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RESEARCH ARTICLE

EXUBERANT RESPONSE TO LATE ONSET OF RECOMBINANT HUMAN GROWTH HORMONE (RHGH) IN PATIENT WITH PAN-HYPOPITUITARISM: CASE REPORT

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ABSTRACT

The Hypopituitarism is a chronic clinical condition of multifactorial etiology, defined as the total or partial function loss of the pituitary gland, leading to a poor secretion of hormones from anterior and posterior pituitary gland. Occurs from pituitary, hypothalamus, and surrounding structures diseases. With varying clinical presentation, the hypopituitarism is often insidious; being that the clinical manifestations are determined by the severity, extent and duration of the disease, furthermore, depends on the severity of hormone deficiency. This clinical condition has high morbidity and mortality, and the diagnosis and treatment when instituted early, change the prognosis of the patient. Hormone replacement therapy should be individualized according to the specific needs of each patient. We describe a case in which the patient with pan-hypopituitarism showed an exuberant response to late start of hormone replacement therapy with GH.

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INTRODUCTION

Hypophysis or pituitary gland is composed by adenohypophysis (anterior hypophysis) which secrete the following hormones: thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin (PRL) and gonadotrophins (follicule stimulant hormone FSH and luteinizant hormone LH); and by neurohypophysis (posterior hypophysis) which stores hypothalamic produced hormones: antidiuretic hormone (ADH) and oxytocin. These hormones have fundamental roles on metabolism, growth, development and reproduction related processes (Du *et al*., 2014; Karaca *et al*., 2010). Hypopituitarism is defined as the deficiency of one or more pituitary gland secreted hormones. Damage superior to 50% of the pituitary gland may inhibit the secretion of anterior gland hormones, which affects organs performances as in ovaries, thyroid and adrenal gland. Most common hormone deficiencies are GH, FSH and LH; ACTH and TSH deficiencies are less common (Dong *et al*., 2009). Being a rare clinical entity, hypopituitarism has a prevalence of 45.5/100 000 and incidence of 4.2/100 000/year in the population (Couto *et al*., 2014; Regal *et al*., 2001). Most common causes are hypothalamic and pituitary tumors or consequence to tumor treatment (radiotherapy and chemotherapy) (Schneider *et al*., 2007). Patients with hypopituitarism present diverse and frequently unspecified clinical manifestations, depending of cause and hormonal dysfunction extent. It may occur insidiously and the subclinical disease may not be recognized (Melmed *et al*., 2011). These patients have a high mortality rate, independent to disease evolution; being the main cause of death cardiovascular and respiratory diseases (Tomlinson *et al*., 2001; Fernandez-Rodriguez *et al*., 2013). The diagnosis of hypopituitarism is made by dosing base level hormones during morning while fasting or, if necessary, by hormonal stimulating tests (Park, 1996). For diagnostic purpose is hard to distinguish pituitary from hypothalamic diseases (vanAken and Lamberts, 2005). Pituitary disease presents primary

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hypopituitarism, as hypothalamic disease presents secondary hypopituitarism. Performing stimulation tests with hypothalamic hormones and imaging like sella turcica MRI may be used to help distinguish hypothalamic and pituitary causes (vanAken and Lamberts, 2005; Prabhakar and Shalet, 2006). The base treatment of hypopituitarism is hormonal replacement therapy of deficient hormones; hormonal replacement order being: glucocorticoid, thyroid hormone, sex hormones and growth hormone. Adult patients with hypopituitarism and hypogonadism must intake hormones to keep secondary sexual characters and reproductive function (Du *et al*., 2014). We describe the case of a patient diagnosed with pan-hypopituitarism presenting exuberant and satisfactory response to late onset of GHreplacement therapy.

