A national registry of thalassemia in Turkey; demographic and disease characteristics of patients, achievements and challenges in prevention

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Introduction

The better management of thalassemia by regular and adequate red cell transfusions, close monitoring of iron loading and appropriate iron chelation therapy (ICT) with deferoxamine (DFO) has changed the prognosis of the disease worldwide (1). Further, there has been a revolutionary development in the management of the disease at the beginning of the twenty-first century with the introduction of magnetic resonance imaging (MRI) as a measure of tissue-specific iron loading and the availability of oral iron chelators deferiprone (DFP) and deferasirox (DFX) (2,3).

In parallel, DFP and DFX were registered in Turkey – in 2004 and 2006, respectively – and gradually replaced DFO. However, dissemination of cardiac T2* MRI as a useful tool for the monitoring and management of iron overload have remained limited.

The cornerstone of relevant public health policies in Turkey was the recognition of thalassemia as a common health problem in 1993. Eventually, a comprehensive national hemoglobinopathy control programme (HCP) was implemented by law and came into force on 24 October 2002 in 33 provinces of Turkey.

In 2012, the Turkish Society of Pediatric Hematology set up the National Registry for Hemoglobinopathies to collate the demographic and disease characteristics of patients, and also quantified and assessed the efficacy of HCP over 10 years in Turkey.

Study design and methods

A website has been prepared to conduct this observational prospective cohort study. The website opened after receiving approval of the ethics committee in October 2012 (B.30.2.EGE.0.20.05.00/OY/ 1747-723 Decision number: 12-5.2/11) and remained open until June 2015. The investigators received a secure entrance to the website. The electronical case report form for each patient with a thalassemia disease and variant hemoglobins and a signed informed consent was completed by the investigators. The system was able to detect repeated registries for any patient receiving health care in more than one centre. The demographic features
and disease characteristics of the patients were reported. Affected births from marriages after 2003 were also questioned and relevant information was collected.

**Results**

The overall population with a major hemoglobinopathy comprised 2046 patients from 27 Thalassemia Centres (TCs) participating in the study. A total of 56 double and one triple registration were excluded. A total of 1988 patients were analysed.

**Distribution of patients throughout Turkey**

The majority of patients came from TCs in the Aegean (n=622), Marmara (n=518), Mediterranean (n=348) and South-eastern Anatolia (n=338) regions. A total of 139 patients were registered from TCs in Central Anatolia and 23 patients were from a single TC serving the whole of Eastern Anatolia. There was no TC in the Black Sea region where a few patients may be living and receiving health care from the nearest TCs outside the region (Table 1). The highest number of registered patients lived in Istanbul (n=265), Izmir (n=207) and Sanliurfa (n=201) provinces.

**Demographic characteristics of patients**

This was a relatively young cohort (51% male) in whom 72% were below 20 years-old (Figure 1). A total of 378 subjects (19%) in the cohort were preschool age (<6 years). The majority of subjects aged ≥6 years were students (n=981, 67%). A total of 480 subjects (33%) were not attending school. Just over half of these (n=256, 53%) were >18 years-old and employed, whereas 224 (47%) were unemployed and 214 of those were >18 years-old. Of the unemployed patients 57% had only completed the 8-year primary education, whereas 33% had graduated from high school and 10% from university. The schooling or employment status was not obtained from 149 subjects. All patients, except for 1% were covered by social security regardless of their social status.

Consanguineous marriage was reported in 48% of parents and 51% of those were first-cousin marriages. Consanguineous marriages accounted for 75% of parents from Sanliurfa, which was the city with the third highest number of thalassemic patients on the registry. In comparison, consanguineous marriages were reported in 38.5% and 29% of parents from Istanbul and Izmir, respectively. Further, the average number of children born to parents with an affected child was 4 in Sanliurfa but 2 in Istanbul and Izmir. A total of 214 families in the registry had more than one thalassemic child.

