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Hypothyroidism.....Beyond Thyroid !

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Thyroxine T4 and tri-iodothyronine T3 are the hormones secreted by the thyroid gland. Secretion of these hormones is regulated by thyroid stimulating hormone (TSH) by the pituitary which in turn is regulated by the hypothalamic thyrotropin releasing hormone (TRH). TSH is the 'set point' in this hypothalamic-pituitary-thyroid feed back axis.

Both these hormones act on their specific receptors. During development, these hormones play a crucial role in cell differentiation. In adults, these hormones are critical for the body metabolism maintaining thermogenic and metabolic homeostasis.

Many structural and functional abnormalities can impair the production of these thyroid hormones with its systemic manifestations. It may be due to primary failure of the thyroid gland with low T4 and elevated TSH levels termed as primary hypothyroidism which accounts for 99 % of cases OR it may be due to insufficient stimulation of the normal thyroid gland as a result of the hypothalamic or pituitary disease or a defect in the TSH molecule itself. This is termed as central hypothyroidism which accounts for less than 1 % of cases.

Till about a decade ago the medicine and endocrinology books enumerated causes of hypothyroidism as----

1. Idiopthic Atrophic hypothyroidism
2. Ablative : surgical or radioablation
3. Impairment of biosynthesis of thyroid hormones with compensatory hyperplasia of the thyroid gland –Goitrous hypothyroidism
4. Transient hypothyroidism :post-partum thyroiditis
5. Hashimoto's autoimmune thyroiditis
6. Central hypothyroidism
7. Resistance to thyroid hormone --RTH

In last decade the scenario has changed due to widespread availability of sensitive diagnostic techniques and better understanding of the pathogenesis. Although Hashimoto described 'struma lymphomatosa' in 1912; it is only in last 10 to 15 years Auto-Immune Thyroid Disease AITD is universally accepted as the commonest cause of primary hypothyroidism in countries with iodine sufficiency and iodine deficiency as a cause in iodine deficient countries.

Being an autoimmune disorder one has to think beyond thyroid for co-existing autoimmune diseases in the patient or his family. Thyroid hormones affect all the organ systems and functions which need to be evaluated before initiating thyroid replacement therapy.

Severe hypothyroidism presents with characteristic features of myxedema facies, slow mentation / response, thick hoarse voice, dry skin, constipation and menorrhagia. However in early stages it may be detected by functional evaluation of a goitre or incidentally in an asymptomatic patient with protean manifestations like hair fall, weight gain etc.

Many studies have documented association between all types of menstrual irregularities and hypothyroidism. Bad obstetric history, repeated miscarriages, primary and secondary infertility may also be associated with hypothyroidism. Serum TSH estimation as a part of pre-operative evaluation and in early pregnancy may detect early asymptomatic cases.

In addition,large number of people voluntarily avail the investigation packages offered by the chain of laboratories.

As a result, many hypothyroid cases are detected in early stages. Treating the elevated TSH report without proper evaluation of the patient has been observed as an increasing trend.

Therefore a study of newly detected hypothyroid cases refered to us was undertaken. The study comprises of 100 consecutive cases in the age group of 15 yrs to 63 yrs. A detailed history including history of galactorrhea along with clinical examination was done.

Each hypothyroid case was investigated for.....

CBC

Serum FT3, FT4,TSH, Anti-microsomal (TPO) antibody

S.Prolactin,S. B 12,Parietal cell antibody

ECG, X-ray chest

OBSERVATIONS

There were 89 women and 11 men.Mean age of the group was 44 yrs,26 cases were less than 25 yrs of age.

Reasons for TSH estimation in this series

Asymptomatic Goitre	33
Weight gain	11
Pregnancy	09
Infertility, scanty menses	09
Schizophrenia /Depression	03
Vague symptoms(hair fall)	25

Voluntary check up	05
Symptomatic hypothy	05

Only 6 women gave history of Galactorrhea. Examination revealed it in 29 additional cases. It can be overlooked unless actively elicited. One was a lactating mother.

Remaining 53 women and 11 men had no evidence of nipple discharge.

S. TSH levels----N range 0.4 to 4.5, TSH > 10 was diagnosed as overt hypothyroidism.

In this series S.TSH ranged from 17 microunits/ml to more than 500 microunits /ml. All the 5 symptomatic cases had TSH levels were more than 400 microunits/ml.

Anti-microsomal (TPO) antibodies—N range 5-34 IU/ml

Antibody levels	Cases (n)
< 34	18
35—100	04
101—300	16
301—600	21
> 601	41

18/100 cases did not have antibodies. 82 cases had raised levels of AMA.

Five symptomatic cases had AMA more than 1000 IU however no correlation was found between antiboby levels and severity of the disease. Once detected these antibodies persist.

HYPERPROLACTENEMIA

S. Prolactin level---N 4.79—23.3 in females, males — 0.04 — 15.2 ng/ml.

70 cases including 11 males had S PRL within normal limits.

18 cases had PRL 24 to 60 ng/ml.

Various reports show 27 % of hypothyroid patients have hyperprolactinemia. The cause of hyperprolactinemia in primary hypothyroidism is uncertain but it is well documented. It may result from the enhanced sensitivity of the lactotrophs to thyrotropin releasing hormone (TRH). Thyroxine replacement therapy controls the galactorrhea and normalizes S. PRL levels if PRL is less than 60 ng/ml.

