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ORIGINAL ARTICLE

Cognitive performance of preschoolers with Congenital Hypothyroidism enrolled in a follow-up program

Desempeño cognitivo en preescolares con Hipotiroidismo Congénito incorporados en un programa de seguimiento

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What do we know about the subject matter of this study?

Untreated congenital hypothyroidism can cause severe sequelae in cognitive development. Timely detection by neonatal screening and early initiation of treatment favors the cognitive development of children within limits of normality.

What does this study contribute to what is already known?

This study shows that early intervention and pharmacological follow-up of patients with Congenital Hypothyroidism encourage active participation of parents in the development of their children and favor cognitive performance in children of low socioeconomic level.

Abstract

The age at treatment initiation is decisive for limiting the neurological sequelae of Congenital Hypothyroidism (CH). Incorporating children into follow-up programs could be very helpful. **Objective**: To evaluate the cognitive performance of preschool children with CH incorporated into a follow-up program. **Patients and Method**: Prospective study of 93 patients with a confirmed diagnosis of CH. Intelligence quotient (IQ) was assessed using the Wechsler Preschool and Primary Intelligence Scale (WPPSI) at 4 and 5 years, and the WISC-R at 6 years of age. Full-Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) scores were analyzed. **Results**: The study sample was 80 children. The average age at starting hormonal treatment was 42 ± 18 days; treatment started early in 25 patients (24 ± 6 days) and late in 55 patients (50 ± 16 days). The mean initial dose of Levothyroxine was 13.5 ± 1.5µg/kg/day. Children with athyrosis and late initiation of treatment had lower scores on

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the VIQ (85 ± 14), the PIQ (89 ± 12), and the FSIQ (86 ± 13) scales at 4 years of age, in comparison with patients with early initiation of treatment. These patients scored within the cut-off point for the normal IQ classification (90-109 points). IQ comparison at 6 years of age revealed differences up to 14 points in the PIQ and 11 points in the FSIQ between children with athyrosis and early initiation of treatment, with and without regular attendance to the follow-up program. **Discussion**: These results support the importance of early initiation of treatment and the incorporation of children in follow-up programs and early stimulation. The etiology of hypothyroidism and the age at initiation of treatment were the most significant factors that affected cognitive performance.

Introduction

The implementation of screening programs for early detection and treatment of Congenital Hypothyroidism (CH) in newborns recommends initiating hormone replacement therapy within the first two weeks after birth to achieve regular cognitive development through normalization of Thyroxine hormone (T4) levels in two weeks and Thyroid stimulating hormone (TSH) levels in one month[1]. The international recommendation indicates the administration of L-thyroxine at initial doses of 10-15 µg/kg/day for severe cases (patients with serum T4 concentrations less than 2 µg/dL and elevated TSH levels) and ~ 10 µg/kg/day for moderate cases. This recommendation is the therapy of choice to reduce the risk of neurological damage characteristic of this group of patients[2].

In 1988, the neonatal screening program for the early detection of CH was implemented in Mexico and then incorporated as mandatory in the Mexican Official Standard 007-SSA2-1993[3]. Vela-Amieva et al.[4] reported that, by 2004, a patient with TSH levels ≥ 10 µIUI/ml in heel blood sample was considered suspicious until confirmed by thyroid profile and scintigraphy. The mean age of initiation of hormone replacement therapy reported in their study was around 55 days; far from the ideal age proposed at the time, which was 30 days of extrauterine life.

To date, new strategies have been implemented to significantly reduce the time elapsed from neonatal screening, diagnostic confirmation (thyroid profile, scintigraphy, T4L concentration or thyroid ultrasound, bone age), and initiation of treatment[5,6].

Several studies have reported that children with CH treated early can obtain IQ scores within the normal range on the global scale[7]; however, other reports show that even when children treated early reach a normal IQ, they obtain lower scores in skills such as postural control, hand-eye coordination, visuospatial skills, auditory discrimination, attention, memory, and language compared with control children[8,9]. It has also been shown that early intervention can prevent some of the cognitive deficits in these cases[10,11].

The objective of this study was to evaluate IQ in preschoolers with diagnosis of CH incorporated into a Neurodevelopmental follow-up program at the National Institute of Pediatrics (INP) in Mexico City.

Patients and Method

Study Design and Patients

Prospective study that included 93 patients with confirmed diagnosis of CH who were born between 2003 and 2004 and were referred to the Neurodevelopmental Follow-up Laboratory by the Endocrinology service of the INP, to be incorporated into the Follow-up Program. 13 patients were excluded because they dropped out of the program or because they presented other conditions affecting neurodevelopment. The final sample consisted of 80 patients who received hormone replacement treatment and met the criteria of having at least two cognitive performance evaluations between four and six years of age.

