GAVIN PUBLISHERS

OPEN ACCESS

# Annals of Case Reports

Prieto-Moreno A and Carbone J. Ann Case Report 6: 683.

DOI: 10.29011/2574-7754.100683

Case Report

# IgG2 Subclass Deficiency and Allergy Contact Dermatitis to Nickel: A Case Report

**Ana Prieto-Moreno Pfeifer[1*], Javier Carbone[2]**

[1]Allergy Department, Hospital Universitario Infanta Leonor, Madrid, Spain

[2]Immunology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain

[*]**Corresponding author:** Ana Prieto-Moreno Pfeifer, Allergy Department, Hospital Universitario Infanta Leonor, Madrid, Spain

**Citation:** Prieto-Moreno A, Carbone J. (2021) IgG2 Subclass Deficiency and Allergy Contact Dermatitis to Nickel: A Case Report. Ann Case Report 6: 683. DOI: 10.29011/2574-7754.100683

**Received Date:** 26 July, 2021; **Accepted Date:** 31 July, 2021; **Published Date:** 03 August, 2021

## Abstract

**Background:** Nowadays contact allergy is increasing rapidly. Its prevalence in general population is 20%, being women more affected than males. Metals are by far the main cause. The pathogenesis of this disease is still not clear.

**Objective:** The purpose of this case report is to describe a patient with allergy contact dermatitis as a main clinical manifestation of deficiency of IgG2 subclass without infections.

**Methods:** We assessed extended blood controls, including proteins, lymphocyte subsets, immunoglobulins, immunoglobulins subclasses and complement. After the study, other pathologies were ruled out.

**Results:** A 68 year-old woman with no major history of infection is presented with recurrent metal allergy for several years. She was referred to our immunology center after a deficiency of immunoglobulins was detected. She didn´t take any drug which could trigger a deficiency of immunoglobulins. She presented dermatitis after at least 20 minutes of contacting with metals (buckles, buttons and customs) and pressure zones. Atopic dermatitis, urticaria, angioedema and others possible dermatology illneses were discarded. The diagnosis was established with Patch test (TRUE test). Finally, she was diagnosed as allergy contact dermatitis to nickel and fragrances. The total immunoglobulin (Ig)E and serology were normal. A deficiency of IgG (542 mg/dL) was observed. IgG2 levels were 117 mg/dL, rest of them (IgG1, IgG3 and IgG4) presented normal tiers. A specific antibody deficiency to pneumococcal antigens was demonstrated. C4 levels (17.3 mg/dL) were decreased. The cellular analyses identified a minimal underlying CD8 decrease (185 cells/ul).

**Conclusion:** This is the first report of allergy contact dermatitis as a principal manifestation of IgG2 subclass deficiency without infections. More investigations are necessary for relating these entities as immune dysregulations of IgG2 subclass deficiency might be associated in some cases.

**Keywords:** Allergy; Contact; Dermatitis; IgG2 subclass deficiency; Immunodeficiency; Nickel

## Introduction

Contact dermatitis is an inflammatory skin disease characterized by pruritus, erythema, vesicles and scale. It can be acute, subacute or chronic. The majority of them (80%) are irritant contact dermatitis (ICD) and rest of them (20%) are allergic contact dermatitis (ACD) [1]. The pathophysiology of this illness is not definitively defined, so the more we study it, the better we could understand the potential mechanisms implicated. ACD is a common type of delayed hypersensitivity reactions, which are mainly caused by small allergens knowns as haptens (<1000 KDa) [2] that also results in a subsequent inflammatory reaction. Haptens are small chemicals groups which need to couple to a carrier protein to become immunogenic and activate T-cells [3]. A recent study describes that the prevalence of ACD in general population is 20,1%, and 19,5% in Europe. The principal haptens implicated are nickel, cobalt and fragrances mix I. Also, in this study they reported that the prevalence of ACD to nickel yielding a prevalence of 11,4%, being by far higher in women (15,7%) than in men (4,3%) [4].

