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Growth hormone deficiency: psychological adjustment from adolescence to young adulthood

Deficit di ormone della crescita: adattamento psicologico in adolescenti e giovani adulti

A. OFFICIOSO, G. GRISO, T. LETTIERO, M. CERBONE, N. IMPRODA, M. SALERNO

Department of Pediatrics, University "Federico II", Naples, Italy

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Riassunto

Obiettivi*. Studi clinici sulle conseguenze comportamentali in adulti affetti da deficit dell'ormone della crescita (GHD) ad insorgenza infantile indicano che il GHD è strettamente associato ad una serie di disturbi psicologici quali depressione ed ansietà che si manifestano con isolamento sociale, difficoltà scolastiche e lavorative. Lo scopo di questo studio è stato valutare gli adattamenti psicologici che intercorrono in adolescenti e giovani adulti affetti da GHD.*

Metodi*. Trenta pazienti in terapia con GH, di età compresa tra 10 e 20 anni, sono stati valutati attraverso un questionario strutturato sul linguaggio e la struttura del corpo, il test del disegno della figura umana, un questionario per ansia e depressione e il Maudsley Obsessional-Compulsive Inventory (MOCI). I pazienti sono stati divisi in 2 gruppi, adolescenti (età 10-16 anni) e giovani adulti (età 16,5-20 anni). Trenta soggetti sani appaiati per età e sesso erano usati come controlli.*

Risultati*. I pazienti con GHD mostravano un livello d'ansia compreso nei valori medi per l'età (adolescenti 47,4 ± 8,6 percentile e giovani adulti 60,2 ± 5,2 percentile) che, tuttavia risultava significativamente più elevato ri-*

Corrispondenza: Mariacarolina Salerno, MD, PhD, Department of Pediatrics, Federico II University of Naples, via S. Pansini 5, 80131 Naples, Italy - Tel. +39 081 7464339 - Fax +39 081 5451278 - E-mail: salerno@unina.it

spetto a quello dei controlli sani (adolescenti 19,1 ± 5,5 percentile P < 0,01; giovani adulti 42,2 ± 4,7 percentile, P < 0,02). Un analogo andamento emergeva per quanto riguarda il livello di depressione, i giovani adulti avevano infatti un punteggio al questionario (66,1 ± 7,3 percentile) più elevato sia rispetto agli adolescenti con GHD (22,7 ± 5,4 percentile, P = 0,0003) che rispetto ai giovani adulti sani (19,3 ± 8,4 percentile, P = 0,001). Gli adattamenti psicologici emersi da tutti i test psicologici utilizzati mostravano un persistente ed eccessivo "controllo" nei pazienti con GHD, adolescenti e giovani adulti, rispetto ai controlli sani. Il punteggio totale al MOCI (15,9 ± 1,5 negli adolescenti e 15,2 ± 1,1 nei giovani adulti con GHD) era significativamente più alto rispetto ai controlli sani (7,1 ± 0,8, P < 0,0001 e 9,4 ± 0,9, P = 0,0003 rispettivamente), indicando un lieve tratto compulsivo.

***Conclusioni**. I pazienti con GHD possono sviluppare disturbi psicologici durante l'adolescenza e/o il periodo di transizione. Pertanto un sostegno psicologico dovrebbe essere offerto a tutti i pazienti con GHD fin dall'infanzia per prepararli ad un trattamento medico che potrebbe durare tutta la vita.*

Introduction

For many years the prominent goal of growth hormone (GH) therapy in children with GH deficiency (GHD) was to improve linear growth and minimize the potential disadvantage of short stature during childhood and adulthood. As a result, patients and their parents had the expectation that GH treatment would conclude once growth had finished. It is now recognized that GH deficiency in adults is associated with significant metabolic derangements, thus patients affected by a severe GHD need to continue or restart GH therapy after the attainment of final height. In addition, adults GHD not on substitutive treatment [1-4] may have an impaired psychological functioning, a reduced sense of well-being and a reduced quality of life [2 3 5-7] which can be improved by GH replacement therapy [5 8-10].

