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Low and Normal IGF-1 Levels in Patients with Chronic Medical Disorders (CMD) is Independent of Anterior Pituitary Hormone Deficiencies: Implications for Treating IGF-1 Abnormal Deficiencies with CMD

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Abstract

Over time, based on evidence–based medicine, a number of hormonal test levels including IGF-1 had been raised or lowered to meet new criteria standards. In particular, IGF-1 plasma levels have been shown in several studies to be an independent diagnostic tool in Adult Growth Hormone Deficiency (AGHD). Many endocrinology studies link low IGF-1 plasma levels with low levels of other anterior pituitary hormones (i.e., LH, FSH, and TSH). Low IGF-1 is considered by most to be between 84-100 µ/l and numerous studies recommend that raising IGF-1 to high normal range reverses Chronic Medical Diseases (CMD), improves bone mineral density (BMD), and fibromyalgia. Moreover, some studies suggest that low levels of IGF-1 by itself independent of anterior pituitary deficiencies is sufficient to determine AGHD in humans. In order to determine the relationship of low IGF-1 with that of LH, FSH, and TSH levels in subjects with CMD, we evaluated these levels (± SD) in 944 patients. Patients with IGF-1 below 84 µ/l, 100 µ/l, and 150 µ/l were accessed. 9.22% had less than 84 µ/l (SD ± 12.52); 19.9% had less than 100 µ/l (SD ± 9.54); and 51.6 had less than 150 µ/l (SD ± 26.0). Specifically, the percentages found for low LH, FSH, and TSH were only 4.2%, 4.8%, and 6.5%. We conclude that IGF-1 deficiencies occur independent of comorbid deficiencies of LH, FSH, and TSH. Finally, we propose that based on the present investigation, IGF-1 low levels between the range of 84-100 µ/l may be too low to be considered as an independent diagnostic marker to treat AGHD with CMD.

Keywords: Adult Growth Hormone Deficiency (AGHD); IGF-1 plasma levels; Chronic Medical Diseases (CMD); Anterior pituitary hormones; Luteinizing Hormone (LH); Thyroid-Stimulating Hormone (TSH); Follicle-Stimulating Hormone (FSH)

Introduction

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) most definitely play essential roles in growth in childhood, and continue to have important metabolic actions in adults [1]. It is well known that Adult Growth Hormone Deficiency (AGHD) is characterized by increased visceral adiposity, abnormal lipid profiles, premature atherosclerosis, decreased quality of life, and increased mortality [2]. GH is generally considered to exert anti-insulin actions, whereas IGF-1 has insulin-like properties [3]. Interestingly, GH deficient adults and those with acromegaly are both predisposed to insulin resistance [4]. High doses of GH treatment have major effects on lipolysis, which plays a crucial role in promoting its anti-insulin effects, whereas IGF-1 acts as an insulin sensitizer that does not exert any direct effect on lipolysis or lipogenesis [5]. Moreover, Growth Hormone Deficiency (GHD) is the most common pituitary hormone disorder, occurring in approximately 20% of patients when multiple tests of GHD are used [6].

One of the most devastating reasons for death among teenagers and young adults is acute brain injury due to trauma. There are 1.5-2.0 million Traumatic Brain Injuries (TBI) in the United States annually, with an associated cost exceeding 10 billion dollars. TBI is the most common cause of death and disability in young adults less than 35 years of age. The consequences of TBI can be severe, including disability in motor function, speech, cognition, and psychosocial and emotional skills. Many studies have consistently demonstrated a 30-40% occurrence of pituitary dysfunction involving at least one anterior pituitary hormone following a moderate to severe TBI [7]. In terms of CMD, there are a number of studies that have shown the relationship between GH; specifically, bone density [8]. According to Amelio et al. [9], bone produces different hormones, like osteocalcin (OC), which influences energy expenditure in humans. The under-carboxylated form of OC has a reduced affinity for hydroxyapatite; hence, it enters the systemic circulation more easily and exerts its metabolic functions for the proliferation of pancreatic β-cells, insulin secretion, sensitivity, and glucose tolerance. Leptin, a hormone synthesized by adipocytes, also has an effect on both bone remodeling and energy expenditure; in fact, it inhibits appetite through hypothalamic influence and in bone,

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it stimulates osteoblastic differentiation and inhibits apoptosis. Finally, amylin (AMY) acts as a hormone that alters physiological responses related to feeding and plays a role as a growth factor in bone. Interestingly, Elbornsson et al. [10] recently showed the benefit of GH replacement therapy over a 15 year period increasing BMD in adults with adult onset of GHD.

