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Case Report

Symptomatic hypoglycemia in a child with common variable immunodeficiency: Deficient anterior pituitary with variable immune deficiency (DAVID) syndrome

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Abstract. Deficient anterior pituitary with variable immune deficiency (DAVID) syndrome is a rare condition characterized by symptomatic ACTH deficiency and primary hypogammaglobulinemia, caused by pathogenic variants of the nuclear factor kappa-B subunit 2 (*NF-κB2*) gene. We report the case of a 9-yr-old boy diagnosed with common variable immunodeficiency at the age of 3, who is under monthly intravenous immunoglobulin. The patient was admitted twice to the pediatric emergency service at the age of 9 due to symptomatic hypoglycemic events. During the hypoglycemic crisis, serum cortisol was low (< 0.1 μg/dL), ACTH level was inappropriately low (4.4 ng/L) and the ACTH stimulation test failed to raise the blood cortisol level. Pituitary magnetic resonance imaging showed a hypoplastic pituitary. Other pituitary deficiencies, primary hyperinsulinism and other metabolic diseases were excluded. He started hydrocortisone replacement treatment while maintaining immunoglobulin substitution and he remains asymptomatic. Molecular analysis revealed the heterozygous nonsense pathogenic variant, c.2557C>T (Arg853Ter) in the *NF-κB2* gene. Thus, symptomatic hypoglycemia in a child with primary immunodeficiency should raise the suspicion of DAVID syndrome, prompting *NF-κB2* molecular analysis, to allow timely and appropriated therapy and genetic counseling.

Key words: NF-κB2 protein, common variable immunodeficiency, ACTH deficiency

Introduction

Deficient anterior pituitary with variable immune deficiency (DAVID) syndrome is a rare autosomal dominant condition characterized by both primary hypogammaglobulinemia and symptomatic ACTH deficit (1).

This disorder was first reported in 2011 in four children with a previous diagnosis of common variable immunodeficiency (CVID), which presented symptomatic hypoglycemia due to central adrenal insufficiency (1). Later, DAVID syndrome was associated with heterozygous pathogenic variants in the nuclear factor kappa-B subunit 2 (*NF-κB2*) gene (2–5). To our knowledge, there are 21 reported cases of DAVID syndrome worldwide (5).

We report the case of a 9-yr-old boy with DAVID syndrome, who presented symptomatic hypoglycemia 6 yr after the diagnosis of CVID.

Case Report

The patient was a 9-yr-old boy without family history of endocrine or immunological diseases (**Fig.**

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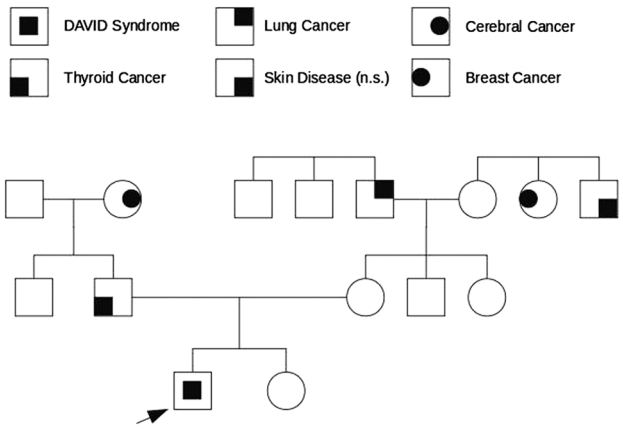

Fig. 1. Pedigree. Males are represented by squares, females by circles, the patient is indicated with an arrow. n.s., not specified.

1), who was diagnosed with CVID at the age of 3. At that time, he had one episode of infectious parotiditis followed by an exuberant thoracic varicella zoster infection two months later. He was referred to the immunodeficiency department and the laboratory evaluation showed decreased serum immunoglobulin (Ig): IgA (7 mg/dL, reference 22–159 mg/dL), IgM (23 mg/dL, reference 47–200 mg/dL) and IgG (314 mg/dL, reference 441–1,135 mg/dL); normal peripheral B-cell counts (CD19+ 18.6%); no signs of autoimmunity were found. He started treatment with intravenous immunoglobulin once a month and remained stable, without respiratory or other infections.

At the age of 9 yr, the patient had a seizure early in the morning; his parents called paramedics, who reported a capillary blood glucose level of 40 mg/dL. Intravenous dextrose was administered immediately with rapid recovery of his mental status. On admission to the pediatric emergency department (PED), his capillary blood glucose had increased to 177 mg/dL and the physical examination was unremarkable. Urine analysis revealed 4+ ketonuria; venous gasometry and the remaining laboratory evaluations were normal. Cerebral computed tomography (CT) was also normal.

