Open Access Library Journal
2017, Volume 4, e4114
ISSN Online: 2333-9721
ISSN Print: 2333-9705

The Novel Patient with BLNK Gene Type of Agammaglobulinemia

Gulnara Mahammadali Nasrullayeva[1], Vafa Rustam Mammadova[1], Afaq Vladimr Khalilova[1], Shabnam Eldar Shahgeldiyeva[2]

[1]Azerbaijan Medical University, Immunology Department, Baku, Azerbaijan
[2]Khazar University, Baku, Azerbaijan
Email: eshahgaldiyev@khazar.org

How to cite this paper: Nasrullayeva, G.M., Mammadova, V.R., Khalilova, A.V. and Shahgeldiyeva, S.E. (2017) The Novel Patient with BLNK Gene Type of Agammaglobulinemia. *Open Access Library Journal*, **4**: e4114.
https://doi.org/10.4236/oalib.1104114

Received: November 3, 2017
Accepted: November 25, 2017
Published: November 28, 2017

Abstract

Background: Agammaglobulinemia (AGM) is a genetic immune system disorder in which the body could not produce antibodies. There are two types of this disease: X-linked AGM (XLA) and autosomal forms. X-linked agammaglobulinemia results from a mutation in the gene for Bruton's tyrosine kinase (BTK), found on the X chromosome. Mutations in BTK result in lack of mature B-cells and immunoglobulins of all classes. There are 8 types of autosomal forms which are reflected in different defective genes. 7-year-old male patient at the age of 1 - 6, was encountered the recurrent broncho-pulmonary and gastro-intestinal infections, furunculosis and recurrent otitis. Also, because of the strain, pain and swelling on the 4th finger of the right hand it was suspected that the patient had rheumatoid arthritis. On immunological investigation, we have found out of absent of B lymphocyte. Level of IgG was 10 times less; IgA, IgM and IgE levels were 3 to 8 times less than the norm. Quantity of T-lymphocytes: absolute number of CD4+ lymphocytes increased, CD3+ and CD8+ lymphocytes were also high. Phagocyte activity in NBT, absolute number of NK cells and IRI index were 2 times lower than the norm. Genetically analysis has discovered the presence of abnormal homozygous BLNK gene.

Subject Areas

Immunology

Keywords

BLNK Gene, Rheumatoid Arthritis, Agammaglobulinemia

1. Introduction

Agammaglobulinemia is a disorder which passed through families when a per-

son has very low levels of protective immune system proteins—immunoglobulins (Ig). Low levels of these antibodies make you more likely to get infected [1] [2] [3]. Mother carrying the defective gene passes this anomaly to the fetus; moreover, the clinical signs of disease are usually observed in boys. There are two types of this disease (**Figure 1**).

X-linked agammaglobulinemia results from a mutation in the gene for Bruton's tyrosine kinase (BTK), found on the X chromosome. BTK is a nonreceptor cytoplasmic tyrosine kinase involved in B-cell receptor intracellular signaling, developing and differentiating [4] [5]. Loss-of-function mutations in BTK result in lack of mature B-cells and immunoglobulins of all classes. 50% of the mutations are new and these patients do not have a family history of the current condition. The other type with low or absent serum immunoglobulins is early onset non-Bruton agammaglobulinemia. Agammaglobulinemias with autosomal recessive/dominant heritage represent a very heterogeneous group, such as common immunoglobulin deficiency with increased only immunoglobulin M (hyper-IgM syndrome), which is also discussed separately. Approximately 90% of patients with early-onset agammaglobulinemia and absence of B cells have abnormalities in the Btk gene [3] [6] [7].

Similar phenotype to that of the X-linked form, autosomal inheritance of agammaglobulinemia, has been detected in a small number of families and accounts for up to 15% of patients with agammaglobulinemia. Males and females are usually affected in equal order. More than 100 cases of autosomal agammaglobulinemia have then been informed to date. Their diagnosis was suspected on the basis of early susceptibility to severe recurrent or persistent infections [8]. The case is particularly true if the parents are consanguineous or the ones belonging to an isolated population. Abnormal laboratory parameters include low Ig levels and low or absent peripheral blood mature B lymphocytes [5] [9]. For determine the genetic defect and to confirm the diagnosis, should be performed molecular genetic testing. **Table 1** shows the existing 8 types of agammaglobulinemia (AGM) which are reflected in defective genes.

