

available at www.sciencedirect.comjournal homepage: www.elsevier.com/locate/rmed

Long-term prognosis of immediate hypersensitivity type of occupational laryngitis

Timo Hannu ^{a,*}, Eeva Sala ^b, Elina Toskala ^c

^a Team of Occupational Medicine, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, FI-00250 Helsinki, Finland

^b Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Turku University Hospital, Kiinamyllynkatu 4-8, FI-20521 Turku, Finland

^c Team of Control of Hypersensitivity Diseases, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, FI-00250 Helsinki, Finland

Received 13 January 2008; accepted 15 July 2008

KEYWORDS

Hypersensitivity;
Laryngeal symptoms;
Occupational asthma;
Occupational rhinitis;
Outcome

Summary

The present study investigated, for the first time, the long-term prognosis of hypersensitivity type of occupational laryngitis (OL).

Thirteen patients with OL diagnosed in 1990–1993 at the Finnish Institute of Occupational Health participated in a questionnaire follow-up study. The records of the primary diagnostic investigations were also reviewed.

The mean follow-up time was 12.5 (range 11–15) years. The mean age of the study subjects was 51.5 (range 32–64) years; nine (69%) were women. In addition to OL during the primary examinations, two patients were diagnosed to have occupational asthma, and nine patients occupational rhinitis. During the follow-up, six additional patients had developed asthma. Asthma had thus been diagnosed in 8 of the 13 (61%) patients. At present, nine patients (69%) were non-employed. Of these, seven were on work disability pension, of whom six had occupational or non-occupational asthma in addition to OL. The remaining four patients (31%) were still working: three had training for some other type of work, and one had been transferred to another job. None of them had developed asthma during the follow-up.

The current study, based on a small series, suggests that many of the patients with previously diagnosed OL developed asthma and were not employed.

© 2008 Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +358 30 474 2575; fax: +358 30 474 2149.
E-mail address: timo.hannu@ttl.fi (T. Hannu).

Introduction

Different types of laryngitis can be grouped according to clinical picture, etiology, and duration, i.e., whether the condition is reversible or non-reversible.¹ For instance, chronic occupational laryngitis is caused by irritant chemical substances, fumes, and dusts^{2,3} and acute occupational laryngitis is caused either by irritant substances, such as ammonia, calcium cyanamide, and metal oxides,^{4–6} or by the immediate hypersensitivity mechanism.^{2–7}

The immediate hypersensitivity type of laryngitis can be classified as an immediate allergic (type I) reaction or other immediate type specific hypersensitivity reaction.² The former term implies that an IgE-mediated hypersensitivity type I allergic reaction to a causative agent could be demonstrated either by skin-prick tests or by specific IgE-antibodies in sera. The latter term can be used when an IgE-mediated or some other immunological reaction mechanism cannot be shown, but the immediate laryngeal reaction is nevertheless confirmed by a positive provocation test. Reports on patients with immediate hypersensitivity type of occupational laryngitis are rare.^{2,7–9} Thus far, the largest series of such patients consisted of 20 patients with etiological agents including flours, obeche wood, decorative flowers, hairdresser's chemicals, acid anhydrides, and other chemicals such as methacrylates and formaldehyde.² The diagnosis in that series was confirmed by specific inhalation provocation tests.

Nasal and bronchial mucosae are very similar,¹⁰ and most patients with asthma have also rhinitis, pointing to the idea of "one airway one disease".¹¹ In this concept, however, the larynx has not been studied and, furthermore, the possibility of allergic reactions of the larynx and the throat is mostly neglected in studies investigating the effects of environmental factors on the respiratory tract. The long-term prognosis of hypersensitivity-induced occupational respiratory diseases, i.e., asthma, rhinitis, or laryngitis, is best known for occupational asthma (OA). To our best knowledge, there are no studies on the prognosis of occupational laryngitis.

