

GENETIC DIAGNOSIS OF PATIENTS WITH PRIMARY AGAMMAGLOBULINEMIA TREATED AT THIRD LEVEL PERUVIAN CENTERS

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ABSTRACT

Primary agammaglobulinemia result from specific alterations in B cells, which lead to low antibody production. Diagnostic suspicion is established with a history of repeated infections, low immunoglobulins, and absence of CD19+ B lymphocytes. The diagnosis is confirmed by genetic analysis and the detection of a mutation linked to the X or autosomal recessive or dominant chromosome. In Peru, there is no literature on primary agammaglobulinemia and no reports on the genotype of patients with suspected primary agammaglobulinemia. Under this scenario, a study was performed to describe the genotype of patients with suspected primary agammaglobulinemia. Twenty (20) patients were found with mutations in the BTK gene and an autosomal recessiveIGHM mutation. Thirteen (13) hereditary mutations and seven de novo mutations were found. It is concluded that the group of primary agammaglobulinemia are mostly mutations in the BTK gene, corresponding to X-linked agammaglobulinemia.

Keywords: *Agammaglobulinaemia; Genotype, Bruton type agammaglobulinemia; Peru (source: MeSH NLM).*

INTRODUCTION

Primary agammaglobulinemia (PA) is a group of diseases caused by alterations in the production of antibodies due to a molecular defect either intrinsic to the B cells or caused by failed interactions between the B cells and the T cells⁽¹⁾. PAs are defined by a CD19+ B lymphocytes count under 1% in the context of a low antibody count⁽²⁾.

Antibody deficiency typically leads to recurrent, often severe, upper and lower respiratory tract infections caused by encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*⁽³⁾. There are three types of PAs: The X chromosome-linked agammaglobulinemia (XLA), which is seen in male patients and is derived from alterations in the Bruton's Tyrosine Kinase (BTK)

gene; the autosomal recessive and the autosomal dominant, which affect both men and women^(4, 5).

The diagnosis of PA is confirmed by genetic studies that seek to identify a mutation in the BTK gene in the case of XLA; at least one of the six genetic variations in the case of the autosomal recessive form, or one of the two genetic variations in the case of the autosomal dominant form⁽⁶⁾. It has been reported that the XLA are the most frequent PAs, most of which are hereditary mutations, defined as the ones that are transmitted through the maternal line, in the context of inheritance linked to the sex. This was reported by Zhang et al., who described the genotype of six patients in China who had PA and confirmed they had XLA by detecting mutations in exons of the BTK gene; he only reported one de novo mutation, defined as a mutation that is not transmitted by maternal or paternal line and that

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occurs spontaneously ⁽⁷⁾. Esenboga et al. reported the results of the genetic analysis of 26 patients with suspected PA and determined there were BTK mutations in all patients, and also described there was no relationship between the genotype and the phenotype of the disease in terms of severity ⁽⁸⁾.

In Peru, primary immunodeficiencies (PID) are underdiagnosed, largely due to the logistical and economic difficulties to arrive to a confirmatory diagnosis ⁽⁹⁾. On the other hand, defects in the production of antibodies are the most frequent PID reported in Peru, and their treatment involves the use of human immunoglobulin, a fundamental medication to alter the natural evolution of the disease and avoid repeated infections and hospitalizations ⁽¹⁰⁾.

The objective of this study was to describe the genotype of patients with suspected PA treated in third level centers; this is the first Peruvian report in which a definitive diagnosis of PA is reached.

THE STUDY

A descriptive study was conducted, which included patients under the age of 18 who visited the National Reference Center for Allergy and Immunology (Centro de Referencia Nacional de Alergia e Inmunología, CERNAAI) of the National Children's Health Institute (Instituto Nacional de Salud del Niño, INSN) and who were clinically suspected of having primary agammaglobulinemia, but who, in many cases, are now being treated at other third-level centers. Patients belong to a previously reported Peruvian registry of patients with primary immunodeficiencies ⁽¹⁰⁾. Patients under the age of 18 who had been diagnosed with primary agammaglobulinemia by a clinical immunologist between June 1, 2011 and June 1, 2014 using criteria of the International Union of Immunological Societies (IUIS), with a compatible clinical picture and absent CD19+ B lymphocytes ⁽¹⁾, were included. Patients with no clinical evidence of primary agammaglobulinemia, with secondary immunodeficiency or who had not accepted to participate through informed consent, were excluded.

The patient's parents or their guardian were contacted to obtain informed consent, following all the guidelines of the Declaration of Helsinki. There were two informed consents: one for patient participation in the study and another one for taking the sample from the patient's mother. This sample was taken to determine whether the mother carried the mutation.

KEY MESSAGES

Research Motivation. Primary agammaglobulinemia (PA) are the most common primary immunodeficiencies and no previous data have been reported regarding their results in genetic analysis in Peru.