Only a few studies have focused on psychological status of GHD children [11], and several behavioural problems such as somatic complaints, anxiety, depression, attention deficit, social problems and aggressiveness were observed at baseline in GHD children compared to healthy children. GH treatment was associated to a significant improvement of these problems, which however remain present compared to healthy subjects. These psychological impairments might be the early expression of psychological disturbances observed in adulthood. In fact, adults who have been treated for GHD during childhood have an unexpected low rate of marriages and high level of unemployment despite comparable educational achievement, that supports an association with lack of motivation and social isolation in these patients [1 12-17]. However, other studies [18] did not find significant

differences when childhood-onset GHD (CO-GHD) adults were compared to their unaffected sibling, except for the rate of marriages that remains significantly lower in GHD subjects.

Moreover depression, psychological complaints and reduced quality of life have also been documented in young adults with CO-GHD at GH discontinuation after having achieved final height [19].

GHD has been considered for many years to be different from other chronic illnesses, because it only temporarily changes the way of life for both the patients and their family, but now the need of appropriate lifelong management and monitoring is well recognized. So that if the challenge for children and adolescents is to learn to cope with their fears and anxieties, the challenge for physicians is to understand and manage the long-term medical needs including the focus on emotional, social, developmental, and educational needs.

The aim of this study was to investigate how control and dependence participate in the psychological adjustment of GHD patients through the follow-up including the period of the transition from childhood to adulthood.

Patients and methods

Patients

The study population consisted of 30 patients (17 males) aged 10-20 years affected with GHD [20] (Tab. I). Sixteen patients were affected by isolated GHD (IGHD) and 14 by combined pituitary hormone deficiency (CPHD); the latter received appropriate stable replacement therapy throughout the follow-up. GHD patients were divided in two groups:

- *Group A*: consisted of 15 patients (10 males) aged 10-16 years, evaluated during adolescence. Ten were affected by IGHD and 5 by CPHD; GH deficiency was diagnosed according to clinical and auxological criteria [21] and by peak GH concentrations < 10 μg/l after two stimulation tests (arginine and clonidine). All patients were receiving a GH dose of 0.2-0.3 mg/kg/week.

Tab. I. Demographic characteristics of patients with GH deficiency compared to control group of healthy subjects.

	GHD patients (n = 30)	**Healthy subjects (n = 30)**
Sex (M/F)	17/13	17/13
Age at the study (yr)	16.9 ± 0.8	17.0 ± 0.8
Age at the diagnosis (yr)	6.5 ± 0.7	-
Duration of therapy (yr)	10.7 ± 1.2	-
Isolated/combined GHD	16/14	-

Data are expressed as mean ± SE

- *Group B*: consisted of 15 patients (7 males) with (CO-GHD), 6 affected by IGHD and 9 by CPHD, aged 16.5-20 years, evaluated during the transition period. Patients had been treated with GH from childhood for a period of 8 to18 years. All subjects in this group were identified to be severe adult GHD, defined as a peak GH response less than 9 μg/l after arginine growth hormone-releasing hormone test (ARG-GHRH) [21] 3–6 months after GH therapy was stopped, at the attainment of their adult height. Patients were enrolled in the study at least 1 year after GH treatment was restarted. All patients were treated with GH at a starting dose of 0.15 mg/kg/week; subsequently the dose was adjusted on the basis of serum insulin-like growth factor-I (IGF-I).

Thirty healthy subjects, matched for age, sex and social class were used as controls (Tab. I).

After oral and written information was provided, informed consent was obtained from the parents and their child.

Psychological evaluation

Non-structured interviews were developed for patients and their parents, to evaluate the level of knowledge and the way they perceive their illness. A structured questionnaire was administered to get information about educational attainment, occupational status, social relationships, and social status of the family.

The human figure drawing test was employed for a variety of assessment purposes, including intellectual development, personality, and emotional adjustment [22-24].

The anxiety scale questionnaire was used to measure anxiety levels in adolescents [25] and young adults [26].

The Children's depression inventory [27] and the Ipat Depression Scale [28], two brief self-report tests were used to assess cognitive, affective and behavioural signs of depression in adolescents and in young adults respectively.