Case report

Patient EJS, 15 years, male, started endocrinological follow up on June/2012, with short stature since early childhood associated with pubertal delay. Diagnosed with hypothyroidism since 3 years old with a daily intake of levotiroxin 50 mcg. Premature at birth, with social and psychological immaturity for his chronological age, used anticonvulsivant for 2 years due to seizures with EEG revealing bilateral centroparietal paroxysmal activity. During physical exam at the initial evaluation was verified: weight 25.9 kg, height 133 cm (standard deviation -4). Tanner staging: P1G1.

Table 1. Exuberant response to rhGH replacement

Data/date	Feb/13	Dec/13	Mar/14	Sep/14	Nov/14	Feb/15	Oct/15	Mar/16
Chronological age	16 years	16 y 10 m	17 y 1 m	17 y 7 m	17 y 9 m	18 y	18 y 8 m	19 y 1m
Bone age	10 years	-	12 y	-	-	12 y 6m	-	-
Height (cm)	135	144	151	155	157	161	165	167
Weight (kg)	27,45	30,8	34	40	42	44,5	52,4	53,5
IGF-1	33,8 (226-903)	174	222	217		240	277	299
Free T4	0,83	0,93	0,89	0,66		0,56	0,86	0,78
Fasting plasma glucose	82	82		80		74	66	
Total testosterone			10			40		
rhGH dose(IU)	3	4	4	4	5	5	5	5
FreeT4 dose (mcg)	50	75	75	100	100	100	112	125

Table 2. Causes of hypopituitarism

Hypophysary causes
- Neoplasia that causes pituitary destruction
Intrasellar tumor: adenoma, craniopharyngioma
Parasellar tumor: meningioma, optic nerve glioma
Metastatic tumor: breast, lungs, melanoma, renal cell carcinoma
- Pituitary ischemic necrosis:
Postpartum (Sheehan syndrome)
Diabetes mellitus
Systemic causes: sickle cell anemia, sickle cell trace, temporal arthritis, atherosclerosis, hemorrhagic fever with renal syndrome
- Pituitary apoplexy (in most cases secondary to a pituitary tumor)
- Cavernous sinus thrombosis
- internal carotid artery aneurysm
- Infections: tuberculous meningitis, fungal diseases, malaria, HIV
- Infiltrative conditions: hemochromatosis, secondary amyloidosis
- Immunologic or inflammatory changes: lymphocytic hypophysitis, granuloma, sarcoidosis
- Primary empty sella syndrome
- Iatrogeny:
Surgical destruction
Cranial radiotherapy: pituitary, nasopharynx, brain
- Idiopathic: Often Monohormonal Disorder (GH, ACTH, TSH)
- Genetic: Pit-1, GH, LH-β, Mutation/deletion GHRH-R
Hypothalamic causes
Pituitary stem and hypothalamic changes, other central nervous system diseases
- tumors: craniopharyngioma, germ cell cancer, metastasis, lymphoma, leukemia
- Infiltrative: hemochromatosis, lipid storage disease
- Head trauma
- Disease-induced hormone: glucocorticosteroid, sex steroids
- Iatrogeny: surgery, irradiation
- Infection: HIV, tuberculosis
- Nutricional: obesity, starvation
- Anorexia nervosa
- Severe systemic disease (interleukin-mediated)
- Psycho-neuro-endocrine: psychosocial dwarfism, stress-induced amenorrhea
- Genetic: KAL1 gene, vasopressin-neurophysin gene

Adapted from Prabhakar *et al*. (2006)
HIV: Human immunodeficiency virus; PIT-1: POU domain, class 1, transcription factor 1; GH: Growth hormone; LH-β: Luteinizing hormone beta; GHRH-R: Growth hormone-releasing hormone receptor; ACTH: adrenocorticotrophic hormone; TSH: thyroid stimulating hormone; KAL 1: Kallmann syndrome gene KAL-1.

