

Occupational Asthma Caused by Chromium and Nickel

María Jesus Cruz,^a Roser Costa,^a Eduard Marquilles,^b Ferran Morell,^a and Xavier Muñoz^c

^aServei de Pneumologia, Hospital Vall d'Hebron, Barcelona, Spain.

^bServei de Pneumologia, Xarxa Hospitalaria, Fundació Althaia, Manresa, Barcelona, Spain.

^cServicio de Neumología, Hospital Vall d'Hebron, Departamento de Biología Celular, Fisiología e Inmunología. Facultad de Medicina, Universidad Autónoma de Barcelona, Barcelona, Spain.

We report the case of a 40-year-old woman who developed occupational asthma following exposure to chromium and nickel in the nickel plating section of a metalworks company. Skin prick tests for specific antibodies proved positive for nickel chloride at a concentration of 1 mg/mL and negative for potassium dichromate. The specific bronchial provocation test confirmed the diagnosis of occupational asthma due to exposure to chromium and nickel. The patient presented a late positive reaction to nickel chloride (0.1 mg/mL) and an immediate positive reaction to a 10 mg/mL solution of potassium dichromate. These results indicate a dual response to nickel and chromium in this patient.

Key words: *Chromium. Nickel. Occupational asthma.*

Asma ocupacional inducida por cromo y níquel

Se describe el caso de una paciente de 40 años que desarrolló asma ocupacional tras la exposición a cromo y a níquel mientras realizaba recubrimientos de níquel en una empresa metalúrgica en la sección de niquelado. Las pruebas cutáneas específicas resultaron positivas a cloruro de níquel a una concentración de 1 mg/ml y negativas a dicromato potásico. La prueba de provocación bronquial específica confirmó el diagnóstico de asma ocupacional debida a la exposición a cromo y a níquel, presentando la paciente una respuesta positiva tardía a una concentración de 0,1 mg/ml de cloruro de níquel, y una respuesta positiva precoz con una solución de 10 mg/ml de dicromato potásico. Estos resultados indican una doble sensibilización a níquel y cromo en esta paciente.

Palabras clave: *Cromo. Níquel. Asma ocupacional.*

Introduction

Occupational asthma (OA) is a disease characterized by variable restrictions in airflow and/or by bronchial hyperresponsiveness to the conditions of a specific working environment.¹ The trigger mechanism may be immunological or nonimmunological. Immunological OA is characterized by a latency period prior to the initiation of symptoms; it is not known whether this kind is mediated by a mechanism that depends on immunoglobulin (Ig) E antibodies or by other non-IgE-dependent mechanisms, some of which are as yet unknown.² Nonimmunological asthma has traditionally been associated with reactive airway dysfunction syndrome, which is caused by an irritation that develops in response to exposure to high concentrations of irritant gases, fumes or vapors.³ This form of OA is characterized by the appearance of asthma symptoms in the hours immediately following inhalation.¹

Correspondence: Dr. X. Muñoz.
Servicio de Neumología. Hospital General Vall d'Hebron.
Pg. Vall d'Hebron, 119. 08035 Barcelona. España.
E-mail: xmunoz@vhebron.net

Manuscript received August 24, 2005. Accepted for publication September 6, 2005.

Exposure to chromium and nickel during industrial electroplating processes is a recognized although poorly characterized cause of OA.^{4,5} Electroplating, which consists of the application of a metallic coating using metal salts, is a process that releases fumes. In the case of chromium these fumes generate a large quantity of chromic acid aerosols; in the case of nickel, fumes are produced in smaller amounts.⁴ Even though the working population exposed to chromium and nickel is significant and dermatitis caused by these agents is a very common occurrence,^{6,7} the prevalence of OA caused by these metals is, in fact, low.^{4,8-25} Even lower is the prevalence of OA caused by exposure to both chromium and nickel.^{4,12,16}

This case report describes a patient whose diagnosis was confirmed by a specific bronchial provocation test and whose symptoms would indicate a case of OA caused by nickel and chromium. We also review the subject, in view of both the few cases that have been reported and of the lack of knowledge of the disease.

