International Journal of Occupational Medicine and Environmental Health 2012;25(4):506–512
DOI 10.2478/S13382-012-0060-4

ANOSMIA AFTER EXPOSURE TO A PYRETHRIN-BASED INSECTICIDE: A CASE REPORT

FABRIZIOMARIA GOBBA and CARLOTTA ABBACCHINI

University of Modena and Reggio Emilia, Modena, Italy
Chair of Occupational Medicine, Department of Diagnostic, Clinical and Public Health Medicine

Abstract
We present the case of a subject developing anosmia, preceded by nasal transient irritation and short lasting phantosmia and torqosmia, upon re-entrance into a room treated with a pyrethrin-based insecticide. The concentration of the insecticide in the room is unknown, but relatively high levels are predicted basing upon the modality of exposure and by the irritation symptoms in the subject. Despite corticosteroids therapy, anosmia has persisted unmodified for more than three years; according to, and based on evidence in the literature on olfactory disturbance prognosis, anosmia in this patient is likely to be permanent. The significance of this case report is related to the current wide use of insecticides containing pyrethrin and pyrethroids and highlights the need for more adequate attention to lowering airborne concentrations of pyrethrins and pyrethroids prior to re-entering the treated rooms. In particular, in a closed space sprayed with pyrethrins and pyrethroids insecticide, any irritant symptoms and/or dysosmia should be immediately considered relevant warning signs, and must be avoided.

Key words:
Insecticides exposure, Adverse effects, Pyrethrins, Irritant symptoms, Anosmia

BACKGROUND

Olfactory impairment has historically been overlooked as a problem of public health, and has been frequently relegated to the status of a mere annoyance, rather than a medical disability. However, olfaction is a critical physiologic function in humans: normal perception is fundamental for detection of many warning signals of life-threatening situations, such as smoke, spoiled food, dangerous chemicals, gas leaks, etc.: in some studies a relation was observed between the degree of olfactory loss and the risk of hazardous events [1,2]. Furthermore, nutritional status and many other topics related to the quality of life may be affected by the impairment of olfactory function [3], and loss of smell is accompanied by an increased risk of depression [4]. In addition, it is present in up to the 90% of Parkinson's Disease patients, and is considered one of the most prevalent troublesome nonmotor problems in this disease [5].

The prevalence of subjects with the impairment of olfactory perception in the general population ranges from 1 up to 20% [6–8]. However, this is likely an underestimation, especially considering the fact that many people with a reduced olfactory sensitivity are unaware of their situation [3].

The terms 'anosmia' and 'hyposmia' are usually applied to describe the absence or diminished smell function, respectively (even if, apparently, 'anosmia' has been occasionally used in a broad sense, to include both conditions). 'Dysosmia' is an altered perception of smell and includes 'cacosmia' (altered perception of a stimulus present) and

Received: January 12, 2012. Accepted: September 26, 2012.
Address reprint request to F. Gobba, Chair of Occupational Medicine, Department of Diagnostic, Clinical and Public Health Medicine, Via Campi 287-41125 Modena, Italy (e-mail: fabriziomaria.gobba@unimore.it).

'phantosmia' (odour perception without stimulus). The sensation of the smell of burnt or metallic smell in the absence of the stimulus is sometimes defined as 'torqosmia' [9].

In a large Swedish study, overall prevalence of hyposmia and anosmia in the general population were 13.3% and 5.8%, respectively [6], and similar proportions were reported in Germany [8].

One of the main factors related to olfactory dysfunction is aging [11], but several other causes are also known. Among the most important are: head trauma [12], infections of the upper respiratory tract, nasal and paranasal sinus diseases [13] and tumours [14]. Loss of olfactory function can be also related to neurodegenerative disease [15], and, in fact, it is an early sign of Parkinson's disease [5,16,17] and Alzheimer's disease [18], and can also be associated with several psychiatric diseases, such as schizophrenia [14].

