Endocrine (2019) 65:710–713
https://doi.org/10.1007/s12020-019-01998-7

RESEARCH LETTER

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Sweat and vitamin D status in congenital, lifetime, untreated GH deficiency

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Received: 22 May 2019 / Accepted: 28 June 2019 / Published online: 10 July 2019

Abstract

Purpose A reciprocal relationship exists between the skin and the GH/IGF-I axis. Skin produces both IGF- I and vitamin D, and GH and IGF-I exert several actions in the skin. Reduced sweating and altered phosphor-calcium homeostasis are occasionally reported in subjects with GH deficiency (GHD), mostly in the setting of hypopituitarism, therefore associated to other hormonal deficiencies. It is unclear whether these findings are due to GHD. The aim of this study was to assess skin function in subjects with isolated GHD (IGHD) due to a mutation in the GHRH receptor gene.

Methods In a cross-sectional study we enrolled 20 IGHD and 20 local controls. Sweating (volume, conductivity and chloride content) was assessed by a 30 min pilocarpine iontophoresis test, using the Macroduct® Sweat Collection System. IGF-I, Insulin, PTH, 25-hydroxyvitamin D, C-reactive protein (CRP), CPK, glucose, calcium, phosphate, alkaline phosphatase, total proteins and fractions, urinary calcium, and insulin were measured. HOMA-IR was calculated.

Results IGHD presented lower sweating, but normal vitamin D and phosphor-calcium homeostasis. Additionally, IGHD subjects presented lower HOMA-IR, higher CRP and reduced CPK.

Conclusion Untreated IGHD cause reduction in sweating, but does not affect phosphor-calcium homeostasis.

KeyWords GH deficiency · skin · sweat · vitamin D

Introduction

Skin has many functions, some protective (against microorganisms, dehydration, ultraviolet light, and mechanical damage) and other homeostatic (sweating and production of vitamin D). A mutual influence exists between the skin and the growth hormone/insulin growth factor I (GH/IGF-I) axis. Skin produces IGF-I and vitamin D, and GH and IGF-I exert several actions on the skin [1, 2]. Therefore, alterations of the GH–IGF-I axis may influence sweating and the phosphorus–calcium homeostasis.

Sweating is essential for thermoregulation, exercise capacity, and exposure to high ambient temperatures [3]. Patients with childhood-onset GH deficiency (COGHD) have impaired sweating ability [3]. Sweating impairment has been also reported in men with adult-onset GHD [4]. Laron's dwarfs, affected by GH insensitivity, also exhibit impaired sweating ability [5].

During exposure to sunlight, ultraviolet radiation penetrates into the epidermis and photolyzes the synthesis of vitamin D. A variable prevalence of vitamin D insufficiency or deficiency has been described in patients with GHD, and the latter was suggested to be a risk factor for vitamin D deficiency [6–8].

We have identified in northeast Brazil a cohort of subjects with severe isolated GHD (IGHD) caused by a homozygous (c.57+1G>A) mutation in the GHRH receptor gene (*GHRHR*) [9]. These individuals have normal longevity and quality of life and are quite active [10], coping well with their environmental challenges, often working outdoor under high solar exposure [11, 12]. The objectives of this study were to evaluate sweating, vitamin D

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production, and phosphorus–calcium homeostasis in this unique IGHD cohort.

Subjects and methods

Subjects

A cross-sectional study enrolled 20 (11 males) IGHD and 20 (11 males) control subjects matched by age and sex, recruited in the Itabaianinha County. This city (latitude 11° 16'22" S, longitude 37°48'57" W, and altitude 225 m) has a warm humid tropical climate, with high level of ultraviolet radiation during most of the day, high temperatures all year long, and small thermal excursion [13].

Inclusion criteria for IGHD was homozygous c.57 +1A→G *GHRHR* mutation; for the control group, individuals of normal height and homozygous for the wild-type *GHRHR* allele. Exclusion criteria were age <25 years and >80 years, use of glucocorticoids, GH replacement therapy (GHRT), and levothyroxine, sedative, or anticonvulsant drugs.

Study protocol

Anthropometric measurements

Height and weight were measured, and body mass index was calculated.

Laboratory analyses

Fasting blood samples were collected between 0700 and 0900 h. Insulin sensitivity was estimated by the homeostasis model assessment index of insulin resistance (HOMA-IR), with the formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5. Following the recommendations of the Brazilian Society of Endocrinology and Metabolism [14], vitamin D deficiency was defined when 25-hydroxyvitamin D was <12 ng/dl, insufficiency from 12 to 20 ng/dl, and sufficiency ≥20 ng/dl. The 24-h urinary calcium was corrected by the body weight.