12 cases had PRL varying from 61 to 300 ng/ml. Of these 12 cases with very high PRL, 8 patients revealed microprolactinoma on MR imaging without any compression.These cases in addition to thyroxine replacement need therapy of hyperprolactenemia with bromocriptin analogs. My patients are treated with thyroxine + cabergolin which normalised PRL levels with disappearance of galactorrhea. Follow up MRI did not show prolactinoma.

Cerebellar Ataxia

Two patients, a 45 yrs woman and 43 yrs old man were found to have cerebellar ataxia. Both of them complained of imbalance, TSH was more than 100, TPO >1000 IU/ml, $S.B_{12}$ was low but they did not show sensory ataxia. It was cerebellar ataxia. Medical literature documents that on autopsy the cerebellum shows neural myxedematous infiltrates of glycogen and mucinous material.The manifestations are milder in adult hypothyroidism and can be controlled with control of hypothyroidism.

Proximal weakness

Difficulty in upsquatting was complained by one patient. Examination revealed 16 cases had difficulty in upsquatting suggesting proximal muscle weakness in hypothyroidism. Only 2% patients present with proximal myopathy but it can be found in about 20% cases.

Vit.D levels were also low in these patients. Vit. D plays an important role in balancing TH_1 and TH_2 cells. Vit. D deficiency has been associated with numerous AIDS.

Cardiomegaly

Sen in 39 cases on chest X-ray. The LVEF estimated in these patients was normal on 2-D echocardiography. Six of these cases had minimal pericardial effusion.

Vitilligo

4 cases had vitilligo which being an autoimmune disorder by itself can coexist in AITD.

Rheumatoid arthritis

It was detected in 4 cases.

S.B 12 levels

Pernicious anemia being an autoimmune disease may be seen in AITD. We measured B 12 conc.in serum of our hypothyroid cases.

$S.B_{12}$---N 211—946 pg/ml		Parietal Cell Antibody Positive
< 211 pg	54 cases	33 cases
212—311 pg	24 cases	17 cases
312----411 pg	03	00 cases
>411 pg	19	03 cases

54 /100 of our Hypothyroid patients were deficient in Vit B 12. Hematology profile of these cases did not show anemia,macrocytosis.Hematological effects of vit B 12 deficiency are seen at lower levels of B 12 viz.<100 pg /ml. Dietary history revealed 16 cases were vegeterians. All the cases were subjected for parietal cell antibody test. 53 out of 100 cases showed antibodies against parietal cells necessitating parenteral B_{12} therapy.A linear relationship between AMA and Parietal cell antibody (PCA) could not be seen however higher the level of AMA, greater were the chances of detecting PCA.

One patient with B_{12}>411pg had PCA,on inquiry he revealed being given Inj. B12 by his family physician just before he was refered for AITD.

12 cases deficient in B_{12} (<211pg)did not have parietal cell antibodies.Two of these cases had TPO around 600 IU/ml. These cases may have nutritional deficiency.

Recent studies show co-existence of various autoimmune

disorders (AID) in AITD. Relative risk of other AIDs is significantly increased more than 10 fold for pernicious anemia, SLE, Addison's disease, celiac disease, vitiligo, Rheumatoid arthritis and Type 1 diabetes.

Although the precise pathogenetic mechanisms are unknown, AITD is believed to reflect a multifactorial mode of inheritance between the product of multiple genes conferring susceptibility. Significant clustering of AID within families of AITD cases is reported with 40-50 % of patients reporting another family members with thyroid disorder.

Autoimmunity in the thyroid gland appear to be inherited defect in immune surveillance leading to an abnormal regulation of immune responsiveness or alteration of presenting Ag in thyroid. Presence of elevated antithyroid antibody titres are diagnostic of AITD. Thyroperoxidase TPO is a main thyroidal microsomal antigen, the other one being thyroglobulin. Presence of TPO (AMA) Abs in subclinical hypothyroidism predicts progression to overt hypothyroidism at 4.3 % per year v/s 2.6 % per year without TPO antibodies.

B_{12} deficiency is seen in 54 % of our cases. Khubchandani et al reported it in 64 % cases of hypothyroidism. Our study correlates B_{12} Deficiency with parietal cell antibodies which in turn are correlated with high levels of AMA Abs. Though haematological manifestations of B12 deficiency appear at a level of B12 <100pg/ml, presence of parietal cell antibodies indicate that these cases will progress to develop pernicious anemia which is reported in 12 % of AITDs as a coexisting AID. The early detection and parenteral correction of B12 deficiency will prevent pernicious anemia in them. Literature reports incidence of rheumatoid arthritis in 4.8 % of cases. The incidence of other AIDs is variable.

Screening for other AIDs might be indicated if subjects of AITDs present with new or non-specific symptoms.

A growing tendency is observed in the community to treat only the biochemical report of thyroid function without evaluating the patient.

Primary hypothyroidism is beyond thyroid which necessitates clinical examination, appropriate investigations and corrective therapy in addition to thyroxin replacement therapy with regular monitoring.

It is desirable that every hypothyroid case should undergo:

S. AMA, ATg antibody test

S. Prolactin, S. $Vit._{D3}$

S.B_{12}, If low then parietal cell antibody test

ECG, X-ray chest.

CBC.