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Is growth hormone deficiency associated with anxiety disorder and depressive symptoms in children and adolescents?: A case-control study

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ABSTRACT

Aim: Children with growth hormone deficiency (GHD) are reported to experience failure in psychological maturation, and to have a lack of self-confidence in social life, and depressive symptoms. The purpose of this study was to investigate the relation between GHD and anxiety disorders and depression in children and adolescents.
Method: 122 children and adolescents aged 7–17, 87 receiving GHD therapy and 35 before treatment, and 122 healthy volunteers were included in the study. All participants were evaluated using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version-Turkish Version (K-SADS-PL-T). Diagnoses falling outside this semi-structured interview were made with clinical evaluation based on DSM-V diagnostic criteria. Participants were also assessed using an information form, the State-Trait Anxiety Inventory for Children (STAI-C), the Social Anxiety Scale for Children-Revised (SASC-R), and the Children's Depression Inventory (CDI), and the results were subjected to statistical analysis.
Results: Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) were significantly more common in children with GHD compared to the control group ($p \leq 0.001$ and $p = 0.033$, respectively). Receipt of treatment significantly reduced GAD and SAD rates in the group diagnosed with GHD ($p = 0.012$, and $p = 0.014$). Being in receipt of GH therapy also caused a significant decrease in STAIC (State) ($p \leq 0.001$), STAIC (Trait) ($p \leq 0.001$), SASC-R ($p \leq 0.001$), and CDI ($p \leq 0.001$) scale scores. Untreated subjects had more adverse scale scores than treated subjects, and treated subjects had more adverse scale scores than the control group. An increase was observed in all scale scores in the form of control group < treated group < pre-treatment group. IGF and GH-PEAK exhibited moderate negative correlation with STAIC-TRAIT, STAIC-STATE, and SASC-R, and weak negative, significant correlation with CDI (Spearman's rho $p \leq 0.05$).
Conclusion: Having GHD and being in receipt of treatment resulted in lower scale scores. Children with GHD had higher GAD and SAD burdens compared to the healthy controls. The etiology of these children's existing psychiatric diseased now requires identification using more variables in psychosocial and hormonal terms.

1. Introduction

Anxiety and depressive disorders are some of the most common conditions affecting children and adolescents [1, 2]. Anxiety and depression are associated with a series of adverse outcomes in young people. They may result in various problems, including emotional disorders, education problems, difficulties at home and in social relations, physical health problems, smoking and substance abuse [3]. The etiology of anxiety and depressive disorders is not fully understood. However, several studies have shown a relation between anxiety and depressive disorders and hormones, and anomalies have been determined in hypothalamicpituitary-adrenal axis systems [4, 5].

Recent studies have suggested that growth hormone (GH) also affects some psychological processes. Children with growth hormone deficiency (GHD) have been reported to experience sleep disorders, failure to mature psychologically and impaired personality development [6, 7]. Failure to thrive, behavioral problems, lack of confidence in social life and depressive symptoms are noteworthy in children with GHD [8, 9]. One review evaluating data from child and adult studies reported that patients with pituitary insufficiency and in receipt of conventional hormone replacement therapy have a suboptimal quality of life and decreased cognition function [10]. In addition, children with

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GHD have been reported to have low quality of life, while improvement occurs in the quality of life self-esteem and emotional well-being domains in subjects receiving GH therapy [11–13]. Hypothalamus involves regulatory peptides such as growth hormone releasing hormone (GHRH), growth hormone inhibiting hormone (somatostatin), and perhaps other neurotransmitters of the dopaminergic and noradrenergic pathways. In addition to the direct effects of GH, therefore, alterations in the secretion of these hypothalamic products may also possibly play a role in the genesis of emotional and behavioral problems [14]. GH treatment of GHD adults reduces the cerebrospinal fluid (CSF) concentrations of vasoactive intestinal peptide and of the dopamine metabolite homovanillic acid [15, 16], and may increase the CSF concentration of beta-endorphin [16]. In addition, increased stereotypical movements and psychological disadvantages have been shown in children with short stature [17, 18]. On the basis of the information in the existing literature, the purpose of this study was to investigate whether or not there is an association between GHD in children and adolescents and anxiety disorders and depression.

2. Methods

One hundred twenty-two patients diagnosed with idiopathic GHD and under monitoring at the Erzurum Regional Training and Research Hospital Pediatric Endocrinology Department, together with 122 healthy children and adolescents without GHD were included in the study. Following receipt of ethical committee approval, participants were selected from children presenting to the Erzurum Regional Training and Research Hospital. All subjects were evaluated in terms of anxiety disorders and depressive symptoms at the Child and Adolescent Mental Health and Diseases Clinic. Children and adolescents aged 7–17 were enrolled. The clinicians and the data handlers were blinded to the diagnoses of the subjects participating in the study. Subjects diagnosed with generalized developmental disorder or mental retardation (IQ < 70), aged other than 7–17, unwilling to take part, or with other hormone deficiencies in addition to GHD were excluded. The control group (CG) consisted of children who were admitted to the outpatient follow-up clinic of healthy children during a period of 1 year. The study was explained to the case and control group members and their families, and informed consent forms were obtained from those enrolled. Once patients' demographic data (age, sex, education, premorbid characteristics and accompanying diseases) had been obtained, all children and adolescents underwent a detailed psychiatric assessment based on The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria.

