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Assessment of Executive Function Skills in Children with Isolated Growth Hormone Deficiency: A Cross-sectional Study

Gülsüm Yitik Tonkaz[1], Atilla Çayır[2]

[1]Giresun Maternity and Children Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, Giresun, Turkey
[2]Erzurum Regional Training and Research Hospital, Clinic of Pediatric Endocrinology, Erzurum, Turkey

What is already known on this topic?

Growth hormone deficiency (GHD) may be accompanied by sleep problems, mood and behavior problems, impairment of cognitive functions, such as attention and memory, and developmental delay in children. It has been suggested that GH may affect individuals' psychological well-being, memory, and cognitive functions by affecting different areas in the central nervous system through specific receptors. In addition, studies have reported that both GH and insulin-like growth factor-1 receptors, through which GH exerts its effects, are important for cognitive functions such as attention and memory. However, studies on executive function (EF), an important element of cognitive function, in children with GHD are limited.

What this study adds?

EF skills in children with isolated GH deficiency (IGHD) were evaluated. EF skills were significantly compromised in the children with IGHD compared to unaffected peers. As EF may influence academic success, we suggest that children with IGHD may benefit from psychiatric evaluation before and during treatment with GH, which may help to ameliorate the effect on school performance and possibly social development.

Abstract

Objective: The aim of this study was to evaluate executive function (EF), such as inhibition and working memory, in children with isolated growth hormone deficiency (IGHD) using performance-based tests and parent-report scales.

Methods: A total of seventy children between the ages of 7 and 12 years were included in the study. Half (n = 35) had children with IGHD and half were healthy controls. To evaluate the EF performances of the participants, the Visual Aural Digit Span Test-B Form (VADS-B) and Stroop task were applied. EF was also evaluated using the Behavior Rating Inventory of Executive Function (BRIEF).

Results: Children with IGHD scored lower on the VADS-B form for short-term memory ($p < 0.05$) compared to healthy controls. In addition, the completion time for the Stroop-color/word test was significantly longer in children with IGHD ($p < 0.05$). For children with IGHD, their parents reported higher scores on all sub-scales of the BRIEF scale, with statistically significant differences for all sub-scales with the exception of "organization of materials" ($p < 0.05$).

Conclusion: In this study, children with IGHD had poorer EF skills compared to unaffected peers. EF skills may influence academic success by affecting children's language skills, mathematical comprehension, cognitive flexibility, and hypothetical thinking. We believe that psychiatric evaluation of children with IGHD before and during treatment may positively contribute to both their academic performance and social relationships.

Keywords: Executive function, isolated growth hormone deficiency

Address for Correspondence: Gülsüm Yitik Tonkaz MD, Giresun Maternity and Children Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, Giresun, Turkey
Phone: +90 506 568 91 38 **E-mail:** gulsumyitik@gmail.com **ORCID:** orcid.org/0000-0001-7195-2293

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Introduction

Executive function (EF) is defined as high-level cognition associated with regulating and controlling cognitive processes. These functions include various cognitive skills that are needed for planning and maintenance of thoughts and behavior in line with a goal, such as orienting attention, inhibition of stimuli irrelevant to the goal, holding processed information in an active state, and switching between information (1). Working memory (WM), inhibition, and cognitive flexibility are among the core components of EF (2).

Growth hormone (GH) deficiency (GHD) is a significant cause of short stature with a prevalence of 1 in 4,000-10,000 births (3). GHD can be isolated or occur with other anterior pituitary hormone deficiencies, and may be congenital or acquired. Clinical findings depend on the specific etiology (3). Congenital causes can be generally classified as isolated GHD (IGHD), anatomical disorders, and genetic pathologies. Acquired causes include trauma, central nervous system tumors, radiation, and infiltrative diseases. However, a large majority of GHD cases are idiopathic (3,4).