Clinical Observations

We report the case of a 40-year-old woman with a smoking history of 20 packet-years, with no other

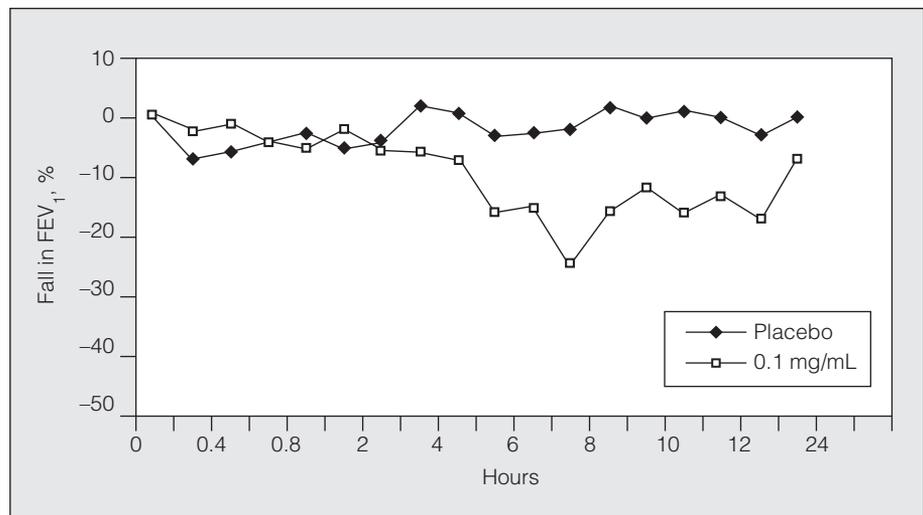


Figure 1. Specific bronchial provocation test for nickel. A late asthmatic reaction can be observed, with a maximum fall of 25% in forced expiratory volume in 1 second (FEV₁) 8 hours after exposure to 0.1 mg/mL of nickel chloride.

history of alcohol or drug abuse, and with no relevant medical history. She had been working in a metalworks company for 3 years, stationed in the nickelplating area, which was located next to, but not physically separated from, the chromium area. For about a year she had had symptoms of predominantly nocturnal wheezing, coughing, and dyspnea, which improved at the weekends and during holidays. At one point she was admitted to hospital for a bronchospasm episode; when she returned to work the symptoms reappeared and so she was once again granted sick leave. From this point on she experienced no new episodes.

A physical examination and blood tests were normal, and total serum IgE titers were 59 U/mL. Chest radiographs were normal, and skin tests with common pneumoallergens proved negative. Lung function was within normal limits, with a forced vital capacity of 4.17 L (114%), forced expiratory volume in 1 second (FEV₁) of 3.31 L (115%), FEV₁% of 79%, and a negative bronchodilator test. A methacholine challenge

test proved negative, with a provocative concentration causing a 20% fall in baseline FEV₁ of over 16 mg/mL. It was not possible to record peak expiratory flow in the workplace as the patient was on sick leave.

Following the recommendations of Bright et al.,⁴ specific skin tests were conducted with saline solutions of nickel chloride and potassium dichromate at concentrations of 1 mg/mL and 10 mg/mL, respectively; results were positive for nickel chloride and negative for potassium dichromate. A suspicion of OA prompted bronchial provocation tests for nickel and chromium, again conducted in accordance with Bright et al.⁴ A solution of 0.1 mg/mL of nickel chloride was nebulized using a de Vilbiss 646 nebulizer (de Vilbiss Co, Somerset, Pennsylvania, USA) with a compressed airflow of 8 L/min. FEV₁ data were recorded every 10 minutes in the hour immediately following the tests and hourly for the next 11 hours. The patient presented with a late asthmatic response to this nickel chloride concentration in the form of coughing and dyspnea, bronchospasm signs on

