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ORIGINAL PAPER

Subclinical hypothyroidism in children with well-controlled epilepsy

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ABSTRACT

Introduction: Epilepsy and epileptic syndromes are common in children. Frequent seizures have a great negative impact on the quality of life in children and their families, and many children with epilepsy need anticonvulsive therapy.

Aim of the study: Despite reducing seizure frequency, anticonvulsive therapy has many complications. Subclinical hypothyroidism has been argued in children with epilepsy as a complication of anticonvulsive therapy and has been proposed as a risk factor for long-term cardiovascular problems. We aimed to determine the relative frequency of subclinical hypothyroidism in children with well-controlled epilepsy.

Material and methods: In a prospective cohort, we assessed subclinical hypothyroidism in 228 children with epilepsy, who were treated with sodium valproate (n = 93), carbamazepine (n = 76), and phenobarbital (n = 59) as monotherapy and compared them with 100 age- and sex-matched healthy children as controls. We defined subclinical hypothyroidism as serum TSH level more than 3.8 μIU/ml and normal serum T4 level.

Results: According to the definition, subclinical hypothyroidism was significantly more frequent in children with epilepsy than in healthy controls. Subclinical hypothyroidism was found in 25 (26.8%) children in the sodium valproate group, 15 (19.7%) in the carbamazepine group, and 13 (22%) in phenobarbital group, but only in four (4%) children in the control group.

Conclusions: These results indicate that in children with epilepsy, who were treated by one of the following: carbamazepine, sodium valproate, or phenobarbital, as monotherapy, subclinical hypothyroidism could occur frequently. Monitoring of thyroid function using T4 and TSH serum level should be considered in these children during anticonvulsive therapy. However, long-term effects of anticonvulsive medications on thyroid function need well-designed, prolonged cohort studies.

KEY WORDS:

children, epilepsy, subclinical hypothyroidism, anticonvulsive therapy.

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INTRODUCTION

Epilepsy is one the most common neurologic disorders in children. Children with infrequent seizures have a better quality of life; therefore, many children with epilepsy need treatment with anticonvulsants to reduce seizure recurrence. First- and second-generation anticonvulsants such as phenobarbital, carbamazepine, and sodium valproate are among the most common anticonvulsants that physicians administer in children with epilepsy. Unfortunately, despite favourable outcomes such as reducing seizure frequency, these anticonvulsants have many adverse side effects. One of the most frequently discussed adverse effects after anticonvulsive administration is thyroid function disturbances and probable subclinical hypothyroidism [1–11].

Subclinical hypothyroidism has been defined by increased thyroid-stimulating hormone (TSH) serum levels while serum levels of T4 and T3 are normal. Subclinical hypothyroidism could lead to long-term complications such as cardiovascular problems. According to this evidence, some of the investigators claimed to find and, if required, to treat subclinical hypothyroidism in patients with chronic conditions to prevent such long-term complications [12–14].

In our country, Iran, many paediatricians and child neurologists administer phenobarbital, carbamazepine, and sodium valproate to manage children with epilepsy. To our knowledge, no study with an acceptable sample size has been conducted to evaluate subclinical hypothyroidism in children with epilepsy, who are treated with these anticonvulsants in our country. Therefore, we conducted a study using an acceptable sample size to assess the frequency of subclinical hypothyroidism in children with epilepsy, who were treated with phenobarbital, carbamazepine, and sodium valproate. We also tried to show a relation between these anticonvulsants and the degree of subclinical hypothyroidism.

MATERIAL AND METHODS

STUDY LOCATION

We conducted this study at Golestan Hospital, a major tertiary university-affiliated centre of child neurology in the south-west of Iran. This centre serves all the population of the Khuzestan province and five other neighbouring provinces. Almost all of the children with epilepsy in these provinces were referred to this centre for better evaluation and treatment. All of these children were evaluated and treated under direct supervision of three child neurologists from the centre. One of these child neurologists has a subspecialty in epileptology and clinical neurophysiology. The study was started in April 2014 and was continued to reach the predetermined sample size by March 2018.

