Original Article

Intelligence Quotient, Anxiety, and Depression in Congenital Hypothyroid Children at School Age

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Abstract

Background: Many studies who evaluated the outcome of the congenital hypothyroidism (CH) screening reported some intellectual and behavioral deficit despite early diagnose and treatment. The aim of the present study was to compare the intellectual and behavioral adjustment of CH children with controls. **Methods:** This study was conducted among a group of 135 children aged 8--12 years in Isfahan, including transient and permanent congenital hypothyroidism (TCH and PCH) and a matched group of their classmate. Demographic characteristics collected using a designed data collecting form completed by parents. Intellectual quotient (IQ) was evaluated using Wechsler Intelligence Scale for Children aged 6--16 years (WISC-III). Depression and anxiety were evaluated using The Children's Depression Inventory (CDI) and the Multidimensional Anxiety Scale for Children (MASC), respectively. The SPSS software version 20.0 was used for data analysis. Nonparametric tests (Mann--Whitney) were used to investigate the association between variables. A significant level of less than 0.05 was considered in all analyzes. **Results:** There was no significant difference in the IQ scores between PCH and TCH groups (P = NS). However, neither of them had intellectual disability (defined as IQ <70). IQ scores were significantly lower in PCH comparing to controls ($P < 0.001$). Total IQ and verbal IQ were significantly differenct between TCH and control group ($P = 0.007$ and $P = 0.001$). No significant difference was found in anxiety and depression scores between CH children and controls. **Conclusions:** There is no significant difference in anxiety and depression scores between congenital hypothyroidism children and controls, although IQ scores in children with congenital hypothyroidism is lower than controls.

Keywords: *Anxiety, congenital hypothyroidism, depression, intelligence*

Introduction

Normal levels of thyroid hormone are critical for physical and mental development, especially in fetal life and post-natal period,[1] Congenital hypothyroidism (CH) is the most common treatable cause of mental retardation, with a prevalence of 1:4000--1:3000 worldwide.[2] However, last studies in Iran demonstrated an overall higher prevalence rate of CH (1:1000).[3]

Many countries perform CH screening as public health national screening programs initiated from 1975.[4] In Iran, CH screening program was established since 2002, and all neonates screened for CH in the first 3--5 days of their lives for early detection and prevention of CH complications such as intellectual disabilities. Neonates with CH were treated early with a high dose of L-Thyroxin [L-T4], and then they reevaluated at the age of three to distinguish between transient CH (TCH) against permanent CH (PCH).[5]

Intelligence quotient (IQ) is the most common scale for evaluating mental development. The mean score of the full-scale IQ test in CH patients before accomplishing of CH screening program was lower than the normal range. In the last decade, researches focused on evaluating the neurological development of CH children after early diagnosis and management. Some of these showed lower IQ level and cognitive deficit in PCH and TCH children.[6] However, some other studies demonstrated that PCH and TCH children have the same mental development and IQ level as controls.[7]

Several studies have assessed the factors that have an impact on the intellectual outcome. For instance, the severity of the disease affects the intellectual outcome.[8] Some authors suggested that a high dose

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of Levothyroxine compared with a low dose treatment is associated with higher IQ scores. On the other hand, the rapid onset of treatment is the most important related factor suggested in other studies.[9]

Animal studies showed that thyroid hormones influence noradrenergic and serotonergic neurotransmission, which play a crucial role in the pathogenesis of depression and anxiety. Increased serotonin levels in the cerebral cortex of rats after T3 administration decreased serotonin synthesis in the brain with hypothyroidism and serotonin inhibitory effect on thyrotropin-releasing hormone (TRH) secretion, suggesting a feedback loop which allows activation of the hypothalamus--pituitary--thyroid axis when serotonin levels in the brain are low.[10] The similarity of symptoms in severely depressed and hypothyroid patients, the therapeutic use of thyroid hormones in the management of depression, and the apparent abnormalities in the hypothalamic--pituitary--thyroid axis of subjects with depression emphasizes this relationship.[11]

An association between thyroid function and depression showed by Saravanan *et al*. found a clear association between higher TSH and lower free T4 and poorer psychological well-being in 697 subjects on thyroxin from the UK.[12]

However, the relationship between anxiety and depression with CH is debatable; one study on CH showed that anxiety and depression, attention problems, mental problems, and aggressive behavior subscale scores were significantly higher in the CH group in which treatment was started at an early age compared with a control group in a child and adolescent sample.[13] More study is needed to draw a definitive conclusion.

