Early chronic ear disease increases the risk of current asthma, but not allergies at 10 years.

Erstad C.¹, Mowinckel P.², Carlsen K-H.³,¹, Lødrup Carlsen KC²,¹.

¹ Faculty of Medicine, University of Oslo.
² Department of Pediatrics, Ullevål University Hospital, Oslo.
³ Voksentoppen center for asthma and allergy, Division of Pediatrics, Rikshospitalet, Oslo

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Corresponding author:

Karin C Lødrup Carlsen

Dpt of Pediatrics,

Ullevål University Hospital and The Faculty of Medicine

NO-0407 Oslo, Norway

Phone: +47 22 11 87 65, Fax: +47 22 11 86 63, e-mail: k.c.l.carlsen@medisin.uio.no

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Abstract

Background

Although allergic diseases in the upper and lower airways often are viewed and treated as separate diseases and by different specialists, the present view favours a common approach. Allergic rhinitis and asthma have a well documented connection, but studies connecting the middle ear and its diseases to this system are few. Within the birth cohort Environment and Childhood Asthma (ECA) Study in Oslo (1992/1993) we aimed to investigate if secretory otitis media (SOM) at 2 years predispose for asthma, and secondarily for allergic rhinitis or allergic sensitisation development at 10 years.

Subjects and methods

The 459 children from a two year nested case-control study within the birth cohort attending a 10 year follow-up visit, underwent at 2 years parental structured interviews, clinical examinations, lung function measurements and skin prick test (SPT). Doctor diagnosed SOM was reported by parents during the two year interview. At 10 years detailed assessments of clinical examination, interview, lung function measurements, exhaled nitric oxide, bronchial hyperreactivity tests, skin prick tests and immunoglobulin E (IgE) were performed.

Results

Children with SOM had increased risk (odds ratio (OR, 95% (confidence interval)) (1.94 (1.10, 3.40)) of current asthma at 10 years, but this tendency was present already in early life, shown by more recurrent bronchial obstruction (rBO) at two years in children with (38 (50%)) compared to without SOM (109 (29%)) (p<0.001). SOM was however not significantly associated with rhinitis (25% versus 16.5%, in children with compared to without SOM, respectively (p=0.08)) or allergic sensitisation at 10 years (34.2 vs 26.1%, respectively (p=0.15)).
Conclusion

Even though children with SOM had an increased risk for current asthma eight years later, SOM appeared not to predispose for asthma development. The connection between asthma and SOM are likely to represent comorbidities.
**Introduction**

Although allergic diseases in the upper and lower airways often are viewed and treated as separate diseases and by different specialists, the present view favours a common approach (1). The allergic infiltration in the nasal mucosa in allergic rhinitis has been shown to be similar to the infiltrate and cytokine profile in the bronchi in asthma (2), expressing Th2 predominance, and asthma develops more commonly in patients with rhinitis than in those without (3) (4). The ARIA collaboration (“Allergic Rhinitis and its Impact on Asthma”) clearly documents the interaction between upper and lower airways in allergic diseases (3).

Secretory otitis media (SOM) is a chronic inflammatory disease in the middle ear, with a serous effusion, most frequently found in children aged 3-6 years. Children with SOM have been found to have a significantly higher prevalence of atopic diseases, specially atopic eczema and allergic rhinitis (2;5). The middle ear effusion during SOM has also been shown to contain high numbers of eosinophils and T lymphocytes like in late allergic inflammation (6), and it is suggested that the inflammation in SOM is TH$_2$ mediated similar to that of allergic rhinitis (2). This would suggest that there is an association between allergic rhinitis and SOM as it is with asthma. Not only is the middle ear continuous anatomically with the nasofarynx via tube Eustachii, but inflammation in the nose during allergic attacks has been shown to give allergic infiltration in the mucosa of Torus tubaris, and following tube dysfunction (2) in atopic patients.

The role of SOM in the development of allergic sensitisation is controversial (7). Although no association between SOM and later development of allergic sensitisation in childhood was shown in a well powered case-control study (5), SOM is nevertheless associated with symptoms of atopic diseases, suggesting such concomitant disease to play a role in SOM (5). Elevated serum IgE antibodies has also been found in children with SOM, suggesting
systemic allergic reactions (8;9), and IgE-sensitization has been shown to be an independent risk factor for SOM (10).