Psychological evaluation

IQ assessments were performed by qualified psychologists, with 90% reliability, using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 4 and 5 years of age[12] and the Wechsler Intelligence Scale for Children-Revised (WISC-R) at 6 years of age[13]. Each patient was assessed in a single session lasting 60-90 minutes. Global (GIQ), Verbal (VIQ), and Performance (PIQ) IQ scale scores were analyzed.

Endocrinological evaluation

Diagnosis and hormonal treatment were performed at the Endocrinology Service of the INP. Thyroid hormone concentrations were quantified according to the standardized method at the institution, and scintigraphy studies were performed to determine the etiology of CH. Late initiation of treatment was considered to be the administration of L-thyroxine after 30 days of life and early when treatment was initiated at 30 days of life or less, considering as a cut-off point the ideal age of initiation according to Vela-Amieva (2004)[3]. These

were the normative criteria for the years when the children entered the study.

Follow-up

The Neurodevelopmental Follow-up Program began at the time of the confirmed diagnosis of CH and included a neurological, developmental, and cognitive evaluation regularly: monthly in the first year, every two months in the second year, every three months in the third year, and then every six months thereafter. Children who required it were provided with early intervention, and speech and cognitive therapy in addition to play and semi-academic activities. Parents were guided on how to manage their children and, most importantly, were encouraged to actively participate in their own children's development. All these activities were carried out by trained personnel assigned to the Neurodevelopmental Follow-up Laboratory, which includes Neurodevelopmental Specialists, Psychologists, Speech Therapists, Diverse Therapists, as well as Social Workers.

Ethical approval

Before joining the study, parents gave written informed consent. All procedures performed in this study were approved by the research and ethics committees of the National Institute of Pediatrics (Reg. INP 059/2014) and were performed according to the standards of the 1964 Declaration of Helsinki and its subsequent amendments, or comparable ethical standards.

Data analysis

The diagnosis and treatment data of the 80 children were used to analyze outcomes at 4 years of age. For the analysis of follow-up outcomes, data from 48 children who had all assessments at 4, 5, and 6 years of age were considered.

The comparison between patients with complete follow-up and those who did not complete it was carried out using the evaluation performed at 6 years of age, considering data from children who had at least two scheduled evaluations which could be at 4 and 5 years, 5 and 6 years, or 4 and 6 years of age (20 children); therefore, data from a total of 68 children were analyzed.

Tables and graphs with mean ± standard deviation were used for descriptive analysis. The strategy for inferential statistical analysis consisted of comparing GIQ, VIQ, and PIQ scores by type of hypothyroidism, age at treatment initiation, and attendance to the follow-up program. Tests for comparing means were performed using the JMP v 12.0 statistical package, SAS Institute.

Results

39 patients (85% female and 15% male) were diagnosed with Athyrosis and 41 (68% female and 32% male) with Thyroid Dysgenesis (ectopia, sublingual nodule, or hypoplasia); 30% of the mothers were under 20 years of age, 92% were housewife, 74% attended elementary school, 14% middle school, and 12% high school. Based on the socioeconomic classification used by the institution, 32% of the families belonged to the low level, 49% to the medium-low level, and 18% to the medium level.

The average age at treatment initiation was 42 ± 18 days (13 to 92 days); 55 patients started after 30 days of age (50 ± 16 days; 31 to 92 days) and 25 before 30 days of age (24 ± 6 days; 13 to 30 days). The mean initial dose of Levothyroxine was 13.5 ± 1.5 μg/kg/day; for patients with athyrosis 13.8 ± 1.4 μg/kg/day, and 13.0 ± 1.8 μg/kg/day for patients with dysgenesis.

Patients with athyrosis who started treatment after 30 days of age had significantly lower scores ($p < 0.003$) at 4 years of age compared with patients with athyrosis with early initiation; these scores are below the cut-off point for normal classification according to the Wechsler scale (< 90 points). Patients with athyrosis and early initiation and patients with dysgenesis with early or late initiation obtained scores within the normal classification (90-109 points) (Table 1).

Analysis by age and type of hypothyroidism showed that patients with athyrosis obtained significantly lower scores ($p < 0.001$) compared with patients with dysgenesis in the VIQ, PIQ, and GIQ scales. A decreasing trend in scores was observed as age increased (Table 2).