The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version-Turkish Version (K-SADS-PL-T) was applied to all cases in the study. This investigates past and existing psychiatric disorders in children and adolescents aged 6–18 in the light of information obtained from subjects and their parents, and clinical diagnosis is established in combination with clinician observations. Decision regarding the presence and severity of symptoms are made by combining the opinions of the adolescent, parents and clinician. If positive symptoms are recorded with a screening interview, then an addition list of symptoms is employed to assess the psychopathology in greater detail. The validity and reliability of the Turkish language version were confirmed by Gökler et al. [19].

The State-Trait Anxiety Inventory for Children STAI-C includes two subscales (state anxiety and trait anxiety), each consisting of 20 multiple-choice items. Study and control group were assessed STAI-C. High scores indicate high levels of anxiety, and low scores, low levels of anxiety. Each item is scored 1, 2 or 3 for an anxiety symptom, and possible total scores thus range from 20 to 60. The scale can be used up to 17 years of age. The Turkish version has been reported to be valid and reliable for use in Turkey [20].

The Social Anxiety Scale for Children-Revised (SASC-R) is an 18-item self-report scale. Possible scores on this five-point Likert type scale range from 18 to 90. Demir et al. reported that the Turkish-language version of the scale is valid and reliable [21].

The Children's Depression Inventory (CDI) can be applied to children aged 6–17. It was administered to all the participants in our study. This is a self-assessment scale used to investigate childhood anxiety. The scale consists of 21 items and provides general information about severity of depression and the depressive symptom profile. A cut-off score of 19 is recommended. The reliability and validity of the Turkish language version of the scale were established by Belma Öy [22].

Standing height was measured in quadruplicate using a wall-mounted Harpenden stadiometer accurate to the nearest 1 mm. Bone age was determined centrally by a single blinded observer using a left hand-wrist radiograph as described by Greulich and Pyle. The clinical diagnosis of GHD was defined by height less than the third percentile and peak GH response < 10 ng/mL after one of two growth hormone stimulation tests using L-dopa, and clonidine. All pre-pubertal patients were primed with sex steroids prior to the GH test. Organic pathology was excluded in all cases with pituitary magnetic resonance imaging (MRI) before treatment.

Serum human GH levels were measured by means of enzyme chemiluminescence assay using the Siemens IMMULITE 2000 xpi system (Diagnostic Products Corporation, Los Angeles, USA). Serum IGF-1 levels were measured with enzyme immunoassay using the Siemens IMMULITE 2000 xpi system (Siemens Healthcare Diagnostics Inc., Los Angeles, USA).

Descriptive statistics (mean, standard deviation, minimum, median and maximum) were used to describe continuous variables. The Kruskal-Wallis *H* test was used to compare continuous independent variables between the three groups. Comparison between two groups of variables determined to be statistically significant was performed using the Dunn test, and analysis was concluded using significance values subjected to Bonferroni correction (Adj. Sig.). The Mann-Whitney *U* test was used to compare two independent and non-normally distributed variables. The chi-square test (or Fisher's exact test when appropriate) was used to assess relations between categorical variables. Student's *t*-test was used in data analysis to compare independent groups. Spearman's rho correlation was used to analyze correlation between two continuous variables not exhibiting normal distribution. The single sample chi square test was used to compare frequency distribution with the expected frequency distribution of a categorical variable. Analyses were performed on MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). Statistical significance was set at 0.05.

3. Results

The case and control group distributions, age, gender and weight data of our study participants are shown in Table 1. The comparison of case group participants according to pubertal and prepubertal status is shown in Table 2. Thirty-five of the 122 patients with GHD consisted of patients who were evaluated during the first presentation that had not yet begun to be treated. The remaining 87 patients were patients who were still on treatment with GH. Generalized Anxiety Disorder (GAD) was diagnosed in 23 of the case group, 12 (34.2%) of the 35 GHD patients before starting treatment and 11 (12.6%) of the 87 GHD patients whose treatment was continuing. Social Anxiety Disorder (SAD) was diagnosed in 10 (28.5%) of the 35 GHD patients before treatment and in 8 (9.1%) of the 87 GHD patients whose treatment was continuing. GAD was diagnosed in 3 (2.4%) subjects in the control group and SAD in 7 (5.7%). Comparison of the case and control group total diagnosis scores revealed that GAD and SAD were significantly higher in children with GHD compared to the control group. Significant variation was determined in distributions of GAD and SAG between the case and control groups at single sample analysis (chi-square $p \leq 0.05$) (Table 3).

At three-way comparisons between individuals diagnosed with GHD receiving treatment or yet to start treatment and the control group,