CLINICAL CASE

LONG-TERM CONSEQUENCES OF PARTIALLY TREATED COMBINED PITUITARY HORMONE DEFICIENCY

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ABSTRACT

Hypopituitarism refers to the insufficient secretion of one or more pituitary hormones, while the clinical elements are different based on the etiology, timing of onset, cluster of endocrine dysfunctions, (related or unrelated) co-morbidities as well as applied therapies over the time. We aim to introduce a case of early-onset hypopituitarism with combined deficiency of growth hormone, gonadotropins and prolactin that lead to early diagnosis of osteoporosis and dyslipidemia as long-term complications after she remained without substitution therapy for a long period of time. Of note, the subject associated a non-functioning pituitary micro-tumor that in pediatric population seems to have a different significance than seen in adults (approximately one out of ten adults might have the condition with an accidental detection). In this case, most probably the genetic form of hypopituitarism might be related to the early presence of this lesion. The diagnosis of hypopituitarism should be promptly followed by hormonal substitution of the associated deficiencies, especially if the condition is discovered early in life. This approach is effective for an adequate development and also for avoiding long term complications that can appear later in life such as high risk of low bone mineral density and cardiovascular elements.

KEYWORDS: *hypopituitarism, pituitary gland, growth hormone, gonadotropins, prolactin, osteoporosis, dyslipidemia*

INTRODUCTION

Hypopituitarism refers to the insufficient secretion of one or more pituitary hormones, while the clinical manifestations of the anterior hypopituitarism particularly manifests as growth hormone (GH) deficiency, central hypogonadism and hypothyroidism, secondary adrenal insufficiency and even prolactin deficiency in certain population subgroups [1-3]. The clinical elements are different based on the etiology, timing of onset, cluster of endocrine dysfunctions and (related or unrelated) co-morbidities [3,4]. The underlying causes vary from congenital and genetic defects (more common in the childhood-onset type) to acquired lesions represented by trauma, tumors, vascular issues, inflammatory lesions, infections [5]. Recently, COVID-19 (coronavirus disease 2019) pandemic revealed us new medical entities in the field of endocrinology, also causing multiple

insufficiencies at different glands [6,7]. Moreover, iatrogenic contributors include surgery of the pituitary gland and radiotherapy (typically seen in adulthood) [8].

Clinical (endocrine) presentation depends on the hormonal axis that is affected, representing either a phenotype of isolated pituitary deficiency or combined pituitary hormone deficiency (CPHD); full blown picture of a syndrome with morphologic anomalies might be present [9-11]. CPHD usually manifests through inadequate secretion of GH in association with one or multiple other (non-GH) pituitary hormones and it is a consequence of genetic background occurring in the transcription factors that play a role in the development of the pituitary gland [12,13]. These factors are, for instance, represented by SOX2, SOX3, PITX2, GLI2, HESX1, BMP4, FGF8, FGF10, LHX4, LHX3, PROP1, OTX2, POU1F1 [14,15]. They have different timing of action during the developmental process; therefore, disturbances in each of them lead to different structural and functional manifestations [16-18]. Among these, PROP1 and POU1F1 are associated with non-syndromic CPHD, with PROP1 pathogenic variant being the most common genetic etiology of hypopituitarism [19,20]. PROP1-related CPHD involves defects of GH, Thyroid Stimulating Hormone (TSH), Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), prolactin and adrenocorticotropic hormone (ACTH) and the first manifestation is usually short stature during childhood, followed by delayed or absent puberty [21,22].

We aim to introduce a case of early-onset hypopituitarism with combined deficiency of GH, gonadotropins and prolactin that lead to early diagnosis of osteoporosis and dyslipidemia as long-term complications after she remained without substitution therapy for a long period of time.

CASE PRESENTATION

This was a 39-year-old female patient admitted for a nonspecific bone pain and frontal headache. Clinically, she had a height of 139 cm, weight of 43 kg (body mass index of 22.27 kg/m^2) with a genetic calculated (target) height of 153.5 cm. The family medical history was irrelevant. Her personal medical history included hypopituitarism with GH deficit and central hypogonadism, elements that were diagnosed during childhood. She did not receive any GH substitution at the time. Also, she did not have any menstrual cycles until the age of 19, when she started substitution with oestrogens and progestative; she has been followed since then (delayed puberty and lack of spontaneous menses were resumed only under medication). Magnetic resonance imaging performed 9 years ago showed a pituitary micronodule of 3 by 5 by 4 mm (the lesion was considered as pituitary incidentaloma and no further imaging follow-up was done since then).

On admission, biochemistry assays revealed a slightly elevated sodium level, high total and LDL (low density lipoprotein) - cholesterol and a mildly increased C-reactive protein (the patient was tested for COVID-19 infection and found negative) (Table 1).