PARTICIPANTS, INCLUSION, AND EXCLUSION CRITERIA

All children with generalised or focal epilepsy according to the International League Against Epilepsy (ILAE) classification [15] were potentially eligible to recruit. To reduce the probable effect of using more than two anticonvulsive medications on the thyroid function tests in a patient, we included only those children with epilepsy, who were treated with one of the following: phenobarbital, or carbamazepine, or sodium valproate generic forms as monotherapy. To reduce the effect of high dosages of anticonvulsive medications on the thyroid function tests, we administered anticonvulsive medications at standard maintenance dosages (phenobarbital 5 mg/kg/dose at bedtime, carbamazepine 10–15 mg/kg/dose every 12 h, and sodium valproate 10–15 mg/kg/dose every 12 h). All the children with epilepsy were well-controlled using these dosages. We excluded all children who had one of the following criteria: 1) uncontrolled epilepsy [16] (more than one seizure event in the last six months) because children with uncontrolled epilepsy need frequent changes in anticonvulsant dosages and even changes in their anticonvulsants, and these changes may have additive effects on thyroid function; 2) anticonvulsive treatment for less than six months; 3) treatment with more than two anticonvulsive agents; 4) a chronic condition other than epilepsy such as cardiovascular, endocrine, renal, and hepatic disease, global developmental delay or confirmed chromosomal abnormalities, and taking medications other than anticonvulsants, because all of these conditions may affect the thyroid function tests; and 5) confirmed thyroid disorders. We also assessed a group of age- and sex-matched children as a control group. We selected these controls from the children who were referred for growth and development monitoring and were residents of the same area as the patients. Many of the children in the control group were siblings of the children with epilepsy.

DESIGN

At least two child neurologists (one of them has a subspecialty in epileptology and clinical neurophysiology) visited all the children with epilepsy and interviewed all the parents and their children seeking medical history for risk factors of epilepsy. When video clips of the events were available, these child neurologists thoroughly reviewed these clips to determine the seizure type. After taking a thorough history of the event, reviewing the video clips, examining the children, reviewing the brain MRI when available, and reviewing the EEG findings, these two child neurologists decided about the epilepsy syndrome according to the ILAE classification [15] if possible. Of note, many of the children with epilepsy were referred to our child neurology clinic for a better decision

and follow-up. After visiting these children with epilepsy, we tried to define the epileptic syndrome and to decide about selecting and administering the best anticonvulsive medication. A child endocrinologist thoroughly interviewed and examined all the participants for the clinical manifestations of hypothyroidism.

We registered the following data from the participants: age, sex, body weight, height, body mass index, seizure type and if possible epilepsy syndrome according to the ILAE classification, EEG and neuroimaging findings, and duration of anticonvulsive therapy.

We obtained informed consent from all the participants and their parents before blood sampling. We referred all the participants to the central endocrine laboratory of the centre for blood sampling between 8:00 and 10:00 a.m. every day except Friday. In each participant, a 5-ml blood sample was collected under standard aseptic conditions. All the samples were stored at –20°C until time of analysis. A thyroid function test (T3, T4, and TSH) was performed for each participant using Thyroid RIA kits (Padyab Teb Co. Apt. 8, No. 17, Eastern Shab boo Aly., 1st Eastern St., Saadat Abad Ave, Tehran, Iran, Telefax: (+9821) 26417197). The normal reference ranges of the thyroid function tests in our area were: TSH (0.2–3.8 μIU/ml), T4 (45–160 μg/dl), and T3 (1.2–3.1 ng/ml) [17]. We defined subclinical hypothyroidism as a serum T4 within the normal range and increased TSH serum levels above the normal ranges. We also graded subclinical hypothyroidism as grade I (TSH 3.9–6 μIU/ml), grade II (TSH 6.1–10 μIU/ml), and grade III (TSH > 10 μIU/ml). [9] To define the precision in assessing thyroid function tests, we measured both intra-assay and inter-assay coefficient of variation for all the thyroid function tests (T3, T4, and TSH). The T4 levels had an intra-assay coefficient of variation < 3.1% and an inter-assay coefficient of variation < 2.5%. The T3 levels had an intra-assay coefficient of variation < 5.1% and an inter-assay coefficient of variation < 6%. The TSH levels had an intra-assay coefficient of variation < 5% and an inter-assay coefficient of variation < 6.4%. In each participant, thyroid function tests were conducted once; however, if the results of thyroid function tests were abnormal, we repeated them after four weeks to confirm that the participant definitely had subclinical hypothyroidism.