We have patient withAGM4 type of disease which caused by homozygous mutation in the BLNK gene on chromosome 10q23.2. In these case B-cell development fails because of mutations B-cell linker protein [2] [8].

The BLNK gene encodes a B-cell linker protein. Linker or adaptor proteins can provide mechanisms by which receptors can increase and regulate to downstream effectors proteins. BLNK has essential role for normal B-cell development. BLNK is exclusively expressed in hematopoietic cells, mainly in progeny-

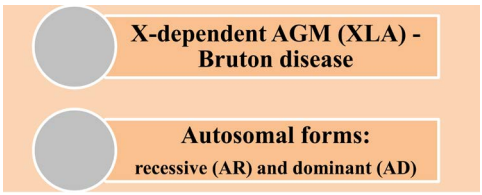

Figure 1. Two types of agammaglobulinemias.

Table 1. Types and defective genes of autosomal agammaglobulinemias.

Disease	Gene/Locus	Location	Inheritance
AGM1	IGHM	14q	AR
AGM2	IGLL1	22q11	AR
AGM3	CD79A	19q13.2	AR
AGM4	BLNK	10q23.2	AR
AGM5	LRRC8	9q34.11	AD
AGM6	CD79B	17q23.3	AR
AGM7	PIK3R1	5q13.1	AR
AGM8	TCF3	19p13.3	AD

AGM: agammaglobulinemia; **AR:** autosomal recessive; **AD:** autosomal dominant

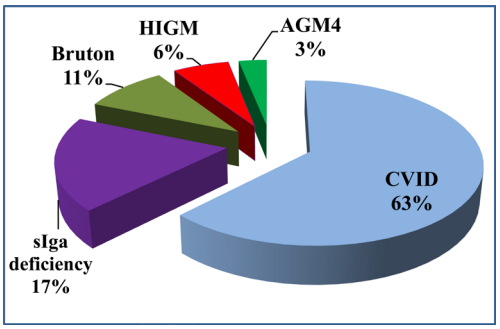

Figure 2. Different types of antibody deficiencies.

tor if myeloid cells, also in B cells [2] [9].

Clinical features on autosomal recessive agammaglobulinemia and X-linked agammaglobulinemia are similarly identical. When maternal transplacentally passed antibodies disappear patients develop recurrent pyogenic infections from 6 months of age. Sinopulmonary infections (especially sinusitis, pneumonia), otitis media are most commonly, followed by skin infections, gastrointestinal infections, sepsis, meningitis and osteomyelitis [3] [8] [10] [11] [12].

2. Patients and Materials

During 2010-2017 years Immunology Department and Pediatric Department of Azerbaijan Medical University have detected 35 patients with Antibody deficiencies, out of which 22 patients with CVID, 6 patients with sIgA deficiency, 4 patients with Bruton disease, 1 patient with AGM4 and 2 patient with HIGM. This investigation had been done in frame of collaboration with biological laboratory of Khazar University research group. Different types of antibody deficiencies are depicted in **Figure 2**.

3. Case Report

7-year-old male patient was born with normal height and weight from the first pregnancy. Parents were close relatives (cousins). Physical and mental develop-

ment of the patient proceeded normally until 1 year. Nevertheless, later, at the age of 1 - 6, he started to face the recurrent broncho-pulmonary and gastro-intestinal infections, furunculosis and recurrent otitis. At the age of 6 patient had pneumonia with high fever and respiratory symptoms. Also, because of the strain, pain and swelling on the 4th finger of the right hand it was suspected that the patient had rheumatoid arthritis (Figure 3).