Parameter	Value	Normal range	Units
Uric acid	5	2.6-6	mg/dL
ALT (alanin aminotransferase)	25	0-55	U/L
AST (aspartat aminotransferase)	21	5-34	U/L
Total cholesterol	267	0-200	mg/dL
LDL-cholesterol	187	60-160	mg/dL
Fasting glycaemia	102	70-105	mg/dL
HbA1c (glycated haemoglobin A1c)	5.1	4.8-5.9	%
Ionic serum calcium	4.12	3.9-4.9	mg/dL
Total serum calcium	9.9	8.4-10.2	mg/dL
Serum phosphorus	3.5	2.5-4.5	mg/dL
Sodium	146	136-145	mmol/L
Potassium	4.83	3.5-5.1	mmol/L
Magnesium	2.08	1.6-2.6	mg/dL
ESR (erythrocyte sedimentation rate)	5.1	1-25	mm/h
C-reactive protein	0.91	0-0.5	mg/dL
Fibrinogen	402.87	200-500	mg/dL

Table 1 - Biochemical assessment in an adult female patient with long term history of hypopituitarism

Endocrine evaluation showed normal thyroid function and no adrenal insufficiency. IGF 1 (Insulin-like Growth Factor) was decreased, as expected for early GH deficiency, also, prolactin levels were also below the normal range. Gonadal axis revealed low estradiol levels

(after 2 months of stopping the hormonal replacement). Bone resorption markers P1NP and CrossLaps were elevated, thus showing an increased bone turnover (Table 2).

Parameter	Value	Normal range	Units
TSH (Thyroid Stimulating Hormone)	1.16	0.5-4.5	µUI/mL
FT4 (free levothyroxine)	14.85	9-19	pmol/L
TPOAb (thyreoperoxidase antibodies)	1.46	0-5.61	UI/mL

Table 2A - Endocrine blood assessment in a patient with early-onset growth hormone and gonadotropin deficiency - Thyroid panel

Parameter (8 a.m.)	Value	Normal range	Units
ACTH (Adrenocorticotropic Hormone)	13.33	3-66	pg/mL
Plasma morning cortisol	15.21	4.82-19.5	µg/dL

Table 2B - Endocrine blood assessment in a patient with early-onset growth hormone and gonadotropin deficiency - Adrenal axis

Parameter	Value	Normal range	Units
IGF 1 (Insulin-like Growth Factor)	63.9	78-274	ng/mL
GH (growth hormone)	0.05	0.02-6.88	ng/mL
Prolactin	3.66	4.79-23.3	ng/mL

Table 2C - Endocrine blood assessment in a patient with early-onset growth hormone and gonadotropin deficiency Somatotropic axis and prolactin status

Parameter	Value	Normal range	Units
FSH (Follicle Stimulating Hormone)	6.52	3.5-12.5	mIU/mL
LH (Luteinizing Hormone)	5	2.4-12.6	mIU/mL
Plasma estradiol	5	12.4-233	pg/mL

Table 2D - Endocrine blood assessment in a patient with early-onset growth hormone and gonadotropin deficiency - Gonadal axis (at stopping hormonal replacement)

Parameter	Value	Normal range	Units
25OHD (25-hydroxyvitamin D)	30.7	20-100	ng/mL
PTH (parathormone)	45.17	15-65	pg/mL
Osteocalcin	25.04	11-43	ng/mL
Alkaline phosphatase	90	38-105	U/L
P1NP	82.71	12.13-58.59	ng/mL
CrossLaps	0.56	0.162-0.436	ng/mL

Table 2E - Endocrine blood assessment in a patient with early-onset growth hormone and gonadotropin deficiency - Mineral metabolism-related hormones and serum bone turnover markers (of formation- P1NP, osteocalcin and alkaline phosphatase, respectively, of resorption – CrossLaps)

Central DXA (Dual-energy X-ray Absorptiometry) according to a GE Lunar Prodigy machine confirmed a decreased bone mineral density (BMD) and an associated Z-score below the expected range for age (Table 3).

DXA region	Bone mineral density BMD (g/cm^2)	Z-score (SD)
Lumbar L1-4	0.860	-1.2
femoral neck	0.740	-1.5
total hip	0.554	**-2.4**

Table 3 - Central DXA of a 41-year-old patient with primary amenorrhea, currently under hormone replacement therapy

Screening plane X-Ray of the thoracic-lumbar spine showed no prevalent vertebral fracture (neither the patient had a history of other spontaneous or low trauma fragility fractures). Imaging evaluation, namely (intravenous contrast) computed tomography showed an asymmetric pituitary gland of normal size and a micro-nodule with maximum coronal diameters of 0.54 cm by 0.28 cm (which seemed stationary with prior evaluation 9 years before). The pituitary stalk was on the median line displaying normal features (Figure 1).