GHD may be accompanied by sleep problems, mood and behavioral problems, impairment in cognitive functions, such as attention and memory, as well as failure to thrive (5). It has been suggested that GH can affect different areas in the central nervous system via specific receptors, impacting the psychological well-being, memory, and cognitive functions of individuals (5). Various studies performed in children with IGHD and children born small for gestational age (SGA) have found low GH levels to be associated with poorer memory and cognitive functions (6). A three-year observational study on children with SGA reported that GH replacement resulted in the development of a normal head diameter, as well as an improvement in intelligence and psychosocial functioning (7,8). Studies conducted on adults with GHD showed that GH treatment affected the neuronal signaling pathways associated with attention and memory in the long term (5,9). Furthermore, in a follow-up study performed on children with GHD, an increase in intelligence quotient (IQ) values associated with fluid intelligence was observed after GH replacement (6). GH was reported to affect the secretion of dopamine (DA) and noradrenaline in experimental rodent model studies (10). GH is also found in the cerebrospinal fluid (CSF) as it penetrates the blood-brain and blood-CSF barrier, and is predicted to affect cognitive processes by mechanisms, such as long-term potentiation via its receptors in different areas of the brain [prefrontal cortex (PFC), amygdala, and hippocampus] (11,12). As a result, it is been demonstrated that both GH and the insulin-like growth factor-1 (IGF-1) receptors, through which GH exerts its effects, are important for cognitive function, such as attention and memory (5).

Upon review of the literature, no studies evaluating EF skills in children with IGHD were found, although there are studies evaluating cognitive skills (5,6,7,8,9,10). Therefore, the aim of this study was to evaluate EF skills in children with IGHD in terms of WM, selective attention, and inhibition skills using performance-based tests and compare the findings with unaffected healthy children. In addition, the parents of the children with IGHD were asked to complete parent report scales related to EF in their children.

Methods

Study Sample

The case group of included 35 children, aged between 7 and 12 years, who attended a tertiary care (University of Health Sciences Turkey, Erzurum City Hospital) pediatric endocrinology outpatient clinic and had been diagnosed with IGHD based on neuroimaging, endocrinological and laboratory evaluation. The control group included 35 healthy children, also aged between 7 and 12 years, who had normal height and weight development, did not have any neurological, psychiatric, genetic, metabolic, or endocrine diseases, and had age-appropriate academic performance as reported by their teachers. This study was a cross-sectional study that was approved by the Erzurum Regional Training and Research Hospital, Local Ethics Committee (decision no: 2022/04-28, date: 11.04.2022) and was performed according to the tenets of the Helsinki Declaration.

Procedure

All participants' standing height was measured in quadruplicate using a wall-mounted Harpenden stadiometer accurate to the nearest 1 mm. In addition, a GH stimulation test was performed with L-dopa and clonidine, and IGF-1, and IGF-binding protein-3 levels were measured. The clinical diagnosis of IGHD was defined by height less than the third percentile and peak GH response <10 ng/mL after one of two GH stimulation tests using L-dopa, and clonidine. All participants diagnosed with IGHD underwent a Diagnostic and Statistical Manual of Mental Disorders-5 based clinical interview to determine psychiatric diagnoses and comorbid conditions before GH replacement therapy (13,14). Based on this psychiatric evaluation, the children had normal language and communication skills. Furthermore, following psychometric testing, those with an IQ level of 80 and above were included in the study. Parents of the participants were asked to complete the Sociodemographic Data Form and the Behavior Rating Inventory of EF (BRIEF)-Parent Form. All children participating in the study underwent the Visual Aural Digit Span-Form-B (VADS-B) and the Stroop test in order. The tests were administered in a quiet and well-lit room without any interaction. The researcher and the child sat on two chairs facing each other during the application of both tests. Time was recorded using a chronometer. The participants had normal or corrected vision and normal hearing. VADS-B was administered starting from the third item of each sub-test. If a successful response was not obtained on the first try, a second sequence of the same length was presented. In case of a correct response, the next sequence was presented. If both trials in the sub-test were answered incorrectly, the sub-test was stopped. Numbers were spoken at 1-second intervals in the auditory sub-test. In the visual sub-test, a booklet that had one number per page was shown to children at 1-second intervals. For sub-tests that needed to be completed by writing, paper and pencil were used and administration time varied between 15-20 minutes. A separate card was used for each of the five parts of the Stroop test. In the first part, individuals were asked to read the names of colors that were written with black ink on a white background. In the second part, individuals were asked to read aloud the names of colors written in a different color on a white background. In the third part, individuals were asked to name the colors of circles printed in different colors. In the fourth part, individuals were asked to name the colors of neutral words written in different colors. In the fifth part, the card used in the second part was re-used, but the individuals were asked to name the colors of the words. The completion time for the relevant task was recorded with a timer for each of the five parts.

