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Walking and postural balance in adults with severe short stature due to isolated GH deficiency

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Abstract

Objectives: Walking and postural balance are extremely important to obtain food and to work. Both are critical for quality of life and ability to survive. While walking reflects musculoskeletal and cardiopulmonary systems, postural balance depends on body size, muscle tone, visual, vestibular and nervous systems. Since GH and IGF-I act on all these systems, we decided to study those parameters in a cohort of individuals with severe short stature due to untreated isolated GH deficiency (IGHD) caused by a mutation in the GHRH receptor gene. These IGHD subjects, despite reduction in muscle mass, are very active and have normal longevity.

Methods: In a cross-sectional study, we assessed walking (by a 6-min walk test), postural balance (by force platform) and fall risk (by the 'Timed Up and Go' test) in 31 IGHD and 40 matched health controls.

Results: The percentage of the walked distance measured in relation to the predicted one was similar in groups, but higher in IGHD, when corrected by the leg length. Absolute postural balance data showed similar velocity of unipodal support in the two groups, and better values, with open and closed eyes and unipodal support, in IGHD, but these differences became non-significant when corrected for height and lower-limb length. The time in 'Timed Up and Go' test was higher in IGHD cohort, but still below the cut-off value for fall risk.

Conclusion: IGHD subjects exhibit satisfactory walking and postural balance, without increase in fall risk.

Key Words

- ▶ GH deficiency
- ▶ balance
- ▶ walking

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Introduction

The ability to walk erect on two legs exerted great evolutionary potential for the human species. Walking and postural balance are extremely important to get around, obtain food and work. Both functions are critical for quality of life and ability to survive in hostile environments with limited access to transport and food. While walking reflects musculoskeletal and cardiopulmonary systems, postural balance depends on body size, muscle tone, visual, vestibular, somatosensory and central nervous systems (1, 2, 3, 4). This complex system favors the equilibrium, guaranteeing postural balance and reducing the risk of falls (5, 6). Several factors such as height, leg length and lean and fat mass (7, 8, 9, 10) may affect walking and postural balance.

Mice with reduced GH signaling have better physical capacity than normal animals (11). It is unclear if humans with isolated GH deficiency (IGHD) in combination with reduced body size have adequate walking and postural balance. If so, they may have advantageous features for obtaining food and saving energy throughout life and in the prevention of falls, especially in older age. It is understandable that these features are not critical for mice living permanently in cages and undergoing standardized experimental conditions.

We have described in Itabaianinha county, in northeastern Brazil, a large cohort of individuals with IGHD, due to the c57+1G→A mutation in the GH-releasing hormone receptor gene (*GHRHR*, OMIM n. 612781), resulting in low serum GH and IGF-I throughout their life (12). Although these individuals are severely short, with reduced lean body mass and increased fat percentage, they perform vigorous daily physical activities such as pottery, farming and domestic work (13). Although these subjects report higher prevalence of dizziness (14), they are not prone to fractures even at advanced ages (15). They also have normal quality of life (16) and longevity (17). Recently, we have shown that these untreated IGHD subjects have better muscle strength parameters adjusted for weight and fat free mass than controls, satisfactory muscle function and greater resistance to fatigue (18), contributing to possible benefits of short stature in these individuals, who live in the real world, with dimensions adapted to people of normal height (19). Therefore, we hypothesized that their walking capacity and postural balance would also be satisfactory, contributing to their environmental adaptation, probably reducing their falls' risk. In an attempt of finding out subtle differences between two, *a priori*, healthy groups (the IGHD subjects and their

normal counterparts), we used the gold standard method to assess the balance, the force plate, which measures postural sway by calculating the center of pressure (20, 21). Measures of balance using questionnaires, like the Berg Balance Scale, are limited by subjective interpretation, ceiling effects and low sensitivity (20, 22, 23) and are more useful in neurological diseases, in which sensitivity is less relevant.

The aims of this study were to assess walking, postural balance and fall risk in congenital, untreated, lifetime IGHD subjects.

