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Thalassemia major between liver and heart: Where we are now ☆

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ABSTRACT

The aim of the study was to assess the current state in terms of liver and heart iron overload as well as of liver and heart related morbidity and mortality in a large cohort of thalassemia patients. Myocardial iron loading was present in 28.9% patients, which was severe in 3.2%. Liver iron was normal in 9.3% and severe in 15%. The rate of cardiac deaths started to decrease between 2000 and 2003 and dropped significantly afterwards. The prescription of combination therapy soon after the hospital admission for decompensated heart failure was associated with a decrease in the short-term mortality. In 111 adult patients who underwent liver elastometry, 14 HCVRNA positive subjects and 2 HCVRNA negative, had stiffness values suggestive of cirrhosis. No cases of hepatocarcinoma were reported. Liver "iron free foci" occurred in a HCV negative patient and the occurrence of a malignant epithelioid hemangioendothelioma led to liver transplantation in another. The study suggests that a subset of patients continues to develop progressive hemosiderosis that may lead to cardiac disease and death. Beyond its key role in preventing myocardial iron overload, liver iron chelation is essential for hampering the onset of hepatic tumors, which may not be limited to hepatocarcinoma.

1. Introduction

Once a universally fatal disease, thalassemia major has turned into a chronic illness, and an excellent long-term prognosis is expected for children who have been chelated at a very young age [1–3]. Assessment of myocardial siderosis and monitoring of cardiac function combined with intensification of iron chelation if necessary, are the main factors responsible for the significant improvement of the life expectancy and quality of life of adult patients with thalassemia. However, if studies on survival have found that heart failure, which was previously the main cause of death, has become rarer, recent analyses have highlighted that liver iron overload is still common in thalassemic patients [4]. The interacting effects of viral infections and iron toxicity are the reasons behind one of the new appearing complications that, with increasing age, are influencing the prognosis. This new complication is liver carcinoma [5]. Of note, studies such as CORDELIA have demonstrated that regarding iron overload, the liver and heart are not two separate and independent entities. On the contrary, at least for deferasirox and partly for desferrioxamine, liver iron concentration (LIC) and more importantly the ability to clear the liver of iron predicts which patients will clear their heart [6].

The aim of this study was to assess the current state in terms of liver and heart iron overload as well as of liver and heart related morbidity and mortality in a large cohort of transfusion-dependent thalassemia patients followed in Cagliari (Italy). Hitherto these aspects had been analyzed only individually in different studies and in different populations.

2. Methods

Data on 697 patients followed at Day Hospital Età Evolutiva-Ospedale Microcitemico, Cagliari (Italy) from 1989 to 2014 were collected and analyzed using Webthal®, a web-based clinical records' software for thalassemia. The use of Webthal for the clinical follow-up of the patients and for scientific purposes was approved by the local Ethics Committee. All patients registered in Webthal signed informed consent to the use of their clinical data for research studies and objectives. Out of the registered patients, 117 were dead at the time of the analysis and 219 had undergone bone marrow transplantation or had moved to other thalassemia centers, while 361 were regularly followed at our center. There were 178 female and 183 male patients,

☆ This work is dedicated to the memory and in honor of Renzo Galanello, who continues to inspire our work every day.

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and their mean age was 29.9 ± 12.4 years (range 0.2–50). Seventy-two of them were <16 years of age. Yearly iron input was 0.43 mg/kg per day in adults and 0.46 mg/kg in pediatric patients. Mean serum ferritin [measured with an automated chemiluminescence immunoassay analyzer (IMMULITE®2000, Siemens-DPC)] was 1447 ± 1030 μg/L (median 1249 μg/L, range 97–5047) in children and 2311 ± 2199 μg/L (median 1648 μg/L, range 208–17,673) in adults. Desferrioxamine monotherapy was prescribed in 16 pediatric patients (22.2%) and in 39 adults (13.9%). All the other children but 3 who took deferiprone monotherapy in 2 cases and combined with desferrioxamine in one, were prescribed deferasirox (44; 61%). Nine children had not started iron chelation yet. Of the adults, 111 (38.4%) were on deferasirox, 89 (30.8%) on deferiprone monotherapy, 47 (16.3%) on deferiprone plus desferrioxamine (15 on alternate scheme) and 3 (1%) on combination of deferasirox and desferrioxamine. To measure myocardial and liver iron levels, patients were scanned with a commercially available 1.5 T General Electric CVi scanner using previously reported techniques [7].

The heavily iron loaded group included patients with T2* <8 ms, moderate ≥8 and <14 ms, and mild ≥14 and <20 ms. Levels ≥20 ms were considered normal. For the liver, we used the conversion from T2* to LIC, by using the formula 0.202 + 25.4 / T2* adapted from Wood et al. [8]. The heavily hepatic iron loaded group included patients with LIC >15 mg/g dw, moderate ≥7 and <15 and mild ≥1.8 and <7 mg/g dw. Levels ≤1.8 mg/g dw were considered normal. Liver transient elastography was performed using FibroScan; Echosens, Paris, France, considering an optimal cut-off of 7.7 kPa for mild fibrosis and an optimal cut-off of 13.0 kPa for cirrhosis, according to the meta-analysis by Friedrich-Rust et al. [9]. The examination was performed on a fasting patient lying flat on his/her back, with the right arm tucked behind the head. Ten successful acquisitions were performed on each patient. The median value represented the liver elastic modulus.