Main Findings. We have found mutations in the Bruton's Tyrosine Kinase (BTK) gene, which correspond to X chromosome-linked agammaglobulinemia. Only one case of autosomal recessive agammaglobulinemia was reported.

Implications. The clinical importance of PA and its previously reported high frequency should be taken into account when defining the guidelines for the diagnosis and treatment of this disease.

The blood samples were taken the day of the interview. Vacuum system tubes with EDTA, after asepsis, were used to obtain 5 ml blood samples. The samples were labeled according to the file number. All samples were sent for processing in an external laboratory using the PCR method and direct sequencing. Blood samples for sequencing did not require any special preservation procedure.

The statistical analysis was performed using the SPSS statistical program, version 24 (IBM Corp., Armonk, NY, USA). Frequencies and percentages were used to describe qualitative variables. The Shapiro-Wilk normality test was applied to determine the distribution of quantitative variables. The mean and standard deviation were used for quantitative variables with normal distribution, and the median and interquartile ranges were used for the quantitative variables without normal distribution.

The study was approved by the Ethics Committee of the National Children's Health Institute CL-28-2017, with institutional administrative authorization for access to information and the development of the study.

FINDINGS

Twenty-one (21) patients meeting the clinical diagnosis of primary agammaglobulinemia were evaluated. The mean age of the patients was 8.67 ± 4.25 years; 20/21 (95.2%) were male and 9/21 (42.9%) came from provinces (Table 1).

All patients underwent genetic analysis; a mutation was found in the p.K36NfsX56 protein, which corresponds to the BTK gene. The patient is currently being treated at

Table 1. Results of the genetic analysis of patients in 21 patients with clinical diagnosis of primary agammaglobulinemia in Lima-Peru, 2018

Patient	Place of origin	Type of Insurance	Gender	Age at time of study (years)	Protein mutation	Change in codon	Exon	Gen	Status of the mother
1	Province	EsSalud	Male	13	p.N72K	c.209-215insA	Exon 3	BTK	Carrier
2	Lima	EsSalud	Male	8	p.T158P fsX17	c.472-475delACAG	Exon 6	BTK	Carrier
3	Province	EsSalud	Male	11	p.K36NfsX56*	c.106-108del A	Exon 2	BTK	Carrier
4	Province	EsSalud	Male	11	p.R520X	c.1558C>T	Exon 6	BTK	Normal
5	Lima	EsSalud	Female	6	p.Y176Lfs.87X	c.525-526 insC	-	IGHM	Not tested
6	Province	EsSalud	Male	10	p.Asn135LysfsX42	c. 537delC	Exon 6	BTK	Carrier
7	Lima	EsSalud	Male	9	p.Phe583Leu	c. 1879T> C	Exon 17	BTK	Carrier
8	Province	EsSalud	Male	13	p.Q196X	c.718C>T	Exon 7	BTK	Carrier
9	Province	EsSalud	Male	9	p.L512P	c.1667T>C	Exon 15	BTK	Carrier
10	Lima	SIS	Male	10	p.Asn135LysfsX42	c.537delC	Exon 6	BTK	Carrier
11	Province	SIS	Male	1	p.Arg544Ger	c.1764G>T	Exon 17	BTK	Normal
12	Province	SIS	Male	5	p.W588X	c.1896 G>A	Exon 18	BTK	Normal
13	Province	EsSalud	Male	12	p.Arg255X	c.895C>T	Exon 8	BTK	Carrier
14	Province	SIS	Male	10	p.Arg255X	c.895C > T	Exon 8	BTK	Normal
15	Lima	SIS	Male	3	p.R288W	c.994C>T	Exon 10	BTK	Normal
16	Province	SIS	Male	7	p.Asn135LysfsX42	c.537delC	Exon 6	BTK	Normal
17	Lima	SIS	Male	9	p.R288W	c.994C>T	Exon 10	BTK	Carrier
18	Province	SIS	Male	20	p.K430E	c.1420A>G	Exon 14	BTK	Normal
19	Lima	SIS	Male	7	p.Asn135LysfsX42	c. 537delC	Exon 6	BTK	Carrier
20	Lima	SIS	Male	6	p.L512P	c.1667 T>C	Exon 15	BTK	Carrier
21	Lima	SIS	Male	2	p.Q196X	c.718C>T	Exon 7	BTK	Carrier

* Mutation not previously reported

SIS: Comprehensive Health Insurance; BTK: Bruton's Tyrosine Kinase; IGHM: Immunoglobulin Heavy Constant Mu.

an EsSalud hospital. Overall, we found 20 patients with mutations in the BTK gene and an autosomal recessive mutation. We found that of all the BTK mutations 13 were hereditary, with a carrier mother, and seven were de novo mutations, with a normal mother (Table 1). The genetic analysis could not be performed in one mother.

