

An ICET- A survey on hypoparathyroidism in patients with thalassaemia major and intermedia: a preliminary report

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Summary. Hypoparathyroidism (HPT) is a rare disease with leading symptoms of hypocalcemia, associated with high serum phosphorus levels and absent or inappropriately low levels of parathyroid hormone (PTH). In patients with thalassemias it is mainly attributed to transfusional iron overload, and suboptimal iron chelation therapy. The main objectives of this survey were to provide data on the prevalence, demographic and clinical features of HPT in thalassemia major (TM) and intermedia (TI) patients living in different countries, and to assess its impact in clinical medical practice. A questionnaire was sent to all Thalassemia Centres participating to the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence

Medicine (ICET-A) Network. Seventeen centers, treating a total of 3023 TM and 739 TI patients, participated to the study. HPT was reported in 206 (6.8%) TM patients and 33 (4.4%) TI patients. In general, ages ranged from 10.5 to 57 years for the TM group and from 20 to 54 years for the TI group. Of the 206 TM patients and 33 TI patients with HPT, 117 (48.9%) had a serum ferritin level >2.500 ng/ml (54.3% TM and 15.1% TI patients) at the last observation. Hypocalcemia varied in its clinical presentation from an asymptomatic biochemical abnormality to a life-threatening condition, requiring hospitalization. Calcium and vitamin D metabolites are currently the cornerstone of therapy in HPT. In TM patients, HPT was preceded or followed by other endocrine and non-endocrine complications. Growth retardation and hypogonadism were the most common complications (53.3% and 67.4%, respectively). Although endocrine complications were more common in patients with TM, non-transfused or infrequently transfused patients with TI suffered a similar spectrum of complications but at a lower rate than their regularly transfused counterparts. In conclusion, although a large international registry would help to better define the prevalence, comorbidities and best treatment of HPT, through the result of this survey we hope to give a clearer understanding of the burden of this disease and its unmet needs. HPT requires lifelong therapy with vitamin D or metabolites and is often associated with complications and comorbidities. Therefore, it is important for endocrinologists and other physicians, who care for these patients, to be aware of recent advances of this disorder. (www.actabiomedica.it)

Key words: hypoparathyroidism, thalassemia major, thalassemia intermedia, clinical manifestations, co-morbidities, iron overload, treatment, survey

Introduction

Low, or inappropriately normal, concentration of serum parathyroid hormone (PTH) in association with hypocalcemia is the hallmark of hypoparathyroidism (HPT) and helps to differentiate this disease from other disorders associated with hypocalcemia. The concentrations of 1,25-dihydroxyvitamin D [1,25(OH)₂ vitamin D] and bone turnover markers including alkaline phosphatase activity are usually in the low normal to low range. The daily urinary excretion of calcium is reduced when patients are hypocalcemic, although the fractional excretion of calcium is increased (1).

In the general population, HPT can be transient or permanent, inherited or acquired, or caused by inability of parathyroid gland to synthesize or secrete PTH. This may be due to abnormal development of the parathyroid gland, destruction of parathyroid tissue, or peripheral resistance to PTH.

It is a rare disease, with leading clinical symptoms of hypocalcemia which is associated with high serum phosphorus levels, and absent or inappropriately low levels of PTH (1). The low extracellular ionized (Ca^{2+})

may have a profound impact on the function of a large number of tissues and organ systems including the brain, muscles, kidneys and heart (2, 3).

In adults, the most common cause of HPT is parathyroid gland injury or inadvertent removal during thyroid surgery whereas in patients with thalassemias it is mainly attributed to iron overload, secondary to multiple blood transfusions and suboptimal chelation therapy (1, 4-6). Iron excess causes tissue damage in the liver, heart, endocrine glands and other organs by generating hydroxyl free radicals that cause oxidative damage to lipids, proteins, and DNA (4-6). Chronic anaemia and magnesium deficiency could be other additional factors causing parathyroid dysfunction (7-9). Other factors, like individual susceptibility to iron toxicity effects, damage secondary to persisting iron overload in the years preceding iron chelation therapy and the severity of hematological phenotype of the disease could also play a role in the development of HPT (4, 10).