Sweat stimulation protocol

Sweat collection was performed using electrodes with pilocarpine gel disks (Pilogel®) applied over the forearm skin and the passage of an electric current of 1.5 mA for 5 min. After iontophoresis, the area was cleaned with distilled water, the macroduct® collector was tightened for 30 min and a minimum amount of 15 μl was collected. A Sweat-Chek® analyzer device measured the conductivity of the sample and converted the measured values into sodium chloride molarity unit equivalents. The value of conductivity was that value when the reading stabilized for approximately 10 s. The sweat chloride content was evaluated using the colorimetric test (Quibasa Química Básica Ltda, Belo Horizonte – MG, CEP 31565-130, Brazil), with sensitivity of 0.960 mEq/l.

Statistics

Kolmogorov–Smirnov and Shapiro–Wilk test were used to test variables that have a normal distribution. The variables with normal distribution were expressed as mean (standard deviation) and compared by Student's t test. The variables with non-normal distribution (IGF-I, sweating volume, C-reactive protein (CRP), insulin, and HOMA-IR) were expressed as median (interquartile range) and compared by Mann–Whitney test. Correlations between sweating and anthropometric or metabolic parameters were assessed by the Pearson or Spearman's (r) correlation coefficients. The number and percentage of patients with vitamin D deficiency, vitamin D insufficiency, and vitamin D sufficiency were compared by Fisher's exact test.

Results

Anthropometric, sweating, 25-hydroxyvitamin D, and phosphorus–calcium homeostasis data are shown in Table 1. As expected, height, weight, and urinary volume were significantly lower in IGHD. Sweating was markedly reduced and significantly altered in IGHD. One IGHD subject did not produce any sweat during two attempts of collection. Serum levels of 25-hydroxyvitamin D and all the phosphorus–calcium homeostasis data were similar to controls. IGHD subjects also showed higher CRP, lower HOMA-IR, and lower levels of creatinine phosphokinase. There were positive correlations between the sweat volume to IGF-I ($r = 0.350$, $p = 0.029$) and to HOMA-IR ($r = 0.278$, $p = 0.023$) in the pooled groups, abolished in each group separately. The number of subjects with vitamin D deficiency, insufficiency, or sufficiency was similar in the 2 groups: 18 sufficient, 1 insufficient and 1 deficient in IGHD; 19 sufficient and 1 insufficient in controls.

Discussion

We describe sweating and phosphorus–calcium metabolism in adults with lifetime, untreated IGHD. We found that IGHD subjects exhibit significant impairment of sweating but have serum levels of 25-hydoxyvitamin D, parathyroid hormone, and phosphorus–calcium levels that are similar to the ones of healthy controls from the same region.

The sweat finding is not surprising, given the fact that GH receptor is widely expressed by several cutaneous cells

Table 1 Anthropometric, sweat, 25-hydroxyvitamin D, and phosphorus–calcium homeostasis data in subjects with isolated GH deficiency (IGHD) and controls

Variables	IGHD	Controls	*p*
Age (years)	49.4 (13.4)	48.9(13.6)	0.898
Males	11	11	1
Height	1.3 (0.1)	1.6 (0.1)	<0.0001
Weight	40.6 (6.4)	77.8 (15.0)	<0.0001
Urinary volume (ml)	686.0 (312.1)	1082 (506.6)	0.006
Sweat volume	20 (19.7)	30 (33.0)	0.012
Sweat chloride	23.4 (17)	14 (5.8)	0.019
Sweat conductivity	43 (14)	31.5 (11)	0.006
IGF-I (ng/ml)	25.0 (6.6)	162.0 (30.5)	<0.0001
Insulin (μU/l)	3.9 (5.7)	7.7 (3.8)	0.003
HOMA-IR	0.9 (1.5)	2.2 (1.2)	0.002
CPK (U/l)	96.9 (48.8)	152.3 (63.4)	0.005
Urinary volume (ml)	686.0 (312.1)	1082 (506.6)	0.006
C-reactive protein	4.0 (4.0)	3.0 (0.0)	<0.001
25-hydroxyvitamin D (ng/dl)	30.2 (8.6)	31.26 (7.5)	0.692
PTH (pg/ml)	56.8 (22.0)	57.5 (20.8)	0.921
Calcium (mg/dl)	10.0 (0.3)	11.0 (0.5)	0.666
Alkaline phosphatase (U/l)	189.8 (70.8)	169. 2 (47.6)	0.290
Phosphate (mg/dl)	3.8 (0.5)	3.6 (0.4)	0.251
Albumin (g/dl)	3.8 (0.5)	4.4 (0.5)	0.185
Urinary Ca (mg/dl/BW Kg)	1.2 (1.2)	1.6 (1.0)	0.224