Data Collection Tools

Socio-demographic Data Form: The form prepared by the authors was designed and administered to collect information regarding the participants and their family members [age, gender, delivery time, delivery type, developmental steps (walking, talking, toilet training), and settlement]. Socioeconomic status was measured with the Hollingshead-Redich scale (15).

Behavior Rating Inventory of Executive Function-Parent Form: BRIEF was developed by Gioia et al. (16) to assess EF, problem-solving skills, and adaptive behavior in children. BRIEF was standardized and validated in Turkish by Batan et al. (17). Scores on eight different subscales of EF and 2 comprehensive indices [Behavioral Regulation Index (BRI) and Meta-Cognition Index (MCI)] can be calculated from this scale of 86 items. The obtained high scores indicate high executive disorder (16,17). Description of BRIEF subscales is as follows (16,17):

- **Inhibition:** Impulse control and ability to stop one's own behavior at the appropriate time

- **Shifting:** Ability to flexibly transition from one situation, activity, mindset or aspect of a problem to another.

- **Emotional Control:** Ability to modulate emotional response.

- **Initiate:** Ability to start a task or activity and generate ideas independently.

- **WM:** Ability to retain information in mind in order to complete a task or make a response.

- **Plan/Organize:** The ability to predict future events, set goals, develop appropriate steps in advance, perform tasks in a systematic way, understand and communicate main ideas.

- **Organizations of Materials:** Ability to manage current and future-oriented task demands within the situational context.

- **Monitoring:** Ability to control work, evaluate performance, and monitor one's own and others' efforts.

- **Behavioral Regulation Index:** It is the total score of inhibition, shifting, emotional control subscale scores.

- **Meta-Cognition Index:** It is the total score of initiate, WM, plan/organize, organizations of materials and monitoring subscale scores.

- **Global Executive Composite Index:** It is calculated by the sum of the BRI and MCI.

Visual Aural Digit Span-Form-B: VADS-B is a neuropsychological test developed by Koppitz (18) that assesses WM and short-term memory (19). Its validity in Turkish was established by Karakaş and Yalın (20) in 1993, and revised in 2002 (21). VADS-B consists of number sequences of two to nine digits. The items are presented orally and visually, and the children are asked to repeat the sequence in forward order, orally and in writing. The scoring considers the number of digits in the number with the most digits that could be accurately repeated. Higher scores indicate better performance. The test is composed of four main sub-tests that are auditory-oral, visual-oral, auditory-written, and visual-written sub-tests.

Stroop Test-TUBITAK Basic Sciences Research Group (TBAG) Form: The Stroop test is used to assess selective attention and response inhibition (21). The test focuses on the interference effect and the reaction time associated with incongruence between the color used in the writing of a word and the color name uttered as the word is read, and offers insight into frontal activation (22,23). The present study used the TBAG version of the Stroop test (23). The TBAG version of the Stroop Test, was developed by Kılıç et al. (24), and was standardized in 2002. In light of earlier published studies, data analysis was performed by taking into account the three sub-sections of the test with the highest reliability: the reading of color names printed in black (Stroop-word), naming of colored circles (Stroop-color), and naming of the colors of colored words, when the color and the meaning may be incongruent for certain words (Stroop-color/word) (25). The critical part, where the interference effect appears in Stroop tests, is the Stroop-color/word section. The test provides completion times for each section, the number of errors, and the corrected number of responses as scores, and comparisons are made based on the completion time for each test (26).

