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Hypoparathyroidism in Adult Patients with Beta-Thalassemia Major

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قُصورُ الدُّرَيْقات لدى المرضى البالغين المصابين بمرض ثلاسيميا الدم الرئيسي نوع بيتا

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الملخص: الهدف: تقييم معدل إنتشار قُصورُ الدُّرَيْقات لدى المرضى البالغين المصابين بمرض ثلاسيميا الدم الرئيسي نوع بيتا والمعتمدين على نقل الدم في مستشفى تعليمي مرجعي في عُمان. **الطريقة:** شملت هذه الدراسة المقطعية جميع المرضى البالغين (أكثر من 13 سنة) والمصابين بمرض ثلاسيميا الدم الرئيسي نوع بيتا ممن تلقوا العلاج في المستشفى السلطاني في عُمان للفترة ما بين 2004 – 2006. تم جمع المعطيات الديمغرافية والدوائية والسريرية والمعلومات المتعلقة بالكيمياء الحيوية لجميع المرضى. تم تحليل البيانات باستخدام التحليل الاحصائي الوصفي والمتغير الاحادي. **النتائج:** شملت الدراسة 31 مريضا متوسط أعمارهم 19 ± 3 سنة ، ومداها مابين 14 - 30 سنة. كان عدد الذكور أكثر من النصف بقليل (52%) (16 مريضا). خضع جميع المرضى لعملية نقل الدم بشكل مفرط ، بالاضافة لعلاج الخَلْب باستخدام ديسفيروكسامين 40-60 ملجرام/كجم لمدة خمسة أيام أسبوعياً ، وديفيربرون 75 ملجرام/كجم يومياً. وجد أن معدل هرمون الدُّرَيقَة كان منخفضاً في 3 مرضى (أقل من 1.6 بيكومول/لتر). بينما كان معدل الهرمون طبيعياً لدى 3 مرضى آخرين (1.6 - 9.3 بيكومول/لتر) مع معدل منخفض لكالسيوم الدم (أقل من 2.1 ملمول/ لتر). تم تعريف هؤلاء المرضى الثلاثة (ممن لديهم معدل عادي من هرمون غدد الدريقة ومعدل منخفض لكالسيوم الدم) كمرضى يعانون من إنخفاض نشاط غدد الدريقة مما يجعل معدل إنتشار المرض في هذه المجموعة من المرضى البالغين والمصابين بمرض ثلاسيميا الدم نوع بيتا الرئيسي يصل إلى 19% (6 من أصل 31). عند مقارنة المرضى المصابين بانخفاض نشاط غدد الدريقة مع غير المصابين, وجد أن المصابين لديهم معدل منخفض من هرمون تلك الغدد (2.7 مقابل 5.3 بيكومول/لتر) (p=0.031) ومعدل منخفض لكالسيوم الدم (1.7 مقابل 2.3 بيكومول/لتر) . كانت النتائج ذات قيمة احصائية. **الخلاصة:** أن معدل إنتشار إنخفاض نشاط غدد الدريقة في المرضى البالغين والمصابين بمرض ثلاسيميا الدم الرئيسي نوع بيتا في هذا المركز المرجعي هو (19%). وهو أعلى بوضوح من المعدلات المسجلة في أماكن أخرى (2.5 و 10.7%).

مفتاح الكلمات: قُصورُ الدُّرَيْقات ، ثلاسيميا الدم الرئيسي ، ثلاسيميا الدم نوع بيتا ، عمان .

ABSTRACT ***Objective:*** To evaluate the prevalence of hypoparathyroidism in adult transfusion-dependent patients with beta-thalassemia major in a teaching referral hospital in Oman. ***Methods:*** All adult (>13 years) patients with beta-thalassemia major seen at Royal Hospital in Oman between 2004 and 2006 were studied. Demographic, pharmaceutical, clinical and biochemical data were collected for all the subjects. Analyses were performed using both descriptive and univariate statistics. ***Results:*** A total of 31 patients were included into the study with an overall mean age of 19±3 years ranging from 14 to 30 years. Just over half of the subjects were males (n=16; 52%). All the patients were on hypertransfusion and combined chelation therapy with desferrioxamine 40-60 mg/kg 5 days per week and deferiprone 75 mg/kg/day. Three of the patients had low levels of parathyroid hormone (<1.6 pmol/l). A further three patients had normal levels of parathyroid hormone (1.6 – 9.3 pmol/l) in the presence of low serum calcium levels (<2.1 mmol/l). These patients (with normal hypoparathyroid hormone levels, but lower calcium levels) were also defined to have hypoparathyroidism bringing the total prevalence of hypoparathyroidism in this cohort of adult patients with Beta-thalassemia major to 19% (6 out of 31). The patients with hypoparathyroidism had statistically significantly lower levels of parathyroid hormone (2.7 versus 5.3 pmol/l; p=0.031) and serum calcium (1.7 versus 2.3 pmol/l; p=0.004) compared to those without hypoparathyroidism. ***Conclusion:*** The prevalence of hypoparathyroidism in adult beta-thalassemia major patients at this referral center was significantly higher (19%) than those reported elsewhere (2.5 and 10.7%).

