

Male hypothyroidism-clinical relevance including role in reproduction

Abstract

Purpose: Overt Hypothyroidism is defined as arise of S.TSH>10mIU/L. Since its incidence is more common in females one generally tends to ignore this diagnosis in males and usually the diagnosis is made in an emergency situation when the patient presents either with coma or with a severe form of Hashimoto's thyroiditis (HT) like IgG4 related thyroiditis.

Methods: A systemic literature search was performed using PubMed for all English articles till Sept 2014 regarding male hypothyroidism using MeSH terms like congenital hypothyroidism, male hypothyroidism and reproduction; subclinical hypothyroidism; Hoffmann's syndrome; myxedemic coma.

Results: To eradicate congenital hypothyroidism all over the world many countries have incorporated in their neonatal screening programme (NNSP), yet occasional cases of cretinism still get diagnosed. Important causes being genes encoding Transcription factor TTX1, TTX2 presenting as Bamforth syndrome, Thyroglobulin gene, Thyroid peroxidase (TPO), TSHR gene abnormalities, Pendred's syndrome coexisting with thyroid developmental abnormalities etc. Context Ig superfamily1 deficiency (IGSF1), Fryns Anophthalmia Plus syndrome (APS), TSH β gene deletion, frame shift mutation in first exon of Fibroblast growth factor8 (FGF8) can present as Central hypothyroidism. The first presentation maybe a neurological emergency like myxedemic coma either secondary to neurofibromatosis, lithium toxicity which responds to L-thyroxin or occasionally may not, responding only to steroids. Some patients may present as different forms of Hoffmann's syndrome or stiff leg syndromes. Subclinical hypothyroidism, (SH) and its aetiology along with TSH R mutations R109 Q reported as causation in 2 brothers and importance of treatment is highlighted. Importance of treatment of SH in children and adults is discussed. Mechanism of reversible kidney dysfunction in hypothyroidism is highlighted along with discussing its relationship with treatment. Changes in serum testosterone and gonadotropins are discussed in a patient of male hypothyroidism and the way it may affect reproduction.

Conclusion: Hypothyroidism may be the primary cause of a male presenting with Hypogonadotropic hypogonadism (HH) and should be suspected in a man presenting with delayed puberty. Untreated hypothyroidism should be suspected as the cause of presentation of myopathies like Hoffmann Syndrome or other myopathies or myxedema coma. SH may warrant treatment in young males with known adverse affects on cardiovascular system although its affect on cognitive function has not been found especially in elderly.

Keywords: congenital hypothyroidism, ttx1, ttx2, central hypothyroidism, igsf1, hoffmann's syndrome, hypogonadotropic hypogonadism, male reproduction, myxedemic coma

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Kulvinder KK,¹ Gautam A,¹ Mandeep S²¹Scientific Director, Centre for Human Reproduction, India²Consultant Neurologist, Swami Satyanand Hospital, India

Correspondence: Kulvinder Kaur, Scientific Director, Centre for Human Reproduction, 721, G.T.B. Nagar, Jalandhar-144001, Punjab, India, Tel 91 1 8198 7204 3422, Fax 91 1 81461 3422, Email kulvinder.dr@gmail.com

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Abbreviations: HT, hashimoto's thyroiditis; HS, hoffmann syndrome; AH, autoimmune hypothyroidism; HH, hypogonadotropic hypogonadism; SCH, subclinical hypothyroidism; CH, congenital hypothyroidism; TG, thyroid gland; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; NNSP, neonatal screening programme; FMD, flow mediated dilatation; DC, coefficient of distensibility; NAFL, non-alcoholic fatty liver; CPK, creatine phosphokinase; APS, anophthalmia-plus syndrome; ES, empty sella; FGF8, fibroblast growth factor 8; H-P, hypothalamo-pituitary; ACC, anterior cingulate cortex; EMG, electromyography; OSA, obstructive sleep apnea; PH, pulmonary hypertension; IR, insulin resistance; MS, metabolic syndrome; CAC, coronary artery calcification; EIA, erythema ab igne; ATT, anti tubercular treatment; TBG, thyroxine binding globulin; DS,

down's syndrome; CeH, central hypothyroidism

Introduction

Although it is well known that hypothyroidism predominantly occurs in females, we have chosen the topic as "male hypothyroidism" as generally its importance gets ignored till the patient presents with a highly worsened disease with coma or severe form of disease or occasionally infertility, impotence or some kind of erectile dysfunction maybe the presenting symptom. To start with we would like to briefly review causes of hypothyroidism in general. Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas where iodine is sufficient, autoimmune disease (Hashimoto's thyroiditis (HT)) and iatrogenic causes are most common.

Causes of Hypothyroidism (Table 1)

Primary hypothyroidism: Primary hypothyroidism refers to hormone deficiency caused by intrinsic dysfunction of the thyroid gland that disrupts the synthesis and secretion of T4 and T3. Overt hypothyroidism is characterized by an elevated TSH levels, usually greater than 10mIU/L, in conjunction with a free T4 level below the lower level of normal reference range. In subclinical hypothyroidism, the TSH levels may be only moderately elevated, the free T4 levels remain in the low normal /normal range. When the condition is severe it is referred to as myxedema. Dietary iodine deficiency is an important cause in children in certain underdeveloped countries. The most important cause of primary hypothyroidism in developed countries is autoimmune or Hashimoto's thyroiditis, a condition in which altered T cell mediated immunity causes destruction of thyroid tissue. This may be a component of type 2 polyglandular autoimmune syndrome

associated with autoimmune adrenal insufficiency and type 1 diabetes mellitus. It is less commonly a component of type 1 syndrome which includes adrenal insufficiency, panhypopituitarism and chronic mucocutaneous candidiasis. Other nonendocrine autoimmune conditions associated with autoimmune thyroiditis include atrophic gastritis, pernicious anemia, systemic sclerosis, sjogren's syndrome, celiac disease, and vitiligo. Individual's treated with interferon Alfa may develop autoimmune thyroiditis with transient or permanent hypothyroidism. Radioactive iodine therapy used for treatment for hyperthyroidism commonly destroys sufficient thyroid tissue to cause post ablative hypothyroidism. Exposure to certain pharmacologic and radio contrast dyes, some expectorants and topical disinfectants can disrupt thyroid function. Lithium inhibits secretion of T3 and T4 leading to hypothyroidism in 10% of people using the same. Other pharmacologic agents include stamuvudine, thalidomide, sutinitib and aminoglutethemide.

