



## ORIGINAL PAPER

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# Cognitive function in patients with childhood-onset combined pituitary hormone deficiency not treated with growth hormone

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### ABSTRACT

**Introduction.** Growth hormone deficiency is a known factor leading to impairment of psychological performance but there are very few studies on cognitive function in adult patients with childhood-onset combined pituitary hormone deficiency (ChO-CPHD). Therefore, the aim of our study was to assess cognitive skills in adult patients with this disorder.

**Material and Methods.** The study was performed in a unique group of 28 adult ChO-CPHD patients, never treated with growth hormone (mean age 42.5 +/- 16.3 years; 12 women and 16 men). The assessment of cognitive performance (WAIS-R) comprised scores of verbal IQ, non-verbal IQ and particular qualitative analysis of subtests.

**Results.** The mean score of full scale (IQ = 81,4) was below the normal when compared to the population norm (IQ = 100, SD +/- 15), although their verbal score (IQ = 85,7) was a bit higher than their nonverbal score (IQ = 81,7).

**Conclusions.** The obtained result of total intelligence quotient (IQ) had shown equable subnormal results and a cognitive level below average in the study group. Decreased subscales of WAIS-R are related to fluid intelligence (this may reflect abnormal brain development or could be linked to the influence of hormonal disorders in early life) as well as, emotional traits of personality.

**Keywords:** cognitive function, intelligence quotient, growth hormone (GH), combined pituitary hormone deficiency (CPHD), Wechsler Intelligence Scale for Adult (WAIS-R).

## Introduction

Hypopituitarism is a clinical syndrome of deficiency in pituitary hormone production. This may result from disorders involving the pituitary, hypothalamus, or surrounding structures [1]. Outcome of this disease depends on the type of hormonal deficiency [2]. Effects of hypopituitarism may be gradual or sudden and calamitous, because pituitary dysfunction affects other endocrine organs. Impaired wellbeing was reported as one of the symptoms in adults with growth hormone (GH) deficiency [3, 4] and improvement of life quality

has been noted after implementation of recombinant human GH (rhGH) treatment [5, 6]. There is evidence from neuropsychological studies that growth hormone has a severe impact on cognitive function. Patients with growth hormone deficiency often complain of attention deficits, as well as poor memory. It seems well established that GH deficiency is associated with emotional and cognitive problems and the presence of a scholastic underachievement [7, 8]. Reasonably, short stature 'itself' might predispose these patients to psychosocial difficulties. The higher incidence of academic failure,

in the presence of normal intellectual performance, has been attributed to environmental and psychosocial factors, including over-protective parents and low self-esteem associated with the short stature [9, 10]. How does everyday existence look to these patients in adulthood? How does combined childhood-onset pituitary hormone deficiency, (not only restricted to GH deficiency), influence their cognitive processes? Which cognitive functions in adult patients with such a deficiency, had been most affected? To answer these questions we undertook a study aiming to assess cognitive skills in the group of adult ChO-CPHD never treated with rhGH.

## Material and Methods

### Patients

The study was carried out on 28 patients (16 males and 12 females) referred to the Department of Endocrinology due to childhood-onset CPHD. Age range at the moment of psychological studies was 17–65 (average 42.5 +/- 16.3) years. The mean age when CPHD diagnosis was made was 11.21 +/- 6.11 years. In all patients, GH, thyrotropin (TSH), and gonadotropins deficiency was diagnosed, and hypoplasia of the anterior pituitary lobe was found on MRI. More than half of the patients were receiving hydrocortisone because of the early or late occurring adrenocorticotropin (ACTH) deficiency. In addition, 12 patients also exhibited prolactin (PRL) deficiency. All individuals were receiving hormonal replacement therapy including levothyroxine and sex hormones, but no one was treated before with recombinant human GH, which determines the importance and unique character of the studied group. This criteria resulted in narrowing down of the overall

number of examined subjects. Patients' characteristics including age at diagnosis, age at start of hormonal replacement therapy and their level of education is shown in **Table 1**.

### Methods

Psychiatric diseases were excluded in the preliminary psychological consultation. The psychologist used the Polish adaptation of the Wechsler Adult Intelligence Scale (WAIS-R) to assess cognitive functions. The WAIS-R (PL) examination consists of 11 subtests, measuring a different facet of intelligence. The patient's attainments on various measures are summarized into three composite scores of IQ: the verbal, nonverbal (performance), and full scale, which provide estimates of the individual's intellectual ability. In addition, the WAIS-R (PL) provides four extra index scores (perceptual organization, freedom from distractibility, processing speed and verbal comprehension) allowing for a more detailed examination of the strengths and weaknesses of an individual's performance. The verbal tests were: Information, Digit Span, Vocabulary, Arithmetic, Comprehension and Similarities. The non-verbal (performance) tests were: Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Digit Symbol. Based on the UK normative data and in line with the IQ scores the Index Scores have a mean of 100 and standard deviation of 15. There are 4 levels of deviations: Mental Retardation (MR) less than or equal to 69, Borderline MR 70–79, Dull Normal 80 to 89, Normal 90 to 109, Bright Normal 110 to 119, Superior 120 to 129, Very Superior 130 and above.