SOM and chest symptoms suggestive of asthma have been found to co-exist in an unselected group of school children (11), but with no indication of one pre-disposing for the other. An association between early adenoidectomy, an operation performed commonly in children with recurrent otitis media or SOM, and later asthma was detected by Mattila PS. *et al* (12), but the association was mainly found in children with infectious recurrent otitis media rather than SOM.

Thus, we aimed to investigate to what extent SOM in the first two years of life was associated with increased risk of current asthma in later school-age. Secondarily we aimed to assess if SOM was associated with later allergic sensitisation or allergic rhinitis.
Subjects and Methods

Study design

The present study is a prospective follow-up study from 0-10 years of a nested case-control study within the “Environment and Childhood Asthma” (ECA) study in Oslo, Norway (13;14). In summary, a cohort of 3754 children was established during 15 months from January 1, 1992 (ECA-1) (15). A nested case-control study with 1-2 clinical visits included children identified with recurrent bronchial obstruction (>1 episode or persistent (at least four weeks) doctors confirmed bronchial obstruction BO)(rBO)(n= 306) by two years of age and 306 controls identified as the child born closest in time to a case, with no history of BO. A two year follow-up study was attended by 516 children including clinical examination, parental interview, lung function (not further described) and skin-prick tests (13;14).

The 10 year follow-up visit (ECA-2) was attended by 459/516 children (89%) , and was completed in 2004 with detailed assessment of clinical examination, lung function measurements, exhaled nitric oxide, bronchial hyperreactivity tests (BHR), skin prick tests and immunoglobulin E (IgE) measures as well as paediatrician guided parental structured interview (14). However, results are not given and methods therefore not further described for lung function and BHR tests in the present paper, except for definition of outcomes, as reported previously (14;15).

Subjects

The subjects in the present study comprise those 459 children (248 (48%) boys) from the two year nested case-control study who attended the 10 year follow-up visit (Table 1).

At 2 years there were no significant differences between children with and without SOM with respect to gender, age, parental atopy at birth, positive skin prick test (SPT) at 2 years or maternal smoking from birth to 2 years (Table 1). However children with compared to
without SOM at 2 years had significantly more often upper respiratory tract infections (URTI) from birth (Table 1). At 2 years the children with SOM also more often presented with an atopic phenotype (atopic dermatitis (AD)/recurrent bronchial obstruction (rBO)) (Table 1). The children lost to follow-up (n=57) did not differ significantly from the included children with respect to age, gender, parental atopy, atopic phenotype at 2 years, number of upper respiratory tract infections (URTI) by 2 years and maternal smoking (data not shown).

Methods

At 2 years:

The two year investigation included a parental paediatrician guided structured interview related to airway symptoms, environmental exposure, lifestyle and diseases. The clinical examination included pulmonary assessment and skin examination. Parents were asked specifically if their child had been seen by a doctor and given the diagnosis of SOM (glue ear), and if they had been submitted to adenectomy and/or insertion of tympanic membrane ventilatory tubes.

Questionnaires were completed by the parents every 6 months from birth to the second birthday, with similar questions related to infectious diseases, family history of disease, socioeconomic factors and environmental exposure (13;14). In particular, the parents were asked to report all illness, including infectious diseases, symptoms of any respiratory illness and contact with doctors with respective diagnosis given. The number of reported URTIs was computed by adding all reported URTIs from each previous six month period from 0-2 years. Maternal smoking at 2 years was given by any versus no smoking.

At 10 years:
Spirometry was performed by forced expiratory flow volume loops according to European standard (14;16).

An exercise challenge test was performed by a 6–8 min treadmill run as previously described (14).

Skin prick test to common inhalant and food allergens were performed with Soluprick® allergens (ALK Albello, Denmark), and the test was considered positive with a wheal diameter $\geq 3$mm larger than the negative control (13;14). Allergens used were: Domestic mites (Dermatophagoides (D. pteronysinus and D. farinae), german cockroach, dog, cat and rabbit dander, birch, timothy (grass) and mugwort pollens, moulds (Cladosporium herbarium and Alternaria alternata), egg white, milk, peanut and codfish.

Asthma was defined (13;14) as in a child who met at least two of the three following criteria: reported dyspnoea, chest tightness and/or wheezing; doctor’s diagnosis of asthma; use of asthma medication ($\beta$-2 agonist, sodium chromoglycate, corticosteroids, leukotriene antagonists and/or aminophylline).