Endocrinopathies are common in β -thalassemia major (TM) patients treated with desferrioxamine therapy, especially in patients with serum ferritin levels >2.500 ng/ml or those splenectomized (11). The

prevalence of overt HPT reported in 1661 TM patients, by the Italian Working Group on Endocrine Complications in Non Endocrine Diseases, was 3.6% (4), whereas a subclinical HPT, utilizing the nocturnal measurements of serum minerals, was observed in almost 100% of 13 TM patients, with normal morning serum calcium levels (12).

There are limited published data on the epidemiology of HPT in patients with thalassaemia intermedia (TI) (13-16). A prevalence of 1% has been reported only in a single Centre from Iran (14).

One of the practical objectives of the International Network of Clinicians for Endocrinopathies in Thalassaemia and Adolescence Medicine (ICET-A) is to encourage research in the field of growth disorders and endocrine complications in thalassaemia and to offer to doctors, taking care of patients with TM or TI, material that can be easily used and applied to practical clinical situations encountered by pediatricians or haematologists (17). Therefore, the main objective of the present study is to provide data on the prevalence, demographic and clinical features of HPT in TM and TI patients living in different countries, and to gain insights into the impact of HPT and approaches to its management in current clinical practice. Through the result of this survey, we hope to give better understanding of the burden of this disease and its unmet needs.

Material and methods

A. First step

In March 2017, the Coordinator of the ICET-A (VDS) prepared a questionnaire to collect data on the "Prevalence, Clinical Presentation and Treatment of hypoparathyroidism (HPT) in Patients with Thalassaemia Major and Intermedia".

HPT was defined "an endocrine disease characterized by failure of the parathyroid glands to produce levels of parathyroid hormone (PTH) sufficient to maintain normal levels of serum calcium characterized by hypocalcemia, phosphate levels in the upper normal or frankly elevated range, inappropriately low or undetectable PTH with normal serum magnesium and alkaline phosphatase" (1, 18).

B. Second step

All ICET-A Members were requested, by mail, to comment on the information and data included in the preliminary questionnaire draft. In particular, the study was planned to fulfil the following information: personal doctors' data (place of work, specialization) demographics and anthropometry of patients, patients' transfusional status, and iron chelation therapy, serum ferritin level on PTH diagnosis, number of TM and TI patients with documented HPT, signs and symptoms registered at diagnosis, investigations potentially required at the diagnosis of HPT in addition to the classic criteria, presence of co-morbidities, recommended treatment of HPT, patients' compliance to treatment, assessment of HPT during the patients' follow-up, and the principal physician taking care of the patients.

Definition of associated complications

The following definitions were used for an homogenous classification of associated morbidities: a) heart disease (defined as the presence of any of the following: history of congestive heart failure, symptoms or signs of congestive heart failure, mild or overt left and/or right ventricular mild or overt dysfunction, arrhythmia with or without myocardial siderosis (MRI T2* <20 msec) (19); b) liver dysfunction (was defined by persistent rise of liver enzymes, greater than twice the normal levels); c) primary hypothyroidism (subclinical and overt were defined by normal or low free thyroxine and abnormally high levels of thyroid-stimulating hormone: >10 mU/L), secondary hypothyroidism (was defined by low free thyroxine and normal or decreased TSH) (13); d) hypogonadism defined according to the criteria reported in our previous publication and literature reports (18, 20); e) short stature (was defined as a Standard Deviation score for height less than or equal to -2, using the tables of WHO for the normal population) (18,20); f) diabetes insulin and non-insulin dependent were defined according to standard of American Diabetes Association) (21), and g) hypoadrenalism was defined in the presence of basal cortisol <4.2 µg/dl (98 nmol/l), serum value associated with the highest negative prediction value against peak post ACTH value >20 µg/dl according to

our experience in Thalassaemic patients (22). Growth hormone (GH) secretion was not included in the survey because the assessment was not performed in all participating Centres.

