Original Article

Hypothyroidism in Children

Subclinical Hypothyroidism in Children on Valproic Acid Montherapy

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ABSTRACT

Objective: To determine the frequency of subclinical hypothyroidism in children on Valproic acid monotherapy.
Study Design: Descriptive / cross sectional study
Place and Duration of Study: This study was conducted at the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi, for duration of twelve months from 1st Jan 2018 to 31st Dec 2018.
Materials and Methods: Male and female children of age 5 to 12 years, having Idiopathic Epilepsy (IE) and using Valproic Acid Monotherapy (VPA monotherapy) for more than one year, were included in this study. Blood samples were collected from these children and sent to hospital laboratory for thyroid function tests. Subclinical hypothyroidism (SCH) was defined as thyroid stimulating hormone (TSH) levels greater than 5U/ml but less than 10U/ml and free thyroxin (FT4) levels within normal range (5-25ng/ml). The data were analyzed on SPSS 16.0 and the frequency of children having subclinical hypothyroidism was calculated.
Results: A total of 122 patients were included in the study. The mean age of the patients was 8.71±1.95 years and the mean duration of treatment with VPA monotherapy was 20.45±5.31 months. The frequency and percentage of male and female patients was 83 (68.0) and 39 (32.0). The frequency and percentage of subclinical hypothyroidism in the study group was found to be 20 (16.4).
Conclusion: The frequency of subclinical hypothyroidism is substantial in children using Valproic acid monotherapy for more than one year.
Key Words: Subclinical Hypothyroidism (SCH), Valproic Acid(VPA) Therapy,Thyroid Stimulating Hormone (TSH)

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INTRODUCTION

Many of the commonly used antiepileptic drugs have been found to cause subclinical hypothyroidism (SCH)[1]. Valproic acid (VPA) is an antiepileptic agent commonly used as monotherapy in the treatment of idiopathic epilepsy and has been found to be related to SCH[1, 2]. The incidence of SCH in patients using VPA monotherapy for a period longer than twelve months varies from 16.7 % to 28 % in different studies [1-3]. There is research based evidence that a longer duration of monotherapy with VPA has a higher prevalence of SCH[4, 6].

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The progression of SCH to clinically overt hypothyroidism has also been documented in the international research[13].
It has been recommended that the patients using VPA should be regularly monitored for thyroid function[5,6]. SCH is defined as normal free thyroxin (FT4) levels in the range 5-25ng/ml along with thyroid stimulating hormone (TSH) levels greater than 5U/ml but less than 10U/ml [(1)].
SCH is generally a self-limiting disorder of thyroid function and does not need treatment. The data in pediatric population is limited and conflicting leading to a difference in treatment approach among different authorities[4]. Normally in children replacement therapy with thyroxin is recommended when the TSH concentration is more than 10 mIU/L but in children with SCH on VPA therapy, an individualized therapy is required. Treatment with thyroxin can be initiated along regular monitoring of the thyroid functiom.[7]
We carried out a study to determine the frequency of subclinical hypothyroidism in children on VPA monotherapy, presenting in outpatient department of our hospital**.**

MATERIALS AND METHODS

This study was carried out in the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi, for

duration of twelve months from 1st Jan 2018 to 31st Dec 2018.

Sample Size: Sample size of 105 is calculated by using WHO software based on confidence interval 95%, margin of error 6% and prevalence of Childhood Ischemic Stroke 11%.

Sampling Technique: Blood samples were collected in paeds OPD using consecutive non- probability sampling technique. The samples were sent to the hospital laboratory for thyroid function studies.

Inclusion Criteria: Children of both sexes of age 5 to 12 years, having idiopathic epilepsy and stable on VPA monotherapy for more than 12 months were included in this study.

Exclusion Criteria: Patients with poor compliance, known cases of hypothyroidism and family history of hypothyroidism or endocrine disease were excluded from the study. The results were recorded individual for every patient.

