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Neurocognitive Profiles of Children with Permanent vs. Transient Congenital Hypothyroidism: A Comparative Study Using the CANTab Assessment

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Abstract

Background: Congenital hypothyroidism (CH) is one of the most common and preventable causes of intellectual disability. Early diagnosis and treatment can prevent severe developmental delays, but subtle cognitive impairments may persist into childhood. Differences in neurocognitive outcomes between permanent and transient congenital hypothyroidism have not been well characterized.

Objective: This study aimed to compare cognitive function in children with permanent versus transient congenital hypothyroidism using the Cambridge Neuropsychological Test Automated Battery (CANTab), a validated and language-independent cognitive assessment tool.

Methods: A total of 60 children aged 7 to 10 years (30 with permanent and 30 with transient congenital hypothyroidism) were recruited from the Isfahan Endocrine and Metabolism Research Center. Three cognitive domains were assessed using the CANTab battery: memory, executive function, and attention & psychomotor speed. Data were analyzed using multivariate analysis of covariance (MANCOVA), adjusting for age, followed by univariate ANOVAs. Effect sizes were reported using partial eta squared (η^2), and statistical power was calculated.

Results: MANCOVA revealed a significant overall difference in cognitive function between groups (Wilks' Lambda = 0.156, F (5,54) = 148.95, $p < 0.0001$, $\eta^2 = 0.844$). Children with permanent hypothyroidism demonstrated significantly lower performance across all domains, with the most pronounced impairments in memory and executive function. Moderate deficits were observed in attention.

Conclusion: Children with permanent congenital hypothyroidism exhibit widespread cognitive impairments compared to those with transient hypothyroidism. These findings underscore the need for ongoing neurocognitive monitoring and early supportive interventions in this high-risk population.

Key Words: Congenital hypothyroidism, Cognitive function, CANTab, Pediatric neurodevelopment, Permanent congenital hypothyroidism, Transient congenital hypothyroidism.

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1- INTRODUCTION

Congenital hypothyroidism (CH), defined by the underdevelopment or dysfunction of the thyroid gland (1), is the most preventable cause of intellectual disability, with an estimated incidence of 1 in 3,000 to 4,000 live births (2). Insufficient thyroid hormone levels during early life disrupt the development of critical organ systems, particularly the central nervous system and skeletal system. Although most affected neonates appear clinically normal at birth, symptoms typically emerge between the sixth and twelfth week of life (3).

CH is divided into permanent (PCH) and transient (TCH) categories, based on the duration of the disease. Permanent forms of hypothyroidism can arise from conditions such as thyrotropin (TSH) resistance, central hypothyroidism, thyroid dysgenesis, defective transport of thyroid hormones, or receptor resistance. In contrast, transient hypothyroidism is typically caused by maternal or neonatal factors.

Maternal factors may include exposure to antithyroid drugs, the presence of transplacental TSH receptor-blocking antibodies, and abnormal iodine intake. Neonatal factors include iodine deficiency, iodine overload from antiseptics, very low birth weight (less than 1500 g), prematurity (less than 37 weeks), and underdevelopment of the thyroid gland. (4).

Since the mid-20th century, newborn screening (NBS) programs have become a cornerstone of anticipatory pediatric care, particularly for the early detection and treatment of congenital hypothyroidism. These programs aim to identify affected infants who may appear asymptomatic at birth, enabling timely intervention to support optimal cognitive development. Regular monitoring of diagnosed children is essential, as early treatment significantly reduces the risk of severe intellectual disability (5). However, despite adequate treatment, mild cognitive impairments may persist, suggesting that early hormone replacement does not fully normalize neurodevelopmental outcomes in all cases (5).

A growing body of evidence has documented a range of cognitive impairments in children suffering from CH. These include deficits in attention (6–14), memory and cognitive flexibility (6–18), working memory (7, 19, 20), visual-spatial skills (6, 8, 10–19), as well as slowed processing speed and reaction time (9, 10, 14).

The present study aims to compare the cognitive performance of children aged 7 to 10 years, regardless of their disease duration. Cognitive function will be assessed using the Cambridge Neuropsychological Test Automated Battery (CANTab), a validated tool that enables detailed evaluation across multiple cognitive domains.

2- MATERIALS AND METHODS

2-1. Study Design

This cross-sectional study included patients aged 7 to 10 years with primary CH detected by the NBS Program. The study was approved by the local clinical research ethics committee, with an ethical code # Approval ID: IR.MUI.MED.REC.1399.091.