4. Discussion

Interestingly, there was not observed any pathological change in the mile-wrist joint in radiography. ASO, RF indexes were negative and CRP was high (110 mg/l). We have detected hepatosplenomegaly on US investigation (hepatomegaly: left part-57mm, splenomegaly: 96 mm). ANA, specific *M. tuberculosis* and brucellosis antibodies were also negative. On X-Ray investigation it was detected pneumonia of left the part of lung and hidrotoraks.

4.1. Immunology

On immunological investigation, we have found out that the type of B lymphocyte was absent. Level of IgG was 10 times less; IgA, IgM and IgE levels were 3 to 8 times less than the norm. There were some noticeable changes in the peripheral blood indexes: leukocytosis, lymphopenia and monocytosis; quantity of T-lymphocytes: absolute number of CD4+ lymphocytes increased, CD3+ and CD8+ lymphocytes were also high. Phagocyte activity in NBT, absolute number of NK cells and IRI index were 2 times lower than the norm. Some these findings are depicted on Table 2.

Figure 3. Clinical fetures of Rheumatoid Arthritis in patient with AGM4.

Table 2. Periodically immunological results of AGM4 patient.

	Before İVİG	After IVIG	Norm
Leukocyte 10^9/l	20.6	14.2	4.0 - 7.3
Lymphocyte %	26	29	36 - 43
İgA (q/l)	0	0.1	0.83 - 2.17
İgM (q/l)	0	0.3	0.55 - 2.10
İgG (q/l) total	0.6	5.0	6.5 - 14.1
İgE (ME/ml)	0	0.8	0 - 60

4.2. Molecular Genetics

HOMOZYGOUS VARIANTS

***BLNK*:** OMIM AR for Agammaglobulinemia 4 (absent pre-B, mature B cells, but normal numbers of pro-B cells; recurrent otitis, pneumonia). *BLNK* is essential for normal B-cell development.

HETEROZYGOUS VARIANTS (only inherited AD or possible compound heterozygous)

***CFI*:** CFI deficiency can cause hemolytic uremic syndrome with clinical impact, such as hemolytic anemia, proteinuria, decreased renal function and hypertension.

***PSTPIP*1:** OMIM AD: Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome.

***C*5:** OMIM AD and AR for complement component 5 deficiency (seborrheic dermatitis, intractable diarrhea, recurrent local and systemic infections) (Table 3).

Genetically analysis has discovered the presence of abnormal homozygous BLNK, heterozygous CFI, PSTPIP1 and C5 genes.

4.3. Treatment

Antibacterial treatment during 2 weeks, non-steroid and steroid medicines, other symptomatic treatment. Replacement therapy by IVIG-Octagam was given in dose 400 - 600 mg/kg, every 4 weeks, but it was not regularly received.

Table 3. Genetic results of our patient M. D., 7 years old.

HOM									
GENE	CHR	POS	SNP ID	IMPACT	AA	ID	MAF	READS	CADD score
BLNK	10	97964346	rs184808145	STOP_GAINED	R282*	ENST00000224337	<0.01	684	38
HET									
GENE	CHR	POS	SNP ID	IMPACT	AA	ID	MAF	READS	CADD score
IL12B	5	158749490	rs139186048	MISSENSE	E132K	ENST00000231228	<0.01	426	26.3
DOCK8	9	418066	.	SPLICE_SITE_ACCEPTOR	NA	ENST00000453981	NA	155	18.77
CFI	4	110682814	.	MISSENSE	D173N	ENST00000394635	<0.01	645	0.001
***PSTPIP*1**	15	77310863	rs201872851	MISSENSE	T68M	ENST00000558012	<0.01	450	25
VPS13B	8	100844858	rs149842139	MISSENSE	R3223W	ENST00000358544	<0.01	559	25.4
NCF4	22	37267701	rs150103256	MISSENSE	V160M	ENST00000397147	<0.01	204	4.579
DNAAF1	16	84208329	rs139519641	SPLICE_SITE_DONOR	NA	ENST00000378553	<0.01	528	11.68
C5	9	123785738	rs34552775	MISSENSE	L354M	ENST00000223642	<0.01	404	25
NCF1	7	74197326	.	MISSENSE	N166D	ENST00000289473	<0.01	673	0.003

GENE: gene name; **MPACT:** consequence of variant (e.g. missense, stop gain, splice-site); **CHR:** chromosome; **POS:** chromosomal position (bases); **ID:** Transcript ID; **SNP ID:** rs number; **R:** base in reference genome; **MAF:** minor allele frequency; **A:** alternative base in sample; **NA:** not annotated; **AA:** change on amino acid level; **READS:** number of sequencing reads covering the variant.