Other uncommon possible causes, including endocrine conditions, immune disorders, pharmaceutical drugs consumption, cocaine addiction and congenital causes have also been reported [1,9].

Smell dysfunction is a common outcome of exposure to some airborne chemicals. This is not unexpected, as receptors of the olfactory neurons are relatively unprotected. A comprehensive list, including more than 120 substances, including drugs, possibly affecting the olfactory function was published several years ago by Amoore [19], however several new chemicals have been recently added [1].

A relevant limit in the current knowledge on the effect of chemicals on olfactory function is that, up to now, it is mainly based on animal studies, on occasional case reports and on the relatively few epidemiological studies in workers [1,20]. Accordingly, the prevalence of olfactory dysfunction caused by airborne exposure to chemicals is difficult to estimate; values ranging 0.5 up 5% of all olfactory disorders have been proposed [21–23], but these data may be an underestimation. In effect, one theory for age-related loss of olfaction invokes cumulative damage to the epithelium from the lifetime toxic exposures [23]. Furthermore, in a large proportion of olfactory disorders no specific cause is identified. Approximately 10–25% of all smell impairments in the general population are currently classified as 'idiopathic' [6,9,21]; some of these idiopathic olfactory losses are likely to be related to unnoticed chemical exposure.

Accordingly, more attention is needed to airborne chemicals as a cause of olfactory dysfunction [1,20].

As there is no particular test for environmental toxins as a source of olfactory loss, the causative agent is commonly based on a detailed history: a significant exposure history in an absence of other common causes of olfactory loss strengthens an argument for environmental toxins as the etiology of the smell loss.

We describe here a case of anosmia following an acute exposure to a pyrethrin-based insecticide.

CASE PRESENTATION AND DISCUSSION

In May 2008, in a large Hospital in North Italy a wall and a part of the examining room used by a 50-year-old male physician was infested by parasites coming from the outside through the windows. To disinfest the parasites, an exterminating company sprayed the room with an insecticide composed of a mixture of pyrethrin, 2-butoxiethanol and 2-etil 6-propilpiperonil ether dissolved in water. The quantity of the insecticide sprayed is unknown, as are its airborne concentrations. After the treatment, the door and the 3 windows of the room were left shut, as requested by the exterminating company.

The subject, as indicated, returned to work in the room 24 hours after the treatment, but no forced exchange of air was provided prior to the work. For practical reasons, only one of the windows could be left open; it was a 'vasistas' type window, i.e. a small secondary window opening in the window. Thus the flow of indoor air was limited.

Upon entering the room, the subject immediately perceived an intense disagreeable odour, qualitatively

described as 'sweetish'. Within a few minutes, subjective nasal irritation, but no nasal discharge, appeared. In the meantime the subject also noted a progressive reduction in odour perception. Despite the symptoms, the subject worked for about 6 hours in the room. According to the medical history, the subject had never smoked, and had no upper respiratory tract infections, allergies or known nasal sinus diseases ongoing, or in the previous weeks. The presence of potential allergens or irritants in the examining room can be ruled out as medical visit to outpatients, but not medical treatments, were performed. Obviously, smoking was strictly forbidden in the whole area.

Some of the patients examined by the physician during the day, in the course of the visit spontaneously referred the perception of an intense odour, but none complained of adverse effects, possibly due to the very limited time they spent in the room.

The subjective intense nasal irritation experienced by the physician persisted also at home, after work and remained substantially unmodified next morning, when the subject went to work.

Over the next few days, the physician carried on his duties in the same examining room for approximately 6 hours/day. The subjective nasal irritation was progressively reduced, but phantosmia persisted, with progressive appearance of *torqosmia* (described as a subjective perception of an intense, unpleasant smell of burnt). At the same time, the perception of odour progressively decreased, and, within a few days, complete anosmia appeared. Concomitantly, taste was also largely compromised.

At the anamnesis, no upper respiratory infections developed, or head trauma occurred at the time of inhalational exposure to the insecticide, or in the weeks before.