Rhinitis was defined as allergic sensitization combined with at least one major and one minor criterion (different from the singular major criterion): Major criteria: Doctors diagnosis of hay fever; at least two of the following: Rhinorrea, itchy/running eyes, nasal congestion or sneezing; Minor criteria: At least one of the following: Rhinorrea, itchy/running eyes, nasal congestion or sneezing; at least one of the following treatments for eye/nose symptoms: Local or systemic antihistamines, local or systemic corticosteroids, sodium chromoglycate, leukotriene antagonists, immunotherapy.

Outcomes

Current asthma: a history of asthma with symptoms and/or medication (by definition above) within the last year and/or a positive exercise test.
Allergic sensitization: a positive skin prick test to at least one allergen.

Current allergic rhinitis: was defined as allergic rhinitis (by definition above) in the last 12 months.

Statistical analysis

Results are given as mean with range (ages) or percentages (for categorical data) as well as by odds ratios (OR) with 95% confidence intervals (CI) when appropriate.

Quantitative data (age) were compared using students T-test, whereas categorical data using \( \chi^2 \) test.

To estimate risk of SOM for outcomes, logistic regression analyses were performed, including the following explanatory variables: SOM, parental atopy and rBO, all at 2 years.

SOM was defined as a positive response in a paediatrician guided structured interview to the question “Has the child had doctor diagnosed secretory otitis”. Report on SOM was missing in seven subjects.

Parental atopy was defined as a history of maternal or paternal asthma and/or hay fever.

Phenotypes at two years were rBO vs no rBO by 2 years.

Statistical analyses were performed by SPSS (statistical package for social sciences), version 14.0.

Level of significance was set to 0.05 (5%).
Results

At 2 years 76 children (42.1% boys) had reported SOM, with no significant gender predominance (Table 1).

Children with SOM at 2 years had significantly more often recurrent bronchial obstruction (rBO) (50%) than children without SOM (29.0%), respectively (p<0.001) (Table 1).

SOM and asthma at 10 years

Current asthma was found in 34% of children (n=25) with SOM compared to 20% (n=74) without SOM, but this was not statistically significant in the overall population (p=0.08). However, girls with SOM had significantly more often current asthma than girls without SOM by two years (31.3% with SOM versus 12.5% without (p=0.014)), whereas SOM was not associated with current asthma at 10 years in boys (35.7% versus 26.4%, respectively (p=0.257)).

Although SOM in a logistic regression analysis (including parental atopy, gender and SOM) was significantly associated with current asthma at 10 years (OR= 1.94, CI 1.10, 3.40) (Table 3) the association disappeared after adjusting for rBO (Table 4), since rBO was already present at two years in all 10 girls and in all but one boy (14/15) with SOM and current asthma.

Similar was found for the combined phenotype rBO and atopic eczema (table 1). Out of the children with SOM and current asthma 37.3% boys were found to have AD/rBO at 2 years compared to those without SOM and current asthma (15.5%) (p<0.001), and similarly did 43.8% of the girls with SOM and current asthma have AD/rBO compared to those without (12.8%) (p<0.001).

SOM and allergic rhinitis at 10 years
SOM by 2 years was not significantly associated with current allergic rhinitis at 10 years, either by univariate analysis (Table 2), or after adjusting for parental atopy and gender (Table 3).

SOM and allergic sensitisation at 10 years

There was no significant association between SOM by 2 years and allergic sensitization (any positive SPT) at 10 years (Table 3), with a positive SPT in 34.2% of children with compared to those without SOM (26.1%), respectively (p=0.15) (Table 2).
Discussion

Although current asthma at 10 years was significantly more common among girls with reported SOM by two years of age, the children had already expressed co-morbidity of obstructive airways disease at two years in all but one child (with atopic eczema). SOM was not associated with later development of allergic rhinitis or allergic sensitization at 10 years.

In the present study 16.6% of the children had SOM. In comparison Zielhuis et al (17;18) reported a prevalence at 2 years at about 20% in children followed up over a 2 years period, which correlates well to our prevalence. Umapathy et al (11) found that in an unselected group of schoolchildren 32.8% of them had SOM, while Raza M. et al (19) detected SOM in 42 % of children with recurrent upper respiratory infection in a secondary care facility. The discrepancy of our prevalence from the two latter studies might be because of selection bias since our study was a selected nested case-control study in a birth cohort population.

