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ORIGINAL ARTICLE

Social, cognitive and psychomotor development in peruvian children with congenital hypothyroidism

Desarrollo social, cognitivo y psicomotor en niños peruanos con hipotiroidismo congénito

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

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability in the pediatric population; however, there are no updated reports on its prevalence, diagnosis, treatment, and prognosis on neurodevelopment in Peru.

What does this study contribute to what is already known?

This study shows that repercussions in social, cognitive, and psychomotor development were more frequent in patients with CH diagnosed and treated after 21 days of age, thus requiring a standardized neonatal screening program.

Abstract

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability in the pediatric population. Early diagnosis and treatment during the first month of life are essential to avoid delaying the neuropsychological development of these patients. **Objective**: to describe the social, cognitive, and psychomotor development of children with CH treated at the National Institute of Child Health (INSN) in Lima, Peru. **Patients and Method**: Retrospective analysis of 26 CH patients seen during 2012-2017 at INSN were reviewed. The aspects of neuropsychological development studied were: cognitive development (IQ), social development (social category), and psychomotor development (gait, speech, and chest control). The IQ was classified according to the result of the Weschler IV scale. An analysis was carried out with the Fisher-Freeman-Halton test to verify if there was a difference in the frequency of the variables according to the age of diagnosis and beginning of treatment. **Results:** Most of the patients presented a borderline IQ (38.5%), the most frequent

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social category was educable (88.7%), and most of the patients presented delay in developing the speech (88.5%). In the Fisher-Freeman-Halton test, there was only a statistically significant increase in the number of cases of speech delay in patients treated between 22 days and 12 months of age ($\chi^2 = 11.246$, $p = 0.002$, V of Cramer = 0.778). **Conclusion:** Neuropsychological developmental delay was more frequent in patients with CH diagnosed and treated after 21 days of age.

Introduction

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability (ID) in the pediatric population[1]. This occurs because thyroid hormones have an important role during the fetal stage and the first two years of life, in the development and maturation of the central nervous system[1,2]. Thus, the absence or insufficiency of these hormones alters neuronal conduction and transmission[2,3].

The prevalence of CH has varied from 1 in 6,500 to 1 in 3,000 newborns after the implementation of screening programs[4,5]. In Peru, the *Instituto Nacional Materno Perinatal* (INMP) has reported that 40 of almost 100,000 newborns screened (1:2,500) were diagnosed with CH[6]. Likewise, a study with data from the *Instituto Nacional de Salud del Niño* (INSN) up to 2005 reported that the average age of diagnosis was 5.9 ± 5.3 months, with a significant decrease in the age of diagnosis compared with studies of previous years[7].

The clinical manifestations are difficulty in sucking coordination, constipation, hypothermia, bradycardia, edema, enlarged fontanelle, macroglossia, prolonged jaundice, umbilical hernia, and growth and developmental delay[8]. There have been attempts at clinical diagnostic algorithms[9]; however, these clinical signs are not always present at birth and develop slowly in the patient[7,8], making universal newborn screening mandatory[2,8].

The appropriate time for CH screening is between the second and fourth days of life. During this period, T4 levels may still be elevated but thyroid-stimulating hormone (TSH) values are at near-normal levels, where they will remain for the first year of life[1,10]. Replacement therapy with levothyroxine should be initiated immediately after confirmation of the diagnosis; the earlier this condition is treated, the less are the repercussions on the patient's development[1,10,11].

The repercussions on the nervous system appear in different aspects of the development of individuals. There is evidenced that intelligence quotient (IQ) is lower in patients with CH compared with healthy children[12,13], however; this evidence could be due to patients who were diagnosed in times when early diagnosis and therapy with high doses of levothyroxine was not widely used[14]. The most frequent alterations occur in visuospatial processing, selective memory, and the sensorimotor system[2,13]. The ability to adapt behavior may also be compromised[15].

The main factors associated with neurodevelopmental deficits include the severity of hypothyroidism according to etiologic diagnosis[8,10,15], delayed initiation of replacement therapy (greater than 15-21 days)[8,10,15,16], and inadequate long-term follow-up[8,10]. Similarly, social factors have been identified such as the sociocultural level of the family[15-17], the level of education of the caregivers[16,17], and coming from a rural area[16].

In Peru, the national technical standard for screening of congenital diseases has recently been approved[18], however, there is no unified national screening program since the health system is fragmented[19]. There are no studies that evaluate the results of treatment in patients with CH. Approximately 2.15% of children attending the Endocrinology Service of the INSN, which is a national referral center, are diagnosed with CH. Consequently, the objective of this study was to describe the social, cognitive, and psychomotor development of children with CH seen at INSN between 2012 and 2017.