The Maudsley Obsessional-Compulsive Inventory (MOCI) [29 30] was employed to evaluate the area of the Checking subscale. Based on the thirty items, the following four clinical sub-scales have been constructed: cleaning (11 items), checking (9 items), slowness (7 items) and doubting (7 items).

Statistical analysis

Data were expressed as mean ± standard error (SE) unless otherwise specified. Statistical analysis was performed using unpaired t-tests. $P < 0.05$ was considered statistically significant.

Results

Non-structured interviews

Group A: Parents of adolescents with GHD were particularly worried about the duration of GH therapy, the perspective of endless treatment and the need for

continuous assessment. The GHD patients expressed emotional suffering when they realized that therapy could be lifelong even if it allowed them to conduct a relatively normal life.

Group B: Several patients of this group overcame the psychological distress of the lifelong treatment and were happy to restart therapy having experienced an impaired sense of health during discontinuation of GH treatment. In others restarting therapy was painful; the narcissistic injury was reopened and they returned to the first every emotion they had experienced, such as anger.

Structured questionnaire

Group A: The majority of patients belonged to the lower social class (60%), 33% to the middle class and only 7% to the upper middle class in which both parents had a degree. All patients, but one, had a scholastic level adequate to their age. The best results were obtained in mathematics (27%) and classics (20%). One patient studied music (piano) with excellent results.

Group B: The majority of patients (60%) belonged to a lower social class, 20% to the middle class and 20% to the upper middle class. The 80% of the patients showed a low self-esteem, a closed attitude towards social relationships, a pessimistic attitude and a sense of detachment from the outside world, which led to a low rate of engagement. Forty percent of young adults with GHD was performing studies adequately to their age, the remaining 60% was unemployed (40%) or only occasionally employed (20%).

The human figure test

Group A: The projected age was the same of chronological age and the maturity level was appropriate to the age in 80% of patients**.** However, in several patients specific traits suggesting an excess of "control" were observed: 20% of them drew shoes in a very precise way, 80% drew with a repeated rhythm, 80% redrew over the same lines, and 33% repeatedly erased and redrew parts of the drawing.

Group B: Also in this group the projected age was the same of chronological age in 82% of patients. As already observed in patients from group A indexes suggesting an excess of "control" were observed: 80% of them drew with a repeated rhythm and 87% redrew over the same lines.

Anxiety questionnaire

As shown in Figure 1, the mean level of general anxiety was within normal for age in adolescents (47.4 ± 8.6 percentile) and young adults with GHD (60.2 ± 5.2 percentile), however in both was significantly higher compared to healthy controls (adolescents 19.1 ± 5.5 percentile $P < 0.01$; young adults 42.2 ± 4.7, $P < 0.02$).

Depression test

As shown in Figure 2, young adults with GHD showed a higher level of depression (66.1 ± 7.3 percentile) compared to both GHD adolescents (22.7 ± 5.4 percentile, P = 0.0003) and healthy controls (19.3 ± 8.4 percentile, P = 0.001). In the 53% of patients the level of depression was above the 75th percentile.

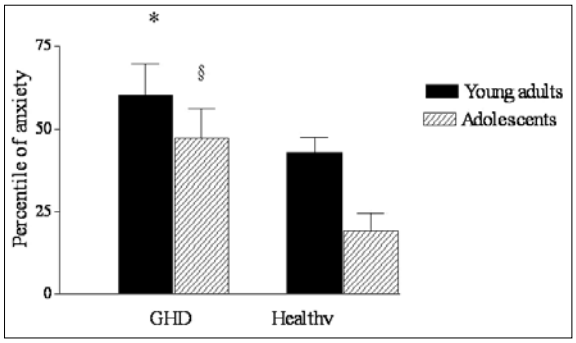

Fig. 1. Mean level of anxiety in adolescents and young adults affected by GHD compared to healthy subjects. * P < 0.02 and §P < 0.0005 vs healthy subjects.

