent samples.

AIT-Group

All children, but one, completed the AIT course. Ten (53%) children had a complete OME resolution, such as type A tympanometry in both ears at T_4. There was a significant reduction at T_3 and T_4 ($p < 0.001$ and < 0.0001, respectively). The tympanometry score's mean value was 3 at baseline and 0.64 at the end of the AIT course. The tympanometry outcomes were confirmed by otoscopic assessment. AIT was well tolerated, and no clinically relevant adverse events occurred.

Control-Group

Three children had a complete resolution of OME. The mean tympanometry score was 3 at baseline and 1.89 at T_4. The score reduction was not significant.

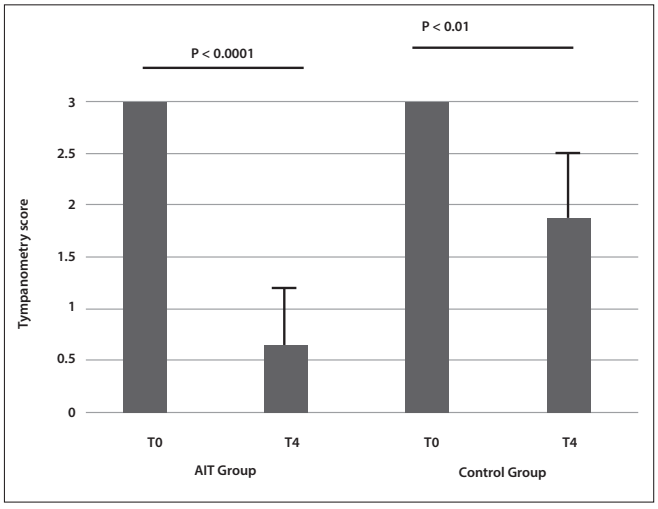
Intergroup analysis

The comparison between groups showed that AIT treatment was significantly more effective than medications alone ($p < 0.01$).
This open study demonstrated that OME completely disappeared in more than half of children after AIT. Tympanometry findings also significantly diminished as of 18 months (**figure 1**). AIT treatment was also more effective than pharmacological therapy.
The tympanometry improvement was consistent with the macroscopic observation of the eardrum. Notably, a relevant improvement was also observed in autumn-winter, such as when OME worsening is common. This fact could support the relevant pathogenic role of persistent AR. AR is characterized by type 2 inflammation (9). Type 2 inflammation is closely dependent on allergen exposure, so it is persistent in patients allergic to *Dermatophagoides* (12). Persistent allergic inflammation causes ET dysfunction and spreads in the middle ear promoting OME. Therefore, the current study provided a positive contribution to support a pathogenic role of allergy in OME development in patients with severe persistent AR.
The main limitations of this study were the open design, the lack of biomarkers assessment, the short AIT course, such as 24 months, the limited number of enrolled children considering the relatively high prevalence of OME, and the concomitant drug therapy, which could make difficult evaluate precisely the AIT effect. However, in clinical practice, only 10-20% of children with clinically relevant OME, such as bilateral tympanometry type B, spontaneously recover. The majority of patients are treated with intranasal corticosteroids, but with slight and transient results. Some OME children with associated adenoid hypertrophy tend to improve in summer and seaside staying, but allergic children do not. For this reason, children with OME and associated severe AR could fruitfully be treated with AIT. Therefore, the current study should be considered a preliminary experience, which should be confirmed by further controlled and randomized trials.
In conclusion, the present preliminary study is the second report showing that AIT could be useful in treating OME associated with severe persistent AR. Moreover, OME is an inflammatory disease, never infectious, frequently depending on persistent allergic inflammation. Thus, adequate treatment of allergy could significantly affect OME.

Conflict of interests

The authors declare that they have no conflict of interests.

Figure 1 *- Tympanometry score assessed at T_0 (baseline) and T_4 (after 24 months) in AIT-Group and Control-group.*



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