All patients were clinically evaluated following the Jeffrey Modell Foundation criteria. The criteria that showed a greater frequency were the occurrence of two or more episodes of pneumonia in one year in 12/20 (60.0%) patients, and low weight gain or growth retardation in 11/20 (55.0%) patients (Table 2).

Table 3 describes other clinical and therapeutic aspects in patients with BTK mutation. A median of total lymphocytes by flow cytometry of 2459 was found, with an interquartile range between 1285.5 and 3670.

In terms of treatment, 18/20 (90.0%) patients received immunoglobulin and all patients received prophylactic antibiotics. Only two patients received the definitive treatment: transplantation of hematopoietic precursors.

DISCUSSION

This has been the first approximation in Peru to a genotypic diagnosis in patients with high suspicion of PA. All the mutations that were found had been previously reported, except the mutation of the BTK gene in the p.K36NfsX56 protein. At the same time, a mutation in the IGHM gene in the p.Y176Lfs.87X protein is being reported. Approximately 60% of autosomal recessive mutations in PA correspond to alterations in the Mu heavy chain, as reported by Silva et al. in 2017 ⁽¹¹⁾.

In connection with the type of mutation, it was found that among the BTK mutations, 13 were hereditary and seven

Table 2. Jeffrey Modell Foundation criteria evaluated in 20 patients with mutations in the BTK gene in Lima- Peru, 2018

Criterion	Hereditary BTK mutation (n=13) n (%)	De novo BTK mutation (n=7) n (%)	Total (n=20) n (%)
Ten or more new ear infections in one year	4 (30.8)	2 (28.6)	6 (30.0)
Two or more serious infections of the paranasal sinuses in one year	4 (30.8)	1 (14.3)	5 (25.0)
Two or more months on antibiotics with poor results	4 (30.8)	2 (28.6)	6 (30.0)
Two or more episodes of pneumonia in one year	6 (46.2)	6 (85.7)	12 (60.0)
Little weight-gain or growth retardation	8 (61.5)	3 (42.9)	11 (55.0)
Recurrent abscesses in dermis or other organs	1 (7.7)	1 (14.3)	2 (10.0)
Persistent mouth sores or fungal skin infections	0 (0.0)	1 (14.3)	1 (5.0)
Need for intravenous antibiotics to fight infections	5 (38.5)	0 (0.0)	5 (25.0)
Two or more deep infections that cause septicemia	0 (0.0)	1 (14.3)	1 (5.0)
Family history of PID	2 (15.4)	2 (28.6)	4 (20.0)

PID: primary immunodeficiencies

were *de novo*. In a study conducted in Turkey, BTK gene mutations were found in 69% of cases and only three were *de novo* mutations⁽¹²⁾. In another study, conducted in China, BTK mutations were found in 16 of 21 patients, and only 2 were *de novo* mutations⁽¹³⁾. *De novo* mutations can influence the severity and mortality of patients, thus having an impact on the clinical phenotype^(14,15); but in our study no relationship was found between the severity of the disease and the type of mutation, in accordance with the findings of Esenboga et al., who states that there is no relationship between the genotype and the phenotype of disease severity⁽⁸⁾.

In the clinical description of the patients, it is stated that the median age at the time of diagnosis was two years. That is in contrast with a study conducted in Peru in 2017, Veramendi et al., in which it was found that the average age at the time of diagnosis was 7.4 years⁽¹⁶⁾. According to previous data, 50.0% of patients develop clinical manifestations at one year of age, and more than 95.0% develop symptoms by five years of age; however, symptoms developed at earlier ages tend to be more severe and carry a greater morbidity and mortality⁽¹⁷⁾. Consequently, the difference found regarding the age at diagnosis could be due to a higher degree of suspicion in the context of a severe disease or to the effectiveness of the training programs on PID carried out in recent years.

Recurrent infections were present in more than 60% of cases and, according to the Jeffrey Modell Foundation⁽¹⁸⁾, this background fact is a fundamental clinical aspect for establishing the diagnostic suspicion of primary immunodeficiency. We assessed these criteria in all patients included in the study and found that two episodes of pneumonia a year and weight loss or growth

retardation were the most frequent events in the patients assessed. The microorganisms a patient with PA is most susceptible to are the encapsulated *S. pneumoniae* and *H. influenzae*⁽³⁾; consequently, our findings show a probable susceptibility to these bacteria; however, it is not possible to determine this with precision given that routine cultures are not taken in this context.

