Original Research Article

Is the clinic pathological profile of hypothyroidism gradually changing: a comparative study from North India

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ABSTRACT

Background: Thyroid dysfunction has been subject of academical and therapeutically interest not only to the endocrinologist but also to the disciplines of medicine. Statistical data and studies on hypothyroidism are scanty, clinical picture is varied, investigations are usually not available at all levels and therefore to enlarge clinical profile of hypothyroidism minimal base line investigation, clinical approach and effects of replacement therapy and complications are to be studied.

Methods: Observational cross-sectional study conducted among patients with hypothyroidism registered at the Air Force Central Medical Establishment (AFCME) New Delhi.

Results: Among 50 patients with hypothyroidism were enrolled in this study during the study period. Idiopathic hypothyroidism was present in 98% patients while only one patient (2%) had Hashimoto’s thyroiditis. Generalized weakness was the commonest presenting symptom followed by lethargy and anorexia. Thyroid swelling was diffuse in nature with no predilection to right or left lobe enlargement. Hypertension (40%) and ischemic heart diseases (36%) were the most common comorbid condition. Mean serum TSH was elevated while serum T3 and T4 values were reduced. Antithyroid antibody titre was positive in more than seventy percentage of patients. X-ray among patients revealed cardiomegaly in ten patients (20%), pulmonary Koch’s in (4%) of patient and in rest of patients x-ray chest PA view was normal. ECG changes showed low voltage on electrocardiogram in (20%) of patients and sinus bradyarrhythmia in (24%) of patients. Most of the patients were put on replacement therapy (L. thyroxine) in dose of 1.6 - 1.7 mcg/kg/day.

Conclusions: Hypothyroidism as a clinical entity is common between 4th and 6th decade of life and seen more among females. Though etiology remained unknown in majority of the patients, weakness, and lethargy were the common clinical presentation.

Keywords: Antithyroid antibody, Hypothyroidism, India, Triiodothyronine, Thyroxine, Serum thyroid-stimulating hormone

INTRODUCTION

Thyroid gland is one of the most important endocrinal glands governing numerous physiological processes. Although its physiology is not completely understood, it has created great interest in many investigations.¹ The derangement in its physiology leads to hyper or hypofunction of the gland.¹ In the past, diagnosis of thyroid disease was possible only by indirect methods like BMR, Serum cholesterol, delayed relaxation of ankle
The use of T3, T4, and TSH assays some more diagnostic methods like PBI, THIST, free thyroxine index, TRH estimation, I131 uptake studies, TC99 Thyroid scan, ant thyroglobulin antibodies, ATS and TSH binding inhibitors are some of the further progressive measures in the field of thyroid disease. With introduction of cellular histochemistry, molecular biology, fluorescent techniques, radio-immune assays, ELISA, CT scan, MRI and digital subtraction angiography, the entire picture of clinical endocrinology has been revolutionized. With further knowledge of genetic engineering, gene therapy and introduction of biotechnology with pharmacology, the theocentric aspects of endocrinial dysfunction has been updated.

Thyroid dysfunction has been subject of academical and therapeutically interest not only to the endocrinologist but also to the disciplines of medicine. Statistical data and studies on hypothyroidism are scanty, clinical picture is varied, investigations are usually not available at all levels and therefore to enlarge clinical profile of hypothyroidism minimal base line investigation, clinical approach and effects of replacement therapy and complications are to be studied. This has resulted interest in the development of this study with the aim to evaluate clinipathological profile of patients with hypothyroidism and study any changing trends and to study the effect and complication during follow up of patients.

METHODS

Design and study center

The present study was an observational cross-sectional study conducted among patients with hypothyroidism registered at the Air Force Central Medical Establishment (AFCME) New Delhi. This is a prestigious defense establishment and cater to a large population of serving defense personnel’s, their families, dependents and retired armed forces personnel’s in Delhi, National Capital Region (NCR) and North India. It is also one of the two centers in India approved by NABH for conducting medical examinations for civil pilots prior to their civil pilot license testing and its periodic renewals. The aim of the study was to collect original Indian data of hypothyroidism and also analyze any change in the trend of the disease. Study duration was the study was conducted over a period of 2 year (April 2014 to March 2016). Ethics committee approval was taken before the start of study.