Data are expressed in mean (standard deviation), except for sweat volume, IGF-I, CRP, insulin, and HOMA-IR that are expressed in median (interquartile range)

Ca calcium, *GH* growth hormone, *BW* body weight, *IGF-I* insulin growth factor I, *HOMA-IR* homeostasis model assessment index of insulin resistance, *CPK* creatinine phosphokinase, *PTH* parathyroid hormone

(melanocytes, keratinocytes, sebocytes, dermal fibroblast, hair matrix cells, endothelial cells, Schwann cells, adipocytes, and the ductal cells of the sweating glands). The reduction of the sweat volume agrees with previous data obtained in patients with GHD associated with other hormonal deficiencies [2, 3]. In a study of adults with COGHD, the sweat volume after pilocarpine was significantly reduced and not fully normalized by GHRT [3]. This study showed that the area of sweat gland glomeruli was significantly decreased in the untreated patients but not different between the GH-treated patients and controls. One explanation for these findings may be that GH exerts both a structural and a functional effect on the sweat glands and that GHRT may be unable to completely revert functional abnormalities [3]. Our data agree with these observations, as the sweating in our IGHD subjects was not only reduced but also qualitatively changed, with both sweat chloride content and conductivity increased in comparison to controls. Curiously, one female IGHD subject did not produce any sweat even after two attempts at collection. Sweating impairment may increase the risk of hyperthermia, particularly important for these subjects living in a tropical climate. As these IGHD subjects are quite active, often working in outdoor environment under high sun exposure, they were informed of the possible consequences of their impaired sweating.

The IGHD subjects have normal 25-hydroxyvitamin D levels and normal phosphorus–calcium homeostasis. These data agree with previous findings of normal volumetric bone mineral density [15] and may contribute to the lack of increased prevalence of vertebral fractures, although currently there is no evidence that fracture risk in GHD is correlated with either vitamin D deficiency or calcium/phosphorus abnormalities [16]. These IGHD subjects are quite active [10] and often work outdoor under direct sun exposure, possibly contributing to their high normal D levels, as expected of their geographic area [13], differently from reports of higher frequency of hypovitaminosis D in GHD individuals [8, 17, 18].

In conclusion, subjects with congenital IGHD exhibit reduction in sweating but normal 25-hydroxyvitamin D levels and phosphorus–calcium homeostasis. While the impairment of sweating capacity may cause increased risk of hyperthermia, the normal 25-hydroxyvitamin D levels and normal phosphorus–calcium homeostasis may contribute to the healthy bone phenotype.

Acknowledgements The authors thank the Associação do Crescimento Físico e Humano de Itabaianinha for assistance.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. C.C. Zoubolis, The human skin as a hormone target and an endocrine. Hormones **3**(1), 9–26 (2004)
2. C. Kanaka-Gantenbein, C. Kogia, M.B. Abdel-Naser, G.P. Chrousos, Skin manifestations of growth hormone-induced diseases. Rev. Endocr. Metab. Disord. **17**(3), 259–267 (2016)
3. M. Lange, J. Thulesen, U. Feldt-Rasmussen, N.E. Skakkebñk, N. Vahl, J.O. Jørgensen, J.S. Christiansen, S.S. Poulsen, S.B.

