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A Review of Endocrine Disorders in Thalassaemia

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ABSTRACT

Endocrine dysfunction in thalassaemia is amongst the most common complication and is principally attributed to excessive iron overload and suboptimal chelation. The prevalence is quite high particularly in multiethnic populations but determining the prevalence is often difficult due to the widespread heterogeneity of the population and timing of exposure to chelation therapy. Disturbances in growth, pubertal development, abnormal gonadal functions, impaired thyroid, parathyroid and adrenal functions, diabetes and disorderly bone growth are commonly encountered. Early detection and institution of appropriate transfusion regimen and chelation therapy and treatment of complications are the keys to managing this population including regular follow. In this article, we review the literature in relation to the various endocrine complications encountered in thalassaemia.

KEYWORDS

Thalassaemia; Chelation; Endocrinopathies; Diabetes; Hypothyroidism

1. Introduction

Thalassaemia major is a hereditary disorder of haemoglobin synthesis and the homozygous state results in severe anaemia. Historically the homozygous condition was known to affect a significant population in Mediterranean countries and the Middle East; however, migration has changed the geographic spread and made it a worldwide health problem. The combination of transfusion and chelation therapy has dramatically extended the life expectancy of thalassaemic patients but is complicated by citrate toxicity and subsequent iron overload resulting in a high incidence of endocrine abnormalities in children, adolescents and young adults [1]. Excessive iron is deposited in most tissues primarily in the liver, heart and the endocrine glands [2]. Bannerman *et al*. in 1967 published the first report of multiple endocrinopathies [3]. Endocrinopathies are now amongst the common complications of thalassaemia but determining the exact prevalence is difficult because of differences in age of first exposure to chelation therapy and the continuing improvement in survival in well-chelated patients [4]. Thus, data regarding the prevalence of endocrine dysfunction in patients with ß thalassaemia major are limited and often depend on compliance with treatment [5-8].

Massive iron deposition is caused by chronic anaemia resulting in profound tissue hypoxia as well as compensatory responses, including increased bone marrow erythropoiesis and increased intestinal iron absorption. Despite the availability of chelation therapy, iron overload remains problematic because of poor acceptability of the currently available agents, which require parenteral administration and close blood monitoring. Disorders of growth, sexual development & fertility, abnormal bone mineralisation, diabetes mellitus, hypothyroidism and hypoadrenalism are the main endocrine complications found in thalassaemic patients [9].

2. Growth in Thalassemia

Thalassaemic children show retardation of growth in the foetal, infantile, the pre-pubertal and the pubertal periods [9]. Approximately 20% - 30% of such patients have growth hormone (GH) deficiency [10]; in the remaining

70% - 80% provocative tests such as clonidine or glucagon stimulation tests have revealed a peak growth hormone levels lower than those found in patients with constitutional short stature. Potential causative factors for growth failure include iron overload, free radical toxicity [11] desferrioxamine toxicity [12], zinc deficiency, anaemia, delayed puberty, primary hypothyroidism [13], liver cirrhosis and defect in the Growth Hormone-Insulin-like Growth Factor-1 (GH-IGF-1) axis [14].

The anterior pituitary gland is particularly sensitive to free radical oxidative stress. Magnetic resonance imaging (MRI) shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function [11]. Twenty-four hour profile of GH in thalassaemic patients and GH response to GHRH is no different from that of idiopathic short stature children [15], but there may be an increased somatostatin tone, which interferes with the GH secretion [16].

Low serum IGF-1 and normal GH reserve in thalassaemic patients imply that a state of relative GH resistance exists and the rise in IGF-1 and improvement in growth with GH therapy suggest that the resistance is only partial at the post receptor level [13]. Moreover linear growth in childhood is disrupted due to anaemia, ineffective erythropoiesis, high ferritin levels & desferrioxamine treatment. This is because desferrioxamine and iron loading at the growth plate may have deleterious effects on local IGF-1 production and paracrine growth regulation [12], hence early chelating agents inhibits cell proliferation, protein synthesis and mineral deposition lowering the activity of alkaline phosphatase. Abnormal body proportions with truncal shortening are commonly seen and could be due to the disease itself, iron toxicity and toxic effects of desferrioxamine [13].

