

Research Article

Can Exist Atopy in Agammaglobulinemia?

Rial Prado MJ^{1*} and Sanchez-Ramon S²

¹Allergy department, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

²Clinical Immunology department, San Carlos Clinical Hospital, Madrid, Spain

Abstract

Background

Recent findings highlight the contribution of the innate immunity to type I hypersensitivity reactions. In order to better determine such contribution in patients with lack of IgE, we aim to study the prevalence and characteristics of allergic manifestations, in the model of agammaglobulinemia. For this purpose, we carefully revised all the medical literature of allergic patients with X-linked agammaglobulinemia (XLA).

Methods

Bibliographic databases sources were used searching the available publications in the last sixty years focused in agammaglobulinemia and allergy.

Results

A total of 752 articles were found with the keywords “agammaglobulinemia” and “allergy”. After applying the inclusion criteria, a total of 20 papers were selected.

Conclusions

Type I hypersensitivity reactions were scarce and limited to XLA patients showing detectable levels of serum IgE. We suggest the necessity of a retrospective observational study based on the supranational registries of XLA to determine the incidence of allergies in this population and try to better understand the immunological mechanisms by which this occurs.

Keywords: Agammaglobulinemia; Atopy; Allergy; Bruton; NKT; Th1; Th2; X-linked Agammaglobulinemia

Background

The contribution of IgE-independent mechanisms mediated mainly by innate lymphoid type 2 cells and NKT cells in allergic processes remains to be elucidated. The absence of IgE, whose closest model in Nature would be X-linked agammaglobulinemia (XLA), may abrogate prototypic IgE-specific responses causing asthma, food allergies, allergic rhinitis or drug allergy. The study of the prevalence and clinical expression of IgE-mediated allergic diseases in this XLA population could confirm the critical role of IgE in their development. In addition, this study would ascertain whether there are other important contributors in the induction of atopic manifestations in the absence of IgE.

XLA is a PID characterized by the severe B-cell deficiency resulting from a differentiation arrest with subsequent agammaglobulinemia[1]. The first description of the disease was

made in 1952 by Bruton[2]. XLA is caused by mutations in the gene for Bruton tyrosine kinase (Btk), essential for B cell differentiation. This genetic defect was discovered in 1993 and since then, several mutations in the Btk gene have been identified [3]. Clinical onset of XLA takes place in early infancy with recurrent bacterial respiratory infections like pneumonia, sinusitis and otitis media, while gastrointestinal infections and in other sites are also common [1,2,4]. Other manifestations, such as arthritis or neutropenia, have been reported in many patients. By contrast, allergic diseases are unusual in this population [4] and very few cases have been described in the literature.

Method

This work was conducted in the form of a classical review with the purpose of evaluating the presence and clinical expression of the allergic diseases in patients with XLA to try to find out the immunological mechanisms that cause allergic symptoms in these patients.

The following steps were followed

Preliminary work

In the first phase, we performed a search in the scientific literature focusing on the object of study. As bibliographic Databases sources we used *Medline* through the portals *PubMed* (<http://www.ncbi.nlm.nih.gov/pubmed/>) and *SciELO* (<http://www.scielo.br/>), searching the available publications in the last sixty years. To conduct our search the following keywords in English and Spanish were used: “agammaglobulinemia and atopy”, “agammaglobulinemia and allergy”, and “agammaglobulinemia and asthma”. Textbooks about the subject were included to complete the searching work [5,6].

Study Selection

We chose case reports, case series and letters to the editor

***Corresponding author:** Rial Prado MJ, Allergy department, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, E-mail: manute-rial@gmail.com

Sub Date: February 3, 2017, **Acc Date:** February 13, 2017, **Pub Date:** February 13, 2017.

Citation: Rial Prado MJ and Sanchez-Ramon S (2017) Can Exist Atopy in Agammaglobulinemia?. BAOJ Aller Immunol 3: 009.

Copyright: © 2017 Rial Prado MJ and Sanchez-Ramon S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

that focused in humans and in experimental animal models. Hypogammaglobulinemia studies were discarded and only papers that associated allergy and agammaglobulinemia were taken into account.