Statistical Analysis

Categorical data are presented as numbers and percentages. The data for continuous variables are presented as mean and standard deviation. The Shapiro-Wilk test was used to determine whether the distributions of continuous variables were normal. The mean differences between two related groups of normally distributed data were compared using the independent sample t-test, while the Mann-Whitney U test was used to compare the non-normally distributed data. The frequencies of categorical variables were compared using the Pearson chi-square, Yates' chi-square, or Fisher's exact test, as appropriate. Statistical significance was considered when $p < 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 21 (IBM Corp., Armonk, NY, USA). Differences in mean subscores of VADS-B, Stroop TBAG form, and BRIEF were analyzed using univariate analysis of covariance (ANCOVA) with participant group as factor and VADS-B, Stroop TBAG form and BRIEF subscores as dependent variables; chronological age in years was set as a covariate.

Results

There was no difference between the groups regarding socio-demographic, data including age, gender, delivery time, delivery type, developmental steps (walking, talking, toilet training), family structure, settlement, and socio-economic status (all $p > 0.05$). Characteristics of the case and control groups including age, gender, and height are presented in Table 1.

Children with IGHD scored lower scores on the VADS-B for assessing short-term memory ($p < 0.05$) (Table 2). Although children with IGHD tended to have longer completion times for the Stroop word and Stroop color sections of the Stroop test to assess selective attention and

Table 1. Age, gender, and height distribution of the participants

		IGHD group (mean ± SD)	Control group (mean ± SD)	p value
Male (n = 16)	**Age (years)**	9.6 ± 1.8	9.4 ± 1.6	0.8
	Height (cm)	117.6 (± 3.01)	133.1 (± 0.31)	**< 0.001**
Female (n = 19)	**Age (years)**	9.5 ± 1.7	9.6 ± 1.7	0.8
	Height (cm)	115.7 (± 3.14)	134.3 (± 0.11)	**< 0.001**

IGHD: isolated growth hormone deficiency, p: probability of significance, cm: centimeter, SD: standard deviation

Table 2. Comparison of the VADS-B and Stroop TBAG subscale scores for children with IGHD and controls

Variables		IGHD group (mean ± SD)	Control group (mean ± SD)	p value	ANCOVA	
					F	p*
VADS-B						
Aural-Verbal		5.61 ± 1.27	6.69 ± 1.13	0.001	15.030	**< 0.001**
Visual-Verbal		4.30 ± 0.95	5.31 ± 0.96	< 0.001	21.785	**< 0.001**
Aural-Written		5.33 ± 1.05	6.26 ± 1.12	0.002	17.375	**< 0.001**
Visual-Written		4.82 ± 1.01	5.46 ± 0.82	0.002	9.287	**0.003**
Total		19.47 ± 5.02	23.71 ± 3.34	< 0.001	22.184	**< 0.001**
Stroop TBAG test						
Stroop-Word	Completion time (sec.)	12.69 ± 6.09	11.10 ± 3.47	0.615	2.985	0.09
Stroop-Color	Completion time (sec.)	17.78 ± 6.62	15.87 ± 4.5	0.390	3.346	0.073
Stroop-Color/word	Completion time (sec.)	36.31 ± 10.29	30.83 ± 10.69	**0.011**	9.532	**0.003**

Analysis of covariance (ANCOVA) was used for comparisons between the two groups after adjusting for chronological age (years).
IGHD: isolated growth hormone deficiency, SD: standard deviation, sec: seconds, VADS-B: Visual Aural Digit Span Test-B Form, TBAG: TUBITAK Basic Sciences Research Group

inhibition, the difference was not significant. However, the completion time for the Stroop-color/word test was significantly longer in children with IGHD.

Parents of children with IGHD reported higher scores on all sub-scales of the BRIEF scale. These scores were significantly worse for all subscales except "organization of materials" (Table 3).

Discussion

The mechanisms underlying the relationship between GH and cognitive functions are still not completely clear. To investigate the potential relationship between EF and GH in this study, we assessed the EF skills of children with IGHD, using both performance-based testing and parent-report tests, and found that EF skills were poorer in children with IGHD when compared to their unaffected peers.

