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Original article

An ICET-A survey on occult and emerging endocrine complications in patients with β-thalassemia major: Conclusions and recommendations

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Summary. In adult thalassemia major (TM) patients, a number of occult and emerging endocrine complications, such as: central hypothyroidism (CH), thyroid cancer, latent hypocortisolism, and growth hormone deficiency (GHD) have emerged and been reported. As the early detection of these complications is essential for appropriate treatment and follow-up, the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) promoted a survey on these complications in adult TM

patients, among physicians (pediatricians, hematologists and endocrinologists) caring for TM patients in different countries. The data reported by 15 countries are presented.The commonest endocrine complications registered in 3.114 TM adults are CH and GHD (4.6 % and 3.0 %, respectively), followed by latent hypocortisolism (1.2%). In 13 patients (0.41%) a cytological papillary or follicular thyroid carcinoma was diagnosed in 11 and 2 patients, respectively, and a lobectomy or thyroidectomy was carried out. Of 202 TM patients below the age of 18 years, the reported endocrine complications were: GHD in 4.5%, latent hypocortisolism in 4.4% and central hypothyrodisim in 0.5%. Transition phase was an area of interest for many clinicians, especially as patients with complex chronic health conditions are responding to new treatments extending their lifespan beyond imagination.. In conclusion, our survey provides a better understanding of physicians' current clinical practices and beliefs in the detection, prevention and treatment of some endocrine complications prevailing in adult TM patients. Regular surveillance, early diagnosis, treatment and follow-up in a multi-disciplinary specialized setting are recommended. (www.actabiomedica.it)

Key words: thalassemia major, central hypothyroidism, latent hypocortisolism, growth hormone deficiency, transition phase, ICET-A

Introduction

Transfusion dependent thalassemia (TDT) patients frequently develop severe endocrine complications mainly due to iron overload, anemia, and chronic liver and heart diseases, which require prompt diagnosis, treatment and close follow-up by specialists (1,2). The incidence of complications is decreasing in younger cohorts of patients who are transfused with blood screened for viruses and also treated with new oral iron chelators that have enhanced the compliance and efficiency of chelation considerably reducing the severity of transfusional hemosiderosis.

On the other hand, in adult Thalassemia Major (TM) patients "occult" and emerging endocrine complications such as central hypothyroidism (CH) (3-5), thyroid cancer (6-9), latent hypocortisolism (10) and growth hormone deficiency (GHD) have emerged and been reported (11,12). As the early detection of these complications is essential for appropriate treatment and follow-up, the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) promoted a survey on these endocrine complications mainly in adult TM patients among physicians (pediatricians, hematologists and endocrinologists) caring for TM patients in different countries. The data from 15 countries are presented in this paper.

Methods used for the ICET-A survey

In September 2017, to ascertain the frequency of some occult and emerging endocrine complications in adult TM patients, the Coordinator (VDS) of ICET-A invited the 18 centers of the network to take part in a study to collect the following information: total number of TM patients followed in their centers; criteria used for the diagnosis of central hypothyroidism (CH), latent hypocortisolism and growth hormone deficiency (GHD), number and sex of TM patients followed with these complications, and of those with diagnosis of thyroid carcinoma and adrenal insufficiency (AI) (***first step***).

An *ad hoc* questionnaire, prepared by VDS in accordance with the Declaration of Helsinki (http://www.wma.net), was distributed by mail to participating centers. The exclusion criteria included: a) non-transfusion-dependent thalassemia; b) acute illnesses; c) bone marrow transplanted patients.

The deadline for sending the requested data was 2 months. In previous ICET-A surveys the patients' ages and the serum ferritin levels at diagnosis of endocrinopathy were not easily available in all centers, and therefore the ICET-A group decided to exclude these data from the questionnaire and to concentrate on the diagnosis and frequency of these complications (***second step***).

After collection and analysis of data, the ICET-A Steering Committee (4 endocrinologists: VDS, ATS, HE, and SDM, and 3 hematologists DC, SD and CK) prepared the first draft of the manuscript (***third step***). Later, the participants from the centers were formally requested to review the manuscript content and participate in the preparation of the final version (***last step***).

Statistical analysis

All numeric variables are reported for individual and sum of the participating centers. Chi-square test was used to compare the frequency of qualitative variables among the different groups. $P<0.05$ was considered statistically significant.