C. Third step

After the final approval by ICET-A Members, the questionnaire was sent to all Thalassaemia Centres taking part to the ICET-A Network of the following Countries: Bulgaria, Cyprus, Egypt, Greece, India, Indonesia, Iran, Italy, Jordan, Malaysia, Qatar, Romania, Kingdom of Saudi Arabia, Sultanate of Oman, Turkey and UK.

Criteria of inclusion and exclusion

The criteria used for patients' inclusion were: 1) patients with TM. The term was applied to patients who had either no β - globin chains synthesis homozygous β^0 thalassaemia) or severely limited, (β^0/β^+ or β^+/ β^+ thalassaemia). The diagnosis of TM was based on haematological, biochemical findings and recently, on molecular characterization of genotype, and on a history of regular transfusion with packed red cells, every 2-3 weeks, in the first years of life; 2) patients with TI. The term was used to define a type of non transfusion-dependent thalassaemia, with mild genotype and clinical phenotype not requiring regular transfusions for survival. As a rule the milder cases had no or occasional blood transfusions while the more severe may need up to 7-8 transfusions annually (11, 23-25).

The exclusion criteria were: a) thalassaemic patients with renal insufficiency; b) bone marrow transplanted patients; c) HIV positive patients; d) patients regularly taking proton-pump inhibitors; e) thyroidectomy and f) patients with questionnaire's incomplete data.

The evaluation of compliance was not included in our survey as it is based on the relationship of personal trust between physician and patient, supported by a few objective data, such as the number of vials or pills distributed by the pharmacy or checking for sites of injection.

The study was in adherence to the tenets of the Declaration of Helsinki and consent was obtained from the subjects aged >18 years or parents/guardians

for subjects <18 years of age, in accordance with the policy of each institution.

Statistical analysis

Standard computer program (SPSS for windows, version 13, SPSS Corp., Tulsa- USA) was used for analysis of data collected. Descriptive statistics are expressed as means \pm standard deviation (SD) medians or percentages and ranges. Chi-square test was used to compare the frequency of qualitative variables among the different groups. Fisher's Exact test was used to calculate the probability value for the relationship between two dichotomous variables. The univariate logistic regression analysis was used to evaluate the odds ratio (OR) with 95% CI. A p value <0.05 was considered significant.

Results

A total of 17 Centers, treating a total of 3023 TM and 739 TI patients, participated in the study. Nine clinicians were pediatric hematologists, 5 pediatric endocrinologists, 4 adult hematologists and 2 adult endocrinologists. In addition, 6 clinicians participated in the analysis of data and the preparation of manuscript, two pediatric hematologists, 2 pediatric endocrinologists, 1 pediatric nephrologist (performing the task of statistical analysis) and 1 medical student.

HPT was diagnosed in 206 (6.8%) TM patients and in 33 (4.4%) TI patients: the difference between the two groups was significant ($p=0.019$). HPT affected more frequently males in the TM group (TM: male/female ratio: 1.48) compared to the TI group (male/female ratio: 1.26) ($p=0.58$). In general, ages ranged from 10.5 to 57 years for the TM group and from 20 to 54 years for the TI group. Data on the distribution of these variables, and the age range at the diagnosis of HPT, reported in different countries, are given in table 1.

At the diagnosis of HPT, 101 patients (42.2%) were asymptomatic, 90 (37.6%) presented with paraesthesia and/or cramps, 41 (17.1%) with tachycardia, 24 (10.0%) with tetany, 26 (10.8%) with cardiac rhythm

Table 1. Demographic and characteristics of patients with thalassaemia major (TM) and intermedia (TI) diagnosed with hypoparathyroidism

