P1-100
Session: Pituitary, neuroendocrinology and puberty

RNPC3 mutations associate prolactin deficiency and ovarian insufficiency: expanding the phenotype beyond isolated growth hormone deficiency type V (MIM#618160)

The authors have nothing to disclose

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Introduction:

- The first three children reported to have biallelic mutations in *RNPC3* presented with growth hormone (GH) deficiency and pituitary hypoplasia (MIM#618160). *RNPC3* encodes a 65-kDa protein that is a structural component of the U11/U12 small nuclear ribonucleoprotein of the minor spliceosome. Mutations in *RNPC3* lead to structural destabilization of the 65-kDa protein, impaired binding of U12 snRNA and global defects in splicing of U12-type introns.
- The underlying mechanism causing GH deficiency (GHD) in these patients is not fully understood. Moreover, whether the association of further hormonal deficiencies occurs throughout lifespan is unknown.

Objective:

We aimed to analyze the evolving hormonal phenotype throughout childhood and adolescence in the first three patients identified with *RNPC3* mutations.

Clinical cases:

We present 3 sisters, compound heterozygous for mutations in *RNPC3* (c.1504C>T / c.1320C>A), born full term with normal length and weight, to non consanguineous parents (target height: 155.6 ± 5 cm) that are heterozygous carriers of the mutations. The patients developed severe postnatal growth failure and typical phenotypic features of GHD. Clinical follow-up and GH replacement of the three sisters started at age 15.5 (**patient 1**), 8.1 (**patient 2**) and 6.0 years (**patient 3**), respectively, resulting in dramatic catch-up growth in all three siblings with their height reaching their target range, as previously reported (*ESPE 2018, P1-P145*).

PUBERTAL DEVELOPMENT

- **Patient-1** was **Tanner stage I** at diagnosis (age **15.5 years**), with baseline **FSH: 30.3 mU/ml** and **LH: 6.7 mU/ml peaking after LHRH stimulation** at **40.1 and 35.5 mU/ml**, respectively, and concomitant **low serum estradiol levels** [7.4 pg/ml]. Three months after rhGH treatment was started, **Tanner stage II spontaneously developed, progressing to Tanner stage IV** after 12 months and presenting a **spontaneous 4-day menarche** after 16 months on therapy.

No further menstrual cycles occurred, with low serum estradiol levels persisting and normal to high FSH and LH levels both at baseline and after LHRH stimulation, thus requiring **hormone replacement**.

- **Patient-2 spontaneously started puberty** (Tanner stage II) at age **11.6 years**, **progressing to Tanner stage IV at age 13** years, but remaining **without menarche up to age 15.7** years, with baseline **estradiol 9.8 pg/ml, FSH 44.2 and LH 12 mU/ml**, **peaking after LHRH stimulation** to **63.1 and 49.5 mU/ml**, respectively; also requiring hormone replacement.

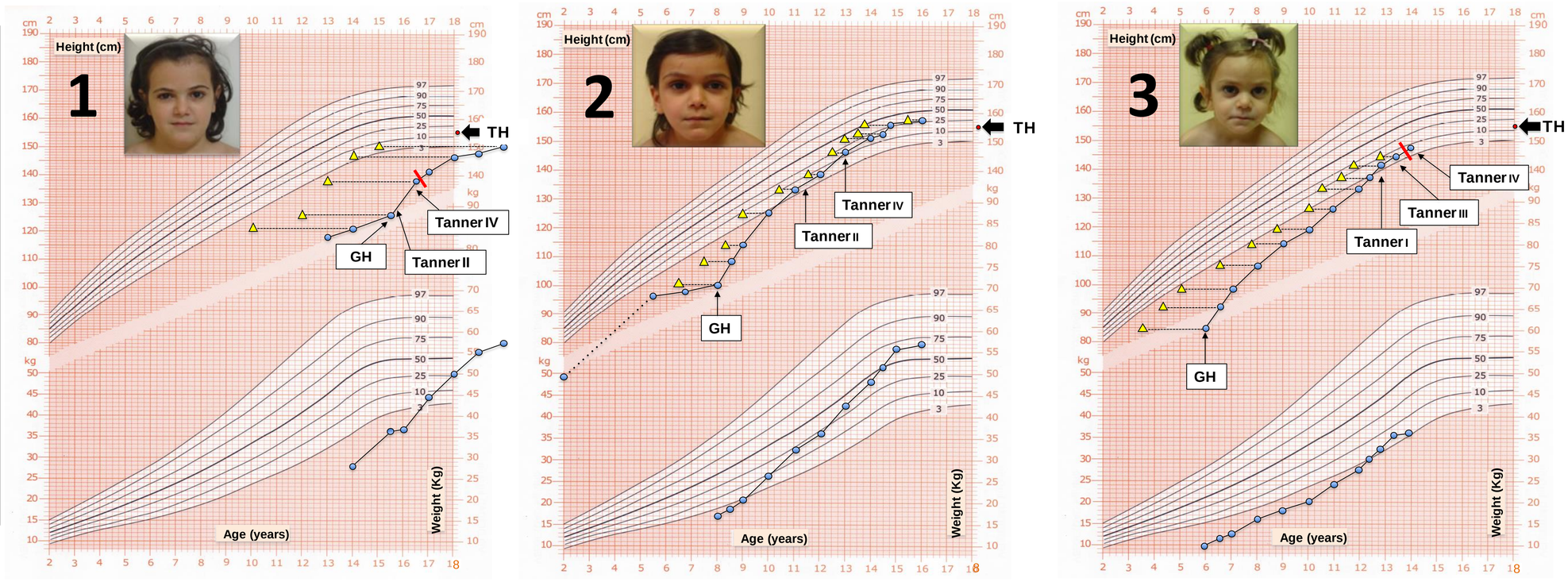
- **Patient-3** started **spontaneous pubertal development** at age 13.0 years, progressing to Tanner stage III in the following 6 months and to Tanner stage IV in 12 month time, with **a single spontaneous menstrual cycle** at age 13 years and 10 months.
- Normal size ovaries but **sparse or absent follicles** were found in the three siblings by ultrasonography.

• **Figure: Patients' growth charts up to their last visit.**

-**Pubertal developmental progression** is shown (Tanner stages) and spontaneous menarche is represented as a red line (\) in patients 1 and 3.

- Yellow triangles represent **bone age** (G&P) at the time of each height measurement.

Abbreviations:
- **GH:** Start on **r**ecombinant human GH treatment.
- **TH**: Target height.



- **Patient 1** showed slightly decreased serum **prolactin** levels at diagnosis [0.78 ng/ml (NV: 1.6-25)], with normal levels in **Patient 2** (2.12 ng/ml) and **Patient 3** (1.83 ng/ml). In contrast, when these patients reached ages of 23, 15.7 and 13.7 years, respectively, in all three serum prolactin was **undetectable** in three separate **baseline** determinations, as well **as after TRH stimulation**.
- The thyrotrophic and corticotrophic axes have shown no impairment during the follow-up to date.

Conclusion:

- Patients with ***RNPC3* mutations**, initially presenting as isolated **GH deficiency**, can develop **additional pituitary (prolactin) or peripheral (estradiol) hormone deficiencies** during their lifespan and should be closely followed.