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CLINICAL PRESENTATION OF HYPOTHYROIDISM: A CASE CONTROL ANALYSIS

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Background: Hypothyroidism is a common endocrinological disorder. Its clinical presentation is variable but well established. However, clinical features vary significantly among different populations owing to their climate, education status and awareness about the disease. This study is designed to evaluate the difference in clinical presentation of our population from already available literature. **Methods:** In this study we have compared the symptoms and signs of hypothyroid and euthyroid patients coming to a diagnostic centre (PINUM, Faisalabad) from January to July 1999. Of the 1594 patients coming to the centre, 394 were included in the study and were examined. After the laboratory investigations, 109 were identified as the cases of hypothyroidism, the rest were declared as euthyroid and selected as controls. We compared the 21 common signs and symptoms of hypothyroidism in our patients. **Results:** Lethargy was the commonest symptom and facial oedema was the most prevalent sign in our population. Old age is reported to be a risk factor for hypothyroidism but in this study we could not find a rising trend with increasing age (odds ratio 1.15, *p*-value 0.71). We also compared the clinical presentation of our patients with the available literature. It was also proved that the signs elicited by the physicians were more reliable and specific for the identification of hypothyroidism. **Conclusion:** Thus, the presentation of hypothyroidism is non-specific and high degree of suspicion is required for its early diagnosis.

KEY WORDS: Hypothyroidism, Age Groups, Signs and Symptoms, Case-Control Studies.

INTRODUCTION

Hypothyroidism is a clinical state resulting from an insufficient amount of circulating thyroid hormone to support normal body function. It may exist in utero or develop in infancy, childhood or even in adult life. The prevalence of unsuspected overt hypothyroidism, defined as the combination of biochemical and clinical findings of hypothyroidism, ranges from 1-18 cases per thousand persons. The female to male ratio in hypothyroidism ranges from 2:1 to 8:1 in various epidemiological surveys[1,2]. In a survey of 2,779 persons carried out in County Durham, England, hypothyroidism was detected in 1.9% of women and was overt in 1.4%. The prevalence in men was less than 0.1 percent[2]. Recent surveys indicate hypothyroidism to be more prevalent in elderly population, reaching as high as 20%[3]. A study of the Framingham population showed that 5.9% of the women and 2.4% of men above the age of sixty had serum TSH levels more than 10mU/L[4]. While in Ireland the prevalence of primary hypothyroidism has been stated as 8.6% in the women above the age of fifty years as compared to only 0.9% in younger females[5]. The incidence of congenital hypothyroidism was reported to be 1 in 2,640 in a study from India[6].

In iodine-replete areas, autoimmune thyroid disease and thyroablative therapy are the major reasons of hypothyroidism. Even in children and adolescents autoimmune thyroiditis is the

commonest cause of non-endemic thyromegaly and acquired hypothyroidism[7]. However, worldwide, iodine deficiency is the leading cause[8].

The clinical manifestations of hypo-thyroidism are variable, depending upon its cause, duration, and severity. The spectrum extends from sub-clinical to overt hypothyroidism to myxedema coma. The classic change is the slowing of physical and mental activities and of all the body systems. The characteristic pathological finding in a hypothyroid patient is the accumulation of hyaluronic acid and other glycosaminoglycans in the interstitial tissues.[9] A high degree of suspicion is thus required in order to appreciate the clinical manifestations of the disorder to reach a diagnosis. Unfortunately, there is very little information available on this subject from our part of the world. The objectives of this study were to look at the presenting clinical features of hypothyroidism in our population and then comparing it to the already available results from other parts of the world.

