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Interferon- β treatment associated with a biochemical profile suggestive of acromegaly. A case report of a patient treated for multiple sclerosis

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Abstract

We describe a 34-year-old female treated with IFN- β for 8 years with a biochemical profile suggestive of acromegaly. The patient presented with elevated serum insulin-like growth factor-I (IGF-I) and insufficient suppression of growth hormone (GH) during oral glucose tolerance test (OGTT). There were no clinical features of acromegaly. A 5-day profile showed higher GH levels on the 3 days following IFN- β injections. Total and bioactive IGF-I were also elevated but did not fluctuate. Four weeks off IFN- β normalized suppression of GH during OGTT but did not reduce serum IGF-I or bioactive IGF-I. In conclusion, IFN- β treatment mimicked acromegaly biochemically. The changes were partially reversible.

Keywords

Multiple sclerosis; interferon- β treatment; growth hormone; insulin-like growth factor-I; insulin-like growth factor I receptor

Introduction

In addition to the modulating effects on the immunesystem Interferon- β (IFN- β) may also have acute effects on the pituitary gland with increased secretion of adrenocorticotrophin (ACTH), prolactin and growth hormone (GH) [1,2]. Moreover a recent investigation reported a modest increase in serum levels of insulin-like growth factor I (IGF-I) in IFN- β -treated patients with multiple sclerosis (MS) suggesting a persistent effect of IFN- β on the GH-IGF-I axis [3]. IGF-I is the primary downstream mediator of the proliferative actions of GH. Consequently, a possible side-effect of IFN- β could be excessive IGF-I action.

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In this case report we present an IFN- β treated MS patient with pathological elevated levels of total (extractable) IGF-I as well as bioactive IGF-I, but without any clinical features of chronic exposure to IGF-I excess.

Patient and methods

We describe a 34-year-old female (height 167 cm, weight 67.9 kg), diagnosed with MS for 9 years and on standard treatment with Rebif[®] 44 μ g three times weekly for 8 years. Rebif is a purified glycoprotein produced by recombinant DNA technology. Rebif[®] has an amino acid sequence identical to human IFN- β 1a. Interferon modulates the immune system through complex mechanisms and its effect in MS has not been fully clarified. At the time when blood samples were collected (2007 and 2008) the patient was classified as secondary progressive due to a minor gradual decline in physical function after the initial phase with attacks.

During a work up for the etiology of infertility, the function of the anterior pituitary gland was evaluated. The initial laboratory results (performed on two occasions with a 2-month interval) showed highly elevated levels of total IGF-I (664 μ g/L (+5.40 SD) and 757 μ g/L (+6.38 SD)). A subsequent oral glucose tolerance test (OGTT) showed an insufficient suppression of GH [4]. On magnetic resonance imaging (MRI) a 3 mm pituitary microadenoma was suspected. The reproductive hormones were compatible with a post-menopausal state. Thyroid function tests suggested subclinical hypothyroidism (Table I) which is a well-known side-effect to IFN- β treatment [5]. Levels of prolactin, ACTH and cortisol were within normal range.

The patient had no symptoms or signs of acromegaly. Fasting plasma glucose was 4.5 mmol/L, HbA_{1c} was 5.1%, and the patient was normotensive. To differentiate between an early phase of acromegaly and elevated levels of IGF-I induced by IFN- β treatment, we performed a 5-day profile of fasting levels of GH, total IGF-I, IGF-binding protein 3 (IGFBP-3) and bioactive IGF-I. Subsequently IFN- β was withdrawn for 4 weeks, and the patient was re-examined with a second OGTT and by measurements of GH, total IGF-I, IGFBP-3 and bioactive IGF-I.