Two months later, he was admitted to the PED with a second episode of symptomatic hypoglycemia (capillary blood glucose level of 24 mg/dL) accompanied by vomiting, diarrhea and extreme fatigue. The symptoms quickly reversed following administration of intravenous dextrose.

The endocrine and metabolic workup at the hypoglycemic crisis revealed low serum cortisol level (< 0.1 µg/dL, reference 6.2–19.4 µg/dL) with inappropriately low ACTH level (4.4 ng/L, reference < 63.3 ng/L). The blood cortisol level failed to rise in response to the ACTH stimulation test (maximal cortisol level of 0.3 µg/dL). Pituitary magnetic resonance imaging (MRI) described a reduced pituitary size and thin pituitary stalk (**Fig. 2**).

Hypothyroidism was excluded (free T_4 level 1.16 ng/dL, reference 0.88–1.58 ng/dL; TSH level 1.74 µUI/mL, reference 0.35–5.00 µUI/mL); IGF-1 (117 ng/mL, reference 95–460 ng/mL), IGF binding protein 3 (3.7 µg/mL, reference 2.4–8.9 µg/mL) and GH (2.72 ng/mL, reference < 3.0 ng/mL) were normal; FSH (2.05 mUI/mL, reference 1.5–12.4 mUI/mL) and LH (2.48 mUI/mL, reference 1.7–8.6 mUI/mL) levels were normal; primary hyperinsulinism was excluded (insulin 0.8 µU/mL, reference 2.6–24.9 µU/mL; C-peptide 0.29 ng/mL, reference 1.1–4.4 ng/mL).

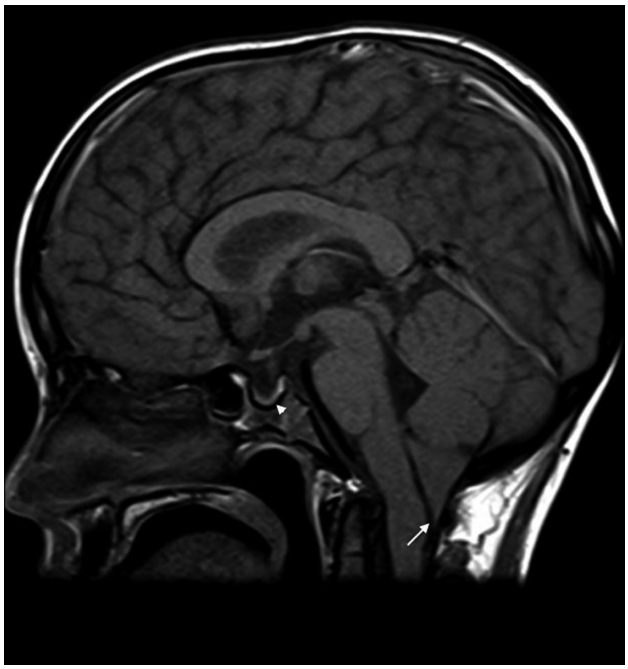

Fig. 2. A midline sagittal T1 magnetic resonance (MR) image showing an hypoplastic adenohypophysis (arrowhead). As an incidental finding, a Chiari I malformation was noted (arrow).

He started hydrocortisone replacement treatment at the dose of 7 mg/m^2/d while maintaining immunoglobulin substitution and he remains asymptomatic.

He is in a pre-pubertal stage and is growing properly in the 10th percentile, according to the CDC growth charts.

The whole exome sequencing identified a germline heterozygous nonsense pathogenic variant in the exon 22 of the *NF-κB2* gene, c.2557C>T (Arg853Ter). The exome sequencing of his parents did not identify any pathogenic variants in the *NF-κB2* gene.

Discussion

The identification of *NF-κB2* pathogenic variants as a molecular cause of DAVID syndrome was a great step in understanding this rare association of CVID with central adrenal insufficiency (2, 6).

The *NF-κB* signaling pathway is a well-known key regulator of innate and adaptive immune responses. NF-κB2 acts in the non-canonical pathway (p52/RelB dimers) of signal transduction and regulates specific aspects of B-cell maturation and T-cell differentiation (6, 7). In mouse models, deletion of *NF-κB2* causes abnormal

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germinal center B-cell formation and differentiation (8).

Chen *et al.* showed that defective processing of p100 to p52, in the presence of heterozygous *NF-κB2* pathogenic variants, results in reduced translocation of p52 to the nucleus (6).

The involvement of *NF-κB2* pathogenic variants in the pathogenesis of CVID can easily be deduced, contrary to its implication in the central adrenal insufficiency, which remains puzzling. The autoimmune etiology seems to be the most acceptable, since circulating autoantibodies against endocrine organs were found in some patients. There are also several reports of ectodermal dysplasia and other autoimmune disorders in these patients (2, 3, 6, 9). However, not all patients have detectable autoantibodies or signs of autoimmunity (4, 5).

