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LETTER TO THE EDITOR

Familial hypogammaglobulinemia with high RTE and *naïve* T lymphocytes

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Abstract

Most of primary immunodeficiencies with hypogammaglobulinemia are associated with reduced memory B cells. T cell development may be interesting as well, but increased recent thymic emigrants are rarely reported in these patients. We report the case of a family (mother and her two sons) diagnosed with common variable immunodeficiency 10 due to a mutation in the *NFKB2* gene. Laboratory findings showed that all three patients presented hypogammaglobulinemia, reduced memory B cells and elevated *naïve* T lymphocytes and recent thymic emigrants. This feature, in the absence of glucocorticoid deficiency, may suggest a primary thymic dysfunction. Interestingly, the mother presented the worst immune phenotype, as regards both antibody production and NK function, indicating that immune function may deteriorate in the course of time. We conclude that close monitoring of immune functions may widen the knowledge on the CVID10 and improve the patients' care.

Keywords Common variable immunodeficiency · NFKB2 · Recent thymic emigrants · NK degranulation · Autoimmunity

To the Editor,

Common variable immunodeficiency 10 (CVID10) is a dominant genetic disorder caused by heterozygous mutations in the *NFKB2* (nuclear factor *kappa* B subunit 2) gene. The disease is characterized by hypogammaglobulinemia with reduced memory B cells, which usually onset in the first decades of life. The clinical spectrum of the disease is remarkably broad and can include a variety of autoimmune features [1].

Low count of memory B cells and inversion of CD4/CD8 ratio can be common features in different forms of CVID, while the involvement of T cell differentiation may characterize specific disorders. Indeed, a low percentage of recent thymic emigrants (RTE) may be found in several CVID that show some degree of T cell deficiency in addition to antibody defect. However, there are scant data about high *naïve* T cells and RTE in CVID forms. Moreover, also NK activity can be affected in this pathology.

Here we report the case of a 29-year-old female diagnosed with CVID because of recurrent infections since adolescence, and her two sons, a 6-year-old boy and a 3-year-old girl, both complaining of recurrent infections.

Flow cytometric analysis of B cells of the woman revealed a low total B cell count and a very low proportion of memory B cells, both IgM memory (CD10–CD27+IgD/IgM+) and switched memory cells (CD10–CD27+IgD/IgM−). Although the two sons showed a normal count and relative number of total B cells, they showed a profound deficiency of cells with memory phenotype (Table 1).

Therefore, genetic analysis and whole exome sequencing were performed revealing in all the patients the heterozygous variant c.C2557T:p.Arg853Ter in the gene *NFKB2* (NM_001077494.2), previously associated with early-onset antibody immunodeficiency (CVID10).

Notably, despite memory B cell deficiency and low total serum IgG (Table 1), protective levels of antibodies to specific antigens were measured (tetanus toxoid and vaccine viruses) indicating some residual immunocompetence of the B cell compartment, which could account for the absence of severe recurrent infections. However, the worse laboratory parameters in the mother compared with her sons suggest that immune function may deteriorate over time. Indeed, the

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Table 1 Clinical and laboratory features of the three patients