Nickel ions are potent haptens which are enabled to cause important inflammation. They penetrate the skin and activate epithelial cells which produce cytokines or chemokines that elicit the activation of antigen-presenting cells (APC) and T cells, which are the main responsible for symptoms. During sensitization, the nickel ion penetrates the skin and can bind directly to toll-like-receptors (TLR4) on dendritic cells (DCs) leading to stimulation of the IKK2 nuclear factor-KB cascade [5,6]. The DCs activated upregulate costimulatory molecules and migrate to the local lymph node, where nickel is presented to naïve T cells by major histocompatibility complex (MHC) II molecules. If the DC activation is enough, allergen specific T cells and memory T cells proliferate and migrate to the blood and the skin resulting in sensitization [7]. The clinical expression of allergic to nickel during the elicitation phase is generated by re-entry of a nickel ion, resulting in visible allergic dermatitis [5]. Nickel induced antibody mediated type I hypersensitivity has rarely been reported [8]. It is not necessary to have an extensive contact, hence rapid skin deposition following contact has been shown to occur after seconds to minutes [9,10]. The same pathophysiology has been studied with mix fragrances [11].

It is described that nickel can induce an autoimmunity process [12,13], but there is nothing that relates ACD to nickel with a primary deficit of immunoglobulins. Nevertheless, deficiency of IgG subclasses is associated with atopic disorders [14]. IgG subclass deficiencies are most strongly associated with IgA deficiency [15]. Approximately 15% of IgA deficient patients also have a IgG subclass deficiency such as combined IgA, IgG2 and IgG4 deficiency [16]. At the same time, deficiency of IgA is also related to allergic diseases and asthma [17,18], but there is none case described about both deficiency of IgG subclass and contact dermatitis.

## Material and Methods

### Case presentation

A 68-year-old woman with no medical comorbidities was referred to us in November 2019. She didn't take any drug which could trigger a deficit of immunoglobulins. The only intervention that she had suffered was due to a cholesteatoma. She didn't have more history of interest. She had been studied by allergists' because 40 years ago started after contacting to metals (buttons, jewelry, metallic chairs, pressure area) with a well-demarcated, intensely pruritic, eczematous eruption localized into the area of skin that had been in contact with the allergen. Over time, the lesions associated blistering and weeping. She also experimented the same symptoms after applying a sticking plaster.

After performing a TRUE test (patching test) study, she was diagnosed as ACD to nickel and fragrances. Likewise, the allergists undertake a blood analysis, of which in the blood count a cytopenia was observed. She presented discreet neutropenia and leucopenia. Also, they observed moderate IgG hypogammaglobulinemia (481mg/dL, normal range 650-1610 mg/dL) that was due to IgG2 deficiency (101 mg/dL, normal range 147-629 mg/dL) and mild low levels of IgA (71 mg/dL). Rest of IgG subclasses (IgG1, IgG3, IgG4), IgM and IgE were normal. Triptasa, total proteins and complement field regular tiers. After this visit she started with bilastin 20 mg/24 hours which reduce the number of episodes, afterwards she was referred to our immunology department.

Firstly, she was re-interviewed. She had never had pneumonia. On a very few occasions, had diarrhea. Once, she passed a cold sore and every year she presented recurrence colds but for respiratory problems. She didn't have urinary infections, neither otitis or herpes or fungal infections. The blood analyses were repeated. Blood count was normal, she didn't present cytopenia. The IgG and IgA levels remain decreased (542 mg/dL and 83.2 mg/dL, respectively), by the way IgG2 kept diminished (117 mg/dL). Additionally, we measured antibody function. Before administered vaccines to 23 pneumococcal polysaccharides and tetanus toxoid, antibody levels were 2.5 mg/dL and 0,35 IU/ml. The postimmunization titers at 3 weeks after vaccination were 4.8 mg/dL to S. Pneumoniae and >7 IU/ml to T. Tetanus which demonstrated specific functional deficiency to polysaccharide antigens which is a common association of IgG2 deficiency. CD3+CD8+T cells (cytotoxic T cells) were decreased while CD4/CD8 ratio was increased (195 cells/ul and 5,56 accordingly). After 8 months we repeated these counts of cells, remaining diminished cytotoxic T cells and elevated CD4/CD8 ratio (185 cells/ul and 5,62). CD3+ T cells (T cells), CD3+CD4+ T cells (T helper cells), CD19+ B cells (B cells) and CD3-CD16/CD56+ LGL/NK cells were regular. CD27-/IgD+ B cells (naïve cells), CD27+/IgD+ B cells (IgM memory) and CD27+/IgD- B cells (switched memory) had common tiers. The complement titers were regular. Finally, we recommend both avoiding contact with nickel and fragrances and receiving every year influenza immunization. No additional treatment was assessed.