Patients and Method

Retrospective study. The medical records of patients with a diagnosis of CH seen between 2012 and 2017 at the INSN, Lima, Peru were reviewed. Patients under 17 years of age who had had a complete follow-up by the endocrinology unit and psychological evaluation were included. Initially, 36 clinical records were identified, of which 4 did not have a psychological evaluation and 6 were of patients with incomplete data, resulting in a final sample of 26 patients.

The data recorded were sex, age at diagnosis, and treatment initiation (≤ 21 days, between 22 days, and 1 year, and > 1 year)[10,11], TSH and free T4 levels[10], family type (nuclear when it consisted of both parents and children, and non-nuclear), IQ, social category, and psychomotor development. None of the children evaluated had history of prematurity.

IQ was classified according to the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) for

children aged 2 years and 6 months to 7 years and 7 months, or the Wechsler Intelligence Scale for Children (WISC) for children aged 6 years to 16 years and 11 months. The following categories were considered for IQ according to the score obtained: very superior (> 130), superior (120-129), superior normal (110-119), average normal (90-109), lower normal (80-89), borderline (70-79), mild ID (60-69), and moderate to severe ID (< 60).

The social category was evaluated according to Vineland Social Maturity Scale (VSMS) as: educable (they present social skills they need to take care of themselves and adapt to society), trainable (they learn to communicate and take care of basic health and safety needs), or custodial (they can be trained in daily routines that contribute to their care, they need direction and close supervision).

Psychomotor development was evaluated according to the *Esquema de desarrollo del Consejo Nacional para la Integración del Impedido* (ED-CONAII) considering the variables trunk control (normal: 7-9 months, delay: > 10 months), onset of gait (normal: 10-12 months, delay > 12 months), and onset of language acquisition (normal: 10-12 months, delay: > 12 months)[20]. The ED-CONAII is an instrument used in public health institutions in Peru because it has been validated for our population[20].

The information was organized in an Excel database and then processed in the SPSS 22 statistical software. For summary measurements, frequency and percentages were used for categorical variables, and means with standard deviation or median with interquartile range according to the normality of the distribution of quantitative variables. The Fisher-Freeman-Halton test was used for verifying the difference in IQ levels, psychomotor developmental delay, and VSMS scores according to the age at the start of treatment.

The protocol for this study was approved by the Ethics Committee of the *Oficina Ejecutiva de Investigación y Docencia* of the INSN, and the handling of patient data was kept confidential.

Results

The median age at diagnosis was 5.5 months (0.66-24) and the most frequent range of age at diagnosis was between 22 days to 12 months of life. For IQ assessment, the WPPSI scale was used in 16 children with a mean assessment age of 4.44 ± 1.32 years, and the WISC in 10 children with a mean assessment age of 9.4 ± 1.84 years. Table 1 summarizes the clinical-epidemiological characteristics.

The evaluation of neuropsychological developmental parameters (table 2) indicated that most of the patients had a borderline IQ level of 70-79 (38.5%), the most frequent social category was educable (80.8%), and most had delayed language onset (84.6%).

Regarding the age at diagnosis (start of treatment) and IQ level (figure 1): 50% of the patients who were diagnosed up to 21 days of birth presented an average normal IQ (90-109) and none presented any type of deficiency. All patients diagnosed after the first year of life presented IQ equal to or below the lower normal level (80-89).

Concerning the relationship of age at diagnosis and social category, all patients diagnosed up to 21 days were qualified as educable and 71.4% of those diagnosed after 21 days were qualified as educable. There was only one patient who was qualified as custodial that was diagnosed after one year of age (figure 2).

Regarding the relationship between age at diagnosis and psychomotor development, none of the patients diagnosed up to 21 days presented delayed trunk control (figure 3). All patients diagnosed after one year presented delayed onset of gait.

When the Fisher Freeman Halton test was performed, there was only a statistically significant higher number of cases of delayed language onset in patients treated between 22 days and 12 months of age ($X^2 = 11.246$, $p = 0.002$, Cramer's $V = 0.778$). Among children according to age at diagnosis and treatment initiation, no statistically significant differences were found in IQ levels ($X^2 = 13.914$, $p = 0.065$), social category ($X^2 = 4.217$, $p = 0.356$), gait delay ($X^2 = 1.657$, $p = 0.559$), or trunk control ($X^2 = 5.894$, $p = 0.060$).

Discussion

CH is a disease that should be diagnosed and treated in the first 15 to 21 days of life. The age ranges of diagnosis identified in this study are higher than those reported in different studies[15-17,21]. The data collected was from a pediatric referral center in which there are no deliveries, which probably explains why most of the diagnoses were made after 21 days of age. On the other hand, in some cases, newborns are discharged after 24 hours of life because there is no standardized national program for neonatal screening that indicates when the tests should be performed, so the screening is performed within this time when thyroid hormone levels may be in normal ranges due to a transient elevation in the first hours of life[1].