Psychometric tests employed for this study are standardized, and therefore additional research conducted in the parallel control group is not required.

**Table 1.** Characteristics of patients with CPHD

Variable	CPHD patients (n = 28)
Sex – n (%):	
– Males	16 (57.1)
– Females	12 (42.9)
Age (years) – mean ± SD (range) at the time of psychological study	41.7 ± 11.1 (18–59)
Age, when the testosterone or estradiol/progesterone therapy was initiated – mean ± SD (range)	19.8 ± 4.6 (9–30)
Age, when the thyroid hormone therapy was initiated – mean ± SD (range)	15.6 ± 6.8 (6–29)
Education – n (%):	
– Elementary level	15 (53.6)
– High school	10 (35.7)
– University level	3 (10.7)

The local Bioethical Committee approved the study and patients gave informed consent.

### Statistical analysis

Continuous variables were expressed as the mean, standard deviation, minimum, median and maximum score. The D'Agostino-Pearson test was used to check the normality of the data distribution. Statistical analysis was performed using paired t-test, Pearson correlation analysis and Spearman rank test. If the p value was below 0.05, the results were considered as statistically significant.

## Results

### Quantitative analysis

Majority of subscale scores were closely centered and decreased. The obtained score of global IQ had shown subnormal and below intelligence quotient (mean 81.4), likewise verbal IQ (mean 85.7) and nonverbal IQ (mean 81.7). No significant variance ( $p > 0.05$ ) between verbal IQ and nonverbal IQ was found in this study, indicating a level of balanced development of different cognitive functions (Table 2).

The principle finding of our study is that CPHD patients have an intellectual performance below average, compared to the population norm. As a reminder, median results of WAIS-R in the normal population is a score of IQ 100 (SD +/- 15). The patients' full-scale IQ scores were all below average (Figure 1). There was no significant difference between verbal IQ and non-verbal IQ, and no statistical discrepancy between women and men was observed.

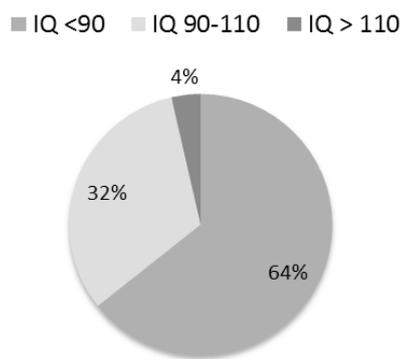


Figure 1. Distribution of WAIS-R test scores in patients with ChO-CPHD

Analysis of total, verbal and non-verbal IQ scores and age when thyroid hormone or appropriate sex hormone treatment was implemented and revealed a weak correlation between the age when testosterone or estradiol/progesterone therapy was started and total IQ, and verbal IQ scores ( $r = -0.4115$ ;  $p = 0.03$  and  $r = -0.3982$ ;  $p = 0.04$  respectively). There was no such correlation between IQ scores and the time of initiation of thyroid hormone therapy. Furthermore, no statistical significant difference between males and females was found.

### Qualitative analysis

However, all subtests were below the average score ( $< 10$ ). The highest scores (best-developed cognitive operations) in the studied group were reported within:

1. Verbal subtests (*Information, Comprehension, Vocabulary*) which estimate: word knowledge and verbal fluency, degree of general information acquired from culture, and long-term memory.

Table 2. Results of WAIS-R test in patients with ChO-CPHD

Test/Subtest	Mean	Standard Deviation (Park. #36)	Minimum	Median	Maximum
Total score	81.43	17.39	45	79	116
Verbal score*	85.75	18.14	45	84	120
Information	8.79	2.88	2	9	14
Digit Span	7.29	2.92	4	6	13
Vocabulary	8.21	2.92	1	8	13
Arithmetic	6.42	3.82	1	6	18
Comprehension	8.43	3.07	1	8	13
Similarities	8.00	3.62	1	9	14
Nonverbal score*	81.71	15.62	52	83	109
Picture Completion	7.04	3.21	1	7	14
Picture Arrangements	7.57	2.83	1	7	13
Block Design	8.25	2.77	1	9	12
Object Assembly	8.34	2.13	5	8	12
Digit Symbol	6.93	3.66	1	6	13

\* Difference between verbal and nonverbal score was not statistically significant ( $p > 0.05$ )

2. Non-verbal subtests (*Object assembly, Block design*) which reflect: visual performance, synthesis, and construction, visual-spatial skills and ability to see how parts make up a whole, they also reveal level of creativeness.