Over the next few days the subject considered the symptoms as nonspecific, transitory effect of irritation. Accordingly, no medical advice was requested. Approximately one month after the exposure the persistence of anosmia convinced the physician to contact a colleague otolaryngologist and seek medical assistance. According to medical history, findings of the visit, including rhinoscopy, did not reveal overt significant clinical picture; accordingly symptom was regarded as the consequence of a non-specific irritation related to inhalation of the insecticide; due to the informal circumstances no written medical report including a description of the conditions of the mucosa was prepared. The patient was prescribed *per os* corticosteroids, nasal spray corticosteroids and nasal washing cycles.

Despite the treatment, anosmia and hypogeusia persisted for several months. The corticosteroids therapy was repeated, but without significant improvement. In Autumn 2010, 20 months after the exposure, the subject once again contacted the otorhinolaryngologist. The latter explained to the patient that he suspected a permanent nervous damage and advised further medical examinations.

In October 2010, a neuropsychological evaluation was performed: no neurodegenerative diseases (as amyotrophic lateral sclerosis, Alzheimer's or Parkinson's diseases) or psychiatric diseases were identified. During the visit, a clinical odour identification test, based on recognition of solutions of 15 substances of common use (lavender, sage, rosemary, mint, mandarin, rose, aniseed, coconut, coffee, ammonia, strawberry, almond, banana and vanilla) was performed, revealing anosmia (0/15 substances identified); the test was not aimed at an evaluation of thresholds, so suprathreshold concentrations of the odorants were tested. No other significant signs or symptoms were observed during neuropsychological evaluation. Based on these finding, the diagnosis was "anosmia probably related to a nervous receptorial damage".

In November 2010, a rhinofibroscopia failed to identify anatomical alterations which could explain anosmia. The morphology of nasal sinus was normal, and significant inflammatory aspects were absent.

In December 2010, a head magnetic resonance imaging (MRI) showed normality of the dimension

and morphology of the ventricular system, regular subaracnoidal spaces over and undertentorial, and normal signal from cerebral parenchyma; a mild hypertrophy of inferior turbinates was observed.

In January 2011, a revised diagnosis was issued. As no known common causes of anosmia were noted at the anamnesis and physical examination, and the results of neuropsychological and ear, nose and throat (ENT) specialist visits and MRI did not show specific pathological conditions inducing anosmia, the final diagnosis was "anosmia probably related to a nervous receptorial damage".

The significant acute exposure and the evolution of the symptoms, in an absence of other common causes of olfactory loss, support the role of insecticide inhalation in the etiology. The mild hypertrophy of inferior turbinates observed at MRI may represent an unspecific consequence of an inflammatory response to the insecticide exposure.

Currently (September 2011), the symptoms are unchanged: due to their long persistence (more than two years), and based on data from the literature on prognosis of patients with olfactory disturbances [24], anosmia in the subject is likely to remain permanent. No symptoms or signs of any other disease are currently present.

In the case presented here, we describe a subject developing permanent anosmia, preceded by nasal irritation and short lasting phantosmia and torqosmia, after working several hours in a room treated with an insecticide sprayed to control infestation of parasites.

The results of medical examinations, including ENT specialist repeated visits, neuropsychological evaluation and head MRI, failed to illuminate the presence of any of the principal known causes of anosmia, including head trauma, upper respiratory infections, tumours, neurodegenerative (e.g. Parkinson's or Alzheimer's disease) or psychiatric diseases, endocrine conditions, immune disorders, and use of pharmaceutical drugs inducing olfactory loss.

Consistent with the course of the patient's clinical presentation, the time sequence of symptoms and the clinical course, suggest a role of insecticide inhalation as the principal cause of his olfactory dysfunction.

The main active components of the insecticide were pyrethrins. In the formulation, 2-etil 6-propilpiperonil ether and 2-butoxiethanol were also present, but these compounds can be considered less relevant from the toxicological point of view, even if butoxiethanol is moderately irritant following inhalational exposure [25].