Methods

Subjects

In a cross-sectional study, adult GH-naïve IGHD subjects and controls with similar socioeconomic conditions and paired by age, sex and BMI were recruited by advertising in the local Dwarfs Association Building and by word of mouth among the inhabitants of Itabaianinha county. Inclusion criteria for IGHD group were age 18 years or above and homozygosity for the c57+1G→A *GHRHR* mutation for the IGHD and for the wild-type allele for controls (13). Exclusion criteria were previous GH replacement therapy, known labyrinth disorders, functional and respiratory limitations and orthopedic diseases.

Thirty-one IGHD and 40 health controls paired by age, sex, blood pressure and BMI were enrolled. Experiments were carried out in a gym in the Itabaianinha municipal seat. The protocol was approved by the Institutional Review Board of Federal University of Sergipe, and all subjects gave their written informed consent.

Anthropometric data and level of physical activity

We used a tetrapolar bioelectrical impedance device with 50KHz (Model 450, Biodynamics, LTDA, and São Paulo, Brazil) to assess fat and fat free mass (18). The International Physical Activity Questionnaire (IPAQ) was used to assess the type and level of physical activity in the last 7 days. The types of activity were walking; activities of moderate intensity (such as carrying light loads, cycling at a regular pace or doubling sneakers) and vigorous intensity activities (such as weight lifting, digging, aerobics or fast cycling). The level of activity was coded at high=3 (at least 1 h of moderate-intensity activity above basal activity level or half an hour of vigorous-intensity activity beyond baseline daily level); moderate=2

(half an hour of moderate intensity on most days); and low=1 (not meeting any of the criteria for any of the previous categories) (24).

Six-minute walk test

This test assesses the global response of all the systems involved during exercise, namely the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism. It measures the distance that a subject can walk quickly on a flat, hard 100-ft hallway in a period of 6 min. The test was performed according to the current American Thoracic Society (ATS) guidelines (25, 26). Individuals were asked to wear comfortable shoes and avoid high-intensity physical activity 2 h prior to the test. Fasting was not requested. They were instructed to ‘walk as far as possible without running for 6 min’. Subjects could slow down and stop if necessary. In case of interruption, they could restart as soon as they felt able, without pausing the countdown. After the first minute, the subject was told ‘You are doing well. You have 5 min to go’. When the timer showed 4 min remaining, the subject was told: ‘Keep up the good work. You have 4 min to go’. When the timer showed 3 min remaining, the subject was told ‘You are doing well. You are halfway done’. When the timer showed 2 min remaining, the subject was told: ‘Keep up the good work. You have only 2 min left’. When the timer showed only 1 min remaining, the subject was told: ‘You are doing well. You have only 1 min to go’. When the timer was 15 s from completion, the subject was told: ‘In a moment I am going to tell you to stop. When I do, just stop right where you are and I will come to you’.

Heart rate (HR) was assessed at rest, at the end of 6 min and at the first and second minutes of recovery.

A self-assessment of the perceived exertion was obtained by the modified Borg Scale (27). In this scale, the ratio properties were graded from 0 (nothing at all), 0.5 (very, very weak), 1 (very weak), 3 (moderate), 4 (somewhat strong), 5 (strong), 7 (very strong) and 10 (very, very strong). The predicted walked distance was calculated by a standardized Brazilian formula: $356.658 - (2.303 \times \text{age}) + (36.648 \times \text{gender}) + (1.704 \times \text{height}) + (1.365 \times \Delta\text{HR})$. Gender was coded 1 for male and zero for females (28). The percentage of the walked distance in relation to the predicted one was calculated.

Postural balance

Postural balance was evaluated by the force platform, which measures the oscillations of the human body in the anteroposterior and mediolateral directions. All tests were performed by a single trained physiotherapist (G A M-B), in a force plate equipment (triaxial digital KINECT P-6000, Porto Alegre, Brazil) with a frequency of 100 Hz, calibrated before each evaluation, following the manufacturer's instructions. Before data collection, individuals were instructed to perform three 30-s tests in the sequence: open and closed eyes, standing with both feet (bipodal support) and with open eyes, standing with one foot (unipodal support). For the correct positioning of the individuals, the force plate was demarcated with adhesive tape at the central point. After individuals climbed barefoot on force plate, no adjustments were made to the feet. The subjects were asked to fix their eyes on a visual marker placed at the mean height of each group. Mediolateral and anteroposterior displacements (mm) and velocity of the center of pressure (mm/s) (29, 30, 31) were measured (Fig. 1). The theoretical assumptions of the postural balance measurement are that individuals with