Country	No. of TM pts	No. of TI pts	No. and % of TM pts. with HPT	No. and % of TI pts. with HPT	Age range (yrs) of TM pts. at diagnosis of HPT	Age range (yrs) of TI pts. at diagnosis of HPT
1. Bulgaria	46	4	9 (19.5)	1 (25)	26-48	40
2. Cyprus	247	39	7 (2.8)	0	38-57	0
3. Egypt	28	4	4 (14.2)	0	13-16	0
4. Iran	750	250	68 (9)	18 (7.2)	18-42	20-45
5. India	206	7	3 (1.4)	0	20-28	0
6. Italy	55	56	4 (7.2)	1 (1.7)	44-48	43
7. Italy	144	85	2 (1.3)	0	39-55	0
8. Italy	72	39	3 (4.1)	0	38-42	0
9. Italy	226	50	24 (10.6)	0	10.5-31.2	0
10. Jordan	355	35	25 (7%)	4 (11.4%)	17-37	21-24
11. Malaysia	82	0	1 (1.2)	0	16.8	0
12. Oman	182	42	11 (6.0)	1 (2.3)	17-30	39
13. Oman	85	17	2 (2.3)	0	18	0
14. Qatar	140	39	12 (2.8)	4 (10.2)	14-28	20-32
15. Turkey	264	38	1 (0.3)	0	14	0
16. Turkey	43	20	14 (32.5)	2 (10)	20-45	24-55
17. UK	98	14	15 (15.3)	2 (14.2)	21-56	26-54
Total number	3023	739	206	33	-	-

disturbance and 6 (2.5%) with cardiac failure. Hyperreflexia, manifested by carpal spasms (Trousseau sign), was present in 15 (6.2%) patients and laryngospasm in 2 patients (0.8%).

In addition to the classical criteria for the diagnosis of HPT the following parameters were assessed by clinicians taking care of thalassaemia patients: serum magnesium (17.6%), 24-hour urinary calcium (17.6%), serum vitamin D (47.0%), electrocardiogram (76.4%), brain computed tomography (CT) or magnetic resonance (MR) (11.7%), bone densitometry (58.8%) and kidney ultrasound (5.8%).

HPT in thalassaemia patients was preceded or followed by other endocrine and non-endocrine complications. The most relevant endocrine complications were: growth retardation and hypogonadism (prevalence of 51.8% and 66.1%, respectively); insulin dependent diabetes mellitus in 78 patients (32.6%) and non-insulin dependent diabetes in 38 patients (17.5%), 78 patients (32.6%) developed primary hypothyroidism and 9 patients (3.7%) central hypothyroidism, and in 8 patients (3.3%) hypoadrenalism was diagnosed.

Liver dysfunction was reported in 41 patients (17.1%) and cardiac involvement in 44 patients (18.4%).

The serum ferritin levels, type of chelation therapy, and the co-morbidities, in both TM and TI patients, registered at the last observation, are summarized in table 2. Of the 206 TM patients and 33 TI patients with HPT, 117 (48.9%) had a serum ferritin level >2.500 ng/ml (54.3% TM and 15.1% TI patients), 71 (29.7%) between 1.000 ng/ml and <2.500 ng/ml (28.1% TM and 39.3% TI patients), and 51 (21.3%) <1.000 ng/ml (17.4% TM and 45.4% TI patients).

A detailed study analysis was possible only in 24 TM patients (12 males and 12 females) followed in an Italian centre (Table 1, no. 10). The mean age at diagnosis of HPT was 18.5±5.8 years (range from 10.5 to 31.2 years). The mean age at onset of blood transfusion was 1.1±1.8 years and the serum ferritin level at the diagnosis of HPT was 5.199±2.635 ng/ml (range 380-14.850 ng/ml). A serum ferritin level above 2.500 ng/ml was present in 19 (79%) patients.

The major risk factor for the development of HPT was the serum ferritin level ($p < 0.002$; OR 2.2;

Table 2. Prevalence and type of co-existence diseases, serum ferritin levels and chelation therapy of the study population (TM versus TI) at last observation