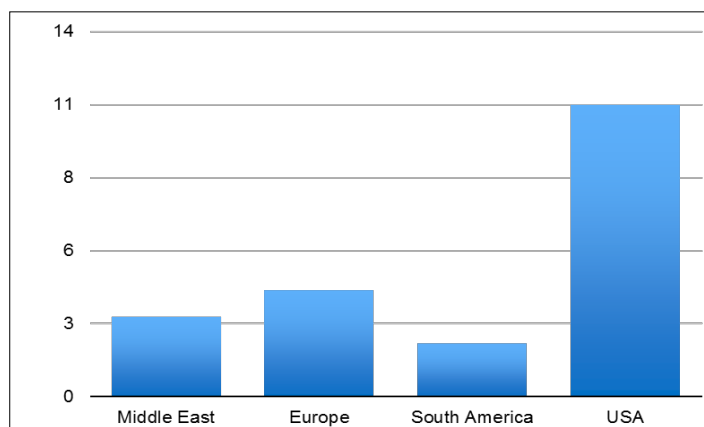
Review

The researchers screened the results of the literature search by the title and abstract. The studies that met the criteria of the Cochrane library were identified and finally only those articles that met the purpose of the study were thoroughly reviewed.

Discussion

A total of 752 articles were found with the keywords "agammaglobulinemia" and "allergy". After applying the inclusion criteria, a total of 20 publications were selected. Of all the items, 11 were written in the USA, 4 in Europe, 3 in the Middle East and 2 in South America (Figure 1). We discuss herein the selected studies in chronological order.

Figure 1: Countries of origin of the articles selected for final review.



One of the most interesting studies found concerning this association is the work of Peterson et al published in 1962, reporting an unusually high frequency of atopic dermatitis in XLA [7]. Atopic dermatitis occurred in 4 out of 23 boys with congenital, X-linked and recessive agammaglobulinemia. None of them had symptoms of respiratory allergy and skin tests were performed with over 200 allergens with negative results. The authors attributed the frequency of atopic dermatitis in this population to the predominance of type IV hypersensitivity reactions. Previously, Porter and Good in 1957 had carefully described the presence of delayed type allergy mechanisms in patients with agammaglobulinemia [8,9].

In 1973, Peczalcsa et al. published a case report of a child with XLA who suffered an immediate urticaria reaction after tetracycline's administration. In addition to that, this child had family history of atopy, positive skin tests to common allergens and detectable IgE levels [10]. The authors suggested that patients lacking the three major serum immunoglobulins and B lymphocytes may have normal levels of serum IgE and IgE-bearing lymphocytes in peripheral blood. Later, in 1975, with the primary objective of evaluating the potential involvement of IgD and IgE in the prevention of infections in patients with PID, a population of

165 patients with diverse ID was analyzed. Twenty-five out of 165 were diagnosed with agammaglobulinemia (X-linked and non X-linked) and none of them had symptoms of atopy. In those 25 patients, IgE levels were low, with a median of 3 U/ml [11]. A couple of years later, a case report of XLA with detectable serum IgE levels was described, disclosing clinical of respiratory allergy with positive skin test for common aeroallergens. This patient suffered anaphylaxis after penicillin G administration and in a second time cutaneous reactivity was demonstrated to major and minor penicillin determinants. Desensitization to penicillin was performed due to recurrent gram-positive infections [12].

In 1985, Lederman and Winkelstein analyzed a population of 96 XLA patients. In this descriptive study, there is no mention of allergy as intercurrent disease, although up to 46% of patients developed chronic pulmonary diseases with both obstructive and restrictive patterns [13]. It could be possible that any of these patients were asthmatic. Many years later, Shabestari et al described a 7 years-old boy with XLA with symptoms of asthma, allergic rhinitis and urticaria [14]. This child had positive skin prick tests to aeroallergens and various foods, despite soluble IgE levels of 0.1 IU/ml with persistence of wheezing, chronic cough, rhinitis and severe papular urticaria after initiation of IVIG. Pulmonary function tests revealed exercise-induced bronchospasm, thus corticosteroids and bronchodilators were added to IVIG, with consequently improvement of chronic cough. The authors concluded that the fact of IgE and others Ig levels were low did not rule out allergy.