2-2. Participants and Sampling

A total of 60 participants were selected through convenience sampling, consisting of 30 children with PCH and 30 children with TCH. The children diagnosed with PCH formed the case group, while those with a history of TCH—defined as children whose levothyroxine therapy had been discontinued under physician supervision—were classified as the control group.

2-3. Cognitive Assessment Procedure

Cognitive function was evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTab), a computerized, language-independent system developed by the University of Cambridge. This battery is widely validated for use in both clinical and research settings and is known for its sensitivity to subtle cognitive impairments.

In this study, five CANTab tasks were administered to assess the following three domains:

1. Paired Associates Learning (memory)
2. Spatial Working Memory (executive function)
3. Stop Signal Task (executive function)
4. Motor Screening Task (attention & psychomotor speed)
5. Reaction Time (attention & psychomotor speed)

All assessments were conducted in a quiet, standardized setting by trained examiners. All participants successfully completed the full CANTab test battery, and no cases were excluded due to technical issues or noncompliance.

2-4. Statistical Analysis

Data was analyzed using Multivariate Analysis of Covariance (MANCOVA) to examine differences in cognitive performance between groups across multiple dependent variables while controlling for potential covariates such as age.

Statistical significance was defined as $p < 0.05$. Effect sizes were reported using partial eta squared (η^2), and statistical power was also calculated to evaluate the reliability of findings. Examination of the data revealed no outlier values (defined as $>\pm 3$ standard deviations from the mean). Prior to conducting MANCOVA, statistical assumptions were evaluated. Residuals demonstrated normal distribution based on the Shapiro–Wilk test, homogeneity of covariance matrices was confirmed using Box's M test, and correlation analyses indicated no evidence of multicollinearity. All assumptions were adequately satisfied.

This methodological approach enabled a structured comparison of cognitive function between children with permanent and transient congenital hypothyroidism, contributing to a deeper understanding of the neurodevelopmental consequences associated with these two forms of the disorder.

3-RESULT

A total of 60 children aged 7 to 10 years participated in the study.This included 30 children with permanent congenital hypothyroidism and 30 with transient congenital hypothyroidism. The mean age in the permanent group was 10.86 years, compared to 9.53 years in the transient group.

3-1. Descriptive Statistics

Table 1 presents the mean and standard deviation of the CANTab test scores for both groups across three cognitive domains and five tests: memory (paired associates learning), executive function (spatial working memory and stop signal task), attention & psychomotor speed (reaction time and motor screening task).

3-2. Multivariate Analysis

MANCOVA was used to examine differences between the two groups across all cognitive domains. The results indicated a statistically significant overall group effect (Table 2).

These findings confirm that the cognitive profiles of the permanent and transient congenital hypothyroidism groups differ significantly when considered as a whole.

Table-1. Mean ± SD of CANTab Test Scores in Permanent and Transient Congenital Hypothyroidism

Cognitive Domain	Test Name	Case group (Mean ± SD)	Control group (Mean ± SD)
Memory	Paired Associates Learning (PAL)	109 ± 21.3	21 ± 9.5
Attention & psychomotor speed	Reaction Time (RTI)	144.21 ± 28.2	68.85 ± 15.6
Attention & psychomotor speed	Motor Screening Task (MOT)	81 ± 19.8	28 ± 10.31
Executive function	Spatial Working Memory (SWM)	78 ± 17.75	35 ± 13.51
Executive function	Stop Signal Task (SST)	10 ± 5.9	18 ± 2.7

Table-2. Multivariate Tests (MANCOVA) Comparing Cognitive Function Between Groups.

Test Statistic	Value	F	Hypothesis df	Error df	p-value	Partial Eta²
Wilks' Lambda	0.156	148.954	5	54	<0.0001	0.844
Pillai's Trace	0.844	148.954	5	54	<0.0001	0.844

3-3. Univariate Tests

Follow-up univariate ANOVAs were conducted for each test to identify where the group differences occurred. All five tests showed statistically significant differences between the two groups.

Children with permanent congenital hypothyroidism performed significantly worse in memory, executive function and attention, compared to those with transient hypothyroidism. The largest differences were observed in Paired Associates Learning (PAL) and Spatial Working Memory (SWM) tasks.

4- DISCUSSION

The main objective of this study was to compare and evaluate cognitive function in children diagnosed with permanent and transient congenital hypothyroidism using the CANTab software. In this discussion, we will focus on the variables that showed statistically significant differences between the two groups.

