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ORIGINAL ARTICLE

Growth development in children with congenital hypothyroidism: the effect of screening and treatment variables—a comprehensive longitudinal study

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Abstract Investigating the screening and early treatment factors potentially affects the growth status of the patients with congenital hypothyroidism. In a longitudinal study, 760 (45 % girl) neonates born in 2002–2009 with congenital hypothyroidism diagnosed by neonatal screening in Isfahan–Iran were followed up to 5 years from the time of diagnosis (i.e., 3–4 records for the first year of age and 2–3 records after that). During follow-up, height, weight, and head circumferences of the patients were measured. Diagnostic and therapeutic factors included serum thyroxine and thyroid stimulating hormone concentration at diagnosis and after treatment initiation, the age at onset of treatment, the first therapeutic dosage, and age at first normalization of thyroxine and thyroid stimulating hormone. Quantile regression for longitudinal data was used for determining the effects of main factors on growth development. Longitudinal growth in height and weight was significantly correlated with the age at onset of treatment and the first therapeutic dosage ($p < 0.01$), while head circumference only with first therapeutic dosage ($p < 0.05$). Growth in weight and head circumference was affected by thyroid stimulating hormone at the time of diagnosis ($p < 0.05$). Also the age of thyroxine normalization had heterogeneous significant impact over the proposed quantiles on weight ($p < 0.05$), height ($p < 0.01$), and head circumference ($p < 0.001$). Among studied factors, the first therapeutic dosage, age at onset of treatment and age of thyroxine normalization seem to be more important for anthropometric development, suggesting that more optimal outcome might be achievable through earlier treatment and appropriate levothyroxine dosage.

Keywords Congenital hypothyroidism · Neonatal screening · Growth · Height · Weight · Head circumferences

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Introduction

Congenital hypothyroidism (CH) is considered as a major treatable cause of mental retardation and growth impairment in newborns [1, 2] and its prevalence varies depending on several factors such as method of screening, gender, birth weight, ethnicity, age, consanguinity, gestational age, parental education, type of labor, birth order, and etc [3]. The incidence of CH is reported as 1:2,000 to 1:4,000 live births in iodine sufficient countries [4, 5] and in different districts of Iran, varies in the range 1–3.4 per 1000 [6, 7].

Most neonates with CH are normal at birth and show no signs and symptoms; however, studies conducted on the follow-up of these patients showed that delay in diagnosis

and late or no treatment may lead to deficits in physical development with incomplete catch-up growth besides seriously well-known neurologic impairments such as mental retardation, poor motor coordination, ataxia, spastic diplegia, muscular hypotonia, strabismus, learning difficulties, and attention deficit disorders [2, 3]. If treatment begins within 2 weeks of age, it leads to normalize physical and cognitive development; accordingly, neonatal thyroid screening programs are performed in many countries, such as Iran, for early diagnosis and treatment of hypothyroid patients [1, 6]. CH screening was started from 2002 in Isfahan as a pilot study, which continued till 2005 and because of its high prevalence in this region, it was adapted as a nationwide screening program in Iran and is continuing until now [3, 8].

There are controversial findings about growth of neonates with CH. Some studies indicated that early treatment leads to normal growth, whereas others did not indicated the same results [9, 10]. It is believed that many factors including screening time, the first dosage of levothyroxine, age of TSH normalization, and disease severity might influence the catch-up growth of neonates with CH [11, 12].

Growth evaluation of CH patients and its related factors has performed in a few studies in Iran, and most of them have evaluated the neurocognitive impairments in CH patients [3, 13–15]. This is while, physical deficits are as important as intellectual disability caused by CH, and they affect untreated patients future life. Given the high prevalence of CH in Iran and particularly in Isfahan, the aim of the current study was to determine the effects of screening program and treatment variables on growth status of CH patients in them of anthropometrics measures using longitudinal quantile regression model for the first time in Iran.

Materials and methods

Study design and participants

In this longitudinal study, 760 (45 % girls) congenitally hypothyroid neonates diagnosed during CH screening program (2002–2009) in Isfahan province, Iran and referred to Isfahan Endocrine and Metabolism Research Center for treatment, who satisfied the inclusion criteria, were enrolled and followed up. CH patients with concomitant diseases or complications such as prematurity, IUGR, genetic disorders (such as Down syndrome), and congenital malformations were excluded. Patients with no data or obvious errors in their demographic information and anthropometric measurements were excluded, too. Totally, among 924 CH patients, 760 were studied. Congenitally hypothyroid neonates with different age-sex combinations were followed from the time of diagnosis, so that the entry time of each patient was different from the other included participants. Among these patients, 65 children were born in 2002, 96 in 2003, 84 in 2004, 78 in 2005, 113 in 2006, 123 in 2007, 111 in 2008, and 90 in 2009. In the present study, duration of follow-up for CH patients, depending on their birth year, was at least 1 and up to 5 years. All parents of CH patients agreed to participate in the study and the Ethics Committee of Isfahan University of Medical Sciences approved the study protocol (research project number: 290217).

