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Climacteric in untreated isolated growth hormone deficiency

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Abstract

Objective—To study the time, intensity of symptoms, hormonal profile, and related morbidity of climacteric in women with untreated isolated growth hormone (GH) deficiency (IGHD).

Design—Women belonging to a large Brazilian kindred with IGHD due to a homozygous mutation in the GH-releasing hormone receptor gene were studied. None of them had ever received GH replacement therapy. A two-step protocol was performed. In the first case-control experiment, aimed to determine the age at climacteric, we compared eight women with IGHD and 32 normal women between 37 and 55 years of age. In the second cross-sectional experiment, aimed to determine the severity of climacteric symptoms, seven women with IGHD (aged 47–65 y) were compared with 13 controls (aged 44–65 y). The Kupperman Index scores, serum follicle-stimulating hormone, luteinizing hormone, prolactin, and estradiol levels were determined, and pelvic and mammary ultrasonography, mammography, and colpocytology were performed.

Results—The number of women with follicle-stimulating hormone above 20 mIU/mL was higher in women with IGHD than controls. Kupperman's Index was not different between the two groups. Menarche had been delayed and parity was lower in women with IGHD. Hormonal profile was similar, but prolactin was lower in women with IGHD. Uterine volume was smaller in women with IGHD, and endometrial thickness and ovarian volume were similar in the two groups. No difference in breast images or in colpocytology was observed between the two groups.

Conclusions—Menarche was delayed and the beginning of climacteric is anticipated in untreated lifetime IGHD, but menopausal symptoms and hormonal profile resemble the normal climacteric.

Keywords

Climacteric; Growth hormone deficiency; Growth hormone; Releasing hormone receptor; Gene mutation

Climacteric usually occurs between 40 and 55 years of age and is characterized by the exhaustion of the ovarian follicles with the reduction of serum inhibin and estradiol and an increase in serum follicle-stimulating hormone (FSH), with menstrual cycle abnormalities usually appearing when FSH is above 20 mIU/mL and menopause occurring when it is above 40 mIU/mL. Climacteric causes several genital, urinary, nervous, metabolic, and cardiovascular alterations.¹

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The relationships between growth hormone (GH) and menopause are not fully understood. In rodents, GH deficiency (GHD) reduces litter size and the number of primordial follicles, suggesting that GH is required for normal female reproductive function female.² In humans, the accomplishment of puberty requires a critical weight,³ and individuals with untreated GHD reach this weight at a later age, and they usually therefore present with delayed puberty. GH has important modulatory effects on gonadotropin-dependent and -independent functions of the ovary, affecting gametogenesis and steroidogenesis.⁴ Accordingly, GH therapy has been used in assisted reproduction with different outcomes.^{5,6} However, the effects of lifetime untreated GHD on climacteric are not known.

In Itabaianinha, a county in the northeastern Brazilian state of Sergipe, we identified an extended pedigree with approximately 100 individuals over eight generations with isolated GHD (IGHD). This is due to a homozygous splice mutation at the beginning of the intron 1 (IVS1 + 1G>A) of the GH-releasing hormone (GHRH) receptor (GHRHR) gene, predicted to result in a severely truncated receptor.⁷ These individuals present with dwarfism (adult height 105-135 cm) with very low serum GH and insulinlike growth factor I (IGF-I).⁸ Despite a risk profile for cardiovascular diseases,⁹⁻¹¹ they do not have premature atherosclerosis or early mortality.¹² The affected women constitute an excellent opportunity to evaluate the effects of a lifetime of severe and untreated IGHD (with otherwise normal pituitary function) on climacteric. In this study, we tested the hypothesis that climacteric is anticipated in women with IGHD, as suggested by animal models, and we evaluated the intensity of menopausal symptoms, sexual and reproductive aspects, the hormonal profile, and the morbidity associated with climacteric.

METHODS

Experiment 1

At present, there are 59 individuals with IGHD living in Itabaianinha, 28 of whom are women. Of these, 14 are younger than 37 years and one is 84 years old. Eight of the remaining 13, between 37 and 55 years of age (45.6 ± 6.8 y), were enrolled in the first study aimed at testing the hypothesis that early climacteric is anticipated in women with IGHD. To this end, we studied their FSH serum levels and compared them with those of 32 age-matched normal individuals (46.1 ± 6.1 y), all from Itabaianinha County. Control women were chosen (by age-matching four controls for each woman with IGHD) from volunteers enrolled in a large protocol designed to analyze the phenotype of normal-appearing individuals who are heterozygous for the IVS1 + 1G>A mutation.¹³ These participants were recruited by ads and word of mouth among the inhabitants of Itabaianinha. The only inclusion criterion was the place of residence (Itabaianinha County). The exclusion criteria were GH and estrogen replacement therapy. All the controls were homozygous for the wild-type allele.