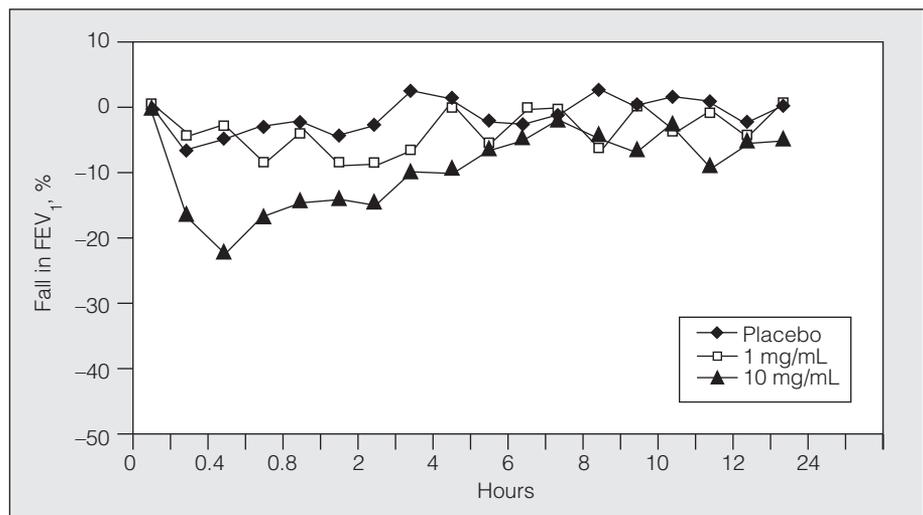


Figure 2. Specific bronchial provocation test for chromium. An immediate asthmatic reaction can be observed, with a maximum fall of 22% in forced expiratory volume in 1 second (FEV₁) 20 minutes after exposure to 10 mg/mL of potassium dichromate.

examination, and a maximum fall of 25% in FEV₁ after 8 hours (Figure 1). Induced sputum samples were obtained prior to conducting the nickel provocation test and in the 24 hours immediately following a positive finding. The samples showed increases of 9% and 2% in neutrophils and eosinophils, respectively.

Three weeks later the bronchial provocation test was performed for chromium using the same method. The protocol consisted of nebulizing 0.1 mg/mL, 1 mg/mL, and 10 mg/mL of potassium dichromate solutions on successive days. The patient developed an early asthmatic response to the 10 mg/mL solution, with the same symptoms as for nickel, and with a maximum fall of 22% in FEV₁ after 20 minutes; after that she subsequently gradually recovered (Figure 2). Given the possibility that this reaction was related to an irritant effect, the same specific provocation was conducted on a healthy volunteer exposed to the same inhaled concentration of metals as the patient, with negative results.

The patient was diagnosed with OA caused by exposure to nickel and chromium, and was advised to avoid these metals. Since then she has remained asymptomatic, and has required neither treatment in an

emergency unit nor admission to hospital. Her lung function, moreover, is within normal limits.

Discussion

OA that develops as the result of the inhalation of metals is not widely recognized. Correct diagnosis requires a confirmation that the patient indeed has asthma, as exposure to metals may trigger other illnesses, such as pneumonitis or chemical tracheobronchitis, chronic obstructive pulmonary disease, alveolitis or metal fume fever. It is also important to rule out other possible exposures, given that there are many other agents in metal-based industrial processes that may cause OA, such as isocyanates, sulfur oxide, chloramine, etc.⁵

Recently published data for France, Canada, the United Kingdom, and Spain indicate that OA caused by exposure to metals may represent between 0.8% and 6.3% of all diagnosed cases of OA.²⁶⁻²⁹ The metals most likely to contribute to the development of OA are platinum, aluminium, chromium, palladium, and nickel, although vanadium, cobalt, zinc, silver, and cadmium also trigger this disease process.⁵ Despite the fact that