Maudsley Obsessional-Compulsive Inventory test

Both adolescents and young adults with GHD exhibited a mean total score above the cut-off level of 12 [31] (15.9 ± 1.5 and 15.2 ± 1.1), significantly higher than healthy controls (7.1 ± 0.8, P < 0.0001 and 9.4 ± 0.9, P = 0.0003 respectively). The clinical subscales particularly affected were checking, cleaning and doubting. No significant differences were observed in the total score and in the subscales between adolescents and young adults (Tab. II).

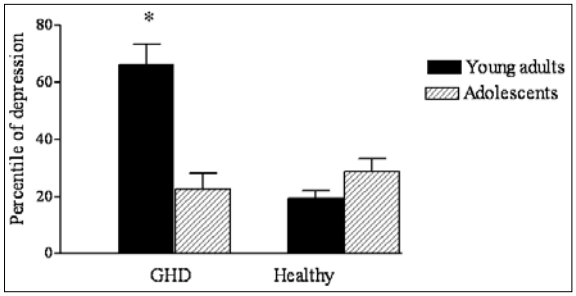

Fig. 2. Mean level of depression in adolescents and young adults affected by GHD compared to healthy subjects. * P = 0.001 vs healthy subjects and P = 0.003 vs adolescents.

Discussion

Our study shows that adolescents and young adults with GHD are at risk of several psychological problems, including social isolation, low rate of engagement, depressed mood, increased anxiety, and a complaint regarding the excessive control, particularly during the transition period.

GHD may affect many aspects of the children's life because it becomes part of their "growing up process" but a full consciousness of their condition begins during puberty, the time when they perceive the deficit as a serious impediment or a threat to their autonomy and ideal self image. This stage, in which the foun-

Tab. II. Mean scores at the MOCI test in patients with GH deficiency compared to control group of healthy subjects.

	Checking	Cleaning	Slowness	Doubting	Total
GHD					
- Adolescents	4.6 ± 0.7[a]	4.4 ± 0.6[a]	3.4 ± 0.3[a]	3.4 ± 0.4[c]	15.9 ± 1.5[c]
- Young adults	4.4 ± 0.4[a]	4.3 ± 0.7[b]	3.4 ± 0.2	3.4 ± 0.4[a]	15.2 ± 1.1[d]
Healthy controls					
- Adolescents	1.8 ± 0.4	2.3 ± 0.3	1.9 ± 0.4	1.1 ± 0.2	7.1 ± 0.8
- Young adults	1.7 ± 0.6	2.6 ± 0.5	3.2 ± 0.8	1.9 ± 0.2	9.4 ± 0.9

Data are expressed as mean ±SE.

[a]P < 0.005; [b]P < 0.04; [c]P < 0.0001; [d]P = 0.0003.

dations of the future are usually built, can be dangerous in their development if their emotional health is not considered and treated as well as their physical health. Most of our patients show an over-estimation of the effects of the illness and take a passive attitude becoming withdrawn. The young adults are in a state of psychosocial transition. They should negotiate the move from dependence to independence and face up to adult decision about relationships and work. Moreover they have to manage the thought of lifelong dependence and the feeling that life is denying them the possibility of developing real independence. The results of the structured questionnaire showed a closed attitude towards social relationships and a low rate of engagement as already reported in previous studies concerning the outcome of CO-GHD subjects [12-17]. While GHD adolescents were all attending school and their educational level was adequate, young adults with GHD showed a high rate of drop out from high school. Moreover the majority of them were unemployed or only occasionally employed.

The observation of psychological adjustment, through all psychological tools, reveal a trait of excessive control that is detectable during adolescence and persists later in life. The level of anxiety, although within average values, is higher than in controls in both adolescents and young adults with GHD. The level of depression that, as in healthy controls, is low in adolescents with GHD, increases with age becoming significantly higher in young adults also compared to controls. The results of this study indicate that patients with GHD may suffer from an anxiety disorder, which takes root in the "control". In fact, the subscale "Checking" of the Maudsley questionnaire is one of the items more affected.