This study designed to compare the depression, anxiety, and IQ of CH children diagnosed by the national program of CH screening with a matched control group of classmates in Iran, Isfahan.

Methods

Ethics

The Ethics Committee of Isfahan University of Medical Sciences (Project No. 191107) approved the evaluations and written informed consent was received from all parents after providing sufficient information. Oral assent was obtained from every included child as well.

Selection and description of participants

CH children were selected from Isfahan Endocrine and Metabolism Research Center according to national neonatal screening program in Iran. Children with a history of meningitis, convulsion, major head trauma, severe asphyxia, severe neonatal jaundice, exchange transfusion, genetic syndromes, and chromosomal abnormalities in their medical documents were excluded. Among 122 children who were diagnosed and were managing 97 CH children were selected according to Cochran formula (N = 132, d = 0.05 n = 97) by random sampling; 46 children with PCH and 45 with TCH children were enrolled in this study (n = 91).

Demographic characteristics including age, sex, parent's monthly income and educational degree, the region of school where the child studying in, consanguineous marriage, gestational age at delivery, type of delivery, and history of hospitalization were collected using a designed data collecting form completed by parents. The region of schools was compared and healthy classmates have been selected from the most frequent regions and schools; 44 healthy classmates with normal CH screening matched by age, sex, and socioeconomic status (considered as family income and educational degree) were included as a control group.

CH screening is a routine national program in Iran and in this way a capillary blood sample from heel prick was collected on filter papers (S&S 903) at 3--5 days of age before hospital discharge. Specimens were sent to a regional newborn laboratory for evaluating TSH level using the cutoff value of 5 mu/L.

Those with 5 mu/L < TSH < 9.9 mu/L was reevaluated for TSH level on filter paper within 48 h after the result. Serum TSH, Free T4 or T4, T3RU at 2--3 weeks of age were check for neonates with TSH level higher than 5 in second filter test or screening TSH level between 10 and 19.9 mu/L, those with screening TSH level was greater than 20 call for serum TSH values and initial treatment.

Definitive diagnose of CH was established by serum TSH and T4. For neonates diagnosed as CH, treatment starts with 10 mg/kg/day of sodium levothyroxine. Follow-up to tight control of disease setups was based on laboratory and clinical findings. Children taking treatment by the age of 3 years reevaluate to distinguish between TCH against PCH by stopping taking pills and TSH level monitoring.[14]

Technical information

A professional psychologist who was unaware of the diagnostic category of patients assessed the IQ using Wechsler Intelligence Scale for Children aged 6--16 years (WISC-III) It was assessed without any reading or writing, and takes 65--80 min to complete and represents a child's cognitive ability by measuring two different scores. One includes verbal IQ covering general knowledge, language, reasoning, and memory skills. The other is performance IQ, which covers problem solving, sequencing, and spatial. The Full Scale (total) IQ score was calculated by summing and converting the verbal and performance IQ scores. WISC-III for children has sufficient and satisfied reliability and validity in Persian (reliability coefficients is higher than 0.95).[15]

Depression and anxiety were evaluated using The Children's Depression Inventory (CDI) and the Multidimensional Anxiety Scale for Children (MASC), respectively,[16] by the same psychologist.