Pyrethrins, the active insecticidal compounds of *pyrethrum* derived from the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum*, and their synthetic analogues and derivatives, the pyrethroids, are commonly used due to their rapid paralyzing activity in insects, but low environmental persistence and low general toxicity to mammals. In humans they are considered to be one of the least poisonous insecticides [26]. A few cases of systemic poisoning due to pyrethrins and pyrethroids have been reported, almost all related to their effect on the nervous system [27]. The main mechanisms of toxicity of pyrethrin and pyrethroids in mammals are well documented, affecting sodium channels and cellular depolarization [28,29]. The effect on sodium channel is related to the loss of olfaction in insects [30]; a critical role for sodium channels in olfactory function has also been recently documented in humans [31].

In reported cases of inhalational exposure in humans, respiratory irritation is the most common effect, but hypersensitivity pneumonitis have also been described [26]. The signs of respiratory irritation, such as shortness of breath, cough, and congestion, were reported among office workers, commencing upon entry into a building that had been 2 days previously treated for termites with a cypermethrin based insecticide [32].

A problem in our study is that the environmental concentration of pyrethrins (and of 2-butoxiethanol and 2-etil 6-propilpiperonil ether) in the subject's inhaled air is unknown, nor it is possible to reliably estimate it. Concentrations in the $\mu g/m^3$ range can be expected after treatment analogous to the one carried out in the case described herein [33]

but higher concentrations, related e.g. to a wrong or inadequate spraying procedure are possible, and the strong nasal irritation referred by the subject is coherent with this hypothesis. It is also difficult to evaluate the real duration of the inhalation exposure; in any case a significant 6-hour exposure during the first day is likely, especially considering the irritant symptoms in the patient, as well as complaints by other patients about the presence of odour. Exposure to significant concentrations over the next few days is less likely, but the persistence of undegraded active compounds of the insecticide on the walls, furniture, door handles and other objects, may have contributed to its persistence in the atmosphere of the room. Nevertheless, the possible risk cannot be reliably evaluated.

To our knowledge, at least one case of permanent anosmia following inhalation of a spray insecticide containing pyrethrum has been previously reported. Analogous to the case reported herein, the symptoms appeared immediately after the first use of the insecticide. An allergic rhinitis was diagnosed based on positive skin test, but the conclusion of the Author was that "It would seem probable that the pyrethrum has damaged the olfactory nerve endings in the nasal mucosa" [34]. In the case described here, the skin test was not available, but symptoms do not suggest an allergic rhinitis.

A large collection of literature suggest that the olfactory neuroepithelium is susceptible to environmental exposures to several chemicals [20], and acute and chronic exposures can induce both temporary as well as permanent olfactory loss [19]. Changes in the olfactory mucosa were described in many experimental studies in animals, including degeneration and necrosis of olfactory neurons and other neurotoxic effects [35].

The capacity for cellular reconstitution after lesion of the olfactory system is remarkable, but recovery can fail in severely injured areas, which subsequently reconstitute as aneuronal respiratory epithelium [36]. Furthermore, a strong genotoxic effect of pyrethrins on the epithelial cells of human nasal mucosa has been observed [37]. These studies lend support to the hypothesis of the insecticide exposure as the primary cause for the permanent anosmia observed.

As no particular test is available to confirm the role of environmental toxins as a source of olfactory loss, the diagnosis is mainly based on an accurate history showing a significant exposure, a coherent time course and the lack of other common causes: all these criteria have been met in this case report. Accordingly, we conclude that the anosmia observed in the physician is very likely related to the exposure to inhalation of relatively high concentrations of pyrethrins, even if the role of 2-butoxiethanol, 2-etil 6-propilpiperonil ether, or a synergistic effect of co-exposure cannot be totally discarded.