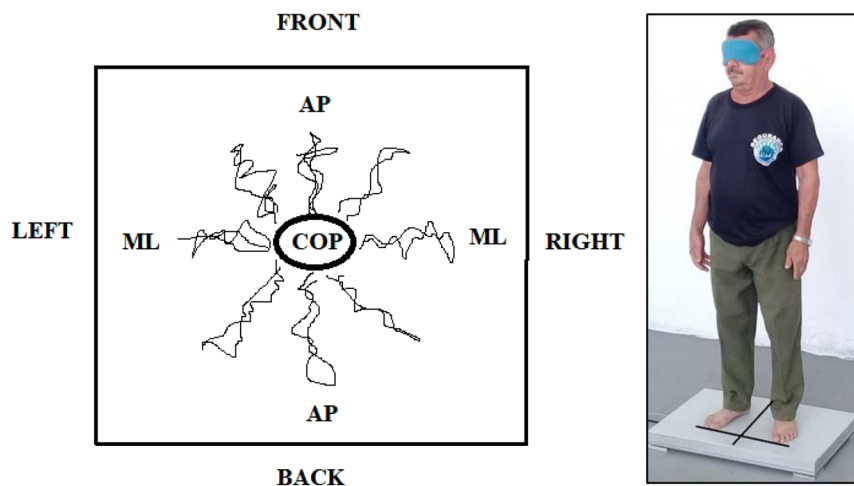


Figure 1

Illustration of the trajectories of the center of pressure (COP) on the force plate during static balance in the anteroposterior (AP), mediolateral (ML) displacement and respective diagonals.

higher amplitudes of oscillation and/or higher oscillation velocity have worse postural balance. Due to the risk of fall, a security technician was available to intervene in cases of large postural oscillations.

Fall risk

Fall risk was assessed by the 'Timed Up and Go' test. Individuals were positioned seated in a chair, with back support, and with their feet in contact with the floor. The IGHD subjects used a smaller chair, according to their size. After verbal command, the individuals got up from the chair, walked a distance of 3 m in a straight line and returned to the initial position. The time is the main outcome of this test. Lower values identify better performance, with 12 s being the usual cut-off point which indicates fall risk (6). The chair used for both individuals with IGHD and for the control group was adjusted to allow the 90° angle of hip and knee flexion when participants took the sitting position (30, 32).

Statistical analysis

Statistical analysis was performed using the statistical software SPSS/PC 8.0 (SPSS, Inc.). Values for continuous variables are expressed as the mean ± standard deviation and frequency for the qualitative variables. Student's *t* test was used for the comparison of the two groups. Significance was established by a *P* value lower than 0.05. We corrected the variables of the force platform and of the time in 'Timed Up and Go' test, by dividing them with the height and the lower-limb length (LLL).

Results

Table 1 shows the anthropometric and blood pressure data. As expected, height, weight and LLL were reduced in the IGHD group. Table 2 shows the data of the 6-min walking test. There was no difference in HR at rest or at the sixth minute of walking nor at 1 or 2 min of recovery, neither in the sensation of dyspnea after exercise. The walked measured and predicted distances were lower in the IGHD group, but the percentage of the walked measured distance in relation to the predicted one was similar between the groups. In addition, the walked distance corrected by the leg length was higher than that in the controls. While both the velocity of the center of pressure with open eye (6.8 ± 1.4 vs 8.0 ± 2.0 mm/s, $P=0.005$) and with closed eye (7.8 ± 2.6 vs 9.9 ± 2.8 , $P=0.002$) were lower in IGHD

Table 1 Anthropometric, physical activity assessed by the international physical activity questionnaire (IPAQ), and blood pressure data in 31 isolated growth hormone deficiency (IGHD) and 40 controls. Data are expressed as mean ± standard deviation.

