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Thyrotropin changes in children under five years of age with chronic malnutrition and their association with neuro-psychomotor development.

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Abstract

Introduction: Malnutrition has a mortality of 45% in pre-schools and predominates in rural areas. Iodine deficiency can lead to hypothyroidism, manifested by elevated TSH, and may be associated with retarded psychomotor neurodevelopment (PMDN). The study's objective was to determine the prevalence of TSH alterations in children with chronic malnutrition and their association with DNPM alterations in the indigenous population under five years of age.

Methods: This cross-sectional study analyzes the database of the " Wawapak-kausay " Project of the indigenous child population in four cantons of the province of Chimborazo-Ecuador from 2018 - 2019. A univariate analysis was carried out with the calculation of frequency and percentages; a bivariate analysis with reporting OR and 95% CI, considering significant *P* <0.05.

Results: There were 350 cases of chronic malnutrition; 50.6% were men, from the lowest quartile of economic income (32%) and the Riobamba canton (44%). 88.6% reported normal TSH, 10.8% high TSH, and 0.6% low TSH. Irregular water supply and TSH disturbance were statistically significant (*P*< 0.01). The Denver II test was applied to 82 children; 70.7% presented normal development, 8.5% suspected delay, and 20.7% psychomotor delay, predominantly in the language area (15.9%); women were more affected (*P*=0.02).

Conclusions: 1 out of 10 children with chronic malnutrition had elevated TSH. No significant association was found between altered TSH values and suspected or delayed psychomotor development.

Keywords: **MESH**: Child Nutrition Disorders, Malnutrition, Protein-Calorie Malnutrition, Thyrotropin, Child Development, Developmental Disabilities.

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Introduction

Child malnutrition is an imprecise, systemic, and potentially alterable pathology that occurs due to a lack of nutrient intake, characterized by a variety of clinical expressions and levels of intensity [1].

In Ecuador for 2018, according to the National Survey on Health and Nutrition (ENSANUT), 23% of children between 0 and 60 months presented chronic malnutrition, the Sierra being the most affected subregion (54.3%), with a higher prevalence (39.4%) in the provinces of Cotopaxi, Tungurahua, and Chimborazo [2].

A significant complication of malnutrition, although little studied, is hypothyroidism. This pathology is mainly associated with a deficit in iodine intake, which leads to various disorders that can be prevented with an adequate diet and supplementation of this mineral, which is found mainly in the ocean. Hence, the areas most likely to be scarce of this element are mountainous areas. Nowadays, thanks to industrialization and diversification of the diet, fewer iodine deficits have been evidenced, and if they occur, the most affected populations are those with fewer economic resources [3].

Thyroid hormones play a fundamental role in essential metabolic processes and contribute to the growth and development of tissues; bone tissue is highly dependent on their action; therefore, if there is evidence of a delay in linear growth during childhood, the investigation of a possible thyroid disorder becomes necessary, to rule out, for example, the presence of hypothyroidism. Likewise, these hormones are essential to the child's brain development [4].

Hypothyroidism is the state that occurs as a consequence of a decrease in the physiological activity of thyroid hormones on tissues. This situation can be derived from the variation in their production, excretion, transport, and metabolism, as well as resistance or lack of response to its effects in target tissues [4]. Worldwide, in children and adolescents, the prevalence of hypothyroidism ranges from 1.72% - 4.94% [5].

It has been observed that those patients who suffer from hypothyroidism have lower scores in cognitive, motor, and language assessments when compared to the healthy population [6]; this could be due to the role played by thyroid hormones in the development of the nervous system from life fetal and during the first two years of life, participating in the processes of myelination, dendritic arborization, synapse development, and neuronal migration.

The purpose of this research is to identify the relationship between the presence of chronic malnutrition with altered TSH values and its alteration with psychomotor development in our child population.

Materials and methods

Type of study

The present study is a non-experimental, cross-sectional analysis of databases.

Database

The database is an investigation in the province of Chimborazo, in rural areas of the Riobamba, Guamote, Guano, and Colta cantons, of the research project "Determinants of malnutrition in children under five years of the Ecuadorian indigenous population: a study based on secondary school at the national and longitudinal level in four cantons of the Chimborazo province, from January 2018 to December 2020, -Wawapakkausay- which included 1,232 indigenous children from rural areas in five cantons of the Chimborazo province [7].