TABLE 1
Specific Diagnostic Tests for Nickel (Literature Review)*

Authors, y	N	Skin Tests		Specific IgE Test	SBPT
		Prick Test	Patch Test		
Sunderman & Sunderman, ⁸ 1961	1	ND	+	ND	ND
McConnell et al, ⁹ 1973	1	+	+	ND; immediate: -	+
Malo et al, ¹⁰ 1982	1	+	ND	+	+
Block & Yeung, ¹¹ 1982	1	+	-†	ND; immediate: -	+
Novey et al, ¹² 1983	1	-	ND	+	+
Malo et al, ¹³ 1985	1	-	ND	-	+
Davies, ¹⁴ 1986	3	ND	ND	ND	ND
Estlander et al, ¹⁵ 1993	1	+	-	+	+
Bright et al, ⁴ 1997	2	1 (+), 1 (-)	ND	ND	2 +
Sastre et al, ¹⁶ 2001	1	+	ND	+	+
Hauteclocque et al, ¹⁷ 2002	1	ND	+	ND	+

*Ig indicates immunoglobulin; ND, not done; SBPT, specific bronchial provocation test.
†Patch test performed using dust collected at workplace. ‡SBPT performed for a mix of cobalt and nickel.

TABLE 2
Specific Diagnostic Tests for Chromium (Literature Review)*

Authors, y	N	Skin Tests		Specific IgE Test	SBPT
		Prick Test	Patch Test		
Novey et al, ¹² 1983	1	-	ND	+	+
Moller et al, ¹⁸ 1986	1	-	-	ND	+
Olaguibel & Basomba, ¹⁹ 1989	5	-	+	ND	1 + early, 3 + dual
Park et al, ²⁰ 1993	4	2 (+), 2 (-)†	2 (-), 2 (-)†	ND	1 + early, 3 + dual
Nemery et al, ²¹ 1995	1	+	ND	ND	+
Shirakawa & Morimoto, ²² 1996	1	ND	+	+	+
Bright et al, ⁴ 1997	7	2 (+)	ND	ND	2 + early, 4 + dual, 1+ late
de Raeve et al, ²³ 1998	1	ND	ND	ND	+
Leroyer et al, ²⁴ 1998	1	ND	-	ND	+
Sastre et al, ¹⁶ 2001	1	+	ND	+	+
Lockman, ²⁵ 2002	1	+	ND	ND	+

*Ig indicates immunoglobulin; ND, not done; SBPT, specific bronchial provocation test.
†Positive results in one test are negative in the other.

chromium and nickel are used in a wide range of industrial processes, the proportion of OA cases attributable to these metals is unknown. As far as we are aware, there are 11 articles each in the literature describing cases of sensitization to nickel^{4,8-17} and to chromium.^{4,12,16,18-25} Tables 1 and 2 summarize the main features of these studies in terms of skin testing, specific IgE testing and specific bronchial provocation testing.

The particular symptoms and work circumstances of our patient indicated a possible diagnosis of OA caused by nickel that was confirmed by the positive results of additional tests performed, which included skin tests and a specific bronchial challenge test. In view of the possibility for transferring the patient to another work station and given the fact that chromium fumes were present in all parts of the plant, a bronchial provocation test for chromium was also performed. The positive result confirmed that our patient was sensitized to chromium as well as to nickel. Although double sensitization has been described for other agents such as enzymes and animal proteins,^{30,31} and for 3 patients exposed to nickel and chromium,^{4,12} the possibility of cross reactivity between these metals has been postulated by Sastre et al.¹⁶ Nonetheless, our patient's particular response to the specific provocation tests would indicate the development of a double sensitization following exposure to both metals. Moreover, the fact that bronchial provocation tests were positive for nickel and chromium at concentrations of 0.1 mg/mL and 10 mg/mL, respectively, is an indication that our patient's principal sensitization is to nickel—as was suggested by Bright et al⁴ in relation to one of their patients.