Selection criteria

The criteria selected for diagnosis of hypothyroidism was presence of clinical symptoms like edema feet, Weight gain, Loss of appetite, Easy fatigue with the generalized weakness, Decreased sweating with the dry and course skin and hoarseness of voice along with clinical signs like delayed relaxation of the ankle jerk, loss of the outer one third of the eyebrow, Sinus bradycardia or low voltage complexes on electrocardiogram.

Inclusion and exclusion criteria

Adult patients with confirmed diagnosis of hypothyroidism with high TSH value with normal or decreased level of T3 or T4. All pediatric patients or patients with post ablative hypothyroidism or those on thyroid replacement therapy or those with drug induced hypothyroidism were excluded from the study. Patients who fulfilled the inclusion and exclusion criteria were enrolled in the study after obtaining written informed consent from them.

Study procedure

All patients underwent hematological evaluation (including hemoglobin, total and differential leukocyte count, platelet count), biochemical (thyroid function test like T3, T4 and TSH, liver function tests, renal function test). Data was presented as percentages for categorical variables and mean (SD) for normally distributed continuous variables.

RESULTS

Among 50 patients with hypothyroidism were enrolled in our study during the study period. Majority of the patients were in the age group of 31-50 years (range 18 to 74 years). Clinical hypothyroidism was more common in females (72%) as compared to those seen in males (28%) (Table1). Idiopathic hypothyroidism was present in 98% patients while only one patient (2%) had Hashimoto’s thyroiditis.

Table 1: Age and gender wise distribution of patients.

| Age group     | No. of patients |
|---------------|-----------------|
| Male no. pts. (%) | Female no. pts. (%) | Total no. pts. (%) |
| Below 20 years |                 |                  |
| 0(0)          | 1(3.84)         | 1(2)             |
| 21-30 years   | 1(7.143)        | 6(23.08)         | 7(14) |
| 31-40 years   | 3(21.42)        | 11(42.30)        | 14(28) |
| 41-50 years   | 7(50)           | 12(46.15)        | 19(38) |
| 51-60 years   | 2(14.28)        | 4(15.38)         | 6(12) |
| 61 onwards    | 1(7.143)        | 2(7.7)           | 3(6)  |
| Total         | 14(28)          | 26(72)           | 50(100)|

Generalized weakness was the commonest presenting symptom followed by lethargy and anorexia. Other common symptoms were breathlessness, weight gain, and change in voice, sensation of cold, palpitations, precordial pain, menorrhagia and impairment of memory.
Bilateral non-pitting edema was seen in 72% patients while puffiness of face and delayed relaxation of ankle jerk was present in 68% patients each. Skin changes varied from 60%-75% (Table 3).

**Table 2: Symptomatology of hypothyroidism in fifty patients (n=50).**

| Symptoms                      | No. of patients | Percentage |
|-------------------------------|-----------------|------------|
| Gen. Weakness                 | 49              | 98         |
| Lethargy                      | 46              | 92         |
| Breathlessness                | 35              | 70         |
| Weight gain                   | 35              | 70         |
| Hoarseness of voice           | 39              | 78         |
| Anorexia                      | 45              | 90         |
| Constipation                  | 29              | 58         |
| Decreased sweating           | 43              | 86         |
| Sensation of cold            | 35              | 70         |
| Palloration                   | 16              | 32         |
| Precordial pain              | 15              | 30         |
| Menorrhagia                   | 8               | 16         |
| Impairment of memory         | 10              | 20         |

Nervousness, bradycardia, thick tongue and thyroid swelling were present only in 10%-30% patients. Thyroid swelling was diffuse in nature with no predilection to right or left lobe enlargement. Hypertension (40%) and ischemic heart diseases (36%) were the most common comorbid condition (Table 4). Erythrocyte sedimentation rate was higher in patients of Hashimoto’s thyroiditis and in patients with associated pulmonary tuberculosis while in others it was within normal limits (Table 5). Mean serum TSH was elevated while serum T3 and T4 values were reduced. Antithyroid antibody titre was positive in more than seventy percentage of patients (Table 6).