Universe and Sample

Sample

The sample consisted of 350 indigenous children under five years of age with symptoms of chronic malnutrition in whom, after their parents' consent, the serum TSH test was performed. The sampling was non-probabilistic of all possible and analyzable cases.

Sampling

The sampling was carried out by the discard method, taking into account the inclusion and exclusion criteria.

Inclusion and exclusion criteria

Serum TSH measurement cases were entered into the study together with the diagnosis of chronic malnutrition. All children in the database had assented to participate in the study. Patients with acute disease at the time of the research or with chronic health problems (such as kidney, heart, metabolic disorders, or disability) that affect their growth and development were excluded.

Variables

The variables were: TSH, age, sex, head circumference, weight, height, altitude of residence, canton of home, family income, overcrowding, water supply, parental education, and neuro psychomotor development.

Instrument

Neuropsychomotor development was measured with the DENVER development test, which classifies the result as normal: when the children met the items within the 25th and 90th percentiles, Uncertain/suspicious of delay if an area has two or more failures, Delay/ abnormal: if there are two or more failures in 2 or more rooms.

Technique

In the Child Care Centers of MIES or the Cáritas social project, safe spaces were conditioned by the DISERLAB laboratory of the Pontificia Universidad Católica del Ecuador, and through biosafety regulations, the trained personnel of the laboratory extracted 2-3 ml of blood on a single occasion from the vein of the child's hand or arm using a suitable needle.

Blood sample analysis

The blood samples were processed in the DISERLAB laboratory of the PUCE, using the IMMULITE 1000 equipment and the third-generation TSH reagent, an immunometric assay with two solid-phase chemiluminescent binding sites. For the analysis of the results, the Reference values provided by the DISERLAB laboratory were used: euthyroid: 0.4 - 4.0 uIU/mL, Hyperthyroid: <0.01 uIU/mL, hypothyroid >4.0 uIU/mL.

The results of the analyzes were delivered in a sealed envelope to the parents/guardians of the children, and abnormal results were reported personally so that they could go to the health service for clinical follow-up.

Results analysis plan

A descriptive analysis of each one of the variables collected (age, sex, canton of residence, altitude of the place of residence, educational level of the parents, economic income, number of children, psychomotor development) was carried out for the total number of children who make up the valid sample. Qualitative variables were described by their distribution of absolute frequencies and percentages.

A bivariate analysis was performed to analyze the association between altered TSH levels and impaired neuropsychomotor development using logistic regression models. The effect measure obtained was the Odds Ratio (OR) and the 95% confidence interval, and the *P- value as a measure of significance, and a P value* <0.05 was considered significant. To carry out the statistical analysis, the Statistical Package for the Social Sciences SPSS 26.0 program (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was used.

Procedure to guarantee bioethical aspects

Once the purpose of the research was disclosed and with prior authorization, the information collected was used solely for the analysis and development of the study. The clinical histories were obtained confidentially and were not disclosed to people outside of this project.

Biases

To avoid possible interviewer, information, and memory biases, the leading investigator always kept the data with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the previous period were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

Results

Participants

There were 350 children entered into the study.

General characteristics of the population

It was an equal distribution between men and women. The mean age was 35 ± months. General descriptions of the group are presented in Table 1.

Prevalence of altered TSH in the study group

The alteration of the TSH was in 40 cases; 38 of the cases were with high TSH related to hypothyroidism. No associations were found with the demographic, socioeconomic, and biological variables (Table 2).

Psychomotor development

The Denver test was applied in 80 cases, with normal psychomotor development in 58 children (70.7%). The qualification by areas of development is presented in Table 3.

There was no association of suspected or delayed psychomotor development with sex, age, the height of residence, canton of living, education of the mother, education of the father, overcrowding, or water supply ($P > 0.1$ in each variable).

At a general level, of the children with altered TSH values, 5 (71.4%) presented normal development, and 2 (28.6%) gave developmental alteration, a deal that was not statistically significant; the same data were obtained in the social area (Table 4).

Table 1. Sociodemographic variables in the study group.