The INSN diagnostic protocol considers an initial TSH and T4 assessment. With the confirmation of the diagnosis, treatment with levothyroxine of 10-15 ug/kg/day is started in children under one month of age, and then the dose is adjusted according to the age at diagnosis[22]. This highlights the need for a standardi-

zed national program of neonatal screening for CH in Peru.

In our study, none of the patients diagnosed before 21 days had any type of ID and 50% had an average normal IQ level. The prevalence of ID levels according to IQ measurement varies among different studies[12,16,21,23]. Cognitive prognosis has been reported to be related to free T4 levels at diagnosis[16,23], treatment dose[11,24], early age of treatment initiation (15 to 30 days from birth)[16,21], etiology, and severity of CH[23]. Seo et al. 2017[21] and Boileau et al. 2004[11] found no significant difference in the IQ of CH patients whose treatment started in the first month of life with the IQ of healthy children. The sample of both studies is from countries with well-established neonatal screening programs.

When evaluated with the Vineland scale, all patients treated before 21 days corresponded to the educable social category. This could imply that early treatment initiation would be associated with reaching a better social category, however; Gottschalk et al. 2008[25] reported that the domain and global scores of the Vineland scale were at the same levels between patients with and without CH. Huo et al. 2011[15] found no difference between the adaptive capacity of CH patients who started treatment after 20 days with those who started treatment earlier, however, they found an association with the severity of CH, the initial dose of treatment, and the time to TSH normalization. These

Table 1. Epidemiological and clinical characteristics of patients with congenital hypothyroidism

Characteristic	n = 26
Sex, n (%)	
Female	21 (81)
Male	5 (19)
Evaluation age (years), median (IQR)	6 (3-11)
Age at diagnosis (months), median (IQR)	5.5 (0.66-24)
Age at diagnosis, n (%)	
≤21 days	6 (23)
22 days - 1 year	13 (50)
>1 year	7 (27)
TSH at diagnosis, n (%)	
< 20mU/L	1 (4)
20 - 100 mU/L	16 (61)
> 100mU/L	9 (35)
Free T4 at diagnosis, n (%)	
< 10ug/dl	23 (88)
Type of family	
Nuclear	10 (38)
No nuclear	16 (62)

IQR: Interquartile range. TSH: Thyroid stimulating hormone.

Table 2. Development evaluation in patients with congenital hypothyroidism according to initiation treatment time

Development indicator	n (%)	Up to 21 days n (%)	After 21 days
Intelligence Quotient			
Superior normal	1 (3.9)	01 (100)	-
Average normal	3 (11.5)	03 (100)	-
Lower normal	5 (19.2)	1 (20)	04 (80)
Borderline	10 (38.5)	01 (10)	09 (90)
Mild ID	5 (19.2)	-	05 (100)
Moderate ID	2 (07.7)	-	02 (100)
Social Category			
Educable	21 (80.8)	06 (28.6)	15 (71.4)
Trainable	4 (15.4)	-	04 (100)
Custodial	1 (3.9)	-	01 (100)
Psychomotor development delay			
Trunk control	11 (42.31)	-	11 (100)
Onset of gait	20 (76.9)	04 (20)	16 (80)
Onset of language acquisition	22 (84.6)	02 (9.1)	20 (90.9)

ID: intellectual disability.

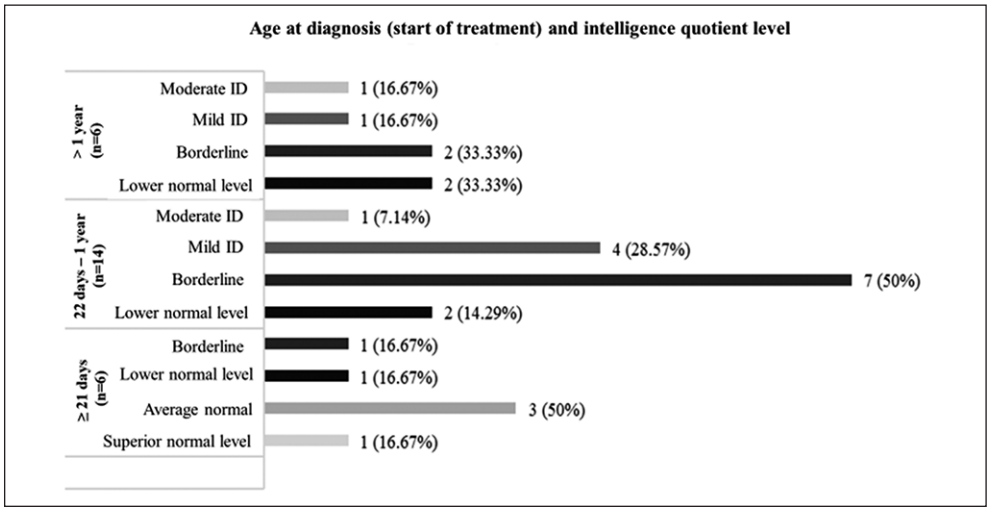

Figure 1. Relationship between diagnosis age and intelligence quotient level.