Although current asthma was more common among girls with SOM in our study, the airways disease was expressed already by the age of two years. The coexistence of SOM and asthma has been suggested by Umapathy et al (11;20), but without discussing if one disease predisposed the other. Thus the present study suggests that SOM did not predispose for asthma later in childhood, since an atopic phenotype was already present at the same time as the SOM.

The lack of association between SOM and allergic sensitization, is in line with, as mentioned above, earlier findings (5;11) which connect SOM to atopic symptoms, but not directly to allergic sensitisation. Our findings is likely not to be a result of less atopy in our population since our previously reported allergic sensitisation prevalence (29.3%) (14) corresponds to
previous Scandinavian reports, where a prevalence of positive SPT’s were found in 31.7% 12-13-year-old Swedish children in 1996 (21).

In our population SOM did not increase the risk of *current allergic rhinitis* (Table 3). Allergic rhinitis is on the other hand suggested to be a risk factor for asthma development (3), supported by The Children’s Respiratory Study (4) that found that the presence of physician-diagnosed allergic rhinitis in infancy was independently associated with a doubling of the risk of developing asthma by 11 years of age. Allergic rhinitis is also often coexisting with SOM, as shown by Umapathy *et al* (11), and support that the middle ear should be regarded as a part of the common airway (2). Allergic rhinitis is also suggested to be a big contributor to SOM development (22), but whether SOM is a risk factor for allergic rhinitis development has not yet, to our knowledge, been considered in a cohort study with a sufficient control group.

*Strengths and limitations of the present study*

Amongst the strengths in this study was the study design, a birth cohort one could follow in a nested case-control study from birth to the age of 10 years. This way one avoided recall-bias and misclassification, and one detected predisposing factors. The subjects, both at 2 and 10 years, were carefully characterized by the interviews and questionnaires, and every case in the case-control study had well matched controls. The study had a statistical power to detect possible associations (with a total of 459 subjects) of at least 70% if we assume a $R^2$ of at least 0.30 between the about 3 covariates. Prevalence of both main explanatory variables as well as outcomes was comparable to other populations. Furthermore, the 10 years follow-up study was well attended (84%) (14). The definitions used were strict with several criteria to fulfil, thus one avoided over- and under-diagnosis of the outcomes in the study. Especially the asthma-definition has been shown to reflect in a good way the child’s clinical state (14;15).
Although the SOM was defined on the basis of parental report of doctors diagnosis and no ear-nose-throat specialist evaluation for SOM during the clinical investigation, the prevalence of SOM was nevertheless similar to that reported by others (17;18).

**Conclusion**

SOM did not individually predispose for the development of later asthma in the overall population in this study. Even though girls with SOM had a greater risk for later asthma than those without, this association was apparent already in early life, presented by rBO. SOM and asthma are most likely to represent comorbidities, as part of the “united airways” starting in early life.
Acknowledgements:

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A particular thanks to the ECA-2 team who performed the 10 year follow-up of these subjects; Geir Håland, Chandra Devulapalli, Monica Cheng-Munthe Kaas, Solveig Knutsen, Trine Stensrud, Ingebjørg Coward and Anne Cathrine Mork Wik
Table 1 Demography over the 459 children examined at 2 years in the Environment and Childhood Asthma study (ECA-study) in Oslo, given by the presence or not of reported secretory otitis media (SOM) by two years of age (452 had SOM).

