Goitrous Hypothyroidism: Changing Clinical Profile

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ABSTRACT

Introduction: On availability of sensitive techniques and better understanding of pathogenesis, hypothyroidism is being detected in early stages in milder forms. The clinical picture is changing in the third millennium compared with what was described 50 years ago.

Materials and Methods: This is a comparative study of goitrous and nongoitrous cases referred for functional evaluation of the thyroid.

Results: One hundred and five cases of goitrous hypothyroidism are studied with hormonal and immunological parameters along with cytology; 80% of the cases were asymptomatic/had protean manifestations. The etiology was autoimmune thyroiditis as evident from raised levels of thyroperoxidase antibodies as well as histopathology.

Conclusion: Autoimmune thyroiditis is the commonest cause of goitrous hypothyroidism, i.e., being increasingly detected in the early stages with milder form. Clinicians need to be aware of the changing profile of goitrous hypothyroidism.

Keywords: Goitrous, Granulomatous thyroiditis, Hypothyroid, Thyromegaly.


INTRODUCTION

Thyroid disorders are the commonest endocrine problems in India.1 Forty years ago, majority of our hypothyroid patients used to be perimenopausal women presenting in severe forms, making a picture of a spot diagnosis (Fig. 1).

Severe hypothyroidism presented with characteristic features of myxedema facies, slow mentation/response, thick hoarse voice, dry skin, and menorrhagia. The only investigation then available at tertiary care centers was radioactive iodine uptake. Over the years, with better understanding of the pathogenesis and availability of ultrasensitive diagnostic tools, the cases are detected much earlier. As a result, there is a change in the profile of hypothyroidism.

In early stages, it may be detected by functional evaluation of a goiter or incidentally in an asymptomatic patient with protean manifestations like hair fall, weight gain, etc.

The cases are referred to our thyroid clinic by various clinical disciplines for evaluation and management of thyroid disorders. In addition, a large number of cases alarmed with the presence of goiter walk in themselves for management. It was observed that a large number of these goitrous cases were clinically asymptomatic; however, they turned out to be hypothyroid on investigations. Therefore, a prospective study was undertaken.

MATERIALS AND METHODS

• A study group comprised males and females above the age of 18 years presenting with goiter.
• A control group comprised age-/sex-matched cases without goiter. All these cases in the control group were referred for thyroid hormone estimations for various indications like obesity, infertility, menstrual irregularities, bad obstetric history, and preoperative evaluation of the thyroid functions.

The study spanned over a period of 18 months. Consecutive cases with goiter and nongoiter were included after informed consent. A detailed clinical history was taken. Duration of thyromegaly was noted. Clinical examination including local examination of the thyroid was carried out. All the cases of control as
well as study group were subjected to thyroid hormone estimation.

Cases with hormone profile revealed overt hypothyroidism (OH) with thyroid-stimulating hormone-sensitive (s-TSH) >15 µIU/mL or subclinical hypothyroidism (SCH) with normal T4 and S. The TSH varying between 5.1 and 14.9 µIU/mL was once again probed with direct questions to find out symptoms suggestive of thyroid hypofunction.

Cases of OH and SCH were further subjected to antithyroperoxidase antibodies (TPO Abs) also known as antinuclear antibodies estimation. Fine-needle aspiration cytology was carried out in all cases with goiter.

Overt hypothyroid cases were then treated with thyroid hormone replacement as per the guidelines of American Thyroid Association with a dose of 1.6 µg/kg/day of the ideal body weight.2

The serum triiodothyronine (T3), thyroxine (T4), and TSH were estimated using enzyme-linked fluorescence assay on mini VIDAS from bioMerieux. Fine-needle aspiration cytology was carried out as an office procedure under strict aseptic precautions. The aspirate was fixed with methanol alcohol and stained with hematoxylin–eosin as well as Giemsa stain. The pathologist was blinded to the clinical, hormonal details.

All the hypothyroid cases were further investigated with electrocardiogram, echo cardiography, and serum lipid profile.