The effect of treatment initiation on the VIQ scale showed that patients with athyrosis and late initiation obtained lower scores than the group with early treatment and significantly lower ($p < 0.005$) than the dysgenesis group with late initiation. The scores obtained (85 mean points) placed them below the normal classification criteria. Patients with athyrosis and early initiation scored within the normal classification range.

In the PIQ scale, there were statistically significant differences ($p < 0.001$) when comparing patients with athyrosis and late initiation with patients with athyrosis and early initiation and patients with dysgenesis. Patients with athyrosis and early initiation scored within the normal classification at all ages and patients with dysgenesis scored within or above the normal classification range at 4 years of age. There was a trend toward lower mean scores on the VIQ and PIQ scales as age increased (Table 3).

In the GIQ Scale, the analysis shows statistically significant differences ($p < 0.005$) at 4 years of age between children with athyrosis and late initiation and patients with dysgenesis and early or late initiation, and marginally ($p = 0.069$) compared with patients with athyrosis and early initiation; these differences remain when compared with the same groups at 5 and 6

years of age ($p < 0.0003$). Patients with athyrosis and early initiation scored within or even above the cut-off point for normality (> 109 points). Scores of patients with athyrosis and late initiation are below the cut-off point for normality (Figure 1).

Differences of up to 14 points on the PIQ scale and 11 points on the GIQ scale were observed when comparing the groups with athyrosis and early initiation, with and without regular attendance to the follow-up program. Although a statistical analysis could not be performed due to the limited number of patients, the scores of patients with early initiation and regular attendance are higher than those who did not regularly attend the follow-up program; the differences recorded from the comparison between the groups with dysgenesis were no more than 9 points (Table 4).

Discussion

Although early initiation of hormone replacement therapy reduces the risk of intellectual disability, some studies have reported that children with CH obtain lower scores on verbal, performance, and global scales than children without CH and IQ variations related to the severity of hypothyroidism[14].

Scores on the verbal and performance scales were closely related to the type of hypothyroidism and age at initiation of therapy, factors that are crucial for cognitive development. Patients with athyrosis with delayed intervention showed on average lower scores, which is a common finding in studies evidencing IQ deficits in children with athyrosis. Published studies on the effect of CH on IQ report that patients with CH obtain lower scores and a score below siblings or classmates[15-17].

We found differences higher than 15 points on the global scale when comparing patients with athyrosis and late initiation with patients with athyrosis and early initiation and patients with dysgenesis, suggesting that a child with these characteristics is at risk of developing cognitive alterations and an IQ lower than at least one standard deviation of the reference mean[12,13].

Language represents a significant indicator of cognitive development. Prolonged exposure to low levels of thyroid hormones represents an important risk factor for alterations in complex cognitive functions, including language[18,19]. Henrichs[20] reported that severe maternal hypothyroxinemia affects fetal brain development and predicts a high risk of delayed development in this area.

Verbal IQ scores in patients with athyrosis were significantly lower than those in patients with thyroid dysgenesis. This difference increases when comparing patients with early initiation of therapy regardless of the type of hypothyroidism, i.e., the effect of early initiation of treatment is more evident in PIQ and even more among patients with athyrosis.

It is important to consider the role played by sociocultural elements in the verbal development of children and especially those with CH. The cases reported in this study are of families coming from sociocultural and economic levels generally considered low or medium-low. In this regard, several studies have shown that variables such as socioeconomic level, available stimulation at home, and the formal education of the parents have an impact on the processes of developmental organization[21-23]. Children of low socioeconomic status tend to be more vulnerable due to poor environmental stimulation compared with those in a more stimulating social environment[24]. This idea is supported by studies that highlight the importance of including children with CH in early care programs, showing that

Table 1. IQ at 4 years of age, by type of congenital hypothyroidism and initiation of treatment

Type of CH and initiation of treatment.	VIQ	PIQ	GIQ
Athyrosis			
Early (13)	101 ± 8	105 ± 13	104 ± 10
Late (26)	85 ± 14*	89 ± 12**	86 ± 13***
Dysgenesis			
Early (12)	103 ± 15	111 ± 15	107 ± 14
Late (29)	103 ± 13	106 ± 10	105 ± 11

*p<0.003, **p<0.0004, ***p<0.002 vs patients with athyrosis and early initiation of treatment, and patients with dysgenesis. (n) = number of patients in each group. CH: Congenital Hypothyroidism; VIQ: Verbal Scale; PIQ: Performance Scale; GIQ: Global Scale.