STATISTICS

We calculated the sample size by using a study conducted by Aggarwal *et al.* [1] To define the differences of thyroid function tests between these three groups of children with epilepsy treated with anticonvulsive monotherapy against control group and for a type I error of 0.05 and type II error of 0.2, we needed to have at least 50 children in each treatment group. We collected all data from the participants in a central computerised registry. We described all data using appropriate descriptive statistics. All data were analysed for normality. To compare subgroups of patients and patients against controls we used ANOVA or an appropriate nonparametric equivalent as required. We considered p-values less than 0.05 as significant. A biostatistician who was blinded to the treatment groups analysed the data.

ETHICS

The review board of the centre approved the study protocol, and we performed the study in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All the parents read and signed written, informed consents before any blood sampling.

RESULTS

BASELINE CHARACTERISTICS

We studied 228 children with epilepsy and 100 healthy children. All children with epilepsy were thoroughly interviewed and examined to define seizure type and, if possible, to define the epilepsy syndrome. From 228 children with epilepsy, 93 received sodium valproate, 76 received carbamazepine, and 59 received phenobarbital. Table 1 shows the baseline characteristics of the two groups.

From 228 children with epilepsy 100 (43.9%) children had generalised seizures and 128 (56.1%) children had fo-

TABLE 1. The baseline characteristics of the two groups

	Children with epilepsy ($n = 228$)	Healthy children ($n = 100$)
Age in year, median (range)	7.5 (3–15)	7 (3–15)
Sex		
Boys (%)	140 (61.4)	51 (51)
Girls (%)	88 (38.6)	49 (49)
Weight in kg, median (range)	24 (11.5–95)	23 (13–70)
Height in cm, median (range)	125 (80–170)	118 (95–164)
BMI, median (range)	17.09 (10.74–37.11)	15.36 (11.16–29.52)

TABLE 2. Thyroid function in children with epilepsy and healthy children

	Children with epilepsy ($n = 228$)	Healthy children ($n = 100$)	p-value < 0.05[a]
T4 in µg/dl; median (range)	Phenobarbital ($n = 59$); 82 (47–141) Valproate ($n = 93$); 91 (55–212) Carbamazepine ($n = 76$); 70 (40–148)	83.5 (30–169)	No Yes Yes
T3 in ng/ml; median (range)	Phenobarbital ($n = 59$); 2 (0.4–3.1) Valproate ($n = 93$); 2 (0.7–3.5) Carbamazepine ($n = 76$); 1.8 (0.9–3.6)	1.95 (0.7–2.4)	No No No
TSH in µIU/ml; median (range)	Phenobarbital ($n = 59$); 2.9 (0.4–7) Valproate ($n = 93$); 3 (0.56–12.3) Carbamazepine ($n = 76$); 2.9 (0.8–6)	2.1 (0.4–7.9)	Yes Yes Yes

[a] *p-values using Kruskal-Wallis One-Way Analysis of Variance on Ranks*

TABLE 3. Thyroid function in boys with epilepsy and healthy boys

	Sex	Healthy boys ($n = 51$)	p-value < 0.05[a]
T4 in µg/dl; median (range)	Phenobarbital ($n = 39$); 80 (47–115) Valproate ($n = 60$); 90 (55–212) Carbamazepine ($n = 41$); 70 (40–148)	80 (30–169)	No Yes No
T3 in ng/ml; median (range)	Phenobarbital ($n = 39$); 2 (0.4–3.1) Valproate ($n = 60$); 2 (1–3.5) Carbamazepine ($n = 41$); 1.9 (1–3.4)	2 (1–2.4)	No No No
TSH in µIU/ml; median (range)	Phenobarbital ($n = 39$); 3 (0.4–7) Valproate ($n = 60$); 3 (0.5–12) Carbamazepine ($n = 41$); 2.8 (0.8–6)	2.2 (0.4–3.8)	Yes Yes No