The lowest scores (least developed, the most decreased cognitive operations) were noticed within:

1. Verbal tests (*Arithmetic, Digit Span*) that indicate mathematical word problems which are performed mentally: immediate auditory restoration and working memory, decreased numerical reasoning, distractibility (sensitive on emotional disturbance and distraction), attention/concentration while manipulating mental mathematical problems logical and abstract reasoning. All these scores could also be influenced by emotional tension and anxiety.
2. Performance subtests (*Picture Completion, Digit Symbol-Coding*) that describe: long-term visual memory, visual perception – ability to quickly perceive visual details, perceptual organization, attention to fine detail, and the ability to differentiate essential from non-essential details, visual-motor coordination, motor, perceptual and mental speed, including learning abilities.

## Discussion

Hormones are the chemical messengers that serve as signal carriers for various cells. Several hormones have the potential for influencing different types of behavioral and psychological symptoms. They can change personal behavior by modulating emotions and mood [11]. Variable expressivity of sex hormones, and their different levels might be associated with cognitive impairment [12]. People with combined pituitary hormone deficiency (CPHD) suffer from quantitative and qualitative abnormalities of pituitary hormone production [13].

Early behavioral descriptions of hormonal effects on emotional disorders have long been disclosed [14]. According to several studies conducted in GHD patients, and only a few reports regarding CPHD, patients show emotional instability, a lack of energy, difficulties in social and sexual functioning, and often suffer from sleeping problems. They exhibit lower marriage frequency, higher unemployment rate and more often, inability to obtain a driving license [15, 16]. However, it was not known until the 1960s that hormones of the pituitary gland influence learning and memory [17]. During the past years several studies have evidenced that growth hormone (GH) may exert distinctive effects

on the central nervous system and induce beneficial effects on psychological capabilities [18]. There is also expanding evidence in the neuropsychological literature that growth hormone (GH) deficiency is associated with cognitive impairment and this impairment may be ameliorated with GH replacement therapy [16, 19, 20]. Recent reports are also concentrating on the cognitive function of those patients including their intellectual functions; the processes of perceiving, imagining, remembering, reasoning, and judging. Most of the studies indicated that GHD can lead to small, but clinically relevant changes in memory, processing speed and attention focus in patients [21]. Children with isolated GHD are reported to have specific educational deficits, in particular learning disability and attention-deficit disorders, which have been tentatively attributed to a compromised intellectual potential [22]. The general picture of cognitive functioning in adult CPHD patients is that their mental status (including IQ) is subnormal. Many of these patients show memory impairment and subnormal intelligence quotient (IQ) scores. Their cognitive functioning appeared subnormal with lapses of attention, difficulty in concentrating and forgetfulness [23]. Also in the present study, the cognitive functions of adult patients with ChO-CPHD never hormonally substituted with rhGH and not systematically treated with other hormones, appeared subnormal. Obtained results show that these patients indeed have apparent cognitive dysfunction, although not severe. The principle finding of this report is that people with CPHD have an intellectual ability that is within the lower than average range when compared to the population norm and with reduced ability to perform tasks involving antidistractory skills. This might suggest educational problems in the past, with necessary special individual attention and lower expectations in school programs, as was confirmed in psychological interviews. Remarkable information provided qualitative analysis of individual psychometric charts with scale score analysis. Decreased scores on arithmetics indicate impaired immediate auditory memory, and at the very least, inadequate attention and concentration.

Although abnormalities of visual-motor integration among children with GHD and hypopituitarism have been described previously [9, 15], the present study also revealed that the lowest results were obtained in tasks comprising the perceptual organization index. This involves the interpretation and organization of visually presented information and is due to process efficiency. In turn, the most decreased subtest Digit Span and Digit Symbol-Coding revealed decreased