Linear regression analysis was used to estimate the relationship between variables and Kaplan–Meier analysis to evaluate the survival function from heart failure in 106 patients who had been and those had not been treated with desferrioxamine plus deferiprone since the acute phase.

Fig. 1 shows the profile of the study performed in this work.

3. Results

3.1. Liver and myocardial iron

Between 2013 and 2014, T2* MRI for liver and heart iron quantification was performed in 246 patients >16 years. If a patient had undergone more than one MRI during this period, the most recent was considered. Thirty-two patients who underwent MRI were on desferrioxamine monotherapy, 64 on deferiprone, 41 on combination desferrioxamine plus deferiprone, 7 on alternate desferrioxamine and deferiprone and 100 on deferasirox. Two patients performed MRI soon after a pregnancy.

Myocardial iron loading (T2* <20 ms) was present in 71 (28.9%) patients, which was mild in 45 (18.3%), moderate in 18 (7.3%) and severe in 8 (3.2%).

Liver iron was within normal limits in 23 subjects (9.3%), while hepatic overload was mild in 104 (42.3%), moderate in 82 (33.3%) and severe in 37 (15%). Among patients with heart T2* >20 ms, the majority (106, 43% of all undergone MR) had no or mild hepatic siderosis and 69 (28%) had moderate to severe liver overload. Out of the 71 patients with heart T2* <20 ms, 50 (20.3%) also had a liver iron concentration of >7 mg/g dw while 21 (8.5%) had a liver iron concentration of <7 mg/g dw (Fig. 2).

3.2. Cardiac iron overload-related mortality

The rate of death from heart failure or iron-related arrhythmias, which had remained high until 2000, started to decrease between 2000 and 2003 and dropped significantly afterwards. The age (years) at the time of acute heart event increased in parallel with the decrease of the number of events (Fig. 3).

The prescription of combination therapy with iv desferrioxamine 50 mg/kg 24-hour-per-day plus deferiprone 75–100 mg/kg per day orally, soon after the hospital admission for decompensated heart failure was associated with a decrease in the short-term mortality [p = 0.04 at 12 months with 2 out of 21 patients who were treated with combined treatment in the acute phase of heart failure and 18 out of 85 who did not, dying in the first 90 days after the hospital admission (Fig. 4)].

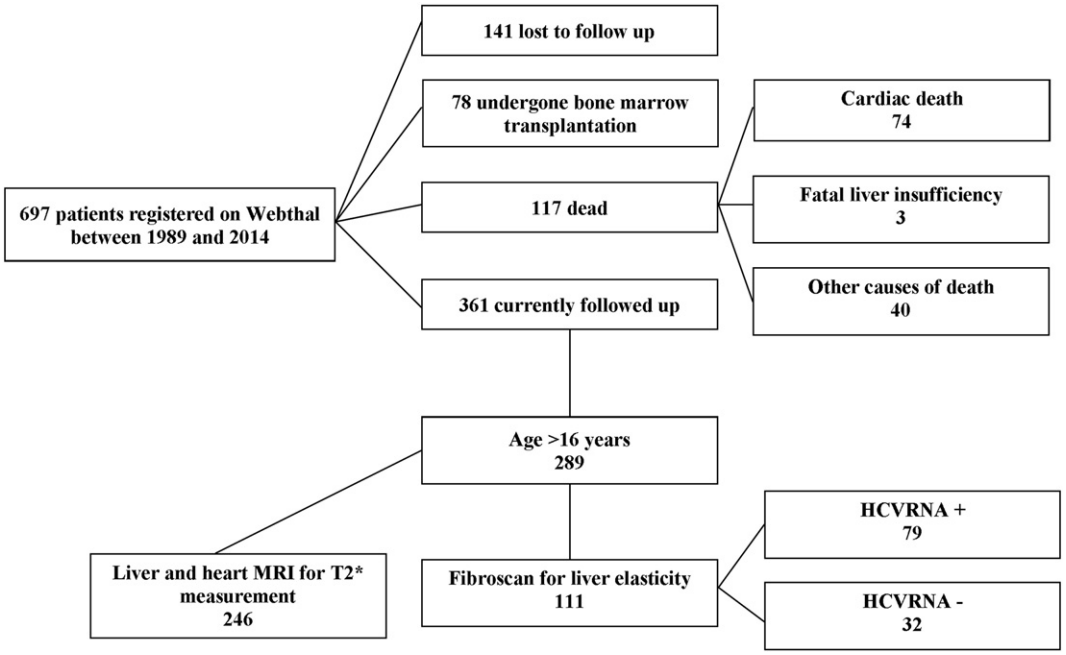

Fig. 1. Profile of study used to evaluate the mortality and morbidity heart and liver related in the 697 patients registered on Webthal.