Data Collection Procedure: After taking approval from hospital ethical committee. Informed written consent for the collection of data and its use in research publication was taken from the parents of the patients. The confidentiality of the patient data was ensured.

Children of both sexes of age 5 to 12 years, having idiopathic epilepsy and stable on VPA monotherapy for more than 12 months were included in this study. Blood samples were collected in paeds OPD using consecutive non- probability sampling technique. The samples were sent to the hospital laboratory for thyroid function studies. Patients with poor compliance, known cases of hypothyroidism and family history of hypothyroidism or endocrine disease were excluded from the study. The results were recorded individual for every patient.

Data Analysis: The data was analyzed on SPSS version 16.0. Descriptive statistics were used to measure qualitative and quantitative data. Qualitative data like gender and subclinical hypothyroidism were measured by percentages and frequencies and quantitative data like age, duration of therapy, and thyroid function test was measured as mean ± standard deviation (SD) if the data were normally distributed, by median and range otherwise. A chi-square test was used for categorical data. Effective modifiers like age, gender and duration of VPA therapy was controlled by stratification. Post stratification Chi square test was applied and p value of less than or equal to 0.05 was considered as significant**.**

RESULTS

A total of 122 patients were included in the study according to the inclusion criteria. The frequency and percentage of male and female patients was 83 (68.0) and 39 (32.0) respectively. Descriptive statistics of age (years), duration of therapy with VPA and thyroid function tests were calculated in terms of mean and standard deviation. The mean age was 8.71±1.95 years with range from 05 to 12 years, as shown in Table I. The mean duration of treatment with VPA was 20.45±5.31 months (Table 2) and mean levels of TSH and T4 were 2.77±1.31 and 15.64±3.44 respectively, as shown in Table 3. The frequency and percentage of children on VPA monotherapy and having subclinical hypothyroidism were calculated and found to be 20 (16.4) as shown in Table 4.

Table No. 1: Descriptive statistics of Age (years) of patients

	n	Minimum	Maximum	Mean	Std. Deviation
Age (years)	122	5	12	8.71	1.95

Table No. 2: Descriptive statistics of Duration of Therapy with VPA months

	n	Minimum	Maximum	Mean	Std. Deviation
Duration of Therapy (months)	122	12	33.00	20.45	5.31

Table No. 3: Descriptive statistics of Thyroid Function Test (TFT)

	n	Minimum	Maximum	Mean	Std. Deviation
TSH (u/ml)	122	0.90	5.40	2.77	1.31
T4 (ng/ml)	122	9.00	22.00	15.64	3.44

Table No. 4: Distribution of Subclinical Hypothyroidism

		Frequency	Percentage
	Yes	20	16.4
	No	102	83.6
	Total	122	100.0

Table No. 5: Effect modifier Gender stratification with Subclinical Hypothyroidism

			Subclinical Hypothyroidism		P-value
			Yes	No	
Gender	male		12	71	0.400
			60.0%	69.6%	
	female		08	31	
			40.0%	30.4%	
Total			20	120	
			100.0%	100.0%	

Effect modifier like gender stratification was compared with subclinical hypothyroidism in children on VPA monotherapy. There were 12 (60.0) male children vs. 08 (40.08) females, who had subclinical Hypothyroidism. Chi-square test was applied and p-value 0.400 was found and taken as insignificant

(Table 5). When age stratification was compared in these children, 9 (45.0) children with SCH were 5-10years of age and 11 (55.0) were 11-12 years of age. Chi-square test was used to compare age stratification and p-value 0.002, (Table 6)

Table No. 6: Effect modifier Age stratification with Subclinical Hypothyroidism

		Subclinical Hypothyroidism		P-value
		Prolonged	Not prolonged	
Age Group	05 - 10 years	09	80	0.002
		45.0%	78.4%	
	11 - 12 years	11	22	
		55.0%	21.6%	
Total		20	102	
		100.0%	100.0%	

DISCUSSION

Subclinical hypothyroidism (SCH) is a mild thyroid failure which is diagnosed when thyroid hormone levels are within normal reference range but thyroid-stimulating hormone (TSH) levels are mildly elevated. These patients usually do not present with clinical manifestations of hypo-thyroidism and the diagnosis is possible with thyroid function tests[7].