Table 2. IQ in patients with complete follow-up, by age and type of Congenital Hypothyroidism

Age and type of CH	VIQ	PIQ	GIQ
4yo.			
Athyrosis (24)	89 ± 15*	94 ± 15*	90 ± 15*
Dysgenesis (24)	104 ± 11	109 ± 11	107 ± 11
5yo.			
Athyrosis (24)	88 ± 14*	93 ± 14*	89 ± 14*
Dysgenesis (24)	99 ± 9	108 ± 12	103 ± 10
6yo			
Athyrosis (24)	88 ± 13*	90 ± 14*	87 ± 14*
Dysgenesis (24)	101 ± 8	104 ± 10	103 ± 8

*p < 0.001 vs dysgenesis for all scales. Comparisons by age within the groups did not show statistically significant differences. (n) = number of patients in each group. CH: Congenital Hypothyroidism; VIQ: Verbal Scale; PIQ: Performance Scale; GIQ: Global Scale.

Table 3. Verbal and performance IQ by type of Congenital Hypothyroidism and initiation of treatment in patients with complete follow-up.

Type of CH and initiation of treatment.	4yo.	5yo.	6yo.
		Verbal IQ	
Athyrosis			
Early (6)	100 ± 11	97 ± 09	100 ± 12
Late (18)	85 ± 15*	85 ± 14*	83 ± 10*.**
Dysgenesis			
Early (7)	102 ± 14	97 ± 13	99 ± 11
Late (17)	105 ± 10	99 ± 07	101 ± 07
		Performance IQ	
Athyrosis			
Early (6)	109 ± 15	107 ± 14	105 ± 14
Late (18)	89 ± 12***	89 ± 12***	85 ± 10***
Dysgenesis			
Early (7)	110 ± 17	108 ± 16	105 ± 12
Late (17)	109 ± 08	108 ± 11	104 ± 09

*p < 0.005 vs groups with late dysgenesis, **p < 0.005 vs all groups. ***p < 0.0001 vs athyrosis with early initiation of treatment and dysgenesis group. (n) = number of patients in each group. CH: Congenital Hypothyroidism; VIQ: Verbal Scale; PIQ: Performance Scale; GIQ: Global Scale.

this type of intervention could be particularly efficient in low-income families[25].

Patients with athyrosis and late initiation of treatment obtained scores below the expected average for their age. However, these scores do not place them within the group of individuals with greater cognitive deficits according to the scales applied (< 79 points). These results support the importance of incorporating children in follow-up and early stimulation programs to reduce cognitive development and learning problems.

It is noteworthy that patients with athyrosis and early initiation achieved throughout development both verbal and performance IQ within normal range, while carriers of other types of dysgenesis with early or late initiation of treatment were located in normal ranges and a group of these patients even reached higher scores (> 110 points) despite coming from families in socially vulnerable conditions.

As reported by other researchers, our results highlight the importance that early initiation of hormone replacement therapy has on cognitive development[2,15,26].