The aim of the present study was to assess the long-term prognosis of patients with hypersensitivity type of occupational laryngitis (hereafter called occupational laryngitis, OL).

Materials and methods

Twenty patients diagnosed with OL were examined at the FIOH during 1990–1993, as described previously.² Ten were women (aged 27–53 years) and 10 men (aged 22–49 years) (Table 1). They were all exposed at work to substances capable of sensitization: flours in five cases, obeche wood in three, decorative plants and vegetables in four, hairdresser's chemicals in four, and various chemicals in four cases (methylhexahydrophthalic acid, formaldehyde, dental adhesive containing methacrylate, and hot melt glue containing resin derivatives, one case of each). They all experienced hoarseness of voice as a work-related symptom. Skin-prick tests to causative substances were performed in 19 cases; 13 displayed positive results. Furthermore, 10 of these 13 patients had an elevated level

of specific IgE-antibodies to the same causative agent. Laryngeal changes corresponding to the symptoms could be verified in all of these patients during specific provocation tests.

Twenty patients were requested by mail to participate in a questionnaire follow-up study. If no response came within 3 weeks, a reminder was sent; altogether, two reminders were sent to the non-responders. The questionnaire inquired current employment status, exposure to work-related substances, smoking habits (status of smoking: current, ex-smoker, or never-smoker; and duration of smoking), and occurrence of asthma. The presence of general or work-related laryngeal and voice symptoms was

Table 1 Characteristics of the patients with occupational laryngitis of immediate hypersensitivity type at the time of the primary examinations at FIOH

	Participated in the present follow-up study (N = 13)	Did not participate in the follow-up study (N = 7)
Age, years	39.0 (19–53)	28.3 (22–45)*
Gender, F/M	9/4	1/6
Duration of exposure, years	13.8 (2–30)	5.8 (1.5–9)
Causative agent		
Flours	4	1
Hairdressing chemicals	4	0
Decorative plants or vegetables	2	2
Obeche wood	0	3
Various chemicals	3 ^a	1 ^b
Positive skin-prick test to the causative agent	7	6
Specific IgE to the causative agent	6	4
History of atopy	2	5**
Other hypersensitivity diseases caused by the same causative agent, yes/no	10/3	7/0
Rhinitis	9 ^c	6 ^d
Asthma	2 ^e	2 ^f
Pharyngitis	2	2
Skin disease	1	3

Data are presented as *n*, or mean (range).

F = female; M = male; FIOH = Finnish Institute of Occupational Health.

**P* = 0.030.

***P* = 0.022.

^a Methylhexahydrophthalic anhydride (MHHPA); methyl-methacrylate; and formaldehyde.

^b Hot melt glue containing resin derivatives.

^c Caused by tulip, MHHPA, rye flour, ammonium persulphate, wheat flour (two cases), jojoba, freesia, and buckwheat.

^d Caused by wheat flour, obeche wood (three cases), spathe plant, and potato with paprika.

^e Caused by tulip and buckwheat.

^f Caused by obeche wood and hot melt glue containing resin derivatives.

also inquired. In addition to the responses to the questionnaire, we reviewed these patients' medical charts of the primary investigations at FIOH.

Data were analysed with the SPSS statistical software system, version 10.0.5 (SPSS, Chicago, IL, USA). The proportional data were compared with Fischer's exact test. The Mann–Whitney *U*-test was used in comparisons of continuous variables. Statistical significance was set at the 5% level. The study was approved by the Ethics Committee of FIOH, and the patients gave their informed consent.

Results

General characteristics

The patients who participated in the follow-up study ($N = 13$) were compared to those who did not ($N = 7$); the data are based on the diagnostic examinations at the FIOH in 1990–1993 (Table 1). In the former group, the mean age of the patients was higher ($P = 0.030$), there were more women ($P = 0.057$), and the mean duration of work exposure before the diagnosis was longer ($P = 0.081$). All patients with OL caused by hairdressing chemicals participated in the follow-up, as well as nearly all patients exposed to flours, but none of the patients exposed to obeche wood.