CDI is a 27-item, self-rated scale appropriate for children aged 7--17 years, which presents cognitive, affective, and behavioral symptoms of depression and has sufficient and satisfied reliability and validity in Persian (Cronbach's $\alpha = 0/87$).[17]

The MASC is a four-point Likert type self-report scale of anxiety including somatic or autonomic, fears and worries, social fears, behavioral avoidance or approach, and separation anxiety[18] and has been translated and approved in Persian as well (Cronbach and test--retest reliability was 0.79 for the whole questionnaire).[19] All the procedures were done free of any charges, and the children were given gifts at the end of the interview and testing.

Statistics

The SPSS software version 20.0 (SPSS Inc., Chicago IL, USA) was used for data analysis. Descriptive data were shown with mean ± SD (standard deviation) or number (%).

Distributions of IQ scores in all three groups were not normal, according to the Shapiro--Wilk test. Correspondingly, log-transformation was applied, yet the data were not following a normal distribution. Therefore, nonparametric tests (Mann--Whitney) were used to investigate the association between variables. A significant level of less than 0.05 was considered in all analyzes.

Results

Table 1 shows the general and perinatal characteristics of CH and control group. Treatment with levothyroxine had begun for all cases before the 20th day of birth. The mean age was 10 years for three subgroups (P = NS), and no therapy was started after 30 days of age. There was no statistically significant difference in parental consanguinity, maturity at birth, type of delivery, hospitalizations, and mother's age at pregnancy, family child order, and number of children in the family between three groups (data not shown).

The mean TIQ score among PCH, TCH, and control group was 109.4 ± 11.2, 110.5 ± 13.5 and 118.0 ± 11.5, respectively. There was no significant difference in the TIQ, PIQ, and VIQ between PCH and TCH groups (P = NS). However, neither of them had intellectual disability (defined as IQ <7 0).

Table 2 shows a comparison of studied variables between control group and PHC and THC groups, respectively.

The severity of disease (defined by serum TSH levels now of diagnosing) was not associated with TIQ, PIQ, and VIQ (data not shown). There was no relationship between anxiety and depression scores of CH children and their IQ scores (data not shown). Table 3 shows that by considering the severity of disease, we found that there were statistically significant differences between all PCH patient's IQ scores (VIQ, PIQ, and TIQ) and those of controls despite the severity of CH.

For those patients with TCH, Mann--Whitney test showed a significant difference only in mild CH patient's IQ scores with control's ($P < 0.001$, $P = 0.040$, and $P = 0.002$). There was no relationship between anxiety and depression scores of CH children and severity of disease ($P > 0.05$, $P > 0.05$).

Patients aged 13 days or less at the onset of treatment and those with age more are not different in IQ, anxiety,

Table 1: General and perinatal characteristics of PCH, TCH, and control group

Variable		PCH	TCH	Control
Gender, *n* (%)	Girl	22 (47.8%)	20 (44.4%)	23 (52.3%)
	Boy	24 (52.2%)	25 (55.6%)	21 (47.7%)
Parental consanguinity, *n* (%)	Yes	12 (26.1%)	18 (40%)	19 (43.2%)
	No	34 (73.9%)	27 (60%)	25 (56.8%)
Maturity At Birth, *n* (%)	Preterm	8 (17.4%)	7 (15.6%)	3 (6.8%)
	Mature	35 (76.1%)	37 (82%)	39 (88.6%)
	Postdate	3 (6.5%)	1 (2.2%)	2 (4.5%)
Type Of Delivery, *n* (%)	NVD	10 (21.7%)	16 (35.6%)	16 (36.4%)
	C/S	36 (78.3%)	29 (64.4%)	28 (63.6%)
Hospitalizations, *n* (%)	Yes	12 (26.1%)	7 (15.6%)	10 (22.7%)
	No	34 (73.9%)	38 (84.4%)	34 (77.3%)
Age	Mean±SD	10.1±1.4	10.0±1.3	10.3±1.3
Number Of Children in Family	Mean±SD	2.0±0.8	2.1±0.8	2.0±0.9
Family Child Order	Mean±SD	1.6±9.4	1.8±0.9	1.5±0.9
Mothers Age at Pregnancy	Mean±SD	25.1±5.4	26.1±5.2	24.6±4.4
Day treatment Begins	Mean±SD	15.1±12.0	20.6±10.2	-