Bone age at 01/27/2012: 9 years (chronological age: 15 years) (Fig. 1 and Fig. 2). Clonidine testing at 02/27/2012: base GH 0.09; > 60 minutes: 0.12; > 90 minutes: 0.12; > 120 minutes: 0.12 (very low GH peak < 1 ng/ml). Hypophysis MRI at 11/06/2009: topical and slightly asymmetrical pituitary gland,with enlargement of the left, without injuries that could be seen after contrast highlight (Fig. 3 and Fig. 4). Laboratory tests at February 2013 show: TSH 0.02, Free T4 0.83, Total T4 6.36, IGF-1 33.8 (226-903), base cortisol 9.8 mcg/dl, ACTH 15, FSH 0.98, LH 0.35, total testosterone 10, prolactine 10.

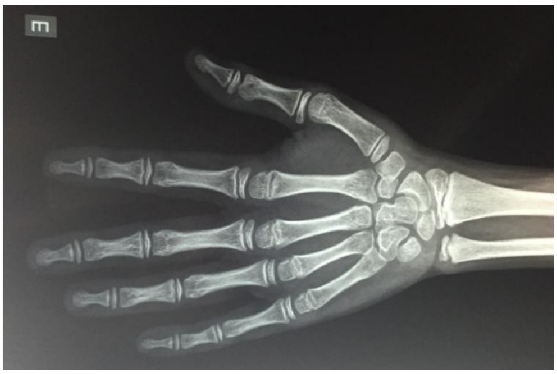

Figure 1. Plain left hand radiography. Inicial bone age: 12 yearsand 6 months

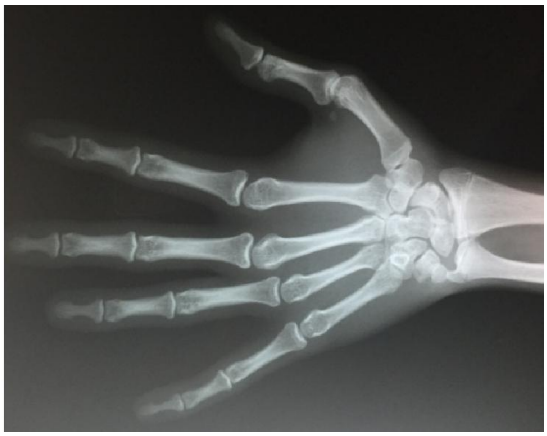

Figure 2. Plain left hand radiography. Final bone age: 18 years

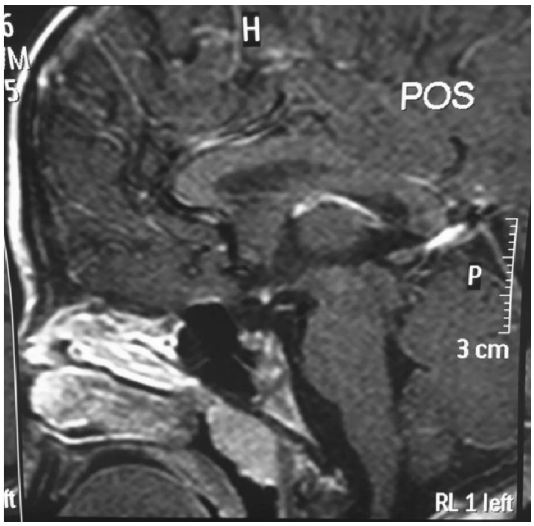

Figure 3. Skull MRI

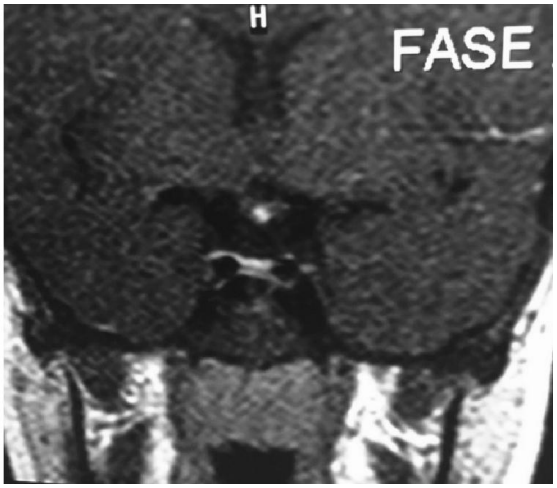

Figure 4. Skull MRI

As the clonidine test already determined GH deficiency (less than 3 ng/ml peak), the insulin tolerance test wasn't performed; furthermore the patient was contraindicated for this test as he presented seizures during his childhood. Base cortisol levels over 3 mcg/dl determined diagnosis of low pituitary reserves of ACTH, choosing to use corticosteroids only in stressful situations. Low height, pubertal delay and central hypothyroidism findings confirm pan-hypopituitarism diagnosis, starting rhGH (somatropin) replacement in February 2013 (doses of 0.14 UI/kg or 0.042 mg/kg/day). On table 1 is shown exuberant response after the beginning of recombinant human GH replacement; sexual steroids replacement than begun in June 2014.

DISCUSSION

Hypopituitarism is defined as total or partial function loss of the anterior and posterior pituitary gland (hypophysis) caused by hypothalamic or hypophysarydysfunctions (Melmed, 2011). With an incidence of 12 to 42 new patients per million per year and prevalence of 300 to 455 patients per million; these values understate the incidence rate, as 30% to 70% of patients with cerebral lesion present symptoms due to low pituitary hormonal secretion (Kim, 2015; Ascoli and Cavagnini, 2006). Hypopituitarism is divided in primary and secondary hypopituitarism. Primary hypopituitarism is defined by the loss, damage or dysfunction of hormone secreting cells; secondary hypopituitarism is caused by hypothalamic or pituitary stem diseases that disrupts neural and vascular connections of the pituitary gland, leading to a reduction of hormonal secretion by hormone secretion cells (Melmed, 2011; Kim, 2015). Hypopituitarism causes are described at Table 2. Posterior pituitary gland decreased hormone secretion occurs due to hypothalamic hormone synthesis or secretion failure; as to the anterior pituitary gland decreased hormone secretion is caused by a deficient activity of any hypothalamic secreted hormones(Melmed, 2011; Kim, 2015).Hypopituitarism patients present signs and symptoms that vary accordingly to the underlying pathology, speed of onset and the severity of hypopituitarism. On major cases, patients presented a slow and progressive loss of pituitary function, with unspecified, vague and mild symptoms; it is worth mentioning that in major cases, patients are late diagnosed (vanAke and Lamberts, 2005; Prabhakar *et al*., 2006; Smith, 2004). GH deficiency is the first

to happen, as GH producing cells (somatotrophs) are vulnerable to pressure. GH deficiency is the most frequent hormonal deficiency between all pituitary hormones, followed by gonadotrophins deficiency (LH, FSH), TSH, ACTH and prolactine[17]. GH, LH and FSH are hormones that show selective deficiencies; children are more likely to suffer GH deficiencies, as adults present gonadotrophins deficiencies (Kim, 2015). Hypopituitarism symptoms may vary from patient to patient, being that the symptoms are associated with the presentation form of hormone deficiency (Vance, 1994). GH deficiency, besides causing low height on children, decreases muscular mass and strength, increased visceral fat and fatigue (Vance, 1994; Shalet *et al*., 1998). ACTH deficiency, if acutely installed, becomes a medical emergency presenting fatigue, weakness, dizziness, nausea, vomit, severe and refractory to volume replacement hypotension associated with hypoglycemia; progressive loss of corticotrophic function, on the other hand, present the same symptoms chronically associated with weight loss (Vance, 1994; Reimondo *et al*., 2008). TSH deficiency present symptoms as: fatigue, cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, slowing of mental processes (Balen and Manning, 1994). Upon gonadotrophin deficiency, men present libido loss, impaired sexual function, decrease of bone mass, eritropoiesis and capilar growth; women, on the other hand, present amenorrhea, oligomenorrhea, infertility, libido loss, dyspareunia, osteoporosis, premature atherosclerosis; children of both sex will present pubertal delay (Vance, 1994). Prolactine deficiency leads to breastfeeding inability (Vance, 1994) and ADH deficiency causes polyuria, nocturia and polydipsia (Prabhakar and Shalet, 2006).