Table 1 Genetic Causes of Congenital Hypothyroidism

Defective gene protein	Inheritance	Consequences
PROP-1	AUTOSOMAL RECESSIVE	Combined pituitary hormone deficiencies with preservation of adrenocorticotrophic hormone
PIT-1	AUTOSOMAL RECESSIVE	Combined deficiencies of growth hormone
TSHB	AUTOSOMAL DOMINANT	Prolactin, thyroid-stimulating hormone (TSH)
TSHB	AUTOSOMAL RECESSIVE	TSH deficiency
TTF-1 (TITF-1) ¹²	AUTOSOMAL DOMINANT	Variable thyroid hypoplasia, choreoathetosis, pulmonary problems
TTF-2 (FOXE-1) ¹³	AUTOSOMAL RECESSIVE	Thyroid agenesis, choanal atresia, spiky hair
PAX-8	AUTOSOMAL DOMINANT	Thyroid dysgenesis
TSH-RECEPTOR ¹⁶	AUTOSOMAL RECESSIVE	Resistance to TSH
G (Albright hereditary osteodystrophy)	AUTOSOMAL DOMINANT	Resistance to TSH
Na ⁺ /I ⁻ -symporter ¹⁹	AUTOSOMAL RECESSIVE	Inability to transport iodide
THOX2	AUTOSOMAL DOMINANT	Organification defect
Thyroid peroxidase ¹⁴	AUTOSOMAL RECESSIVE	Defective organification of iodide
Thyroglobulin ¹⁵	AUTOSOMAL RECESSIVE	Defective synthesis of thyroid hormone
Pendrin ¹⁸ (SLC26A4)	AUTOSOMAL RECESSIVE	Pendred syndrome: sensorineural deafness & partial organification defect in thyroid
Dehalogenase I	AUTOSOMAL RECESSIVE	Loss of iodide reutilization

TSH, thyroid-stimulating hormone

Secondary hypothyroidism or central hypothyroidism: May be caused by a number of disorders that impair the hypothalamic-pituitary control of TG. Infiltrative disorders affecting the hypothalamus that can interfere with TRF secretion include sarcoidosis, hemochromatosis, and histiocytosis. Masses that impinge on the pituitary stalk can impede TRH delivery through the hypophyseal portal system. Compression of thyrotrophic cells by pituitary adenoma and other masses of sella turcica can inhibit synthesis and secretion of TSH. Surgery/radiotherapy used to treat pituitary adenoma can destroy thyrotrophic cells which lead to secondary hypothyroidism that can develop into pan hypopituitarism. Other women pituitary causes include lymphocytic hypophysitis, pituitary metastasis from primary malignant neoplasms, apoplexy, Sheehan's syndrome in women.

Methods

For this review we included data and relevant information obtained

through a PubMed database search for all articles published in English from 1950 upto 2014 which included the terms "male hypothyroidism," "subclinical hypothyroidism," congenital hypothyroidism", myxedema, cretinism and autoimmune hypothyroidism, Hoffmann syndrome.

Results

The electronic searches yielded a total; of 16,399 articles of which a total of 1648 were relevant to males. After ruling out the animal studies and the ones pertaining to female hypothyroidism and duplicate studies we finally selected 117 studies suitable for this review. No meta analysis was conducted.

Autoimmune Hypothyroidism (AH)

AH may be associated with a goiter (HT), or at later stages of the disease, minimal residual thyroid tissue (atrophic thyroiditis). Because

the autoimmune process gradually reduces thyroid's function, there is a phase of compensation when normal TH levels are maintained by a rise in TSH. This state is called subclinical hypothyroidism (SH), though some patients might have minor symptoms. Later unbound T4 levels fall and TSH levels rise further and symptoms become more readily apparent at this stage (usually TSH>10mIU/L) which is referred to clinical or overt hypothyroidism. The mean annual incidence of AH is 4/1000 women and 1/1000 men. It is more common in Japanese populations possibly due to genetic factors and chronic exposure to high iodine diet.

Li et al investigated IgG4 related thyroiditis in a surgical series of 70 patients with HT, 19 of whom immunostained positive for IgG4. This subgroup was characterized by a higher male: female ratio, more rapid progression and a higher level of circulating antibodies with no clinical evidence of other organ involvement concluding that IgG4 related thyroiditis constituted a distinct and more aggressive form of HT.¹ A similar case of IgG4 related thyroiditis was presented in a 55year old male pilot by Salook et al.² who presented with a previous history of hypothyroidism treated with L-thyroxin stabilized for several years with family history of hypothyroidism in his sister, admitted with history of pain in neck and feeling of pressure along with sub acute thyroiditis. He had a decreased TSH levels increased ESR, and CRP levels, along with very high antithyroid antibodies. Patient underwent hemithyroidectomy for pressure symptoms due to enlarging goiter. Diagnosis of IgG4 related thyroiditis got confirmed by elevated IgG4-737mg/dl (μ 3-201mg/dl) and high IgG4/igG plasma cell ratio on immuno histochemistry. Hence they concluded IgG 4 thyroiditis and IgG-related disease should be considered in all patients with aggressive form of HT.²

Congenital hypothyroidism

Definition and aetiopathogenesis

Congenital hypothyroidism (CH) is a common disease with a worldwide incidence of 1 in 3000-4000 newborns³ Permanent primary CH can be caused by abnormal thyroid differentiation (athyreosis), migration (ectopy) or functioning (leading to goitre formation).⁴ Goiters follow an autosomal recessive pattern of inheritance, whereas ectopy and athyreosis are considered as a singly sporadic activity with a family preponderance. Devos et al.⁴ studied 73 newborns over a period of nine years of which 230 had a permanent primary CH. On scintigraphy scan 141 had ectopy (104girls), 38 had athyreosis (21girls), 42 had goiter (18girls), 10 (3girls) had normal scan. Only in the ectopies was the proportion of girls significantly higher than 0.5($p<0.0001$), isolated cardiac malformations were observed in 7 patients (3%) a prevalence 5 fold higher than in general population, this was largely due to ASD'Ss and VSD's which were only observed in ectopy and athyreosis.⁴

Thyroid gland (TG) development is orchestrated by the coordinated expression of several developmental transcription factors. Thyroid transcription factor 1 (TTF1, TTF2 and paired homeobox 8(PAX 8) are expressed selectively, but not exclusively in the TG. In combination, they dictate the thyroid cell development and the induction of thyroid specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na⁺/I, NIS) and the TSH-receptor. Mutations in these developmental TF's or their downstream target genes are rare causes of thyroid agenesis or dysmorphogenesis, though the cause of most forms of congenital hypothyroidism remains unknown (Table1). Detection and treatment of congenital

hypothyroidism (CH) within the first few weeks of life will prevent the complications of this disorder. Since the clinical features of CH are subtle, many newborns remain undiagnosed at birth.⁵