We can conclude that in children with CH detected

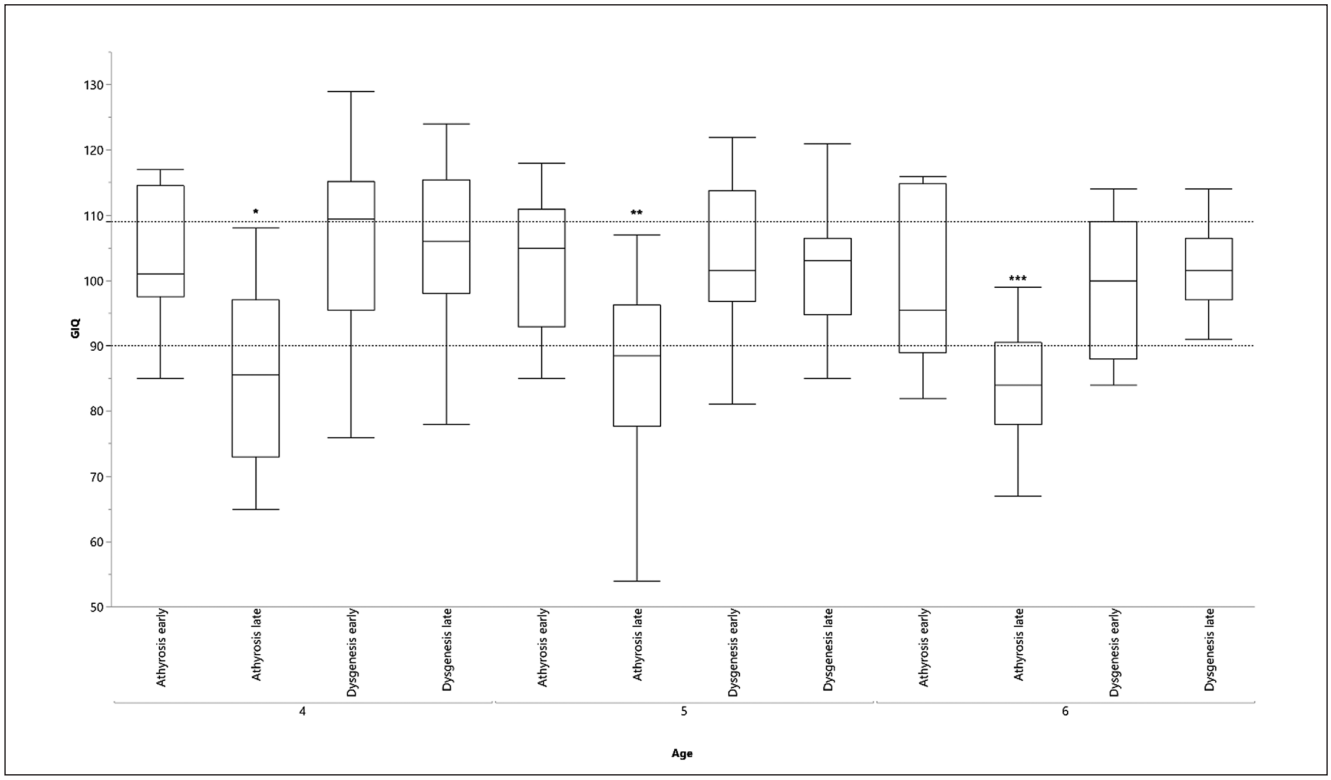

Figure 1. Mean global scale IQ scores in patients with complete follow-up with athyrosis and late initiation of treatment (N = 17) were below the cut-off point for normality (dashed lines) at all ages. *p < 0.005 at 4yo compared to dysgenesis patients with early (N = 7) or late (N = 17) initiation of treatment. **,***p < 0.0003 compared to the same groups at 5yo and 6yo. Patients with arthrosis with early initiation of treatment scored within or even above the cut-off point for normality (90-109 points); scores in these patients were similar to those in the dysgenesis group.

at birth by neonatal screening, who are incorporated into early care programs, even if they come from socially vulnerable conditions and hormone replacement treatment is initiated before 30 days (ideally before 15 days), the impact on cognitive development will be more satisfactory. Future research should specifically study the components of the WPPSI and WISC-R test subscales to identify the presence of subtle difficulties in specific areas that could affect cognitive performance.

Regarding the limitations of the study, as happens in most follow-up studies, the loss of patients is a major limitation when analyzing the results; in our case, we were unable to incorporate the data of 12 patients at 6 years of age into the analysis because we did not have at least 2 of the scheduled evaluations.

The program is designed to provide neurodevelopmental follow-up to children from the time the diagnosis is confirmed until 14 years of age; however, we only included follow-up data from 4 to 6 years of age, and this, of course, somewhat limits the conclusions regarding the benefits of the follow-up and early stimulation program.

The families of the patients were in the low and lower-middle socioeconomic levels, so the impact of the full range of socioeconomic variables on cognitive development, particularly language development, may not be fully reflected.

Table 4. IQ in patients with or without regular attendance to the follow-up program

Regular attendance to program		VIQ	PIQ	GIQ	CIG
Athyrosis early	Sí	(6)	100 ± 12	**105 ± 14**	**102 ± 14**
	No	(2)	93 ± 2	**91 ± 2**	**91 ± 2**
Athyrosis late	Sí	(18)	83 ± 10	85 ± 10	82 ± 10
	No	(3)	85 ± 14	95 ± 6	88 ± 9
Dysgenesis early	Sí	(7)	99 ± 11	105 ± 12	102 ± 12
	No	(6)	90 ± 9	102 ± 9	96 ± 8
Dysgenesis late	Sí	(17)	101 ± 7	104 ± 9	103 ± 5
	No	(9)	100 ± 12	106 ± 10	103 ± 11

Differences of 14 points in PIQ and 11 in GIQ in the groups with athyrosis and early initiation of treatment, when comparing patients with regular attendance vs. without regular attendance (**bold**). In the groups with dysgenesis, differences of 9 points in the verbal scale (VIQ) and 6 points in the global scale (GIQ) between the early treated group with regular attendance vs. those without regular attendance (italics). (n) = number of patients in each group. VIQ: Verbal Scale; PIQ: Performance Scale; GIQ: Global Scale

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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