Other studies highlighting IgE-dependent mechanisms of allergy in XLA focused on the cytokines secreted by T cells in response to allergens, which can play an important role in the induction and maintenance of airway inflammation and hyperresponsiveness [15]. In addition, Amedei et al suggested a preferential Th1 profile in XLA patients. The authors concluded that Th1 bias could explain the increased prevalence of autoimmune diseases and the low incidence of allergy manifestations [16]. In another study, Özcan et al analyzed a population of 113 children with antibody deficiencies. Of these 113 children, 3 had XLA with median detectable levels of total IgE 8 IU/ml. One of them had positive skin tests to aeroallergens and two of them had personal history of wheezing with positive bronchial provocation with methacholine [17]. This implies that in some XLA patients, type Th2 responses are indeed predominant.

In 2006, an extensive review of the infection profile of 201 XLA patients in the US was published [18]. There is however no reference to the development of atopy, so we cannot rule out that these patients had any allergies since it was not the focus of the study. McGinnitie et al, performed a retrospective study to evaluate the clinical characteristics of 141 children diagnosed with PID [19], including just 2 children with XLA. Again, no references to the development of atopy were given.

Finally, another interesting paper is a clinical study that analyzed 7 children that had been diagnosed with cow's milk allergy and were subsequently diagnosed of were different PIDs [20]. One such patient was finally diagnosed as XLA and clinical signs of

suspected allergy to cow's milk were failure to thrive and eczema. Skin tests with cow's milk were negative and total IgE levels were less than 1 IU/ml.

Conclusion

The prototypical sequence of events in type I immediate hypersensitivity involves exposure to an antigen, activation of Th2 cells and specific B lymphocytes to the antigen, production of specific IgE antibodies, IgE binding to the high affinity Fcε receptors on mast cells and basophils. In a second time, Ag-IgE binding and crosslinking inducing mast cell activation by antigen challenge, leading to the release of mast cells mediators and subsequent local and systemic reaction [5]. Therefore, the role of IgE appears fully central to the development of allergic disease and theoretically, a patient with absence of IgE should not have ability to produce hypersensitivity type I responses.

The immunoglobulin class switch recombination deficiencies (Ig-CSR-D) also called Hyper IgM syndromes (HIGM) are a group of primary immune deficiencies (PID) that have in common a normal or elevated serum IgM level and diminished switched immunoglobulin isotypes (IgG, IgA and IgE). The molecular basis of Ig-CSR-D includes failures in CD40L-CD40 signaling pathway, activation-induced cytidine deaminase (AID) catalytic activity, as well as DNA repair mechanisms[33]. The Ig-CSR-D would be a very interesting study model since the few IgE expressing B cells would not be able to undergo affinity maturation for allergens. However, the low prevalence of HIGM makes very difficult to study the presence of allergy in a large population sample.

XLA is characterized by blockage of B lymphocytes' maturation in the bone marrow not beyond the stage of B prelymphocyte, given that Btk participates in signal transduction from the B prelymphocyte receptor necessary for its survival and differentiation. The main feature is the absence of serum immunoglobulin, a marked decrease of B cells in peripheral blood and lymphoid tissues and the absence of plasma cells in tissues. The number and function of T cells are usually normal in these patients, although they may show reduced number of activated T cells due to low antigen presenting cells in the absence of B lymphocytes [6].

In line with the theoretical framework of allergy in the setting of agammaglobulinemia, it is striking the occurrence of many allergic reactions such as asthma, urticaria, atopic dermatitis or drug allergy in this patients' population. In fact, most of the commented patients that developed allergy symptoms showed normal or detectable levels of IgE. There is only one patient in all the medical literature revised with undetectable serum IgE described by Shabestari et al [14]. One possible explanation is that the levels of IgE necessary for allergen sensitization and subsequent development of symptoms were much lower than those currently believed (total IgE 0.1 IU/ml in this patient). Other hypothesis is suggested by Nonoyama et al [34] could be that leaky B cells from XLA patients with missense mutations of Btk keep very low but functional Btk. In addition, CD40 signaling is intact in B cells lacking demonstrable Btk and it is possible that XLA patients have specific antibody producing cells. For the same reason, the review of the literature shows that

there is a predominant Th1 response and delayed hypersensitivity, as in atopic dermatitis or asthma, in XLA [7,8,9,14,17]. Another intriguing fact is the existence of drug allergy in a few patients. In two of the articles analyzed two immediate reactions were described, one in which the hypersensitivity mechanism could be proven by reactivity to the major and minor penicillin determinants. In these two patients, IgE levels were normal, suggesting that adverse reactions were mediated by a type I hypersensitivity mechanism, which is rare when one consider the low incidence of type I penicillin hypersensitivity in children population (APENIN study, unpublished data).