CONCLUSIONS

The case discussed herein shows the possibility that an acute inhalational exposure to a pyrethrin-based insecticide can induce permanent anosmia. The environmental concentration of the insecticide is unknown, but relatively high levels are suggested by exposure modality (spraying for parasites disinfestations, no forced exchange of air before re-entering the room and limited exchange of indoor air), and by the irritant effect reported by the subject.

This case report is of significance, as pyrethrins and pyrethroids are ubiquitously applied in many commercial products used to control insects, including household insecticides, pet sprays and shampoos, potentially involving an exposure in both, workers and general population. Our case report emphasizes the need for focused attention on lowering pyrethrins' concentrations in the air to safe levels as well as the importance of adequate exchange of air, prior to re-entering the rooms sprayed with the insecticide, and for considering the appearance of any subjective irritant symptoms after re-entrance as a relevant warning sign.

ACKNOWLEDGEMENTS

We would like to thank Dr. Michael Aschner for his invaluable comments and revision of the manuscript, and the Patient, that consented the presentation of the case.

REFERENCES

1. Doty RL. *Olfactory dysfunction and its measurement in the clinic and workplace.* Int Arch Occup Environ Health 2006;79:268–82.
2. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. *Hazardous Events Associated With Impaired Olfactory Function*. Arch Otolaryngol Head Neck Surg 2004;130:317–9.
3. Frasnelli J, Kummel T. *Olfactory dysfunction and daily life.* Eur Arch Otorhinolaryngol 2005;262:231–5.
4. Temmel AFP, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. *Characteristics of Olfactory Disorders in Relation to Major Causes of Olfactory Loss.* Arch Otolaryngol Head Neck Surg 2002;128:635–41.
5. Haehner A, Hummel T, Reichmann H. *Olfactory Loss in Parkinson's disease* [cited 2011 Nov 25]. Parkinsons Dis 2011;2011:450939. Epub 21 Apr 2011. Available from URL: http://www.hindawi.com/journals/pd/2011/450939.
6. Bramerson A, Johansson L, Ek L, Nordin S, Bende M. *Prevalence of Olfactory Dysfunction The Skovde Population-Based Stud*y. Laryngoscope 2004;114:733–7.
7. Hoffman HJ, Ishii EK, MacTurk RH. *Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS*). Ann NY Acad Sci 1998;855:716–22.
8. Landis BN, Konnerth CG, Hummel T. *A study on the frequency of olfactory dysfunction.* Laryngoscope 2004;114:1764–9.
9. Schiffman SS. *Taste and smell losses in normal aging and disease.* JAMA 1997;278:1357–62.
10. Cullen MM, Leopold DA. *Disorders of smell and taste*. Med Clin North Am 1999;83:57–74.
11. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. *Prevalence of olfactory impairment in older adults.* JAMA 2002;288:2307–12.
12. Ottaviano G, Marioni G, Marchese Ragona R, Trevisan CP, de Filippis C, Staffieri A. *Anosmia associated with hearing loss and benign positional vertigo after head trauma.* Acta Otorhinolaryngol Ital 2009;29:270–3.
13. Wang JH, Kwon HJ, Jang YJ. *Detection of Parainfluenza Virus 3 in Turbinate Epithelial Cells of Postviral Olfactory Dysfunction Patients.* Laryngoscope 2007;117:1445–9.
14. Doty RL. *Studies of Human Olfaction from the University of Pennsylvania Smell and Taste Center***.** Chem Senses 1997;22:565-86.
15. Hawkes C. *Olfaction in Neurodegenerative Disorder*. Mov Disord 2003;18:364–72.
16. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters EC, Berendse HW. *Idiopathic Hyposmia As a Preclinical Sign of Parkinson's Disease.* Ann Neurol 2004;56:173–81.
17. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. *Olfactory Loss May Be a First Sign of Idiopathic Parkinson's Disease.* Mov Disord 2007;22:839–42.
18. Bacon AW, Bondi MW, Salmon DP, Murphy C. *Very early changes in olfactory functioning due to Alzheimer disease and the role of apolipoprotein E in olfaction.* Ann N Y Acad Sci 1998;855:723–31.
19. Amoore JE. *Effects of chemical exposure on olfaction in humans.* In: Barrow CS, editor. *Toxicology of the nasal passages.* Washington, DC, USA: Hemisphere Publishing; 1986. p. 155–90.
20. Gobba F. *Olfactory toxicity: long-term effects of occupational exposures.* Int Arch Occup Environ Health 2006;9:322–31.
21. Mott AE, Leopold DA. *Disorders in taste and smell.* Med Clin North Am 1991;75:1321–53.
22. Heiser C, Grupp K, Hörmann K, Stuck BA. *Loss of olfactory function after exposure to barbituric acid*. Auris Nasus Larynx 2010;37:103–5.
23. Upadhyay UD, Holbrook EH. *Olfactory loss as a result of toxic exposure.* Otolaryngol Clin N Am 2004;37:1185–207.