Fibromyalgia (FM) is another CMD characterized by widespread pain and fatigue and is considered a syndrome with different pathogenic mechanisms. Controversial data on GH axis disturbances have been published. Some preliminary trials have shown promising effects of GH therapy on tender points and quality of life in FM [11]. In fact, Cuatrecasas et al. [12] showed patients with FM had an IGF-1 of 150 µg/l or less. The mean peak of GH during an insulin tolerance test (ITT) was 13.3 ± 9.9 ng/ml in 127 patients in which the test was performed. In 22 of the 127 (17.3%), ITT peak GH was 5 ng/ml or less, and in 8 (6.3%), the peak GH was 3 ng/ml or less. Mean baseline GH (n=127) was 1.47 ± 2.58 ng/dl, and 8 of 120 (6.8%) showed an insufficient IGF-1 response (<50% over baseline) to the IGF-1 generation test.

The GH-IGF-1 axis plays a role in normal brain growth, but little is known of the effect of growth hormone deficiency on brain structure. However, Webb et al. [13] reported on 15 children (mean of 8.8 years of age) with isolated growth hormone deficiency [peak growth hormone <6.7 µg/l (mean 3.5 µg/l)] and 14 controls (mean of 8.4 years of age) with idiopathic short stature [peak growth hormone >10 µg/l (mean 15 µg/l) and normal growth rate]. Compared with controls, they found children with isolated GHD had lower Full-Scale IQ ($P < 0.01$), Verbal Comprehension Index ($P < 0.01$), Processing Speed Index ($P < 0.05$), and Movement-Assessment Battery for Children ($P < 0.008$) scores. Verbal Comprehension Index scores correlated significantly with IGF-1 ($P < 0.03$) and insulin-like growth factor binding protein-3 ($P < 0.02$) standard deviation scores in isolated GHD. Moreover, they also found that in patients with isolated GHD, white matter abnormalities in the corpus callosum and cortico-spinal tract and reduced thalamic and globus pallidum volumes relate to deficits in cognitive function and motor performance.

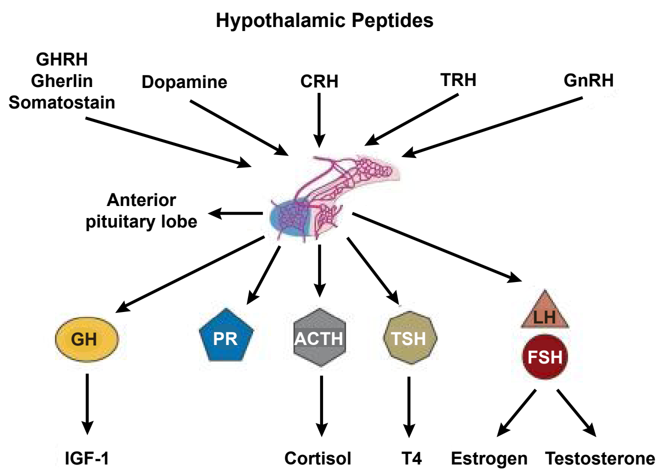
Finally, Polish scientists Tołwińska et al. [14] evaluated with high resolution echocardiography selected parameters of endothelial function and measured medial thickness in carotid communis arteries (IMT) in children with GHD before replacement therapy. They found that IMT in patients with GHD showed a more advanced degree of atherosclerotic changes in this group compared to healthy controls. In addition, Tołwińska et al. [14] suggest that ultrasonographic evaluation of premature atherosclerosis in children with GHD is a basis for future estimation of positive effects of replacement therapy.