ability to receive, store, process, and use information through a series of cognitive ordering procedures called sequential processing. These building blocks are not only essential for listening, learning, reading and communication, but also every mental process that is dependent on these processing abilities. Factor comparisons showed that impaired verbal comprehension and perceptual organization were not significantly varying in the studied group, and both of them are essentially equivalent to working memory, which is consistent with the level of general intellectual abilities. According to D. Wechsler, intelligence is an individual's ability to adapt and constructively solve problems in the environment [24] and is also influenced by personal traits and other non-intellective components, such as anxiety, persistence and goal awareness. Therefore the assessment of intellectual performance depends on emotional dependence. These personal traits could significantly decrease scores of Arithmetic and Digit span. The WAIS-R subtests were classified into two categories: fluid intelligence and crystallized intelligence. Fluid intelligence is related to biology. This is the ability to find meaning in confusion and solve new problems, the ability to draw inferences and understand the relationships of various concepts, independently of acquired knowledge [25]. This is also the ability to reason in an abstract way, defined as our "on-the-spot reasoning ability, a skill not basically dependent on our experience." Belsky [1990] indicated this type of intelligence, being active when the central nervous system (CNS) is at its physiological peak [26]. Fluid intelligence includes such abilities as problem-solving, learning, and pattern recognition, that generally correlates with measures of abstract reasoning. Fluid intelligence includes those types of basic intelligence that make learning quick and thorough. Underlying abilities such as short-term memory, abstract thought, and speed of thinking are usually considered as a component of fluid intelligence. Crystallized intelligence in contrast, is the ability to utilize previously acquired knowledge and experience. Crystallized intelligence correlates with abilities that depend on knowledge and experience, appearing as a function of brain regions responsible for the storage and usage of long-term memories (such as the hippocampus) [27]. It is the store of information that a given society has accumulated over time. Crystallized intelligence includes those types of intellectual abilities that reflect accumulated learning [28]. The WAIS measures fluid intelligence on the performance scale and crystallized intelligence on the verbal scale. Results of our study group suggest that patients with

CPHD have impaired fluid intelligence more significantly than crystallized intelligence, because the higher scores were noted in the verbal part (comprehension, vocabulary, information). The study group could better deal with understanding social conventions, common sense, and social rules and expressions (Verbal comprehension), rather than perceptual organizational learning, and pattern recognition.

As mentioned before, abnormalities of visual-motor integration among patients with hypopituitarism have been described previously [15]. A range of assessments, including the WAIS, was used in this study. Authors concluded that overall performance of patients was in the low-average range. A link between academic performance and socioeconomic status and short stature is indicated and might predispose CPHD patients to some of their psychosocial difficulties, such as educational and professional achievements. The higher incidence of academic failure in presence of normal intellectual skills has been attributed to environmental and psychosocial factors, including over-protective parents and low self-esteem resulting from the impact of short stature. But, it is possible that their problems are related to congenital predispositions; for example impaired fluid intelligence. If so, then an overprotective approach by family members should not be recommended and children with hypopituitarism should be encouraged to intensive and systematic compensatory stimulation of the CNS.

Congenital disturbances in pituitary development, as well as postnatal and later life insults such as hypoglycemia, hypothyroidism, abnormal delayed growth and sexual development in patients with CPHD could all impact normal developmental processes. In summary, our results suggest that patients with ChO-CPHD have lower than average cognitive function with specific difficulties in attention, working speed, memory and perceptual organization. Diminished cognitive functions such as deterioration in memory, reduced ability to process information quickly, and reduced verbal fluency has been observed. An important question is whether the cognitive dysfunction seen in CPHD patients can be related to other common symptoms of CPHD. For example, these patients often are also depressed, and cognitive dysfunction occurs in people who are depressed. Conceivably, the cognitive dysfunction in CPHD could be simply present due to depression. Depressed patients are often slow and the score of speed performance tasks were significant decline in our group of patients. Due to those reasons, we excluded depressive symptoms in our study.

The lowest scores were in tasks sensitive to emotions, tension and anxiety, comprising: concentration, attention, numeric reasoning, short term memory, visual perception, perceptual organization, visual memory, visual-motor coordination, motor and mental speed. Educational attainments of parents were not recorded, but genetic factors as well as social class might provide some explanation for the lower IQ scores in patients.

## Conclusions

In addition to decreased overall cognitive performance in the study group, moderate deficits in terms of verbal and performance scales were also observed. Furthermore, the study showed decreased IQ and associated reduced scores of subtests, primarily concerning conscious perceptual processing (Perceptual Organization and Working Memory). Patients also appeared to have more impaired fluid intelligence than crystallized intelligence; but this may be related to purely biological disturbances, such as impaired brain development or other dysfunctions (hypoglycemia, low thyroxin concentrations) particularly appearing in early life. One noteworthy problem is also the relationship between fluid intelligence and the emotional component of personality.

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## Conflict of interest statement

The authors declare no conflict of interest.

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