APMB - Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Medico Biologiche
Vol. 112(1) 2024

ISSN 1828-6550

DOI: 10.13129 / 1828-6550 / APMB.112.1. 2024.CCS2

Clinical case Seminar **CCS 2 (1-5)**

The challenge of pituitary hyperplasia differential diagnosis in a young girl with growth arrest.

Aurora Lanzafame, Tiziana Abbate, Giuseppina Zirilli, Flavia Caime, Domenico Corica, Malgorzata Wasniewska.

Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy.

Abstract

Growth arrest is an alarming condition which requires precise and tempestive investigations in order to provide accurate diagnosis. Long-standing primary hypothyroidism (PHT) may rarely occur as a growth arrest as the only clinical sign at onset in children. The most common cause of PHT in children and adolescents is represented by Hashimoto's thyroiditis (HT), an autoimmune disease which frequently presents clinically with goitre. Rarely, HT may present as an atrophic variant without goitre, which may delay the diagnosis of PHT. Long-standing PHT is an unusual cause of pituitary hyperplasia (PH) and it has to be differentiated from severe conditions, including neoplasms. Loss of thyroxine feedback determines overproduction of thyrotropin releasing hormone, thyrotropin (TSH)-releasing cells hyperplasia and a consequent pituitary enlargement. Levothyroxine replacement therapy usually determines regression of PH.
This report describes a case of an 11-year-old girl suffering from PHT and secondary PH due to autoimmune atrophic thyroiditis whose only onset symptom was growth arrest.
Thyroid hormone evaluation should be included in the first step of evaluations in patients with growth arrest even in the absence of clear clinical signs suggestive of thyroid disfunction. In patients with pituitary enlargement, thyroid function tests are important to recognize PH secondary to PHT and to avoid unnecessary surgery.

Keywords: pituitary hyperplasia, primary hypothyroidism, growth arrest, autoimmune thyroiditis

Introducing Member: Malgorzata Wasniewska

Corresponding Author: Aurora Lanzafame - auroralanzafamemd@gmail.com

Introduction

Autoimmune thyroiditis (AIT) is the most common cause of acquired primary hypothyroidism (PHT) in non-iodine deficient areas. The most frequent clinical manifestations of AIT include goiter, fatigue, weight gain, constipation, cold intolerance, menstrual disturbances, headache and growth retardation (1). Delayed or missed diagnosis of PHT can lead to complications such as growth arrest or pubertal disorders. The absence of goiter, typical of atrophic variant of AIT, is one of the main causes responsible for the diagnostic delay of PHT. Long-standing PHT could be a rare cause of pituitary hyperplasia (PH) in children (2). PH differential diagnosis includes several conditions which can be hard to distinguish radiologically, especially adenomas and physiological hypertrophy (3), requiring a multidisciplinary approach. Pituitary enlargement in PHT is usually related to thyrotropin (TSH)-releasing cells hyperplasia caused by overproduction of thyrotropin releasing hormone (TRH) due to loss of thyroxine feedback. In these cases, levothyroxine replacement therapy has been shown to usually determine regression of the PH (2).

We report the case of an 11-years-old girl suffering from PHT and secondary PH due to autoimmune atrophic thyroiditis whose only onset symptom was growth arrest.