	Thalassemia major patients with HPT (n. 206) no. of pts (%)	Thalassemia intermedia patients with HPT (n. 33) no. of pts (%)	p
Short stature <3 rd centile	110 (53.3%)	14 (42.4%)	0.24
Hypogonadism	139 (67.4%)	19 (57.5%)	0.26
Primary hypothyroidism	70 (33.9%)	8 (24.2%)	0.27
Central hypothyroidism	9 (4.3%)	0	0.14
Diabetes insulin dependent	71 (34.4%)	8 (24.2%)	0.24
Diabetes non-insulin dependent	38 (18.4%)	4 (12.1%)	0.38
Hypocortisolism	6 (2.9%)	2 (6.0%)	0.35
Liver dysfunction	40 (19.4%)	1 (3.0%)	0.02
Cardiac disease	41 (19.9%)	3 (9.0%)	0.14
Serum ferritin values below 1.000 ng/ml	36 (17.4%)	15 (45.4%)	0.0003
Serum ferritin values between 1.000 ≤2.500 ng/ml	58 (28.1%)	13 (39.3 %)	0.19
Serum ferritin values >2.500 ng/ml	112 (54.3%)	5 (15.1%)	0.00003
Chelation therapy with desferrioxamine	76 (36.8%)	6 (18.1%)	0.04
Chelation therapy with deferiprone	35 (16.9%)	5 (15.1%)	0.79
Chelation therapy with deferasirox	90 (43.6%)	18 (54.5%)	0.24
Chelation therapy with desferrioxamine plus deferiprone	5 (2.4%)	0	0.37

CI 95%: 2.9-1.6) and the major protective factor was the good compliance (>80%) to iron chelation therapy ($p<0.002$; PR 0.16; CI 95%: 0.5-0.005) whereas the age at the start of chelation therapy was a minor risk factor for the development of HPT ($p<0.002$; OR 1.1; CI 95%: 1.2-1).

Comparing the data of these 24 TM patients with HPT to 162 TM patients, without HPT, followed in the same Centre, emerged that hypogonadism, primary hypothyroidism, insulin dependent diabetes and cardiac iron overload were the most common associated complications. No significant differences were observed between the two groups of patients regarding the low bone mass (69.2% vs 56.6%: $p>0.05$).

When we divided these two groups of patients into 3 cohorts (C), according to the year of birth (C1=1954-1964; C2=1965-1974; C3=1975-2001) and as a consequence to the beginning on iron chelation therapy, the prevalence of HPT showed a progressive decline from 18.5% to 10.9% and 3.4% in C1, C2 and C3. Furthermore, an intensive iron chelation therapy induced a recovery of HPT in 2 female TM patients, aged 23 and 15 years. Their serum ferritin level, at the diagnosis of HPT, was 14.850 and 4.739 ng/

ml, respectively. After intensive subcutaneous chelation therapy with desferrioxamine the levels dropped to 1.474 ng/ml and 580 ng/ml, respectively. Over 25 years of follow-up, one out of 24 TM patient (4.1%) developed a symptomatic hypercalcemia, two patients nephrolithiasis (8.3%), one patient nephrocalcinosis (4.1%) and one patient on treatment with 1,25-dihydroxyvitamin D3, with persistent hypocalcemia and hyperphosphatasemia, developed a cerebral calcinosis (4.1%).

The prescribed medications in the Centres participating to the survey are reported in table 3. The

Table 3. Medications used in thalassemic patients with hypoparathyroidism

Medications	n. (%)
1,25-dihydroxyvitamin D3	159 (66.5%)
1-hydroxy-vitamin D3	63 (26.3%)
Dihydroxyvitamin D3	8 (3.3%)
Calcium carbonate	191 (79.9%)
Calcium citrate	5 (2%)
Low phosphate diet	142 (59.4%)
Teriparatide	1 (0.48%)
Others	none

majority of thalassaemic patients were taking Calcium supplements and vitamin D (calcitriol). Calcium carbonate (containing 40% elemental calcium) and citrate (containing 21% elemental calcium) were the most commonly prescribed. One Italian patient (0.48%) was on treatment with teriparatide.

No patients were on treatment with phosphate binders, hydrochlorothiazide or magnesium supplementation.

The patients' care was often provided jointly between specialists (pediatrician or haematologist and endocrinologist, in 76.4% of Centres). In two Centres the pediatrician and the haematologist declared the personal management of their patients and in another two Centres the haematologists preferred to refer the patient to an endocrinologist only for consultation or when the patient was not responding to treatment.