Measurements

Screening program for congenital hypothyroidism in Isfahan

In this program, which was initiated in May 2002, all infants who were born in 17 different hospitals and maternity wards (public–private) were referred to the Isfahan (Iran) Endocrine and Metabolism Research Center for screening. Venous blood samples were taken on the day of referral (3rd–7th day of birth), by trained nurses, from the cubital vein. A pediatric endocrinologist and collaborating general practitioners evaluated the laboratory results and the medical file of each newborn consists of gestational age, sex, anthropometric measures, and date of birth. After physical examination and lab evaluation, the neonates who needed to be recalled were determined. Serum concentrations of thyroxine (T4) and thyroid stimulating hormone (TSH) were measured by radioimmunoassay and immuneradiometric assay, respectively, using Kavoshyar (Iran–Tehran) kits. Thyroid function tests were performed by Berthold-LB2111 unit gamma counter equipment using serum samples. The sensitivity of the T4 and TSH tests were 0.38 µg/dl and 0.05 mIU/L, respectively. During this period, term neonates weighing more than 2500 g with TSH > 20 mIU/L or a T4 < 6.5 µg/dL were recalled. For immature infants, the recall was based on the elevated TSH to the age of newborns and the lowered T4 to the weight of newborns. Beyond day 7, neonates with TSH > 10 were recalled again and those with abnormal T4 and TSH levels on their second measurements (between days 7 and 28 with TSH > 10 mIU/l and T4 < 6.5 µg/dl) were diagnosed as CH patient [16–18]. In both preterm and full-term neonates whose T4 measurements were low according to their weight [19], further tests including T3 resin uptake and free T4 index were performed, and abnormal results were identified. Then, treatment was started after confirming hypothyroidism. Hypothyroid neonates underwent treatment within 15–30 days with LT4 at a single dose of 10–15 µg/kg/day as soon as the diagnosis was confirmed, and were followed regularly. Monitoring of TSH and T4 was done every 1–2 months during the first year of life and every 1–3 months during the second and third years.

Cases of permanent and transient congenital hypothyroidism were determined at the age of 3 years by measuring TSH and T4 concentrations 4 weeks after the withdrawal of LT4 therapy. Children with normal TSH level (TSH < 10 mIU/l) considered as transient CH and patients with elevated TSH levels (TSH > 10 mIU/l) and decreased T4 levels (T4 < 6.5 μg/dl) were diagnosed as permanent CH (PCH) sufferers. Then, treatment processes were continued for PCH children.

Thyroid scanning and/or ultrasound was performed before starting treatment in the neonatal period or at the age of 3 years after confirming the permanency of CH. In cases where the scan was performed after treatment, or the results of scan and the follow-up data not compatible it was repeated. In some cases parents did not give permission to perform of scanning at birth, so it was performed at 3 years old. The etiology of CH among PCH patients was also determined [8, 20].

For evaluating the impact of different variables on outcome anthropometric measures during the follow-up period; serum T4 and TSH concentration at diagnosis and after treatment initiation, the age at onset of treatment (early, ≤ 30 days or late, > 30 days), the first dosage of levothyroxine (low, < 33.33 μg/day or high, ≥ 33.33 μg/day), and age at first normalization of T4 and TSH (normT4 and norm TSH, in months) were recorded. More details about diagnosis criteria over the screening program can be found elsewhere [3, 6, 8].

Anthropometric measurements

At baseline (birth) and during each follow-up time point, in addition to evaluating thyroid function tests, anthropometric evaluation of CH patients was done by measuring length/height, weight, and head circumference. Supine length until the age of 2 years (before walking) and then standing height were measured without shoes by using a tape meter against a wall with a precision of 10 mm. Patients' weight was measured to the nearest 10 g on an electronic scale that was placed on a flat ground and subjects were motionless and wearing light clothing. Head circumference was measured using a non-elastic tape with a precision of 10 mm. At each follow-up all these parameters were measured in the same scale. Anthropometric measurements were obtained by a trained endocrine nurse specialist at each clinic visit.

Statistical analysis

In longitudinal studies, measurements of the same subject are assessed repeatedly to characterize the changes in response over time and the factors that influence these changes. [21]. In current study, advanced statistical method, i.e., quantile regression for longitudinal data was used for investigating the effects of main factors determining the growth development and providing empirical evidence of effects heterogeneity depending on patient location on the distribution of growth status. In quantile regression, unlike linear regression, the effect of the predictor variables on the dependent variable is going to be evaluated separately in different quantiles. Such model enables the investigator to explore various forms of heterogeneity associated with the covariates under less stringent distributional assumptions [22, 23]. Thus, in the current study, this method provides comprehensive perspective on how various diagnosis and treatment factors of CH patients affect the growth status of subjects (anthropometric measurements) in different quantiles. The included empirical percentiles were the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th for each anthropometrics variable. We modeled the relation between interest factors and responses variables during 3–4 records for the first year and 2–3 records after 2 years of age. All model estimation was performed in R free statistical software version 3.2.2 by means of the following model specific function: rq from package quantreg for distribution free quantile regression [24].