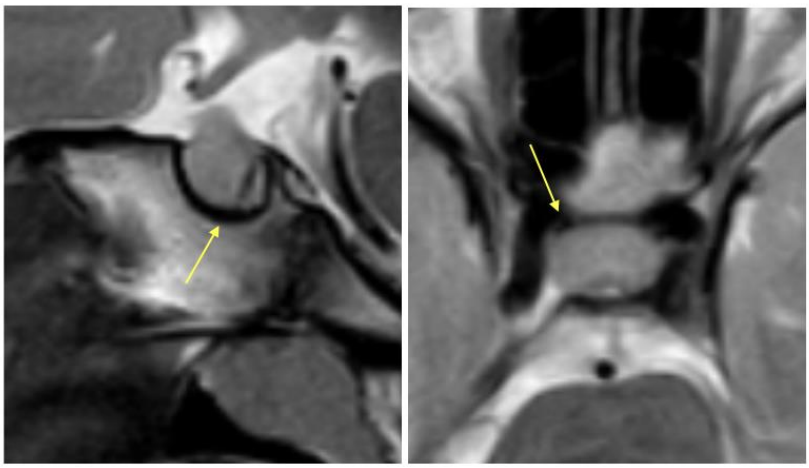
Case Report

An 11-years-old girl referred to Outpatient Clinic of Pediatric Endocrinology because of statural growth arrest over the last year. Her familiar and personal medical history could not be studied in detail since the patient had been adopted when eight years old. Growth velocity of the last year was 0.9 cm and her stature declined from the -1.50 SD to -2.32 SD, while her BMI increased from 0.47 SD to 1.15 SD according to WHO growth charts (4). Bone age and chronological age agreed.

At the first evaluation, on physical examination she was pre-pubertal and thyroid gland was not palpable; neurological examination was normal. She did not complain of tiredness, headache, nausea or any other symptoms. School performance was constantly satisfied over the last years, according to parents' opinion.

Concurrently with the carrying out of the biochemical investigations, brain MRI was urgently performed to exclude an intracranial organic lesion as the cause of growth arrest. MRI showed a symmetrical enlargement of pituitary gland (pituitary volume = 648.9 mm^3). Particularly, an expansion of the pars tuberalis was detected extending into the suprasellar cistern with a mild compression of the optic chiasm. The pituitary stalk and the posterior pituitary were dislocated. After Gadolinium-DTPA administration, the gland homogeneously enhanced.

Fig. 1 MRI sagittal and coronal planes



Thyroid function tests documented markedly elevated TSH (319 µUI/ml, normal range 0.27-4.2 µUI/ml), very low free thyroxine, FT4 (2.79 pmol/L, normal range 12-22 pmol/L), positive antibodies to thyroglobulin and thyroid peroxidase, suggesting AIT. Thyroid ultrasonic evaluation revealed diffusely hypoechogenic, coarse and heterogeneous parenchymal echotexture, increased parenchymal vascularization, in absence of thyroid enlargement, leading to atrophic autoimmune thyroiditis (AAT) diagnosis. Other basal hormonal evaluations (Tab. 1) demonstrated slight hyperprolactinemia and low concentrations of cortisol and insulin-like growth factor-1 (IGF-1); gonadotropins and estradiol were in pre-pubertal range. Chronic systemic diseases and celiac

diseases were excluded. Levothyroxine treatment (2 µg/kg/day) was promptly started.

Table 1 Main biochemical findings

Analyte	Value at diagnosis	Six months-follow up	Normal Range
TSH	319 µUI/ml	0.239µUI/ml	0.27-4.2
FT4	2.79 pmol/L	18.7pmol/L	12-22
AbTPO	4580UI/mL	1755 UI/mL	<34.00
AbTG	289 UI/mL	291.00 UI/mL	<115.00
PRL	497 µ[IU]/ml	88.6 µ[IU]/ml	102-496
IGF-1	88,5 ng/ml	182.8 ng/ml	118-413
Cortisol	5,3 µg/dl	11.8 µg/dl	5-25
FSH	2,15 mIU/ml	4.01 mIU/ml	<11.1*
LH	<0,3 mIU/ml	0.88 mIU/ml	<11.9*
Estradiol	<5 pg/ml	42.3 pg/ml	

TSH= thyroid-stimulating hormone, FT4= free thyroxine, AbTPO= thyroid peroxidase antibodies, AbTG= thyroglobulin antibodies, PRL= prolactin, IGF-1= insulin-like growth factor-1, FSH= follicle-stimulating hormone, LH= luteinizing hormone. *Normal Range refers to pre-pubertal age

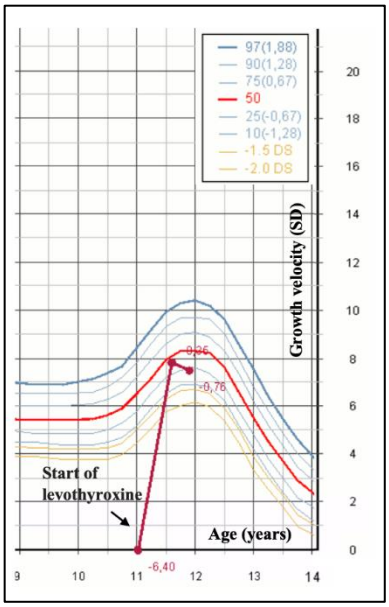
Once thyroid functionality was normalized, hypothalamic-pituitary function was thoroughly investigated. Specifically, sub-normal growth hormone (GH) secretion was revealed both at arginine and glucagon stimulating tests (GH peak was 6 ng/ml and 7 ng/ml, respectively), while prolactin (PRL) serial sampling appeared normal.