Experiment 2

We identified seven menopausal women (two from the IGHD group in experiment 1 and five additional ones) with IGHD (FSH >20 mIU/mL and hot flushes or the presence of menstrual cycle irregularities during the past year) aged 47 to 65 years and compared them with 13 controls homozygous for the wild-type allele aged 44 to 65 years (no overlap with the control group in experiment 1). The controls were recruited by an ad posted in the local health clinic, and they were all confirmed to be homozygous for the wild-type GHRH-R allele. Estrogen replacement therapy was an exclusion criterion. The individuals were transported from the municipal district of Itabaianinha to the University Hospital of Federal University of Sergipe in Aracaju, the capital of Sergipe. Body mass index (BMI) was calculated with the formula: $BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$. We defined climacteric in two phases based on the menstrual history in the past year: premenopause (menstrual cycles were maintained) and postmenopause

(spontaneous amenorrhea lasting 12 consecutive months or more). To evaluate the prevalence and intensity of the climacteric symptoms, we used the Kupperman Index,¹⁴ which consists of 11 items (hot flushes, paresthesia, insomnia, nervousness, melancholy, vertigo, weakness, arthralgia, headache, palpitation, and formication); weighted score (WS) of the 11 items of the Kupperman Index were calculated as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Hot flushes are weighted (multiplied) by a factor of 4. Paresthesia, insomnia, and nervousness are weighted by 2 and the others by a factor by 1. The total sum is the final score, graded as mild (up to 19), moderate (20-35), and intense (>35).

The protocol was approved by the ethical committee of the Federal University of Sergipe. All individuals signed informed consent.

Hormonal measurements were obtained after overnight fasting. If the women had menses, blood was collected at the fifth day of the cycle. Fluoroimmunoassays were used to measure FSH, luteinizing hormone, estradiol, and prolactin (Perkin Elmer Life and Analytical Science, Wallac Oy Turku, Finland). The sensitivities were 0.05 mIU/L, 0.05 mIU/L, 8.17 pg/mL, and 0.04 ng/mL, respectively. The intra- and interassay variabilities were 1.4% and 2.6%, 4.3% and 2.6%, 4.2% and 2.0%, and 1.4% and 2.6%, respectively.

Mammography was performed with a Medicor apparatus (Median HFG) using the Bi-Rads (breast imaging reporting and data system) categories.¹⁵ The colpocytology smear was obtained in a triple sampling, removing the scraped bottom of the vaginal sack, ectocervix, and endocervix, using an Ayres spatula and brushing the cervical collection.

Data are presented as mean $\pm$ SD for number and frequency of nominal variables. In experiment 1, a binomial test was used. In experiment 2, Student's *t* test, Mann-Whitney *U* test (Kupperman Index), and χ^2 test (nominal variables) were used to compare the two groups. The level of significance was set at $P < 0.05$.

RESULTS

The number of women with FSH above 20 mIU/mL was higher in the IGHD group than in the control group (5/8, 62.5% vs 14/32, 43.7%; $P = 0.02$) (Table 1), suggesting that climacteric starts earlier in women with untreated IGHD.

Anthropometric, body composition, and blood pressure data for experiment 2 are shown in Table 2. There was no significant difference in the total Kupperman Index score between IGHD and control groups (13.17 ± 9.28 vs 16.00 ± 10.50). There were no differences in the intensity of Kupperman Index between IGHD and controls: mild 71.4% vs 76.9%, moderate 28.6% vs 15.45%, and intense 0.0% vs 7.7%, respectively. The weighted score of hot flushes in IGHD was higher than in the control group; the scores of paresthesia, nervousness, vertigo, and headache were higher in the control group than the IGHD group, with no differences in the others symptoms (Table 3).

Dyspareunia was reported less frequently in the IGHD group than in controls (0% vs 23.1%). There were no differences in other sexual aspects: coital bleeding (0% vs 7.7%) and the presence of libido (85.7% vs 84.6%) and orgasms (100% vs 69.2%). Reproductive aspects are presented in Table 4. Menarche and first sexual relationship were delayed in the IGHD group in comparison with controls. Table 5 displays the hormonal levels of the groups. Only prolactin was lower in the IGHD group than in the control group.

Uterine volume was smaller in the IGHD group than the control group (42.26 ± 9.78 vs 88.68 ± 63.13 cm³, $P < 0.05$), whereas endometrial length (0.64 ± 0.14 vs 0.68 ± 0.30 cm) and the volumes of the right (3.13 ± 1.52 vs 3.93 ± 2.86 cm³) and left (3.49 ± 2.34 vs 4.61 ± 2.62

cm³) ovaries were not different between the two groups. One women with IGHD and three control individuals presented with one uterine fibroma. One women with IGHD and two controls had a breast cyst. Two cases of fibrocystic mammary disease were found in the control group. There was no significant difference in colpocytology findings between the two groups.