<table>
<thead>
<tr>
<th></th>
<th>SOM yes</th>
<th>SOM no</th>
<th>p-value</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=76</td>
<td>n=376</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years n=459</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, months (min – max)</td>
<td>27 (21,39)</td>
<td>27 (20.41)</td>
<td>0.50</td>
<td>27 (20,41)</td>
</tr>
<tr>
<td>Gender (boy), n (%)</td>
<td>44 (57.9)</td>
<td>199 (52.9)</td>
<td>0.43</td>
<td>243 (53.8)</td>
</tr>
<tr>
<td>Parental atopy at birth, n (%)</td>
<td>36 (47.4)</td>
<td>149 (40.6)</td>
<td>0.28</td>
<td>185 (41.8)</td>
</tr>
<tr>
<td>AD and rBO at 2 years, n (%)</td>
<td>23 (30.3)</td>
<td>65 (17.3)</td>
<td>&lt;0.001</td>
<td>88 (19.5)</td>
</tr>
<tr>
<td>rBO at 2 years, n (%)</td>
<td>38 (50.0)</td>
<td>109 (29.0)</td>
<td>&lt;0.001</td>
<td>147 (32.5)</td>
</tr>
<tr>
<td>No. URTI at 0-2 years, mean no (n)</td>
<td>10.06 (31)</td>
<td>6.28 (203)</td>
<td>&lt;0.001</td>
<td>6.78 (234)</td>
</tr>
<tr>
<td>Maternal smoking 0-2 years (any smoking), n (%)</td>
<td>23 (30.3)</td>
<td>125 (33.4)</td>
<td>0.59</td>
<td>148 (32.9)</td>
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<tr>
<td>SPT positive at 2 years, n (%)</td>
<td>6 (9.7)</td>
<td>29 (10.1)</td>
<td>0.92</td>
<td>35 (10.0)</td>
</tr>
<tr>
<td>10 years n=459</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, year (min-max)</td>
<td>10.32 (8.8, 11.9)</td>
<td>10.34 (9.0, 12.3)</td>
<td>0.88</td>
<td>10.3 (8.8, 12.3)</td>
</tr>
</tbody>
</table>

AD: Atopic dermatitis
rBO: Recurrent bronchial obstruction
URTI: Upper respiratory tract infection
SPT: Skin prick test
Table 2 The demography of the 459 children followed-up at 10 years, given by the presence or not of reported secretory otitis media (SOM) (in 452 children) by two years of age.

<table>
<thead>
<tr>
<th></th>
<th>SOM positive</th>
<th>SOM negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=76</td>
<td>n=376</td>
<td></td>
</tr>
<tr>
<td>Current asthma, n (%)</td>
<td>25 (33.8)</td>
<td>74 (19.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Allergic sensitisation (at least one positive skin prick test), n (%)</td>
<td>26 (34.2)</td>
<td>97 (26.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Current allergic asthma</td>
<td>13 (17.6)</td>
<td>32 (8.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>(current asthma + allergic sensitisation), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current allergic rhinitis, n (%)</td>
<td>19 (25.0)</td>
<td>62 (16.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Allergic rhinitis (ever), n (%)</td>
<td>21 (27.6)</td>
<td>68 (18.1)</td>
<td>0.056</td>
</tr>
</tbody>
</table>
Table 3

Logistic regression analysis (including SOM, parental atopy and gender) to estimate the effects of SOM by 2 years for asthma, allergic sensitisation and current allergic rhinitis in 10 year old children.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Current asthma</th>
<th>SPT positive</th>
<th>Current allergic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>SOM (no)</td>
<td>1.94 1.10, 3.40</td>
<td>0.73 0.42, 1.25</td>
<td>0.63 0.35, 1.15</td>
</tr>
<tr>
<td>Parental atopy (no)</td>
<td>1.77 1.11, 2.81</td>
<td>2.02 1.31, 3.11</td>
<td>1.93 1.18, 3.16</td>
</tr>
<tr>
<td>Gender (girl)</td>
<td>2.25 1.39, 3.65</td>
<td>0.47 0.30, 0.74</td>
<td>0.60 0.36, 1.0</td>
</tr>
</tbody>
</table>

SOM: Secretory otitis media

SPT: Skin prick test

Table 4 Logistic regression analysis of the 459 children (452 with SOM) to show how rBO as a variable interferes with the SOM and current asthma connection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Current asthma</th>
<th>SPT positive</th>
<th>Current allergic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>SOM (no)</td>
<td>1.24 0.69, 2.25</td>
<td>1.28 0.73, 2.23</td>
<td>1.45 0.79, 2.67</td>
</tr>
<tr>
<td>rBO (no)</td>
<td>9.86 5.02, 19.3</td>
<td>1.29 0.82, 2.02</td>
<td>1.37 0.82, 2.31</td>
</tr>
<tr>
<td>Parental atopy (no)</td>
<td>1.67 1.02, 2.76</td>
<td>1.99 1.29, 3.07</td>
<td>1.90 1.16, 3.11</td>
</tr>
<tr>
<td>Gender (girl)</td>
<td>2.09 1.24, 3.51</td>
<td>2.06 1.31, 3.22</td>
<td>1.61 0.97, 2.68</td>
</tr>
</tbody>
</table>
SOM: Secretory otitis media

rBO: Recurrent bronchial obstruction

SPT: Skin prick test
Reference List