Karamifar *et al*. [17] have demonstrated that 62.9% of girls and 69% of boys affected with thalassaemia were less than 2SD below the mean for normal height. Roth *et al.* [18] showed that 40.6% of patients were short in stature (height below third percentile). Similarly Soliman *et al.* [19] reported a prevalence of short stature (<2SD) in 49% of their thalassemic patients. Moayeri *et al*. [20] showed that 62% were less than 2SD and 49% were 3SD below the mean and also confirmed decreased growth hormone response to two provocative tests and low levels of IGF-1 in a majority of their thalassaemic patients. Moreover Gulati *et al*. [21] and Theodoridis *et al*. [10] have also reported similar reduced responses to provocative tests in 51% and 20% of thalassaemic patients respectively. Borgna-Pignatti *et al*. [22] have also confirmed short stature in 40.6% of their thalassaemic subjects. A more recent study by Vogiatzi *et al*. has shown that 25% of the 361 subjects regardless of the thalassaemia syndrome had short stature. [23]

Although the results of short term GH therapy are encouraging, the impact of treatment on final height of non-GH deficient thalassaemic children remains uncertain [13] and often GH produces uncertain clinical response [24,25]. Most patients lack the pubertal spurt and have reduced GH peak amplitude [26], hence responses to recombinant human GH therapy is poor when compared with that of children with GH deficiency, idiopathic short stature or Turner Syndrome.

3. Hypogonadism and Puberty in Thalassaemia

Sexual immaturity is a profound complication of severe thalassemia. Multiple gonadal and pituitary-gonadal function studies have confirmed primary gonadal failure due to gonadal iron deposition [27]. Secondary hypogonadism results from iron deposition on gonadotrophic cells of the pituitary gland as shown by poor response of FSH and LH to GnRH stimulation [28-30] or a combination of both primary and secondary hypogonadism [31]. The incidence rate of failure of onset of puberty is 50% in some studies and may approach even 100% [9]. Evidence suggests those with more severe defects have a greater rate of iron loading possibly due to increased vulnerability to free radical toxicity. Iron toxicity on adipose tissue has also been shown to cause impaired synthesis of Leptin and consequently a delay in sexual maturation [32]. Leptin is a polypeptide hormone produced by adipose cells due to expression of the ob gene and acts as a permissive signal to initiate puberty. Gross iron overload in the pituitary, hypothalamus and gonads is progressive even with chelation therapy [33]. Patients with low gonadotropin levels have significant unresponsiveness to gonadotropin releasing hormone compatible with a hypothalamic and pituitary damage [34]. Delayed onset of menarche, oligomenorrhoea, secondary amenorrhoea, attenuated testicular size (of 6 - 8 ml) and breast size at Tanner Stage 2 or 3 are common manifestations of significantly elevated serum iron and ferritin levels [5, 35].

The yearly growth velocity in thalassaemic patients is either markedly reduced or completely absent [35]. Up to 20% of such patients have short stature [10] and the absence of pubertal growth spurt during spontaneous or induced puberty is detrimental to the achievement of a normal final height [13]. Disproportionate body proportions and changes in spinal growth [36] further impair truncal growth.

Chern *et al*. [37] have demonstrated a high prevalence of hypogonadotropic hypogonadism in their study subjects. The overall prevalence was 72%, with 45% prevalence in boys and 39% in girls. Considerable delay or arrest in development of secondary sexual characters and menstrual cycle was also noted. Similar results of decreased gonadal function were also noted in 75% girls

and 62% boys in a cross sectional study conducted at Hong Kong [38].

Moayeri *et al*. [20] reported puberty failure in 69% of thalassaemic patients with low levels of FSH and LH (73.2% in males and 64.8% in females) and their results were consistently similar to the multicentre study that was being conducted at Italy [35], which showed hypogonadism in 47% females and 51% males. Soliman *et al.* [19] have also reported lack of puberty in 73% males and 42% in thalassaemic patients with age less than 21 yrs. Moreover Borgna-Pignatti [22] and colleagues have also reported puberty failure in 67% males and in 38% females respectively. Notably, women who are well chelated may still conceive successfully.

Chelation therapy initiated early prior to the onset of adrenarche and administration of low dose sex steroids during adolescence may promote growth of bones, growth velocity and sexual maturation [9]. Chatterjee *et al*. 2011 [39] have since confirmed feasibility for low dose sex steroid priming in their Indian cohort as 80% reached pubertal maturation which was most effective in younger patients with minimal iron overload.