When we asked to describe the major problems met during the care of 239 HPT thalassaemia patients, 15 Centres (88.2%) reported, as the major problem, the patients' compliance to treatment, 7 Centres (41.1%) the control of calcium and/or phosphate levels, 5 Centres (29.4%) the cost of treatment or tests, 5 Centres (29.4%) the difficulty to require tests, 3 Centres (17.6%) the availability for an endocrinologist consultation, and 2 Centres (11.7%) the management of acute symptomatic hypocalcemia.

Discussion

This survey was carried out to investigate the prevalence, demographic and clinical features of patients with thalassaemias who developed HPT in different countries, to gain insights into the differences of the impact of HPT and the approach of its management in current clinical practice.

β thalassaemia is an inherited disorder of hemoglobin synthesis wherein mutations of the β globin gene lead to various degrees of defective β chain production, resulting in an imbalance of α/β globin chain synthesis, ineffective erythropoiesis, and a wide spectrum of anemia. Extremely diverse phenotypes exist within the β thalassaemia syndromes among populations (11, 23, 24). In our survey TI included patients who had clinical manifestations that were too severe

to be termed minor yet too mild to be termed major (15, 16, 24).

We documented that 6.8% (range: 0.3%-32.5%) of TM patients and 4.4% (range: 0%-14.2%) of TI patients had HPT. Hypoparathyroidism affected males more frequently in the TM group (TM: male/female ratio: 1.48) supporting a potential different compliance to iron chelation therapy. The suggested hypothesis, reported in the literature that females tolerate better iron toxicity, probably as an effect of reduced sensitivity to chronic oxidative stress (25), seems to be unlikely in the TI group because the male/female ratio was 1.26.

In TM patients HPT was preceded or followed by other endocrine and non-endocrine complications. Hypogonadism was the most commonly associated complication (Table 2) followed by short stature (53.3%), insulin dependent diabetes mellitus and non-insulin dependent diabetes (52.8%). The prevalence and type of other co-existent diseases was as follows: primary hypothyroidism (33.9 %), central hypothyroidism (4.3 %) and hypocortisolism (2.9 %). Although endocrine complications were more common in patients with TM, non-transfused or infrequently transfused patients with TI suffered a similar spectrum of complications but at a lower rate than their regularly transfused counterparts (Table 2).

It is well known that the differences in the frequencies of endocrine disturbances between TI and TM is due to the different impact of iron overload on the two diseases. Severe iron-overload related endocrine dysfunction is universally described in TM, compared to those with TI, who are either not transfused or are inadequately transfused (15, 16, 24, 26).

Of the 206 TM patients and 33 TI patients with HPT enrolled in our study, 117 (48.9%) had a serum ferritin level >2.500 ng/ml (54.3% in TM and 15.1% in TI patients), 71(29.7%) between 1000 ng/ml and <2.500 $\mu\text{g/l}$ (28.1% in TM and 39.3 % in TI), and 51 (21.3%) <1.000 ng/ml (17.4% in TM and 45.4% in TI patients). These findings indicate that a high ferritin levels were the major factor responsible for the development of HPT. In addition, most patients with HPT, also had multiple associated endocrine disorders. Unexpectedly, 15 infrequently transfused patients with TI and HPT had, at the last observation, a serum ferritin

level <1.000 ng/ml. Further investigations on these patients are needed to explain this discrepancy.

We acknowledge that ferritin measurements are poorly correlated with organ iron stores although Behoul et al. (11), using a multivariate logistic regression analysis, found that patients with a serum ferritin levels >2.500 ng/ml were: 3.27 times (95% CI 1.27-8.39) more likely to have HPT; 3.53 times (95% CI 1.09-11.40) to have diabetes mellitus; 3.25 times (95% CI 1.07-10.90) to have hypothyroidism, and 2.75 times (95% CI 1.38-5.49) more likely to have hypogonadism compared to patients with a serum ferritin level \leq 1.000 ng/ml. Possible contributing factors causing a variability of cellular iron overload are: a) the cell surface transferrin receptors and the capacity of the cells to deploy defence mechanisms against inorganic iron; b) individual susceptibility to iron toxic effect; c) the development of organ(s) damage secondary to persisting severe iron overload in the years preceding iron chelation therapy; d) the hematological phenotype of the disease and e) liver disorders, chronic hypoxia and associated endocrine complications, such as diabetes (10).