Incidence and sex ratio

With the advent of screening of newborn populations using heel prick technique of Guthrie and Saunders the incidence of CH was initially reported in range of 1:1000 to 1 in 4000 newborns,⁶ neonatal screening is now performed in most developing countries. The incidence in USA has increased from 1:4094 in 1987 to 1:2372 in 2002.^{7,8} The reason for increased incidence although not clear has been attributed to change in testing strategy from cord blood to heel prick and with increased sensitivity and accuracy of TSH measurements as compared to thyroxin concentrations, many countries have switched from T4 follow up TSH approach to a primary TSH test. Dilli et al.⁹ studied from 2008-2010 for evaluation of national newborn screening programme 3223765 newborns where samples were collected by heel prick on a filter paper keeping a cutoff value for recall as 20mU/L initially and 15mU/L subsequently. They found that the mean annual incidence of possible CH showed a gradual increase over the years (1:888 in 2008, 1:529 in 2009 and 1:469 in 2010) with noting of regional differences. Male to female ratio was constant for all 3years being 1.04, 1.1, 1.1 and unlike all screening programmes where female preponderance is reported with a 2:1 female: male ratio,⁸ they did not find a female preponderance.⁹ One of the reasons for the female preponderance occurring is mostly in thyroid ectopy and occurs less with agenesis as given by a report from Canada.⁴ Similarly in Iran the female: male was 1:1.4.¹⁰ Hence although they concluded an increased performance measures for CH screening in their neonatal screening programme (NNSP) the incidence of confirmed CH is not available in database at national level. In a study in Egypt, Bakhit 2013 found 79% of permanent CH due to thyroid dysgenesis and dysmorphogenesis accounted for remaining 21% which was similar to results of Nair et al in India.¹¹ Of 248 patients diagnosed with CH by NSP; 204(82.3%) patients were diagnosed to have permanent CH and 14(17.7%) transient CH. As compared to other studies female to male ratio was 0.8 and 0.7 in permanent and transient CH respectively 161(65%) patients had thyroid dysgenesis (107 ectopic TG, 28 athyreosis and 26 thyroid dysplasia). 87(35%) patients had intact gland in thyroid scan and were considered to have dysmorphogenesis. Of these 87 patients 44 proved to have transient CH and 43 had permanent CH similar to worldwide reports.¹² They concluded the slight higher incidence of transient CH in their study could be due to iodine deficiency and further difference in male: female ratio unlike earlier studies quoting higher female: male ratio,^{13,14} could be explained by higher incidence of parental consanguinity in that region and undiagnosed family history of CH as reported in study by Constanet et al.¹⁵

Prevention

Despite cretinism being completely eliminated in developed countries by early diagnosis of newborn screening programmes, a 22year old male was reported from Kolkata, India. This case presented as the most severe form of untreated CH presenting as the myxedematous form of cretinism along with mental retardation secondary to thyroid aplasia. He had stunted physical features with height-83cm (SDS-16.98) and weight 13.9kg (<3rd percentile), along with severe stunted mental growth, delayed milestones, delayed bone (x-ray hands showing bone age<1year) and sexual maturation.¹⁶ Early diagnosis of either form of neurological/myxedematous cretinism should be attempted in case CH is not diagnosed initially. Treatment

even in newborns is using thyroxine tablets, as liquid oral suspensions can't be depended on reliable dosing. Crushed T4 tablets, mixed with breast milk/formula milk is ideal and frequent monitoring every 2-3 weeks is recommended during first months of life keeping infants with CH within the high end of range.¹⁷ Transplacental passage of maternal TH occurs before the fetal TG begins to function and provides partial TH support to a fetus with CH. Early TH replacement in newborns with CH prevents potentially severe developmental abnormalities. CH may be transient, especially if the mother has TSH-R blocking antibodies or has received antithyroid drugs, but permanent hypothyroidism occurs in the majority. Neonatal hypothyroidism is due to TG dysgenesis in 80-85%, to inborn errors of TH synthesis in 10-15%, and is TSH-R mediated in 5% of affected newborns. Developmental abnormalities in males are half as compared to those in female newborns.

Mutations

Mutations that cause CH are increasingly being identified, but the vast majority remains idiopathic. Eg:

- i. Salerno et al identified a heterozygous mutation of c.334G>T on analysis of 3 exons of TTF1, which results in replacement of glycine in position 112 with stop codon, generating a nonsense protein that lacks the correct transactivational domain in the C terminal region. Since NK2 homeobox 1 (NKX2.1) gene encoding the TTF1 plays a critical role in lung, thyroid and CNS morphogenesis and function; mutations cause a rare form of progressive respiratory failure associated with surfactant synthesis, compositions and homeostasis. Hence concluding with the case report of this male child that screening for TTF1 deletions or mutations should always be considered in children with CH and unexplained neonatal respiratory distress or neuro developmental deficits.¹⁸
- ii. Similarly Sandal et al reported Bamforth syndrome – a rare syndrome caused by mutations in the gene encoding TTF2, whose main features are CH due to thyroid dysplasia, cleft palate and spiky hair, with or without choanal atresia and bifid epiglottis and in this child additionally pencephaly was observed.¹⁹
- iii. Mutations in the thyroid peroxidase (TPO) gene are the most common cause for dysmorphogenesis. So far more than 80 mutations in the TPO gene have been described, resulting in variable decrease in TPO bioactivity. Clinically these TPO defects manifest with congenital primary goitrous hypothyroidism. Altmann et al.²⁰ reported 2 German children with CH who were identified to have compound heterozygous TPO mutations. They both shared the same novel mutation in the TPO gene (C756R) in exon 13. One case presented with an apparently dominant inheritance of thyroid dysmorphogenesis.²⁰
- iv. Similarly CH due to thyroglobulin (TG) deficit, an autosomal recessive disease (OMIM#274700) was reported in 2 sisters born from consanguineous parents, but the father's (euthyroid) analysis showed that he was a heterozygous carrier of the novel point mutation of the TG gene determining a stop codon at 768 of the protein identified in the 2 sisters.²¹
- v. A nonsense mutation (W520X) was identified in a child in the third transmembrane domain of the TSHR that causes the lack of the C terminus portion of the receptor. Moia et al.²²

concluded that the mechanism through which W520X mutation exerts its effects is more likely to be haploinsufficiency rather than a dominant effect, which could explain the phenotype of their patient, having a hormonal pattern of a mild subclinical hypothyroidism without overt disease phenotype.²²

- vi. In humans PAX8 gene maps to chromosome 2q12-q14 and consists of at least 10 exons. So far several PAX8 mutations and a rare sequence variant had been reported, in patients with hypoplastic normally located TG associated with renal anomalies. But Vincenzi et al.²³ studied a male patient of hypothyroidism with his family members presenting with various phenotypes varying from CH to just subclinical hypothyroidism and the genetic variant R133W-PAX8 was not directly involved in the development of the thyroid phenotype.²³
- vii. Recently by exomic sequencing Kuhnen et al.²⁴ 2014 unexpectedly identified mutations in patients with structural thyroid defects (p.Leu597Ser) and (p. Gln 413 Arg); the latter patient in addition having severe hearing loss; both missense homozygous mutations in SLC 26A4 gene, both mutations which were previously described as loss of function mutations in patients with Pendred syndrome and nonsyndromic enlarged vestibular aqueduct. Thus they suggested extending analysis to SLC 26A4 in patients with apparent thyroid dysgenesis.²⁴ Montanelli et al.²⁵ described late onset goiter and a novel mutation in sodium iodide symporter of the proband and family members of a 16yr old girl inherited from her parents and recommended that thyroid ultrasonography be performed in CH patients with low radioactive iodine uptake and elevated serum Tg.²⁵