In the present study, WM was assessed with both VADS-B and the BRIEF scale and both tasks determined poorer WM in children with IGHD. The effects of GH on cognitive skills, such as learning and memory, have been investigated by various earlier studies, including prospective studies that reported cognitive improvement after GH replacement in adults followed up for GH deficiency (26,27,28). Experimental animal studies observed improvement in spatial memory with GH and replacement with GH secretagogue, ghrelin (29,30). Moreover, an impairment in the Morris water maze performance test was found in spontaneous dwarf rats with an inbred variant of the GH gene that causes GH deficiency (31). In contrast to these studies, an experimental animal study examining the effect of GH on cognitive performance showed that GH excess also had a negative effect and inhibition of GH action had a beneficial effect on spatial learning and memory and thus cognitive performance in male mice (32,33). These different results obtained after GH replacement were attributed to the variable effects of systemic GH on different tissue types (34). However, in another study where 99 prepubertal children (aged 3-11) were monitored for idiopathic short stature and GH deficiency-related short stature, IQ levels were found to significantly increase (6). In recent years, neuroimaging studies have been performed to investigate memory performance in GH deficiency (35,36). Arwert et al. (36) compared the GH/IGF-1 axis and memory performance between two groups with high and low IGF-I among 24 elderly adults and determined that, although error rates on a WM task were similar between the two groups, those with high IGF-I levels had faster memory performance with more blood flow to the task-related prefrontal areas on positron emission tomography. Moreover, the same group using functional magnetic resonance imaging (fMRI) in a study of adults with childhood-onset GH deficiency showed that, although the groups were not different in terms of WM, the imaging results of adults with childhood-onset GH deficiency showed higher activity in dorsolateral/ventrolateral PFC, anterior cingulate cortex, parietal cortex, complementary motor and motor cortex, as well as in the thalamus and precuneus. The authors interpreted these results as GH-deficient patients having a lower-than-normal WM speed, which could be compensated for by dorsal prefrontal regions through different mechanisms with no disruption

Table 3. Comparison of BRIEF Scale scores of children with IGHD and control

Variables	IGHD group (mean ± SD)	Control group (mean ± SD)	p value	ANCOVA	
				F	p*
BRIEF					
Inhibition	22.53 ± 6.46	17 ± 2.86	< 0.001	19.886	**< 0.001**
Shifting	18.94 ± 4.19	15.73 ± 3.56	0.001	11.115	**0.001**
Emotional control	19.91 ± 4.32	14.94 ± 3.01	< 0.001	29.167	**< 0.001**
Initiate	13.82 ± 3.25	11.39 ± 2.79	0.003	10.584	**0.002**
Working memory	19.65 ± 5.31	15.39 ± 4.10	0.001	13.250	**0.001**
Plan	25.29 ± 6.84	19.45 ± 5.33	< 0.001	14.805	**< 0.001**
Organization of materials	12.65 ± 3.94	10.97 ± 3.05	0.090	3.650	0.061
Monitoring	13.53 ± 3.93	10.76 ± 2.96	0.002	10.386	**0.002**
BRI	61.38 ± 12.69	47.67 ± 7.3	< 0.001	28.637	**< 0.001**
MCI	72.29 ± 17.6	57 ± 13.95	< 0.001	15.154	**< 0.001**
GEC	133.68 ± 29.29	104.67 ± 19.64	< 0.001	22.070	**< 0.001**
Total scores	146.35 ± 31.93	115.73 ± 21.58	< 0.001	18.377	**< 0.001**

Analysis of covariance (ANCOVA) was used for comparisons between the two groups after adjusting for chronological age (years).
BRIEF: Behavior Rating Inventory of Executive Function, IGHD: isolated growth hormone deficiency, SD: standard deviation, BRI: Behavioral Regulation Index, MCI: Metacognition Index, GEC: Global Executive Composite

in the quality of memory performance (35). In another study, those with childhood-onset GHD were reported to have more pronounced impairment in cognitive functions compared to those with adult-onset GH deficiency (37). The data obtained in the present study supports the studies that have demonstrated poorer WM in children with IGHD. The difference in the errors on WM tasks, which was not found in adult GHD, was quite prominent in the children with IGHD in our study. It is possible that this may because there is no increased prefrontal blood flow in children that was observed in neuroimaging studies of adults, although there is no empirical evidence to support this as yet.