The knowledge acquired in recent years, driven by the medical use of anti-IgE monoclonal antibody (omalizumab) in moderate to severe asthma and other severe allergic conditions, has allowed to unravel the magnitude of IgE role blockage in advanced allergic diseases and also the potential contribution of IgE-independent mechanisms. NKT cells, innate lymphocytes type 2 cells (ILC2s) could account for the development of allergic diseases in patients with agammaglobulinemia through the release of cytokines such as IL-4, IL-9, IL-5 or IL-13, which are heavily involved in allergic lung inflammation [21,22].

The investigation of IgE production and regulation is complicated because of the very low blood frequencies of IgE B cells and IgE plasma cells. Furthermore, IgE B cells are extremely hard to identify. Also, most serum IgE is linked to high affinity receptors in mast cells and basophils, and to low affinity receptor on the surface of B cells. Current studies in murine models have provided new understanding of how IgE is produced and regulated *in vivo* [31]. Two principal pathways of immunoglobulin class-switching have been characterized for IgE: a predominantly direct pathway from the IgM to the IgE isotype and a sequential pathway from IgM to an IgG1 intermediate and then to IgE[32].

Currently, they are missing data to answer all these questions and more rigorous studies focused on this goal are needed to establish more solid conclusions. We suggest the necessity to carry out a retrospective observational study based on supranational registries of XLA as an excellent approach to determine the incidence of allergies in this population and to try to better understand the immunological mechanisms by which allergy may occur. XLA seems a good model to evaluate IgE-independent contributors in atopy manifestations.

References

1. Conley ME, Broides A, Hernandez-Trujillo V, Howard V, Kanegane H, Miywaki T, et al. (2005) Genetic analysis of patients with defects in early B cell development. *Immunol Rev* 216-234.
2. Bruton OC (1952) Agammaglobulinemia. *Pediatrics* 9:722-728.
3. Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, et al. (1993) Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell* 72:279-90.
4. Moin M, Aghamohammadi A, Farhoudi A, Pourpak Z, Rezaei N, et al. (2004) X-linked agammaglobulinemia: A survey of 33 Iranian patients. *Immunol Invest* 33:81-93.

