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Research Article

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

Yitik Tonkaz G and Çayır A. Executive Functions and Isolated Growth Hormone Deficiency

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What is already known about this topic?
GH deficiency (GHD) may be accompanied by sleep problems, mood and behavior problems, impairments in cognitive functions such as attention and memory, and developmental delay in children. It is suggested in the literature that growth hormones can affect individuals' psychological well-being, memory, and cognitive functions by affecting different areas in the central nervous system through specific receptors. In addition, different studies emphasize that both growth hormone and insulin-like growth factor I (IGF-I) receptors, on which growth hormone exerts its effects, are important for cognitive functions such as attention and memory. However, studies on executive functions, an important element of cognitive functions, in children with GH deficiency are limited.

What this study adds to the literature?
Based on this literature gap, we evaluated executive function skills in children with isolated GH deficiency (IGHD). Executive function skills may influence academic success by affecting children's language skills, mathematical comprehension, cognitive flexibility, and hypothetical thinking. Therefore, we think it would be useful concerning a holistic approach if the psychiatry department evaluated the children we diagnosed with isolated GH deficiency (GHD). We think that psychiatric evaluation of IGHD children before and during treatment will make positive contributions to both their academic and social relationships.

ABSTRACT
Objectives: This study aims to evaluate executive functions 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 were included in the study. To evaluate the executive functioning (EF) performances of the participants, the Visual Aural Digit Span Test-B Form (VADS-B) and Stroop task were applied. Executive functioning was also evaluated using the Behavior Rating Inventory of Executive Function (BRIEF).
Results: Children with IGHD received lower scores on the VADS-B administered to assess short-term memory ($p<0.05$). And, the completion time for the Stroop-color/word test was significantly longer in children with IGHD ($p<0.05$). Children with IGHD were determined to receive higher scores on all sub-scales of the BRIEF scale completed by the parents of the participants, with statistically significant differences for all sub-scales except for "organization of materials" ($p<0.05$).
Conclusions: We determined poorer executive function skills in children with IGHD. Executive function skills may influence academic success by affecting children's language skills, mathematical comprehension, cognitive flexibility, and hypothetical thinking. Therefore, we think that psychiatric evaluation of children with IGHD before and during treatment will positively contribute to both their academic performance and social relationships.
Keywords: Executive Function, Isolated Growth Hormone deficiency,

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1. Introduction
Executive functions (EF) define high-level cognition associated with regulating and controlling cognitive processes. These functions include various cognitive skills that are needed for the planning and maintenance of thoughts and behaviors 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 executive functions (2).
Growth hormone deficiency (GHD) is a significant cause of short stature with a prevalence of 1 in 4000-10000 births (3). GHD can be isolated or occur with other anterior pituitary hormone deficiencies, congenital or acquired. Clinical findings depend on whether the cause is congenital or acquired, and whether it is accompanied by other anterior pituitary hormone deficiencies or isolated (3). Congenital causes can be generally classified as isolated growth hormone deficiency (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, impairments in cognitive functions such as attention and memory as well as failure to thrive (5). The literature proposes that growth hormones 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 on children with isolated growth hormone deficiency and children with small gestational age (SGA) have found low growth hormone (GH) levels to be associated with poorer memory and cognitive functions (6). A three-year observational study on children with SGA determined 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 GH deficiency 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 the intelligence quotient (IQ) values associated with fluid intelligence was observed after GH replacement (6). GH was reported to affect the secretion of dopamine and noradrenaline in experimental animal model studies in rodents (10). It 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 (LTP) via its receptors in different areas of the brain (prefrontal cortex, amygdala, and hippocampus) (11, 12). As a result, it is emphasized that both growth hormone and the insulin-like growth factor I (IGF-I) receptors through which growth hormone exerts its effects are important for cognitive functions such as attention and memory (5).

Upon review of the literature, no studies evaluating executive function skills in children with IGHD were found although cognitive skills have been previously evaluated. Based on this gap in the literature, we aimed to evaluate children with IGHD's executive function skills according to parent-report scales, as well as their working memory, selective attention, and inhibition skills according to performance-based test results.

2. METHODS

2.1 Study Sample

The case group of our study included 35 children, aged between 7 and 12 years, who applied to the tertiary care (Health Sciences University - Erzurum City Hospital) pediatric endocrinology outpatient clinic and were diagnosed with isolated GH deficiency based on endocrinological and laboratory evaluation. The control group included 35 healthy children 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. Our study is a cross-sectional study that was approved by the local ethics committee (2022/04-28) and planned according to the Helsinki Declaration.