### Results and Discussion

To the best of our knowledge, this is the first reported case of ACD to nickel as a main manifestation of IgG2 subclass deficiency. Diminished generation of specific antibody titers in response to a polysaccharide vaccine is a functional humoral immunity correlate of this disease [19]. IgG subclass deficiency refers to a significant decrease in the serum concentrations of one or more subclass of IgG [20]. The proportion of each subclass is maintained within a relatively narrow range: IgG l, 60-65%; IgG2, 20-25%; IgG3, 5-10%; IgG4, 3-6%. Hence, a meaningful reduction of one of the major subclasses (IgG1 and IgG2) could cause a decrease of total levels of IgG [16] as we could see in our case. Typically, deficit of IgG2 is related to recurrent sinopulmonary or bronchial infections

because it is predominantly responsible for the antibody response against polysaccharide capsular antigens [21]. Its prevalence in patients with deficit of immunoglobulins is around 17%. However, our patient only presented contact allergy to nickel and a cholesteatoma which was intervened few years ago. There are some studies which related these molecules to allergic diseases. Principally asthma, rhinitis and atopic [22-24]. It has been proved that desialylated IgG are related to allergic disease, fundamentally with asthma [25]. Studies defend that primary immunodeficiencies diseases are related to asthma and rhinitis, without preference of subclass deficit [24,26]. Indeed, hiper IgE syndrome, that is a primary immunodeficiency, present atopic dermatitis or urticaria [27], nevertheless our patient didn't present symptoms compatible with these entities. It is described that the pathophysiology of ACD is mediated principally by T cells [28], but our patient had a deficiency of IgG2 but for infections. So, her ACD might be associated to this deficiency in as much as, there are cases of IgG2 deficiency and atypical forms of presentation [29,30]. Even so, more studies are necessary into this field to assess the potential role of the primary antibody deficiency in the development of this type of allergy.

On the other hand, it is known that allergy to nickel is mediated by both CD4+ and CD8+ T cells. Studies have emphasized that CD8+ T cells were the main effector cells of CHS while CD4+ T cells behave as down-regulatory cells. The difference between CD8+ T cells and CD4+ T cells mediating ACD may relate to the molecular mechanisms by which antigens are processed and presented to the T cells. Antigens external to the cell are phagocytosed and processed for presentation on MHC class II molecules (eg, HLA-DR) to CD4+ T cells. In contrast, internal cytoplasmic antigens are processed by the endogenous pathway for presentation on MHC class I molecules (eg, HLA-A, -B, and -C) to CD8+ T cells. External allergens can also enter the endogenous pathway to be presented to CD8+ T cells [31]. In our patient, we observed that CD3+CD8+T cells were decreased, but sometimes, especially where there is a deficient CD8 T cell pool, CD4+ T cells can be effector cells of ACD, but not for all haptens [32]. This could explain both the diminished titers of CD8 T cell in our patient and the increased of CD4/CD8 ratio which was observed. Also, these were observed in another study which defends that patients with severely allergy to nickel present both an increase in the proportion of naïve CD4+T cells and a decrease of naïve CD8+T cells with corresponding decreases in the effector memory cells re-expressing CD45RA (EMRA) and effector memory cell populations [33].