5. Abbas AK, Lichtman AH, Pillai S (2015) Cellular and Molecular Immunology. Elsevier Saunders.
6. Ochs HD, Smith CIE, Puck JM (2014) Primary Immunodeficiency Diseases A Molecular and Genetic Approach. Oxford University Press.
7. Peterson RDA, Page AR, Good RA (1962) Allergy in agammaglobulinemia. *J Allergy* 33:406.
8. Good RA, Zak J, Jensen DR, Pappenheimer AM (1957) Delayed Allergy and Agammaglobulinemia, *J Clin Invest* 86: 894.
9. Porter HM (1957) Immunologic Studies in Congenital Agammaglobulinemia with Emphasis on Delayed Hypersensitivity. *Pediatrics* 20: 958.
10. Peczalcsa G, Ballow M, Hansen JA (1973) IgE-bearing lymphocytes and atopy in a patient with X-linked infantile agammaglobulinemia. *Lancet* 1:1254.
11. Buckley RH, Fiscus SA (1975) Serum IgD and IgE concentrations in immunodeficiency diseases. *The Journal of Clinical Investigation* 55:157-165.
12. Ganier M, Lieberman P (1997) Infantile agammaglobulinemia and immediate hypersensitivity to Penicillin G. *JAMA* 237: 1852-1853.
13. Lederman HM, Winkelstein JA (1985) X-linked agammaglobulinemia: An analysis of 96 patients. *Medicine* 64: 145-156.
14. SadeghiShabestari M, Rezaei N (2008) Asthma and Allergic Rhinitis in a Patient with BTK Deficiency. *J Invest Allergol Clin Immunol* 18(4): 300-304.
15. Hamelmann E, Takeda K, Schwarze J, Vella AT, Irvin CG, et al. (1999) Development of eosinophilic airway inflammation and airway hyperresponsiveness requires interleukin-5 but not immunoglobulin E or B lymphocytes. *Am J Respir Cell Mol Biol* 21:480-9.
16. Amedei A, Romagnani C, Benagiano M, Azzurri A, Fomia F, et al. (2001) Preferential Th1 profile of T helper cell responses in X-linked (Bruton's) agammaglobulinemia. *Eur J Immunol* 31:1927-34.
17. Özcan C, Metin A (2015) Bronchial hyperreactivity in children with antibody deficiencies. *Allergol Immunopathol* 43(1):57-61.
18. Winkelstein JA (2006) X-linked agammaglobulinemia. Report on a United States registry of 201 patients. *Medicine* 85:193-202.
19. MacGinnitie A, Aloï F, Mishra S (2011) Clinical characteristics of pediatric patients evaluated for primary immunodeficiency. *Pediatr Allergy Immunol* 22: 671-675.
20. Melo KM, Dantas E, De Moraes-Pinto MI, Condino-Neto A, Gonzalez IG, et al. (2013) Primary Immunodeficiency May Be Misdiagnosed as Cow's Milk Allergy: Seven Cases Referred to a Tertiary Pediatric Hospital. *ISRN Pediatr* 2013: 470286.
21. Neill Daniel R, See Heng Wong, Agustin Bellosi, Robin J Flynn, et al. (2010) "Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity". *Nature* 464 (7293): 1367-1370.
22. Gold, Matthew J, Antignano, Frann (2014) "Group 2 innate lymphoid cells facilitate sensitization to local, but not systemic, TH2-inducing allergen exposures." *J Allergy Clin Immunol* 133 (4): 1142-8.
23. Papadopoulou A, Mermiri D, Taousani S, Triga M, Nicolaidou P, et al. (2005) Bronchial hyper-responsiveness in selective IgA deficiency. *Pediatr Allergy Immunol* 16:495-500.
24. Agondi RC, Barros MT, Rizzo LV, Kalil J, Giavina-Bianchi P (2010) Allergic asthma in patients with common variable immunodeficiency. *Allergy* 65:510-515.
25. Mehra A, Sidi P, Doucette J, Estrella L, Rouvelas H, et al. (2007) Subspecialty evaluation of chronically ill hospitalized patients with suspected immune defects. *Ann Allergy Asthma Immunol* 99: 1430-50.
26. Villa A, Notarangelo LD, Roifman CM (2008) Omenn syndrome: inflammation in leaky severe combined immunodeficiency. *J Allergy Clin Immunol* 122: 1082-6.
27. Crowder RV, Thompson WT, Jr Kupfer HG (1959) Acquired Agammaglobulinemia With Multiple Allergies and Pernicious Anemia. *AMA Arch Intern Med* 103: 445.
28. Freedman SO, Brown EB, Myers P (1958) Hypogammaglobulinemia and Bronchial Asthma. *Am J Med* 25: 961.
29. D Mac Glashan Jr (2011) Inhibition of IgE-mediated secretion from human basophils with a highly selective Bruton's tyrosine kinase, Btk, inhibitor. *International Immunopharmacology* 11: 475-479.
30. Burcu Bestas, Turunen JJ, Emelie K, Blomberg M, Qing Wang (2015) Splice-Correction Strategies for Treatment of X-Linked Agammaglobulinemia. *Curr Allergy Asthma Rep* 15:4.
31. Wu LC, Zarrin AA (2014) The production and regulation of IgE by the immune system. *Nature Reviews Immunology* 14: 247-259.
32. Geha RS, Jabara H, Brodeur SR (2003) The regulation of immunoglobulin E class-switch recombination. *Nature Rev Immunol* 3: 721-732.
33. Ouadani H, Ben-Mustapha I, Ben-Ali M, Ben-Khemis L (2015) Novel and recurrent AID mutations underlie prevalent autosomal recessive form of HIGM in consanguineous patients. *Immunogenetics* 6.
34. Nonoyama S, Tsukada S, Yamadori T, Miyawaki T (1998) Functional analysis of peripheral blood B cells in patients with X-linked agammaglobulinemia. *J Immunol* 161(8):3925-9.
35. S Nasser, R Sorouri, Z Pourpak, M Yeganeh, A Aghamohammadi, et al. (2011) Molecular Characterization of Bruton's Tyrosine Kinase Deficiency in 12 Iranian Patients With Presumed X-Linked Agammaglobulinemia. *J Invest Allergol Clin Immunol* 21(7):571-577.
36. H Zeng, Y Tao, X Chen, P Zeng, B Wang, et al. (2013) Primary Immunodeficiency in South China: Clinical Features and a Genetic Subanalysis of 138 Children. *J Invest Allergol Clin Immunol* 23(5):302-308.