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Physical activity as measured by accelerometry in children receiving growth hormone

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Aim: Parents of children treated with growth hormone (GH) frequently report to the paediatrician that their children have become more physically active. In the present study, activity patterns of GH-treated children were measured and compared to those of healthy controls. *Methods:* Subjects were 25 children at the start of GH treatment (age 8.4 ± 2.6 y) and 19 age- and gender-matched controls (age 8.8 ± 3.2 y). Physical activity was assessed with a tri-axial accelerometer for movement registration over two separate 2-wk intervals, one before the start of GH treatment and one 2 wk after the start of treatment. GH-treated subjects were categorized as poor responders (change in height over 1 y <0.7 SDS, $n = 15$) or good responders (change in height over 1 y >0.7 SDS, $n = 10$). *Results:* Before therapy, good responders showed a significantly lower physical activity compared to healthy controls, spending significantly less time on high-intensity activities. This difference disappeared 2 wk after the start of therapy. Physical activity in poor responders was not significantly different from controls before and after 2 wk of GH therapy.

Conclusion: Children who respond well to GH therapy (change in height >0.7 SDS) showed a reduced amount of physical activity before therapy, which was normalized after 2 wk of GH therapy.

Key words: *Growth hormone deficiency, physical activity intensity, physical activity frequency, Tracmor*

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Since the FDA approved the use of recombinant growth hormone (rGH) in 1985, the number of prescriptions of growth hormone has risen dramatically (1). It was no longer only severely growth hormone deficient (GHD) patients who were treated, but also children suffering from partial GHD. The eligibility of patients for GH treatment is decided on the basis of anthropometric parameters and endocrine testing.

In paediatric patients, growth hormone therapy is used to correct height deficit. However, it is also remarkable that parents frequently report to physicians that their child has become livelier after the start of treatment. This may be based on metabolic effects of GH, as have been described in the literature. Gregory et al., for example, found a significant increase in basal metabolic rate (BMR) (2) and total daily energy expenditure (TDEE) in children receiving GH therapy.

An increase in TDEE can be attributed to growth as well as to increased physical activity. Possible changes in this component of TDEE can be measured by accelerometry. Accelerometers measure the occurrence and intensity of body movements. The method is easy applicable and does not interfere with the child's daily activities. Two kinds of accelerometers are distinguished: one-axial and tri-axial accelerometers. One-axial accelerometers measure accelerations in one direction in contrast to tri-axial accelerometers, which measure accelerations of the body in three dimensions.

Since data about physical activity patterns in children receiving GH therapy are lacking, the present study investigated the short-term effect of GH on spontaneous physical activity. For this purpose, the Tracmor, a tri-axial accelerometer, which has been proven to be a reliable tool for the assessment of physical activity in adults (3–4) as well as in children (5), has been used. The patients were divided into two groups (good responders and poor responders), according to their response to GH therapy, to see whether the short-term changes in activity patterns were comparable between the two groups. In addition to the intensity of physical

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activity, Tracmor data have been used to calculate the fraction of time spent on a given activity at low, moderate or high levels of intensity (3–4).

Methods

Subjects

Eligibility for therapy was based solely on one or more anthropometric criteria as visible in GH-deficient patients: height SDS at start of treatment <-2.5 SDS, deviation from target height >1.3 SDS and growth in the year before treatment >-0.25 SDS. Additional endocrine testing was performed (arginine, clonidine and sleeping test) to measure maximum GH concentrations. Some children did not undergo all tests because they were submitted from other hospitals. The clonidine test could not be performed in one child indicated to be hypersensitive to clonidine.

To minimize the influence of environmental factors, healthy controls were selected from friends or relatives of the patients living in the same neighbourhood. They were measured simultaneously with the patients, but did not receive GH therapy. Parents and children were informed about the study and written informed consent was obtained. The study was approved by the Ethical Committee of the University Hospital Maastricht.

All patients were prepubertal by physical examination. Two control patients were already pubertal.

Study design

The Tracmor was worn twice (M1 and M2) during a 2-wk period, before the start of therapy in the patients and during weeks 3 and 4 of this therapy. The children received 0.7 mg hGH/m^2/d (Humatrope®). Two girls with Turner syndrome received 1.3 mg hGH/m^2/d (Humatrope®), in accordance with Dutch treatment criteria. After 1 y, growth was evaluated and expressed as Z-scores (SDS) (6). The difference in SDS (SDS_{t1year}- SDS_{t0}) was used to divide the patient group into good and poor responders. A change in SDS >0.7 was considered to be a good response, based on the mean response to GH therapy found in the study by Ranke et al. (7).

