Prevalence of diabetic ketoacidosis (DKA) in thalassemia major patients in Iran due to secondary iron overload

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Summary

Introduction. Thalassemia is considered the most common genetic disorder worldwide. The main treatments for thalassemic patients are transfusion and iron chelation therapy. Diabetes mellitus (DM) is a frequent complication in thalassemia major due to iron overload. Some patients may develop diabetic ketoacidosis (DKA) and expire.

Aim. To determine the prevalence of diabetes and the rate of DKA in thalassemia major patients in the south of Iran.

Methods: We reviewed data of thalassemic patients who were treated in our area over a 13 year period (one year prospectively and 12 years retrospectively). In addition we investigated 37 patients with thalassemia major and DKA. We used descriptive study for data analysis.

Results. Among 820 thalassemia major patients receiving transfusion in Shiraz (a capital center in the South of Iran), 70 individuals (8.5 %) had a fasting blood sugar of 126 mg/dl or higher and thus were diagnosed as diabetic. The incidence of DKA in the year 2004 was 8 per approximately 2500 major thalassemic patients (0.3%) in Fars province in the South of Iran, with 5 of these patients developing DKA for the first time (0.2 %). The mean ages of developing diabetes and DKA in thalassemic patients were 18.2 and 15.5 years, respectively. The most common symptoms were polyuria and polydipsia (94.5%). There were more female thalassemic patients (73%) than males (27%) in the group that developed DKA, and this difference was significant.

Discussion. Our study has demonstrated that a significant number of thalassemia major patients had diabetes, and some of them were complicated with DKA. Diabetes developed at the same age as in other countries. We suggest that blood sugar should be checked routinely in all thalassemia major patients after the age of 9 years to prevent life-threatening conditions such as DKA.

Key words: thalassemia major, diabetes mellitus, ketoacidosis, iron overload, Iran.
Introduction

Iran is one of the countries in which thalassemia is endemic. According to the data released by the Center of Disease Control, the overall carrier rate of the gene is 5% (1). Patients with thalassemia major suffer not only from the consequences of the anemia itself (such as reactive bone changes and splenomegaly), but also from complications caused by the repeated blood transfusions they receive for the correction of the anemia. The majority of these complications are due to chronic iron overload in body tissues, with subsequent pathologic changes leading to disturbances in the function of various organs.

Diabetes mellitus is one of the most common complications in thalassemic patients and is caused by the following factors, either alone or in combination: destruction of pancreatic cells and decreased insulin release, damage to hepatocytes, peripheral resistance to insulin, and genetic factors (2). Insulin resistance is one of the factors leading to hemochromatosis-induced diabetes. However, studies have shown that diminished insulin release is much more important. Familial predisposition is also an important predictor of glucose intolerance, at least in patients with primary hemochromatosis (3). Other reports have found that noncompliance of patients in using chelating agents, increased body iron, and liver cirrhosis are related factors (4, 5). Another study showed that the prevalence of glucose intolerance was higher in patients who were older and had more blood transfusions (6).

Diabetes ketoacidosis (DKA) is a major acute emergency in diabetics, and can be life threatening in thalassemic patients already compromised by the anemia and its complications. For this reason, screening for diabetes and effective control of blood sugar, plus rapid and proper management of ketoacidosis are of utmost importance in these patients.

The present study was performed to determine the prevalence of diabetes and the incidence of ketoacidosis in thalassemic patients under therapy in Shiraz and 18 affiliated Centers in the south of Iran. No previous data were available for this group of patients.

Patients and Methods

Our project was based on a population of approximately 2500 thalassemia major patients receiving blood transfusions in the south of Iran (Fars Province), with Shiraz as the main thalassemia center, and 18 other university affiliated centers.

The study was designed with both prospective and retrospective branches. In the retrospective branch, the documents of all thalassemia major patients with the diagnosis of DKA admitted in three major hospitals affiliated with Shiraz Medical School (Nemazee, Saadi and Dastgheib Hospitals) from 1991 to 2003 were selected and the required information (age, sex, medical history, signs and symptoms, and laboratory data) was recorded. All patients with DKA are referred to these hospitals. The criteria for diagnosis of DKA were a blood sugar level above 300 mg/dl, serum positive for ketones in dilutions above 1/2, metabolic acidosis (PH less than 7.30 and bicarbonate level below 15 mEq/l), ketonuria and glycosuria. Clinical manifestations including vomiting, polyuria, dehydration, abdominal pain, and decreased level of consciousness were also documented.

In the prospective branch, we included all patients with thalassemia who were admitted over a one year period (2003-2004) to the Nemazee Hospital Pediatric Endocrinology Ward with the diagnosis of diabetic ketoacidosis, and recorded their clinical and laboratory manifestations, liver function tests and prothrombin time (PT).

Thalassemic-diabetic patients with a history of
DKA were assessed for their age, sex, liver span, history of splenectomy and serum ferritin level, plus their clinical manifestations, blood sugar, PH, bicarbonate level, and serum ketones during the episode of DKA.

In addition, all thalassemic patients receiving transfusions in the thalassemic ward of Dastgheib Hospital were tested for serum ferritin and fasting blood sugar during the period of our study, and those individuals with a blood sugar level of 126 mg/dl or higher were diagnosed with diabetes. All data were analyzed with SPSS version 13 and a p value less than 0.05 were considered as significant.

**Results**

In 2004, there were nearly 2500 registered thalassemia major patients in Fars province (Shiraz and 18 affiliated centers), in the south of Iran. In the same year, eight of these patients developed DKA, five of them for the first time. Thus, the incidence of DKA in year 2004 was 8 per 2500 major thalassemic patient (0.3%) and the rate of first occurrence of DKA among these patients was 5 per 2500 (0.2%).