Results

In this longitudinal study, 760 CH patients consisting of 345 girls (45 %) and 415 boys (55 %) were evaluated. Mean age of starting treatment was 23.5 ± 18.7 days. In 82.7 % of patients, treatment was begun before the 30th day of life and remaining after that. Of CH patients, 55.7 % were determined as permanent CH and remaining was diagnosed with transient CH. The mean starting dosage of levothyroxine was 35.4 ± 9.6 μg/day. Tables 1–3 present the quantile regression estimates to evaluate the effects of different predictors on the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles of height, weight, and head circumference of CH patients.

The association between "age and baseline of height, weight and head circumference" with all three response variables were highly positive and significant ($p < 0.01$). Also, height, weight, and head circumference of boys were significantly higher than girls in all percentiles ($p < 0.01$).

The quantile estimates indicated that "the first dosage of levothyroxine (LT4)" had strong, positive and significant effects on the distribution of height, weight, and head circumference of CH patients ($p < 0.01$). In other words, based on our results, height, weight, and head circumference of those patients whose first dosage of levothyroxine had been greater than or equal to 33.33 (μg/day) were more than those whose first dosage of LT4 was less than 33.33 (μg/day) ($p < 0.01$). The magnitude of the effects increases when one moves from lower percentiles to higher percentiles of the conditional head circumference distribution (Figs. 1–3).

Table 1 Quantile regression estimates of predictor variables for height (cm)

Predictor variables	Percentile													
	3rd		10th		25th		50th		75th		90th		97th	
	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value
Intercept	35.685	12.396***	37.049	19.711***	39.215	24.362***	42.266	26.011***	43.899	23.381***	43.911	19.757***	48.780	16.058***
Age	0.895	71.611***	0.892	93.840***	0.889	100.242***	0.895	89.922***	0.926	75.823***	0.961	65.625***	0.976	53.574***
Baseline height (cm)	0.350	5.888***	0.371	10.059***	0.364	12.073***	0.341	10.979***	0.339	9.699***	0.368	9.010***	0.303	5.152***
Sex (Reference: girl)	1.285	2.803***	1.317	4.310***	1.171	4.471***	1.301	6.157***	1.274	4.363***	0.816	2.434**	1.014	1.824*
Serum T4 concentration at diagnosis (μg/dl)	0.041	1.334	0.031	2.142**	0.009	0.827	0.019	1.739*	0.011	0.757	0.003	0.217	0.008	0.341
Serum TSH concentration at diagnosis (mIU/l)	−0.004	−1.415	−0.003	−1.085	−0.001	−0.347	0.001	0.446	0.001	0.670	0.001	0.247	0.000	−0.045
Serum T4 concentration after treatment initiation (μg/dl)	−0.006	−0.280	−0.011	−0.952	−0.001	−0.096	−0.001	−0.196	−0.004	−0.622	−0.008	−1.684*	−0.018	−1.856*
Serum TSH concentration after treatment initiation (mIU/l)	0.151	0.941	0.189	1.685*	0.024	0.231	−0.012	−0.145	0.093	1.001	0.162	1.211	0.170	1.159
The age at onset of treatment (Reference: ≤ 30 days)	−1.101	−1.825*	−1.397	−3.220***	−1.532	−3.526***	−1.260	−3.847***	−1.203	−3.192***	−0.803	−1.761*	−1.981	−3.116***
The first dosage of levothyroxine (Reference: < 33.33 μg/day)	1.242	1.913*	0.845	2.231**	1.146	3.498***	1.196	4.190***	0.995	2.951***	0.866	1.658*	1.713	2.457**
Age of T4 normalization	−0.001	−0.140	−0.003	−0.828	−0.005	−1.693*	−0.005	−2.127**	−0.007	−2.049**	−0.007	−1.784*	−0.006	−0.939
Age of TSH normalization	−0.004	−0.938	0.000	0.030	0.002	0.555	−0.001	−0.317	−0.002	−0.655	−0.003	−0.782	−0.001	−0.277
Type of thyroid dysfunction (Reference: transient)	−0.004	−0.009	−0.772	−2.201**	−0.379	−1.374	−0.576	−2.480**	−0.493	−1.794*	−0.269	−0.825	−0.201	−0.422

*** $P < 0.01$; ** $P < 0.05$; * $P < 0.1$

Table 2 Quantile regression estimates of predictor variables for weight (cm)