**Disease characteristics**

The majority of subjects (95%) had homozygous β-thalassemia (Table 2). A total of 1385 β-thalassemia alleles reported from 724 patients contained 22 different β-thalassemia mutations. The most common 11 mutations represented 90% of all β-thalassemia alleles. IVS1-110(G->A) was the most prevalent mutation (Table 3).

Although, β-thalassemia intermedia (TI) was reported in 215 (11.5%) of 1873 patients with β-thalassemia, only one-third of subjects (33.3%) were entirely transfusion-free. Whereas, regular (>8 times/year), frequent (5–8 times/year) or occasional (0–4 times/year) transfusions were reported in 79 (37.6%), 30 (14.3%) and 31 (14.8%) patients, respectively.

Splenectomy was defined in 79 (38%) of 207 patients with TI and 590 (37%) of 1594 patients with β-thalassemia major (TM). The patients were divided into four age cohorts by decades, and splenectomy indication during the first decade has been compared between age cohorts II, III and
IV. The splenectomy frequency in the age cohort-III displayed a slight decrease compared to cohort-IV and simply shifted to the second decade. However, the frequency of splenectomy has not changed in the age cohort II- compared to III (Table 4).

A total of 115 patients with TM were aged <2 years at the time of registration and had not met the criteria for starting ICT. A total of 150 patients with TI, hemoglobin H (HbH) disease, sickle-cell disease (SCD) and β/S thalassemia were not receiving ICT. The history of ICT was not obtained for 78 patients. Overall, 1561 of 1645 patients (95%) with TM (n=1473), TI (n=128), SCD (n=31), β/S thalassemia (n=9) and HbH disease (n=4) were receiving a monotherapy regimen. DFX was the most prevalent chelator, prescribed to 1337 (81.3%) patients, followed by DFO to 131 (8%) and DFP to 93 (5.7%) patients. Combined therapy of DFO+DFP was reported in 58 (3.5%), DFX+DFO in 20 (1.2%) and DFX+DFP in 6 (0.3%) patients. The highest DFX administration of 93.6% was reported in patients aged <10 years and remained as the most prevalent chelator in all age cohorts. The use of DFO and DFP was least in patients aged <10 years and increased gradually in older age cohorts (Table 5).

Hemopoietic stem cell transplantation (HSCT) was reported in 96 patients in whom all but one (SCD) had TM. The average age of HSCT was 8.1 years (median 7 years) and the oldest patient was 18 years old. The source of HSCT was matched sibling donor (MSD) in 87 of 92 patients, whereas three family- and two unrelated-donor transplantations were reported. Overall, 70 of 91 patients (77%) had thalassemia-free survival after HSCT whereas 20 patients had graft rejection with autologous recovery (22%) and 1 died (1.1%). There were 115 patients with an MSD but who had not yet had HSCT, of whom 84 were <17 years old. Further, there were 417 patients with a healthy sibling whose human leukocyte antigen (HLA) compatibility had not been evaluated.

There were 34 deaths (5%) out of 680 patients from 3 TCs. The causes of death were heart disease (n=17), infections (n=8), hepatic failure (n=2), anemia (n=1), HSCT (n=1) and unknown (n=5). The earliest cardiac death was at 11 years-old. The rates of cardiac deaths in the population at risk (age>10 years) has improved gradually in 5-year cohorts, since 1999 (Table 6).

The impact of the hemoglobinopathy control program on thalassemic births

There were 619 thalassemic births after 2004. The number of new cases has shown a consistent decrease only since 2009 (Figure 2). The year of marriage was recorded in 482 of 619 parents of whom 242 have been married ≥2003. According to the statements of couples, overall 142 of 242 (58.7%), married in provinces covered by the HCP but haven’t had premarital screening. The remaining 100 couples had premarital screening but 40% of those either received no feedback information (n=25) or were misinformed (n=15) regarding screening results and 60% had been informed as couples at risk of having thalassemic offspring but these parents either had not had a prenatal diagnosis (n=49) or had consciously given birth to a thalassemic child (n=11).