4. Glucose Intolerance and Diabetes Mellitus

Effective management of patients suffering from homozygous beta thalassaemia has led to improved life expectancy and hence manifestations of haemosiderosis related complications, notably, disturbances of the exocrine and endocrine function of the pancreas [40]. But unlike haemochromatosis, where the incidence of diabetes is as high as 80% [41], the incidence is lower in thalassaemics due to better diagnosis and treatment of the condition [9]. Four out of eight patients of Lassman *et al*. [42] had diabetes. 50% of twenty patients studied by Suadek *et al*. [43] had abnormal glucose tolerance. Sixteen of eighty two patients interviewed by Chern *et al*. had diabetes and risk was increased by co-infection with hepatitis C [44]. Gamberini *et al*. [44] followed up 273 thalassaemic patients over a period of thirty years and have shown that 42 patients developed insulin dependent diabetes mellitus. They demonstrated that prevalence progressively increased with time. Noetzil *et al*. [45] found almost 50% of patients studied had confirmed diabetes or abnormal glucose tolerance and that pancreatic iron was the strongest predictor of beta cell toxicity. The main risk factors were poor compliance with desferrioxamine treatment ($p < 0.05$), advanced age at the start of intensive chelation therapy, liver cirrhosis or severe fibrosis. Prevalence of impaired glucose tolerance (IGT) was also high and was associated with male sex, poor compliance with desferrioxamine therapy and a very high liver iron concentration. The Italian working group [46] demonstrated diabetes in 4.9% of patients whereas Aydinok *et al*. [47] showed IGT in 10.8% of their study subjects. A multicentre study in Cyprus [48] showed that 9.4% of thalassaemic patients had diabetes. Najafipour *et al*. [49] have shown the prevalence rates of diabetes mellitus, impaired fasting glucose and impaired glucose tolerance in their group of thalassaemic patients to be 8.9%, 28.6% and 7.1% respectively. Overall prevalence ranges from 6.4% to 14.1%. The development of glucose intolerance is progressive; this is related to poor compliance with chelation therapy and presence of hepatic fibrosis or cirrhosis. Guidelines recommend screening with the oral glucose tolerance test (OGTT) and studies have shown those with higher responses are more likely to have deteriorating glucose tolerance [50,51]. However OGTT compliance is often poor. Pancreatic iron overload can be assessed my MRI [52] but doesn't seem to correlate with siderosis in other organs.

Although inadequate insulin release has been reported by several groups [42,53,54], hyperinsulinaemia and decreased insulin sensitivity [55] with reduced hepatic release of insulin [9] has been presumed to be the main pathogenic mechanism. Siklar *et al*. [56] propose impaired insulin secretion precedes development of insulin resistance. Moreover selective oxidative damage to pancreatic beta cells may also occur as a result of autoimmunity [56]. Beta cell function remains normal until the later stages of disease [9] but insulin sensitivity correlates inversely with iron overload and age [57]. Fasting pro-insulin and pro-insulin to insulin ratio is significantly increased and correlate positively with hepatic iron [58] but C-peptide levels are variable indicating variable beta cell function [59,60]. Evaluation of exocrine function of the pancreas shows decreased serum trypsin and lipase levels [61] with normal activity of alpha amylase. The onset of diabetes mellitus tends to follow the development of other endocrine and cardiac complications [62]. Glucose intolerance correlates with at least 50% decline in beta cell function which is not entirely reversible even after intensive iron chelation but paradoxically, high transfusion regime not accompanied by effective iron chelation can increase the incidence of diabetes mellitus further.

5. Thyroid Dysfunction

Thyroid dysfunction is a frequently occurring endocrine complication in thalassaemia major, but its prevalence and severity is variable and the natural history is poorly described [63]. Autoimmunity has no role in the pathogenesis of thalassaemia related hypothyroidism [64]. Up to 5% of thalassaemic patients develop overt clinical hypothyroidism that require treatment [35] whereas a much greater percentage have sub-clinical compensated hypothyroidism with normal T4 and T3 but high TSH