MATERIAL AND METHODS

This was a case control study, carried out at the Punjab Institute of Nuclear Medicine (PINUM), Faisalabad, Pakistan. All the patients coming to PINUM for their thyroid work up from January to July 1999 were interviewed and examined by a group of trained physicians with the help of a standard questionnaire, after obtaining a verbal consent. All patients with already established diagnosis of hypothyroidism, thyroid ablation or thyroidectomy, co-existing infections, thyroid or other malignancies, other systemic illnesses like, diabetes mellitus, cardiac, renal and liver failure etc., hyperthyroidism, sub-clinical hypothyroidism, pregnancy and those already on thyroid hormone replacement therapy were excluded from the study. There was no age limit specified for inclusion in the study. Both the doctors and the patients were unaware of the thyroid status of the patients at the time of interview. The diagnosis of hypothyroidism was established after the availability of results of laboratory investigations on the basis of both clinical judgment and the laboratory investigations. The laboratory tests comprised of serum T_3, T_4, FT_4, and TSH by radioimmunoassay, and thyroid scan where required. The questionnaire looked at the common symptoms and signs of hypothyroidism as mentioned in the literature. The symptoms asked were dyspnoea, hoarseness, odynophagia, changes in bowel habits, temperature intolerance, lethargy, change in body weight, appetite, paresthesia, hair loss, body aches, depression, anxiety and menstrual abnormalities, mainly menorrhagia. The signs included general physique of the patient [divided into three categories of normal physique (Body mass index [BMI] 20–25 kg/m^2), thin (BMI<20 kg/m^2) and fat (BMI>25 kg/m^2)], pulse, deep tendon reflexes, skin changes like dry/coarse skin and coarse hair, non-pitting peripheral oedema, and oedema of face.

The data were entered and analyzed using SPSS statistical software package, version 10.0 for Windows (SPSS. Inc, Chicago, IL). The results of the above mentioned variables were compared between hypothyroid and euthyroid patients using Chi Square analysis.

The cases and the controls were further divided into two groups; group A with age more than fifty years and group B with less than fifty years of age. The frequency of hypothyroidism was compared in both the groups by using chi square test.

RESULTS

A total of 1594 patients were registered in PINUM in the above-mentioned period for their thyroid work up. Out of which, 394 patients fulfilled the inclusion criterion and were selected. After undergoing the laboratory tests 109 were identified to have primary hypothyroidism and thus were selected as cases. The rest of 285 were euthyroid and labelled as controls. In hypothyroid patients the mean age was 33.5±16.3 years, while in euthyroid patients it was 31.2±13.8 years. Three patients from the cases were too young to answer some part of the questionnaire. Females were equally predominant in both cases and controls; with 88 (80.79%) females and 21 (19.3%) males in the cases and 248 (87%) females and 37 (13%) males in the controls. Eighty-two (75.23%) patients were married among the hypothyroid patients; while in control group 184 patients (64.56%) were married. The results of their laboratory investigations (Mean±SD) are shown in Table-I.

Table-1: The results of the laboratory investigations performed on Hypothyroid and Euthyroid patients.

Laboratory Investigations	**Hypothyroid** Mean±SD (n)	**Euthyroid (Controls)** Mean±SD (n)	***p* value**
TSH (mU/L)	99.95±59.31 (109)	1.52±1.31 (285)	<0.001
T_3 (ηmol/L)	0.85±0.65 (102)	1.95±0.67 (271)	<0.001
T_4(ηmol/L)	5.06±4.75 (8),	65.73±38.51 (15)	<0.001
FT_4 (pmole/L)	4.03±4.45 (101)	14.75±4.84 (263)	<0.001

The mean pulse of the hypothyroid patients was 74.6±10.3 beats per minute (bpm) while that of euthyroids was 84.2±12.4 bpm. The commonest symptom complained by our patients was lethargy; a total of 72 (67.9%) patients among the cases while 98 (34.4%) of the normal control subjects complained of it. Oedema of the face was the commonest sign present in hypothyroid patients and was found in 69 (63.3%) of the hypothyroid patients and 9 (3.2%) of the euthyroids. The other symptoms complained by our patients and the signs elicited by the physicians in both cases and controls are shown in Table-II. The symptoms of menstrual abnormalities were asked from premenopausal female population only. Twenty two out of 57 (38.6%) premenopausal females among the cases had menorrhagia while only 15 out of 188 (8.0%) of the controls complained of it.

The age above 50 years were analyzed as a risk factor for developing hypothyroidism as mentioned in literature[3-5]. There were 11 (10.4%) of the hypothyroid patients, and 26 (9.1%) of the controls whose age was more than 50 years. The odds ratio from two by two contingency table

came out to be 1.15 (95% confidence interval of odds ratio 0.55–2.42) that was insignificant statistically (p=0.706).