OBSERVATIONS

During a study period of 18 months, 150 cases with goiter formed the study group with a control group of nongoitrous 100 cases.

Control Group

There were 76 females and 24 males. The mean age of this group was 26.8 years; obviously none had thyromegaly. Only 4/100 cases had s-TSH varying between 5.6 and 9.7 µIU/mL; however, their free T4 and TPO antibodies were within normal limits. These cases were advised 6 monthly follow-up with s-TSH estimation.

Study Group

This group had 150 consecutive cases of thyromegaly. There were 140 females and 10 males, confirming the female preponderance in thyroid disorders; 45/150 cases were functionally euthyroid as shown by their hormone profile. Remaining 105 cases were diagnosed as goitrous hypothyroidism and studied in detail. There were 98 females and 7 males. The mean age of the study group was 27.6 years. All these cases were again probed for symptomatology, suggestive of hypofunction of the thyroid.

Symptoms like lethargy, depression, change in voice, constipation, and menorrhagia raised the index of suspicion for hypothyroidism. The present study had only 12 cases having one or two of these symptoms along with goiter. Moreover, all these patients were not menopausal but were in their thirties. The main indication for evaluation of thyroid functions was presence of goiter.

The remaining 93 cases did not volunteer any symptoms, suggestive of hypofunction. In other words, they were asymptomatic. They came to the health care facility for reasons shown in Table 1. These reasons were revealed only on direct questioning.

Slow relaxation of the ankle jerk was noted only in six cases.

Cases of infertility, bad obstetric history, irregular/scanty periods, sec. amenorrhea were referred for thyroid studies firstly because of the presence of the goiter and secondly because of the increasing awareness among the clinicians about the changing clinical profile of the thyroid dysfunction.

There were 27 young females with obesity/weight gain. Weight gain in hypothyroidism is due to myxedema, but these 27 cases had no evidence of puffiness, edema-pitting/nonpitting. More than clinicians, the weight loss programmers are increasingly referring obese females for thyroid hormone estimation because the hypothyroidism has protean manifestations.

Five cases with menstrual disorders had galactorrhea. The serum prolactin (PRL) levels in them ranged from 33 to 47 ng/mL.

Zulewski’s clinical scoring3 system was used for the study group, and the results are shown in Table 2.

As can be seen, only 12 cases had a hypothyroid score, 53/105 cases of OH were clinically asymptomatic despite

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Table 1: Clinical profile (n = 93)

<table>
<thead>
<tr>
<th>Clinical profile</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparently asymptomatic</td>
<td>93</td>
</tr>
<tr>
<td>Goiter</td>
<td>93</td>
</tr>
<tr>
<td>Weight gain</td>
<td>27</td>
</tr>
<tr>
<td>Lethargy</td>
<td>16</td>
</tr>
<tr>
<td>Constipation</td>
<td>03</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>02</td>
</tr>
<tr>
<td>Irregular/scanty menses</td>
<td>14</td>
</tr>
<tr>
<td>Sec. amenorrhea</td>
<td>02</td>
</tr>
<tr>
<td>Infertility</td>
<td>04</td>
</tr>
<tr>
<td>Bad obstetric history</td>
<td>04</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>05</td>
</tr>
</tbody>
</table>

Table 2: Zulewski’s score

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of cases</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5</td>
<td>12</td>
<td>Hypothyroid</td>
</tr>
<tr>
<td>3–5</td>
<td>40</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&lt;3</td>
<td>53</td>
<td>Euthyroid</td>
</tr>
</tbody>
</table>
probing history. The clinical scoring system of Zulewski lacks sensitivity and specificity (Table 3).3

One case had a multinodular goiter.

Hormone Profile

Table 4 shows the hormone profile of the study group. Serum T3 levels ranged from 0.4 to 2.46 nmol/L. Similarly, the serum T4 levels ranged from 9.85 to 77.7 nmol/L. Very low T3 and T4 levels were characteristically noted in 12 symptomatic cases. The 93 asymptomatic cases had normal T3, which is a metabolically active hormone. Serum T4 being low in these cases, the TSH was elevated by biofeedback mechanism confirming primary hypothyroidism. Serum TSH varied from 18 to 292 µIu/mL.