Results

The completed questionnaires were returned from 15 out of 18 ICET-A centers following a total of 3.156 TM patients (2.964 adults and 202 children and adolescents). Experienced physicians in thalassemia participating in the study were: 14 pediatric hematologists, 4 adult hematologists, 7 pediatric endocrinologists and 3 adult endocrinologists working in strict collaboration with the thalassemia centers, 1 pediatrician and 2 medical students.

Criteria used for the diagnosis of hypocortisolism

The lowest basal cortisol threshold reported to exclude hypocortisolism was ≤3 μg/dl (88 nmol/l). For a better assessment of adrenal function, 9 out of 15 (60 %) of the participating centers employed a standard-dose (SDT) corticotropin stimulation test (Synacthen 250 μg intravenously) and 2/15 (26.6 %) a low dose (LDT) stimulation test (Synacthen 1 μg). In one center LDT or insulin tolerance test were used. The diagnostic cut-off value used in 10/15 centers was between 18 to 20 μg/dl (495 -550 nmol/l).

Assessment of growth hormone secretion in adults

The most common tests used for the diagnosis of GHD were glucagon stimulation test and growth-hormone releasing hormone (GHRH) plus arginine test (combined test). Arginine alone or clonidine was also used for the assessment of GH reserve. The insulin tolerance test (ITT) was performed only in one center (UK). The cut-off limit for the diagnosis of GHD was < 3 ng/ml in adults and <10 ng/ml in children and adolescents, using an ultrasensitive chemiluminescence-based immunometric assay.

Criteria used for the diagnosis of central hypothyroidism and the evaluation of thyroid nodule

The diagnosis of central hypothyroidism was based on low circulating levels of free thyroxin (FT4) in the presence of low to normal TSH levels.

Thyroid ultrasound was performed almost in all TM patients followed in one Italian center; in the other centers the scan was requested only in selected patients. Fine-needle aspiration biopsy (FNAB) and microscopic evaluation was considered the best first-line diagnostic procedure for a thyroid nodule. The cytological classification of malignancy risk was based on the Bethesda system criteria (13).

Endocrine complications in different countries

The commonest endocrine complications registered in TM adults were CH and GHD (4.6 % and 3.0 %, respectively, followed by subclinical hypocortisolism and thyroid cancer (1.2 % and 0.41 %, respectively) (Table 1 and 2).

The age range at the diagnosis of adults endocrine complications was 22.3-54 years for CH, 18-56 years for GHD, 18.4-53 years for latent hypocortisolism, and 21-52 years for thyroid nodules. The cytological diagnosis was compatible for papillary or follicular carcinona (11 patients and 2 patients, respectively). A lobectomy or thyroidectomy was carried out in all patients.

Of 202 TM patients below the age of 18 years, endocrine complications reported were: GH deficiency in 4.5%, latent hypocortisolism in 4.4% and central hypothyrodisim in 0.5%.

A summary of total endocrine complications registered in children, adolescents and adult TM patients is reported in table 2.

All TM patients with latent hypocortisolism were asymptomatic and had no history of adrenal crisis.

Table 1. Distribution of endocrine complications in different countries (cont. in Table 2)

Endocrine complication and total TM (n.)	UK (180) Adults	Romania (180) Adults	Italy (444) Adults	Turkey (41) Adults	Iran (750) Adults	Kingdom of Saudi Arabia (145) Adults	India (46) Adults	Cyprus (293) Adults	Greece (383) Adults
Central hypothyroidism	9 4 M 5 F	14 10 M 4 F	3 1 M 2 F	10 5 M 5 F	6 4 M 2 F	15 5 M 10 F	2 2 M -	0 - -	64 36 M 28 F
Thyroid cancer	0 - -	0 - -	7 3 M 4 F	0 - -	0 - -	0 - -	0 - -	0 - -	5 2 M 3 F
Latent hypocortisolism	1 1 M -	1 1 M -	5 2 M 3 F	0 - -	4 3 M 1 F	16 9 M 7 F	1 1 M -	0 - -	0 - -
GH deficiency	45 25 M 20 F	Not tested - -	16 12 M 4 F	7 3 M 4 F	6 4 M 2 F	5 3 M 2 F	Not tested - -	2 1 M 1 F	Not tested - -

Table 2. Distribution of endocrine complications in different countries and summary data reported in two groups of thalassemia major (TM) patients