Long term consequences

Long term follow up of CH is of particular interest. CH is an umbrella term for several congenital thyroid disorders usually characterized by pathologically low concentrations of thyroxine that may or may not be accompanied by elevated concentrations of thyroid stimulating hormone (TSH), TH's act on such processes as neuronal migration and differentiation, myelination, and synaptogenesis, which are essential for proper neurodevelopment and are also involved in maintenance of normal physiological functions such as bone maturation. Pathologically low concentrations of TH's experienced during critical stages of development may cause severe mental retardation and skeletal growth abnormalities.²⁶⁻²⁹ The deleterious outcomes of untreated CH are well known.³⁰⁻³³ In a long term follow up study on hearing since neonatal period Lichtenberger et al.³⁴ found hearing loss to be three times higher than the reference population. Hearing impairment was diagnosed at a median age of 7 (25th and 75th percentile 34-19yrs) 17% of affected patients required hearing support in early adulthood. Hearing loss was associated with type of CH (patients with athyreosis and gland in situ were more frequently affected than that with an ectopic TG, with disease severity as assessed by bone maturation delay at the time of diagnosis with at least one knee epiphyseal ossification center absent in the most severe form and with other associated chronic diseases. Hearing loss was mostly bilateral (90%), mild to moderate (96%), of the sensorineural type (76%) and concerned high or very high frequencies. Hence they concluded that despite major improvements in prognosis, hearing loss remained a significant problem particularly in patients with severe CH. With parents and primary care physicians being aware of this risk, early diagnosis and intervention could improve long term prognosis of these patients.³⁴

With rapid institution of high dose levothyroxine 10-15µ/Kg/day producing prompt normalization of thyroid function, Albert et al.³⁵ found normal intellectual and motor development in 54 CH cases and 53 control siblings aged 9.6+/-3yr. They found that severity of CH did not influence outcome but greater time to normalize free T4 was associated with worst motor balance. Therefore they suggested that subtle negative impact on motor function associated with time to normalize free T4 levels is consistent with benefit from rapid initial correction³⁵ whereas Bongers-Schokking suggests that CH overtreatment during first 2years leads to lowered cognitive outcomes at 11 years whereas under treatment if not complicated by over treatment results in normal cognitive development and that fast TSH normalization at initial treatment leads to above developmental scores at a younger age but affect IQ at age 11.³⁶ Bagatti N et al.³⁷ studied the requirement of L-T4 in 36 patients (27 females/9 males), where 13 had CH (athyreosis), while rest 23 had acquired hypothyroidism (AH, n=14 due to previous thyroid nodule, n=9, thyroid carcinoma) found a higher requirement (dose/kg) in CH as compared to AH despite a higher TSH in adult patients. They proposed that the difference in requirement of replacement therapy between adult patients of CH and those with surgical athyroidism could be explained by a lack of TH's since fetal life in CH which could determine a different set point of the hypothalamic-pituitary-thyroid axis.³⁷ Young adults with CH treated with long term L-T4 replacement therapy may have significant impairment of flow mediated dilatation (FMD) and brachial artery distensibility with the measurement of coefficient of distensibility (DC). Oliviera et al.³⁸ studying 32 young adults with CH aged 18.9 and 32age/sex matched controls suggested that high TSH levels, inadequately corrected by L-T4 replacement therapy, especially during puberty, can exert significant effects on the elastic and functional vessel properties.³⁸

The importance of treating primary hypothyroidism is revealed by the first report in a 27year old man with chronic untreated primary hypothyroidism who presented with delayed puberty, marked short stature (ht-133cm) with severe almost continuous headache for last 6years. MRI revealed pituitary hyperplasia. This patient was diagnosed as primary hypothyroidism at 21yrs age and L-T4 therapy lead to resolution of symptoms and a gain in height of 28cm over 6years. Evaluation for lack of pubertal progression along with chronic nausea, vomiting, fatigue and weight loss revealed secondary hypocortisolism (at 9am-4.8µg/dl, ACTH-3.2pg/ml, GH deficiency (IGF1-65ng/ml (RR-117-325ng/ml) and HH (9AM Testosterone98ng/dl (RR-280-1500ng/dl) LH-.01 (1.14-5.75miu/l) with empty sella (ES)on MRI brain. Uncontrollable thyrotroph hyperplasia due to chronic untreated primary hypothyroidismx 15years may have been damaging adjacent corticotrophs, gonadotrophs leading to panhypopituitarism and ES.³⁹

Other causes of male hypothyroidism

Central Hypothyroidism

I. Context Ig superfamily member 1 (IGSF 1) deficiency was recently discovered as a novel X linked cause of central hypothyroidism (CeH) and macroorchidism. Joustra et al.⁴⁰ studied 24 males from 10 families examined in university of Leiden, Amsterdam, Cambridge and Milan. 17 index cases showed CeH (100%), Hypoprolactinaemia (n=16.67%) and transient partial GH deficiency (n=3.13%). Pubertal testosterone production was delayed, as were the growth spurt and pubic hair development. However testicular growth started at a normal age and attained macro orchid state size in all evaluable adults. BMI, percent fat and waist circumference

tended to be elevated. Metabolic syndrome was present in 4 out of 5 patients in 55year age. Heterozygous female carriers (32-80yrs) also showed CeH (6/18,33%), hypoprolactinaemia in 2(11%) and no case of GH deficiency. Thus they concluded that male patients in IGSF1 deficiency is characterized by CeH, hypoprolactinaemia, delayed puberty, macroorchidism and increased body weight. A subset of female carriers also exhibit CeH.⁴⁰ Further Nakamura et al.⁴¹ studying 4 Japanese boys with congenital CeH found 3 novel IGSF1 mutations. In patients 1&2 p.R1189X, and patient 3 and 4 distinct missense (p.V1082E) or nonsense (p.Q645X) mutations in IGSF. The mothers of patients 1, 3 and 4 were heterozygous for these mutations which provides additional genetic evidence that loss of function mutations in IGSF1 causes an Xlinked C-CeH and variable prolactin deficiency.⁴¹

II. Fryns Anophthalmia-Plus syndrome (APS) was reported in a 3year old child by Cayir et al.⁴² who presented with central hypothyroidism, chiari type 2 malformations, conductive hearing loss and developmental regression. He had asymmetry of face and head, left choanal atresia, a sunken facial appearance microphthalmia in left eye, severe microphthalmia in left eye, bilateral low set ears scarring from cleft palate surgery. MRI revealed decreased right globe volume, an undeveloped left globe, decreased left optic nerve thickness, chiari type 2 malformations and left choanal atresia. Summary of the presented case reported here and 14 previous cases might be defined as APS.⁴²

III. Hermann et al.⁴³ reported a novel deletion in Thyrotropin β subunit gene identified by array comparative genomic hybridization (aCGH) analysis as a cause of isolated central CH (ICCH) in a 51 days old boy originating from Turkey. ACGH using specific probes around TSH β gene showed him to be homozygous for a 6kb deletion spanning all exons and parts of 5'UTR of the gene. Thus they concluded infants clinically suspected of hypothyroidism should be evaluated thoroughly even if TSH based screening is normal. In cases with ICCH and undetectably low TSH serum concentrations, a TSH β gene deletion should be considered and aCGH should be performed.⁴³