DISCUSSION

Although it has been reported that GHD causes delay in the age at menarche, no data are available on the age at and symptoms of menopause in women with untreated IGHD. This is because IGHD is a rare disease and most individuals with GHD receive GH replacement therapy or have multiple pituitary hormone deficiencies, including gonadotropins. The Itabaianinha population offers the unique opportunity to study the effect of lifetime untreated, severe IGHD on reproductive function.

The first part of our work suggests that climacteric occurs sooner in women with IGHD than in normal women of the same region, as assessed by the increased number of middle-aged women with elevated FSH. These data are in agreement with data from rodents, in which GHD reduces the number of primordial follicles, suggesting that reproductive function requires adequate concentrations of GH and/or of its principal mediator IGF-I and that reduced concentrations of these hormones may have caused the anticipation of the climacteric age in our IGHD participants.²

The second part of this study evaluated the climacteric symptoms in seven women with IGHD compared with age-matched controls from the same community. Women with IGHD had reduced weight and height, as previously reported.^{7,8} Both groups were slightly overweight (by BMI), similar to other Brazilian climacteric women (63.5%).¹⁶

The Kupperman Index scores were not different between the IGHD and control groups. The percentages of symptoms of mild intensity were also similar, apparently less severe than that previously reported in other Brazilian women.¹⁷

Most of the Kupperman Index scores were not different between the two groups. The weighted score of hot flushes (multiplied by a factor of 4) and of three less weighted scores (paresthesia and nervousness multiplied by 2 and headache by 1) were, respectively, higher and lower in the IGHD than the control groups. Insomnia was not different between the two groups. These results show an overall similar symptomatology of climacteric in the two groups.

Animals with defects in the GHRH axis have a reduction in nonrapid eye movement sleep, which is not reversed by the GH administration,¹⁸ suggesting a direct effect of GHRH on sleep. We did not find any difference in the weighted score for insomnia in our IGHD group despite the absence of GHRH activity. Although the accuracy of sleep perception can vary,¹⁹ the prevalence of insomnia was similar to that previously reported (29%) in normal climacteric Brazilian women.²⁰

Menarche in the IGHD group occurred later than in controls. To reach menarche and to start the reproductive cycle, it is necessary to reach a critical weight above 40 kg.^{21,22} In a Brazilian study, 43% of the girls reached menarche by age 12 years and 75% by age 13 years, with a mean weight of 44 and 47 kg, respectively.²³ Therefore, it is likely that the delay in menarche in our IGHD women was due to a delay in reaching a critical weight.

Age at menopause (expressed as the age of the complete disappearance of menstruation) was nonstatistically different between the IGHD and control groups. The age of menopause in controls was within the age range of normality reported in different ethnic groups.²⁴

Women with IGHD had lower parity and number of offspring than the control group. This may be related to the need for cesarean births performed on all the IGHD women because of cephalic-pelvic disproportion. A shorter reproductive life due to the late menarche and earlier climacteric and later occurrence of first intercourse can also contribute to the lower parity.

FSH, LH, and estradiol levels were similar in the two groups and in the range expected at the climacteric age.²⁵ However, prolactin levels were lower in IGHD women. This is likely due to the reduction of the pituitary volume observed in these women.²⁶ Although no pathology data are available, such hypoplasia is likely predominantly due to a reduction in somatotroph cells, as seen in a mouse model of GHRH-R deficiency.²⁷ As the nighttime secretion of prolactin is also regulated by GHRH,²⁸ the lack of GHRH action may also explain the reduced level.

The uterine volume was smaller in the IGHD group than in the control group. This could be a consequence of reduced parity or of the effect of the lack of GH and/or IGF-I on uterine development. The dimensions of the ovarian volume were within normal limits for woman in the climacteric age for both groups.²⁹

Mammography density is a strong risk factor for breast cancer, and it correlates with serum GH and IGF-I levels.³⁰ In addition, a correlation between the prevalence of breast cancer and serum IGF-I levels has been reported in women older than 50 years,³¹ and a higher prevalence of squamous intraepithelial lesions was reported in women with serum IGF-I in the highest quartile.³² Therefore, we would expect a reduced risk of breast and cervical cancer in IGHD women. We found that 82.5% of IGHD women had normal breasts with mammographic evidence of fat infiltration and one case of a mass that was diagnosed by ultrasonography as a cyst. In the control group, breasts with fat infiltration were observed in 69.5%, with three cases of nodules that the ultrasound scan found to be cysts or fibrocystic mammary disease. No woman in either of the two groups had any evidence of breast or cervical cancer. For this reason, we cannot comment on the antiproliferative effects of IGF-I deficiency on female cancer risk in our women with IGHD.