Predictor variables	Percentile													
	3rd		10th		25th		50th		75th		90th		97th	
	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value
Intercept	3078.160	6.884***	4137.100	17.854***	4642.030	24.647***	5168.520	27.181***	5571.300	25.487***	5795.440	20.283***	5822.590	13.285***
Age	181.040	36.988***	177.740	59.428***	179.030	67.395***	185.790	52.149***	200.040	54.111***	217.620	50.971***	237.720	45.380***
Baseline height (cm)	0.290	3.221***	0.210	3.769***	0.220	4.291***	0.220	4.353***	0.210	3.407***	0.230	3.007***	0.270	2.559**
Sex (Reference: girl)	905.870	5.837***	793.890	8.710***	862.330	11.159***	765.310	10.860***	726.100	8.022***	655.680	6.277***	797.890	5.298***
Serum T4 concentration at diagnosis (μg/dl)	1.610	0.233	−1.870	−0.429	−2.280	−0.742	−2.730	−1.167	−1.020	−0.254	−3.790	−1.005	−7.560	−2.419**
Serum TSH concentration at diagnosis (mIU/l)	0.980	0.708	2.120	2.116**	1.800	2.899***	2.180	4.343***	2.260	3.871***	1.570	2.485**	0.980	1.037
Serum T4 concentration after treatment initiation (μg/dl)	−1.760	−0.236	0.520	0.122	1.760	1.241	0.280	0.233	−0.090	−0.050	−1.390	−0.927	−2.110	−1.695*
Serum TSH concentration after treatment initiation (mIU/l)	−5.570	−0.075	16.780	0.410	14.790	0.435	19.930	0.628	1.070	0.032	1.600	0.051	63.240	1.054
The age at onset of treatment (Reference:≤ 30 days)	−610.360	−2.965***	−494.660	−3.158***	−432.730	−3.321***	−322.650	−3.444***	−472.810	−4.291***	−608.600	−4.770***	−693.680	−2.869***
The first dosage of levothyroxine (Reference: < 33.33 μg/day)	719.210	3.407***	610.360	4.490***	619.920	5.051***	583.050	5.401***	724.420	5.403***	676.740	4.356***	745.980	3.566***
Age of T4 normalization	−1.070	−0.781	−1.530	−1.591	−2.620	−4.007***	−3.160	−7.034***	−3.120	−5.451***	−2.500	−2.984***	−1.970	−1.535
Age of TSH normalization	2.400	1.428	1.340	1.202	1.500	1.682	1.100	1.605	1.060	1.225	0.970	1.078	0.200	0.151
Type of thyroid dysfunction (Reference: transient)	−161.950	−0.977	−142.370	−1.356	−126.710	−1.568	−190.930	−2.771***	−243.640	−3.092***	−215.960	−2.498**	−175.910	−1.281

*** $P < 0.01$; ** $P < 0.05$; * $P < 0.1$

Table 3 Quantile regression estimates of predictor variables for head circumference (cm)

Predictor variables	Percentile													
	3rd		10th		25th		50th		75th		90th		97th	
	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value
Intercept	32.976	21.166***	32.089	26.718***	34.063	33.560***	35.959	34.848***	38.573	37.084***	39.851	34.490***	40.460	28.638***
Age	0.268	38.741***	0.253	60.760***	0.241	56.239***	0.227	55.578***	0.213	47.402***	0.200	33.445***	0.213	30.151***
Baseline height (cm)	0.136	3.043***	0.192	5.516***	0.164	5.763***	0.143	5.056***	0.101	3.597***	0.095	2.879***	0.087	2.145**
Sex (Reference: girl)	1.350	7.348***	1.359	10.914***	1.412	12.640***	1.468	12.783***	1.603	13.932***	1.432	10.107***	1.399	9.611***
Serum T4 concentration at diagnosis (μg/dl)	0.004	0.383	0.001	0.257	0.001	0.106	0.001	0.151	0.001	0.232	−0.002	−0.419	−0.004	−0.789
Serum TSH concentration at diagnosis (mIU/l)	0.003	1.187	0.004	4.632***	0.004	5.188*	0.004	5.541***	0.003	4.023***	0.003	3.667***	0.003	3.628***
Serum T4 concentration after treatment initiation (μg/dl)	−0.006	−0.685	0.001	0.137	0.000	0.010	−0.003	−0.589	−0.001	−0.282	−0.001	−0.433	−0.002	−1.079
Serum TSH concentration after treatment initiation (mIU/l)	0.085	1.425	0.048	1.225	0.024	0.780	0.025	0.736	0.031	0.771	0.006	0.143	0.019	0.389
The age at onset of treatment (Reference: ≤ 30 days)	−0.413	−1.380	−0.407	−1.946*	−0.257	−1.825*	−0.348	−2.627***	−0.372	−2.468**	−0.192	−0.970	−0.356	−1.739*
The first dosage of levothyroxine (Reference: < 33.33 μg/day)	0.798	2.854***	0.688	4.276***	0.725	4.421***	0.848	5.409***	0.815	5.434***	0.987	5.415***	1.040	6.317***
Age of T4 normalization	−0.005	−1.501	−0.005	−2.912***	−0.006	−4.143***	−0.005	−4.176***	−0.006	−4.423***	−0.007	−4.840***	−0.008	−4.988***
Age of TSH normalization	0.002	0.942	0.002	0.860	0.002	1.414	0.001	0.677	0.001	0.642	0.001	1.045	0.001	0.825
Type of thyroid dysfunction (Reference: transient)	−0.098	−0.470	−0.054	−0.378	0.002	0.022	0.046	0.442	0.050	0.477	0.006	0.049	0.061	0.428