IV. Suzuki et al.⁴⁴ reported a De novo frame shift heterozygous p.S192fsX204 mutation in last exon of fibroblast growth factor 8 (FGF8) in a patient who presented with gonadotropin deficiency with multiple malformations with primary hypothyroidism, with micropenis, craniofacial anomalies and ventricular septal defect at birth. Patient examined at 8months and 16years of age revealed delayed puberty, hyposmia, borderline mental retardation and, mild hearing difficulties. Thus concluding that frame shift mutations in FGF8 can account for the etiology of hypothalamo-pituitary (H-P) dysfunction.⁴⁴

V. CeH is generally related to a H-P disorder or arising as an iatrogenic condition. Usually it is difficult to diagnose CeH because it lacks specific change clinical signs and they may be masked by other pituitary hormone deficiencies. Treatment is with L-T4 replacement therapy after exploration of circadian TSH cycle index and confirming diagnosis of low free T4 with low/normal or mildly increased TSH levels.⁴⁵ Similarly patients with thalassemia major present with CeH by age of 18 with equal incidence in both sexes.⁴⁶ CeH and hypogonadism was part of the presenting complaint of a stage IV small cell

carcinoma along with secondary adrenal insufficiency in a 66year old man who was a chronic smoker.⁴⁷

Neurological

- I. Myxedemic coma in a patient with neurofibromatosis has been reported, in a 51year old male to reverse with thyroid hormone replacement therapy and other additional measures in shock and hypoventilation.⁴⁸ Also a case of primary hypothyroidism with deteriorating consciousness that did not respond to thyroxine and ultimately responded to steroids was reported in a 60year old male and was diagnosed as a case of Hashimoto's encephalopathy.⁴⁹ In addition lithium induced toxicity and myxedemacrisis has been reported in a 70year old male subject on lithium for bipolar disorder, hence emphasizing the importance of monitoring thyroid function tests in patients on lithium therapy.⁵⁰
- II. Experimentally PET Scans examining glucose metabolism in 13 hypothyroid subjects with 10 healthy controls show lower regional activity in the amygdale, hippocampus and perigenual anterior cingulated cortex (ACC), left subgenual ACC, and right posterior cingulated cortex and this activity corrects after thyroxine replacement.⁵¹
- III. Thyroid disorders can present with varied neurological manifestations affecting the entire neuraxis. Hypothyroidism can present as coma^{48,52} when it involves the brain and at the other end of the spectrum can produce neuropathies and myopathies, when it involves the peripheral nerves and muscles. It may resemble polymyositis. Rarely, stiffness and tautness of muscles may be the only manifestation of hypothyroidism. Sowmini et al.⁵³ reported a 30year old young male who presented with generalized muscle stiffness, involving the limbs, facial and paraspinal muscles. The stiffness was so severe that it restricted all daily activities and increased progressively with movements and produced recurrent falls. This clinical picture resembled one of stiff person syndrome. Since he had hypertrophy of calf muscles and generalized muscle tautness a differential diagnosis of Hoffmann's syndrome or other disorders which resemble stiff person syndrome was ruled out. Investigations revealed severe hypothyroidism with elevated thyroid antibodies. Importance of identifying such a condition is because it is completely treatable with thyroid replacement therapy and this patient could lead normal life following treatment.⁵³
- IV. Myopathic changes are observed in 30-80% of patients with hypothyroidism.⁵⁴ Patients with more severe or longstanding untreated hypothyroidism are more likely to develop clinically significant muscle disease. Slowed muscle contractio, in hypothyroid myopathy, may be caused by a shift in the distribution of muscle fiber types from fast-twitch to slow twitch fibres. A reduction in muscle mitochondrial oxidative capacity and β -adrenergic receptors, as well as the induction of an insulin resistant state, may result in these changes.⁵⁵ The global inhibition of the main oxidative pathways (substrate incorporation, substance oxidation) and of the respiratory chain within cells may also cause myopathic symptoms.⁵⁶ There are four variants of hypothyroid myopathy known as Hoffmann Syndrome, Kocher-Debre-Semelaigne syndrome, atrophic form and myasthenic syndrome.^{57,58} Hoffmann syndrome (HS) is a rare form of hypothyroid myopathy in adults

characterized by presence of muscle weakness, stiffness and pseudo hypertrophy. Senanayke et al.⁵⁹ reported a 39year old male with primary hypothyroidism diagnosed at childhood and not on regular thyroxine therapy who presented with fatigue, cold intolerance, constipation, exertional breathlessness, progressive muscle weakness and swelling of the legs for one year. Examination revealed pseudo hypertrophy of calf muscles with marked symmetrical proximal upper and lower limb weakness. His TSH and creatine phosphokinase (CPK) were significantly elevated and electromyography (EMG) was compatible with myopathic disorder. After institution of thyroxine therapy his weakness improved markedly and pseudo hypertrophy regressed in two months.⁵⁹ Besides that a rare case of HS was reported in a 12year old male child along with pituitary hyperplasia. This child presented with headache, besides the other features with which HS patients present. Bilateral papilloedema was present and MRI revealed enlargement of pituitary glands and Hashimoto's thyroiditis was confirmed on thyroid studies. Treatment with TH's resulted in complete improvement of symptoms in three months.⁶⁰ Two cases of long duration HS were reported by Nalini et al.⁶¹

Miscellaneous

Autoimmune

- a) Cetinkaya et al.⁶² reported a rare association of monosomy 18p Syndrome in a 34year old male subject who presented with polyglandular autoimmune (PAS) Type III A. The patient presented with mental retardation, short stature, wide earlaps, old looking face atrophic mouth, drooping cheeks with full teeth loss and weak, soft sparse hair. Chromosome analysis revealed 46XY, del 18(p11,2). He was also found to have autoimmune thyroiditis, primary hypothyroidism, diabetes mellitus type1 besides GH deficiency and hypogonadotropic hypogonadism.⁶²
- b) Mostly hypothyroidism is autoimmune, but a rare case is reported of a 2year old boy of ulcerative colitis on sulfasalazine therapy that subsequently developed type1 diabetes mellitus, autoimmune hepatitis and autoimmune hypothyroidism. This highlights the role of immune related mechanisms in the pathophysiology of disease like ulcerative colitis.⁶³
- c) Hypothyroidism had been part of polyendocrinopathy syndrome in a 27yr old boy who presented with reversible adrenal insufficiency with hypothyroidism with falsely raised TSH because of presence of heterophilic antibodies.⁶⁴
- d) Recent data have shown a relationship between obesity and thyroid autoimmunity, with the adipocyte hormone leptin appearing to be the key factor linking the two conditions. Duntas et al.⁶⁵ explain how leptin has variably been implicated in thyroid function, while recent findings suggest that leptin resistance may mitigate leptin deficiency and enhance autoimmunity in obese subjects via mechanisms operating independent of thyroid function. The development of resistance to the weight lowering effects of leptin in obesity may well be initiated by activation of inflammatory signaling which substantially contributes to the derangement of immune response and propagation of autoimmunity in susceptible individuals. Thus they concluded that the regulation of inflammasome derived cytokines in obesity is an important step in controlling the trigger of thyroid autoimmunity. The

clarification of the pathways may offer innovative therapeutic targets in obesity as well as thyroid autoimmunity.⁶⁵ Further Rotondi et al.⁶⁶ on the basis of study of 55 morbidly obese (BMI>40KG/M2) and 55 nonobese with raised TSH concluded that the impact of raised S.TSH on the lipid profile differs in morbidly obese as compared to nonobese patients, suggesting that obese patients might not be truly hypothyroid. Measuring total cholesterol could be a helpful tool for deciding whether a morbidly obese patient with a raised serum TSH should be given levothyroxine treatment or not.⁶⁶