In a broader sense, GHD in adults is associated with considerable morbidity and mortality. The diagnosis of GHD is generally straightforward in children as growth retardation is present; however, in adults, diagnosis of GHD is often challenging. Therefore, other markers are needed to identify adults who have GHD and could potentially benefit from GH replacement therapy. Consensus guidelines for the diagnosis and treatment of adult GHD recommend provocative testing of GH secretion for patients who have evidence of hypothalamic-pituitary disease, patients with childhood-onset GHD, and patients who have undergone cranial irradiation or have a history of head trauma [15].

Many report that suspicion of GHD is also heightened in the presence of other pituitary hormone deficits. Tests for GHD include measurement of the hormone in urine or serum or measurement of stimulated GH levels after administration of various provocative agents [16]. The results of several studies indicate that non-stimulated serum or urine measurements of GH levels cannot reliably predict deficiency in adults, especially related to Body Mass Index (BMI) [17]. In fact, Ghigo et al. [18] and Petersenn et al. [19] have suggested that based on consensus of the literature, the GH Research Society Consensus (RSC) from Port Stevens in 1997 [18] and its Consensus Statements should be appropriately amended. Accordingly, they further suggest one should evaluate patients with hypothalamic or pituitary disease as well as those with childhood-onset GHD to identify obvious risk as adults for severe GHD (Figures 1 and 2).

In terms of testing for AGHD, there has been much controversy as to the most appropriate measure. Specifically, Aimaretti et al. [20] reported that total IGF-1 levels are often normal even in patients with total anterior hypopituitarism. They suggested that this does not rule out severe GHD and therefore, ought to be verified by provocative testing of GH secretion. However, they further believe despite the low diagnostic sensitivity of this parameter, very low levels of total IGF-1 can be considered definitive evidence of severe GHD in a remarkable percentage of total anterior hypopituitary and as such, these patients could therefore skip provocative testing of GH secretion.

Feletti et al. [21] performed a meta-analysis showing the unequivocal link between GHD and cognitive performance as well as improvements with GH replacement therapy. In addition, there have been numerous studies showing improvement with GH replacement therapy (raising IGF-1 levels) for a number of abnormalities including: BMD (from 138.1 to 279.4); fibromyalgia (from 98.6 to 173.3); brain processing speed and memory (from 150 to 250); head trauma (from 74 to 362.6); cognitive function (from 135 to 213); carotid intimal media thickness (from 51.8 to 234.4); insulin sensitivity (from 103.5-231.1); reduction of abdominal fat accumulation (from 146 to 267); and 100



GHRH: Growth-Hormone-Releasing Hormone; CRH: Corticotropin-Releasing Hormone; TRH: Thyrotropin-Releasing Hormone; GnRH: Gonadotropin-Releasing Hormone; GH: Growth Hormone; IGF-1: Insulin-Like Growth Factor 1; PR: Prolactin; ACTH: Adrenocorticotropic Hormone; TSH: Thyroid-Stimulating Hormone; T4: Thyroxine; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone

Figure 1: Hormones of the anterior pituitary lobe, their regulation by hypothalamic peptides, and the hormones of the peripheral endocrine glands that are under their control.

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point increases of IGF-1 levels are associated with a 7 point increase in IQ (Table 1).

Finally, many endocrinology studies link low IGF-1 levels with low levels of other anterior pituitary hormones (i.e., LH, FSH, TSH) [22], but in terms of CMD, the relationship between GH and these other anterior pituitary hormones, to our knowledge, have not received adequate attention. Thus, our laboratory decided to investigate the relationship of low IGF-1 levels with that of LH, FSH and TSH plasma levels in subjects with CMD.