In our patients with β -thalassemias, hypocalcemia varied in its clinical presentation from asymptomatic biochemical disturbances to a life-threatening condition, requiring hospitalization. Symptoms of hypocalcemia most commonly included paresthesia and/or cramps, tachycardia, and neuromuscular irritability. Laryngospasm, cardiac rhythm disturbance, and cardiac failure occurred in 34 patients (14.2%), requiring immediate and aggressive intervention. Seventeen out of 426 TM patients (3.9%), reported by Karimi et al. were admitted to the hospital for convulsions due to HPT. Their age was between 11 to 20 years and the calcium level was below 8.5 mg/dl (2.125 mmol/L) (27).

HPT requires lifelong therapy with vitamin D or metabolites. Vitamin D3 is the most economical treatment of HPT; however, vitamin D3 has a very long biologic half life with the subsequent danger of chronic vitamin D intoxication. Dihydroxyvitamin D, an analogue of vitamin D, acts similarly, and can be used as an alternative. 1,25-dihydroxyvitamin D3, the biologically active metabolite of vitamin D3, is very potent, but has the danger of causing acute intoxica-

tion. It has a short half life and is more expensive than vitamin D3. A further metabolite, 1-hydroxy-vitamin D3 is also available for therapeutic use. Both under- and overtreatment can lead to unintended outcomes that can be irreversible. In undertreated or late treated patients with HPT, where there is a combination of chronic hypocalcemia and hyperphosphatemia, ectopic calcifications in organs may occur (28, 29). In over treated patient the risk of kidney stones and nephrocalcinosis is markedly increased (30).

To date, three guidelines on the management of hypoparathyroidism have been published, including those of the International Consensus Conference guidelines based on the first international conference on hypoparathyroidism held in Florence, Italy, in May 2015 (31), the European Society of Endocrinology Clinical Guidelines (32), and the American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinic Review (33). Although the number of trials is small and the number of patients enrolled in them is few, endocrinologists now have at least three documents to address management of acute and chronic HPT across the world.

Our study carries some limitations. Firstly, it is retrospective in nature and the genotype of patients was not available for the majority of them. Secondly, the quantification of iron overload was undertaken indirectly from serum ferritin levels, using stratification levels (<1.000 ng/ml, 1.000-2.500 and >2.500 ng/ml). Thirdly, a detailed study analysis was possible only in 24 TM patients followed in a single Italian Centre. Finally, we recognize that one additional limit of our study is the lack of statistical analysis, which did not allowed us to study correlations with splenectomy, and drugs used for iron chelation therapy. For the same reason, we did not divide TI patients into groups according to transfusional status to avoid an excessive fragmentation of the population.

With these limitations in mind, the present study describes in details HPT in TM and TI patients and stimulating for further prospective studies, such as: natural PTH history, renal function impairment, fracture incidences, ectopic calcifications, effects of replacement therapy and patients' quality of life. Clinical trials are also necessary to establish whether intensive

iron chelation therapy is able to prevent or reverse hypoparathyroid function.

In conclusion, iron overload remains a critical problem, even in countries where chelation therapy is widely available and adequately implemented recently. An early recognition and prevention of the endocrine complications, by early and regular chelation therapy, is mandatory for the improvement of the quality of life of these patients. Because asymptomatic hypocalcemia is common in these patients and may be potentially missed, it is important to check for hypocalcaemia, especially in the second decade of life, particularly when other iron overloaded associated complications occur. For HPT, Calcium and vitamin D metabolites are currently the cornerstone of therapy.

The scenario reported in TI patients makes optimal and early intervention extremely essential, and reflects the need for further studies to better explain the current findings observed in our patients and the beneficial effects of new chelation therapy on endocrine complications.

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