- e) In assessing the relation of non-alcoholic fatty liver (NAFL) disease with insulin resistance (IR), metabolic syndrome (MS) and hypothyroidism Misra et al.⁶⁷ studied 40 cases of NAFLD with 30 controls. He found that NAFLD patients demonstrated significantly higher IR, TSH values and a significantly lower FT4 levels as compared to controls, demonstrating prevalence of IR and hypothyroidism in patients. A significant positive correlation between TSH and IR and a negative correlation between FT4 and IR were established in the cases. Moreover TSH was significantly related to LDL-cholesterol, independent of IR. Hence earlier detection of risk factors in NAFLD coexisting with hypothyroidism maybe helpful in preventing cardiovascular diseases.⁶⁷ Similarly Posadas et al.⁶⁸ studied 753 patients (45% males, aged 35-70yrs) with no history of DM, renal, Sub clinical hypothyroidism(SCH) was defined as raised TSH with normal free T4 levels, coronary artery calcification and abdominal visceral obesity defined by computed tomography. They found SCH was present in 17.7% of studied population. The prevalence of fatty liver (FL) was similar in euthyroid and SCH subjects (31.8% vs 27.8%).But FL with SCH patients were heavier and had more metabolic abnormalities as compared to SCH plus normal liver subjects. SCH along with FL was associated with MS, IR and coronary artery calcification (CAC) independent of potential confounders.⁶⁸ Although overt and SCH are risk factors for atherosclerosis. Zhang et al.⁶⁹ found increased coronary artery disease with greater degree of CAC in a large cohort study of 41403 euthyroid subjects as well. Dahiya et al.⁷⁰ estimated nitric oxide and ischemia modified albumin in 50 newly diagnosed patients of hypothyroidism and found it to be significantly raised in hypothyroid patients as compared to controls. Hence they concluded that estimation of nitric oxide and ischemia modified albumin (markers of oxidative stress) in hypothyroidism may help to throw light on pathogenesis and severity of the disease although further research is needed to establish their role as biomarkers in hypothyroidism.⁷⁰
- f) The acute Wolff Chaikoff effect^{71,72} suggests that iodine induced hypothyroidism especially in patients with amiodarone therapy is caused by a chronic acute inhibition of thyroid gland.^{73,74} Although till recently it was not clear how excessive iodine use is linked to thyroid autoimmunity. Latrofa et al.⁷⁵ answered the question by studying thyroglobulin auto antibodies (TgAb) epitopes in 16 iodized salt (IS) users out of 906IS users and 17 IS nonusers (of389IS-nonusers) by inhibition binding assay to Tg using human monoclonal TgAb-Fab directed to A, B, C and D epitopes on Tg and found a significantly higher iodine excretion in IS users with TgAb and not TPOAb more frequent in IS users. HT ultrasound to identify thyroid hypoechogenicity was found in 87 patients and TgAb directed to the epitope B of Tg were more frequent in IS users than IS nonusers and they

concluded Iodine induced thyroid autoimmunity is related to TgAb and the unmasking of a cryptic epitope on Tg contributes to this relationship in humans.⁷⁵

Other miscellaneous

- A) Consumptive hypothyroidism is a rare condition, usually described in association with diffuse infantile haemangioma of the liver, over expressing type 3 iodothyronine deiodinase. DeCorti et al.⁷⁶ reported a case of acquired hypothyroidism associated with a parotid haemangioma in a male child who was initially evaluated at 48 days of age due to persistent jaundice. Despite replacement therapy, resolution of clinical and hormonal characteristics occurred only after introduction of propranolol at 3 months of age to the therapeutic regimen. In their review of literature they only found one case of proven consumptive hypothyroidism associated with infantile parotid haemangioma, thus concluding how underestimated it maybe and it should be considered a real possibility if infantile parotid haemangioma found.⁷⁶
- B) Erythema ab igne (EIA) is a dermatosis characterized by reticulate red brown pigmentation and telangiectasia resulting from long term exposure to infra red irradiation. Turan et al.⁷⁷ also reported a 42 year old male, who presented with red brown spots and blisters on both thighs and behind legs. He was diagnosed with EAI based on clinical, historical and histopathological features presented and they concluded that a final diagnosis of bullous EAI associated with normocytic normochromic anemia and subclinical hypothyroidism was the presenting feature of this case preferring hot environments.⁷⁷
- C) Obstructive sleep apnea (OSA) and hypothyroidism are two diseases that can be associated with pulmonary hypertension (PH). Studying the effect of combination of hypothyroidism with OSA Araz et al.⁷⁸ found that the combination of hypothyroidism with OSA is associated with an increased frequency and severity of PH. When PH is found out of line with the severity of OSA, thyroid dysfunction should be investigated. Of the 236 patients studied 167 were male and69 female participants-of which Group I was OSA with 81.9% (n=149) males, Group II (n=56, 44.6% males) only hypothyroidism while Group III (n=31, 64.6%males where both hypothyroidism and OSA present.⁷⁸
- D) In a study on HIV infected patients coinfectd with multidrug resistant tuberculosis receiving antitubercular treatment (ATT) and antiretroviral treatment, Andries et al.⁷⁹ found hypothyroidism to be a common side effect of patients receiving ethionamide, p-amino salicylic acid and stavudine in a study conducted in Mumbai ,India. 61%of the 116 patients enrolled in this study from Oct 2006-Mar 2013 were male of which 37/69(54%) had hypothyroidism after atleast 90days of treatment. Co administration of PAS and ethionamide was found to double the risk of hypothyroidism. Therefore they recommended to screen at baseline, 3months, 6months and then every 6monthly thereafter for HIV infected persons on MDR-TB treatment containing PAS and/or ethionamide until newer safer and more efficacious MDR-TB regimens become available.⁷⁹
- E) In a cross sectional retrospective study Hadlow et al.⁸⁰ analyzed TSH and free T4 results from 152261 subjects collected over 12years by a single laboratory and found the relationship

between log TSH and free T4 was nonlinear. For free T4 within reference the reference range (10-20pmol/l) median TSH was higher in men than in women and increased across age bands with the highest values in those 80years and older ($p < 0.001$). In contrast in overt hypothyroidism ($n=4403$) TSH was lower in older age groups than in those aged 20-39years and thus concluded that the TSH-freeT4 relationship is not inverse log-linear but can be described by 2 overlapping negative physiological curves. At physiological free T4 concentrations, TSH is higher in men, and in older people, whereas the TSH response to hypothyroidism is more robust in younger people.⁸⁰

