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Case Report Article

NFKB2 mutation in a patient with lymphopenia and extreme cold sensitivity (a case report)

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Abstract

NF-κB pathway is a complex protein playing an important role in regulating lymphocyte development, immune responses, inflammation, cell proliferation, and cell death. The NF-kB signaling pathway has been described to be associated with canonical and noncanonical pathway. The canonical pathway utilizes NF-kB1, whereas the latter pathway involves NF-kB2, which is the cornerstone of the non-canonical NF-kB pathway, and has been shown to be critical for the development of secondary lymphoid organs, B cell development, and the humoral response to T-dependent and T-independent antigens. In this study, we investigated the patient with chief complain of low body temperature as well as feeling cold even in the warm seasons since 15 years ago. We reported a middle age man with mild lymphopenia and no significant infection, but hypothermia with significant chills even in the warm seasons with a mutation in NF-κB2 pathway.

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Keywords NF-κB, NFKB2, Lymphopenia, Chills.

Introduction

NF-κB pathway (nuclear factor kappa-light-chain-enhancer of activated B cells**)** is a complex protein that functions as controlling transcription of DNA and cytokine production (1). NF-κB transcription factors are coded by five genes as follows: *NFKB1*, *NFKB2*, *RELA*, *RELB,* and *REL, and* Their products are p50, p52, p65 (RelA), RelB, and c-Rel, respectively. Factors p50 and p52 (the products of *NFKB1* and *NFKB2*, respectively) are considered as functional transcription factors (2). The NF-κB pathways play vital roles in many normal cellular functions including inflammation, apoptosis, cell survival, proliferation, angiogenesis, and innate and acquired immunity (1).

NF-κB proteins are inactive cytoplasmic proteins attached to an inhibitors molecules of κB (IκB) family (3). NF-κB pathways activation occurs in two ways as following: the canonical and the non-canonical. The canonical pathway responds to stimulation of immune receptors, and also directs rapid and transient activation of NF-κB pathways (4). It is activated by some receptors such as antigen receptors, cytokine receptors, and pattern-recognition receptors (5). The main canonical NF-κB family members are the NF-κB1 p50-RELA and NF-κB1 p50-c-REL dimers (6).

In contrast to the canonical pathway, the activation of non-canonical NF-κB pathway is slow and durable. The main Non-canonical NF-κB family members are NF-κB2 p52 and RELB (7). Established roles of the non-canonical NF-κB pathway consist of thymic epithelial cell (TEC) differentiation, secondary lymphoid organogenesis , B-cell maturation and survival, regulating T-cell differentiation, DC maturation, and bone metabolism (7).

Case presentation

In the present survey, we reported a 58 years old man born of consanguine parents who were distant relatives. The patient was the ninth child of his family and other family members were all healthy. The onset of his disease was in the age of 7 years old and at the time of diagnosis, he was 56 years old. The patient came with chief complain of low body temperature and feeling cold even in the warm seasons since 15 years ago. The patient also had history of recurrent URI; however he had no other significant infection. The patient had frequent sinusitis and common cold in his juvenile period. He had herpes zoster in 55 years old. Also, He had a history of hospitalization due to kidney stone. His tonsils were atrophic. Both kidneys had normal diameter, shape, and differentiation of corticomodular in CT scan. Also, prostate size was larger than normal. Complete endocrinologic, rheumatologic, and neurologic works up were normal. However, there was lymphopenia in CBC (absolute lymphocyte=870), with normal count of other cells. The results of other immunologic tests including Ig M, G, A, E levels, antibody response, NBT, complements, HIV, and ANA were normal. In spite of lymphopenia, the percentage of immunologic cells was normal (CD 3=65%, CD 19= 11%); however the absolute counts of CD 3 and CD 19 were low (CD 3=565, CD19=95) (**Table 1**). In genetic evaluation, we found a nonsense mutation (c.1831C > T) in *NF-KB2* gene (p.Arg611∗).

Discussion

The NF-κB pathway plays a key role in many normal cellular functions including inflammation, apoptosis, cell survival, proliferation, angiogenesis, and innate and acquired immunity (1). This pathway is observed in all cells. The NF-κB pathway has significant functions in many diseases including asthma, bone and muscular diseases, age-related diseases, and in some kinds of cancers (1). Previous studies conducted on patients with the same molecular defect presented only mild to moderate laboratory and clinical complications (8).