Endocrine complication and total TM (n.)	Oman (100) Adults	Qatar (90) Adults	Turkey (302) Adults	Egypt (34) Children and Adolescents	Malaysia (82) Children and Adolescents	Oman (86) Children and Adolescents	Total: TM patients (2954) Adults	Total: TM patients (202) Children and Adolescents	Chi square p value
Central hypothyroidism	2 1 M 1 F	7 4 M 3 F	12 8 M 4 F	0 - -	1 - 1 F	0 - -	144 (4.8%) 80 M (55.5%) 64 F (44.5%)	1 (0.5%)	8.27 0.004
Thyroid cancer	1 - 1 F	0 - -	0 - -	0 - -	0 - -	0 - -	13 (0.44%) 5 M (38.4%) 8 F (61.5%)	0 - -	12.94 0.0003
Latent hypocortisolism	0 - -	10 4 M 6 F	0 - -	2 1 M 1 F	6 3 M 3 F	1 1 F	38 (1.3%) 21 M (55.2%) 17 F (44.8%)	9 (4.4%) 4 M (44.4%) 5 F (55.5%)	0.893 0.345
GH deficiency	Not tested - -	12 8 M 4 F	3 3 M -	0 - -	9 6 M 3 F	0 - -	96 (3.2%) 59 M (61.4%) 37 F (38.6%)	9 (4.5%) 6 M (66.6%) 3 F (33.3%)	0.854 0.355

However, it is important to note that only CH was systematically checked by all participating centers every 6-12 months, whereas the assessment of other complications (e.g. growth hormone deficiency and hypocortisolism) was done occasionally or not at all. In one center (UK) the assessment of GH secretion was done frequently and was based on a combination of low insulin growth factor-1 (IGF-1) and GH de-

termination, after stimulation with ATT or glucagon test, in the context of other anterior pituitary hormone deficiencies.

The answers to the multiple choice question *"what are the major problems that you are going to face for diagnosis and treatment of endocrine complications in thalassemia?"* were: eight clinicians (53.3%) cited the transition phase, five (33.3%) the availability of drugs for performing the tests [e.g. exogenous corticotropin (ACTH) and growth-hormone releasing hormone (GHRH)], four (26.6%) the availability of drugs for treatment (e.g. testosterone gel), four (26.6%) the cost of endocrine drugs, and three (20.0 %) the unaivalability of endocrine consultation.

Additional comments were: lack of solid evidence base for modern therapies, poor compliance of some patients to treatment due to low economic circumstances, multiple drug ingestions causing feeling of depression, poor quality of some local iron chelation agents, and reimbursement of GH treatment in adults with GHD.

Discussion

Before the implementation of transfusions, TM was considered a pediatric disease with a severe clinical course and short survival, not exceeding the first decade of life. Today in developed countries, survival of patients on conventional treatment with appropriate transfusion and chelation, has increased to 40-50 years and is expected to extend soon to the geriatric age group (14). This advancement has been attributed to improved efficacy of chelation therapy as well as to enhanced management strategies, focusing on optimum treatment of the disease and its complications. However, prolonged survival of TM patients, in recent years, has resulted in a new set of challenges for both the patients and the treating staff from increasing prevalence of endocrine complications (15).

In fact, recent data indicate that 88.4% of 43 adult TM patients (aged 45-60 years) suffer from at least one endocrine complication (14). The commonest complications, in a group of young adult patients (mean age 29 years), were hypogonadism (16/21-76%), hypoparathyroidism (9/21-43%), osteoporosis (9/21-43%), diabetes mellitus (8/21-38%), and hypothyroidism (8/21-38%) (16).

Although there have been several studies describing the experience of dedicated centers treating adult thalassemia patients (17-22), only few have reported the prevalence of the occult and emerging endocrine complications in non selected adult TM patients, such as: central hypothyroidism (3-5), thyroid cancer (6-9), hypocortisolism (10,18) and growth hormone deficiency (GHD) (11, 12).

Therefore, taking in consideration that there is a need for increasing awareness of these endocrine problems in transfusion dependent thalassemia patients of advanced age, the ICET-A (23) promoted a survey on occult and emerging endocrine complications in TM patients among pediatricians, hematologists and endocrinologists taking regularly care of TM patients in different countries. Furthermore, the doctor's need in the management of these complications were also registered.

In spite of the limitations from the retrospective nature of the study and the scanty data source, we believe that it has some value for physicians taking care of adult TM patients.

Essentially, what do we know and what shall we do?