**Table 3: Clinical signs of hypothyroidism in fifty patients (n=50).**

| Symptoms                                      | No. of patients | Percentage |
|-----------------------------------------------|-----------------|------------|
| Bilateral peripheral non-pitting edema         | 36              | 72         |
| Puffiness of face                             | 34              | 68         |
| Delayed relaxation of ankle jerk              | 30              | 60         |
| Pallor of skin                                | 28              | 56         |
| Cold skin                                     | 30              | 60         |
| Boggy eyelids                                 | 28              | 56         |
| Slow speech                                   | 16              | 32         |
| Loss of hairs                                 | 14              | 28         |
| Pallor of lips                                | 14              | 28         |
| Dry skin                                      | 36              | 72         |
| Coarse skin                                   | 36              | 72         |
| Coarse hairs                                  | 14              | 28         |
| Thick tongue                                  | 06              | 12         |
| Nervousness                                   | 10              | 20         |
| Sinus bradycardia                             | 18              | 36         |
| Thyroid swelling                              | 4               | 8          |

**Table 4: Comorbid condition among enrolled patients.**

| Co-existing disease | No. of patient | Percentage |
|---------------------|----------------|------------|
| Hypertension        | 12             | 24         |
| Ischemic heart disease | 11         | 22         |
| Pulmonary tuberculosis | 2              | 4          |
| Bronchial asthma     | 5              | 10         |

**Table 5: Blood parameters in hypothyroid patient (n=50).**

| Indices                        | Mean value | Normal value | No. of patients | %    |
|--------------------------------|------------|--------------|-----------------|------|
| Hemoglobin (GM %)              | 10.0 %     | 9.6%         | 50              | 100% |
| Total count (CMM)              | 8012       | 6021         | 50              | 100% |
| Differential count             | P64 L30 E4 M2 BO | P64 L30 E4M2 BO | 50 | 100% |
| ESR (MM/1st HR.)               | 12.00      | 16.34        | 50              | 100% |

**Table 6: Serum thyroid parameter among enrolled patients.**

| Tests                           | Observed mean value | Normal value | |
|---------------------------------|---------------------|--------------|---|
| Serum T3                        | 0.473 nmol/l        | 1.1-2.9 nmol/l |    |
| Serum T4                        | 2.05 mcg/dl         | 5-11 mcg/dl  |    |
| Serum TSH                       | 43.72 mu/l          | 0.5-5 mu/l   |    |
| Antithyroid antibody titre     | ++ (>70%)           | -            |    |

Thyroid swelling was observed only in three patients (8%). All these 4 patients were submitted for FNAC. Out of these, one patient had classical changes of Hashimoto’s thyroiditis (2%). X-ray among patients revealed cardiomegaly in ten patients (20%), pulmonary Koch’s in (4%) of patient and in rest of patients x-ray chest PA view was normal. ECG changes showed low voltage on electrocardiogram in (20%) of patients and sinus bradycardia in (24%) of patients (Table 7). Twelve patients (24%) had ST-T changes while fifteen patients...
(30%) had normal electrocardiogram. ECHO findings revealed seven patients (14%) had pericardial effusion, while CCF and Hypertensive heart disease was seen in four (8%) patients and five (10%) patients respectively. Otherwise all patients had normal echocardiography (Table 8).

Table 7: ECG changes among enrolled patients.

| ECG changes          | No. of patients (n=50) | %   |
|----------------------|------------------------|-----|
| ST-T changes         | 12                     | 24% |
| Within normal limit  | 15                     | 30% |
| Low voltage          | 10                     | 20% |
| Sinus bradycardia    | 12                     | 24% |
| Chamber hypertrophy  | 1                      | 2%  |
| Disturbance of rhythm| -                      | -   |
| Av dissociation      | -                      | -   |
| Complete heart block | -                      | -   |
| Atrial/ventricular   | -                      | -   |
| premature beats      | -                      | -   |

Management among enrolled patients revealed, most of the patients were put on replacement therapy (L. thyroxine) in dose of 1.6-1.7 mcg/kg/day. Patient of Hashimoto’s thyroiditis who also treated with prednisolone 40-60 mg/day, there was decrease in levels of thyroid hormones in initial phase of disease, followed by state of hypofunction of gland, at that time replacement therapy was added.