	IGHD	Controls	<i>P</i> value
Sex (Males)	16	20	1.000
Age (years)	46 ± 12	43 ± 11	0.992
Weight (kg)	38 ± 7	67 ± 11	<0.001
Height (cm)	125 ± 8	166 ± 10	<0.001
Standard deviation score for height	-8.6 ± 1.3	-0.3 ± 1.5	<0.001
BMI (kg/m ²)	23.4 ± 3.4	24.1 ± 2.8	0.354
Fat mass (%)	36.5 ± 13.2	23.17 ± 8.5	<0.001
Fat free mass (kg)	25.6 ± 7.2	53.8 ± 12.1	<0.001
Lower-limb length (cm)	59.0 ± 5	81 ± 7	<0.001
Physical activity level	1.45 ± 0.5	1.51 ± 0.5	0.616
Systolic blood pressure (mmHg)	111 ± 9	115 ± 10	0.065
Diastolic blood pressure (mmHg)	79 ± 5	80 ± 4	0.079

The scoring system and the domains of IPAQ questionnaire were detailed in the 'Methods' section.

than controls, the velocity of the unipodal support of the center of pressure was similar in the groups (30.4 ± 7.1 vs 32.4 ± 6.4 , $P=0.214$). Table 3 shows the displacement of the static postural equilibrium and the 'Timed Up and Go' test in absolute and corrected values for height and LLL. The absolute values were significantly better in the IGHD group in comparison to controls, but when corrected for height and LLL, these differences disappeared. The 'Timed Up and Go' test was higher in IGHD than controls in both absolute value and in value corrected for height or LLL, but was still below 12 s, the cut-off point which indicates fall risk.

Discussion

This work shows that adult individuals with congenital, untreated severe IGHD have similar walking and postural balance to normal controls, paired by sex, age and degree of physical activity. These data expand our previous observation that these IGHD subjects have better muscle strength parameters when adjusted for weight and fat free mass than controls. They also exhibit greater peripheral resistance to fatigue, demonstrating satisfactory muscle function (18), in spite of having marked reduction of fat free mass and increase of fat percentage (33, 34), throughout the life.

Table 2 Six-minute walk test in 31 isolated GH deficiency (IGHD) subjects and 40 controls. Data are expressed as mean \pm standard deviation.

	IGHD	Controls	P value
Heart rate of rest (bpm)	83 \pm 11	88 \pm 13	0.106
Heart rate at the sixth minute (bpm)	103 \pm 19	100 \pm 16	0.456
Heart rate at 1 min recovery (bpm)	90 \pm 14	83.8 \pm 13	0.065
Heart rate at 2 min recovery (bpm)	85 \pm 13	83 \pm 13	0.483
Dyspnea (Borg)	4.7 \pm 1.3	4.6 \pm 1.2	0.808
Walked distance (m)	348 \pm 64	393 \pm 40	0.001
Predicted distance (m)	508 \pm 54	575 \pm 41	<0.0001
Distance walked based on prediction (%)	68 \pm 12	69 \pm 7	0.978
Distance walked/leg length (meter/cm)	6 \pm 1	5 \pm 1	<0.0001

Our data expand the benefits of lifetime IGHD in terms of health and longevity (19). Walking and postural balance are extremely important for small people who survive in potentially hostile environments, to get around, obtain food, work and reduce falls. To our knowledge, the IGHD people of Itabaianinha are the only available model to evaluate the consequences of lifetime lack of GH.

We had previously studied in these subjects the maximal cardiac stress test, with a treadmill Bruce protocol, performing stress echocardiograms to assess coronary atherosclerosis (35). This and subsequent studies showed no evidence of premature atherosclerosis (despite increase in total and LDL cholesterol) (36). Accordingly, they have normal longevity (17). However, the Bruce protocol produces a stress condition that mirrors major

physical effort, surgery, emotional trauma or accidents, not ordinarily found in daily life. In this paper, we aimed to assess the submaximal level of functional capacity, as most activities of daily living are performed at submaximal levels of exertion. Therefore, we used the 6-min walking test, which better reflects the functional exercise level for daily physical activities (25). Our data show that the walked measured or predicted distances are lower in the IGHD group, but the percentage of the walked measured distance in relation to the predicted one was similar between the groups. In addition, the walked distance corrected by the LLL was indeed higher in IGHD subjects. These data show that when corrected for height, these IGHD subjects walk similar to normal statured controls, and when corrected by the lower member length, they seem to walk better.