In brief,

1) The prevalence of occult and emerging endocrine complications in adults differed among participating centers; the prevalence of CH (4.6 %), GHD (3.0%) and latent hypocortisolism (1.2%) was lower compared to other reports (3-5,10, 24-31). Of 202 TM patients below the age of 18 years, the reported endocrine complications were: GHD in 4.5%, latent hypocortisolism in 4.4% and central hypothyrodisim in 0.5%. All TM patients with latent hypocortisolism were asymptomatic and none had a history of adrenal crisis.

In general, the clinical manifestations of CH are usually milder than those of primary hypothyroidism and, therefore, the clinical diagnosis can be difficult because the chronic disease *per se* and the presence of signs and symptoms of other pituitary hormone deficiencies may mask underlying CH (4). The diagnosis is usually based on a biochemical testing either inci-

dentally or in patients under evaluation for mild signs similar to those of primary hypothyroidism, which include fatigue, constipation, dry skin and weight gain.

Transient or reversible forms of CH may be observed during non thyroidal illnesses (NTI), in which hypothalamic thyrotropin releasing hormone (TRH) synthesis and feedback set points may be down regulated to result in CH. In these patients the biochemical testing must be repeated (4).

Therefore, clinicians should be alert for the diagnosis of CH through accurate interpretation of thyroid function tests. We recommend L-thyroxine therapy if the level of FT4 is consistently low provided that the patient has normal cortisol levels.

2) The symptoms of latent hypocortisolism often go unnoticed at first because they tend to be non-specific. When levels of cortisol reach critically low levels, life-threatening symptoms might develop.

One of the reasons for less severe symptoms is the fact that aldosterone, a product of the outer glomerular zone of the adrenal cortex, is secreted in almost normal amounts in patients with secondary adrenal insufficiency because the glomerular zone is mainly regulated by renin and angiotensin II rather than ACTH. Adrenal androgens and estrogens are also missing in secondary adrenal insufficiency because, like cortisol, they are regulated by ACTH (27, 29, 30).

The pathophysiological basis of latent hypocortisolism has not yet been well-defined. Chronic transfusions induce iron overload in several organs, including adrenal and pituitary gland. Therefore, it is most possible that pituitary iron deposition might reduce ACTH secretion leading to AI. Furthermore, the adrenal glands might also be directly affected by iron toxicity leading to primary adrenal insufficiency.

A combination of morning plasma ACTH and cortisol levels can be used for initial screening of adrenal function (30). In our previous guidelines, the optimal threshold that maximizes sensitivity plus specificity for morning basal cortisol against peak post-ACTH value >20 μg/dl (>550nmol/L) was 10 μg/dl (275 nmol/L) (30). However, the possibility of a partial adrenal insufficiency, in spite of adequate but probably less than expected cortisol synthesis before and after surgical stress, should be considered in every TM patient (31), and a pre-operative administration of glucocorticoids should be considered before a stressful event (30-32).

In summary, the lack of treatment guidelines and published research often leave hematologists and internists hesitant to approach TM patients presenting uncommon endocrine complications. The ICET-A recommendations provide helpful information on laboratory parameters and their interpretation, as well as adrenal hormone replacement dosages and management strategies. The guidelines emphasize that clinicians need to suspect AI earlier in TM patients with risk factors, such as: sepsis, advanced age, severe iron overload and/or poor compliance to therapy, low cardiac T2*, and multiple endocrine complications (30).

3) A considerable variability in the utilization of endocrine tests for the assessment of GH secretion was reported. GHD in adults is a clinical syndrome associated with lack of positive well-being, depressed mood, feelings of social isolation, decreased energy, alterations in body composition with reduced bone and muscle mass, diminished exercise performance and cardiac capacity and altered lipid metabolism with increase in adiposity.

Essentially there is no pathognomonic clinical feature to suspect GHD in adults. In patients with chronic diseases, the clinical evaluation of GHD is difficult because signs and symptoms may be subtle and nonspecific, and universal provocative testing in all patients is difficult because the approach is cumbersome and expensive. In addition, TM patients with GHD may have deficiencies of other pituitary hormones, further complicating the clinical picture. This contrasts with childhood-onset GHD where growth failure acts as a useful biological marker of GHD. Furthermore, the potential risks for performing ITT in patients with thalassemia, the lack of availability of drugs for testing GH secretion (e.g. GHRH), and the poor collaboration with endocrinologists are potential factors for the differences reported by the participating centers.