The mean follow-up time of the 13 patients participating in the follow-up study was 12.5 (range 11–15) years after the diagnosis of OL. The mean age of these patients was 51.5 (range 32–64) years; nine (69%) were women. During the primary diagnostic examinations, in addition to being diagnosed as having OL, two patients were diagnosed to have concurrently OA, and nine patients occupational rhinitis (OR) (Table 1). One of the subjects with only OL after the primary investigations was a never smoked 27-year-old hairdresser, who has been exposed to hairdressing chemicals for 7 years. After the diagnosis of OL, she was re-educated. Other of the subjects with only OL was an ex-smoker 49-year-old foreperson with a 20 years history of work-related exposure to formaldehyde. After the diagnosis of OL, he was not able to continue his job and was granted disability pension by an insurance company.

Development of asthma

During the follow-up period, six additional patients had developed asthma. Three of these six patients were diagnosed to have OR during the primary investigations at FIOH. There were no significant differences between these six patients and the two patients, which were diagnosed to have asthma during the primary investigations at FIOH, regarding to age, gender, smoking status, and duration of exposure (data not shown). The causative agents of OL included flours (rye, wheat), hairdressing chemicals (ammonium persulphate, jojoba), and other chemicals (methacrylates, formaldehyde) in the first group, and flours (buckwheat) and decorative plans (tulip) in the latter group. Of the six additional patients with asthma, three had developed OA caused by the same agent (rye, wheat, ammonium persulphate, one case each) as their OL, and one by a different agent (OL caused by methacrylates and

OA by resin in a dental restorative material). In these four patients, the time interval between the primary investigations and the later investigations (including bronchial challenge tests at the FIOH) was a few months at the most, during which time they were no longer exposed to the causative agents. The asthma of the remaining two patients was not regarded to be of occupational origin after diagnostic investigations; the time interval between the primary investigations and the pulmonary investigations at the FIOH was a few months in one case (a hairdresser whose OL was caused by jojoba); and in the other case, the time interval between the primary investigations at the FIOH and the later pulmonary investigations performed at a local central hospital was 12 years. The latter patient retired on work disability pension because of his OL (caused by formaldehyde) after the primary investigations at the FIOH, and was therefore not exposed to the causative agent after that. All in all, eight of the 13 (61%) patients with OL developed asthma.

Those who developed asthma either after the primary investigations at FIOH or during the follow-up time were older (mean age 55.5 versus 45.2 years), and their mean exposure time prior to the diagnostic examinations was longer (16.2 versus 9.9 years) than of those who did not develop asthma, but these differences were not statistically significant ($P = 0.127$ and $P = 0.284$, respectively) (Table 2). Seven of the eight (88%) patients who developed asthma were not employed (six were on disability pension due to the occupational disease, and the reason for the non-employment of one patient, who had been re-trained, was not known). Only one of the eight (12%) patients was employed (a 37-year-old male baker who had been re-educated after his occupational disease to be an instructor). The employment situation of the five who did not develop asthma was better. Three of these five (60%) were employed (two of them were re-educated, and one was relocated in the same organization after the occupational disease) but two of them (40%) were not (one had retired, but not because of the occupational disease, and the other, who had been re-trained for another job, was unemployed).

We also assessed the occurrence of laryngeal symptoms (hoarseness of voice), nasal symptoms (nasal discharge, blockage, or sneezing), and lower respiratory symptoms (dyspnoea, coughing, phlegm, or wheezing) in those who had developed asthma based on the primary investigations at FIOH. In all of these eight patients, laryngeal symptoms preceded the lower respiratory symptoms ($N = 4$) or occurred simultaneously ($N = 4$). Five of these eight patients had also OR. In these five patients, nasal symptoms preceded ($N = 4$) or occurred simultaneously ($N = 1$) with the lower respiratory symptoms, and they also preceded ($N = 1$) or occurred simultaneously ($N = 4$) with the laryngeal symptoms.