Sneppen, A. Juul, Skin morphological changes in growth hormone deficiency and acromegaly. Eur. J. Endocrinol. **145**(2), 147–153 (2001)
4. S.A. Pedersen, K. Welling, K.F. Michaelsen, J.O. Jørgensen, J.S. Christiansen, N.E. Skakkebaek, Reduced sweating in adults with growth hormone deficiency. Lancet **2**(8664), 681–682 (1989)
5. K. Main, K.W. Kastrup, N.E. Skakkebaek, Reduced sweating in Laron's dwarfism. Arch. Dis. Child. **65**(12), 1380 (1990)
6. P. Ameri, A. Giusti, M. Boschetti, G. Murialdo, F. Minuto, D. Ferone, Interactions between vitamin D and IGF-I: from physiology to clinical practice. Clin. Endocrinol. (Oxf.) **79**(4), 457–463 (2013)
7. E. Witkowska-Sędek, A. Kucharska, M. Rumińska, B. Pyrżak, Relationship between 25 (OH) D and IGF-I in children and adolescents with growth hormone deficiency. Adv. Exp. Med. Biol. **912**, 43–49 (2016)
8. A. Ciresi, F. Cicciò, C. Giordano, High prevalence of hypovitaminosis D in Sicilian children affected by growth hormone deficiency and its improvement after 12 months of replacement treatment. J. Endocrinol. Invest. **37**(7), 631–638 (2014)
9. R. Salvatori, C.Y. Hayashida, M.H. Aguiar-Oliveira, J.A. Phillips 3rd, A.H. Souza, R.G. Gondo, S.P. Toledo, M.M. Conceição, M. Prince, H.G. Maheeshwari, G. Baumann, M.A. Levine, Familial dwarfism due to a novel mutation of the growth hormone-releasing hormone receptor gene. J. Clin. Endocrinol. Metab. **84**(3), 917–923 (1999)
10. A.L. Andrade-Guimarães, M.H. Aguiar-Oliveira, R. Salvatori, V. O. Carvalho, F. Alvim-Pereira, C.R.A. Daniel, G.A.M. Brasileiro, A.A. Santana-Ribeiro, H.A. Santos-Carvalho, C.R.P. Oliveira, E. R. Vieira, M.B. Gois-Junior, Adult individuals with congenital, untreated, severe isolated growth hormone deficiency have satisfactory muscular function. Endocrine **63**(1), 112–119 (2019)
11. M.H. Aguiar-Oliveira, A.H.O. Souza, C.R.P. Oliveira, V.C. Campos, L.A. Oliveira-Neto, R. Salvatori, Mechanisms in endocrinology: the multiple facets of GHRH/GH/IGF-I axis: lessons from lifetime, untreated, isolated GH deficiency due to a GHRH receptor gene mutation. Eur. J. Endocrinol. **177**(2), R85–R97 (2017)
12. M.H. Aguiar-Oliveira, A. Bartke, Growth hormone deficiency: health and longevity. Endocr. Rev. **40**(2), 575–601 (2019)
13. C.G. Marinho, L.M. Mermejo, R. Salvatori, J.A. Junior Assirati, C.R.P. Oliveira, E.G. Santos, Â.C.G.B. Leal, C.S. Barros-Oliveira, N.P. Damascena, C.A. Lima, C.T. Farias, A.C. Moreira, M. H. Aguiar-Oliveira, Occurrence of neoplasms in individuals with congenital, severe GH deficiency from the Itabaianinha kindred. Growth Horm. IGF Res. **41**(2018), 71–74 (2018)
14. C.E.S. Ferreira, S.S. Maeda, M.C. Batista, M. Lazaretti-Castro, L. S. Vasconcellos, M. Madeira, L.M. Soares, V.Z.C. Borba, B.C.C. Silva, C.A. Moreira, Consensus – reference ranges of vitamin D [25(OH)D] from the Brazilian medical societies. Brazilian Society of Clinical Pathology/Laboratory Medicine (SBPC/ML) and Brazilian Society of Endocrinology and Metabolism (SBEM). J. Bras. Patol. Med Lab. **53**(6), 377–381 (2017)
15. C.C. Epitácio-Pereira, G.M. Silva, R. Salvatori, J.A. Santana, F.A. Pereira, M.B. Gois-Junior, A.V. Britto, C.R. Oliveira, A.H. Souza, E.G. Santos, V.C. Campos, R.M. Pereira, E.H. Valença, R.A. Barbosa, M.I. Farias, F.J. de Paula, T.V. Ribeiro, M.C. Oliveira, M.H. Aguiar-Oliveira, Isolated GH deficiency due to a GHRH receptor mutation causes hip joint problems and genu valgum, and reduces size but not density of trabecular and mixed bone. J. Clin. Endocrinol. Metab. **98**(11), E1710–E1715 (2013)
16. G. Maziotti, S. Frara, A. Giustina, Pituitary diseases and bone. Endocr. Rev. **39**(4), 440–488 (2018)
17. R.T. Hamza, A.I. Hamed, M.T. Sallam, Vitamin D status in prepubertal children with isolated idiopathic growth hormone deficiency: effect of growth hormone therapy. J. Invest. Med. **66**(5), 1–8 (2018)
18. M. Kužma, N. Binkle, A. Bednárová, Z. Killinger, P. Vaňuga, J. Payer, Trabecular bone score change differs with regard to 25 (OH) D levels in patients treated for adult-onset growth hormone deficiency. Endocr. Pract. **22**(8), 951–958 (2016)