During the period from 1991 to 2004, 37 of these β-thalassemia major patients were admitted to the hospital for DKA, including the 8 patients admitted in 2004.

Among thalassemia major patients receiving transfusion in Shiraz (820 patients), 70 subjects (8.5%) had a fasting blood sugar of 126 mg/dl or higher and thus were considered diabetic; 12 individuals among these diabetic-thalassemic patients (17.1%) were admitted at least once due to DKA. Therefore, the rate of DKA in thalassemic patients receiving transfusions in Shiraz was 1.46 % while the prevalence of thalassemia major in patients with DKA was 8.5 %.

The average age of thalassemic patients developing diabetes was 18.2 years (range 9 to 34 years). In females the mean age was 17.5 years compared to mean of 19.3 years in males. The mean age for thalassemic patients with diabetes admitted for DKA was 15.5 years old. Their distribution by sex is shown in Figure 1. Clinical manifestations of these patients are presented in Figure 2.

Among the 70 patients with diabetes, 47 had had splenectomy (67.1%) while 84% of thalassemic patients admitted for DKA had undergone splenectomy. Only 19% had normal liver span; liver was palpable 2 to 5 cm below the costal margin in 43% of these patients and more than 5 cm in 38%.

The average blood sugar in patients with DKA was 542 mg/dl at the time of admission. Their average pH was 7.08 and mean bicarbonate level was 6.04 mEq/l.

The average serum ferritin level was 2320 ng/ml in thalassemic patients with diabetes on transfusion in Shiraz and 2760 ng/ml in those admitted due to DKA. The average protein in thalassemic patients with diabetes was 7.2 g/dl and the average albumin 3.85 g/dl. Hypoalbuminemia was seen in 10.5 % of cases, but no patient had hypogammaglobulinemia. All patients had elevated liver transaminases and 33 % had prolonged prothrombin time.

**Discussion**

Beta thalassemia major is a serious genetic disease, but with regular transfusion and iron chelating therapy patients generally reach adulthood. Unfortunately, the prevalence of complications due to iron overload is still high(1-4). Deposition of iron in the pancreas has been well documented and development of diabetes in thalassemic patients has generally thought to be due
to direct toxic effect of iron on the pancreas islet cells that leads to insulin deficiency (7, 8). However, insulin resistance (from iron deposition in both liver and muscles) is also involved in the changes in glucose metabolism observed in thalassaemia (7-15).

In present study we found that of 820 thalassemic patients receiving transfusion in Shiraz, 70 individuals (8.5%) had diabetes according to our criteria. Different reports have been issued on this prevalence, ranging from 49 to 138 per 1000 patients (16-19).

A study in Taiwan (12) showed that the prevalence of diabetes was as high as 19.5% in 89 thalassemia major patients on transfusion therapy and that of impaired glucose tolerance was 8.5%. According to this study, presentation with DKA among patients with diabetes was as high as 31.1%.

In an early study by McIntosh reported in 1976(14), 4 out of 9 prepubertal thalassemic youth had diabetic glucose tolerance tests. In Italy, a prevalence of diabetes of 6% was reported in β-thalassemia major patients in 1990 (2). In another study done by De Sanctis et al. (13) in 2004 on 3817 thalassemic patients, diabetes was present in 3.2 % of patients.

A study in Saudi Arabia by El-Hazmi et al. (15) on 50 thalassemia major patients, in 1994, showed prevalence of diabetes of 6%, which was attributed to insulin insensitivity produced by iron overload, that eventually leads to exhaustion of β cells in the pancreas. Among our patients with diabetes, 12 individuals (17.1%) were admitted at least once due to DKA. Not many studies have reported the incidence of DKA in thalassemic patients. The manifestation has been as high as 31.1 % in Taiwan (12).

In our group of patients, the incidence of DKA in year 2004 was 8 per 2500 thalassemia major patients (0.3%) and the rate of first occurrence of DKA among these patients was 5 per 2500 (0.2%). The annual incidence of DKA in non-thalassemic diabetic population is 3 to 8 per 1000 (20). Seventy-three percent of patients presenting with DKA in this study were females (female to male ratio of 2.7) while this proportion was 51% in diabetic patients without DKA (Figure 1). The difference was significant (p<0.05). The reasons for this difference are yet to be determined; nevertheless, these findings point out the need for careful monitoring of the metabolic state of female thalassemic patients. Two previous studies done in other regions reported mean ages of 18 and 18.1 years for the development of diabetes in thalassemic patients (9, 19).

In our study the mean age was 18.2 years, almost exactly the same as in the other studies, which may indicate similarities in the progression of the disease and/or screening methods among the different Centers. The mean age of our thalassemic patients who developed DKA was 15.5 years; we know of no other report of the age of thalassemics with DKA.

Eighty-one percent of thalassemic patients with a history of DKA had hepatomegaly and their average serum ferritin level was 2760 ng/ml, both of which suggest the role of inadequate control of iron loading in pathogenesis of diabetes. In one study, the average ferritin level in thalassemic patients with diabetes was 5600 ng/ml (21). It has been shown that endocrine sequelae tend to develop at older ages and with higher ferritin levels. Life expectancy can be increased if ferritin level is kept below 2000 ng/ml, which requires regular iron chelating therapy (21).

In the light of the results of our study, we strongly suggest surveillance and follow-up of patients with β-thalassemia for endocrine and liver disorders in order to detect and prevent or alleviate associated complications.

References


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