- F) Although hyperprolactinaemia due to hypothyroidism is known to result in gynecomastia in adults, this observation is not seen in prepubertal children. Dayal et al.⁸¹ reported a boy who developed gynecomastia after the first year of age and was later diagnosed to have CH along with hyperprolactinemia.⁸¹
- G) Kyrysiak et al.⁸² reported different effects of methyl testosterone administration on thyroid function in 2 twin brothers with transient hyperthyroidism developing in one of the brothers with hypothyroidism following methyl testosterone (a non aromatizable androgen). MT resulted in a marked reduction of thyroxine binding globulin (TBG), irrespective of the patients hormonal status whereas the impact on free TH's depended on baseline thyroid function. They concluded that in any hypothyroid patient receiving levothyroxine in whom TH's suddenly change without any apparent reason use of non aromatizable androgen or any other drugs which affect TBG should be suspected or taken into consideration.⁸²
- H) The association of down's syndrome (DS) and thyroid is well recognized with patients of DS have an increased prevalence of both CH and acquired thyroid function.^{83,84} Earlier studies reported that frequency of CH was 28times higher than in general population.⁸⁴ Cebeci et al.⁸⁵ studied 62 patients with DS (32 male and 30 female) retrospectively from hospital records of patients with DS and hypothyroidism. They found a high prevalence of thyroid dysgenesis in patients with DS and hypothyroidism and advised further studies as no such previous association had been reported.⁸⁵
- I) Hypothyroidism induced reversible kidney dysfunction has been reported in three cases with 2 males 68 and 72yrs with serum creatinine and TSH being elevated to 1.4-3mg/dl and 94-181miu/l along with low free thyroxine levels (undetected to 0.4ng/dl). Initiation of increased doses of levothyroxine led to return of serum creatinine to baseline in several months (2-10mths), concluding a reversible relationship between thyroid gland and kidney function which maybe missed if the interplay is not kept in mind.⁸⁶ This can be explained by the findings of Tsuda et al.⁸⁷ suggesting low thyroid function even within normal range is associated with reduced renal plasma flow (RPF), regional blood flow (RBF) and glomerular filtration rates (GFR) which might be caused by a preferential increase in vascular resistance in the afferent arteriole (Ra). This conclusion was on the basis of studying 26 patients with serum creatinine<1mg and without thyroid disease and on basis of serum TSH was positively correlated with Ra but not at the efferent arteriole (Re). Serum TSH was significantly and negatively correlated with TPF, RBF and GFR and in multiple regression analysis TSH was significantly positively associated with Ra after adjustment for age and mean BP.⁸⁷

J) In a 20year period a single centre retrospective study Klose M emphasized the importance of improved awareness of thyroid status and optimal thyroid replacement of hypo pituitary patients to reduce cardiovascular risk in hypo pituitary patients with secondary hypothyroidism, irrespective of age, gender and IGF1 status.⁸⁸

K) Childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy alone present with hyperthyrotropinemia without antithyroid antibodies with a prevalence comparable to the control group as shown by Delvecchio et al.⁸⁹ after study of 84 cases of ALL and concluded that a thyroid follow up in all off therapy as thyroid gland seems to be more prone to be damaged by chemotherapy at a younger age and it should be differentiated on the basis of age at the end of treatment with more frequent tests in younger patients.⁸⁹

Subclinical Hypothyroidism (SH)

Subclinical hypothyroidism (SH) is an asymptomatic condition defined by increased serum TSH with serum free T4 and free T3 levels within their respective reference range. The treatment and management of SCTD and population screening are controversial despite potential risk of progression to overt disease. It can have repercussions on the cardiovascular system and bone as well as on other organs and systems.⁹⁰ The prevalence has been reported to be between 4 and 20% of adult population⁹¹ and 1.7% in US children.⁹² It seems to be a benign remitting condition in childhood with a low risk of progression to overt hypothyroidism. A slight increase in TSH levels with normal TH's maybe transient and sometimes causes a false positive at neonatal screening for CH.⁹³ The most frequent cause of persistent SH in childhood is represented by autoimmune thyroiditis. However iodine deficiency, obesity, non thyroid chronic diseases or inherited syndromes may also be responsible for mild increase in TSH levels. Mutations in genes encoding proteins involved in TSH pathway are thought to be involved in some cases of idiopathic SH, particularly in familial setting.⁹⁴⁻⁹⁶

TSH exerts its activity by binding to the extracellular domain of TSHR. TSHR is a member of the G protein-coupled receptor family, which also includes calcitonin or PTH receptors. Cerbone et al.⁹⁷ reported non autoimmune SH in 2 brothers carrying the same mutation in the extracellular domain of TSH-R but presenting with different clinical, biochemical and morphological features. The first one had only a slight persistent elevation of TSH, abnormal thyroid on ultrasound and did never require l-thyroxine (L-T4) replacement treatment and had a normal IQ of 108 at age 16. The second one has a neonatal persistent moderate TSH levels increase associated with a thyroid gland hypoplasia and was treated with L-T4 since the first months of life although had an IQ of 80 at age 16, possibly due to initial low dosage/delay in starting treatment which its known to be associated with such outcomes.⁹⁷ The mutation R109Q in the extracellular domain of TSH-Xr, found in these 2 brothers was described by Clifton-Bligh et al in a child with compound heterozygous for another missense mutation in the fourth transmembrane segment of receptor.⁹⁸ In the 2 siblings reported by Nicoletti et al.⁹⁵ having the same R109Q mutation, milder phenotype was found, characterized by slight increase in serum TSH, normal thyroid gland at ultrasound and no clinical features of thyroid dysfunction.⁹⁵

Rapa et al.⁹⁹ evaluated the clinical characteristics and TSH-R gene variants in children with mild to moderate elevations of TSH with normal TH due to nonautoimmune SH. TSHR gene non-synonymous

mutations/polymorphisms were found in 21.5% cases.⁹⁹ Cerbone et al.¹⁰⁰ studying 47 caucasian children (25 males) with long term idiopathic SH found that persistent SH in children is not associated with alteration in growth, bone maturation, BMI, and cognitive function or other complaints that could be attributed to SH even after several years without therapeutic intervention.¹⁰⁰ In further extension of this study their group found no effect on bone health as evaluated by lumbar spine dual X-ray absorptiometry (DXA) and phalangeal quantitative ultrasound (QNS) as revealed by a study of 25 caucasian children and adolescents (11 males age 9.8+/-3yrs) and from their data concluded that QUS are comparable to those provided by DXA and QUS may represent a good, cheaper and safer screening test for bone evaluation in children with SH.¹⁰¹ There is no clear cut benefit of L-thyroxine therapy in adults or children.^{102,103} Sunbul et al.¹⁰⁴ found untreated SH is associated with impairment in left ventricular longitudinal myocardial function by two dimensional speckle tracking echocardiography.