## Conclusion

In the present case report, we report a patient with ACD to nickel with IgG2 subclass deficiency without typical clinical symptoms of humoral immunodeficiency. There is a possibility that more cases of ACD to nickel with these features have occurred, even though no previous reports have been published. We suggest that measurement of immunoglobulins in patients with severe ACD could be indicated, inasmuch as the relation between these two entities could be much deeper than what we think.

### Ethics Approval and Consent to Participate

The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in the study.

### Human and Animals Rights

This case was regular clinical practice and approved by Ethics committee of our Hospital and confirmed by the patient. All clinical investigations were conducted according to the Declaration of Helsinki principles.

### Conflict of Interest

The authors declare they have no financial relationships with biotechnology and/ or pharmaceutical companies interested in the subject matter or materials discussed in this manuscript.

## References

1. Fonacier L, Noor I. (2018) Contact dermatitis and patch testing for the allergist. Ann Allergy, Asthma Immunol [Internet]. 120: 592-598.
2. Uter W, Werfel T, White IR, Johansen JD. (2018) Contact allergy: A review of current problems from a clinical perspective. Int J Environ Res Public Health. 15: 1108.
3. Gefen T, Vaya J, Khatib S, Rapoport I, Lupo M, et al. (2015) The effect of haptens on protein-carrier immunogenicity. Immunology. 144: 116-126.
4. Alinaghi F, Bennike NH, Egeberg A, Thyssen JP, Johansen JD. (2019) Prevalence of contact allergy in the general population: A systematic review and meta-analysis. Contact Dermatitis. 80: 77-85.
5. Ahlström MG, Thyssen JP, Wennervaldt M, Menné T, Johansen JD. (2019) Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. Contact Dermatitis. 81: 227-241.
6. Saito M, Arakaki R, Yamada A, Tsunematsu T, Kudo Y, et al. (2016) Molecular mechanisms of nickel allergy. Int J Mol Sci. 17: 1-8.
7. Kaplan DH, Igyártó BZ, Gaspari AA. (2012) Early immune events in the induction of allergic contact dermatitis. Nature Reviews Immunology. 12: 114-124.
8. Saluja SS, Davis CL, Chong TA, Powell DL. (2016) Contact Urticaria to Nickel: A Series of 11 Patients Who Were Prick Test Positive and Patch Test Negative to Nickel Sulfate 2.5% and 5.0%. Dermatitis. 27: 282-287.
9. Erfani B, Lidén C, Midander K. (2015) Short and frequent skin contact with nickel. Contact Dermatitis. 73: 222-230.

10. Ahlström MG, Thyssen JP, Menné T, Midander K, Julander A, Lidén C, et al. (2018) Short contact with nickel causes allergic contact dermatitis: an experimental study. Br J Dermatol. 80: 259-260.

11. Periyasamy M, Sekar S, Rai R. (2019) Analysis of hypersensitivity in fragrance series by patch testing. Indian Dermatol Online J. 10: 657-662.

12. Al-Mogairen SM, Meo SA, Al-Arfaj AS, Hamdani M, Husain S, et al. (2010) Nickel-induced allergy and contact dermatitis: Does it induce autoimmunity and cutaneous sclerosis? An experimental study in Brown Norway rats. Rheumatol Int. 30: 1159–1164.

13. Sterzl I, Procházková J, Hrdá P, Bártová J, Matucha P, et al. (1999) Mercury and nickel allergy: Risk factors in fatigue and autoimmunity. In: Neuroendocrinology Letters. 20: 221-228.

14. De Moraes Lui C, Oliveira LC, Diogo CL, Kirschfink M, Grumach AS. (2002) Immunoglobulin G subclass concentrations and infections in children and adolescents with severe asthma. Pediatr Allergy Immunol. 13: 195-202.

15. Yount WJ, Seligmann M, Hong R, Good R, Kunkel HG. (1970) Imbalances of gamma globulin subgroups and gene defects in patients with primary hypogammaglobulinemia. J Clin Invest. 49: 1957-1966.

16. Oxelius VA, Laurell AB, Lindquist B, Golebiowska H, Axelsson U, et al. (1981) IgG Subclasses in Selective IgA Deficiency. N Engl J Med. 304: 1476-1477.