Physical activity

Physical activity was assessed with the help of a triaxial accelerometer for movement registration (Tracmor, Philips Research, Eindhoven, The Netherlands). The Tracmor is a small device ($7 \times 2.8 \times 0.8$ cm), which is worn on a belt at the back of the waist. The triaxial accelerometer calculates the sum of the rectified and integrated acceleration curves from the anteroposterior, mediolateral and vertical directions of the trunk. The integration period was set at 1 min, and the final output is expressed as counts per minute (cpm) (3)

The Tracmor was worn during waking hours, except while showering and during swimming. The parents of the children recorded in a log the times when the children woke up, when they put the Tracmor on and off, and when they went to bed. If the sum of the time during which the device was worn and the duration of sleep was less than 22 h, the day was excluded from the analysis (mean number of recorded days was 11).

Activities were defined at three intensity levels, as described before (3–4), Low-intensity, associated with an accelerometer output $\leq$200 cpm, represents lying, sitting and standing. Moderate-intensity, associated with an accelerometer output ranging from 200 to 500 cpm, includes walking at a velocity of 1.5–2.0 km/h. High-intensity activities are associated with an accelerometer output $\geq$500 cpm. The fraction of time spent at a given intensity level was calculated as the time spent at this intensity level divided by total activity time.

GH stimulation tests

Arginine test. The arginine test was performed in the morning after an overnight fast. Arginine hydrochloride (0.5 g/kg) was infused for 30 min. Blood samples were taken to measure growth hormone levels at -15, 0, 30, 45, 60, 75, 90 and 120 min after the start of the infusion (8).

Clonidine test. The clonidine test was performed in the morning after an overnight fast. After an oral dose of clonidine (0.15 mg/m^2, max. 0.15 mg), blood samples were taken every 30 min for the next 2 h to measure growth hormone levels (8)

Sleeping test. Because natural peaks of growth hormone secretion occur during the first hours of sleep, blood samples were taken every 10 min during the first 2 h of sleep to measure growth hormone levels.

Statistics

Tracmor data were expressed as counts/min, mean Tracmor counts per day were divided by the time during which the device was worn, to correct for possible differences in activity time. For each group of children, a paired *t*-test was used to see if there was a significant difference in the Tracmor data before and after 2 wk of therapy. The treated groups were compared with each other and with the control group using an independent *t*-test.

Results

Patient characteristics before and after 1 y of GH therapy are given in Table 1. The mean growth response after 1 y for the entire growth hormone treatment group ($n = 25$) was $+0.59$ SDS (± 0.45), while the change in SDS in the control group was $+0.02$ (± 0.21). On the

Table 1. Patient characteristics.

	Controls[a]	Poor responders	Good responders
Height before therapy (cm)	130.5 (19.9)	123.2 (13.9)	105.1 (9.6)
Height 1 y after therapy (cm)	135.2 (19.4)	130.3 (14.2)	116.0 (10.4)
Height before therapy (SDS)	−0.89 (1.2)	−2.71 (0.97)	−3.52 (0.77)
Height 1 y after therapy (SDS)	−0.95 (1.1)	−2.44 (0.94)	−2.41 (0.83)
Weight before therapy (kg)	28.1 (11.0)	23.0 (6.1)	15.0[b] (3.3)
Weight 1 y after therapy (kg)	30.8 (12.0)	26.1 (6.8)	18.3 (3.4)
Weight before therapy (SDS)	−0.61 (0.98)	−1.92 (0.79)	−2.73 (1.1)
Weight 1 y after therapy (SDS)	−0.59 (0.94)	−1.79 (0.73)	−2.01 (0.77)
Weight-for-height (SDS) before therapy	−0.17 (1.05)	0.25 (1.11)	−1.02 (1.52)
Weight-for-height (SDS) after therapy	0.09 (1.37)	0.15 (0.73)	−1.14 (1.61)
GH concentration, arginine test (mU/l)		23.1 (11.1) ($n = 15$)	17.0 (8.4) ($n = 10$)
GH concentration, clonidine test (mU/l)		38.2 (29.2) ($n = 13$)	31.5 (13.1) ($n = 7$)
GH concentration, sleeping test (mU/l)		18.3 (9.4) ($n = 15$)	14.0 (12.2) ($n = 7$)

[a] Anthropometric data of one control subject after 1 y of therapy were missing.
[b] To calculate weight data, one patient was excluded because of an abnormal increase in weight during the first year of therapy.
Values are means (SD).

basis of the response to GH therapy, three groups could be distinguished: 1) control group ($n = 19$) (mean age 8.8 ± 3.2 y); 2) patient group with a response to GH therapy <0.7 SDS/y ($n = 15$) (mean age 9.7 ± 2.4 y); 3) patient group with a response to GH therapy >0.7 SDS/y ($n = 10$) (mean age 6.5 ± 1.7 y).

Of the 25 children who started GH therapy, 17 had a height below −2.5 SDS (9 were good responders), 21 deviated more than 1.3 SDS from their target height (10 were good responders) and 8 children (6 were good responders) showed a deviating growth chart.

Although the mean age of the two patient groups did not differ significantly from that of the controls, the children with a poor response to GH therapy were significantly older than the good responders (9.7 ± 2.4 vs 6.5 ± 1.7 y; $p < 0.01$). The number of recorded days did not significantly differ between the two measurements periods.