According to clinical, biochemical and radiological findings, long-standing PHT caused by AAT, leading to secondary PH, was identified as the cause of growth arrest.

Six months after the beginning of levothyroxine, an increase of growth velocity (4.4 cm, 0.42 SD), the onset of puberty (Tanner stage B2), a normalization of thyroid and pituitary function and of GH secretion at clonidine stimulation test were demonstrated.

PH regression was also documented by MRI with a decrease of pituitary volume (218.4 mm3) within the normal range for age and sex.

Fig. 2 Improvement in growth velocity after hormonal replacement therapy start



Discussion

AIT is a common etiology of acquired PHT in children and adolescents, that most frequently occurs with euthyroidism or subclinical hypothyroidism (5) (6) (7).In our patient, AIT determined a severe hypothyroidism that clinically appears only with growth arrest. AAT variant at onset of AIT is extremely rare in childhood (8). Clinically, AAT is characterized by the absence of goiter that may delay the diagnosis, leading to severe consequences of long-standing PHT including PH and growth impairment.

The prevalence of PH in PHT cases varies widely according to data available in the literature (9) and it seems to be directly related to TSH levels in terms of adenohypophysis volume (9) (10). Hormonal replacement therapy with levothyroxine leads to PH regression up to about 85% of cases (10).

The mechanisms involved in growth impairment related to long-standing PHT include the loss of thyroxine stimulating action on GH synthesis, and mechanical factors including pituitary stalk and infundibulum compression resulting in the crushing of somatotroph cells by hyperplastic thyrotrophs and lactotrophs.

Furthermore, another pathophysiological mechanism that has been suggested to be related to these findings is TRH-induced transdifferentiation of somatotroph to thyrotroph cells (11). This hypothesis is supported by the common origin of the somatotroph and thyrotroph pituitary mammals cells in ontogeny (12) and the detection of TRH and endogenous TRH receptors (TRHR) in both thyrotrophic and somatotrophic pituitary cells (13) (14). Bi-hormonal cells, expressing both GH and TSH due to the transdifferentiation, have been detected in adenohypophysial biopsies from humans with long-standing PHT (11). The transdifferentiation process is reversible, as seems to be confirmed by the resumption of statural growth and normalization of GH secretion in our patient.

As regards PH diagnostic work-up, the lack of specific radiological criteria among with the existence of physiological hypertrophic phases during pituitary maturation process remarkably complicate differential diagnosis. More specifically, pituitary gland volume normally increases at birth and during puberty (15) (16). Pathological conditions causing sellar mass include neoplasms, non-neoplastic cystic lesions, inflammatory and infectious lesions, aneurysms and pituitary haematomas (17). Pathognomonic radiological findings (such as suprasellar or infrasellar extension, T1-T2 weighed signal variations) in combination with age, clinical and biochemical findings help to correctly identify specific aetiology (17).

In conclusion, thyroid disfunction should always be considered when approaching patients with growth arrest even in the absence of clear clinical signs suggestive of thyroid disfunction.

The combination of growth monitoring, thorough physical examination and hormonal evaluation, including thyroid function tests, must be performed in order to correctly direct the differential diagnosis of PH and avoid unnecessary surgery (3).