Table 8: Echo findings among enrolled patients.

| Echo findings                 | No. of patients | Percentage |
|-------------------------------|-----------------|------------|
| Normal study                  | 34              | 68%        |
| Pericardial effusion          | 7               | 14%        |
| CCF                           | 4               | 8%         |
| Hypertensive heart disease    | 5               | 10%        |

Co-existing conditions like hypertension with hypothyroidism were treated by L-thyroxine + calcium channel blocker in two patients and L-thyroxine + ACE-inhibitors in two patients. Ischemic heart disease with hypothyroidism was treated with L-thyroxine + Nitrate + Antiplatelet agent + tranquilizer. Pulmonary tuberculosis with hypothyroidism was treated with L-thyroxine + AKT containing HERZ regime. Bronchial Asthma with hypothyroidism was treated with L-thyroxine + bronchodilators. Iron-preparation, vitamins, calcium, zinc were given as a supportive therapy. There was no mortality among study patients during the study period (Table 9).

Table 9: Side effect profile among enrolled patients.

| Disease                      | Drugs used                         | Side effect  | No. of patients | Percentage |
|------------------------------|------------------------------------|--------------|-----------------|------------|
| Hypothyroidism               | LT                                 | Chest pain,  | 5               | 10%        |
|                              |                                    | Palpitation  | 3               | 6%         |
| Hashimoto’s thyroiditis      | LT with steroids                   | None         | NIL             | NIL        |
| Hypertension                 | LT with (1) calcium channel blockers,(2) ace inhibitors| Constipation,| 1               | 2%         |
|                              |                                    | Dry cough    | 2               | 4%         |
| Ischemic heart disease       | LT with (1) nitrates,(2) anti-platelet agent| Headache,   | 4               | 8%         |
|                              |                                    | None         | NIL             | NIL        |
| Pulmonary tuberculosis       | LT with AKT                        | None         | NIL             | NIL        |
| Bronchial asthma             | LT with bronchodilators            | Gastritis,   | 2               | 4%         |
|                              |                                    | Rhythm       | 1               | 2%         |
|                              |                                    | disturbance  |                 |            |

DISCUSSION

Hypothyroidism is the most common disorder of thyroid gland. The clinical syndrome of hypothyroidism is the result of deficient production of thyroid hormone or very rarely the defect in its receptor. In hypothyroidism, virtually every tissue, every organ and every in the body is affected to a greater or lesser extent.

Table 10: Comparing age distribution in the hypothyroid patients.

| Age groups (years) | Vairamanikandan et al\(^3\) | Present study |
|--------------------|-------------------------------|---------------|
| 0-40               | 28                            | 22            |
| 41-60              | 17                            | 25            |
| >60                | 5                             | 3             |
| Total              | 50                            | 50            |

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Table 11: Gender distribution of hypothyroid patients.

| Studies                     | Gender | Total no. of patients | (%)   |
|-----------------------------|--------|-----------------------|-------|
|                             | M      | F                     |       |
| Vairamanikandan et al³      | 17     | 33                    | 50    |
| Sinha and bhattachar⁴       | 12     | 44                    | 56    |
| Present series              | 14     | 36                    | 50    |
| V.c. matthew⁵               | 7      | 21                    | 28    |
| Rakesh dhadhal⁶             | 25     | 3                     | 28    |
| Arindam bose⁷               | 515    | 1614                  | 2129  |

Hydrophyroidism was more common amongst female patients in all series (66-89.28%) and clinical hypothyroidism is 3 times more common in female compare to males in present study and also in other studies (Table 11). Most of patients were having primary (idiopathic) hypothyroidism, while secondary hypothyroidism due to Hashimoto’s thyroiditis varied from 3-11% (Table 12).