The results of our study were similar to some of the international studies. The mean age (years) in our study was 8.71±1.95, whereas in a study by Kim et al[3] the mean age was 9.7 ± 4.7. The frequency and percentage of male and female patients were 34(55.7) and 27(44.2) in Kim's study and 83 (68.0) and 39 (32.0) in our study. The mean reading of TSH and T4 in our study was 2.77±1.31 and 15.64±3.44 respectively and in Kim's study the mean TSH value was 4.64±2.81and T4 value was 1.28±0.34. A recent study from Turkey[1] has reported 28% children with subclinical hypothyroidism after 12 months of therapy with VPA whereas in our study, there were 16.4% of patients with subclinical hypothyroidism in children on VPA therapy for more than one year. Over period of time SCH can progress to clinically overt state[7, 13] .The clinical implications of SCH besides progression to overt hypothyroidism[13] include psychiatric and cognitive dysfunction[14], lipid abnormalities [12, 15], endothelial dysfunction and insulin resistance[16, 17], adverse cardiac end points[18-20] and neuromuscular dysfunction[24].

In view of the wide range of possible complications of the hypothyroid state, it is important to define normal serum TSH levels, so that the decision of intervention with thyroxin therapy can be made. This avenue has always been open to discussion [9]. Levothyroxin therapy (LT) is generally agreed to be appropriate when the TSH level is greater than 10 mIU / L [10]. In the management of SCH patients with a serum TSH level less than 10mIU/L some authorities recommend routine[11] whereas others recommend selective use of Levothyroxin Therapy (LT) [12].

Villar HC conducted a meta-analysis of 14 randomized clinical trials enrolling a total of 350 patients and concluded that LT for SCH does not result in improved survival or decreased cardiovascular morbidity but improves some parameters of lipid profiles and left ventricular function.[12]

Haentjens P and colleagues did an analysis of 7 cohort studies and concluded that the relative risk of all-cause mortality was increased in hypothyroidism compared with euthyroid controls, particularly in patients with co-morbid conditions[26] Razvi S, worked on the influence of age on the relationship between SCH and ischemic heart disease. It was a meta-analysis of 15 studies and showed an increased prevalence and incidence of cardiovascular mortality only in a relatively younger population.[22]

Biondi B etal in their work on cardiovascular effects of mild hypothyroidism have shown increased left ventricular relaxation time, vascular tone at rest, and left ventricular systolic dysfunction with exercise and impaired endothelial function.[23]Some studies, like Christ-Crain M study have shown improvement of cardiac contractibility and systolic time interval with LT. It has been suggested in this study that neuromuscular symptoms and dysfunction, common in patients with SCH, can be reversed by LT.[24]

The clinical implications of SCH were beyond the scope of our study, but reconfirmation of increased frequency of subclinical hypothyroidism in children using VPA monotherapy, was important and stressed a long term monitoring of thyroid function in these patients. These children could be followed for longer periods and decisions could be taken for early intervention with LT**.**

CONCLUSION

The study concludes that the frequency of subclinical hypothyroidism in children on Valproic acid monotherapy for longer than twelve months is substantial. The risk of conversion to clinical hypothyroidism and associated complications is documented in international studies. Therefore long term follow up of thyroid function in epilepsy patients on Valproic acid monotherapy is needed**.**

Author's Contribution:

Concept & Design of Study:	Fazeel Shahzad
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Final Approval of version:	Fazeel Shahzad

Conflict of Interest: The study has no conflict of interest to declare by any author.

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