GOLIATH, a variant of DAVID syndrome?

Caroline Hasselmann[1,2], Mark Samuels[2,3], Guy Van Vliet[2,4]

[1]CHU Tours, France, [2]Endocrinology Service and Research Center, CHU Ste-Justine, Montreal, Departments of Medicine[3] and Pediatrics[4], Université de Montréal, Montréal H3T1C5, Québec, Canada

Background

DAVID syndrome[1] (Deficit in Anterior Pituitary Function and Variable Immune Deficiency) is a rare condition combining anterior pituitary deficiencies and common variable immune deficiency (CVID). It can be caused by *NFKB2* mutations[2,3].

All patients described so far have an orthotopic posterior pituitary (PP) and most only ACTH deficiency.

Objectives

To describe a girl with common variable immunodeficiency (CVID), ectopic PP (EPP) and multiple pituitary hormone deficiencies, and to demonstrate genetic heterogeneity of DAVID syndrome.

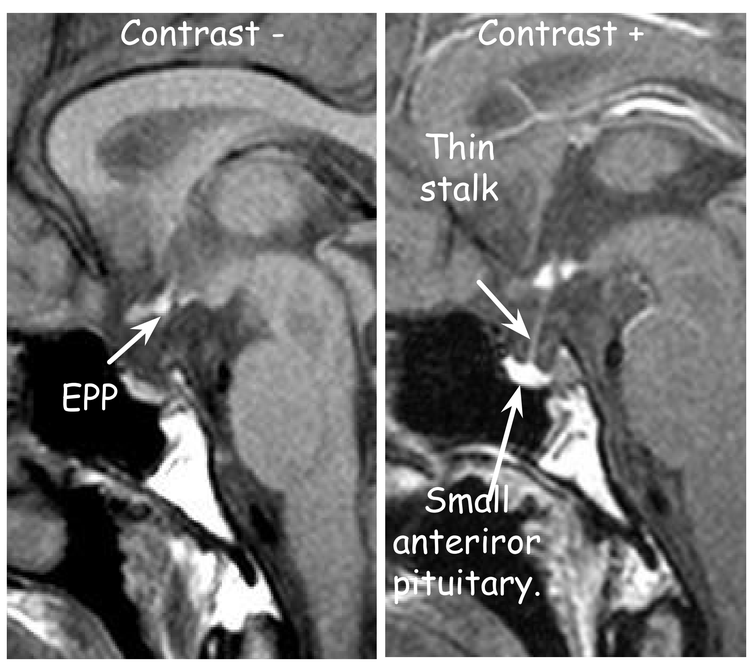

Figure 1: Magnetic resonance imaging (sagittal T1 images)

Case Presentation

- Clinical presentation at age 17 y:
  - Unexplained intellectual disability
  - Glomerulonephritis → Dx: CVID[4].
  - Endo consult for 1[ary] amenorrhea
  - Tanner B2P1
  - Height 165 cm (target 165-182)
- Imaging:
  - US: uterus small, ovaries normal.
  - Hand X-ray: epiphyses fused.
  - MRI: EPP, thin stalk and small anterior pituitary (Fig 1).
- Baseline labs:
  - Cortisol: < 11.1 nmol/L
  - DHEAS: < 0.5 µmol/L
  - ACTH: 0.8 pmol/L
  - fT_4: 9.2 pmol/L
  - IGF-I: < 3.2 pmol/L
- Pituitary function testing:
  - *LHRH*:
    - LH: 3.2 to 28.8 mUI/L
    - FSH: 5.3 to 13.5 mUI/L
  - *TRH*:
    - TSH: 7.2 to 31.2 mU/L at 30 min. and still high at 90 min. (15.5 mU/L)
    - PRL: 10.4 to 45.2 µg/L at 10 min.
    - peak GH after arginine: 0.02 µg/L.
- Treatment : cortisol & estrogens
- Evolution: between 17 and 20 y, BMI increased from 24 to 31 kg/m^2.
- Genetic investigation:
  - *NFKB2* (Fig. 2): normal.
  - Exome sequencing: potentially disease-causing variant in one of the genes of the NFKB pathway (Fig. 3).