Almost all reported patients carrying *NF-κB2* pathogenic variants have primary immune deficiency (1–5), but only 44% have ACTH deficiency (5).

Recently, Klemann *et al.* described 15 previously unreported cases of primary immunodeficiency associated with *NF-κB2* pathogenic variants. To our knowledge and according to Klemann *et al.* there are 50 reported cases of *NF-κB2* pathogenic variants worldwide and only 21 of them have DAVID syndrome (5).

The nonsense *NF-κB2* pathogenic variant identified in our patient (c.2557C>T) causes the mutation, Arg853Ter at the protein level, resulting in an abnormal protein. It is the most common pathogenic variant described in case of DAVID syndrome (2, 5, 6, 9, 10). However, there are other *NF-κB2* pathogenic variants reported in DAVID syndrome patients, including nonsense, missense and frameshift mutations in exons 22 and 23 (2–7).

Like most reported cases, in this patient as well, clinical manifestation of ACTH insufficiency was seen a few years after the diagnosis of immunodeficiency (2, 5, 6). There are, at least, two other cases of symptomatic hypoglycemia being the first presentation of DAVID syndrome (4, 7). Other concomitant endocrinopathies, like GH deficiency and hypothyroidism, have also been described (2, 4, 5, 7, 9) but those were not found in our patient.

The hypoplastic pituitary identified in our patient was also reported in other cases [2], but most patients have a normal pituitary in the MRI (5). Studies in Lym1 mouse models carrying homozygous nonsense pathogenic variants in *NF-κB2* also show normal pituitary anatomy (2). Therefore, the hypothesis that *NF-κB2* pathogenic variants affect pituitary development is not consistent.

Conclusion

In conclusion, the association of CVID and ACTH deficiency is a rare condition. Thus, the presence of symptomatic hypoglycemia in a child with previously or later diagnosed primary immunodeficiency should raise the suspicion of DAVID syndrome. *NF-κB2* genetic analysis should be carried out in order to establish the diagnosis. This will allow timely and appropriated therapy as well as genetic counseling and avoid potentially fatal consequences.

References

1. Quentien MH, Delemer B, Papadimitriou DT, Souchon PF, Jaussaud R, Pagnier A, *et al*. Deficit in anterior pituitary function and variable immune deficiency (DAVID) in children presenting with adrenocorticotropin deficiency and severe infections. J Clin Endocrinol Metab 2012;97: E121–8. [Medline] [CrossRef]
2. 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;15: 139. [Medline] [CrossRef]
3. Shi C, Wang F, Tong A, Zhang XQ, Song HM, Liu ZY, *et al*. NFKB2 mutation in common variable immunodeficiency and isolated adrenocorticotropic hormone deficiency: A case report and review of literature. Medicine (Baltimore) 2016;95: e5081. [Medline] [CrossRef]
4. Lal RA, Bachrach LK, Hoffman AR, Inlora J, Rego S, Snyder MP, *et al*. A case report of hypoglycemia and hypogammaglobulinemia: DAVID syndrome in a patient with a novel NFKB2 mutation. J Clin Endocrinol Metab 2017;102: 2127–30. [Medline] [CrossRef]
5. Klemann C, Camacho-Ordonez N, Yang L, Eskandarian Z, Rojas-Restrepo JL, Frede N, *et al*. Clinical and immunological phenotype of patients with primary immunodeficiency due to damaging mutations in *NFKB2*. Front Immunol 2019;10: 297. [Medline] [CrossRef]
6. 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;93: 812–24. [Medline] [CrossRef]
7. Kuehn HS, Niemela JE, Sreedhara K, Stoddard JL, Grossman J, Wysocki CA, *et al*. Novel nonsense gain-of-function *NFKB2* mutations associated with a combined immunodeficiency phenotype. Blood 2017;130: 1553–64. [Medline] [CrossRef]
8. Carragher D, Johal R, Button A, White A, Eliopoulos A, Jenkinson E, *et al*. A stroma-derived defect in NF-kappaB2-/- mice causes impaired lymph node development and lymphocyte recruitment. J Immunol 2004;173: 2271–9. [Medline] [CrossRef]
9. 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;135: 1641–3. [Medline] [CrossRef]
10. Nagai M, Imai Y, Yamanishi K. Psoriasiform dermatitis associated with common variable immunodeficiency 10 due to an Arg853* mutation in the NFKB2 gene. J Dermatol 2019;46: e24–6. [Medline] [CrossRef]

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