Sixty-two of these 242 (25.6%) couples were married in Sanliurfa. Premarital screening was performed in only 17 (27%) of these 62 marriages. Although 12 out of those 17 were informed that they were at-risk couples, only one had a prenatal diagnosis but consciously gave birth to the affected child. Whereas 19 (7.8%) of the 242 couples were married in Izmir, of whom 15 (79%) had premarital screening and 10 of those 15 were informed that they were at-risk couples, but only 5 of those had a prenatal diagnosis.

Discussion
Previous epidemiological studies from Turkey reported that the Cukurova region was the most prevalent for hemoglobin S (HbS) carriers (up to 10%) and the majority of patients with SCD were from the region (4-6). Because the TCs that participated from Cukurova have not registered patients with SCD, the current registry mainly included patients with homozygous β-thalassemia. TI was composed of 11.5% of the cohort and the majority of those were receiving transfusions. It remains to be elucidated whether the milder forms have been missed.

Although the prevalence of β-thalassemia carriers was stated as 2.1% overall in Turkey (7), the epidemiological data demonstrated regional differences, with a higher prevalence in coastal areas (5,8-10). In concordance with this, the majority of patients came from the Marmara, Aegean and Mediterranean regions. Although epidemiological data from South-eastern Anatolia did not indicate a high prevalence of thalassemia carriers (11, 12), homozygous forms in the region were found to be as high as those in the coastal areas, most probably because of the higher number of consanguineous marriages and the higher fertility rate. The considerable number of families with more than one affected child indicated that preventive measures have not been implemented even for the families with a proven risk. After implementation of the HCP, the highest number of affected children were born in Sanliurfa. It was revealed that the majority of these couples had not had premarital screening and further, prenatal diagnosis was either not offered or not accepted by the at-risk families. The number of newborns with thalassemia and hemoglobinopathies was reported as being reduced from 272 in 2002 to 25 in 2010, which accounted for a 90% reduction over these years (13). We considered that report with caution since in the current registry, 79 affected births were reported from 27 TCs in Turkey in 2010. This inconsistency can be explained by insufficient reporting of new cases to the official registry system conducted by the Ministry of Health in Turkey. Nevertheless, the number of affected newborns per year demonstrated a trend towards a consistent decrease since 2009. This achievement can be improved by auditing all components of the programme carefully and applying appropriate corrective measures.

This was a relatively young cohort where 72% of the registry was <20 years-old and mostly were either of preschool age (19%) or students (67%). Approximately one half of the remaining thalassemics were employed while just under half were neither employed nor in education or training (NEET). The Organisation for Economic Co-operation and Development (OECD) reported that nearly 30% of young people in Turkey aged 15–29 were NEET, which is well above the OECD average of 15%, and low skills were a key barrier to achieving better labour market outcomes for youth in Turkey (14). In fact, 57% of NEET in the registry were early school-leavers. Although, regardless of their social status, all patients were covered by social security, effective policies are needed to improve the education, job and career prospects of the patients up to at least the average of their peers. Taking into account that most children and adolescents in this cohort will be moving from childhood to adulthood in the near future, the transition from pediatric to adult care should also be adjusted appropriately.

A wide molecular heterogeneity of the Turkish thalassemics has been confirmed by this registry. The most common seven mutations accounted for less than 80% of all thalassemia alleles and were consistent with the previous reports from Turkey (15-20). The IVS-I-110(G->A) substitution was the commonest defect with a frequency of 47% within all β-thalassemia alleles in the cohort. Five of the seven most common β-thalassemia alleles were either β0 (Codon 39[C->T], IVSI-1[G->A], FSC8[-AA]) or severe β+ thalassemia (IVSI-110[G->A], IVSII-745[C->G]), whereas only two prevalent alleles (IVSI-6[T->C], IVSII-1[G->T]) were composed of mild β++ -thalassemia mutations.
It is suggested that improved tissue oxygenation by adequate transfusion regimens has considerably reduced the incidence of splenectomy within the first 10 years of life in thalassemics (21,22). The unchanged needs for splenectomy in our patients from the mid-1970s to mid-2000s may be related to the low transfusion policy in Turkey.