The definitive treatment of PAs is the transplantation of hematopoietic precursors (TPH); however, logistical difficulties limit the application of this therapy in our environment, reason why the initial treatment of PA is based on the use of human immunoglobulin, as well as on the prescription of prophylactic antibiotics⁽¹⁷⁾. Two patients underwent transplantation of hematopoietic precursors, which was done outside the country. All patients received immunoglobulin. When THP is not possible, the use of immunoglobulin is the only treatment that can alter the natural course of the disease, decreasing morbidity and mortality⁽³⁾. More than 90% of patients received antibiotic prophylaxis. In addition to immunoglobulin replacement therapy, patients with XLA require aggressive antibiotic treatment for any suspected infection and, in some cases, prolonged antibiotic therapy may be prescribed to treat ongoing lung infections and chronic sinusitis or as prophylaxis⁽¹⁹⁾.

Since the study had a small number of patients, the chance of establishing inferences from the information obtained is limited. It should be considered that there is still an underdiagnosis of patients with primary immunodeficiencies⁽⁹⁾, reason why this report is a first approximation to PA, and continuous registration will be necessary, as will be necessary to have the necessary

Table 3. Sociodemographic and clinical description of 20 patients with mutations in the BTK gene in Lima-Peru, 2018.

Characteristics	Hereditary BTK mutation (n=13) n (%)	De novo BTK mutation (n=7) n (%)	Total (n=20) n (%)
Age in years at time of diagnosis*	2.91 (1.1-5.8)	1.9 (1.5-7.2)	1.98 (1.3-5.8)
Age in years at time of study*	9 (7.5-11.5)	7 (3.0-11.0)	9 (6.3-11.0)
Survival time in months***	151.2 (115.4-186.94)	126.3 (83.7-169.0)	145.8 (116.6-175.0)
Place of origina			
Lima	7 (53.9)	1 (14.3)	8 (40.0)
Province	6 (46.1)	6 (85.7)	12 (60.0)
Institution where being treated			
INSN	5 (38.4)	5 (71.4)	10 (50.0)
HNERM	7 (53.9)	1 (14.3)	8 (40.0)
Another EsSalud Hospital	1 (7.7)	0 (0.0)	1 (5.0)
HAMA	0 (0.0)	1 (14.3)	1 (5.0)
Type of current insurance			
EsSalud	8 (61.5)	1 (14.3)	9 (45.0)
SIS	5 (38.5)	6 (85.7)	11 (55.0)
Background			
Malignancy	3 (23.1)	1 (14.3)	4 (20.0)
Autoimmunity	1 (7.7)	1 (14.3)	2 (10.0)
Consanguinity	1 (7.7)	0 (0.0)	1 (5.0)
Ancillary Exams			
Total lymphocytes by flow cytometry+*	1863 (1232.0-3343.0)	3670 (1795.0-4250.0)	2459 (1285.5-3670.0)
Lymphocytes CD19+*	3 (0.0-16.5)	9 (3.0-24.0)	8 (0.3-18.8)
IgG*	65.4 (35.0-89.5)	72 (49.0-75.0)	73 (40.0-82.5)
IgM**	32.5 (17.7)	38.1 (11.2)	34.5 (15.7)
IgA*	8 (2.5-14.5)	10 (3.0-12.0)	8 (3.0-11.5)
IgE*	21 (11.0-37.0)	48 (39.0-58.0)	29 (17.0-48.5)
Treatment			
Use of immunoglobulin	12 (92.3)	6 (85.7)	18 (90.0)
Antibiotic prophylaxis	13 (100)	7 (100)	20 (100)
Hematopoietic precursor transplantation	1 (7.7)	1 (14.3)	2 (10.0)

*Medium (IQR)

**Average (SD)

***Average (95% CI)

Normal values of total lymphocytes by flow cytometry+: 1200 to 4100 mg/dl. Normal values of lymphocytes CD19+: 220 to 1300 mg/dl.

Normal IgG values: 650 to 1600 mg/dl. Normal IgM values: 54 to 300 mg/dl. Normal IgA values: 40 to 350 mg/dl. Normal IgE values: 0 to 100 IU/ml.

IQR: interquartile range; SD: standard deviation; 95% CI: 95% confidence interval; INSN: National Child Health Institute; HNERM: National Hospital Edgardo Rebagliati Martins; EsSalud: Seguro Social del Perú; HAMA: Hospital María Auxiliadora.

logistics to establish the definitive diagnosis of PA in all the cases that can be reported. Only in such circumstances could the genotypic profile of patients with PA be reported, in addition to its clinical implications and its impact on prognosis.

In conclusion, the present study shows that XLA are the most frequent PAs with mutations in the exons of the BTK gene, being mostly hereditary, although there is an unusual high number of de novo mutations. The usual clinical presentation of PAs is with repeated pneumonias and concurrent growth retardation. All the patients in the study received human immunoglobulin; it is, therefore,

essential to ensure the availability of the drug in settings where PA patients receive care.

Authors' Contributions: EMB and DGG conceived the research project. RIM and DGG elaborated the research project to approval. WCC, EMB, and JAB actively participated in the review of the project to approval. DGG performed the data analysis. The entire team took part in the preparation of the final report.

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