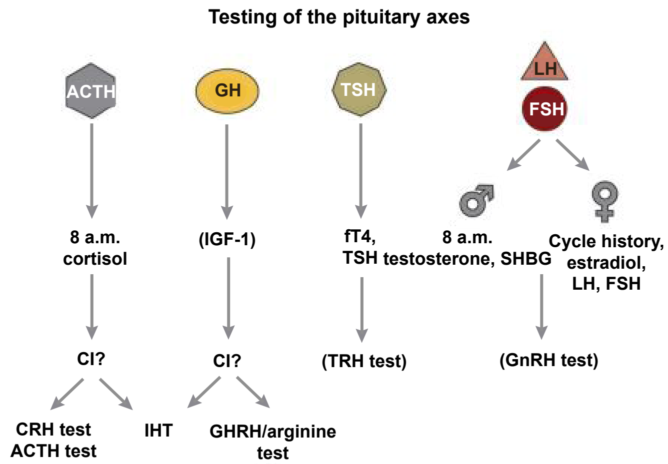
Methods

Subjects and testing

This study was approved by the PATH Foundation NY Institutional Review Board (IRB) with an improved consent form that each patient filled out prior to any treatment or data retrieval. This was a post-hoc analysis of all presenting data. All subjects signed an approved IRB consent form based on an approval from the PATH Foundation NY IRB committee (registration #IRB00002334) and ethics board approval from PATH Foundation NY. The criterion for study inclusion was at least one P300 test for each patient. Trained EEG medical and psychometric technicians conducted the tests. All test interpreters were blinded to other patient results. All subjects were part of a catchment study involving brain electrical activity mapping and aging research.

The data set consisted of both genders (male and female) from the age range of 18-90 years with mixed race including: Caucasian, Hispanic, Asian and African–American. A total of 944 patients were recruited from the PATH Medical clinic over a two-year period ending on March 24, 2009. The diagnosis of CMD was carefully derived from a number of clinically relevant tests, such as a complete biochemical panel analysis (CBC, etc.) and neuropsychological tests including: Test of Variables of Attention (TOVA); Wechsler Memory Scale-III (WMS); The Central Nervous System Vital Signs Memory Test (CNSM); Mini-Mental State Examination (MMSE); Brain Event–Related Potentials (P300); and echocardiograms (ECHO), electrocardiogram (EKG or ECG), DEXA (Dual-energy X-ray absorptiometry measuring percent body fat) along with a number of diagnostic parameters (Table 2).

We evaluated plasma levels of IGF-1, LH, FSH and TSH (x=± SD) on all 944 subjects. In order to analyze the relationship between anterior pituitary hormones and levels of IGF-1, we divided patients



The relevant anterior pituitary axes are shown in the upper portion of the diagram as in figure 1, while the steps to be followed in endocrinological assessment are shown in the lower portion.

CI: Contraindications; IGF-1: Insulin-Like Growth Factor 1; fT4: Free Thyroxine; TSH: Thyroid-Stimulating Hormone; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; CRH: Corticotropin-Releasing Hormone; ACTH: Adrenocorticotropic Hormone; IHT: Insulin Hypoglycemia Test; GHRH: Growth-Hormone-Releasing Hormone; TRH: Thyrotropin-Releasing Hormone; GnRH: Gonadotropin-Releasing Hormone; SHBG: Sex-Hormone Binding Globulin

Figure 2: Structured assessment of basal pituitary hormones followed by evaluation with dynamic testing methods.

Disorder Improved with Raising IGF-1 Levels	Start Level of IGF-1 µ/l**	Post Treatment Level IGF-1 µ/l
Bone Mineral Density	138.1	279.4
Fibromyalgia	98.6	173.3
Brain Processing Speed/Brain Memory	150-	250
I.Q.	There is a 7 point increase in IQ for every 100 point increase in IGF-1 level	There is a 7 point increase in IQ for every 100 Point Increase in IGF-1 level
Head Trauma (improvements in anxiety, depression and short and long term memory	74	362.6
Insulin sensitivity	103.5	213
Carotid intimal media thickness (Reduction)	51.8	234.4
Abdominal fat reduction/HIV	146	267
Cognition	135	213

Table 1: GH replacement therapy showing improvement as a function of increased IGF-1 levels.

according to the following IGF-1 cut-offs: below 84 µ/l; 100-84 µ/l; and below 150 µ/l.