The cognitive disparities observed may be explained by underlying mechanisms in permanent congenital hypothyroidism, including a reduced number of myelinated axons, subtle alterations in myelin ultrastructure, and decreased axon diameter, all of which may result from thyroid hormone deficiency. Notably, myelination is initiated based on specific axon size thresholds (21).

Moreover, the proper development of executive functions depends on adequate myelination, which is essential for the maturation of the prefrontal cortex and the formation of efficient connections between cortical and subcortical brain regions (22).

Table-3. Univariate ANOVA Results for CANTab Test Domains.

Cognitive Domain	F (1, 58)	p-value	Partial Eta²	Power	Interpretation
Memory (PAL)	609.34	<0.0001	0.755	1.00	large effect
Attention & psychomotor speed (RTI)	6.67	0.011	0.033	0.73	Small effect
Attention & psychomotor speed (MOT)	11.87	0.001	0.057	0.93	Moderate effect
Executive function (SWM)	142.36	<0.0001	0.418	1.00	Large effect
Executive function (SST)	10.98	0.001	0.053	0.91	Moderate effect

Children diagnosed with permanent congenital hypothyroidism demonstrate weaker visual-spatial abilities compared to those with transient congenital hypothyroidism. This difference is likely related to the absence of thyroid hormones in the primary motor cortex during critical periods of postnatal development. Additionally, inadequate thyroid function before birth may disrupt the maturation of the occipital-striatal pathway to the superior parietal region, which plays a key role in spatial localization and processing (17).

According to the model proposed by Rourke et al., children with permanent congenital hypothyroidism show more pronounced visual-spatial dysfunction than individuals with nonverbal learning disabilities. This may be due to abnormalities in myelin formation or synaptogenesis (23).

Consistent with the findings of Ramírez et al. (18), our study further supports the presence of attention impairments in children with congenital hypothyroidism. The results indicate that these children have a shorter attention span compared to healthy peers (9–11, 24, 25). This deficit becomes especially apparent in tasks that require sustained or divided attention. Since subcortical storage systems are closely related to attentional processes, and thyroid hormones are essential for the proper distribution of cortical cells, a prenatal hormone deficiency may interfere with the normal development of prefrontal cortical layers, leading to attention deficits in affected children (6, 7).

Cognitive flexibility is a mental process that depends on age-related cognitive abilities, particularly inhibitory control and working memory. Our study shows that children with permanent congenital hypothyroidism exhibit weaker cognitive flexibility compared to those with transient hypothyroidism. This may be attributed to the role of the prefrontal cortex, which is critical for both working memory and cognitive flexibility and is influenced by thyroid hormone levels (11). These findings are consistent with previous research demonstrating deficits in working memory and response inhibition among individuals with congenital hypothyroidism (11, 17, 19, 26).

The results of this study offer valuable insight into the challenges experienced by children with congenital hypothyroidism. These challenges may explain why parents and teachers often report difficulties with school tasks, the need for greater supervision and extended time to complete assignments, inattentiveness, and delays in fine motor activities such as writing.

This study has several limitations. First, the control group consisted of children with transient congenital hypothyroidism rather than healthy peers. This may have underestimated the true extent of cognitive impairment, as subtle deficits have also been reported in transient cases. Second, the relatively modest sample size (n=60) may restrict the generalizability of our findings and the robustness of multivariate analyses, although strong effect sizes and adequate univariate power support the validity of the observed differences. Finally, potential confounders such as socioeconomic status, parental education, and treatment adherence were not measured and could have influenced cognitive outcomes.

Overall, the findings highlight the importance of regular cognitive evaluation in children diagnosed with permanent congenital hypothyroidism, with the goal of guiding timely cognitive rehabilitation. The present results may also serve as a tool for predicting cognitive status and can assist healthcare providers and psychotherapists in adopting appropriate strategies for treatment and support—ultimately helping to prevent declines in intellectual function in this vulnerable population.

5- DECLARATION

5-1. Ethical Approval

The study protocol and all related procedures were reviewed and approved by Isfahan University of Medical Sciences with Approval Number IR.MUI.MED.REC.1399.091. Informed consent was obtained from all participants involved in the study.

5-2. Conflict of Interests

The authors declare that they have no conflicting interests that could potentially influence the research findings, data interpretation, or objectivity of this article.

5-3. Availability of Data and Materials

The datasets analyzed during the current study are available upon reasonable request.

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