REVERSIBLE GROWTH HORMONE EXCESS (GHE) IN TWO GIRLS WITH NEUROFIBROMATOSIS TYPE 1 (NF-1) AND OPTIC PATHWAY GLIOMA (OPG)

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BACKGROUND:

- Twelve cases of NF-1 children with OPG and GHE are reported to-date.
- So far, to our knowledge, no data exist on the longitudinal course of NF-1 children with OPG and GHE.
- The aetiology of GHE is unknown.
- Our aim is to increase awareness of GHE in NF-1 children with OPG and help its management.

CASES PRESENTATION:

We describe two NF-1 girls with OPG and reversible GHE. After completing chemotherapy, the diagnosis of GHE was established from auxological data, high IGF-1 and lack of GH suppression during an oral glucose tolerance test (OGTT).

Case1: A tall, obese and pre-pubertal 6.9 yrs girl with NF1 and treated OPG was found to have GHE. She started somatostatin analogue (SSa) and her growth decelerated and IGF1 levels normalised. At 7.8 yrs she developed central precocious puberty (CPP), which was suppressed with GnRHa. At 10.2 yrs she had acute pancreatitis and SSa was stopped. Off SSa, IGF1, GH profile and growth velocity remained normal. GnRHa was stopped at 13.5 yrs and menarche occurred at 14.3 yrs. Final height was -0.6 SDS, BMI +1.8 SDS. She developed type 2 diabetes at 15.5 yrs. IGF1 remains normal 8.2 yrs after stopping SSa.

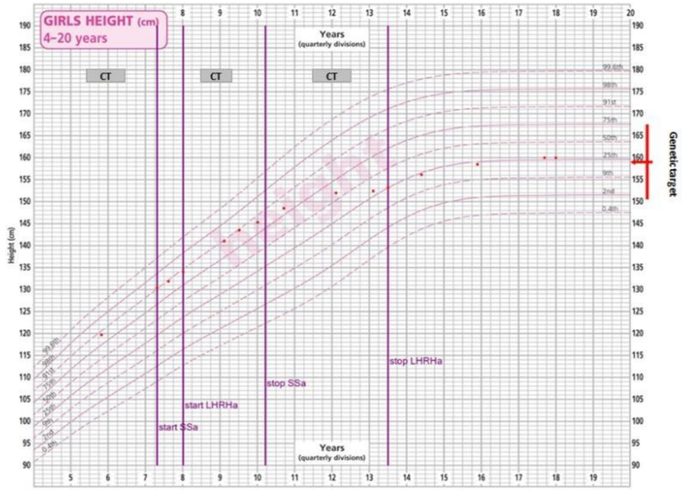

Fig 1: Case 1: Height chart and timing of chemotherapy (CT horizontal bars), SSa and LHRHa tratments (vertical lines)

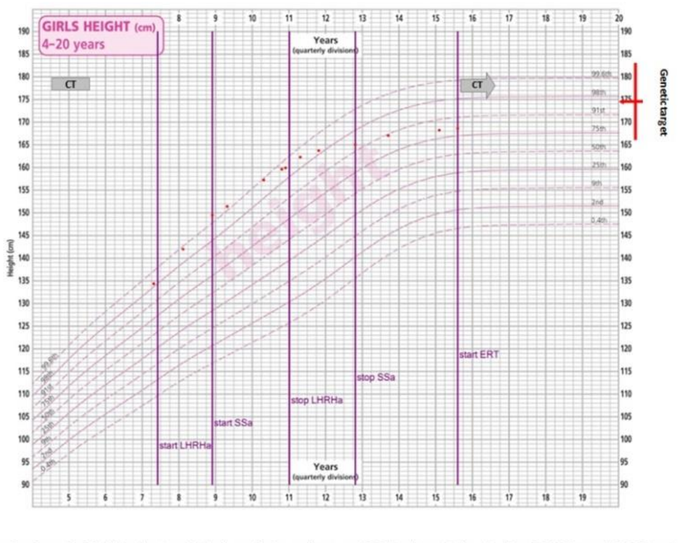

Fig 2: Case 2: Height chart and timing of chemotherapy (CT, horizontal bars), SSa, LHRHa and ERT treatments (vertical lines). The arrow bar represents an ongoing CT on last follow up.

Case2: An obese, tall 7.4 yrs girl with NF1 and OPG, treated for CPP with GnRHa after completing chemotherapy, continued to grow at a faster rate despite clinical and biochemical pubertal suppression. IGF1 was high and GHE was proven by lack of GH suppression during an OGTT. She started SSa at 8.9 yrs and her growth rate and IGF1 levels normalised. Because of the clinical history of case 1, at 12.8 yrs SSa was stopped in case 2 and GHE reassessed. IGF1 remained normal with GH suppression on OGTT at 2.8 yrs follow-up. At 11 yrs GnRHa was stopped but subsequently she developed hypogonadotropic hypogonadism and started on HRT. She remained obese (BMI 2.6 SDS), final height +0.9 SDS.

DISCUSSION:

GHE is rare in childhood but may be more frequent in NF1 patients with OPG. In these patients, who are already at risk of developing tumors, an endogenous GHE might increase their oncologic risk and induce existing tumor growth. In pre-pubertal or pubertal NF1 children with OPG whose puberty is biochemically and clinically suppressed with GnRHa therapy, persistent high levels of IGF-1, tall stature and growth acceleration should trigger further investigations to rule out GHE. The diagnosis of GHE may be challenging considering the lack of established biochemical diagnostic criteria in childhood. Only a careful interpretation of clinical and biochemical data can successfully lead to an appropriate diagnosis of GHE allowing SSa treatment to be considered. Our cases show that the GHE, that occurs in NF-1 children with OPG after completion of oncological treatment, can be reversible. Therefore if GHE resolution is confirmed, only short term therapy with SSa may be needed, reducing patient's discomfort, cost and potential side effects. Our two cases are the first NF-1 patient with OPG and GHE reported in the literature with a normal GH-IGF1 axis respectively 8.2 and 2.8 years (mean 5.5) after stopping SSa. The pathogenesis of GHE in NF-1 patients with OPG is still unclear. As the regulation of GH secretion normally depends on the interaction between the stimulatory hypothalamic GHRH and the inhibitory somatostatin, it has been speculated that the GHE could derive from a hypothalamic dysfunction due to a "functional geographic" effect of the OPG on the hypothalamus-pituitary axis signal pathway. Supporting this hypothesis of a functional "geographical" effect of OPG both our patients developed CPP, hyperphagia and obesity, all manifestations of hypothalamus-pituitary axis signal pathway dysfunction.

CONCLUSION:

- Due to the potential increased oncologic risk, every effort should be made to identify and consider treatment in NF1 children.
- GHE that occurs in NF-1 children with OPG after the end of oncological treatment can be reversible and only short term therapy with SSa might be needed.
- The aetiology remains unknown but its reversible course, unrelated to the cancer treatment, supports the hypothesis of a hypothalamic dysfunction.

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