[a] *p-values using Kruskal-Wallis One-Way Analysis of Variance on Ranks*

TABLE 4. Thyroid function in girls with epilepsy and healthy girls

	Girls with epilepsy ($n = 88$)	Healthy girls ($n = 49$)	p-value < 0.05[a]
T4 in µg/dl; median (range)	Phenobarbital ($n = 20$); 84 (54–141) Valproate ($n = 33$); 91 (70–143) Carbamazepine ($n = 35$); 70 (48–140)	84 (55–140)	No No Yes
T3 in ng/ml; median (range)	Phenobarbital ($n = 20$); 1.9 (1.2–2.9) Valproate ($n = 33$); 2 (0.7–3) Carbamazepine ($n = 35$); 1.8 (0.9–3.6)	1.9 (0.7–2.3)	No No No
TSH in µIU/ml; median (range)	Phenobarbital ($n = 20$); 2.7 (1.2–7) Valproate ($n = 33$); 2.3 (0.6–8.8) Carbamazepine ($n = 35$); 3 (1.4–5.9)	2 (0.7–7.9)	No No No

[a] *p-values using Kruskal-Wallis One-Way Analysis of Variance on Ranks*

cal seizures. We could define Rolandic epilepsy spectrum in 40 children, generalised tonic-clonic seizures alone in 10 children, childhood absences in eight children, juvenile absences in nine children, juvenile myoclonic epilepsy in 11, and frontal lobe epilepsy in three children. We could not define an epilepsy syndrome in the rest of the children with epilepsy (147 children). From 228 children with epilepsy, 102 (44.7%) had a family history of epilepsy.

From 228 children with epilepsy, 156 children (68.4%) had abnormal epileptiform findings in their EEG, and in the rest, the EEG findings were normal, especially the background rhythm. From 228 children with epilepsy, brain MRI (non-epilepsy protocol) was conducted in only 175 and the main MRI findings were arachnoid cyst in four children, cavum vergae in six children, colpocephaly in two children, benign external hydrocephaly in four children, and probable focal cortical dysplasia in three children. The brain MRI was normal in the rest of the studies (156 children).

Table 2, Table 3, and Table 4 show thyroid function in children with epilepsy and compare them with healthy children according to the anticonvulsive agents and sex of the participants.

We defined subclinical hypothyroidism as serum TSH level more than 3.8 µIU/ml and normal serum T4 level [17]. According to this definition, 25 (26.8%) children in the sodium valproate group, 15 (19.7%) in the carbamaz-

TABLE 5. The frequency of subclinical hypothyroidism in the participants according to sex and anticonvulsant

Sex and grade	Valproate ($n = 25$)	Carbamazepine ($n = 15$)	Phenobarbital ($n = 13$)	Healthy ($n = 4$)	p-value < 0.05[a]
Boys	17	5	7	1	Yes
Grade 1	8	5	6	1	
Grade 2	8	0	1	0	
Grade 3	1	0	0	0	
Girls	8	10	6	3	Yes
Grade 1	1	10	4	2	
Grade 2	7	0	2	1	
Grade 3	0	0	0	0	

[a] *χ^2 tests between anticonvulsive agents and the healthy children*

epine group, 13 (22%) in the phenobarbital group, and only four (4%) children in the control group had subclinical hypothyroidism. Table 5 shows the frequency and the grade of hypothyroidism in different groups of the participants and compares them.

Subclinical hypothyroidism was significantly ($p < 0.05$) more frequent in children who took anticonvulsive agents than in the healthy controls; however, the frequency of subclinical hypothyroidism among groups of anticonvulsive agents was not significantly different. Of note, none of the children with epilepsy or the healthy controls showed clinical manifestations of hypothyroidism.