24. London B, Nabet BA, Fisher AR, White B, Sammel MD, Doty RL. *Predictors of Prognosis in Patients with Olfactory Disturbance.* Ann Neurol 2008;63:159–66.
25. World Health Organization. *Concise International Chemical Assessment Document no.10. 2-Butoxyethanol* [cited 2012 Jan 12]. Geneva: World Health Organization; 1998. Available from URL: http://www.who.int/ipcs/publications/cicad/cicad_10_revised.pdf.
26. U.S. Department Of Health And Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological profile for pyrethrins and pyrethroids* [cited 2012 Jan 12]. Atlanta, GA, USA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry; 2003. Available from URL: http://www.atsdr.cdc.gov/ToxProfiles/tp155.pdf.
27. Ray D, Fry JR. *A reassessment of the neurotoxicity of pyrethroid insecticides.* Pharmacol Ther 2006;111:174–93.
28. Soderlund DM. *Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent avances* [cited 2012 Jan 12]. Arch Toxicol 2012;86(2):165–81. Available from URL: http://www.springerlink.com/content/kx4322m77815h184/fulltext.pdf.
29. Du Y, Khambay B, Dong K. *An important role of a pyrethroid-sensing residue. F1519 in the action of the N-alkylamide insecticide BTG 502 on the cockroach sodium cannel.* Insect Biochem Mol Biol 2011;41:446–50.
30. Kadala A, Charreton M, Jakob I, Le Conte Y, Collet C. *A use-dependent sodium current modification induced by type I pyrethroid insecticides in honeybee antennal olfactory receptor neurons.* NeuroToxicology 2011;32:320–30.
31. Weiss J, Pyrski M, Jacobi E, Bufe B, Willnecker V, Schicket B, et al. *Loss-of-function mutations in sodium channel Nav1.7 cause anosmia.* Nature 2011;472:186–90.
32. Lessenger JE. *Five office workers inadvertently exposed to cypermethrin*. J Toxicol Environ Health 1992;35:261–7.
33. Siebers J, Mattusch P. *Determination of airborne residues in greenhouses after application of pesticides.* Chemosphere 1996;33:1597–607.
34. Brain DJ. *Toxic insecticides.* Br Med J 1965;1(5432):450.
35. Duncan HJ, Smith DV. *Clinical disorders of olfaction*. In: Doty RL, editor. *Handbook of olfaction and gustation.* New York: Marcel Dekker; 1995. p. 345–65.
36. Jang W, Youngentob SL, Schwobje JE. *Globose Basal Cells Are Required for Reconstitution of Olfactory Epithelium after Methyl Bromide Lesion.* J Comp Neurol 2003;460:123–40.
37. Tisch M, Faulde MK, Maier H. *Genotoxic Effects of Pentachlorophenol, Lindane, Transfluthrin, Cyfluthrin, and Natural Pyrethrum on Human Mucosal Cells of the Inferior and Middle Nasal Conchae*. Am J Rhinol 2005;19:141–51.