*** $P < 0.01$; ** $P < 0.05$; * $P < 0.1$

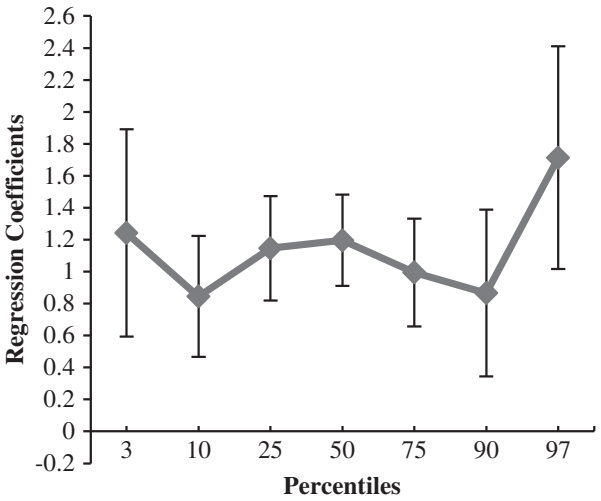

Fig. 1 The effect of "The first dosage of levothyroxine (LT4)" across percentiles of the CH patients' height

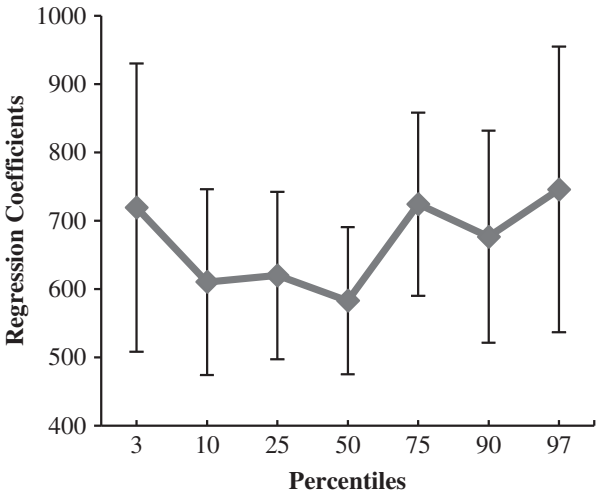

Fig. 2 The effect of "The first dosage of levothyroxine (LT4)" across percentiles of the CH patients' weight

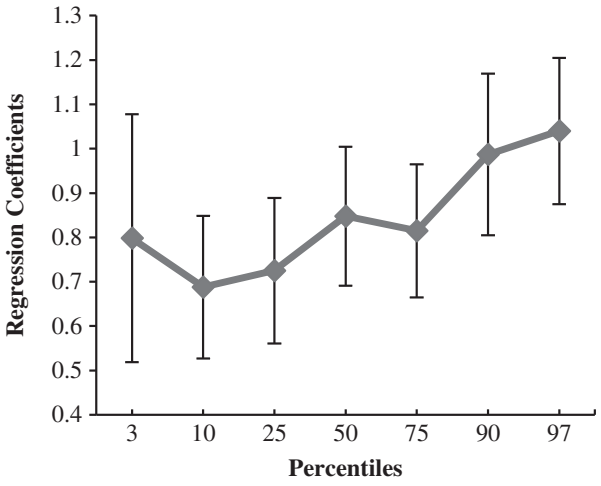

Fig. 3 The effect of "The first dosage of levothyroxine (LT4)" across percentiles of the CH patients' head circumference

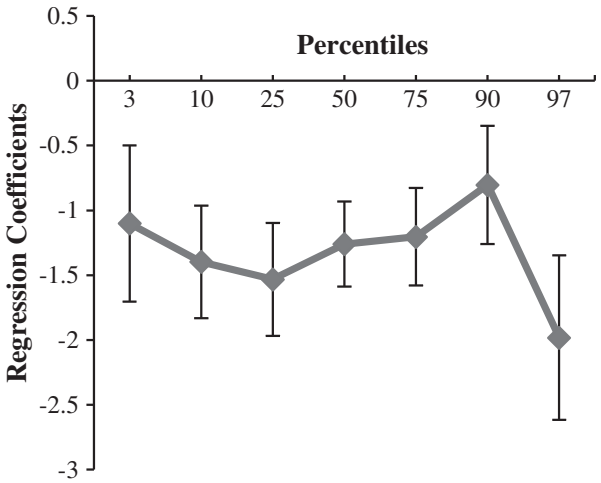

Fig. 4 The effect of "The age at onset of treatment (days)" across percentiles of the CH patients' height

The coefficients of "the age at onset of treatment" were highly negative and significant for all percentiles in distribution of the patients' weight and height ($p < 0.05$). In other words, the weight and height of patients whose age at onset of treatment was greater than 30 days were significantly lower than those participants with onset age of therapy was less than 30 days ($p < 0.05$). The same picture was observed for all percentiles of the patients' head circumference, too ($p < 0.05$). (Figs. 4–6)

Other significant predictors for height were "type of thyroid dysfunction and age of T4 normalization" (Table 1). The type of thyroid dysfunction had only significant negative effects on height at "10th, 50th, and 75th" percentiles ($p < 0.05$). In other words, the height of patients with transient CH was significantly higher than PCH. The coefficients of "age of T4 normalization" were negative for all percentiles of the patients' height distribution (Fig. 7). In other words, based on our findings, it is expected that the more the delay in "T4 normalization", the shorter the final height of patients. However, only at the median of the height distribution, a significant association was observed ($p < 0.05$).