	Mother (age-related normal range)	Son (age-related normal range)	Daughter (age-related normal range)
Clinical features			
Age (years)	29	6	3
Autoimmunity	Psoriasis	None	None
ACTH levels	Normal	Normal	Normal
Immunoglobulin levels			
IgG (mg/dL)	437 (700–1600)	304 (510–1260)	170 (300–1070)
IgA (mg/dL)	< 10 (70–400)	18 (50–230)	18 (30–150)
IgM (mg/dL)	13 (40–230)	38 (40–130)	18 (50–170)
Specific antibodies	+ Tetanus toxoid Vaccine viruses	+ Tetanus toxoid Vaccine viruses	+ Tetanus toxoid Vaccine viruses
Lymphocyte subsets			
Total lymphocytes			
Cells/mcL	1270 (1000–4000)	5870 (1500–6800)	3010 (2000–8000)
% of total leukocytes	19.9 (27.0–44.1)	52.2 (26.0–49.6)	53.5 (36.3–60.5)
T cells			
CD3+			
Cells/mcL	1037 (1000–2200)	3766 (1200–2600)	2024 (1400–3700)
% of total lymphocytes	81.7 (59.0–83.0)	64.2 (43.0–63.0)	67.3 (46.2–67.8)
CD3+CD4+			
Cells/mcL	870 (560–110)	2580 (640–1400)	1400 (650–2300)
% of CD3+	68.5 (31.0–59.0)	44.0 (26.5–41.4)	46.5 (18.3–42.7)
RTE CD45RA+CD31+			
Cells/mcL	450 (200–590)	1908 (250–900)	1011 (300–1500)
% of CD4+	51.7 (6.4–51.0)	74.0 (43.9–66.4)	72.2 (52.7–73.9)
Naïve CD45RA+CCR7+			
% of CD4+	75.9 (20.5–54.8)	91.0 (20.5–54.8)	89.9 (20.5–54.8)
Effector CD45RA+CCR7−			
% of CD4+	1.8 (1.4–17.0)	1.6 (1.4–17.0)	2.0 (1.4–17.0)
Effector memory CD45RA−CCR7−			
% of CD4+	8.4 (19.9–52.4)	3.2 (19.9–52.4)	2.8 (19.9–52.4)
Central memory CD45RA−CCR7+			
% of CD4+	13.9 (8.4–32.8)	4.2 (8.4–32.8)	5.2 (8.4–32.8)
CD3+CD8+			
Cells/mcL	118 (200–500)	1042 (250–1200)	531 (370–1300)
% of CD3+	9.3 (12.0–38.0)	17.8 (13.8–28.8)	17.6 (14.7–27.2)
Naïve CD45RA+CCR7+			
% of CD8+	38.5 (18.8–71.0)	74.7 (18.8–71.0)	74.5 (18.8–71.0)
Effector CD45RA+CCR7−			
% of CD8+	10.9 (4.5–33.7)	12.0 (4.5–33.7)	14.9 (4.5–33.7)
Effector memory CD45RA–CCR7−			
% of CD8+	33.4 (14.6–63.0)	11.0 (14.6–63.0)	9.2 (14.6–63.0)
Central memory CD45RA–CCR7+			
% of CD8+	17.3 (1.2–7.3)	2.3 (1.2–7.3)	1.4 (1.2–7.3)
B cells			
CD19+			
Cells/mcL	71 (120–440)	781 (280–790)	650 (360–1500)
% of total lymphocytes	5.6 (2.8–17.4)	13.3 (8.5–20.2)	21.6 (14.4–25.1)
RBE CD10+CD27−IgD/IgM+			
% of CD19+	20.7 (0.6–3.0)	25.8 (3.4–9.0)	30.0 (6.8–11.5)

Table 1 (continued)

	Mother (age-related normal range)	Son (age-related normal range)	Daughter (age-related normal range)
Naïve CD10–CD27−IgD/IgM+			
% of CD19+	76.6 (42.0–82.2)	69.3 (47.8–69.8)	66.9 (52.3–72.1)
IgM memory CD10–CD27+IgD/IgM+			
% of CD19+	0.4 (1.7–29.3)	3.0 (6.3–22.0)	1.8 (6.7–18.1)
Switched memory CD10–CD27+IgD/IgM−			
% of CD19+	1.3 (3.0–26.5)	0.9 (1.8–14.2)	0.5 (1.8–14.2)
NK cells			
CD3–CD16+CD56+			
Cells/mcL	149 (70–480)	1252 (100–480)	308 (130–720)
% of total lymphocytes	11.7 (6.0–27.0)	21.3 (4.0–17.0)	10.2 (4.0–17.0)
NK degranulation activity			
% CD107a+ (mean ± SD) of age-matched controls	7.3 (23.0 ± 6.5)	18.3 (16.2 ± 6.9)	17.2 (16.2 ± 6.9)

two children did not present increased frequency or severity of infections before the start of Ig replacement therapy.

Moreover, the same mutation in *NFKB2* has also been associated with hypogammaglobulinemia with Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)-like autoimmunity. Indeed, altered NFkB signaling due to genetic defects causes an impairment in thymic development and in T cell tolerance. Consequently, altered expression of AIRE (autoimmune regulator) may cause a defective removal of self-reactive cells inducing the onset of autoimmune manifestations [1], as seen in patients with CVID10. Nevertheless, no autoimmune disease was reported in the three patients apart from mild psoriasis in the mother. It is questionable if psoriasis can represent a feature of NFKB2-specific autoimmunity, maybe due to a reaction to the accumulation of unprocessed NFkB in skin cells, or just a CVID-associated autoimmune disorder favored by an imbalance in T cell development.