Laboratory methods

Blood samples were collected during fasting and stored at -20°C . Serum GH was measured by a immunofluorometric assay (TR-IFMA Delfia; Perkin Elmer Life Sciences, Turku, Finland). The GH assay is based on direct sandwich technique using two monoclonal antibodies directed against two different antigenic determinants of the GH molecule. The assay is specific for the 22 KD isoform of human GH. The intra-assay and inter-assay coefficients of variation (CV) were 2.7% and 5.2%, respectively. The initial two serum total IGF-I values were measured by an in-house radioimmunoassay, intra-assay and inter-assay CV 5.4 % and 10.4% [6]. The subsequent measurements of total IGF-I were made by a commercially available method, intra-assay and inter-assay CV 2.1% and 8.2% (Immulite; Siemens Healthcare Diagnostics, Deerfield, Illinois, USA), and confirmed by an in-house IGF-I TR-IFMA, intra-assay and inter-assay CV 5% and 10% [7]. This approach was chosen to verify that our findings were assay independent. It is well recognized that different IGF-I immunoassays yield different IGF-I levels. This is readily explained by the use of different IGF-I calibrators, different methods to circumvent interference from the IGFBPs and different antibodies [8]. Therefore, we decided to use three different assays: a polyclonal-based RIA using des-IGF-I as tracer and acid ethanol extraction and precipitation of the IGFBPs [6], an in-house sandwich assay using monoclonal antibodies and acid ethanol extraction and precipitation of the IGFBPs [7] and finally a commercial sandwich assay using IGF-II blocking of the IGFBPs (Immulite, Siemens). IGFBP-3 was measured by a

commercially available method, intra-assay and inter- Diagnostics, Deerfield, Illinois, USA). IGF-I bioactivity was measured by an in-house IGF-I kinase receptor activation (KIRA) assay, intra-assay and inter-assay 10% and 15% [9].

The reference range used to calculate Z-scores for IGF-I bioactivity was based on 11 lean healthy females with a mean age of 30.7 ± 7.6 years [10].

Results

On the five consecutive days during which IFN- β was injected every second day, higher levels of fasting GH were observed on the 3 days following IFN- β injections (Table I). INF- β also seemed to stimulate secretion of some of the other pituitary hormones (Table I). Serum IGF-I and particularly bioactive IGF-I were highly elevated and showed no fluctuations in relation to IFN- β administrations.

The nadir GH level of the initial OGTT during IFN- β treatment (36 h after last IFN- β injection) was 0.58 $\mu\text{g/L}$ (Figure 1) – an insufficient suppression according to strict criteria [4], suggesting acromegaly as a possible diagnosis. In recent published guidelines a nadir GH level below 0.4 ng/mL is considered a normal response [11]. After 4 weeks off IFN- β treatment, the suppression of GH during OGTT normalized, with a nadir GH of 0.13 $\mu\text{g/L}$ (Figure 1). By contrast to GH levels, there were no changes in serum IGF-I, IGFBP-3 or bioactive IGF-I after withdrawal from IFN- β treatment (Table I). The initial MRI was re-evaluated and now considered normal without any obvious pituitary microadenoma.

Discussion

This case suggests that IFN- β can attenuate suppression of GH by glucose and cause severely elevated levels of total IGF-I (measured by different immunoassays) and bioactive IGF-I similar to that observed in overt acromegaly [9]. Furthermore, four weeks without treatment normalized the suppression of GH during OGTT, whereas IGF-I levels remained elevated. Based on our investigations we have concluded that this patient most likely had increased serum IGF-I secondary to IFN- β treatment and not as a result of a GH-secreting pituitary adenoma. The two OGTTs were made on two different hospitals (but GH levels analysed at the same laboratory) with different local guidelines for GH measurements, i.e. every 30 min or every 15 min. Importantly, if the standard procedure (30 min intervals) had been used at the 2nd OGTT it would not have changed the results or conclusions since the 90 min GH value was also clearly below 0.40 ng/mL (0.18 ng/mL).

The presence of IGFBP-proteolysis, may explain why bioactive IGF-I was relatively more increased than immunoreactive IGF-I (Table I). A previous study in pregnancy indicates that bioactive IGF-I becomes elevated as a result of an increased IGFBP-3 proteolytic activity [12]. This may also apply to MS, which has been associated with an increased activity of numerous proteases that may cleave the IGFBPs and in this way increase levels of bioactive IGF-I [13].