All guidelines provide age-specific recommendations for the initiation of ICT. In children <6 years old, all guidelines recommend DFO as the first-line choice and DFX as the second-line option for patients where DFO is ineffective or not tolerated. DFP is recommended for children >6 years old and/or as a second-line option if patients are resistant or intolerant to DFX (21, 23). Under the regulations of Turkey, all chelators have been approved as first-line treatment at the age ≥2 years and DFX has been the first-line choice for more than 90% of patients.

HSCT has remained the only curative treatment for TM. The Turkish Pediatric Bone Marrow Transplantation Group specifically collected the data of 245 thalassemic children who underwent HSCT and of whom 68% achieved thalassemia-free survival (24). In this registry, only 96 patients were reported as having undergone HSCT. The missing registration may result from the loss of follow-up of these patients because their health care is usually moved from the TC to the transplantation centre after HSCT. Nevertheless, there were 115 TM patients with an MSD but not yet transplanted and a further 417 patients with healthy sibling(s) with unknown HLA compatibility. This figure indicates that the awareness of physicians and parents should be increased for this curative option.

The widespread implementation of cardiac T2* MRI and appropriate intensification of chelation in those with cardiac iron overload reduced cardiac mortality significantly (2,3). Survival data from three major TCs indicated that despite a gradual improvement in cardiac deaths in the at-risk population in 5-year cohorts since 1994, cardiac disease is still major cause of early deaths and a sustained effort in dissemination of cardiac T2*MRI and optimum use of ICT should be maintained. The compliance with ICT remained the most important factor in ensuring the desired outcome for thalassemic patients that may be strengthened by individualizing treatment, careful monitoring and continuous psychosocial support (2, 25).

In conclusion, many efforts have been directed toward optimizing patients’ management and implementing a prevention programme in Turkey in the new millennium. The current data indicate that these efforts should be maintained to achieve further improvement in the survival and quality of life associated with better integration into social life for thalassemics. The developing strategies are also essential for further achievements in the prevention programme.

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References


Table 1. Regional distribution of the registered patients

<table>
<thead>
<tr>
<th>Regions</th>
<th>Provinces</th>
<th>Centres (n)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marmara</td>
<td>Istanbul</td>
<td>3</td>
<td>416</td>
</tr>
<tr>
<td></td>
<td>Bursa</td>
<td>2</td>
<td>102</td>
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<tr>
<td>Central Anatolia</td>
<td>Ankara</td>
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<td>36</td>
</tr>
<tr>
<td></td>
<td>Kayseri</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Eskisehir</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Konya</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>South-eastern Anatolia</td>
<td>Urfa</td>
<td>2</td>
<td>187</td>
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<td>Diyarbakir</td>
<td>2</td>
<td>105</td>
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<tr>
<td></td>
<td>Gaziantep</td>
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<td>Aegean</td>
<td>Izmir</td>
<td>4</td>
<td>495</td>
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<td></td>
<td>Denizli</td>
<td>1</td>
<td>73</td>
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<td></td>
<td>Aydin</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>Antalya</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Mersin</td>
<td>1</td>
<td>92</td>
</tr>
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<td></td>
<td>Adana</td>
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<td>90</td>
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<td>Antakya</td>
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<td>49</td>
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<td></td>
<td>Isparta</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Eastern Anatolia</td>
<td>Erzurum</td>
<td>1</td>
<td>23</td>
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Table 2. The diagnosis of registered patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
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<tr>
<td>β-thalassaemia major</td>
<td>1658</td>
<td>83.4</td>
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<tr>
<td>β-thalassaemia intermedia</td>
<td>215</td>
<td>10.8</td>
</tr>
<tr>
<td>β/S thalassemia</td>
<td>16</td>
<td>0.8</td>
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Table 3. The most common beta thalassemia mutations in the cohort