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

References

1. de Vries, L., Bulvik, S., Phillip, M. (2009). Chronic autoimmune thyroiditis in children and adolescents: at presentation and during long-term follow-up. Arch Dis Child, 94(1), 33-7. doi: 10.1136/adc.2007.134841.
2. Cao, J., Lei, T., Chen, F., Zhang, C., Ma, C., Huang, H. (2018) Primary hypothyroidism in a child leads to pituitary hyperplasia: A case report and literature review. Medicine (Baltimore). 97(42), e12703. doi: 10.1097/MD.0000000000012703.
3. Sapkota, S., Karn, M., Sapkota, S. (2021). Pituitary hyperplasia in childhood primary hypothyroidism: a review. Childs Nerv Syst. 37(3), 749-762. doi: 10.1007/s00381-020-05014-6.
4. de Onis, M., Onyango, A.W., Borghi, E., Siyam, A., Nishida, C., Siekmann, J. (2007) Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 85(9), 660-7. doi: 10.2471/blt.07.043497.
5. Crisafulli, G., Aversa, T., Zirilli, G., Pajno, G.B., Corica, D., De Luca, F. et al. (2019) Subclinical Hypothyroidism in Children: When a Replacement Hormonal Treatment Might Be Advisable. Front Endocrinol (Lausanne). 10, 109. doi: 10.3389/fendo.2019.00109.
6. De Luca, F., Santucci, S., Corica, D., Pitrolo, E., Romeo, M., Aversa, T. (2013) Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. Ital J Pediatr. 39, 8. doi: 10.1186/1824-7288-39-8.
7. Wasniewska, M., Corrias, A., Salerno, M., Mussa, A., Capalbo, D., Messina, M.F., et al. (2012). Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. Horm Res Paediatr. 78, 232-236. doi: 10.1159/000343815.
8. Matsuura, N., Konishi, J., Yuri, K., Harada, S., Fujieda, K., Nohara, Y., Mikami, Y., Kasagi, K., Iida, Y., Hosoda, A., et al. (1990). Comparison of atrophic and goitrous auto-immune thyroiditis in children: clinical, laboratory and TSH-receptor antibody studies. European Journal of Pediatrics. 149(8), 529-533. doi: 10.1007/BF01957685.
9. Beck-Peccoz, P., Brucker-Davis, F., Persani, L., Smallridge, R.C., Weintraub, B.D. (1996). Thyrotropin-secreting pituitary tumors. Endocrine Rev. 17, 610-638. doi 10.1210/edrv-17-6-610.
10. Khawaja, N.M., Taher, B.M., Barham, M.E., Naser, A.A., Hadidy, A.M., Ahmad, A.T., et al. (2006). Pituitary enlargement in patients with primary hypothyroidism. Endocr Pract.12, 29-34. doi: 10.4158/EP.12.1.29.
11. Vidal, S., Horvath, E., Kovacs, K., Cohen, S.M., Lloyd, R.V., Scheithauer, B.W. (2000). Transdifferentiation of somatotrophs to thyrotrophs in the pituitary of patients with protracted primary hypothyroidism. Virchows Arch. 436(1), 43-51. doi: 10.1007/pl0000819.
12. Radiana, S., Coculescua, M., Morriss, J.F. (2003). Somatotroph to thyrotroph cell trans differentiation during experimental hypothyroidism- a light and electron-microscopy study. J Cell Mol Med. 7, 297-306. doi:10.1111/j.1582-4934.2003.tb00230.x.
13. Kim, K., Arai, K., Sanno, N., Teramoto, A., Shibasaki, T. (2001). The expression of thyrotrophin-releasing hormone receptor 1 messenger ribonucleic acid in human pituitary adenomas. Clin Endocrinol (Oxf). 54, 309-16. doi: 10.1046/j.1365-2265.2001.01237.x.
14. Bruhn, T.O., Rondeel, J.M., Bolduc, T.G., Jackson, I.M. (1994). Thyrotropin-releasing hormone (TRH) gene expression in the anterior pituitary. I. Presence of pro-TRH messenger ribonucleic acid and pro-TRH-derived peptide in a subpopulation of somatotrophs. Endocrinology. 134(2), 815-820 doi: 10.1210/endo.134.2.8299576.
15. Cox, T.D., Estler, A.D. (1991) Normal pituitary gland: changes in shape, size and signal intensity during the first year of life at MR imaging. Radiology. 179, 721-724. doi: 10.1148/radiology.179.3.2027981.
16. Elster, A.D., Chen, M.Y.M., Williams, D.W. III, Key, L.L. (1990). Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. Radiology. 174, 681-685. doi: 10.1148/radiology.174.3.2305049.
17. Connor, S.E., Penney, C.C. (2003). MRI in the differential diagnosis of a sellar mass. Clin Radiol. 58(1), 20-31. doi: 10.1053/crad.2002.1119.

Communicated April 16, 2024, received May 3, 2024, revised June 4,2024, published on line July 1, 2024