Keywords: Hypoparathyroidism; Thalassemia major; Beta-thalassemia; Oman.

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Advances in Knowledge

Despite the small sample size, this study provides the only available published literature on the prevalence estimate of hypoparathyroidism in adult patients with beta-thalassemia major in the Arabian Gulf. It also adds to the current scant evidence that no correlation exists between serum ferritin and parathyroid hormone levels.

Application to Patient Care

Because of its significant prevalence (19%), all adult beta-thalassemia major patients should be routinely monitored for any signs and symptoms of hypoparathyroidism. Serum ferritin is not a good or reliable indicator of the development of hypoparathyroidism. It is therefore recommend that the parathyroid function be tested periodically, particularly when iron overload-associated complications occur.

Beta-thalassemia major, first described by Cooly and Lee in 1925,[1] is a haemoglobinopathy caused by a defect in the production of the B globin chain. The disease is manifested by anaemia, hepato-splenomegaly, growth retardation, bone changes and jaundice. The combination of regular blood transfusion and chelation has extended the life span of these patients.[2,3] However, despite chelation therapy, regular blood transfusion led to iron overload, that resulted in frequent endocrine complications including hypogonadism, diabetes mellitus, hypothyroidism and hypoparathyroidism.[4]

Hypoparathyroidism secondary to siderosis, first described by Gabriele in 1971,[5] is now a well recognized complication of regular blood transfusion occurring in the second decade of life; however, the incidence of hypoparathyroidism varies from centre to centre.[6] Asymptomatic hypocalcaemia is common in these patients and may be missed for some; thus it is important to check for hypocalcaemia in the presence of mild hypoparathyroidism, especially in the second decade of life. Improvement in chelation therapy has largely resulted in the reduction of the prevalence of hypoparathyroidism, but has yet to eliminate it entirely.[7,8]

The current study was conducted to determine the prevalence of hypoparathyroidism as well as the description of the various clinical and biochemical parameters in a group of adult patients with beta-thalassemia major at the Royal Hospital, a tertiary care hospital in Muscat, Sultanate of Oman.

METHODS

The study included all adult patients (>13 years) with beta-thalassemia major being treated at the Royal Hospital in Oman. All the patients were on a hypertransfusion regimen and combined chelation therapy with desferrioxamine 40-60 mg/kg 5 days per week and deferiprone 75 mg/kg/day. The demographic and clinical data of all the patients studied were obtained including age, sex, height, body weight, age at first blood transfusion , age at start of regular desferrioxamine chelation, duration of iron chelation, compliance, history of splenectomy and laboratory investigations, including average serum ferritin level in the last year and hepatitis C virus (HCV) seropositivity. All patients were tested to detect whether they are hypoparathyroid. The tests included serum calcium (total), phosphorus, alkaline phosphatase and parathyroid hormone levels. Hypoparathyroidism was defined as low levels of parathyroid hormone (<1.6 pmol/l) or normal levels of parathyroid hormone (1.6-9.3 pmol/l) in the presence of low serum calcium levels (<2.1 mmol/l).

RESULTS

A total of 31 patients were included in the study. The demographic and clinical characteristics of the study cohort are shown in Table 1. Just over half of the patients were males (n=16; 52%). The overall mean age of the cohort was19±3 years; the age range being from 14 to 30 years. The mean age at first blood transfusion and start of iron chelation therapy was 18±18 months and 9±6 years, respectively. Less than half of the cohort had good compliance with iron chelation therapy (n=13; 42%). Nearly two thirds of the cohort had hepatitis C antibodies (n=18; 58%), while just under a third of the patients had had their spleens removed (n=9; 29%). Three of the patients had low levels of parathyroid hormone (<1.6 pmol/l). A further three patients had normal levels of parathyroid hormone (1.6-9.3 pmol/l) in the presence of low serum calcium levels (<2.1 mmol/l). These were also considered to be in a

Table 1: ***Demographic and clinical characteristics of the major beta-thalassemia cohort stratified by hypoparathyroidism* status (N=31)***