Because the appropriate selection of patients at risk of GHD is the crucial first step in making a correct diagnosis, the ICET-A proposed the following recommendations for GH testing in adults with TM (33):

- Short stature (height SDS <–2.5),
- Severe and/or prolonged iron overload,

- Dilated cardiomyopathy,
- Very low IGF-1 levels, especially in those patients with childhood-onset GHD, in the presence of pituitary iron deposition and/or atrophy,
- Severe osteoporosis and/or serum IGF-1 level <–2 standard deviations (34, 35),

In adults, GHD has been associated with: an adverse lipid profile; increased cardiovascular and cerebrovascular events; and decreased bone mineral density, muscle strength, exercise capacity, cognitive function and quality of life (QoL) (36). At present, there are no guidelines in the literature for the use of recombinant human GH administration in adult patients with TM and GHD. However, the reports of heart failure and left ventricular dilatation in two TM patients with GHD (a 21-year-old woman and a 23-year-old male patient) with improvement of heart failure during recombinant GH replacement therapy, suggest that GHD due to iron-induced damage to the hypothalamic-pituitary axis can contribute to heart failure in adult patients with TM (11,12). Given the possible positive effects of GH on the heart, it could be speculated that GH treatment may be useful in some patients with cardiac failure.

GH plays a positive role in maintaining the structure and function of the normal adult heart, by stimulating cardiac growth, heart contractility, and the normal structure of vascular endothelium. When GHD appears in adults, it causes impaired cardiac performance and exercise capacity (36). Despite these promising studies, the current situation is still far from being clear necessitating further and intensive investigation.

In an international multicentre study conducted in a large series of children and adolescents TM, a diagnosis of GHD was made in 7.9% of males and 8.8% of females (37). Whereas, in the present survey the prevalence was lower (4.5%) and higher in males (66.6 vs. 33.3% in females).

Growth hormone replacement therapy has been reported, with variable results, in TM patients. Therefore, large well-designed randomised controlled trials over a longer period with sufficient duration of follow up are needed (38, 39).

4) The occurrence of malignancies in TM patients is also an emerging concern. In the last five years, in a single Thalassaemia Unit following 195 thalassemic 11 carcinomas were diagnosed: (4 of liver, 1 of lung, 1 of adrenal gland and 5 of the thyroid gland) and the mean age was 42.6 years (9).

In our survey, the prevalence of thyroid papillary and follicular carcinoma was 0.41%. The highest prevalences were registered in Greece and Italy (1.3% and 1.57%, respectively), followed by Oman (1.0%).

In summary, it seems that patients with thalassemia have a substantial risk for malignancies. Further studies are needed in these patients to clarify the possible link between cellular iron content, hepatitis C virus infection and cancer development (9). A thyroid ultrasonography is recommended for all adult TM patients in addition to the annual FT4 and TSH assessment.

5) Transition from paediatric to adult care has become an area of interest for many clinicians, particularly as so many patients with complex chronic health conditions are responding to new treatments that have improved their lifespan beyond any imagination. Half of the participating centers raised this point taking in consideration that the aging patients' conditions creates new challenges for adults with thalassemia and for the providers who care for them. Considering that the management of thalassemia patients requires multidisciplinary and collaborative interventions, it is urgent to identify the appropriate dimensions of Centers of Expertise (CEs), based both on the number and mainly on the age of patients, and on their specific clinical and therapeutic and research needs. Legislation is required to endorse and organise the individual units and CEs. An efficient schedule for medical care and transition phase for patients with thalassemia should be carefully organized to meet the national health system structure and socio-economic capabilities for precise treatment, prevention, and patients' social adaptation, as well as the epidemiology of thalassemia in the population. Therefore, optimal care for adults must be placed as a priority program and will require hard work, commitment, and collaboration by all involved.

A previous ICET-A survey has shown that there is heterogeneity in the organization of existing health services with anticipated effects on patients' expectancies and wellbeing. Only a few countries have dedicated transition phase programmes and specialised

centers for thalassemia care (40). Thus, the medical community needs to work in a non-dogmatic way with the providers to find the best solution for reaching an undisputable common goal: to provide optimal treatment for all patients.

In conclusion, our survey provides an understanding of current physician clinical practices and beliefs in the detection of some occult and emerging endocrine complications in TM patients. While waiting for more extensive adequately powered and targeted studies, physicians should remember that thyroid cancer and GHD are not rare diseases among adult TM patients and are probably under-diagnosed. We hope that our data will be valuable for physicians taking care of adult TM patients. Regular surveillance, early diagnosis, treatment and follow-up in a multi-disciplinary specialized setting are recommended for upgrading the management of these complications.

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