DISCUSSION

The clinical manifestation of chronic hypothyroidism may develop insidiously as compared to the severe hypothyroidism, resulting from ablation or thyroiditis, associated with rapid onset of symptoms. The wide variability in the presentation further confounds the recognition of this condition. Among patients in general medicine practice presenting with the common complaints relating to hypothyroidism like constipation, weight gain, menstrual irregularities, fatigue, cold intolerance, depression and galactorrhea etc., only 4% are actually hypothyroid, and fewer than 2% have a TSH level at least 5mU/L above normal[10]. In contrast, more specific symptoms and signs include slow movement, coarse skin, decreased sweating, hoarseness, paresthesia, cold intolerance, periorbital oedema, and delayed deep tendon relaxation[11,12].

Table-2: Frequency of the clinical features observed in hypothyroid and euthyroid patients.

Symptoms	**Hypothyroid** No. (%)	**Euthyroid (Controls)** No. (%)	***p*-value**
Sample size	106*	285	
Lethargy	72 (67.9)	86 (30.1)	<0.001
Bowel habits			
Constipation	70 (66.0)	38 (13.3)	<0.001
Loose motion	3 (2.8)	23 (8.07)	
Normal	36 (33.9)	224 (78.6)	
Body aches	64 (60.4)	152 (53.3)	>0.05
Depression	57 (53.7)	62 (21.7)	<0.001
Increased sensations of			
Cold	54 (50.9)	21 (7.4)	<0.001
Heat	8 (7.5)	84 (29.5)	
Normal	44 (41.5)	180 (63.1)	
Weight changes†			
Gain	49 (44.9)	24 (8.4)	<0.001
Loss	7 (6.4)	44 (15.4)	
Stable	53 (48.6)	217 (76.1)	
Paresthesia	49 (46.2)	86 (30.2)	0.001
Menorrhagia‡	22 (38.6)	15 (8.0)	<0.001
Hoarseness	40 (36.7)	62 (21.8)	<0.001
Appetite changes†			
	35 (32.1)	44 (15.4)	<0.001

Decreased	63 (57.8)	217 (76.1)	
Normal	7 (6.4)	24 (8.4)	
Increased			
Dyspnea	32 (30.2)	96 (33.7)	>0.05
Odynophagia	13 (12.2)	62 (21.8)	0.002
Nervousness / Anxiety	13 (12.2)	78 (27.4)	<0.001
Hair loss+	9 (8.3)	9 (3.2)	0.008
Mean Pulse (beats/min)	74.6 ± 10.3	84.2 ± 12.4	<0.001
Edema of face	69 (63.3)	9 (3.2)	<0.001
Peripheral edema	66 (60.6)	9 (3.2)	<0.001
Apperance			
Fat	40 (36.7)	27 (9.5)	<0.001
Normal	65 (59.7)	238 (83.5)	
Thin	4 (3.7)	20 (7.0)	
Skin changes	16 (14.7)	3 (1.1)	<0.001
Delayed relaxation of deep tendon reflexes	22 (20.9)	6 (2.1)	<0.001
Exopthalmos	2 (1.8)	7 (2.5)	>0.05

*There were three cases among hypothyroidism that were unable to answer the questions, so are removed from the denominator.

†The denominator taken is 109 for hypothyroid patients; and the symptoms are documented from attendants in case of children.

‡Fraction of symptoms of menorrhagia was calculated from the reproductive age group female patients only. (For Hypothyroidism N=57; For Euthyroidism N= 188)

In this study, we have found the female preponderance in hypothyroidism as expected. The female to male ratio in cases was 4:1 which is similar to what has been reported in the literature. The female to male ratio in control group was 6:1, making the results comparable with cases and decreasing any bias in clinical symptoms coming from different gender.

There had been reports that indicate that the prevalence of hypothyroidism increases in the elderly[3,4]. In contrast to that, we had 37 patients above fifty years of age in this study with hypothyroidism in only 29.7%, while its frequency was 26.8% among other 354 patients below 50 years of age. Though this study clearly shows an increasing trend of hypothyroidism with growing age, more data from different community based studies is required to call it statistically significant. The reason for the smaller sample size in the older age group could be that lesser number of elderly patients is brought to a diagnostic centre in our setting.