Table 3 Displacements (mm) of the static postural equilibrium with open eye (OE), closed eye (CE) and unipodal support (US) and the time (s) of the 'Timed Up and Go' test in absolute and corrected values for height (cm) and lower-limb length (LLL, cm), in 31 isolated GH deficiency (IGHD) and 40 controls. Data are expressed as mean \pm standard deviation.

	IGHD	Controls	P value
Displacement OE mediolateral	14.6 \pm 4.0	19.2 \pm 5.3	<0.001
Displacement OE mediolateral/height	0.13 \pm 0.05	0.12 \pm 0.04	0.382
Displacement OE mediolateral/LLL	0.28 \pm 0.10	0.26 \pm 0.08	0.358
Displacement OE anteroposterior	8.5 \pm 3.2	14.1 \pm 4.5	<0.001
Displacement OE anteroposterior/height	0.06 \pm 0.03	0.08 \pm 0.04	0.077
Displacement OE anteroposterior/LLL	0.14 \pm 0.07	0.18 \pm 0.09	0.083
Displacement CE mediolateral	14.9 \pm 3.1	17.2 \pm 2.5	<0.001
Displacement CE mediolateral/height	0.13 \pm 0.10	0.14 \pm 0.05	0.753
Displacement CE mediolateral/LLL	0.29 \pm 0.21	0.30 \pm 0.10	0.771
Displacement CE anteroposterior	7.7 \pm 2.0	12.9 \pm 3.6	<0.001
Displacement CE anteroposterior/height	0.07 \pm 0.08	0.08 \pm 0.04	0.519
Displacement CE anteroposterior/LLL	0.15 \pm 0.17	0.17 \pm 0.09	0.502
Displacement US mediolateral	28.4 \pm 6.1	33.5 \pm 5.2	<0.001
Displacement US mediolateral/height	0.29 \pm 0.20	0.28 \pm 0.13	0.694
Displacement US mediolateral/LLL	0.65 \pm 0.45	0.61 \pm 0.30	0.729
Displacement US anteroposterior	25.8 \pm 4.7	31.4 \pm 4.7	<0.001
Displacement US anteroposterior/height	0.28 \pm 0.29	0.21 \pm 0.1	0.211
Displacement US anteroposterior/LLL	0.62 \pm 0.64	0.47 \pm 0.3	0.237
Timed Up and Go test	11.3 \pm 2.1	7.1 \pm 1.4	0.010
Timed Up and Go test/height	0.09 \pm 0.03	0.05 \pm 0.01	<0.001
Timed Up and Go test/LLL	0.19 \pm 0.7	0.10 \pm 0.02	<0.001

The relationship between height and distance traveled and the length of the lower limb is intuitive. Walking speed is also an objective measure of lower-limb neuromuscular function and physical performance. It relates to functional abilities, morbidity and mortality, being a potent 'vital sign' in older adults (37). We believe that the normal walking of these IGHD subjects, coupled with their better muscle strength parameters (18) contributes to their environmental adaptation, keeping a large number of subjects alive in a rural and potentially hostile environment for more than two centuries.

The 6-min walking test has become a standard tool in clinical practice and research because it is considered a tool that can evaluate the performance, function and response to treatment of individuals with cardiorespiratory disorders (25, 26). For instance, patients with pulmonary hypertension with values less than 332m have shorter survival rate than those walking farther (38). To our knowledge, this is the first report of this test being performed in individuals with severe IGHD and marked short stature. Although we did not intend to establish limits of normality of this test in people with severe short stature, these data can be useful to researchers interested in walking of proportionate short stature of any causes.

Animal data in GH receptor-knockout (GHRKO) (11) and GHRH-knockout (GHRHKO) mice (39) show an increase in locomotor and thermogenic activities. We have shown that our IGHD subjects have a higher caloric intake corrected by body weight (40). We think that their greater peripheral resistance to fatigue (18) coupled to satisfactory walking, may have beneficial consequences, improving cardiopulmonary function and avoiding excessive fat accumulation in individuals with severe impairment of the lipolysis due to GH deficiency.