Descriptive statistic of Multinomial Logistic Regression, PCH=Permanent Congenital Hypothyroid, TCH=Transient Congenital Hypothyroid, NVD=Natural Vaginal delivery, C/S=Cesarean Section

Table 2: The comparison of the control group in some clinical variables with PCH and TCH

Variable	Control	PCH		TCH	
	Median (min-max)	Median (min-max)	*P*	Median (min-max)	*P*
VIQ	122.0 (79.0-131.0)	117.0 (79.0-123.0)	<0.001	106.0 (75.0-125.0)	<0.001
PIQ	118.0 (85.0-131.0)	107 (77.0-124.0)	<0.001	117.0 (75.0-125.0)	0.114
TIQ	121.0 (86.0-134.0)	113.0 (80.0-121.0)	<0.001	111.0 (84.0-130.0)	<0.001
ANX	51.0 (29.0-82.0)	47.0 (29.0-98.0)	0.169	50.0 (21.0-81.0)	0.404
DEP	12.0 (5.0-30.0)	14.0 (2.0-35.0)	0.613	10.0 (2.0-26.0)	0.086

Mann-Whitney Test, PCH=Permanent Congenital Hypothyroid, TCH=Transient Congenital Hypothyroid, VIQ=Verbal Intelligent Quotient, PIQ=Practical Intelligent Quotient, TIQ=Total Intelligent Quotient, ANX=Anxiety, DEP=Depression

Table 3: The comparison of IQ scores between Congenital Hypothyroid children and control group

	Severity of congenital hypothyroidism±	VIQ		PIQ		TIQ	
		Median (min- max)	*P*	Median (min- max)	*P*	Median (min-max)	*P*
PCH	Mild/control	117.0 (79.0-120.0)/*	0.002	108.0 (77.0-120.0)/**	0.008	114.0 (80.0-121.0)/***	0.004
	Moderate/control	117.0 (90.0-120.0)/*	0.020	104.0 (81.0-118.0)/**	0.007	103.0 (88.0-121.0)/***	0.006
	Severe/control	115.0 (95.0-123.0)/*	0.028	107.0 (88.0-124.0)/**	0.018	112.0 (101.0-118.0)/***	0.007
TCH	Mild/control	106.0 (75.0-125.0)/*	<0.001	113.0 (75.0-125.0)/**	0.040	109.0 (84.0-120.0)/***	0.002
	Moderate/control	114.0 (113.0-116.0)/*	0.397	105.0 (85.0-125.0)/**	0.773	113.0 (103.0-124.0)/***	0.591
	Severe/control	125.0 (125.0-125.0)/*	0.756	103.0 (103.0-103.0)/**	0.400	121.0 (121.0-121.0)/***	0.987

Mann-Whitney Test, PCH=Permanent Congenital Hypothyroid, TCH=Transient Congenital Hypothyroid, VIQ=Verbal Intelligent Quotient, PIQ=Practical Intelligent Quotient, TIQ=Total Intelligent Quotient. *122.0 (79.0-131.0). **118.0 (85.0-131.0). ***131.0 (86.0-134.0) ±Mild: neonatal first serum TSH level <50; Moderate: 50< neonatal first serum TSH level <100; and Severe: Neonatal first serum TSH level >100

and depression scores. There was no association between general and perinatal characteristics of CH children and their IQ scores (data not shown).

Discussion

There was no significant difference in anxiety and depression scores between CH children and controls. By Bisachi in Italy, the behavioral scale in CH children using self-reported method was not significantly different with controls, yet parent-reported assessments showed an improved risk of the behavioral problem at school age in CH patients. However, youth with early diagnosing of CH showed more behavioral problem than their age-matched controls.[18] We suggest that the effect of chronic disease as a risk factor for such psychological disorders must be considered. Parents of children with the chronic treatment and follow-up requirement may feel worried or anxious more about every small difficulty their children might have and starting the school may emphasize the problem. It is noteworthy that the condition may lead to complicated relationships and behavioral issues in patients and families.[20] It seems that early and high dose treatment may eradicate many physiological reasons of behavioral problems, but a longitudinal design with multi-factor considerations and a higher number of patients are needed for a definitive conclusion.