The mechanism through which patients become sensitized to these metals is disputed. Some authors have postulated the existence of an irritant mechanism due to the high oxidation capacity of these metals, given that these play important roles in catalyzing biological oxidation reactions.³² Other authors, however, have suggested that, acting as haptens, these metals may trigger the development of an IgE-dependent immunological mechanism.³³ The literature includes 14 reported cases^{4,8-17} of nickel-induced OA (Table 1); specific skin prick tests were performed for 9 of these patients and positive results were obtained for 6 patients (67%).^{4,9-13,15,16} Moreover, serum specific IgE values were positive for 4 out of 5 of these patients.^{10,12,13,15,16} Of the 10 patients who underwent the inhalation challenge test, 2 presented an early reaction,^{10,11} 6 a late reaction,^{9,13,15,17} and 2 a dual reaction.^{12,16} Observed in 2 out of 3 of the patients, moreover, was an increase in bronchial hyperresponsiveness to methacholine or histamine following the specific test.^{10,11,13} These reports would seem to support the argument that, in most patients, OA develops through an IgE-dependent immunological mechanism. In our patient, the positive skin prick test and the 2% increase in eosinophils in induced sputum would be consistent with this hypothesis. Note that an increase in induced sputum eosinophil counts was also reported by Sastre et al.¹⁶

Although chromium as a metal is not allergenic, its salts are and consequently have been widely researched

as a cause of contact dermatitis.^{6,7} As for OA caused by chromium, 24 cases have been reported to date^{4,12,16,18-25}; in 7 out of 12 of these patients (58%) the skin prick test was positive^{4,12,16,18-21,25}; moreover, high levels of specific IgE were found in the 3 patients on which this test was performed.^{12,16,22} A specific bronchial provocation test was performed in all 24 patients in question, with an early response observed in 8 patients,^{4,12,19-22,24} a dual response in 10 patients,^{4,16,19,20} and a late response in 5 patients.^{4,18,19,23} (For 1 patient the type of reaction was not recorded.²⁵) As with nickel, it seems that an IgE-dependent immunological mechanism may explain most of the cases described. In our case, skin tests with chromium were negative and an early reaction was observed to the provocation test. A control subject had a negative challenge test, ruling out the possibility of an irritant mechanism. Note that our patient received a higher dose of chromium than of nickel—a similar dose to that used by Bright et al⁴ and a lower dose than that used by Sastre et al.¹⁶

In conclusion, our studies of the patient described indicate a probable diagnosis of double sensitization to nickel and chromium, although we can not entirely rule out the possibility of cross reactivity occurring between these 2 metals. The results obtained for the skin, specific bronchial provocation, and induced sputum tests support the hypothesis put forward by other authors of a possible IgE-dependent immunological mechanism being the trigger for this kind of OA. However, we cannot rule out the possibility of other pathogenic mechanisms being responsible for OA.

REFERENCES

- Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. Definition and classification of asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. *Asthma in the workplace*. New York: Marcel Dekker Inc.; 1993. p. 1-4.
- Chan-Yeung M, Malo JL. Occupational asthma. *N Engl J Med*. 1995;333:107-12.
- Alberts WM, do Pico GA. Reactive airways dysfunction syndrome. *Chest*. 1996;109:1618-26.
- Bright P, Burge PS, O'Hickey SP, Gannon PF, Robertson AS, Boran A. Occupational asthma due to chrome and nickel electroplating. *Thorax*. 1997;52:28-32.
- Bernstein IL, Nemery B, Brooks S. Metals. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. *Asthma in the workplace*. New York: Marcel Dekker Inc.; 1993. p. 1-4.
- Hansen MB, Rydin S, Menne T, Dues Johansen J. Quantitative aspects of contact allergy to chromium and exposure to chrome-tanned leather. *Contact Dermatitis*. 2002;47:127-34.
- Basketter DA, Angelini G, Ingber A, Kern PS, Menne T. Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact Dermatitis*. 2003;49:1-7.
- Sunderman FW, Sunderman FW Jr. Loffler's syndrome associated with nickel sensitivity. *Arch Intern Med*. 1961;107:405-8.
- McConnell LH, Fink JN, Schlueter DP, Schmidt MG Jr. Asthma caused by nickel sensitivity. *Ann Intern Med*. 1973;78:888-90.
- Malo JL, Cartier A, Doepner M, Nieboer E, Evans S, Dolovich J. Occupational asthma caused by nickel sulfate. *J Allergy Clin Immunol*. 1982;69:55-9.
- Block GT, Yeung M. Asthma induced by nickel. *JAMA*. 1982; 247:1600-2.

12. Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. *J Allergy Clin Immunol.* 1983;72:407-12.
13. Malo JL, Cartier A, Gagnon G, Evans S, Dolovich J. Isolated late asthmatic reaction due to nickel sulphate without antibodies to nickel. *Clin Allergy.* 1985;15:95-9.
14. Davies JE. Occupational asthma caused by nickel salts. *J Occup Med.* 1986;36:29-30.
15. Estlander T, Kanerva L, Tupasela O, Heskinen H, Jolanki R. Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. *Clin Exp Allergy.* 1993;23:306-10.
16. Sastre J, Fernández-Nieto M, Marañón F, Fernández-Cladas E, Pelta R, Quirce S. Allergenic cross-reactivity between nickel and chromium salts in electroplating-induced asthma. *J Allergy Clin Immunol.* 2001;108:650-1.
17. Hauteclocque C, Morisset M, Kanny G, Kohler C, Mouget B, Moneret-Vautrin DA. Asthme professionnel par hypersensibilité aux métaux durs. *Rev Mal Respir.* 2002;19:363-5.
18. Moller DR, Brooks SM, Bernstein DI, Cassidy K, Enrione M, Bernstein IL. Delayed anaphylactoid reaction in a worker exposed to chromium. *J Allergy Clin Immunol.* 1986;77:451-6.
19. Olaguibel JM, Basomba A. Occupational asthma induced by chromium salts. *Allergol Immunopathol.* 1989;17:133-6.
20. Park HS, Yu HJ, Jung KS. Occupational asthma caused by chromium. *Clin Exp Allergy.* 1994;24:676-81.
21. Nemery B, de Raeve H, Demeds M. Dermal and respiratory sensitisation to chromate in a floorer. *Eur Respir J.* 1995;8 Suppl 19:222.
22. Shirakawa T, Morimoto K. Brief reversible bronchospasm resulting from bichromate exposure. *Arch Environ Health.* 1996;51: 221-6.
23. de Raeve H, Vandecasteele C, Demeds M, Nemery B. Dermal and respiratory sensitization to chromate in a cement floorer. *Am J Ind Med.* 1998;34:169-76.
24. Leroyer C, Dewitte JD, Bassanets A, Boutoux M, Daniel C, Clavier J. Occupational asthma due to chromium. *Respiration.* 1998;65:403-5.
25. Lockman LE. Case report: allergic contact dermatitis and new-onset asthma. Chromium exposure during leather tanning. *Can Fam Physician.* 2002;48:1907-9.
26. Ameille J, Pauli G, Calastreng-Crinquand A, Vervloët D, Iwatsubo Y, Popin E, et al, and the corresponding members of the ONAP. Reported incidence of occupational asthma in France, 1996-99: the ONAP programme. *Occup Environ Med.* 2003;60: 136-41.
27. Provencher S, Labrèche P, de Guire L. Physician based surveillance system for occupational respiratory diseases: the experience of PROPULSE, Québec, Canada. *Occup Environ Med.* 1997;54:272-6.
28. McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989-97. *Occup Environ Med.* 2000;57:823-9.
29. Kogevinas M, Antó JM, Soriano JB, Tobias A, Burney P, and the Spanish Group of the European Asthma Study. The risk of asthma attributable to occupational exposures. *Am J Respir Crit Care Med.* 1996;154:137-43.
30. Santaolalla M, de Barrio M, de Frutos C, Gandolfo M, Zuberdiá J, Rubio M, et al. Double sensitization to enzymes in a baker. *Allergy.* 2002;57:957.
31. Muñoz X, Gómez-Ollés S, Cruz MJ, Morell F. Occupational asthma related to mouse allergen exposure and rhinoconjunctivitis due to collagenase inhalation in a laboratory technician. *Respiration.* In press 2006.
32. Bernstein IL, Nemery B, Brooks S. Metals. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. *Asthma in the Workplace.* New York: Marcel Dekker Inc.; 1993; p. 501-21.
33. Dolovich J, Evans SL, Nieboer E. Occupational asthma from nickel sensitivity. I. Human serum albumin in the antigenic determinant. *Br J Ind Med.* 1984;41:51-5.