IGHD subjects showed lower non-corrected oscillation in the postural balance for open eye, close eye and unipodal support variables when compared to the control group. It is important to note that individuals with short stature and consequently LLL may present lower postural oscillation. Biomechanically, these lower values of postural oscillation can be explained by the fact that the human body functions as an inverted pendulum (41). Joint amplitudes of the ankle and proximity of the gravitational center to the base of support promote an increase in the internal torque favorable to the postural balance. The proximity of the gravitational center to the base of support promotes an increase in the internal torque favorable to the postural equilibrium. Accordingly, when we corrected these

measures of postural balance for height and LLL, these differences disappeared, suggesting a role of height or LLL in these measures.

However, two other important factors that seem to directly influence postural balance oscillation are fat mass content and BMI. Studies have shown that overweight individuals present greater postural balance due to hypersensitivity of foot mechanoreceptors (42, 43). This fact is explained by somatosensory stimulation, which causes neuroplasticity in the motor cortex by proprioceptive increase in the area of plantar contact (44). Other studies have shown that increased fat mass promotes greater postural oscillation (45). Conversely, a recent study showed that fat mass and BMI are not able to influence postural oscillation parameters in the unipodal support (8). Although our IGHD subjects present higher fat mass percentage, they exhibit normal or more frequently low BMI values (18, 34) due to the small size of muscles and bones. Therefore, we cannot draw final conclusions on the role of BMI on the body oscillation in these subjects.

The proprioceptive systems are of great relevance for the maintenance of postural balance (2). Previously, we reported that these IGHD individuals had normal visual acuity (46) and mild hearing loss, but complained more of dizziness than controls (14). This subjective complain of mild dizziness contrasts with the lack of hip fracture even in individuals older than 90 years (36). Indeed, going back as far as 1892, there is no death certificate reporting hip fracture as cause of death in any of the IGHD subjects (17). In addition, we have previously shown that the mean number of vertebral fractures in individuals older than 60 years was lower in IGHD than in controls (36). It is well known that one-third of normal people over 65 years of age will suffer falls at least once a year, some resulting in serious injuries, and the majority leading to impaired mobility, loss of function and decreased quality of life (47). Data of the present work show normal postural balance in these IGHD subjects, contributing to their low fall risk, excellent health and high quality of life (16), including in advanced age (19).

The 'Timed Up and Go' test was higher in IGHD cohort than the controls, likely reflecting their shorter limb length, causing longer execution time (44). Nevertheless, this time remains within the predicted normal range for normal statured people and below the threshold of fall risk (9).

One study with 8300 women aged 65–89 years with a wide variation in physical function and lifestyles from four large metropolitan areas in the United States concluded

that lifestyle factors (not smoking, going outdoors frequently, walking at a fast usual-paced walking speed and high physical activity) and shorter body height may reduce the fall risk (48). Our IGHD subjects rarely smoke (49) and have all the other protective factors against the fall risk. The satisfactory walking and postural balance contribute to the good quality of life, overall health and no evidence of falls in this IGHD cohort. Therefore, we do not think that walking and postural balance need to be routinely evaluated in individuals with IGHD. Our data will be useful to compare with other forms of congenital or acquired GH deficiency, GH insensitivity syndromes or other causes of dwarfism.

Our work has one major limitation. We cannot separate the consequences of lack of GH from short stature. To study this aspect, one would need a group of individuals with similar stature and normal GH secretion, as we used in a voice study (50). However, most causes of severe short stature (e.g. achondroplasia and 3-M syndrome) have trunk/limb disproportion and specific orthopedic problems and are therefore not adequate controls for well-proportioned patients with no relevant orthopedic problems.

In conclusion, our data demonstrate that adults with severe short stature due to IGHD show satisfactory walking and postural balance, without increase in fall risk. These data expand previous observations of adequate muscle function in these subjects, despite marked reduction in muscle mass. These data exemplify another dissociation between muscle mass and function and contribute to establish an overall beneficial health profile of these subjects living with markedly reduced GH and IGF-I levels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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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.

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