Characteristic	All (n=31)	Hypoparathyroidism*		
		No (n=25)	Yes (n=6)	*p*-value
Age, years, mean±SD	19±3	18±3	21±5	0.172
Male gender, n (%)	16 (52%)	13 (54%)	3 (43%)	1.000
Age at first blood transfusion, months, mean±SD	18±18	14±11	31±30	0.170
Age at start of iron chelation therapy, years, mean±SD	9±6	8±5	10±8	0.297
Number of patients with good compliance, n (%)**	13 (42%)	11 (44%)	3 (43%)	1.000
Ferritin, mcg/l, mean±SD	5461±3268	5271±2775	5340±2738	0.788
Calcium, mmol/l, mean±SD	2.2±0.26	2.3±0.08	1.7±0.28	0.005
Phosphorous, mmol/l, mean±SD	1.7±.35	1.6±0.26	2.1±0.47	0.072
Alkaline phosphatase, iu/l, mean±SD	135±58	125±44	182±91	0.182
Parathyroid hormone, pmol/l, mean±SD	4.8±2.1	5.3±1.7	2.7±2.2	0.031
Hepatitis C infection, n (%)	18 (58%)	11 (46%)	6 (100%)	0.028
Splenectomized, n (%)	9 (29%)	6 (25%)	3 (50%)	0.320

*Hypoparathyroidism was defined as those who had low levels of parathyroid hormone (<1.6 pmol/l) or those with normal levels of parathyroid hormone (1.6 – 9.3 pmol/l), but with lower levels of serum calcium (<2.1 mmol/l).

**Good compliance was defined as the regular use of subcutaneous desferrioxamine in a dose of 40-60 mg/kg 5 times per week.

SD = Standard deviation; Percentages are column percents; *p*-values were generated using Student's t-tests, Pearson's χ^2test, and Fisher's Exact test whenever appropriate.

hypoparathyroidism state bringing the total prevalence of hypoparathyroidism in this cohort of major beta-thalassemia patients to 19% (6 out of 31).

The patients with hypoparathyroidism had statistically significantly lower levels of parathyroid hormone compared to those without hypoparathyroidism, (2.7 versus 5.3 pmol/l; p=0.031). All the patients in the hypoparathyroidism group had hepatitis C antibodies compared to only 48% in the cohort without hypoparathyroidsm, and this difference was statistically significant (100% versus 48%; p=0.025). The cohort with hypoparathyroidism also had statistically significantly lower levels of serum calcium than those without hypoparathyroidism (1.7 versus 2.3 pmol/l; p=0.004). The hypoparathyroidism group had also higher levels of serum ferritin (5967 versus 5340 mcg/l; p=0.788), phosphorous (2.1 versus 1.6 mmol/l; p=0.072), and alkaline phosphatase (182 versus 124 iu/l; p=0.182). However, the differences were not statistically significant. Furthermore, there was also no correlation between serum ferritin levels and parathyroid hormone levels (r=-0.015; p=0.935).

DISCUSSION

Endocrinopathies, of which hypoparathyroidism is one of the most common, are a well recognized complication of beta-thalassemia major due to chronic anaemia, hypoxia and iron overload.[9,10] The prevalence of hypoparathyroidism in our study was 19%, which is significantly higher compared to other studies (2.5% and 10.7%).[11,12] One of the possible explanations of this finding is the older age at which regular home chelation by desferrioxamine was initiated in our patients.

Contrary to expectations of a positive correlation between serum ferritin levels and hypoparathyridism, there were no significant differences in serum ferritin levels between those with hypoparathyridism and those without hypoparathyridism. Several explanations can be put forth for this finding. The serum ferritin level can be subjected to changes with intercurrent infection and hence it is not a reliable indicator of the development of hypoparathyroidism. Another explanation is the individual susceptibility to iron toxic effect or the development of organ damage by severe iron overload in the many years preceding the initiation of chelation therapy. Angelopoulos et al.[13] also found no correlation between serum ferritin levels and hypoparathyroidism. They went on to recom-

mend that the parathyroid function to tested periodically, particularly when other iron overload-associated complications occur.

Several studies have implicated genetic risk factors in the development of chronic complications of beta-thalassemia major. Filosa et al. [14] have shown that hypogonadism and severity of osteoporosis in patients with transfusion dependant beta-thalassemia major are related to the haematologic phenotype; patients with B^0/B^0 phenotype presented more frequently with hypogonadism and severe osteoporosis. Previous published reports have already demonstrated a reasonable correlation between hypoparathyroidism and other endocrinopathies; [15, 16] therefore, it is reasonable to assume that the beta-thalassemia genotype is also responsible for the expression of endocrinopathies. However, this is only an assumption and further studies are needed to corroborate this hypothesis. The results of this study should only be applied in the context of its limitations, namely: small sample size, testing of B^0/B^0 genotyping, as well as lack of the details of some of laboratory measurements such as vitamin D and magnesium.

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