Employment status

At the time of the follow-up study, nine (69%) patients were not employed and four (31%) were employed. The reasons that the patients gave for their non-employment were retirement in seven cases (six patients had been granted disability pension by an insurance company due to their

Table 2 Comparison of the patients with occupational laryngitis of immediate hypersensitivity type who developed asthma and those who did not during the follow-up

	Developed asthma during the follow-up time (N = 8)	Did not develop asthma during the follow-up time (N = 5)
Characteristics at the time of the follow-up study		
Age, years	55.5 (39–64)	45.2 (32–62)
Gender, F/M	5/3	4/1
Smoking status (current/ex/never)	1/2/5	2/1/2
Working status		
Employed	1	3
Not employed	7	2
Characteristics at the primary investigations at FIOH		
Duration of exposure, years	16.2 (3.5–30)	9.9 (2–23)
Causative agent of OL		
Flours	Rye 1, wheat 1, buckwheat 1	Wheat 1
Hairdressing chemicals	Ammonium persulphate 1, jojoba 1	Ammonium persulphate 2
Decorative plants or vegetables	Tulip 1	Freesia 1
Various chemicals	Methacrylates 1, formaldehyde 1	MHHPA 1
Positive skin-prick test to the causative agent of OL	4	3
Specific IgE to the causative agent of OL	4	2
Other hypersensitivity diseases caused by the same causative agent		
OR	5	4
OA	2	0
Pharyngitis	2	0
Skin disease	1	0

Data are presented as *n*, or mean (range).

F = female; FIOH = Finnish Institute of Occupational Health; M = male; MHHPA = methylhexahydrophthalic anhydride; OA = occupational asthma; OL = occupational laryngitis; OR = occupational rhinitis.

occupational disease, and one patient was on a normal old-age retirement pension); one patient was unemployed, and the reason for the non-employment of one patient was not available. None of the six patients who had developed asthma during the follow-up time were employed. Of the four patients who were still working, three had been re-educated and one had been transferred in the same organization to work tasks not including exposure to the causative agent. None of these four patients had developed asthma during the follow-up time.

The non-employed patients were older (mean age 54.9 versus 44.0 years; $P = 0.050$) than the employed patients. Although the majority of the former group were women (seven of nine versus two of four) and had a longer mean exposure time prior to diagnostic examinations (15.2 versus 10.5 years) than the latter group, these differences were not statistically significant ($P = 0.530$ and $P = 0.414$, respectively) (Table 3).

Vocal symptoms

All except one patient (92%) had hoarseness of voice as a vocal symptom during the primary investigations at FIOH, whereas, at the time of the follow-up study, nine patients reported persistent vocal symptoms. There were no significant differences between the nine patients with and the four patients without persistent vocal symptoms at the follow-up regarding to age, gender, smoking status, duration of exposure, and working status (data not shown). However, a trend was found regarding the development of

asthma during the follow-up time between these two groups (six of nine versus null of four; $P = 0.070$). Two of the nine were still working, and they both suffered from work-related laryngeal symptoms: one, an electrician whose OL was caused by methylhexahydrophthalic anhydride and who was then transferred to other work, from chemicals (such as adhesives, cleaning substances, and glues), and the other one, a hairdresser whose OL was caused by ammonium persulphate, in the dust of the workplace. Vocal symptoms affected the performance of both persons in their daily speaking situations, for instance when louder speaking or prolonged voice use is needed. The remaining seven patients were no longer working, but all of them still had vocal symptoms, which in four cases disturbed daily speaking.