Our finding indicated lower IQ scores in children with CH comparing to controls, although all CH patient's IQ scores were within the normal range. Our results are in accordant with many previous studies. In Zurich, Dimitropoulos *et al*. reported that full-scale IQ, PIQ, and VIQ scores of CH children lied in the normal range but significantly lower than in controls.[6] In a study by Ordooei *et al*. mean of IQ scores in all participants were within the normal range yet CH children had lower mean in IQ scores than the control group. More to the point there were no statistically significant differences observed between PCH and TCH mean IQ scores.[6] By the same token, several studies have revealed the significantly lower mean of IQ scores in CH children comparing to controls.[7,21]

In a survey by Maria-Carolina, considerably lower mean IQ levels in both the CH children and their sibling control group were detected, yet no significant difference was found between them. They showed that the low IQ score between CH children was associated with lower familial IQ.[22] Many studies showed no significant relation between CH children intellectual outcome and their sibling controls.[23] Using of sibling controls would account for controlling the genetic influence and environmental factors, and therefore it can be assum that relative low IQ scores in siblings are a considerable factor be taken into account. Although in our study we tried to consider and match the socioeconomic status based on parental occupation and education, which may affect the intellectual outcome,[24] it was found that SES matching is not a good enough method to eliminate the effect of potential confounders related to the intellectual issue. So, further investigations with the association of family IQ were recommended.

Several factors such as age at onset of treatment could affect the intellectual outcome.[25] Van Vliet documented that CH children diagnosed by neonatal screening still

showed a clinically significant intellectual deficit (loss of 6--19 IQ points). Recent studies indicate that this gap may be close by earlier treatment and a higher initial dose of levothyroxine. In recent years of screening era, rapid starting of treatment (2 weeks instead of 4--5 weeks) and a high initial dose (10--15 instead of 5--8 mg/kg/day) were recommended.[8] In the present study, all patients take 10 mg/kg/day of levothyroxine at the onset of diagnosing, and no association was detected between IQ scores of children starting treatment before 13 days of age or at 13--30 days after birth. Many studies in Iran highlight the success of national screening program of neonates for detection and treatment of CH due to the normal range of CH children IQ scores, yet the IQ of CH children is lower than healthy children.[21] Possible explanations for these are race, genetics of children, and familial IQ. The other factors contributing to intellectual outcome must be taken into consideration.

Some studies indicated that severity of CH is one of the significant risk factors for neuropsychological development.[18] The result of the screening program in Berlin stated that early and efficient treatment could normalize the intellectual outcome of patients with CH independent of the severity of disease.[24] Duburis *et al*. have reported that with early treatment and a high initial dose of levothyroxine, the psychomotor development of infants with severe CH is indistinguishable from that of controls.[8] It seems that early and optimal substitution treatment may be able to eliminate the effect of severity of CH on intelligence and CH children intellectually function well within the normal range. Broadly speaking, in the critical ages, careful monitoring and tight dose adjustment is necessary, yet tight controlling and follow-ups do not guarantee counterbalance IQ scores of CH children relative to a healthy control group. Therefore, other factors affecting IQ status have to be considered.

There are some major limitations in this study that could be addressed in future researches. Insufficient sample size for statistical measurement in order to conclude a valid research result was an important limitation. Moreover, the effect of chronic illness on children's intelligence, anxiety, and depression which could act separately from CH must be considered.[26] In this study, comparing the affected children with normal controls eliminates the chance of comparing the variables between two chronically affected children groups with different disease which future studies can focus on it.

Conclusions

In our study, there was no significant difference in anxiety and depression scores between CH children and controls, although IQ scores in children with CH were lower than controls but were within the normal range.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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