In addition to defective memory B cells, we reported a high percentage of RTE in all three patients. An increase of this subset of T lymphocytes is rarely reported in subjects with antibody deficiency, and for this reason, we further investigated T cell subsets. All the patients had an expanded proportion of *naïve* CD45RA+CCR7+ (Table 1).

These features are quite unusual in CVID and thus may deserve attention. Therefore, we speculate that this immunological profile, already reported in three cases by Lee et al. [2], if not specific for NFKB2 immunodeficiency may be highly supportive of this genetic defect, likely reflecting the underlying thymic dysfunction. It could also be hypothesized that increased RTE could depend on defective adrenocorticotropic hormone secretion, as autoimmune adrenal insufficiency has been associated with NFKB2 deficiency in the DAVID syndrome [3]. Notably, our three patients showed no anti-adrenal gland antibodies and normal adrenocorticotropic hormone and cortisol, thus indicating that RTE expansion was a primary immune defect and was not related to glucocorticoid deficiency. Besides, the rise in RTE and in *naïve* populations is likely due to a defective or impaired progression towards mature populations since NFkB signaling is commonly engaged in peripheral maturation and differentiation of T cells [4]. However, both activation and proliferation after phytohemmoagglutinin and anti-CD3/anti-CD28 stimulation resulted comparable between patients and control, thus confirming previous literature data [2].

Moreover, there is controversial evidence in the literature on NK function in NFKB2 deficiency [5, 6]. We measured CD107a expression on NK cells stimulated with K562 cells to assess NK degranulation in a cytometric assay. Our results revealed a decreased activity in the mother when compared with age-matched healthy controls, while the two children showed NK activity within the range of healthy pediatric controls (Table 1). These results are consistent with a possible worsening of this function during age. To date, NK activity has been reported to be lower in adults than in children, and it is likely beginning to decrease from adolescence (we knew that the case in Ref. [5] was 15 years old at the time of analysis).

Although NK degranulation test has some technical limitations and can show a slight variability also in healthy controls, our findings, according with previous reports, suggest that it could be worth evaluating NK cytotoxicity in patients with NFKB2-related CVID, especially in adulthood.

Overall, our results together with previous data from the literature may suggest that NFKB2-related hypogammaglobulinemia is an immunodeficiency with progressive deterioration of antibody production accompanied by defective development of T cell memory. Adults with NFKB2 immunodeficiency seem more likely to meet some impairment in

NK function compared with controls. Finally, NKFB2 has been associated with APECED-like autoimmunity; however, the presence of such autoimmune disorders may have biased the detection of the genetic cause in published cases. Thus, the real risk of autoimmunity will be determined only when a larger number of cases will be included in clinical databases.

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Compliance with ethical standards

Conflict of interest All the authors declare no conflicts of interest.

References

1. Chen K, Coonrod EM, Kumánovics A, Franks ZF, Durtschi JD, Margraf RL, et al. Germline mutations in NFKB2 implicate the noncanonical NF-κB pathway in the pathogenesis of common variable immunodeficiency. Am J Hum Genet. 2013. https://doi.org/10.1016/j.ajhg.2013.09.009.
2. Lee CE, Fulcher DA, Whittle B, Chand R, Fewings N, Field M, et al. Autosomal-dominant B-cell deficiency with alopecia due to a mutation in NFKB2 that results in nonprocessable p100. Blood. 2014. https://doi.org/10.1182/blood-2014-06-578542.
3. Brue T, Quentien MH, Khetchoumian K, Bensa M, Capo-Chichi JM, Delemer B, et al. Mutations in NFKB2 and potential genetic heterogeneity in patients with DAVID syndrome, having variable endocrine and immune deficiencies. BMC Med Genet. 2014. https://doi.org/10.1186/s12881-014-0139-9.
4. Oh H, Ghosh S. NF-κB: roles and regulation in different CD4(+) T-cell subsets. J Immunol Rev. 2013. https://doi.org/10.1111/imr.12033.
5. Lougaris V, Tabellini G, Vitali M, Baronio M, Patrizi O, Tampella G, et al. Defective natural killer-cell cytotoxic activity in NFKB2-mutated CVID-like disease. J Allergy Clin Immunol. 2015. https://doi.org/10.1016/j.jaci.2014.11.038.
6. Montin D, Licciardi F, Giorgio E, Ciolfi A, Pizzi S, Mussa A, et al. Functional evaluation of natural killer cell cytotoxic activity in NFKB2-mutated patients. Immunol Lett. 2018. https://doi.org/10.1016/j.imlet.2017.12.006.