Discussion

Previous studies have investigated the impact of OR on the development of asthma. In a Finnish epidemiological study, workers seeking compensation for OR had a 4.8-fold relative risk of developing asthma as compared with patients receiving compensation for any other occupational disease.¹² It has been estimated that the positive predictive value of rhinoconjunctivitis in the development of OA is close to 30%.¹³ According to the present study, which is the first series reporting on the late prognosis of occupational laryngitis of immediate hypersensitivity type, 60% of patients with OL had developed asthma. It should be kept in mind, however, that 60% of these OL patients have also OR.

Table 3 Comparison of the patients with occupational laryngitis of immediate hypersensitivity type who were currently employed and those who were not at the time of the follow-up

	Not employed (N = 9)	Employed (N = 4)
Characteristics at the time of the follow-up study		
Age, years	54.9 (39–64)	44.0 (32–52)*
Gender, F/M	7/2	2/2
Smoking status (current/ex/never)	2/2/5	1/1/2
Developed asthma during the follow-up time	6	0
Characteristics at the primary investigations at FIOH		
Duration of exposure, years	15.2 (3.5–30)	10.5 (2–20)
Causative agent of OL		
Flours	Rye 1, wheat 2	Buckwheat 1
Hairdressing chemicals	Ammonium persulphate 1, Jojoba 1	Ammonium persulphate 2
Decorative plants or vegetables	Tulip 1, freesia 1	
Various chemicals	Methacrylates 1, formaldehyde 1	MHHPA 1
Positive skin-prick test to the causative agent of OL	5	2
Specific IgE to the causative agent	4	1
Other hypersensitivity diseases caused by the same causative agent		
OR	6	3
OA	1	1
Pharyngitis	1	1
Skin disease	1	0

Data are presented as n, or mean (range).

F = female; M = male; MHHPA = methylhexahydrophthalic anhydride; OA = occupational asthma; OL = occupational laryngitis; OR = occupational rhinitis.

* $P = 0.050$.

In line with the previous studies on OR, the present study indicates that OL either alone or concurrently with OR is a risk factor for asthma, too.

Upper respiratory allergic symptoms often precede or coincide with the onset of allergic asthma from the sensitizer.¹⁴ In our series, all patients who developed asthma had laryngeal symptoms before or concurrently with asthmatic symptoms. Moreover, the nasal symptoms of the patients with asthma and OR preceded or occurred simultaneously with the lower respiratory symptoms as well as with the laryngeal symptoms. These findings indicate that a sequence of events may be involved, i.e., the nasal symptoms are followed by laryngeal symptoms, and thereafter by lower respiratory symptoms, if the exposure to a sensitizing agent continues. This finding emphasizes the importance of early intervention as soon as the laryngeal symptoms appear, before they can develop into asthma.

In the present series, about 70% of the patients with OL were not employed. Of these patients, nearly all (eight out of nine) had asthma already at the primary investigations at FIOH or had developed asthma since then. It is difficult to estimate whether either their laryngitis or asthma was the principal cause of their non-working status. Asthma apparently seems to be the main cause, because most of these patients were entitled to a work disability pension. The contributing role of OL cannot be excluded, however. On the other hand, none of the remaining four patients who were still working had developed asthma during the follow-up. Assessment of the occupational rehabilitation of these patients has been started, and has been found successful in all: three of them were re-educated and one was relocated

within the same organization. This demonstrates the importance of early diagnosis and subsequent necessary intervention measures.

At the follow-up, nearly 70% of the patients still had laryngeal symptoms. This was a much higher rate compared to patient series in other studies, which have shown that the 1-year prevalence of vocal symptoms is 37% in the teachers of children's day care centres, 29% in school teachers, and 17% in nurses,^{15,16} whereas the lifetime prevalence of vocal symptoms in the general population is about 30% and the point prevalence in the general population is 6.6%.¹⁷ In our series, those with persistent vocal symptoms at the follow-up had a higher risk for the development of asthma during the follow-up time than those without these symptoms.