Analysis of hormones

IGF-1 and IGFBP-3 were used as the hormone measures. Venipuncture was done in non-fasting subjects between 8:30 AM and 7:30 PM at baseline examination of the PATH Medical Clinic Program. Blood samples were collected in 5 ml tubes containing a 0.5 ml sodium citrate solution. All tubes were stored on ice before and after blood sampling. Platelet-free plasma was obtained by 2-stage centrifugation (10 minutes at 1600 g at 4°C and 30 minutes at 7000 g at 4°C). Platelet-free samples were immediately frozen in liquid nitrogen and stored at −80°C. Assays were performed blinded to information on the subject. Plasma levels of estradiol and sex hormone-binding globulin were estimated with double anti-body radioimmunoassays (Bioreference Lab, New York, NY). As measures of the levels of bio-available and free estradiol, testosterone, and nonprotein-bound estradiol were respectively calculated in the basis of hormone and binding protein levels, for the analysis of GH and IGFBP-3, the laboratory performed standardized procedures [23,24]. For this particular study, we are only reporting the IGF-1 plasma levels.

Results

Table 3 represents the results of our systematic analysis showing the relationship of the IGF-1 (N=944) and percentage (%) (SD ± X) denoted as a function of our arbitrary cut-off points. We found the following in our patient population diagnosed with CMD: 84 µ/l=9.22 µ/l (SD ± 12.52); 100 µ/l= 19.9 (SD ± 9.54); and 150 µ/l= 56.1 (SD ± 26.0).

Most interestingly, when we calculated the plasma levels of LH, FSH and TSH using a low reference range as represented in Table 4 and as such, we surprisingly found only a small percentage of patients had comorbid anterior pituitary hormone deficiencies (between the range 84–100 µ/l of IGF-1 plasma levels: low LH=4.2%; FSH=4.8%; and TSH=6.5%). Specifically, only 0.3% had more than one hormone deficiency and none had three or more.

* Visual and auditory P300 brain evoked potentials (the positive spike in an EEG wave 300ms after a stimulus): Amplitude and Latency
* Fluorodeoxyglucose (FDG) Positron Emission Topography (PET) Brain Hypometabolism
* Computed tomography (CT) Scans
* Mini-Mental State Examination (MMSE)
* Central Nervous System Vital Signs Memory Test (CNSM)
* Test of Variables of Attention (TOVA): Omissions, Commissions, Response Times, and Variability
* Wechsler Memory Scale-III (WMS): Immediate Memory Index (combining Immediate Verbal with Immediate Non-Verbal Memory scores) and the Wechsler Working Memory Index Score
* Additional clinical and cognitive interviews
* Evidence of cognitive deterioration indicated by subjective report of decline by self and/or informant

Table 2: Tests to Diagnose Chronic Medical Disease (CMD).

IGF-1 Levels (n=944)	Percentage (%) (SD ± X)
84 µl	9.22 (SD ± 12.52)
100 µl	19.9 (SD ± 9.54)
150 µl	56.1 (SD ± 26.0)

Table 3: IGF-1 levels and percentage breakdown.

Hormone	Baseline Range (Males)	Baseline Range (Females)
LH	1-10 U/L	Follicular, 1-20 U/L
		Midcycle, 25-100 U/L
		Postmenopausal, 20-100 U/L
FSH	1-10 U/L	Follicular, 1-10 U/L
		Midcycle, 6-30 U/L
		Postmenopausal, 1-8 U/L
		Postmenopausal 20-100 U/L
TSH	0.4-4.2 mIU/L	0.4-4.2 mIU/L

Table 4: Normal and low ranges for anterior pituitary hormones tested.

Reference: Wallach JB (2000) Interpretation of Diagnostic Tests (7th edn) Lippincott Williams and Williams, Philadeplphia, Baltimore, New York.

Discussion

To reiterate, AGHD is marked by a number of neuropsychiatric, cardiac, metabolic, muscular, bone symptoms and clinical features. The most common of these are increased body fat (particularly abdominal fat), decreased lean body mass (including muscle), functional strength, thin skin and cool extremities, decreased psychological well-being and energy, reduced bone density, an increase in c-reactive protein, low-density lipoprotein (LDL), fibrinogen, plasminogen activator inhibitor-1 (PAI-1), a decrease in high-density lipoprotein (HDL), decreased insulin sensitivity, and decreased quality of life [25].