The coefficient of "serum TSH concentration at diagnosis" was negative and it was statistically insignificant at lower percentiles of the height distribution. This implies that for a patient whose height is below the median, an increase in serum TSH concentration at diagnosis is accompanied by a significant decrease in height. On the other hand, serum T4 concentration at diagnosis had significant effects at 10th and 50th quantiles ($p < 0.05$). At the 10th percentile, serum

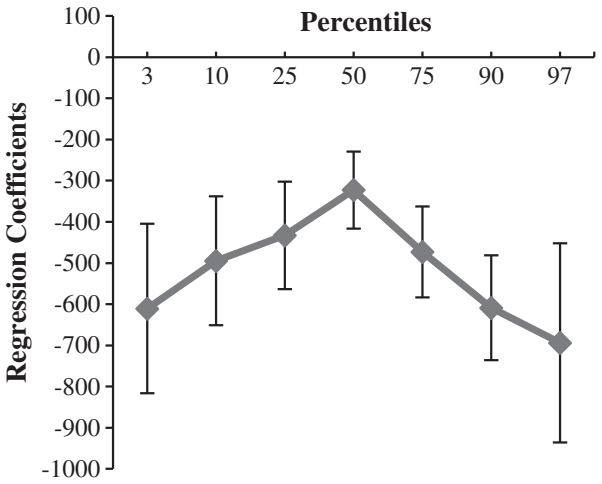

Fig. 5 The effect of "The age at onset of treatment (days)" across percentiles of the CH patients' weight

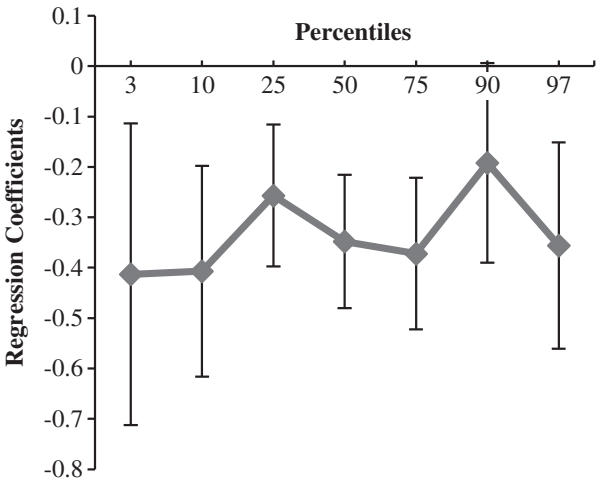

Fig. 6 The effect of "The age at onset of treatment (days)" across percentiles of the CH patients' head circumference

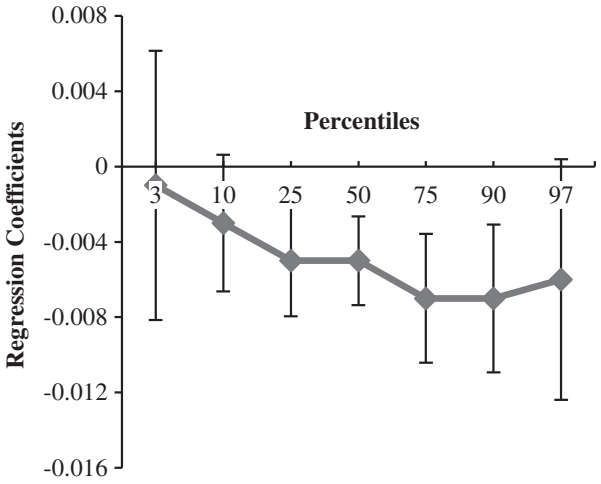

Fig. 7 The effect of "Age of T4 normalization" across percentiles of the CH patients' height

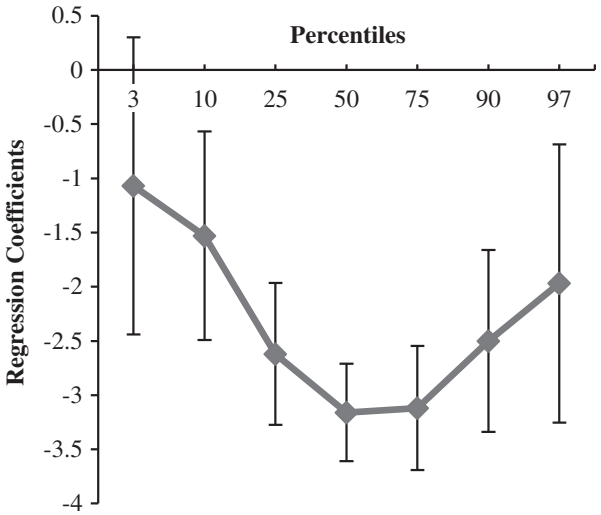

Fig. 8 The effect of "Age of T4 normalization" across percentiles of the CH patients' weight

TSH concentration after treatment initiation and at the 90th and 97th quantiles, serum T4 concentration after treatment initiation were marginally associated with increment in height ($p < 0.1$). There is no clear impact of serum TSH concentration on the various percentiles of the height distribution after treatment initiation (the positive and negative coefficients).