levels. It usually occurs in severely anaemic and/or iron overload thalassaemics but is uncommon in optimally treated patients [7,65]. The pathogenesis is again unclear but thought to relate to lipid perioxdiation, free radical release and oxidative stress [65]. The incidence of hypothyroidism is directly related to the degree of iron overload and most patients have ferritin levels close to 2000 µg/l. Typically the thyroid gland is impalpable, thyroid antibodies are negative and often clinical features of the disease are absent. Thyroxine levels have been reported normal in majority of patients [5,27,31,66] suggesting insensitivity of the thyroid gland to iron overload. However low or normal T4 values with elevated TSH have been also reported suggesting sub-clinical primary hypothyroidism [5,31,67,68]. An exaggerated TSH response to stimulation by thyrotrophin-releasing-hormone (TRH) was found by De Sanctis *et al*. [69] in 8 of 24 thalassaemics studied and a third of those went on to develop subclinical or overt hypothyroidism three to eleven years later. This suggests the development of thyroid disease may have a fairly protracted course. De Sanctis *et al*. [69] reported predominance of the mildest form of primary hypothyroidism in their cohort of 97 patients with thalassaemia where the disease course was mostly stable. Thyroid ultrasonography usually shows reduced echogenicity of the gland due to reduced volume with thickening of thyroid capsule. Chirico *et al*. [70] followed up 72 thalassaemic patients over a period of eight years and demonstrated ferritin levels correlate positively with both TSH and thyroid volume on ultrasonography and can predict progression of thyroid disease. This is contrary to previous studies [71,72] including a 12-year longitudinal study by Filosa *et al*. [72] 7 years earlier which showed no association between ferritin levels or transfusion statuswith worsening thyroid function.

Some studies have reported a high prevalence of primary hypothyroidism reaching up to 17% - 18% [7,73] whereas others have reported a low prevalence of 0% - 9% [74,75]. Shamshirsaz *et al*. [1] demonstrated a prevalence of 7.7% in their study similar to the Italian study group [35] who found 6.2% patients to be hypothyroid where as Aydinok *et al*. [47] showed the prevalence to be higher at 16%. A more recent study by Toumba *et al*. [48] showed that the prevalence of acquired hypothyroidism was 5.9% which was consistent with other studies.

Investigation of thyroid function should be performed annually beginning at the age of 12 years. Elevated levels of TSH and reduction in T4 and T3 result from increased sensitivity of the gland to pharmacological doses of Iodine [76] which may result in rapid progression of subclinical hypothyroidism into a severe disease [77]. This is more detrimental in those with concomitant cardiomyopathy and thus caution is required with co-prescription of Iodine based anti-arrhythmic agents such as amiodarone. It is questionable as to what action should be taken in mild hypothyroidism. De Sanctis *et al*. [78] showed that good compliance with chelation therapy appeared to improve thyroid function and routine surveillance for hypothyroidism is unnecessary in thalassaemia major [79].

6. Hypoparathyroidism

Hypocalcaemia due to hypoparathyroidism is a recognized late and rare complication principally due to iron overload. It has a higher incidence in males and usually evident after 10 years of age [35]. The loss of diurnal variation in parathyroid hormone (PTH) levels is the first evidence [9]; patients typically have low calcium, PTH & Vitamin D levels and high phosphate levels. Zamboni *et al*. [80] demonstrated decreased PTH levels and subsequently impaired vitamin D synthesis in their older thalassaemic patients. The manifestations are primarily noted in the second decade. Iron toxicity may cause overt hypoparathyroidism in 3% - 4% of thalassaemia patients whereas preclinical hypoparathyroidism was recently reported to occur in close to 100% of thalassaemic patients [81]. Angelopoulos *et al*. [82] in their study of transfusion dependant patients with β thalassaemia have demonstrated hypoparathyroidism in 13.5% subjects with significant low levels of intact parathyroid hormone and total and ionized calcium. Similarly Aleem *et al*. [83] have shown that 20% of their patients had hypoparathyroidism which was much higher compared to the multicentre study in Italy [35] involving 25 centres which showed the prevalence to be 3.6%. A French study from 1993 showed the prevalence to be as high as 22.5% [84]. Shamshirsaz *et al*. [1] in their multicentre study in Tehran have shown a prevalence of 7.6%, which was higher than the 3.6% - 7%, reported by other workers [8,35,85] and the male: female ratio was 4:1, which was higher than several other reports [35,86].

