Measuring complications of sickle cell disease
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One third of newly diagnosed children with sickle cell disease in the Netherlands evades neonatal screening

Submitted

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ABSTRACT

In 2007 a national neonatal screening program for sickle cell disease (SCD) was launched in The Netherlands as the population at risk has increased over the last two decades. The aim of this study was to estimate the prevalence, the number of newly diagnosed children with SCD as well as the proportion of cases that evade neonatal screening.

Cross-sectional survey of three data sources were used to estimate the prevalence and incidence of SCD in The Netherlands: the Dutch Paediatric Surveillance Unit (DPSU), a survey among laboratories and a survey among Dutch paediatric practices. To correct for potential underreporting by the paediatricians we used the capture-recapture method. Children with SCD aged <18 years, either born before 2003 or newly diagnosed children in the period 2003-2007 were included in the study.

The prevalence of SCD in children living in the Netherlands at January 1st 2003 was 1:5152 (95%CI 1:4513 - 1:6015). In the 4 years thereafter, the yearly incidence was 1:2011 (95%CI 1:1743 - 1:2376). Nearly one third (27%) of the newly diagnosed cases was born outside the Netherlands and thus evaded neonatal screening. Approximately 60% of the newly diagnosed SCD children were not reported by paediatricians.

The number of children with SCD in the Netherlands is much higher than previously estimated. A considerable number of children is born abroad and does not benefit from neonatal screening. As these children are at risk of serious infant morbidity physicians and health planners should be aware of the risk of disparities in the care for these children and adequate measures to approach this should be considered.
INTRODUCTION

In 2007 a national neonatal screening program for sickle cell disease (SCD) was launched in The Netherlands, prompted by the increase of the population at risk from 0.5 to 1.7 million people over the last two decades (1). SCD is an inherited disorder of haemoglobin with its highest incidence in people of African ancestry and an increasing prevalence in Europe (2). Presently, it is one of the most common genetic disorders in the United Kingdom (3;4). SCD is characterised by chronic haemolytic anaemia and vascular occlusion, causing painful crises and irreversible damage to vital organs at an early age (2). Auto-infarction of the spleen leads to life-threatening infections with encapsulated bacteria in 7-10% of the cases (5;6). With daily prophylactic penicillin administration and immunization, the risk of serious infections has been substantially reduced (6;7). Children with SCD benefit from neonatal screening because this enables administration of these preventive measures before patients suffer from any symptoms. It is recommended that children with SCD are cared for by specialised clinicians and receive periodic evaluation by a multidisciplinary team in a comprehensive medical care setting (8-11). Therefore all children diagnosed with SCD by neonatal screening are referred to a paediatric haematologist. As the screening program is performed in the first week of life, children with SCD that are born abroad and immigrate to The Netherlands at a later age will evade the screening and only be identified when they become symptomatic.

The aim of the present study was to estimate the prevalence of paediatric SCD and the number of newly diagnosed SCD children in The Netherlands. Furthermore, we aimed to estimate the proportion of children with SCD receiving paediatric care in a comprehensive care setting.

METHODS

In order to estimate the number of newly diagnosed children (age < 18 years) with SCD, we first tracked the children in whom the diagnosis was already established at January 1st 2003. Secondly, we estimated the number of newly diagnosed children in the four years after January 2003.

Estimation of prevalence of SCD in children < 18 years in 2003

The estimation of prevalence of SCD in children in The Netherlands at January 1st 2003 was based on two national surveys: a survey among paediatric practices and a survey among laboratories. In March 2004 all 107 Dutch paediatric practices (including 8 university hospitals) were requested information on SCD patients (<18 years of age) who were under their care in January 2003. For non-responding practices, data were
collected by a site visit. Data collection included initials, date of birth, date of diagnosis, final diagnosis and country of parental origin.

In December 2006, a confidential enquiry was sent to all 37 Dutch laboratories (including 8 university hospitals) that perform haemoglobinopathy testing (by High Performance Liquid Chromatography or Haemoglobin electrophoresis). For all patients born after January 1st 1985 (<18 years of age in January 2003) with HbS > 40%, the following data were collected: initials, date of birth, postal code of home address, date of test and final diagnosis. If more then one diagnostic test was available, data from the initial test were used, as the diagnosis was presumed to have been established by this test. Children who had their first diagnostic test performed before January 1st 2003 were used to validate prevalent cases. The total population of children< 18 years of age in The Netherlands in 2003 was 3.2 million (12).

**Estimate of newly diagnosed children (incidence) in the period 1-1-2003 to 1-1-2007**

This estimate was also based on two datasets: one dataset was collected by the Dutch Paediatric Surveillance Unit (DPSU) and the other was the laboratory dataset described above. The DPSU collected data on newly diagnosed patients with SCD through surveillance using a monthly electronic card sent to all Dutch practising paediatricians (13). The following data were collected from the cases: initials, date of birth, date of diagnosis, final diagnosis and the country of birth of mother and child. Children diagnosed after January 1st 2003 were used to validate the estimation of newly diagnosed cases after 2003.

No ethical approval was required. The datasets were filed at the Dutch Data Protection Authority (www.cpbweb.nl) with number m1339945.