5. Outcomes

The patient is under our control for 2 years. In this period the number of diseases, especially pneumonia, decreased against the background of immunological treatment. Pain in the joints falls and can open the finger. The patient's parents were informed of the illness, and a prenatal diagnosis was recommended during the next pregnancy.

6. Conclusion

Thus, based on the detection of a serious deficiency of humoral immunity and BLNK gene mutation, patient has rarely diagnosed disease—agammaglo-bulinemia type 4 (AGM4).

References

[1] Schwartz, R.A. (2017) Bruton Agammaglobulinemia. http://emedicine.medscape.com/article/884942-overview

[2] Kniffin, C.L. (2010) Agammaglobulinemia 4, Autosomal Recessive. http://www.omim.org/entry/613502

[3] Pituch-Noworolska, A., Mach-Tomalska, H., Szaflarska, A. and Adamek, D. (2016) Shulman Disease (Eosinophilic Fasciitis) in X-Linked Agammaglobulinemia. *Polish Journal of Pathology*, **67**, 183-188. https://doi.org/10.5114/pjp.2016.61456

[4] Abolhassani, H., Vitali, M. and Lougaris, V. (2016) Cohort of Iranian Patients with Con-genital Agammaglobulinemia: Mutation Analysis and Novel Gene Defects. *Expert Review of Clinical Immunology*, **12**, 479-486. https://doi.org/10.1586/1744666X.2016.1139451

[5] Ferrari, S., Zuntini, R., Lougaris, V., *et al.* (2007) Molecular Analysis of the Pre-BCR Complex in a Large Cohort of Patients Affected Byautosomal-Recessive Agammaglobulinemia. *Genes and Immunity*, **8**, 325-333. https://doi.org/10.1038/sj.gene.6364391

[6] Vickery, J., Michael, C. and Lew, D. (2013) Evaluation of B Lymphocyte Deficiencies. *Cardiovascular & Hematological Disorders-Drug*, **13**, 133-143. https://doi.org/10.2174/1871529X11313020006

[7] Chin, T.W. (2014) Agammaglobulinemi. http://emedicine.medscape.com/article/884942-overview

[8] Conley, M.E. (2013) Autosomal Agammaglobulinemia. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=33110

[9] Yuvaraj, S. and Hendriks, R.W. (2012) Blnk (B-Cell-Linker). http://atlasgeneticsoncology.org/Genes/GC_BLNK.html

[10] Agarwal, S. and Mayer, L. (2009) Pathogenesis and Treatment of Gastrointestinal Disease in Antibody Deficiency Syndromes. *Journal of Allergy and Clinical Immunology*, **124**, 658. https://doi.org/10.1016/j.jaci.2009.06.018

[11] Slotta, J.E., Heine, S., Kauffels, A., *et al.* (2011) Gastrectomy with Isoperistaltic Jejunal Parallel Pouch in a 15-Year-Old Adolescent Boy with Gastric Adenocarcinoma and Autosomal Recessive Agammaglobulinemia. *Journal of Pediatric Surgery*, **46**, e21-24. https://doi.org/10.1016/j.jpedsurg.2011.06.005

[12] Vancikova, Z., Freiberger, T., Vach, W., Trojanek, M., Rizzi, M. and Janda, A.

(2013) X-Linked Agammaglobulinemia in Community-Acquired Pneumonia Cases Revealed by Immunoglobulin Level Screening at Hospital Admission. *Clin Padiatr*, **225**, 339-342. https://doi.org/10.1055/s-0033-1354415