Sociodemographic variables		Frequency No.=350	Percentage
Sex	Man	177	50.6%
	Women	173	49.4%
Age group	< 12 months	9	2.6%
	13 - 24 months	63	18.0%
	25 - 36 months	136	38.9%
	37 – 48 months	63	18.0%
	49 – 60 months	74	21.1%
Residence height (masl)	<2945	69	20.1%
	2945-3200	92	26.7%
	3201-3400	122	35.5%
	>3400	61	17.7%
canton of residence	riobamba	154	44.0%
	Guamote	94	26.9%
	Colta	66	18.9%
	Guano	36	10.3%
family income	Q4	82	25.0%
	Q3	57	17.4%
	Q2	84	25.6%
	Q1	105	32.0%
mother's instruction	Superior	16	4.6%
	Baccalaureate	105	30.0%
	basic	193	55.1%
	Initial	14	4.0%
parent instruction	Superior	22	6.3%
	Baccalaureate	106	30.3%
	basic	169	48.3%
	Initial	14	4.0%

Discussion

This study focused on finding the prevalence of changes in thyroid-stimulating hormone (TSH) levels in children diagnosed with chronic malnutrition; of 350 registered cases with malnutrition, 40 (11.4%) had an altered result, and 38 children (10.8%) presented an elevated TSH.

The elevated TSH was in a higher percentage (37.2%) among the children between 27-48 months.

Later were younger and older infants, with 11.1% and 7.9%, respectively. There are no specific comparative studies for this variable in regional reports.

Theoretically, chronic exposure to high altitudes could affect the endocrine system, including the thyroid axis; At high altitudes, hypoxia characterized by low oxygen availability could affect blood T4 and T3 concentrations depending on the altitude level and duration of exposure.

Table 2. Demographic, socioeconomic, and biological characteristics associated with altered TSH in the study group.

Variables		TSH altered No.=40	TSH Normal No.=310	OR (95% CI)	*P*
Provenance	Riobamba	18 (11.7%)	136 (88.3%)	reference	-
	Guamote	7 (7.4%)	87 (92.6%)	0.61 (0.24-1.52)	0.28
	Colta	10 (15.2%)	56 (84.8%)	1.35 (0.59-3.10)	0.48
	Guano	5 (13.9%)	31 (86.15)	1.22 (0.42-3.5)	0.72
Residence height (masl)	<2945	7 (10.1%)	62 (89.9%)	0.58 (0.21-1.62)	0.30
	2946-3200	8 (8.7%)	84 (91.3%)	0.49 (0.18-1.31)	0.15
	3201-3400	14 (11.5%)	108 (88.5%)	0.66 (0.27-1.59)	0.36
	>3400	10 (16.4%)	51 (83.6%)	reference	
Mother's instruction	Greater than bachelor	12 (9.9%)	109 (90.1%)	reference	
	Basic or high school	25 (12.1%)	182 (87.9%)	1.25 (0.60-2.58)	0.55
Parent instruction	Greater than bachelor	13 (10.2%)	115 (89.9%)	reference	
	Basic or high school	31 (12.6%)	160 (87.4%)	1.27 (0.62-2.63)	0.51
Economic income	Q4	8 (9.8%)	74 (90.2%)	0.65 (0.21-1.62)	0.35
	Q3	7 (12.3%)	50 (87.7%)	0.49 (0.18-1.31)	0.72
	Q2	8 (9.5%)	76 (90.5%)	0.66 (0.27-1.57)	0.32
	Q1	15 (14.3%)	90 (85.7%)	reference	
Overcrowding	Yes	17 (9.2%)	168 (90.8%)	reference	
	No	22 (14.2%)	133 (85.8%)	1.64 (0.83-3.20)	0.15
Water supply	Permanent	26 (9.4%)	251 (90.6%)	reference	
	Irregular	13 (21.0%)	49 (79.0%)	0.39 (0.10-0.81)	0.01
Sex	Man	19 (10.7%)	158 (89.3%)	0.87 (0.45-1.68)	0.68
	Women	21 (12.1%)	152 (87.9%)	reference	
Age	0-12 months	1 (11.1%)	8 (88.9%)	1.19 (0.13-11.01)	0.87
	13-24 months	5 (7.9%)	58 (92.1%)	0.83 (0.25-2.74)	0.75
	25-36 months	16 (11.8%)	120 (88.2%)	1.28 (0.50-3.26)	0.61
	37-48 months	10 (15.9%)	53 (84.1%)	1.81 (0.64-5.05)	0.26
	49-59 months	7 (9.5%)	67 (90.5%)	reference	
Weight (z-score)	High weight	0 (0%)	1 (100%)	…	1
	Normal weight	17 (13.1%)	13 (86.9%)	1.05 (0.12-9.09)	0.96
	Underweight risk	17 (10.1%)	151 (89.9%)	0.79 (0.91-6.80)	0.83
	Low weight	5 (13.5%)	32 (86.5%)	1.09 (0.11-10.08)	0.94
	Severe underweight	0 (0%)	6 (100%)	reference	
Size	Tall stature	0 (0%)	1 (100%)	…	1
	Regular size	3 (15.8%)	13 (84.2%)	1.63 (0.40-6.59)	0.49
	Risk of short stature	1 (4.2%)	23 (95.8%)	0.38 (0.05-3.11)	0.37
	Low stature	25 (12.4%)	177 (87.6%)	1.23 (0.57-2.67)	0.90
	Severe short stature	10 (10.3%)	87 (89.7%)	reference	
Head circunference	Microcephaly	0 (0%)	5 (100%)	0.53 (0.07-4.13)	0.54
	Normocephaly	6 (11.3%)	47 (88.7%)	0 (0-0)	1.00
	Macrocephaly	0 (0%)	1 (100%)	0.94 (0.37-2.37)	0.90