As can be seen in Table 2, the number of Tracmor counts/min before the start of the GH therapy was significantly lower in the good responders than in the controls ($p < 0.05$). After 2 wk of therapy, this difference had disappeared, because of a significant increase in the number of counts/min among the good responders ($p < 0.05$) (Table 2).

The proportion of time the three groups spent on low-, moderate- and high-intensity activity is listed in Table 2. This shows that before therapy, good GH therapy responders spent less time on high-intensity activities than controls and poor responders ($p < 0.05$ and $p < 0.01$, respectively). After 2 wk of GH therapy, there was no longer a significant difference between the three groups. Good GH therapy responders showed a significant increase in high-intensity activities ($p < 0.05$). Tracmor data of poor GH responders did not significantly differ from controls before as well as after start of therapy. Excluding the Turner patients did not influence the outcome of the results.

A comparison of the two patient groups in terms of the maximum growth hormone values found during the endocrine tests revealed no significant difference between the good and poor responders as regards the

Table 2. Tracmor data output of three subject groups: controls, poor GH responders (change in height <0.7 SDS) and good GH responders (change in height >0.7 SDS)

	Controls		Poor responders		Good responders		
	M1	M2	M1	M2	M1		M2
Tracmor (counts/min)	61[a] (17)	57 (17)	67[a] (16)	64 (15)	48[b] (11)	*	55 (12)
Low activity (%)	56 (10)	56 (12)	56 (11)	58 (11)	62 (8)		58 (11)
Moderate activity (%)	25 (6)	25 (6)	23 (5)	23 (5)	25 (6)		26 (6)
High activity (%)	19[a] (7)	19 (8)	21[a] (7)	19 (7)	13[b] (5)	*	17 (7)

M1: first measurement period, before start of GH treatment in the patients; M2: second measurement period, 2 wk after the start of GH treatment in the patients.

Values are means (SD). Tracmor data were expressed as counts/min; mean Tracmor counts per day were divided by the time during which the device was worn, to correct for possible differences in activity time.

A paired *t*-test was used to see if there was a significant difference in the Tracmor data before and after 2 wk of therapy.

* Denote within groups differences compared to baseline values ($p < 0.05$).

An independent *t*-test was used to test the difference between the three different patient groups. Lower-case letters represent between-group differences; means with different letter superscripts are significantly different ($p < 0.05$).

maximum GH concentrations found during the sleep, arginine or clonidine tests.

Discussion

Growth hormone is known to have an anabolic effect, which is associated with increased energy expenditure (9). Although it is the general experience of paediatricians that children become more active after the introduction of GH therapy, Gregory et al. were unable to demonstrate an increase in activity. The measured increase in TDEE in their study reflected the increase in BMR (2).

In the present study, the children were divided into two groups according to their response to growth hormone therapy. Before the start of GH therapy, good GH therapy responders showed a lower number of Tracmor counts per minute and spent less time on high-intensity activities. The observed difference had disappeared after 2 wk of GH therapy. This means that children with a good response to GH therapy were less physically active than healthy controls until GH was supplemented. The lower amount of activity before start of treatment might be partly explained by an impaired erythropoiesis, as was demonstrated in GHD adults (10). Erythropoiesis increases during GH therapy, which may lead to an increase in oxygen capacity and thereby contribute to an improved exercise performance capacity (10–11). In addition, an increase in plasma volume and total blood volume, as was measured in GH-deficient adults on GH therapy (10, 12), might contribute to an increase in VO_{2max} (13). Another explanation might be a change in body composition, which is observed after start of GH treatment (14).

However, as the present study showed, the amount of spontaneous physical activity differed between good and poor responders. In contrast to the good responders, poor responders were comparable to controls before start of GH treatment. GH therapy did not influence their activity patterns. Probably, in these children, their retarded growth was not based on growth hormone deficiency. The present results show that additional exogenous GH therapy does not influence activity levels in these children in contrast to the good responders in which GH therapy causes an increase in growth and physical activity.

The effect of GH therapy on activity was observed over a relatively short period of time because metabolic effects of GH therapy become apparent soon after its start (12, 15), as was confirmed in the present study. The good responders adapted similar activity levels as their control counterparts after 2 wk of GH supplementation. However, it would have been of interest to measure physical activity after 1 y of therapy to see if the increase in physical activity in the good responders was maintained. Unfortunately, this was not possible because of practical limitations and should be the subject of future studies.

In the present study, intensity of physical activity was measured using a tri-axial accelerometer, which is a non-invasive method of measuring activity under free-living conditions. It confirmed the increase in activity reported by some parents after the introduction of GH therapy. Good responders were less active than controls before the introduction of GH therapy, which was normalized 2 wk after the start of therapy. In the poor responders group, GH therapy had no effect on activity. The increase in physical activity in responders was mainly attributable to an increase in high-intensity activities.

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