<table>
<thead>
<tr>
<th>(\beta^T) mutation</th>
<th>Homozygous</th>
<th>Compound heterozygous</th>
<th>Total (\beta^T) allele</th>
<th>%</th>
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<tbody>
<tr>
<td>IVSI-110 (G-&gt;A)</td>
<td>234</td>
<td>184</td>
<td>652</td>
<td>47.1</td>
</tr>
<tr>
<td>IVSI-1 (G-&gt;A)</td>
<td>26</td>
<td>53</td>
<td>105</td>
<td>7.6</td>
</tr>
<tr>
<td>IVSI-6 (T-&gt;C)</td>
<td>24</td>
<td>56</td>
<td>104</td>
<td>7.5</td>
</tr>
<tr>
<td>Codon 39 (C-&gt;T)</td>
<td>22</td>
<td>35</td>
<td>79</td>
<td>5.7</td>
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<tr>
<td>IVSII-745 (C-&gt;G)</td>
<td>19</td>
<td>40</td>
<td>78</td>
<td>5.6</td>
</tr>
<tr>
<td>IVSII-1 (G-&gt;A)</td>
<td>20</td>
<td>36</td>
<td>76</td>
<td>5.5</td>
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<tr>
<td>Codon 8 (-AA)</td>
<td>23</td>
<td>26</td>
<td>72</td>
<td>5.2</td>
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<td>Codon 44 (-C)</td>
<td>17</td>
<td>11</td>
<td>45</td>
<td>3.3</td>
</tr>
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<td>Codon 5 (-CT)</td>
<td>12</td>
<td>17</td>
<td>41</td>
<td>3.0</td>
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<td>-30 (T-&gt;A)</td>
<td>10</td>
<td>13</td>
<td>33</td>
<td>2.4</td>
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<tr>
<td>IVSI-5 (G-&gt;C)</td>
<td>10</td>
<td>9</td>
<td>29</td>
<td>2.1</td>
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Table 4. Changes in frequency and age of splenectomy in age cohorts by decades

<table>
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<th>Age of Splenectomy (year)</th>
<th>Age cohorts of patients</th>
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<tr>
<td></td>
<td>I- (0–10 y) n=685 (%)</td>
</tr>
<tr>
<td>0–10</td>
<td>37 (5.5)</td>
</tr>
<tr>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>20–30</td>
<td></td>
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<td>30–40</td>
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Table 5. Changes over time in percentage of chelator use in patients with hemoglobinopathies

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>DFO (%)</th>
<th>DFP (%)</th>
<th>DFX (%)</th>
<th>DFP+DFO (%)</th>
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<tbody>
<tr>
<td>0–10</td>
<td>486</td>
<td>3.3</td>
<td>2</td>
<td>93.6</td>
<td>1.1</td>
</tr>
<tr>
<td>11–20</td>
<td>637</td>
<td>7</td>
<td>4</td>
<td>85</td>
<td>4</td>
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<tr>
<td>21–30</td>
<td>317</td>
<td>12</td>
<td>11.3</td>
<td>69.4</td>
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<td>31–40</td>
<td>112</td>
<td>21.4</td>
<td>14.2</td>
<td>60</td>
<td>4.5</td>
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Table 6. Changes over time in the number and age of cardiac deaths

<table>
<thead>
<tr>
<th>Cardiac deaths</th>
<th>n</th>
<th>Average age (years)</th>
<th>% of deaths At-risk population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994–1998</td>
<td>6</td>
<td>17.2</td>
<td>3.26</td>
</tr>
<tr>
<td>1999–2003</td>
<td>3</td>
<td>13.7</td>
<td>1.98</td>
</tr>
<tr>
<td>2004–2008</td>
<td>4</td>
<td>19.8</td>
<td>1.53</td>
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<tr>
<td>2009–2013</td>
<td>3</td>
<td>23.3</td>
<td>0.85</td>
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Figure 1. The age distribution of the registered patients.
Figure 2. The number of affected births prior and after the implementation of the Hemoglobinopathy Control Programme.