Most importantly, in some patients with AGHD, IGF-1 elevation is resistant to direct GH treatment. However, as we reported earlier [26], the interaction of IGF-1 and IGFBP-3 is quite complex, but seems to involve the integrity of the GH receptor. Previous work from Wilson's laboratory has shown that the constant subcutaneous infusion of IGF-1 to monkeys with normal pituitary glands results in a sustained elevation in circulating concentrations of IGFBP-3; whereas, the acute administration of IGF-1 to monkeys pretreated with a GH receptor antagonist produces a brief, but significant, elevation in serum IGFBP-3. Experiments from Wilson's group [27] indicate that IGF-1 administration during GH receptor antagonism restores circulating levels of IGFBP-3. It remains to be determined whether IGF-1 directly affects hepatic synthesis and secretion of IGFBP-3 [27].

Therefore, the use of IGF-1 alone may not be enough to raise IGFBP-3 levels, but in combination with GH receptor agonistic activity, it may induce the increases as we observed in earlier reports from our laboratory [26] and others [28]. These benefits, which are consistent with literature findings [28], and based on unpublished work in our laboratory (a subject of another paper to be published elsewhere), an increase of IGF-1 levels to the high normal range seems to reverse CMD and associated illnesses (Table 1).

Conclusion

Since we now found that only a small percentage of CMD patients have abnormal low levels of LH, FSH and/or TSH between lGF-1 levels of 84-100 µ/l, we cautiously propose that IGF-1 low levels may be too low to be considered as an independent diagnostic marker to treat AGHD with CMD patients. More research is required to determine any difference we observed in our clinical study and what has been observed in the current literature.

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Conflict of Interest

The authors report no conflict of interest and approved this manuscript with equal contribution. The authors are appreciative for the funding support of Life-Extension Foundation.