However, the physiology in the heights seems to condition in a chronic way from the pediatric age. The present study did not find an association between a height of more than 3400 meters above sea level with a higher prevalence of hypothyroidism.

When analyzing the relationship between family income and TSH changes, it was found that 41.7% of the children belonging to the lowest income quartile (Q1) had TSH levels ≥4μIU/ml. These data agree with the association between poverty and hypothyroidism [3].

Another interesting finding from the present study was the association between water quality and hypothyroidism. (Modarelli, 2019) carried out a study in Argentina with 57 people aged 12 to 19 in which physicochemical analyses of the water were carried out regarding the composition of nitrates, observing levels of these above the safety limit for human consumption in the samples. Of the water reserve wells, which was related to a higher prevalence of subclinical hypothyroidism (TSH greater than 3.59 mIU/l) (52.6%) and goiter (77.2%) in those who drank groundwater compared to those who drank drinking water (*P*:0.001*)*.

In the present study, it was determined that children who had irregular access to water obtained from cisterns, wells, rivers, etc., had a 61% higher probability of presenting altered TSH compared to children who had permanent access to water (public network), statistically significant value (OR 0.39, 95% CI 0.10-0.81, *P* =0.01).

Even though in this investigation there is no data on water quality, a line of research is opened in which it is proposed that irregular supply could be associated with low consumption of drinking water, forcing the population to consume water untreated and thus predispose to exposure to endocrine disruptors such as nitrates, which are considered worldwide as the significant contaminants of surface and groundwater, in turn, these have been found to cause alterations in the levels of thyroid hormones, the latter occurs due to the interruption generated by nitrate in the uptake and accumulation of iodine by the thyroid, due to the ability of nitrate to compete with iodine for the sodium-iodine transporter present in the thyroid cell membrane, which is responsible for capturing and fixing iodine within the gland's follicles, an essential ion for thyroid function.

In the current database of a total of 350 children with a diagnosis of chronic malnutrition, 82 children had neurodevelopmental screening through the Denver Test, through which the social, motor, and language areas were evaluated, obtaining a total of 17 children (20.7%) presented delay in global development; Upon identifying each valued area, it was determined that 15.9% given the uncertainty in the language area, 4.9% in the social area, 2.4% in the fine motor area, and no delay was found in the gross motor area; According to these results, we can show that the most affected area was language, a finding similar to that obtained in a Mexican study carried out on 576 children from rural and marginalized localities of Mexico City between the ages of 7 to 26 months, where it was observed direct association between short stature and delayed language development with a *P value* < 0.001 [8].

Table 3. Psychomotor development test (Denver) in the study group.

Variable		Frequency N=82	%
Social development	Normal	65	79.3%
	suspected delay	13	15.9%
	Delay	4	4.9%
fine motor development	Normal	69	84.1%
	suspected delay	eleven	13.4%
	Delay	2	2.4%
language development	Normal	53	64.6%
	suspected delay	16	19.5%
	Delay	13	15.9%
gross motor development	Normal	79	96.3%
	suspected delay	3	3.7%
	Delay	0	0%
Total	Normal	58	70.7%
	suspected delay	7	80.5%
	Delay	17	20.7%

Table 4. Association between altered TSH and child development.