2.2 Procedure

All participants' standing height was measured in quadruplicate using a wall-mounted Harpenden stadiometer accurate to the nearest 1 mm. Also, a GH stimulation test performed with L-dopa and Clonidine, IGF-1, and IGF-binding protein-3 (IGFBP-3) levels were measured. The clinical diagnosis of isolated GH deficiency (IGHD) 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 participants diagnosed with IGHD underwent a Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V)-based clinical interview to determine psychiatric diagnoses and comorbid conditions before GH replacement therapy. According to the psychiatric evaluation, the children had normal language and communication skills. As a result of the psychometric test, 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 Executive Function (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 (spectacles, contact lenses, etc.) 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 were asked to be filled in 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.

2.3 Data Collection Tools

Sociodemographic 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 has been measured with the Hollingshead-Redich scale.

Behavior Rating Inventory of Executive Function (BRIEF) - Parent Form: BRIEF was developed by Gioia (200) to assess executive function, problem-solving skills, and adaptive behaviors in children (13). Scores on 8 different subscales of executive functions can be calculated from this scale of 86 items. This scale was standardized in Turkish by Batan et al. in 2011 (14).

Visual Aural Digit Span -Form B (VADS-B): VADS-B is a neuropsychological test developed by Koppitz (1970) (15) that assesses working memory and short-term memory (16). Its validity in Turkish was established by Karakaş and Yalın, and revised in 2002 (17). 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: In the literature, the Stroop test is used to assess selective attention and response inhibition (18). 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 (19, 20). The present study used the TBAG version of the Stroop test (20). The TBAG version of the Stroop Test, was developed by Kılıç et al., and was standardized in 2002 (21). In light of the studies in the literature, 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, here the color and the meaning are incongruent for certain words (Stroop-color/word) (22). 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 (24).

2.4 Statistical analysis

The categorical data were presented as numbers and percentages. The data for continuous variables were 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, when appropriate. Statistical significance was considered when the p-value was<0.05. Statistical analysis was performed using the Statistical Package of Social Sciences version 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY). Differences in mean subscores of VADS-B, Stroop TBAG form, and BRIEF were analyzed using the univariate analysis of covariance (ANCOVA) with participant group as factor and VADS-B, Stroop TBAG form and BRIEF subscores as dependent variables; chronological age (years) was set as a covariate.

3. 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 (p>0.05). Characteristics of the case and control groups including age, gender, and height are presented in **Table 1**.

Children with IGHD were found to receive lower scores on the Visual Aural Digit Span Test (VADS-B) that was administered to assess short-term memory **(p<0.05) (Table 2)**. Although children with IGHD had longer completion times for the Stroop word and Stroop color sections of the Stroop test that was administered to assess selective attention and inhibition, the difference was not statistically significant (p>0.05). However, the completion time for the Stroop-color/word test was significantly longer in children with IGHD **(p<0.05) (Table 2)**.

Children with IGHD were determined to receive higher scores on all sub-scales of the BRIEF scale completed by the parents of the participants, with statistically significant differences for all sub-scales except for "organization of materials" **(p<0.05) (Table 3)**.

4. Discussion

The mechanisms underlying the relationship between GH and cognitive functions are still not completely clear. To investigate the potential relationship between executive functions and GH in this study, we assessed the executive function skills of children with IGHD using both performance-based testing and parent-report tests and determined that executive function skills were poorer in children with IGHD.