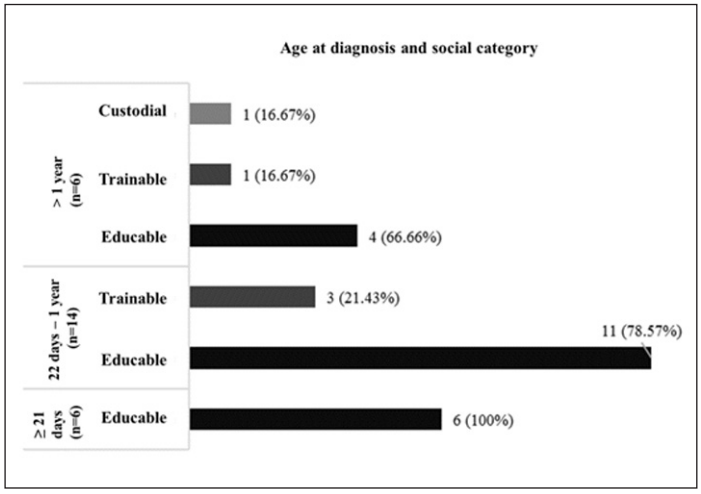

Figure 2. Relationship between the age at diagnosis and the social category.

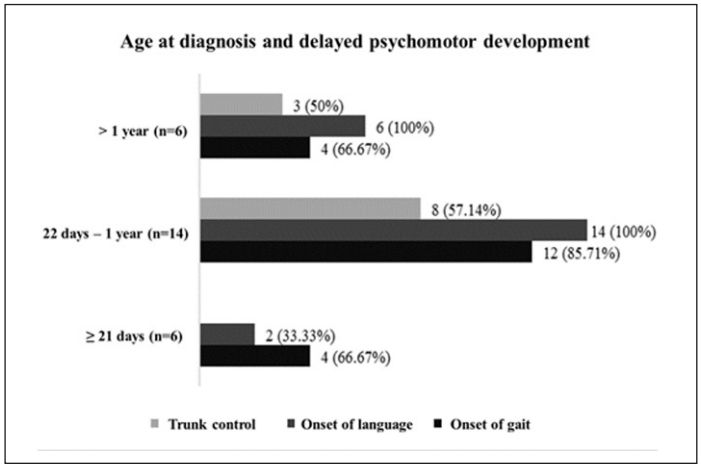

Figure 3. Relationship between diagnosis age and delayed psychomotor development.

differences could be explained by the notable influence of the environment on behavioral modeling, where the sociocultural level of the family is a factor associated with this[15,17].

Regarding psychomotor development, none of the children who started treatment before 21 days of age presented a delayed trunk control. All patients who initiated treatment after 12 months presented gait delay. Bulus et al. 2017[13] reported gross motor impairment (motor control, sitting, walking, jumping, and other movements) in CH patients and a higher number of patients with abnormal Denver Test in patients who initiated treatment after 15 days. Kempers et al.[23] and Baysal et al. 2017[26] reported that CH severity was more determinant in the long term on cognitive and motor functions than the time of treatment initiation. Regarding language development, it was observed that 90.9% of patients treated after 21 days presented delay in this area. This coincides with what has been reported in other studies that report that patients with CH present a frequent delay in language and that in those treated early, this frequency decreases[15,17].

Important limitations of the study were the small sample size and that all patients came from a single health institution. In addition, variables associated with the neurodevelopment of patients with CH such as the educational level of the parents and the degree of stimulation received by the children could not be identified in the medical records that were reviewed. Another limitation was that for the extrapolation and comparison of the results of this study there is an absence of studies comparing the ED-CONAII (Peruvian test) with other standardized tests such as Bayley or Battelle.

Studies with larger cohorts of patients with CH and

from different cities in Peru are recommended to evaluate the impact of the implementation of the technical standard for neonatal screening. Similarly, the use of standardized psychomotor development assessment tools is suggested in order to extrapolate and compare data with the international literature.

In conclusion, according to what was observed in this study, the greatest impact on the social, cognitive, and psychomotor development of patients with CH was observed in patients diagnosed and treated after 21 days of age. Therefore, it is important to implement a unified neonatal CH screening program in Peru for timely diagnosis and treatment.

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: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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