variables		TSH altered no=7	TSH Normal No.=75	OR (95% CI)	*P*
Overall development	Altered	2 (28.6%)	23 (30.7%)	0.90 (0.16-5.00)	0.91
	Normal	5 (71.4%)	52 (69.3%)	Reference	
Social development	Altered	2 (28.6%)	15 (20.0%)	1.60 (0.30-9.06)	0.60
	Normal	5 (71.4%)	60 (80.0%)	Reference	
Fine motor development	Altered	0 (0%)	13 (17.3%)	0 (0-0)	0.10
	Normal	7 (100%)	62 (82.7%)	Reference	
Gross motor development	Altered	1 (14.3%)	2 (2.7%)	6.0 (0.50-77.10)	0.10
	Normal	6 (85.7%)	73 (97.3%)	Reference	
Language development	Altered	2 (28.6%)	27 (36.0%)	0.7 (0.13-3.90)	0.70
	Normal	5 (71.4%)	48 (64.0%)	Reference	

Thyroid hormones play an essential role in the development and maturation of the central nervous system from the last months of fetal life and during the first two years of life, in addition to their importance in central and peripheral neuronal conduction. The present study could not demonstrate an association between alterations in psychomotor neurodevelopment and hypothyroidism in children with malnutrition.

When carrying out a bivariate analysis, the relationship between altered TSH values and alterations in psychomotor development was sought, finding that 28.6% of the children presented alteration in global growth, 14.3% in the gross motor area, and 28.6% in language. While in a fine motor area, no disorder was found. 25.6% of the boys and 35.9% of the girls studied presented altered psychomotor development (suspicion/delay). Regarding the areas of development that had alteration, it was evidenced that in the social area, 14% corresponded to boys and 28.2% to girls; in the fine motor area, 23.3% were boys and 7.7% girls; Gross motor 2.3% boys and 5.1% girls, finally in the area of language 23.2% of boys and 48.7% of girls presented alteration, determining that being a man is a protective factor against language disorders, data statistically significant with *P* =0.02 (OR 3.1 CI 1.2-8). (Buluş & Tiftik, 2017) [6] in a study consisting of a total of 228 children aged 24 to 56 months, of whom 112 were diagnosed with congenital hypothyroidism and 116 were healthy children, the two participating groups applied the Denver Development Test, obtaining as a result that in both there was no statistically significant relationship about the social area, fine motor, and language. However, a significant difference was found concerning the gross motor area of development (*P*=0.001). Although this research is not explicitly based on the study of congenital hypothyroidism, since no studies were found closely related to this topic during the bibliographic search, these results were taken as part of the final analysis.

Conclusions

After data analysis, it was found that 1 out of 10 children with chronic malnutrition had elevated TSH for the reference range. The biological variables female sex, low weight, short height, average head circumference, and mother's height <150 cm obtained a higher percentage of thyroid function alteration. Statistically significant data was obtained when relating irregular water supply with TSH alteration, with a *P value*: of 0.01. In the children to whom the Denver test was applied, it was determined that 2 out of 10 children (20.7%) presented psychomotor retardation, with a higher prevalence in the language area (15.9%).

Abbreviations
SD: Standard deviation DPM: Psychomotor development FA: Absolute frequency
GH: growth hormone
CI: confidence interval
IGF-1: Insulin-like growth factor 1
WHO: World Health Organization
OR: Odds ratio
TRH: thyrotropin-releasing hormone
TSH: thyroid stimulating hormone.

Supplementary information
No supplementary materials are declared.

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Author contributions
Alexandra Gabriela Valenzuela Astudillo: Conceptualization, data curation, formal analysis, fundraising, research, writing - original draft.
Alejandra Estefania Torres Yajamin: Methodology, project administration, resources, Software, supervision, validation, visualization, writing - review and edition.
Maria Fernanda Rivadeneira: Methodology, project administration, resources, software, supervision, validation, visualization.
Ana Lucia Moncayo: Methodology, project administration, resources, software, supervision.
All authors read and approved the final version of the manuscript.

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Availability of data and materials
Data were collected from medical files and are not publicly available due to patient confidentiality but are available through the corresponding author under clearly justified academic requests.

Statements

Ethics committee approval and consent to participate
The Research Committee and the Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Católica del Ecuador approved it.

Publication Consent
Not required when patient-specific images, radiographs, and studies are not published.

Conflicts of interest
The authors declare they have no conflicts of interest.

Author Information
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