Two previous papers have reported data on total IGF-I levels in MS patients treated with IFN- β . In a study by Hosback et al. IGF-I levels were increased in a group of patients with a longstanding history of MS [3]. In that study no data concerning the specific INF- β medications were provided. In the other study patients were exclusively treated by Avonex[®] (another medication with an amino acid sequence identical to human IFN- β 1a) and no changes in IGF-I levels were reported during 3 months of treatment [2]. Thus, it is possible that the modulating effect on the GH-axis may vary between the different IFN- β medications and that duration of INF- β treatment might also be of importance. Compared to the data reported by Hosback et al. [3] our patient seemed to have more severely elevated

levels of IGF-I. Hence, pronounced inter-individual differences might contribute to the discrepant results reported in the literature. An early study from 1995 reported an increase in IGF-I levels in IFN- α treated patients with hepatitis C, supporting a link between IFN and the GH/IGF-I system [14].

The mechanisms connecting IFN- β treatment and the GH/IGF-I system have not been elucidated. The 5-day GH profile lends some support to the hypothesis that IFN- β has an acute stimulating effect on GH secretion [1,2]. The normalization of GH suppression by OGTT after withdrawal from IFN- β is consistent with this hypothesis. However, an apparent paradox was that 4 weeks without treatment did not reduce IGF-I levels despite normalization of GH suppression by oral glucose. A recent *in vitro* study has shown that IFN- β down regulates the expression of IGF-I receptors on the cell surface [15]. Therefore, it could be speculated that the increased activity of the GH/IGF-I axis could be compensatory to a down regulation of IGF-I receptors and that 4 weeks without treatment does not normalize the number or function of IGF-I receptors. This hypothesis is consistent with the clinical presentation of the patient, who had no discernible symptoms or signs of GH and IGF-I excess despite 8 years on IFN- β treatment. We acknowledge that further studies are required to test this hypothesis.

In conclusion, IFN- β treatment mimicked acromegaly biochemically with attenuated suppression of GH after oral glucose administration and severely elevated levels of immunoreactive and bioactive IGF-I. Thus, it appears that there is a discrepancy between *in vitro* IGF-I bioactivity and the effect *in vivo*.

References

1. Goebel MU, Baase J, Pithan V, Exton M, Saller B, Schedlowski M, Limmroth V. Acute interferon beta-1b administration alters hypothalamic-pituitary-adrenal axis activity, plasma cytokines and leukocyte distribution in healthy subjects. *Psychoneuroendocrinology*. 2002; 27:881–92. [PubMed: 12383450]
2. Then BF, Kumpfel T, Yassouridis A, Lechner C, Holsboer F, Trenkwalder C. Acute and chronic neuroendocrine effects of interferon-beta 1a in multiple sclerosis. *Clin Endocrinol (Oxf)*. 2007; 66:295–303. [PubMed: 17224002]
3. Hosback S, Hardiman O, Nolan CM, Doyle MA, Gorman G, Lynch C, O'Toole O, Jakeman P. Circulating insulin-like growth factors and related binding proteins are selectively altered in amyotrophic lateral sclerosis and multiple sclerosis. *Growth Horm IGF Res*. 2007; 17:472–9. [PubMed: 17697791]
4. Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Bruce JN. Basal and glucose-suppressed GH levels less than 1 microg/L in newly diagnosed acromegaly. *Pituitary*. 2003; 6:175–80. [PubMed: 15237928]
5. Caraccio N, Dardano A, Manfredonia F, Manca L, Pasquali L, Iudice A, Murri L, Ferrannini E, Monzani F. Long-term follow-up of 106 multiple sclerosis patients undergoing interferon-beta 1a or 1b therapy: predictive factors of thyroid disease development and duration. *J Clin Endocrinol Metab*. 2005; 90:4133–7. [PubMed: 15811929]
6. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, Muller J, Hall K, Skakkebaek NE. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab*. 1994; 78:744–52. [PubMed: 8126152]
7. Frystyk J, Dinesen B, Orskov H. Non-competitive time-resolved immunofluorometric assays for determination of human insulin-like growth factor I and II. *Growth Regul*. 1995; 5:169–76. [PubMed: 8745141]
8. Frystyk J, Freda P, Clemmons DR. The current status of IGF-I assays – a 2009 update. *Growth Horm IGF Res*. 2010; 20:8–18. [PubMed: 19818658]