IMMUNOLOGICAL PARAMETERS

The mean anti-TPO antibody level was 836.94 ± 302.3. Attempt to correlate TPO Abs with severity of the hypothyroidism based on serum TSH levels showed nonlinearity (Table 5).

Infiltration of thyroid parenchyma by inflammatory infiltrates containing small lymphocytes, plasma cells, and well-developed germinal centers is the cytological picture of thyroiditis which was seen in all the cases. In addition, many thyroid follicles showed atrophic changes. The hallmark of Hashimoto’s4 thyroiditis was Askanazy / Hürthle cells (Fig. 2). These are epithelial cells characterized by abundant eosinophilic, granular cytoplasm. It is a metaplastic response to inflammatory injury.5

Six cases revealed clusters of lymphocytes, histiocytes with few giant cells lining the follicles diagnosed as granulomatous thyroiditis (Fig. 3).

Twenty-seven cases revealed abundance of colloid within the follicles with normal follicular epithelial cells, hence, reported as colloid goiter (Fig. 4), although hormonally and immunologically these cases had autoimmune thyroiditis.

DISCUSSION

Hypothyroidism results from inadequate production or inadequate action of thyroid hormone in target organs. Primary hypothyroidism is the commonest disorder, while secondary and tertiary hypothyroidisms are rare. Low levels of circulating T4 with increased levels of serum TSH are the diagnostic criteria of primary hypothyroidism.

It had been more prevalent in elderly women, commonly presenting at menopause. However, the mean age of the study group in this series is only 27.8 years. Hypothyroidism is being detected at a much earlier age simply because of the presence of the goiter and availability of sensitive diagnostic techniques, although these patients had no symptom or sign of hypothyroidism.

Table 3: Grades of thyromegaly

<table>
<thead>
<tr>
<th>Grades</th>
<th>Thyromegaly</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Goiter visible with extended neck</td>
<td>40</td>
</tr>
<tr>
<td>II</td>
<td>Goiter visible with neck in normal position</td>
<td>46</td>
</tr>
<tr>
<td>III</td>
<td>Goiter extending up to sternomastoid</td>
<td>14</td>
</tr>
<tr>
<td>IV</td>
<td>Goiter extending beyond sternomastoid</td>
<td>04</td>
</tr>
</tbody>
</table>

Table 4: Hormonal profile

<table>
<thead>
<tr>
<th>Type</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum T3</td>
<td>1.18 ± 0.28 nmol/L</td>
<td>0.92–2.33 nmol/L</td>
</tr>
<tr>
<td>Serum T4</td>
<td>42.06 ± 22.74 nmol/L</td>
<td>60–120 nmol/L</td>
</tr>
<tr>
<td>Serum TSH</td>
<td>103 ± 72.56 µIu/mL</td>
<td>0.25–5.0 µIu/mL</td>
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</tbody>
</table>

Table 5: Thyroid cytology

<table>
<thead>
<tr>
<th>Cytology</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic thyroiditis</td>
<td>72</td>
</tr>
<tr>
<td>Granulomatous thyroiditis</td>
<td>06</td>
</tr>
<tr>
<td>Colloid goiter</td>
<td>27</td>
</tr>
</tbody>
</table>
Female preponderance in thyroid disorders continues to remain the same.

The clinical profile of menopausal hypothyroid women had been described for all these years. These patients had symptoms like lethargy, depression, menorrhagia, constipation, hoarseness of voice. However, goiter was absent (atrophic thyroid). Over the years, it has been realized that there is a great symptom overlap between hypothyroids and normal population. The attempts to clinical scoring system have also turned out to be unsuccessful.