On studying 23 consecutive SH (both treated and untreated SH with 7 males in each group and controls all around 40years), they concluded that speckle tracking echocardiography appears to be useful both for early detection of left ventricular impairment in patients with SH and documentation of improvement in myocardial deformation parameters with treatment.¹⁰⁴ Although a prevalence of the minor allele of phosphodiesterase 8B (PDE8B) gene polymorphism associated with elevated serum levels of TSH was demonstrated in patients affected by sporadic nonautoimmune SH, significant differences in circulating TSH in patients with minor or major alleles for each polymorphism were not identified demonstrating a lack of association between the polymorphisms and serum TSH levels in these 58 patients studied.¹⁰⁵ Despite the negative impact of SH on CVS in young adults (<55-60yrs) the decision to treat elderly people still remains an unresolved clinical challenge due to a lack of appropriately powered RCT of L-T4 in SH patients examining cardiovascular hard endpoints in various classes of age and 2nd because of the negative effects of possible overtreatment in moderately old (70-75 and oldest old >85yrs).¹⁰⁶

Role in male reproduction

Velasquez & Arata¹⁰⁷ found no changes in free testosterone (T) levels in hypothyroid men, whereas several other studies have shown a fall in circulating T levels in hypothyroid patients.^{108,109} Velasquez and Arata found a rise in only FSH without a concomitant rise in LH levels, whereas Jaya Kumar found a rise in both serum FSH as well as LH levels.¹⁰⁹ However Donnelly and White found no changes in either serum FSH/LH levels in hypothyroid men.¹⁰⁹ GnRH administration to hypothyroid patients resulted in attenuated LH responses.¹¹⁰ In hypothyroid males Morris et al.¹¹¹ found a significant decrease in gonadal steroids, namely, progesterone (P), and total T. Bioavailable T (Bio T), calculated by Morris's formula was reduced in hypothyroid men. Morris et al.¹¹¹ measured serum total T, SHBG by ELISA, BioT by Tremblay and Dude method,¹¹² calculated percent free T and free T by Nanjee's formula¹¹³ and Vermulelen's computer¹¹⁴ respectively. On the basis of these calculations, they developed and validated an equation for calculation of Bio T. On this basis they concluded that total T has the best predictor of Bio T. They proposed the following for the cause of fall in T:

- Low cholesterol uptake in Leydig cells as evident from high serum cholesterol levels
- Lower conversion of progesterone (P) to T as evidenced by low T/P ratio

- Higher conversion of estradiol (E2) to T as suggested by high E2:T ratio and
- Hyperprolactinaemia.

High prolactin suppresses 17 α -hydroxylase enzyme in rat testicular cells which catalyzes the conversion of P to 17 α hydroxyl P.¹¹⁵ Although this raised a question about the role of T on the feedback inhibition of pituitary gonadotropin release,^{116,117} in studies of Kumar et al.,¹¹⁷ serum E2 levels were similar in hypothyroid as well euthyroid men, which suggested that E2 is the prime regular of negative feedback on pituitary level of gonadotropins, instead of T as has been corroborated by studies by Rochira et al.^{118,119} They showed that basal and GnRH stimulated LH and FSH secretion was higher than normal in aromatase deficient men with normal T levels. Rochira et al.,¹¹⁸ reported 4 cases of tall stature without growth hormone deficiency who had a impaired response of GH to GHRH-ARG as compared to normal subjects and who had significantly lower IGF1 levels as compared to normal subjects and both IGF1 peak and concentrations were not modified by estrogen therapy in men with aromatase deficiency and concluded insulin as the cause of tall stature rather than GH for the marked increase in height due to nonclosure of epiphyses.¹²⁰ Besides that for normal physiology, Pitteloud et al.,¹²¹ showed that for Inhibition of LH secretion by T in men aromatization is required for its pituitary effect but not its hypothalamic effect as shown by studying 11 men with GnRH deficiency normal (NL).^{121,122}

Discussion and interpretations

Although it is clear that AH is 4times more common in females the particular type of AH, namely IgG4 related thyroiditis, which appears to be associated with male hypothyroidism is a more aggressive form of HT. As for CH, with the NNSP now in most countries it is a crime to have any case presenting with cretinism in adulthood and although the prevalence of female: male CH varies from 2:1,1:1,1:1.4 from various geographical regions, a screening programme for every child has become essential rather than excluding male children thinking of low incidence of hypothyroidism in males with the idea of eradicating cretinism from globe in view of the essential role of thyroid hormone in the development of various important organ systems.

Central Hypothyroidism (CeH) is generally a H-P disorder, where IGSF1 has been noted to be an important X linked disorder as a cause of CeH and affecting male hypothyroidism as well as reproduction. Other rare disorders which can present with CeH can be APS, deletion in Thyrotropin β subunit, heterozygous mutations with FGF8, with thalassemia major and more rarely as long with stage IV small Cell Carcinoma. Neurological complications include extreme presentation with coma where patients may/may not respond to levothyroxine therapy, where steroid therapy may be of help. Thus high index of suspicion should be kept when a male patient presents unconscious without any known cause. Other manifestations include neuropathies and myopathies of which stiff person syndrome, Hoffmann syndrome have been the common manifestations and presenting complaints in variable manner in males having hypothyroidism of untreated hypothyroidism of long term origin which responds to therapy with TH. Hypothyroidism maybe the presenting complaint of multiple autoimmune syndromes like chromosome18p syndrome, associated with ulcerative colitis, be part of a polyendocrinopathy syndrome. Obesity has also been correlated with thyroid autoimmunity and the explanation of how excessive iodine use is linked to thyroid autoimmunity has finally been explained by Latrofa et al.,⁷⁵ who explained iodine induced thyroid autoimmunity is related to TgAb and

the unmasking of cryptic epitope on Tg contributes to this relationship in humans.⁷⁵ Other miscellaneous disorders like consumptive hypothyroidism, EIA, OSA can present with hypothyroidism, or as complications following patients who have been on ATT (specifically PAS and PAS with ethionamide), treatment for ALL. Recently it has been emphasized that hypothyroidism induced reversible kidney function gets corrected just by treating hypothyroidism. No effect of persistent SH in children was found in growth, bone maturation, BMI, cognitive function or other complaints that could be attributed to untreated SH even after several years without therapeutic intervention, suggesting no need of therapy in children with SH. However in young adults some effect on left ventricular function suggested which warrants treatment. Thus despite effect on CVS function the decision to treat SH in elderly remains unresolved because of fear of over treating in moderately old and oldest of old. As far as reproduction is concerned both primary hypothyroidism should be considered as a cause of HH, and SH needs to be treated in infertile males with the known effects on sperm motility, morphology parameters^{123,124} as well as effects on gonadal hormones as well as serum prolactin.

Conclusion

Although hypothyroidism is common in females it may be the primary cause of male HH especially CeH and should be looked for in a man with delayed puberty as a primary cause with importance of IGSF highlighted recently. Also untreated hypothyroidism may be the cause of presentation as myopathies like Hoffmann's syndrome or other myopathic syndromes. Subclinical hypothyroidism in young males may warrant treatment with the known adverse affects on cardiovascular system in young males although its effects on cognitive function has not been found especially in old age.¹²⁵

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Conflict of interest

Author declares that there is no conflict of interest.

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