17. Jorgensen GH, Gardulf A, Sigurdsson MI, Sigurdardottir ST, Thorsteinsdottir I, et al. (2013) Clinical symptoms in adults with selective IgA deficiency: A case-control study. J Clin Immunol. 33: 742-747.

18. Janzi M, Kull I, Sjöberg R, Wan J, Melén E, et al. (2009) Selective IgA deficiency in early life: Association to infections and allergic diseases during childhood. Clin Immunol. 133: 78-85.

19. Orange JS, Ballow M, Stiehm ER, Ballas ZK, Chinen J, et al. (2012) Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 130: S1-24.

20. Jefferis R, Kumararatne. (1990) Selective IgG subclass deficiency: quantification and clinical relevance. Clin Exp Immunol. 81: 357-367.

21. Escobar-Pérez X, Dorta-Contreras AJ, Interián-Morales MT, Noris-García E, Ferrá-Valdés M. (2000) IgG2 immunodeficiency: Association to pediatric patients with bacterial meningoencephalitis. Arq Neuropsiquiatr. 58: 141-145.

22. De Jose Gomez MI, Gonzale De Dios J, Hernando De Larramendi C, Jimenez Garcia A, Vidal Lopez ML, et al. (1990) Deficit de IgG2 asociado a neumonías de repetición y asma. An Esp Pediatr. 33: 258-264.

23. Dadkhah M, Aghamohammadi A, Movahedi M, Gharagozlou M. (2015) Atopic manifestations: Dermatitis, allergic rhinitis and asthma in patients with hypogammaglobulinemia. Iran J Pediatr. 25: e2786.

24. Khokar A, Gupta S. (2019) Clinical and Immunological Features of 78 Adult Patients with Primary Selective IgG Subclass Deficiencies. Arch Immunol Ther Exp (Warsz). 67: 325-334.

25. Braza F, Chesne J, Castagnet S, Magnan A, Brouard S. (2014) Regulatory functions of B cells in allergic diseases. 69: 1454-1463.

26. Özcan C, Metin A, Erkoçoğlu M, Kocabaş CN. (2014) Allergic diseases in children with primary immunodeficiencies. Turk J Pediatr. 56: 41-47.

27. Gaudinski MR, Milner JD. (2017) Atopic Dermatitis and Allergic Urticaria: Cutaneous Manifestations of Immunodeficiency. Immunology and Allergy Clinics of North America. 27: 1-10.

28. Esser PR, Martin SF. (2017)Pathomechanisms of Contact Sensitization. Current Allergy and Asthma Reports. 17: 83.

29. Oi R, Takeichi T, Okuno Y, Kojima D, Sugawara K, Kono M, et al. (2018) An infant with generalized pustular psoriasis and geographic tongue had a heterozygous IL36RN mutation and IgG2 deficiency. Journal of Dermatological Science. 90: 216-218.

30. Garg V, Lipka S, Rizvon K, Singh J, Rashid S, Mustacchia P. (2012) Diffuse nodular lymphoid hyperplasia of intestine in selective IgG 2 subclass deficiency, autoimmune thyroiditis, and autoimmune hemolytic anemia: Case report and literature review. J Gastrointest Liver Dis. 21: 431-434.

31. Saint-Mezard P, Bérard F, Dubois B, Kaiserlian D, Nicolas JF. (2004) The role of CD4+ and CD8+ T cells in contact hypersensitivity and allergic contact dermatitis. European Journal of Dermatology. 14: 131-138.

32. Martin S, Lappin MB, Kohler J, Delattre V, Leicht C, et al. (2000) Peptide immunization indicates that CD8+ T cells are the dominant effector cells in trinitrophenyl-specific contact hypersensitivity. J Invest Dermatol. 115: 260-266.

33. Wicks K, Stretton C, Popple A, Beresford L, Williams J, et al. (2019) T lymphocyte phenotype of contact-allergic patients: experience with nickel and p-phenylenediamine. Contact Dermatitis. 81: 43-53.