CONCLUSION

In conclusion, climacteric seems to start earlier in women with untreated lifetime IGHD than in normal women, but its symptom-intensity, clinical aspects, sexual behavior, and hormonal profile resemble normal climacteric.

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TABLE 1

Age and FSH in eight individuals with IGHD and 32 age-matched controls

	IGHD		Control	
	Age, y	FSH, mIU/mL	Age, y	FSH, mIU/mL
IGHD1	37	5.10	37	11.4
			37	9.1
			37	3.1
			37	12.3
IGHD2	38	8.62	38	5.69
			38	22.3
			39	8.2
			39	5.2
IGHD3	39	3.77	39	67.8
			41	11.6
			41	22.4
			41	7.0
IGHD4	47	21.0	47	2.96
			48	11.4
			48	2.97
			48	13.5
IGHD5	48	52.3	49	6.62
			49	38.4
			49	61.7
			49	3.1
IGHD6	49	53.9	50	55.2
			50	75.4
			51	8.0
			51	94.9
IGHD7	52	103.0	52	41.6
			52	14.2
			52	78.0
			52	52.3
IGHD8	55	68.6	53	46.7
			53	115.0
			53	4.9
			54	68.1

FSH levels higher than 20 mIU/mL are in bold. IGHD, isolated growth hormone deficiency; FSH, follicle-stimulating hormone.

TABLE 2

Anthropometric and blood pressure data on seven growth hormone-deficient women and 13 control climacteric women

Variables	IGHD	Control	<i>P</i>
Age, y	55.86 ± 8.69	53.31 ± 5.25	0.497
Weight, kg	36.41 ± 7.29	62.26 ± 11.42	<0.0001
Height, cm	117.43 ± 4.08	154.12 ± 6.38	<0.0001
BMI, kg/m ²	26.55 ± 5.83	26.31 ± 4.90	0.926
Systolic BP, mm Hg	131.43 ± 19.52	129.23 ± 12.56	0.794
Diastolic BP, mm Hg	84.29 ± 20.70	83.85 ± 5.06	0.958

Data are mean ± SD. IGHD, isolated growth hormone deficiency; BMI, body mass index; BP, blood pressure.

TABLE 3

Weighted score (WS) of the 11 items of the Kupperman Index in seven isolated growth hormone-deficient (IGHD) women and 13 control climacteric women

Symptom	IGHD	Control	<i>P</i>
	WS/total (%)	WS/total (%)	
Hot flush	36/84 (43)	36/156 (23)	<0.0001
Paresthesia	6/42 (14)	30/78 (38)	0.001
Insomnia	12/42 (29)	28/78 (36)	0.205
Nervousness	12/42 (29)	48/78 (61.5)	<0.0001
Melancholy	7/21 (33)	10/39 (26)	0.278
Vertigo	0/21	0/39	Not feasible
Weakness	5/21 (24)	11/39 (28)	0.433
Arthralgia	8/21 (38)	13/39 (33)	0.398
Headache	3/21 (14)	14/39 (36)	0.028
Palpitation	6/21 (28.5)	8/39 (20.5)	0.249
Formication	6/21 (28.5)	10/39 (26)	0.459

Score range includes 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Hot flushes are weighted (multiplied) by a factor of 4. Paresthesia, insomnia, and nervousness are weighted by 2 and the others by a factor of 1. In each group, the WS for each symptom and the rate of the maximal possible amount are indicated.

TABLE 4

Reproductive aspects in seven growth hormone deficient-and 13 control climacteric women

Variable	IGHD	Control	<i>P</i>
Age at menarche (y)	17.57 ± 2.23	13.62 ± 1.33	<0.0001
Age at menopause (y)	52.20 ± 4.21	48.25 ± 3.06	0.075
Age at first intercourse (y)	28.20 ± 13.14	19.69 ± 5.60	0.065
No. of gestations	2.00 ± 0.00	5.50 ± 3.50	0.005
No. of births	1.75 ± 0.50	4.67 ± 2.90	0.006
Breast-feeding (d)	145.25 ± 186.04	402.75 ± 581.88	0.201

Data are mean ± SD. IGHD, isolated growth hormone deficiency.

TABLE 5

Hormonal profile in seven growth hormone deficient-women and 13 control climacteric women

Variables	IGHD	Control	<i>P</i>
FSH, mIU/mL	55.91 ± 37.01	52.76 ± 27.25	0.830
LH, mIU/mL	32.09 ± 22.19	23.32 ± 14.91	0.304
Prolactin, ng/mL	3.86 ± 1.91	6.58 ± 3.26	0.030 ^a
Estradiol, pg/mL	24.89 ± 20.29	49.13 ± 38.22	0.080

Data are mean ± SD. IGHD, isolated growth hormone deficiency; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

^aStatistically significant difference.