References

1. Stochholm K, Juul S, Christiansen JS, Gravholt CH (2012) Mortality and socioeconomic status in adults with childhood onset GH deficiency (GHD) is highly dependent on the primary cause of GHD. Eur J Endocrinol 167: 663-670.
2. Capalbo D, Esposito A, Di Mase R, Barbieri F, Parenti G, et al. (2012) Update on early cardiovascular and metabolic risk factors in children and adolescents affected with growth hormone deficiency. Minerva Endocrinol 37: 379-389.
3. Williams NG, Interlichia JP, Jackson MF, Hwang D, Cohen P, et al. (2011) Endocrine actions of myostatin: systemic regulation of the IGF and IGF binding protein axis. Endocrinology 152: 172-180.
4. Wexler T, Gunnell L, Omer Z, Kuhlthau K, Beauregard C, et al. (2009) Growth hormone deficiency is associated with decreased quality of life in patients with prior acromegaly. J Clin Endocrinol Metab 94: 2471-2477.
5. Yuen KC, Dunger DB (2007) Therapeutic aspects of growth hormone and insulin-like growth factor-I treatment on visceral fat and insulin sensitivity in adults. Diabetes Obes Metab 9: 11-22.
6. Urban RJ (2006) Hypopituitarism after acute brain injury. Growth Horm IGF Res 16: S25-29.
7. Reimunde P, Quintana A, Castañón B, Casteleiro N, Vilarnovo Z, et al. (2011) Effects of growth hormone (GH) replacement and cognitive rehabilitation in patients with cognitive disorders after traumatic brain injury. Brain Inj 25: 65-73.
8. Tritos NA, Hamrahian AH, King D, Greenspan SL, Cook DM, et al. (2012) A longer interval without GH replacement and female gender are associated with lower bone mineral density in adults with childhood-onset GH deficiency: a KIMS database analysis. Eur J Endocrinol 167: 343-351.
9. Amelio PD, Panico A, Spertino E, Isaia GC (2012) Energy metabolism and the skeleton: Reciprocal interplay. World J Orthop 3: 190-198.
10. Elbornsson M, Götherström G, Bosæus I, Bengtsson BÅ, Johannsson G, et al. (2012) Fifteen years of GH replacement increases bone mineral density in hypopituitary patients with adult-onset GH deficiency. Eur J Endocrinol 166: 787-795.
11. Yuen KC, Bennett RM, Hryciw CA, Cook MB, Rhoads SA, et al. (2007) Is further evaluation for growth hormone (GH) deficiency necessary in fibromyalgia patients with low serum insulin-like growth factor (IGF)-I levels? Growth Horm IGF Res 17: 82-88.
12. Cuatrecasas G, Gonzalez MJ, Alegre C, Sesmilo G, Fernandez-Solà J, et al. (2010) High prevalence of growth hormone deficiency in severe fibromyalgia syndromes. J Clin Endocrinol Metab 95: 4331-4337.
13. Webb EA, O'Reilly MA, Clayden JD, Seunarine KK, Chong WK, et al. (2012) Effect of growth hormone deficiency on brain structure, motor function and cognition. Brain 135: 216-227.
14. Tolwinska J, Bossowski A, Szczepanska-Kostro J, Glowinska B, Urban M (2005) Ultrasonographic evaluation of atherosclerotic changes in carotid and brachial arteries in children with growth hormone deficiency before GH replacement therapy. Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw 11: 85-90.
15. Gabellieri E, Chiovato L, Lage M, Castro AI, Casanueva FF (2010) Testing growth hormone deficiency in adults. Front Horm Res 38: 139-144.
16. Abs R (2003) Update on the diagnosis of GH deficiency in adults. Eur J Endocrinol 148: S3-8.
17. Corneli G, Di Somma C, Baldelli R, Rovere S, Gasco V, et al. (2005) The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. Eur J Endocrinol 153: 257-264.
18. Ghigo E, Aimaretti G, Corneli G (2008) Diagnosis of adult GH deficiency. Growth Horm IGF Res 18: 1-16.
19. Petersenn S, Quabbe HJ, Schöfl C, Stalla GK, von Werder K, et al. (2010) The rational use of pituitary stimulation tests. Dtsch Arztebl Int 107: 437-443.
20. Aimaretti G, Corneli G, Baldelli R, Di Somma C, Gasco V, et al. (2003) Diagnostic reliability of a single IGF-I measurement in 237 adults with total anterior hypopituitarism and severe GH deficiency. Clin Endocrinol (Oxf) 59: 56-61.
21. Falleti MG, Maruff P, Burman P, Harris A (2006) The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a meta-analysis of the current literature. Psychoneuroendocrinology 31: 681-691.
22. Chen S, Léger J, Garel C, Hassan M, Czernichow P (1999) Growth hormone deficiency with ectopic neurohypophysis: anatomical variations and relationship between the visibility of the pituitary stalk asserted by magnetic resonance imaging and anterior pituitary function. J Clin Endocrinol Metab 84: 2408-2413.
23. Södergård R, Bäckström T, Shanbhag V, Carstensen H (1982) Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 16: 801-810.
24. Buonomo FC, Lauterio TJ, Baile CA, Campion DR (1987) Determination of insulin-like growth factor 1 (IGF1) and IGF binding protein levels in swine. Domest Anim Endocrinol 4: 23-31.
25. Lasaite L, Bunevicius R, Lasiene D, Lasas L (2004) Psychological functioning after growth hormone therapy in adult growth hormone deficient patients: endocrine and body composition correlates. Medicina (Kaunas) 40: 740–744.
26. Braverman ER, Bowirrat A, Damle UJ, Yeldandi S, Chen TJ, et al. (2010) Adult growth hormone deficiency treatment with a combination of growth hormone and insulin-like growthfactor-1 resulting in elevated sustainable insulin-like growthfactor-1 and insulin-like growth factor binding protein 3 plasma levels: a case report. J Med Case Rep 4: 305.
27. Wilson ME (2000) Insulin-like growth factor I (IGF-I) replacement during growth hormone receptor antagonism normalizes serum IGF-binding protein-3 and markers of bone formation in ovariectomized rhesus monkeys. J Clin Endocrinol Metab 85: 1557–1562.
28. Lo J, You SM, Canavan B, Liebau J, Beltrani G, et al. (2008) Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. JAMA 300: 509–519.