9. Chen JW, Ledet T, Orskov H, Jessen N, Lund S, Whittaker J, De MP, Larsen MB, Christiansen JS, Frystyk J. A highly sensitive and specific assay for determination of IGF-I bio-activity in human serum. *Am J Physiol Endocrinol Metab.* 2003; 284:E1149–E55. [PubMed: 12604504]
10. Frystyk J, Brick DJ, Gerweck AV, Utz AL, Miller KK. Bioactive insulin-like growth factor-I in obesity. *J Clin Endocrinol Metab.* 2009; 94:3093–7. [PubMed: 19470623]
11. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab.* 2010; 95:3141–8. [PubMed: 20410227]
12. Fuglsang J, Sandager P, Moller N, Fisker S, Frystyk J, Ovesen P. Peripartum maternal and foetal ghrelin, growth hormones, IGFs and insulin interrelations. *Clin Endocrinol (Oxf).* 2006; 64:502–9. [PubMed: 16649967]
13. Scarisbrick IA. The multiple sclerosis degradome: enzymatic cascades in development and progression of central nervous system inflammatory disease. *Curr Top Microbiol Immunol.* 2008; 318:133–75. [PubMed: 18219817]
14. Del MP, Bernasconi D, De CV, Randazzo M, Meozzi M, Badaracco B, Mesiti S, Marugo M. Endocrine evaluation in patients treated with interferon-alpha for chronic hepatitis C. *Horm Res.* 1995; 44:105–9. [PubMed: 7590639]
15. Vitale G, van Koetsveld PM, de Herder WW, van der Wansem K, Janssen JA, Colao A, Lombardi G, Lamberts SW, Hofland LJ. Effects of type I interferons on IGF-mediated autocrine/paracrine growth of human neuroendocrine tumor cells. *Am J Physiol Endocrinol Metab.* 2009; 296:E559–66. [PubMed: 19141687]

Figure 1.

GH suppression by oral glucose administration during INF- β treatment and after 4 weeks off treatment. A nadir GH level below 0.4 ng/mL was considered as a normal response.

Table 1

Levels of pituitary hormones, thyroid hormones, cortisol, estradiol, total IGF-I, IGFBP-3 and bioactive IGF-I during INF- β treatment and after 4 weeks off treatment. Bolded values indicate samples obtained in the morning after administration of INF- β . The Z-scores for each measurement of IGF-I, IGFBP-3 and bioavailable IGF-I were calculated according to age and assay specific reference ranges.

	Initial results		5-days profile, INF- β treatment				No INF- β treatment	
GH, $\mu\text{g/L}$			20.7	0.83	3.3	2.51	6.0	5.7
Total IGF-I, $\mu\text{g/L}$, in-house RIA	664	757						
Z-score	+5.40	+6.38						
Total IGF-I, $\mu\text{g/L}$, Immulite, Siemens			408	459	420	451	402	436
Z-score			+3.16	+3.70	+3.29	+3.62	+3.10	+3.46
Total IGF-I, $\mu\text{g/L}$, in-house TR-IFMA			426	418	416	457	458	457
Z-score			+5.84	+5.66	+5.61	+6.55	+6.57	+6.55
IGFBP-3, $\mu\text{g/L}$, Immulite, Siemens			5670	5520	5540	5650	5470	5030
Z-score			+1.27	+1.09	+1.11	+1.25	+1.02	+0.47
IGF-I bioactivity, $\mu\text{g/L}$, in-house KIRA			4.9	5.7	5.4	4.7	3.8	5.1
Z-score			+13.3	+15.8	+14.8	+12.5	+9.5	+13.8
Prolactin, mIU/L (<600 mIU/L)	76	73	176	99	144	103	140	106
FSH, U/L	41	57	57	49	51	51	52	56
LH, U/L	32	41	49	38	43	41	42	42
Estradiol, nmol/L	0.06	0.04	<0.026	<0.026	<0.026	<0.026	<0.026	<0.026
ACTH, ng/L (0–46 ng/L)	14							
Cortisol, nmol/L (200–600 nmol/L)	309							
TSH, mIU/L (0.5–4.0 mIU/L)	7.1	4.1	9.3	5.0	6.4	5.5	5.2	4.6
Free T3, pmol/L (4.0–6.8 pmol/L)	5.1	4.9						
Free T4, pmol/L (12.8–20.4 pmol/L)	13.0	12.0						
Total T3, nmol/L (1.0–2.6 nmol/L)			2.2	2.0	2.4	2.3	2.2	2.5
Total T4, nmol/L (60–140 nmol/L)			90	96	91	84	83	82