Table 12: Etiology of hypothyroidism.

| Studies                     | Etiology | No. of patients | Percentage (%) |
|-----------------------------|----------|-----------------|----------------|
|                             | Idiopathic | Hashimoto’s    | Idiopathic | Hashimoto’s |
| Kikuchi et al⁸              | 16        | 2               | 18          | 88.8        | 11.2        |
| Present studies             | 49        | 1               | 50          | 98          | 2           |

Table 13: Symptomatology of hypothyroid in patients (n=50).

| Symptom           | Larson et al⁸ | Present study (%) |
|-------------------|---------------|-------------------|
| Generalized weakness | 99             | 98                |
| Lethargy          | 91            | 92                |
| Decreased sweating | 89            | 56                |
| Cold sensation    | 89            | 70                |
| Memory impairment | 66            | 20                |
| Constipation      | 61            | 58                |
| Weight gain       | 59            | 70                |
| Breathlessness    | 55            | 70                |
| Hoarseness        | 52            | 78                |
| Anorexia          | 45            | 90                |
| Menorrhagia       | 32            | 16                |
| Palpitation       | 31            | 32                |
| Precordial pain   | 26            | 30                |

Generalized weakness and lethargy were predominant symptoms with patients presented. Other symptoms were anorexia, weight gain, change of voice (hoarseness of voice) and breathlessness. Decreased sweating, sensation of cold, impairment of memory, were not common in present series (Table 13).

Table 14: clinical signs of hypothyroid patients.

| Clinical sign         | Larsen et al⁸ | Present study (%) |
|-----------------------|---------------|-------------------|
| Dry skin              | 97            | 72                |
| Coarse skin           | 97            | 72                |
| Coarse hair           | 95            | 72                |
| Slow speech           | 91            | 72                |
| Boggy eyelids         | 90            | 72                |
| Cold skin             | 83            | 60                |
| Thick tongue          | 82            | 12                |
| Puffiness of face     | 79            | 68                |
| Pallor of skin        | 67            | 60                |
| Loss of hairs         | 57            | 32                |
| Pallor of lips        | 57            | 28                |
| Bilateral non-pitting edema | 55        | 72                |
| Nervousness           | 35            | 72                |

Patients presenting with bilateral non-pitting edema and puffiness of face, skin changes and changes in hair were common in Lippincott study. Most patients were having overt hypothyroidism in Lippincott study while they were less common in our study because subclinical signs like S. bradycardia, thyroid swelling and delayed relaxation of
ankle jerk were not taken into consideration in their study. Dr. A. M. Somalwal has noticed patients having gradual onset of progressive cerebellar syndrome without involvement of cranial nerves or pyramidal tract involvement. This study had none (Table 14).

Table 15: Cholesterol level in hypothyroid patients

| Studies             | Normal value | Hypercholesterolemia | Mean value |
|---------------------|--------------|----------------------|------------|
| Vairamanikandan et al1 | 57.14%       | 42.8%                | 233.18     |
| Present study (n=30) | 42%          | 58%                  | 215.22     |

Hypercholesterolemia was seen in about 58% of patients in this study. In hypothyroid state, LDL fraction and triglyceride were mostly affected, and HDL fraction was decreased. This was mostly because of both lipid synthesis and degradation of lipid were at slower rate. Caraccio N. Ferrannini concluded in his study that only serum LDL levels are increased specifically and reversibly in association with subclinical hypothyroidism. Altered Lipoprotein (a) values reflect a genetic influence rather than a reduced thyroid hormone action (Table 15).

In hypothyroidism, there is decreased amount of circulating levels of serum T3 and T4, that leads to stimulation of pituitary gland and hypothalamic region both of which leads to increase level of serum TSH which result in increased synthesis of thyroid hormone in blood.

Serum TSH is most sensitive parameter for diagnosis of hypothyroid state. Ditta A and Tauyab M proposed from their study that estimation of TSH in the patients with type-1 diabetes may be useful in the early identification of thyroid dysfunction. It is observed that mean value of S. TSH increased in both of series while S. T3 and S. T4 levels were reduce in both the series (Table 16).