DISCUSSION

Our results show that, compared to healthy children, subclinical hypothyroidism as defined by normal T4 and elevated TSH (more than 3.8 μIU/ml) [17] was significantly more common in children with epilepsy (more than 23%, 53/228), who were treated using either sodium valproate, carbamazepine, or phenobarbital as monotherapy. For better assessment, we found subclinical hypothyroidism in only 4% of healthy controls. Despite the relatively high frequency of subclinical hypothyroidism in children with epilepsy, none of the children among those with epilepsy and healthy controls showed clinical signs of hypothyroidism.

According to Table 5, in children who were treated by sodium valproate, subclinical hypothyroidism was more common in boys than in girls (17 boys vs. eight girls). In children who were treated with carbamazepine, subclinical hypothyroidism was more common in girls than in boys (five boys vs. 10 girls), and in those who were treated with phenobarbital, the frequency of subclinical hypothyroidism was the same in boys and in girls. We have no explanation for these differences; however, these results may be accidental, and precisely designed studies in the future could explain these differences.

Our results are in accordance with some of the previous studies. One of the main studies conducted by Eiris-Punal *et al.* showed that subclinical hypothyroidism could occur in 8.2% of children with epilepsy, who were treated with carbamazepine (61 children) and 26% of children who were treated with sodium valproate (51 children), compared to 3.6% (148) of healthy controls [4]. A study conducted by Kim *et al.* compared 61 children with epilepsy, who were treated with sodium valproate, with 144 healthy controls. They found that 52.4% (32/61) of children with epilepsy had subclinical hypothyroidism compared to healthy controls (16.7%, 24/144) [8]. Another study conducted by Turan *et al.* showed that subclinical hypothyroidism was more common in children who were treated with sodium valproate (39.2%, 20/51) compared to those who were treated with carbamazepine (6.7%, 3/45) and phenobarbital (12.5%, 6/48), and only 2.3% (1/44) of healthy controls showed subclinical hypothyroidism [10]. Another study conducted by Sahu *et al.*, showed subclinical hypothyroidism in 26.3% (15/57) of children who were treated by sodium valproate as monotherapy [9]. However, two studies conducted by Verroti *et al.* found that in children with epilepsy, carbamazepine and sodium valproate could alter thyroid function tests; however, interestingly, none of their children showed subclinical hypothyroidism [18, 19].

A group of studies has tried to explain the mechanisms of subclinical hypothyroidism in patients treated with anticonvulsants. The main mechanism that has been proposed is GABA (γ aminobutyric acid) stimulating properties of anticonvulsive medications. GABA could inhibit the release of somatostatin which itself inhibits TSH secretion [4, 20].

Subclinical hypothyroidism is important and has serious long-term complications such as cardiovascular problems. Although only severe subclinical hypothyroidism (TSH more than 10 μIU/ml) requires urgent treatment, we need to follow-up patients with mild and moderate subclinical hypothyroidism (TSH 4–10 μIU/ml) and closely monitor clinical signs and symptoms of overt hypothyroidism in them [12–14]. In our study, only one boy (14 years old, BMI 21.05) had grade 3 subclinical hypothyroidism (TSH 12.3 μIU/ml). He had juvenile myoc-

lonic epilepsy, and our endocrinologist decided to treat him by levothyroxine.

Our results should be interpreted in the face of certain limits. We did not assess baseline thyroid function in our children before treatment by anticonvulsive agents; however, we had a group of healthy controls to compare subclinical hypothyroidism in the normal population. We also did not follow thyroid function in children who were candidates for drug withdrawal. Another study showed that after withdrawal of anticonvulsive medications thyroid function disturbances are reversible [11]. We did not measure serum levels of anticonvulsive medications to correlate these serum levels by thyroid function tests; therefore, we could not define a correlation between serum levels of these anticonvulsive medications and grades of subclinical hypothyroidism in our patients.

CONCLUSIONS

In conclusion, our results indicate that in children with epilepsy who were treated by either carbamazepine, sodium valproate, or phenobarbital as monotherapy, subclinical hypothyroidism could occur and is relatively common (about 20%). Our results indicate that monitoring of thyroid function using T4 and TSH serum levels should be considered in these children during anticonvulsive therapy. However, understanding the long-term effects of anticonvulsive medications on thyroid function requires well-designed, prolonged cohort studies.

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DISCLOSURE

The authors declare no conflict of interest.

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