Hormonal deficiencies are diagnosed through specific hormone testing. The screening for GH deficiency is done through insulin-like growth factor 1 (IGF-1) dosage; confirmation may be done through two tests: insulin tolerance test (ITT), consider gold standard, or through clonidine test. GH and ACTH deficiencies can be diagnosed through ITT, as hypoglycemia (lower than 40 mg/dl) is a powerful stimulus to GH and cortisol secretion. GH levels inferior to 3.0 g/L indicate a severe deficiency, levels between 3.0 to 4.9 g/L indicate partial deficiency, and levels superior to 5.0 g/L are considered normal (vanAken and Lamberts, 2005), excluding GH deficiency in both children and adults. ACTH deficiency is diagnosed with a cortisol peak inferior to 18 mcg/dl. Insulin tolerance test consists of a bolus injection of 0.05-0.1 U/Kg of regular insulin, with dosing samples of GH, cortisol and basal glycaemia at 30, 60, 90, 120 minutes after insulin administration (Geloneze and Tambascia, 2006). The ITT adverse effects are sweating, palpitation, tremors, seizure (due to hypoglycemia) and because of that is contraindication for the elderly, patients with cardiovascular diseases, cardiopaths and individuals with a history of seizures. Clonidine is an alpha-2 adrenergic capable of stimulating GH secretion by inhibiting of somatostatin and stimulating GHRH neurons, being the most common agent used to diagnose GH deficiency on children (Lee *et al*., 2013). A low dosage of clonidine (0.1 mg/m^2) is effective as a GH-stimulant agent, and so this low dosage results in fewer adverse effects like hypotension and torpor (Borges *et al*., 2016). TRH stimulating test is not clinically administrated however it can distinguish between hypophysary and hypothalamic injuries, being that hypothalamic injuries causes delay on rising TSH levels (Allahabadia and Weetman, 2003). TSH deficiency is confirmed through normal or low TSH concentration associated to low levels of free T4, characterizing central hypothyroidism (vanAken and Lamberts, 2005). Primary hypothyroidism on the other hand presents high levels of TSH (Prabhakar and Shalet, 2006). Dosing free T4 makes treatment control, as the TSH levels are compromised. Hypopituitarism is treated with hormone replacement, which is a simple solution but it can't be done to physiological levels, and besides it is difficult to monitor treatment response (Smith, 2004). GH replacement treatment was formerly used only in children with growth disorder due to GH deficiency; however, with the development of recombinant human growth hormone (rhGH) it became possible to treat adults with hypopituitarism and patients with low GH secretion, for example, old age, burn injury, obesity or catabolic disease (Prabhakar and Shalet, 2006; Kim, 2015). Patients that undertook treatment with rhGH presented body mass reduction, increase of muscular mass, increase on physical strength, bone density, decreased cardiovascular risk, improvement of dyslipidemia, cardiac function and mental health (Prabhakar and Shalet, 2006; Kim, 2015). The initial GH dosage utilized was 0.03 to 0.05 mg/kg or 0.1 to 0.2 UI/kg/day, being adjusted by the IGF-1 levels and corrected by his bone age to achieve a growth rate according to his age group and pubertal staging. Men have a better response to drug therapy than women, due to increased IGF-1 levels mediated by testosterone; so women, especially those with Turner syndrome, may require a higher dosage, as estrogen decreases IGF-1 production (vanAke and Lamberts, 2005). The therapy with rhGH must be implemented as soon as diagnosis is established for a better prognosis and clinical outcome, as hypopituitarism patients have a higher cardiovascular death incidence rate. The satisfactory response with late onset of rhGH replacement therapy was surprising and reveals the importance of early diagnosis, once low height and pubertal delay causes countless psychological and social problems.

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