In our study, working memory was assessed with both VADS-B and the BRIEF scale and both tasks determined poorer working memory in children with IGHD. The effects of GH on cognitive skills such as learning and memory have been investigated by various studies in the literature. Prospective studies determined cognitive improvement after GH replacement in adults followed up for GH deficiency (23-25). Experimental animal studies observed improvement in spatial memory with GH and GH secretagogue ghrelin replacement (26, 27). Moreover, an impairment in the Morris water maze performance test was determined in spontaneous dwarf rats with a variant of the GH gene that causes GH deficiency (28). In contrast to these studies, an experimental animal study examining the effect of GH on cognitive performance emphasized that GH excess had a negative effect and inhibition of GH action had a beneficial effect on spatial learning and memory and therefore cognitive performance in male mice (29). These different results obtained after GH replacement were attributed to the variable effects of systemic GH on different tissue types (30). On the other hand, 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 (31). In recent years, neuroimaging studies have been performed to investigate the memory performance of GH deficiency. Arwert et al. compared Growth Hormone/Insulin-Like Growth Factor 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 working memory 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 (PET) (6). Moreover, Arwert et al. determined in a functional Magnetic Resonance Imaging (fMRI) study conducted on adults with childhood-onset GH deficiency that, although the groups were not different on the working memory task, the imaging results of adults with childhood-onset GH deficiency showed higher activity in dorsolateral/ventrolateral prefrontal cortex (PFC), anterior cingulate cortex, parietal cortex, complementary motor and motor cortex, as well as in the thalamus and precuneus. The author interpreted these results as GH-deficient patients having a lower-than-normal working memory speed, which could be compensated for by dorsal prefrontal regions through different mechanisms with no disruption in the quality of memory performance (32). 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 (33). The data we obtained support the studies that have demonstrated poorer working memory in children with IGHD. The difference in the errors on working memory tasks, which was not found in adult GHD, was quite prominent in child GHD in our study. This may be attributed to the absence of the increased prefrontal blood flow that was observed in neuroimaging studies of adults, to the incomplete development of compensatory mechanisms in childhood (34).

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 BRIEF scale. The results of both assessments determined poorer inhibitory control in children with IGHD. Patients with isolated GH deficiency also had lower scores (poor executive function skills) on the components of other executive functions 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 impairments in neurocognitive networks associated with attention and executive function (33). Also, it has been generally emphasized that cognitive skills and attention improve after GH replacement (35). Further studies employing different neuropsychological tests accompanied by neuroimaging are needed to evaluate the effects of GH deficiency on the executive functions of children in more detail.

Lastly, the Stroop TBAG test also provides information regarding selective attention (24). In the present study, we determined poorer selective attention in children with isolated GH deficiency. GH is thought to enter a mutually excitatory interaction with dopamine (DA) and influence the ventral tegmental area (VTA)-nucleus accumbens (NA)- hippocampus-cingulate cortex axis through the amplification of dopaminergic effects, playing a role in reward and conflict processing (26). It has also been suggested that GH deficiency could affect cognitive functions such as conflict monitoring, working memory, and selective attention by causing DA deficiency (22). Sartorio et al. reported that children with IGHD had certain academic impairments, especially learning difficulties and attention deficit disorders (36). Although different studies that used the Stroop test to evaluate the relationship between GH and attention did not find a significant difference (36-38); studies that used different measurement tools such as the trail-making test (TMT), the divided attention task, and the Go/no go task obtained significant results (26, 34, 39). In line with the results of our study, a review on GH and selective attention stressed that GHD was associated with poor selective attention (40). Prospective studies that will evaluate cases of childhood-onset GHD in adulthood are needed to better understand the relationship between GH and selective attention.

5. Limitations

Our study has several limitations. The first of these is that the executive function skills of cases with isolated GH deficiency participating in our study could not be evaluated after GH replacement. One of our limitations is that the scales used to evaluate executive functions vary in the literature. Another limitation is that the parent-child relationship, attachment, and parental attitudes, which are known to affect executive function skills, were not evaluated in the study. Further studies are needed in this context (33). Lastly, the participants were administered

neuropsychometric tests, however 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 executive function skills.

Despite all of these limitations, our study is the first that has examined executive functions in school-age children with isolated GH deficiency based on both performance and parent reports. In this context, we think that it will contribute to the literature on isolated GH deficiency.

6. Conclusion

We determined poorer executive function skills in children with IGHD. Executive function skills may influence academic success by affecting children's language skills, mathematical comprehension, cognitive flexibility, and hypothetical thinking. Therefore, we think that a holistic approach, including psychiatric evaluation, would be beneficial for children with IGHD. We think that psychiatric evaluation of children with IGHD before and during treatment will positively contribute to both their academic performance and social relationships.

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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, p< 0.05, cm: centimeter

Table 2. Comparison of the VADS-B and Stroop TBAG test's subscale scores of Children with IGHD and control

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)
p = Probability of significance, $p < 0.05$
IGHD: Isolated Growth Hormone Deficiency ***SD****: standard deviation* ***sec:*** *second* **VADS-B:** Visual Aural Digit Span Test-B Form

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**
Behavioral Regulation Index (BRI)	61.38 ± 12.69	47.67 ± 7.3	<0.001	28.637	**<0.001**
Metacognition Index (MCI)	72.29 ± 17.6	57 ± 13.95	<0.001	15.154	**<0.001**
Global Executive Composite (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*