Discussion

In addition to the cardinal features of DAVID syndrome (CVID and severe ACTH deficiency), our patient has severe GHD and hypothalamic hypogonadism.
In contrast to all patients with DAVID syndrome reported so far, she has an EPP, suggesting developmental, rather than autoimmune, endocrine deficits.

Conclusions

DAVID syndrome is clinically and genetically heterogeneous. While a search for an alternative genetic etiology is underway, we suggest describing our patient's condition as GOLIATH syndrome: **G**HD, **O**besity, **L**ow IQ, **I**gG and **A**CTH deficiency, **T**riad and **H**ypogonadism.

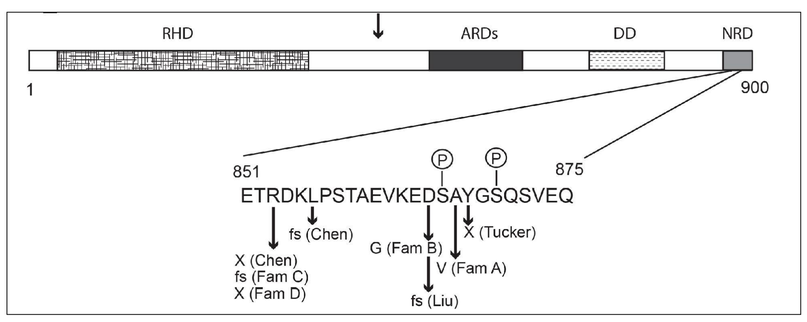

Figure 2: known mutations in NFKB2 in patients with DAVID syndrome including our own unpublished data on families A, B, C and D from ref. 1 and in the mouse Lym1 mutant (Tucker, ref .5)

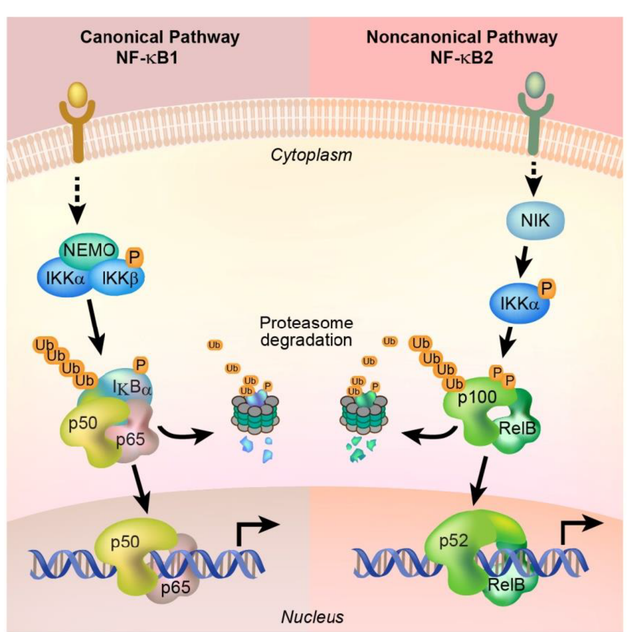

Figure 3: NFKB pathway (from Chen et al. AJHG 2013)

References

1. Quentien et al. JCEM 97:E121, 2012
2. Chen et al. AJHG 93:13, 2013
3. Liu et al, J Clin Immunol 34: 686, 2014
4. Benoit et al. Pediatr Nephrol 24:601, 2009
5. Tucker et al, J Immunol 179:7914, 2007

We call on clinicians to communicate with us (guy.van.vliet@umontreal.ca) if they have a patient with a similar phenotype: should a variant in the same gene be found, it would greatly strengthen the argument about its disease-causing role.