**Capture-recapture method**

To correct for potential underreporting by the paediatricians we used the capture-recapture method (14;15). With this method the total number of cases in the population (n) is estimated using the number of cases identified by two independent sources. Independency of the sources implies that cases have the same probability of being recorded in each database. The first source was the combined paediatric survey and DSPU set and the second source the laboratory survey. Duplicate entries were removed from each database by computer sorting and visual inspection and data were then merged using date of birth and initials. Children that were already present in one of the databases were excluded from the database of newly diagnosed cases after 2003.
The estimate of the prevalence of children with SCD in 2003 and the number of newly diagnosed cases thereafter were both calculated as follows. The number of cases reported separately by two sources and the number of cases common to both sources were entered into the following formula:

$$\hat{n} = \frac{c_1c_2}{m},$$

Where $\hat{n}$ is the estimated total number of cases, $c_1$ and $c_2$ are the number of diagnosed SCD cases in the first (paediatric surveys) and the second (laboratory survey) source respectively, and $m$ is the number of diagnosed SCD identified in both sources (matches).

The following formula was then used to calculate the standard deviation (sd) for $\hat{n}$:

$$sd = \sqrt{\frac{c_1c_2(c_1 - m)(c_2 - m)}{m^3}}.$$

A simple approximate $(1-\alpha)$ 100% confidence interval is given by where $\hat{n} \pm z_{1-\alpha/2}sd$, where $z_{1-\alpha/2}$ is the $(1-\alpha/2)$ quantile from a normal distribution.

RESULTS

Prevalence of children with SCD in 2003

The survey among paediatric practices had a response rate of 91% and identified 258 children age <18 years with SCD living in The Netherlands on January 1st 2003. The majority of these children originated from West Africa (48%) or from Surinam/ Dutch Antilles (31%). For the laboratories, the response rate was 100% in eight laboratories of university hospitals and the national referral laboratory and 40% for laboratories of local hospitals. Non-responding laboratories were all situated in areas where prevalence is known to be low. The laboratory survey identified 190 cases, with 79 cases overlapping the survey among paediatricians. The capture-recapture method yielded an estimate of 621 (95% CI 532-709), based on these datasets (Table 1).


The response rate of the DPSU surveillance was 95%. Between 2003 and 2007 the number of reported newly diagnosed SCD patients was 120 with an annual range of 21 to 41 children.

Thirty two newly diagnosed cases (27%) were born outside The Netherlands. The laboratory survey identified 173 cases, with 58 cases overlapping the survey among paediatricians. The capture-recapture method yielded an estimate of 358 (95% CI 303-
Chapter 2

Table 1 Estimates for the total number and newly diagnosed children with SCD using capture – recapture method in the Netherlands.

<table>
<thead>
<tr>
<th>Group</th>
<th>Paediatricians n</th>
<th>Laboratories n</th>
<th>Both n</th>
<th>Estimated number n (95% CI)</th>
<th>Incidence/Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases &lt;18 years at 1-1-2003</td>
<td>258</td>
<td>190</td>
<td>79</td>
<td>621 (532-709)</td>
<td>Prevalence 1:5,152 (6,015 - 4,513)</td>
</tr>
<tr>
<td>Newly diagnosed cases 2003-2007</td>
<td>120</td>
<td>173</td>
<td>58</td>
<td>358 (303-413)</td>
<td>Incidence 1:2,011 (2,376 - 1,743)</td>
</tr>
</tbody>
</table>

Incidences: Newly diagnosed cases per live births per year

413) newly diagnosed SCD children in The Netherlands over the 4 year period (mean 94/year; 95% CI 61-127) (Table 1). Of this estimated number only 120 cases (34%) were reported by paediatricians.

**DISCUSSION**

This study showed that the estimated number of children in the Netherlands that have SCD is much higher than expected with a total number of 621 children in 2003, and an average of 94 newly diagnosed children each year since then. It also revealed that not all SCD patients received optimal care. Our study revealed that less than half of the paediatric SCD patients are reported by paediatricians. Nearly one third (27%) of the newly diagnosed children is born outside the Netherlands and therefore evades the neonatal screening program.

The number of affected children is estimated using a capture-recapture method with two independent sources. The first source is the paediatric practices and the second source is the laboratories. These sources are independent as laboratory tests may be requested not only by paediatricians but by general practitioners and other specialists as well.

In 2003, the estimated total number of children with SCD living in The Netherlands is 621, which is five-fold higher compared to estimations a decade earlier (16). This may be explained by the effect of demographic changes and by underestimation in previous studies, as these used a single data source (16;17).

The estimated number of total and newly diagnosed children with SCD from 2003 (621 and 358 respectively) is more than twice the number of cases identified by paediatricians (258 and 120 respectively). This difference cannot solely be explained by underreporting
within the paediatric practices and suggests that not all children with SCD are under the care of a paediatrician. This is disquieting, as regular paediatric follow up of SCD patients in a specialized comprehensive care setting is necessary for an adequate quality of care (11;13;14).

Most newly diagnosed children live in urban parts of The Netherlands in newly immigrated families, originating from Central- or West Africa. As their parents have a limited knowledge of the Dutch language, culture and health care system, special efforts are needed to ensure that these children have sufficient access to the health care system.

We demonstrated that almost one third of the newly diagnosed patients is not born in The Netherlands. These children, unidentified by neonatal screening, are at increased risk for serious infection or other life-threatening complications of SCD prior to diagnosis and subsequent installation of preventive measures. This finding implies that disparities in the care of these children may occur and therefore the initiation of other screening programmes should be considered (e.g. directed at children that are adopted or children of immigrant families). We are not aware of any data on this issue from other countries that perform neonatal screening for SCD and it would be interesting to study whether this problem is more widespread.

Moreover, despite the availability of a neonatal screening program, clinicians need to remain alert for yet undiagnosed children presenting with symptoms that may suggest SCD (5).
REFERENCES