It has been observed that young adults GHD rarely appear satisfied, in spite of their efforts, the pursuit of the "maximum" seems to be born out of a need, rather than out of real goals. Depression and their need for control coexist and contribute to interpersonal conflict and isolation from peers. The doubt is at the basis of control. It rise from the necessity of a constant hyper control of their

size, from an excessive concern of the patient's mothers that persist even when a satisfactory height has been reached. Almost all the mothers persist to accompany their "children" even when they became of age. The patients get entangled in a snare of excessive concern; they get discouraged easily for an autonomous exploration. The excess of mother's concern is characterized by instability, contradictions and uncertainties that confirm to the patient a missing trust in himself.

The GHD patient has already a missing trust in his body due to both, the deficit of his size and the deficit of his GH secretion. The effect of lacking in self confidence pushes him to the continuous pursuit of "perfection", well expressed in the human figure test, where 80% of both adolescents and young adults drew with a repeated rhythm, while 80% and 87% respectively redrew over the same lines. The pursuit of "perfection" of these patients seems functional to the unconscious persuasion that only the achievement of such a state will get them the approval and therefore the acceptance.

Our findings indicate that anxiety, depression and a trait of excessive control can be observed in GHD patients despite GH replacement therapy. Several studies have reported psychological problems in children and adults with GHD not on replacement therapy, some of which can be ameliorated by GH treatment [5 8-11 19]. We do not have data on psychological trait of GHD patients before substitutive treatment or at discontinuation of treatment, however, our results indicate that psychological problems get worse with age, adolescents being less affected than young adults. These traits can lead to impairment of self-esteem, emotional distress and concerns or uncertainty about future health.

It is important to support GHD children and to provide experiences that promote self-esteem. It is necessary to inform appropriately the GHD children on the nature of their illness and properly prepare them to a lifelong treatment. It is also important to give psychological assistance to parents as patients develop emotional issues according to the parents emotional issues. Early intervention, ideally starting at the time of diagnosis, with an appropriate psychological support, in addition to medical treatment will hopefully ameliorate present and future life of patients with GHD.

Summary

Objective. Clinical studies concerning the behavioural outcome in adults with childhood-onset (CO) growth hormone deficiency (GHD) indicate the GHD is strongly associated with a range of psychological effects including social isolation, low rate of academic progress, low rate of engagement, depressed mood and increased anxiety. The aim of this study has been to investigate the psychological adjustment of patients with CO-GHD from adolescence to young adulthood.

Methods. Thirty patients aged 10-20 years were evaluated during GH treatment through a structured questionnaire, a structured body language and body structure checklist, the human figure drawing test, the anxiety and depression

questionnaires, and the Maudsley Obsessional-Compulsive Inventory (MOCI). Patients were divided into 2 groups, adolescents and young adults. The latter group included only patients in the transition period affected by severe GHD when retested as adults. Thirty healthy subjects matched for age and sex were used as controls.

Results. Patients affected with GHD showed an average level of anxiety (adolescents 47.4 ± 8.6 percentile, young adults 60.2 ± 5.2 percentile, respectively) which, however, resulted significantly higher when compared to healthy controls (adolescents 19.1 ± 5.5 percentile $P < 0.01$; young adults 42.2 ± 4.7, $P < 0.02$). A similar trend was observed for depression; young adults with GHD had an higher score of depression (66.1 ± 7.3 percentile) compared to both GHD adolescents (22.7 ± 5.4 percentile, $P = 0.0003$) and healthy young adults (19.3 ± 8.4 percentile, $P = 0.001$). In adolescents with GHD the level of depression was very close to healthy controls (28.8 ± 4.5 percentile). The psychological adjustment, carried out by all the psychological tools showed an excessive control in patients with GHD which increased from adolescence to young adulthood, and a slight compulsive trait as shown by the mean total score at MOCI (15.9 ± 1.5 and 15.2 ± 1.1, respectively), significantly higher than healthy controls (7.1 ± 0.8, $P < 0.0001$ and 9.4 ± 0.9, $P = 0.0003$ respectively).

Conclusions. Patients with GHD are at risk of some psychological problems, which can be observed during adolescence and persist or increase during the transition period. Behavioural counseling and psychological support from childhood should, therefore, be considered in patients with severe GHD to adequately prepare them to a lifelong medical treatment.

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