Another parameter evaluated in the present study was self-regulation or inhibitory control, which is defined as the ability to suppress irrelevant responses. We assessed the inhibitory control ability in children with IGHD using both the Stroop TBAG test and the parent-reported BRIEF scale. The results of both assessments suggested poorer inhibitory control in children with IGHD. Patients with IGHD also had lower scores (poor EF skills) on the components of other EFs, such as shifting, emotional control, initiating, planning/organizing, and monitoring, which were evaluated in our study with the BRIEF sub-scales. In line with the results of our study, a meta-analysis reported that GH deficiency caused impairment in neurocognitive networks associated with attention and EF (38). Moreover, it has been generally reported that cognitive skills and attention improve after GH replacement (5). Further studies employing different neuropsychological tests accompanied by neuroimaging are needed to evaluate the effects of GH deficiency on the EF of children with GHD in more detail.

Lastly, the Stroop TBAG test also provided information regarding selective attention (25). In the present study, we determined poorer selective attention in children with IGHD. GH is thought to enter a mutually excitatory interaction with DA and influence the ventral tegmental area-nucleus accumbens-hippocampus-cingulate cortex axis through the amplification of dopaminergic effects, playing a role in reward and conflict processing (39). It has also been suggested that GHD could affect cognitive functions, such as conflict monitoring, WM, and selective attention, by causing DA deficiency (39). Sartorio et al. (40) reported that children with IGHD had certain academic impairment, especially learning difficulties and attention deficit disorders. Although different studies have used the Stroop test to evaluate the relationship between GH and attention and found no significant difference (39,40,41), studies that used different measurement tools, such as the trail-making test, the divided attention task, and the go/no go task, obtained significant results (37,42,43). In line with the results of our study, a review of GH and selective attention found that GHD was associated with poor selective attention (43). Prospective studies that will evaluate cases of childhood-onset GHD in adulthood are needed to better understand the relationship between GH and selective attention.

Study Limitations

Our study has several limitations. The first of these is that the EF skills of cases with IGHD participating in our study were not evaluated after GH replacement. A further limitation was that the scales used to evaluate EF functions vary between studies. Another important limitation was that the parent-child relationship, attachment, and parental attitudes, which are known to affect EF skills, were not evaluated. Further studies are needed in this context (35). Lastly, the participants were administered neuropsychometric tests, but neuroimaging methods, such as fMRI, were not used. Follow-up studies that will use similar scales, incorporate neuroimaging methods, and encompass the childhood period, the treatment process, and the adulthood period are needed to better understand the relationship between GH deficiency and EF skills.

Despite these limitations, this study is the first that to examine EF in school-age children with IGHD, based on both child performance and parent reports. In this context, we believe that the present study will contribute to the literature on IGHD and potentially stimulate future comprehensive prospective studies.

Conclusion

The results of this study demonstrated poorer EF skills in children with IGHD compared to unaffected peers. EF skills may influence academic success by affecting children's language skills, mathematical comprehension, cognitive flexibility, and hypothetical thinking. We believe that psychiatric evaluation of children with IGHD before and during treatment may positively contribute to both their academic performance and social relationships, although this suggestion requires data from future prospective studies before it can be adopted widely.

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Ethics

Ethics Committee Approval: This study was a cross-sectional study that was approved by the Erzurum Regional Training and Research Hospital, Local Ethics Committee (decision no: 2022/04-28, date: 11.04.2022) and was performed according to the tenets of the Helsinki Declaration.

Informed Consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Authorship Contributions

Surgical and Medical Practices: Gülsüm Yitik Tonkaz, Atilla Çayır, Concept: Gülsüm Yitik Tonkaz, Design: Gülsüm Yitik Tonkaz, Atilla Çayır, Data Collection or Processing: Gülsüm Yitik Tonkaz, Analysis or Interpretation: Gülsüm Yitik Tonkaz, Atilla Çayır, Literature Search: Gülsüm Yitik Tonkaz, Writing: Gülsüm Yitik Tonkaz, Atilla Çayır.

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