The effect of "age of TSH normalization" was negative but insignificant at almost all percentiles of patient's height, except 10th and 25th percentiles. In contrast, the coefficient of "age of TSH normalization" was positive but non-significantly associated with weight and head circumference distributions.

According to Table 2 and Fig. 8, it appears that "age of T4 normalization and type of thyroid dysfunction" had relatively large negative effects on weight at the median and upper percentile of distribution. Type of thyroid dysfunction had a negative strong association with weight at 50th, 75th, and 90th percentiles ($p < 0.05$). Our findings imply the achievement of weight for patients with transient thyroid disorders have been higher than patients with permanent thyroid disorders.

Different from height, the effect of "serum T4 concentration after treatment initiation" was more heterogeneous across quantiles of weight and head circumference distributions. In particular, patients seem to be affected by "serum T4 concentration after treatment initiation" at 97th percentile of weight distribution ($p < 0.1$), while this effect was not statistically significant in other quantiles (Table 2).

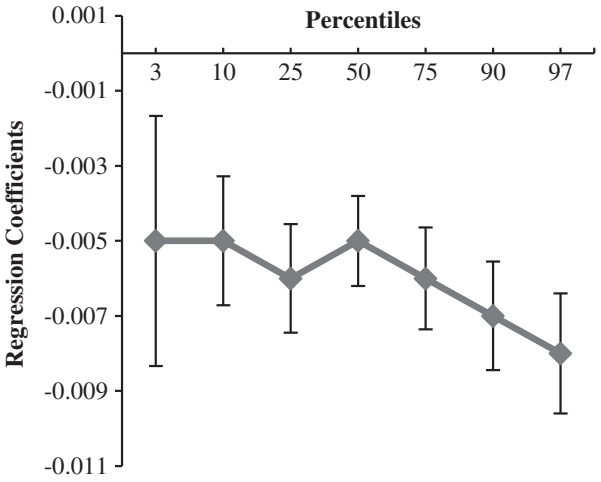

Fig. 9 The effect of "Age of T4 normalization" across percentiles of the CH patients' head circumference

The coefficients of "serum TSH concentration at diagnosis" were strong, negative and significant in most of the percentiles of patients' weight distribution ($p < 0.05$). In other words, based on our findings, it is expected that increasing of "serum TSH concentration at diagnosis" is associated with a significant increase in weight for CH patients. Similar results were also obtained about head circumference.

According to Table 3 and Fig. 9, the effect of "age of T4 normalization" on the distribution of head circumference was negative and statistically significant ($p < 0.01$). In other words, based on our findings, it is expected that the lower of "age of T4 normalization" is associated with a significant increase in head circumference ($p < 0.01$). The impact's estimates for the type of thyroid dysfunction on head circumference were insignificantly negative at 10th percentile and insignificantly positive at 25th percentile and upper. Finally, "serum TSH concentration at diagnosis" had a significant association with head circumference at all percentiles except in the 3rd percentile ($p < 0.01$).

Discussion

In current comprehensive longitudinal study, the effect of treatment and timing factors on growth development of CH patients, diagnosed during the CH screening program and followed up from 2002 to 2009, using an advanced statistical model, i.e., quantile regression models for longitudinal data, was investigated. This modeling approach enables us to achieve more comprehensive picture about the effects of various predictors of height, weight, and head circumference of CH patients in their different percentiles of distribution.

Although several studies have reported that the majority of CH patients detected by neonatal screening had normal growth and it is well known that growth retardation is prevented by early detection and treatment of CH [3, 12, 17, 25, 26], Grant reported that catch-up growth of the CH patients depends on many factors such as age of treatment, dosage of treatment, and the severity of the disorder [3, 12]. The results of the current study indicated that longitudinal growth in height and weight was significantly associated with the "the age at onset of treatment and the first dosage of levothyroxine" in all percentiles, while head circumference was only associated with the first dosage of levothyroxine. Recent data clearly indicate that patients with CH diagnosed by neonatal screening and promptly treated with a sufficient large LT4 daily dose grow normally and attain normal adult height [18, 27, 28]. In Brook's study, it was mentioned that a high initial dose of LT4 in the treatment of CH could cause an increase in caloric intake that results in acceleration of growth [29]. Some studies showed that by the age of 3–4 years, stature became normal in children with early treated congenital hypothyroidism [12, 16]. The results of Chiesa et al.'s study indicated that the initiation of treatment in CH patients as late as 24 months corrects the short stature and delayed bone age by age 5 years [30, 31]. However, Delvecchio et al. showed that the daily LT4 requirement progressively decreases during the follow-up, irrespective of etiology; reflecting a decreasing need of thyroxine with growth [32]. Some studies reported that delayed height growth improves during treatment, which was also dependent on the dose of LT4 and the age at onset of treatment [33, 34]. For instance, in Morin et al.'s study, the children had a high initial dose of LT4, but they showed a lower height at 1 year of age and reached normal height value at 3 years of age [34]. Based on our results, the weight and height of patients whose age at onset of treatment was less than or equal to 30 days had been significantly higher than others. Moschini et al.'s study reported that CH patients reached normal height at 6 years of age if treatment initiation would be in 33 days after birth [25]. In accordance with our results, Heyerdahl and colleagues in their study on linear growth of early treated CH patients concluded that childhood growth impairment associated with the age at onset of treatment and initial LT4 dose [10]. However, the findings of Delvecchio et al.'s study suggest that earlier diagnosis and replacement therapy do not significantly modify final height in CH patients [35]. In Adachi et al.'s study, no significant relationship was observed between the final height standard deviation score (FHSDS) with the current LT4 dose and the date of initiation of LT4 therapy, too [33]. Salerno et al. confirmed that adult height is not correlated with the severity of CH at diagnosis, the initial LT4 dosage or the etiology of the defect [36]. Results of aforesaid studies [36] indicated that