Limited data [87,88] shows that early supplementation with Vitamin D or calcitriol treatment for three months is sufficient to normalize plasma calcium and phosphate levels. Tetany, seizures or cardiac failure due to severe hypocalcaemia is rare and requires immediate correction with intravenous administration of calcium.

7. Adrenal Function

Histological and imaging studies have shown that iron deposits in the adrenal cortex of thalassaemic patients are mainly confined to the zona glomerulosa with rare involvement of the zana fascicularis [89]. Most studies have revealed intact pituitary adrenal axis in thalassaemics [27,31,53,54,66]. Prevalence of adrenal insufficiency is variable and depends both on the degree of iron overload and cut off values for cortisol measurement. McIntosh [54] found raised ACTH levels suggesting

primary adrenal failure, but Costin *et al*. [5] found reduced ACTH and adrenal reserve even in the absence of clinical signs. To support this finding baseline serum and urinary cortisol levels are frequently normal which may reflect reduced ability of the adrenal cortex to respond to additional pulses of ACTH [90]. Patients usually have dissociation between androgen, cortisol and aldosterone synthesis leading to low serum Dihydroepiandrostenedione (DHEA), Dihydroepiandrostenedione Sulphate (DHEAS), androstenedione and testosterone levels, which also explains absence of adrenarche in these patients [91]. Patients usually demonstrate an intact secretory pattern of cortisol and aldosterone but abnormal circadian patterns of ACTH secretion [92]. Also, thalassaemics with chronic liver disease may have falsely low serum cortisol levels as it is normally bound to cortisol binding globulin (CBG) which is synthesised by hepatocytes [93]. To date CBG level in thalassaemics hasn't been reported, however, a normal level in the presence of low cortisol excludes its role in adrenal insufficiency. Inaccurate cortisol levels in women may be a reflection of oestrogen induced elevation in CBG levels. Imaging studies using MR have frequently identified adrenal hypointensity without alteration of morphology in thalassaemia patients and verified autopsy findings of correlation between adrenal iron and liver iron [94]. However, despite high sensitivity, histology still remains the gold standard for diagnosis of iron deposition.

8. Osteoporosis

Beta thalassemia is associated with marrow expansion, osteopaenia with cortical thickening, trabecular coarsening and bone deformity [95]. Factors implicated in its cause include hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, iron overload and its treatment [96]. Malnutrition, inadequate exercise and absence of adrenal sex hormones during adrenarche and gonadal hormones during puberty are other contributory factors [97]. There is a high incidence of osteoporosis of the spine and hip in both sexes. In men the lumbar vertebrae and femoral neck are affected while in women it is the spine [96]. Due to significant reduction in cortical and trabecular bone mineral density, pathological fractures are commonly encountered in more than 20% of cases [98].

A multi centre study group in Tehran [1] demonstrated that the prevalence of osteoporosis and osteopaenia in the lumbar region (L1 - L4) region were 50.7% and 39.4% respectively; the prevalence was 10.8% and 36.9% respectively in the femoral neck region. Similar results from other studies have also been reported [99,100]. Jensen *et al.* [96] showed that the overall prevalence of "severely low" bone mass was 51%; the prevalence of "low" bone mass to be 45%. Further studies like one performed by Vogiatzi *et al*. [101] showed that amongst the 31 patients studied (26 major and 5 intermedia), 22.6% had reduced bone mass (Z = −1 to –2) and 61.3% had low bone mass (Z </= −2).

Diagnosis is established early by BMD measurements using various densitometry modalities. Prevention, early diagnosis and effective chelation therapy is most effective in arresting the progression of the disease. Diet rich in calcium and Vitamin D and exercise can improve the outcome [57]. Patients with hypogonadism should be treated with hormone replacement therapy.

9. Conclusion

Thalassemia patients have a high prevalence of endocrinological abnormalities. Several studies at different centres have demonstrated the increased prevalence of endocrinopathies in patients with thalassaemia. Regular follow-up is essential for the early detection and appropriate treatment of associated complications. Improvements in protocols of transfusion regime and chelating therapy should hopefully improve the care and quality of life of these patients. Increasing awareness of endocrinological problems in thalassemic patients is essential not only because such patients are living longer now, but also because much of the morbidity and mortality from these complications can be reduced with regular surveillance, early treatment and follow-up in a multi-disciplinary setting.

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