Functional (overt) hypothyroidism was detected in 105/150 (70%) of young asymptomatic goitrous patients. Overt hypothyroidism was detected on functional evaluation of the goiter. Only 12 cases presented with symptoms suggestive of hypothyroidism. More than 80% of the hypothyroid cases are asymptomatic, thus emphasizing the need for high index of suspicion with increased awareness of the changing profile of the hypofunction.

Thyromegaly was mild, grade I to II, in 82.5% of the cases. As the thyroid starts failing, the inadequate production of T4 results in increased TSH secretion leading to thyromegaly in early stages of the disease process. But over the years, the gland goes on diminishing as a result of immunological destruction.

The hormone profile showed low T4 with high TSH. The paucity of symptoms may be explained based on the normal serum T3 levels seen in these cases. The presence of goiter also indicates early stage of autoimmune thyroiditis.

Hyperprolactinemia, serum PRL levels not exceeding 60 ng/mL, have been reported in about 20% of the hypothyroid patients, and it normalizes with thyroid replacement therapy. This series had five cases with galactorrhea, with serum PRL varying from 33 to 47 ng/mL. The exact cause of hyperprolactinemia is not understood; probably, it depicts the hypersensitivity of the lactotrophs to the raised levels of thyrotropin-releasing hormone.

Autoimmune thyroiditis has now been recognized as the commonest etiology of primary hypothyroidism. Detection of serum anti-TPO Abs (antimicrosomal antibodies) and antithyroglobulin antibodies is a vital component of diagnosing autoimmune thyroiditis. Antimicrosomal antibodies (TPO antibodies) are more sensitive than anti-Tg Abs. Antibodies are known to be involved in thyroid cell destruction through cytotoxic mechanisms mediated by the complement and killer cells. The autoimmune process appears to be due to an inherited defect in immune surveillance, which leads to dysregulation, chronicity, and destruction of the gland.

Autoimmune mechanism is evident in this study by increased levels of TPO antibodies varying from 50 to more than 1,000. However, there was no linearity between levels of elevated serum TSH and antibodies.

Although thyroid cytology is not necessary for diagnostic and therapy purposes, it gives the confirmation of the etiology. The hallmark of the autoimmunity is extensive infiltration of inflammatory cells, including small lymphocytes, plasma cells, follicular atrophy, and fibrosis.

Hashimoto’s thyroiditis is caused by a breakdown in self-tolerance to thyroid autoantigens, which is evident by the circulating autoantibodies against TPO and thyroglobulin. The autoimmunity has a strong genetic predisposition. Approximately 50% of the siblings show raised levels of thyroid antibodies.

In the early stages of autoimmune thyroiditis, the lesions are focal. Twenty-seven cases in this series were diagnosed as colloid goiter because the aspiration needle missed the focal lesion. It is the pitfall of the technique.

Six cases had granulomatous thyroiditis, but there was no history of pain. The granulomatous thyroiditis (de Quervain’s) is less common. It usually occurs in the fifth decade. It is supposed to be triggered by the presence of viral infection. Clinically, the patient complains of pain in the thyroid region.

The clinician may also look for other autoimmune disorders like systemic lupus erythematosus, Sjögren’s syndrome, type II diabetes mellitus, rheumatoid arthritis, and Grave’s disease.

A rare cause of goitrous hypothyroidism is Pendred syndrome, which is a genetic disorder with organification defect presenting in family members with sensorineural deafness, goiter, and hypothyroidism. Radioactive iodine uptake with perchlorate washout test clinches the diagnosis of organification defect.

CONCLUSION

A study of 105 cases of goitrous hypothyroidism revealed that: (1) The age of presentation was second and third...
decade. (2) More than 80% of cases were asymptomatic/had protean manifestations. (3) Patients with goiter, menstrual irregularities, bad obstetric history should be subjected to serum TSH estimation as a screening test. In addition, serum TSH estimation should be a parameter of preoperative evaluation. (4) Anti-TPO Abs were high in all of them. (5) Fine-needle aspiration cytology confirmed lymphocytic thyroiditis.

Clinicians of various disciplines need to be aware of the changing profile of hypothyroidism.

REFERENCES