Table 1. Laboratory and immunologic data of the patient

Laboratory test	patient	normal
Complete blood count		
White blood cells (10^3/μL)	4.1	4-10
Red blood cells (10^6/μL)	4.91	3.5-5.5
Neutrophils (%)	74.7	20-70
Lymphocytes (%)	22.7	45-75
Monocytes (%)	2.6	4-10
Eosinophils (%)	3.6	0.5-5
Basophils (%)	0.01	0-1
Hemoglobin (gr/dl)	13.7	11-16
Platelets (10^3/μL)	244	150-450
Erythrocyte sedimentation rate 1h	25 (the highest NL limit)	0-10
Hematocrit (%)	40.4	37-50
RDW-CV (%)	11.9	11-16
Platelet distribution width (%)	19.4	6.1-21.2
Mean platelet volume (f lit)	4.2	7-11
Sodium (meq/L)	138	135-145
Potassium (meq/L)	4.08	3.5-5.1
Lymphocytes subsets		
$CD3^+$ (%)	13	30-78
$CD4^+$ (%)	8	22-58
$CD8^+$ (%)	5	10-37
$CD19^+$ (%)	2	9-38
$CD20^+$ (%)	2	5-15
$CD56^+$ (%)	4	2-10
Serum immunoglobulins		
C3	173	83-177 mg/dl
C4	35	15-45 mg/dl
CH50	120	70-150 U
IgM (mg/dL)	90	37-286
IgG (mg/dL)	1424	639-1349
IgA (mg/dL)	310	61-356
IgE (IU/ml)	10	<188
Nitroblue tetrazolium test (%)	100(the highest NL limit)	90-100
Vaccine antibodies		
Anti-tetanus (IU/mL)	4.4	<0.1 basic immunization recommended
Anti-diphtheria (IU/mL)	<0.1	<0.1 basic immunization recommended
Infection panel		
Human immunodeficiency virus Ab	0.3(non-reactive)	<1.0 Non-Reactive >=1.0 Reactive
Immunoassays-Autoimmune diseases		
ANA	Negative	<1/80
Kidney function test		
Blood urea nitrogen (mg/dl)	37	13-43
Creatinine (mg/dl)	1.4	0.3-0.7
Hormones		
P.S.A (ELFA)	1.56	3.42
Free PSA (ELFA)	0.53	0.05-1.1

RDW-CV; Red blood cell distribution width reported statistically as coefficient of variation, CD; cluster of differentiation, Ig; immunoglobulin, Ab; antibody, μL; microliter, dL; deciliter, fL; femtoliter, pg; pictogram, IU; international unit, mg; milligram, RU; relative units, U; units, U/l; units per liter, NL; normal

There are different reports of NF-κB2 mutations related diseases. The first report of NF-κB2 mutation was a patient with common variable immunodeficiency (CVID) and adrenocorticotropic hormone (ACTH) insufficiency (DAVID-syndrome) (9, 10). Also, some patients had autoimmunity and trachyonychia (9). There is also another report of NF-κB2 mutation as the cause of CVID (11-13).

Also, nonsense mutations in NF-κB2 (in E418X and R635X) have been demonstrated to cause a combined immunodeficiency (CID) without ectodermal or endocrine manifestations in three patients, due to prolonged activation of both canonical and non-canonical pathways (14). Also, a 13-year-old girl with CVID has been reported with cytomegalovirus (CMV) pneumonia and decreased NK cell cytotoxicity with normal NK cell numbers due to heterozygous nonsense mutation in *NF-κB2* (c.2611C>T, p.Gln871*) (15). There is also a report of central diabetes insipidus in a 3 years old patient with NF-κB2 mutation who firstly presented hypogammaglobinemia and alopecia totalis at the first year of age, as well as central adrenal insufficiency at fourth year of age (16).

Another study showed that heterozygous nonsense mutation in *NF-κB2* caused by c.1831C > T was asymptomatic (17). This mutation in *NF-κB2* gene has been previously reported by Chen et al. in CVID patients [18]. They investigated NFKB2 in 33 unrelated CVID-affected patients and found c.2557C>T (p.Arg853 (∗)), in just one simplex case. There is also a report of neutrophilic dermatosis in NF-κB2 mutation (19). NF-κB1 deficiencies have vast phenotypic variations ranging from mild to severe autoinflammatory disorders (20). Altogether, these findings show that mutation in *NFKB2* gene could be involved as a genetic etiology for patients with primary immunodeficiency, especially for the patients with hypogamaglobulinemia.

In conclusion, we reported a middle age man with mild lymphopenia and no significant infection who had also hypothermia with significant chills even in the warm seasons with a mutation in NF-κB2 pathway. So, this pathway may play roles in hypothalamic temperature control. Our data show that the NF-κB2 has a critical role in development of acquired and innate immunity.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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