high LT4 starting doses rapidly normalized serum TSH concentrations even in patients with severe CH at diagnosis but growth and bone age maturation were not affected by such a high dose. In Darendeliler et al.'s study, no significant correlation was found between height at all ages and the initial dosage of LT4 [9]. Only at the age of 2 years there was a significant positive correlation between height and serum T4 levels measured up to that age [9]. The doses used in this study were in the lower limits of the recommended dose ranges [9]. The results of Jones et al. confirmed our findings [37].

We found that height, weight, and head circumference of boys were significantly higher than girls in all percentiles. Results of Morin et al.'s study indicated that girls tend to be longer than boys at all ages, but the difference was significant only at age of 6 months. Also, the aforesaid study showed that boys had some delay in growth during the first year of life [34]. The difference between males and females in growth, particularly in physical development, may be attributed to socioeconomic status of different communities and likely much attention and care to male gender in developing countries.

In our study, growth in weight and head circumference were affected by serum TSH concentration at diagnosis, but these parameters were not affected by serum T4 concentration at diagnosis. Also, the age of T4 normalization had heterogeneous impact on weight, height, and head circumference over the proposed quantiles, but the age of TSH normalization, did not have significant effect on growth status of CH patients. Several studies have reported findings about the influence of hypothyroidism and hormonal patterns on intellectual outcome in CH patients [38, 39]. However, a few studies have been performed regarding the influence of these factors on the catch-up growth of the CH patients. Ng and colleagues in the United Kingdom studied the head circumference and linear growth of 125 patients with CH from diagnosis up to 3 years of age [40]. In contrast with our findings, they found that initial confirmatory T4 at diagnosis is an independent factor influencing head circumference's growth in the first 3 years of life [40]. We found no correlation between height and age of TSH normalization, but Bain and Toublanc reported that age of TSH normalization is significantly delayed in patients with a shorter final height than the standard height [11]. They also found that the main factors for a taller height in adulthood were the age at the start of treatment and compliance with treatment [11]. In our study, there were positive correlations between growths in weight and head circumference and serum TSH concentration at diagnosis. However, Adachi and colleagues in their study on growth follow-up investigating the final heights and pubertal growth patterns of 27 CH patients have found no significant association between the FHSDS and the initial TSH value [33].

Study strengths and limitations

It is important to recognize some strengths as well as potential limitations of the present study. The current longitudinal study can be considered as the first comprehensive study to investigate the effect of treatment and timing factors on growth development of the patients with CH in Iran by using an advanced statistical model, i.e., longitudinal quantile regression model. This advanced statistical method enables us to achieve more comprehensive pictures about the effects of different predictors of weight, height, and head circumference on patients with CH. However, our study had some limitations. Hormonal assay was conducted at specific ages that it was better to assess their effects in different ages in order to increase the accuracy of the results. Longitudinal nature of the study led to lack of data in some follow-up time points and missing data. Also, we did not have information about the anthropometric indices of parents; therefore we could not adjust their impact as confounding variables.

Conflicting evidences are available about the impacts of starting dosage of LT4 and timing of TSH normalization on anthropometrics growth in patients with CH, detected by neonatal screening; some studies suggest that the amount of replacement LT4 received during first 3 years of life, particularly in the first 6 months of life, may strongly influence the attainment of normal catch-up growth and a predictor of future requirements [28, 32], and some others suggest lack of relationship [35, 41], therefore incorporating data about LT4 dosage and TSH levels over the follow-up as a time varying covariates and possible interaction between these variables, as well as their interaction with CH severity in the used model in our study could increase reliability of findings; however we did not have data about LT4 requirement and serum's TSH levels during the follow-up.

Concluding remarks

In summary, the findings of our study showed that among studied factors, the first dosage of LT4 and the age at onset of treatment seem to be more important factors for growth development, suggesting that more optimal outcome might be possible through earlier treatment and appropriate LT4 dosage. The early treatment of CH patients leads to improving growth outcomes and proved the efficacy of the screening programs as a tool to achieve better growth in these children.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethical approval After explaining all aspects of study propose for who met the inclusion criteria; a written informed consent was

obtained from all parents of CH patients agree to participate in our study. Regional bioethics committee of our university approved the study protocol.

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