A limitation of our study is its small sample size, as it comprised only 13 patients. This partly reflects the rarity of this disease condition. In our study, we included patients diagnosed at the FIOH in 1990–1993. By extending this time period, we might have gained a larger study population, but this might nevertheless have influenced the uniformity of the diagnostic procedures, which may change in the course of time. To avoid this possibility, we chose the afore-mentioned shorter time period. Based on biological differences, the predominantly female population may have had an influence on our results. The small sample size also hampered statistical analysis, which was restricted to basic operations. Therefore, we could not unfortunately determine the causative agents of OL with an increased risk to develop asthma, which information would be important when designing interventions for prevention.

In conclusion, this study addressed for the first time the late prognosis of OL. Development of asthma was high among patients with previously diagnosed OL. Nearly all of the patients who had OL as well as OA were out of the workforce, whereas the patients who were still working had either been re-educated or transferred to other work tasks after their diagnosis of OL, and none of them had developed asthma during the follow-up time. Further studies with a larger sample size are needed to confirm our findings.

References

1. van den Broek P. Acute and chronic laryngitis. In: Kerr AG, editor. *Scott-Browns's otolaryngology*. London: Butterworths; 1987. p. 99–188.
2. Sala E, Hytönen M, Tupasela O, Estlander T. Occupational laryngitis with immediate allergic or immediate type specific chemical hypersensitivity. *Clin Otolaryngol* 1996;**21**:42–8.
3. Baletic N, Jakovljevic B, Marmut Z, Petrovic Z, Paunovic K. Chronic laryngitis in glassblowers. *Ind Health* 2005;**43**:302–7.
4. Anonymous. Cyano compounds. In: Stellman JM, editor. *Encyclopedia of occupational health and safety*. 4th ed. Geneva: ILO; 1998. p. 104.133–5.
5. Baxter PJ. Primary irritant gases. In: Baxter PJ, Adams PH, Aw T-C, Cockcroft A, Harrington JM, editors. *Hunter's diseases of occupations*. London: Arnold; 2000. p. 123–78.
6. Elmer P, Cockcroft A, Nemery B. Inorganic dusts. In: Baxter PJ, Adams PH, Aw T-C, Cockcroft A, Harrington JM, editors. *Hunter's diseases of occupations*. London: Arnold; 2000. p. 663–708.
7. Piirilä P, Kanerva L, Keskinen H, Estlander T, Hytönen M, Tuppurainen M, et al. Occupational respiratory hypersensitivity caused by preparations containing acrylates in dental personnel. *Clin Exp Allergy* 1998;**28**:1404–11.
8. Roto P, Sala E. Occupational laryngitis caused by formaldehyde: a case report. *Am J Ind Med* 1996;**29**:275–7.
9. Hannu T, Piipari R, Toskala E. Immediate hypersensitivity type of occupational laryngitis in a welder exposed to welding fumes of stainless steel. *Am J Ind Med* 2006;**49**:402–5.
10. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;**111**:1171–83.
11. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003;**58**:691–706.
12. Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest* 2003;**123**:283–8.
13. Gautrin D, Ghezzi H, Infante-Rivard C, Malo JL. Natural history of sensitization, symptoms, and disease in apprentices exposed to laboratory animals. *Eur Respir J* 2001;**17**:904–8.
14. Malo J-L, Lemièr C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;**10**:1513–5.
15. Sala E, Laine A, Simberg S, Pentti J, Suonpää J. The prevalence of voice disorders among day care center teachers compared with nurses: a questionnaire and clinical study. *J Voice* 2001;**15**:413–23.
16. Simberg S, Sala E, Rönnemaa A-M. Comparison of the prevalence of vocal symptoms among teacher students and other university students. *J Voice* 2004;**18**:363–8.
17. Roy N, Merrill RM, Gray SD, Smith EM. Voice disorders in the general population: prevalence, risk factors, and occupational impact. *The Laryngoscope* 2005;**115**:1988–95.