According to our study, dyspnoea, and weight loss, are the symptoms that were not significantly different in hypo- and euthyroid patients (p>0.05) (Table-II). The symptoms that were highly suggestive of hypothyroidism, in decreasing order of significance, included increased sensation of cold, generalized lethargy, constipation, weight gain, appetite loss, depression, menorrhagia, and hoarseness. While hair loss and body aches were just significantly more prevalent

in the cases (p<0.01). Interestingly, anxiety and odynophagia were noticeably more prevalent in the control (p<0.01). The signs of hypothyroidism as elicited by the physicians were more specific and helpful in identification of hypothyroid patients (Table-II). These comprised of skin changes (dry coarse skin and coarse hair), obese or fat appearance, facial oedema, non-pitting peripheral oedema (p<0.001). The delayed relaxation of ankle jerk reflex was present in 21% cases only, but it was very specific for hypothyroid patients. A modest measurable exopthalmos has been described in the patients of myxedema[13, 14]. It was present in 2 of our cases.

When we compare our study to already available data on this subject, we come across some very interesting observations. We realize that most of the signs and symptoms have the same trend though the prevalence might be different. For example, weakness has been reported as one of the commonest symptoms of hypothyroidism with a prevalence of 98%, and 99% in Murray's and Lermann's series respectively and 25.5% in Watanakunakorn's study[15,16,17] (Table-III).

Table-3: The symptoms and signs reported in literature by different series and studies.

	Murray series		**Lermann**	**Watanakunakorn**
	Cases (%)	Controls (%)	Cases (%)	Cases (%)
Sample size	100	100	77	400
Weakness	98	21	99	26
Lethargy	85	17	91	25
Constipation	54	10	61	37
Body aches	36	17	-	10
Depression	60	41	-	-
Increased sensations of				
Cold	95	39	60-95	58
Heat	2	12	-	-
Weight changes				
Gain	76	36	50-75	48
Loss	9	23	-	6
Paresthesia	56	15	-	-
Palpitations	23	20	31	-
Menorr-hagia	33	-	32	16
Hoarseness	74	18	52	48
Decreased appetite	40	15	-	14
Dyspnea	72	52	55	12
Odyno-phagia	-	-	3	8
Nervousness / Anxiety	51	42	35	13
Hair loss	41	21	57	32
Edema of face	95	27	79	67
Peripheral edema	57	2	55	-
Skin changes	70-79	10-26	97	89
Delayed relaxation of deep tendon reflexes	-	-	-	43
Exopthalmos	11	4	-	1

In our study too, lethargy was mentioned by 67.9% of the cases and was the most prevalent feature. Similarly, cold intolerance, that was found in 89% of the Lermann's series and 93% of the

Murray's, was prevalent in about half of our cases, which is quite comparable to the 58.25% in Watanakunakorn's[15,16,17]. While skin changes like dry, coarse skin, hoarseness and hair-loss were not mentioned as commonly in our study as they had been in other series (Table-II and III). However, we found that these symptoms were significantly specific for hypothyroidism, which was similar to what has been described in the literature. On the other hand, constipation, weight gain, oedema of the face and non-pitting peripheral oedema, had quite comparable prevalence to all the studies. Slow relaxation of deep tendon reflexes was found in 21% of our population as compared to the 43.5% in literature[17]. This was a subjective measurement and the results could be subjected to error.

Most of the information that we get about the clinical manifestations of hypothyroidism is from literature of the western countries. Their level of education, awareness about the diseases, and health care facilities are quite different from ours. The climate and cultural norms are also very dissimilar. The pathophysiology of the disease always remains the same, but the perception of symptoms, their recognition and expression differ in every population as governed by the above mentioned determinants.

Hence, there is a need for every community to define the expression and prevalence of their common disorders in order to recognize them early and correctly. The diagnosis of hypothyroidism may be overlooked for several years because of the insidious and non-specific nature of symptoms that further complicates the detection of hypothyroidism. Therefore, it is very critical to have a high degree of suspicion in assessing the patients having such a vague presentation. The importance of clinical picture cannot be stressed more; however, a support from laboratory investigations should be sought whenever and wherever required.

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