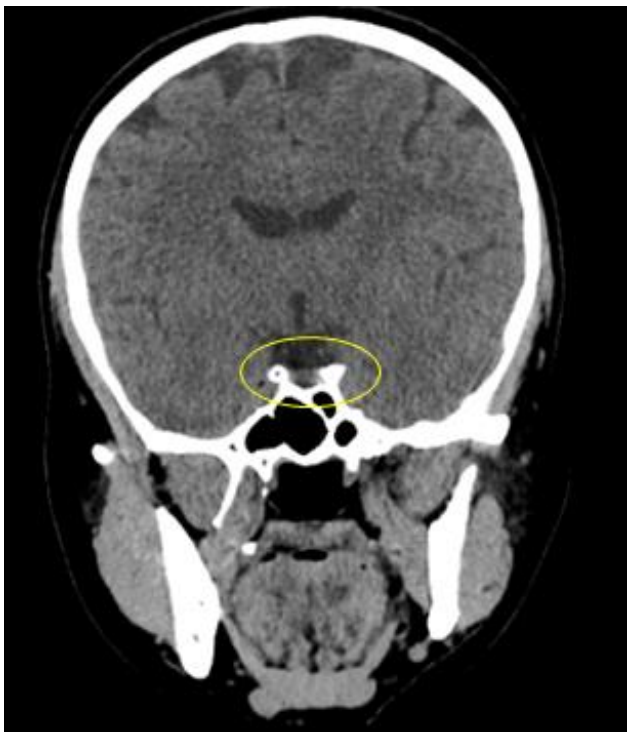

Figure 1 - Computed tomography showing a pituitary micro-nodule in a patient with early-onset hypopituitarism - Frontal plan

The patient re-started substitution with oral contraceptives. Supplementation with calcium and vitamin D (1000 cholecalciferol per day) was added to the anti-resorptive medication (weekly 70 mg alendronate). The next DXA assessment was planned within one year in order to decide drug continuation based on BMD change and (if any) incidental fragility fractures. A cholesterol lowering agent was initiated (atorvastatine 20 mg per day). For the pituitary incidentaloma, the adequate approach was surveillance; no specific surgical intervention is needed. Lifelong follow-up is required. Replacement of GH deficiency in adults represents an off-label solution in our country thus it was not recommended.

DISCUSSION

Due to the timing of onset and the absence of other lesions that could interfere with pituitary hormones secretion, the cause for hypopituitarism in this patient is, most probably, genetic. Therefore, genetic testing (currently not available in this specific instance) would identify the specific transcription factor mutation and correlate it with the hormonal axes that are affected. Moreover, the lack of GH substitution and delayed estro-progestative treatment in this case synergistically acted as negative factors for bone health that become the main issue as an adult [23,24].

Both GH and IGF 1 contribute to normal mineral metabolism; therefore, insufficient levels are directly correlated to altered bone microarchitecture, decreased bone mass and increased fracture risk, an aspect that is prone to become clinically manifested in adults with long term untreated (early) GH deficiency (either isolated, but, mostly in association with hypogonadism) [25,26]. At the same time, uncorrected hypogonadism decreases BMD and women with premenopausal hypo-estrogenic status must be evaluated with a complete panel of investigations regarding skeleton health in terms of bone turnover markers, mineral metabolism-associated hormones, central DXA, and screening spine X-Ray [27,28]. A most important pitfall in adults with dwarfism is using an adequate reference database for BMD (nomogram) and a correct positioning of the patient amid using the DXA device [29,30].

Another comber stone is defining osteoporosis in premenopausal population, especially in the absence of prevalent low trauma fracture (as in seen here), but in association with a secondary cause of low BMD such as hypogonadism [31,32]. Starting specific anti-osteoporotic medication represents another challenging issue in this specific matter. In these patients, the first line of treatment for acquiring normal bone status should be hormone replacement therapy, followed by anti-resorptive medication and selective use of teriparatide (only in a distinct, high fracture risk subgroup confirmed with complicated osteoporosis) [33,34]. For other situations, the correction of underlying factor such as glucocorticoids arrest for glucocorticoids-induced osteoporosis or parathyroidectomy for primary hyperparathyroidism should be enough not to associate specific drugs against osteoporosis in uncomplicated cases [35,36].

Regarding the treatment of GH deficiency, early substitution during childhood is the most adequate management in order to achieve the targeted genetic-based stature and avoid later complications, such as cardiovascular events, dyslipidemia (as found here), reduced exercise capacity, and excessive body fat mass [37,38]. However, compliance to medication

among GH-deficient patients is relatively low, due to the necessity of daily injections for years and access to this treatment that was not feasible in this female case [39,40]. For this reason, long-acting GH preparations should increase the compliance to therapy [41,42]. In addition, the use of GH replacement for adults with hypopituitarism is restricted in some countries thus adult GH deficiency syndrome actually remains untreated [42,43].

Of note, the subject associated a non-functioning pituitary micro-tumor that in pediatric population seems to have a different significance than seen in adults (approximately one out of ten adults might have the condition with an accidental detection). In this case, most probably the genetic form of hypopituitarism might be related to the early presence of this lesion. However, the management includes only serial imaging follow-up with a low-to-zero expected rate of growth as far as we know by now [44,45].

CONCLUSION

The diagnosis of hypopituitarism should be promptly followed by hormonal substitution of the associated deficiencies, especially if the condition is discovered early in life. This approach is effective for an adequate development and also for avoiding long term complications that can appear later in life such as high risk of low BMD and cardiovascular elements.

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