Table 16: Thyroid function test of hypothyroid patients.

| Tests                     | Sinha and bhattacharya4 (n=56) | Present series (n=50) |
|---------------------------|--------------------------------|-----------------------|
| Serum T3                  | 0.51 +/- 0.05 nmol/l            | 0.473 nmol/l          |
| Serum T4                  | 20.31 +/- 2.4 ng/ml             | 2.05 ng/ml            |
| Serum TSI                 | 52.61 mu/l                     | 43.72 mu/l           |

Table 17: Changes in X-ray chest PA view in hypothyroid patients

| Studies                  | Cardiomegaly | No. of patients | %   |
|--------------------------|--------------|-----------------|-----|
| V.C. Mathew Roy4         | 22           | 28              | 78.75% |
| Present study            | 12           | 50              | 24%  |

Cardiomegaly was considered when cardiothoracic ratio was more than 0.5. They could be due to peri-cardial effusion, cardiomyopathy, CCF, anemia etc. There were differences in patients having cardiomegaly in present series and V.C. Mathew Roy study group, it may be due to the fact that most of the patients were having full blown picture of myxedema and study was targeted for study of pericardial effusion in latter series (Table 17).

Table 18: Electrocardiographic changes in hypothyroid patients

| ECG changes                | V.C. Mathew Roy series4 (N=28) | Present series (N=50) |
|----------------------------|--------------------------------|-----------------------|
|                            | No. of patient | Percentage | No. of patient | Percentage |
| ST-T changes               | 13              | 46.42      | 12             | 24         |
| Low voltage complex        | 2               | 7.15       | 10             | 20         |
| Sinus bradycardia          | 7               | 25         | 12             | 24         |

Table 19: Echocardiographic findings in hypothyroid patients

| Pericardial effusion       | V.C. Mathew Roy series4 (n=16) | Present series (n=50) |
|----------------------------|--------------------------------|-----------------------|
|                            | No. of patients | %   | No. of patients | %   |
| Mild                       | 6               | 37.5 | 4             | 8   |
| Moderate                   | 8               | 50   | 3             | 6   |

The findings were similar in both V.C. Mathew Roy series and in present series. Common ECG findings in study groups were sinus bradycardia, low voltage ECG and ST-T changes which are 24%, 20%, and 24% respectively (Table 18).

Moderate amount of pericardial effusion was seen in 50% of patients in V.C. Mathew Roy series and it could be mainly due to most of patients having overt hypothyroidism. In present series 8% of patients were having mild pericardial effusion while 6% of patients had moderate pericardial effusion (Table 19). All the patients after confirmation of hypothyroidism by clinical data and supported laboratory investigations,
were put-on lowest dosage of Levo-thyroxine (0.1 mg). Then dosage of replacement therapy was increased in subsequent follow-up visits at interval of 6-8 weeks. Reviewing patient’s symptoms, particularly paying attention to development of new symptoms, like angina pain, palpitation and by keeping watch on patient wellbeing, dosage of Levo-thyroxine had been adjusted individually. Thyroid function tests, particularly TSH estimation were done after six weeks of starting therapy. Then it was repeated annually or when required. Side effects of L-thyroxine were chest pain and palpitation. Chest pain was in 10% patients and it was non-specific, non-cardiac and not due to coronary artery disease. No definite explanation can be offered for this and therefore it was assumed to attribute as side effect of L-thyroxine. Palpitation is a well-known side effect of L-thyroxine and was observed in 6% patients. This was commonest amongst the patients of Ischemic Heart Disease and anaemia. Palpitation appeared to be related with dosage L-thyroxine as increase in the dosage resulted in palpitation. However, it was tolerated well. Conditions co-existing with hypothyroidism like hypertension, Ischemic Heart Disease, pulmonary Koch’s, Bronchial asthma were treated accordingly with addition of L-thyroxine. On follow-up examination at three weeks, none of the patients were having side effects due to treatment regime used for co-existing medical disease. None of the complications were observed during follow-up examination and there was no mortality.

CONCLUSION

This study thus concludes, hypothyroidism as a clinical entity is common between 4th and 6th decade of life and seen more among females. Though etiology remained unknown in majority of the patients, weakness, and lethargy were the common clinical presentation and pedal edema with puffiness of face being the common clinical findings. Hypertension and heart disease were the commonest comorbidities in this study.

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