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One-third of the new paediatric patients with sickle cell disease in The Netherlands are immigrants and do not benefit from neonatal screening

M Peters,¹ K Fijnvandraat,¹ X W van den Tweel,¹ F G Garre,² P C Giordano,³ J P van Wouwe,² R R Pereira,² P H Verkerk²

¹Department of Paediatric Haematology, Academic Medical Center, Emma Children's Hospital, Amsterdam, The Netherlands

²TNO Quality of Life, Prevention and Care, Leiden, The Netherlands

³Human and Clinical Genetics Department, Haemoglobinopathies Laboratory, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to

Dr Marjolein Peters, Department of Paediatric Haematology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands; m.peters@amc.nl

MP and KF contributed equally to this study

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ABSTRACT

Objectives To estimate the prevalence of children with sickle cell disease (SCD) in The Netherlands. To estimate the annual number of children newly diagnosed as having SCD and the proportion with diagnoses through neonatal screening. To estimate the proportion of children with SCD receiving paediatric care in a comprehensive care setting.

Design Data from two sources, a survey of paediatric practices (n=107) and a laboratory database (n=20), were analysed by the capture–recapture method.

Participants Children with SCD aged <18 years, either born before 2003 or newly diagnosed as having SCD between 2003 and 2007.

Main outcome measures Prevalence, annual number of children newly diagnosed as having SCD, proportion of children with diagnoses through neonatal screening, proportion of children receiving paediatric care.

Results The prevalence of SCD in children living in The Netherlands on 1 January 2003 was 1:5152 (95% CI 1:4513 to 1:6015). In the next 4 years, the annual incidence was 1:2011 (95% CI 1:1743 to 1:2376). Nearly one-third (27%) of the children newly diagnosed as having SCD immigrated to The Netherlands after birth and would, therefore, be missed by the neonatal screening programme. Approximately 60% of all children with SCD were not reported by paediatricians.

Conclusion The number of children with SCD in The Netherlands is much higher than previously estimated, and the majority of these children seem not to be reviewed regularly by a paediatrician. Children born abroad (27% of new cases) do not benefit from neonatal screening and are at high risk of life-threatening complications before SCD is diagnosed. As this introduces disparities in healthcare, the initiation of adequate measures should be considered.

In 2007, a national neonatal screening programme 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, SCD is the most common genetic disorder in the UK and is increasingly common in The Netherlands, with a carrier incidence of 0.4%.^{3–5} 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

What is already known on this topic

- ▶ Neonatal screening of SCD enables early prevention.
- ▶ Evaluation of SCD patients in a comprehensive care setting reduces morbidity and mortality.

What this study adds

- ▶ Nearly one-third of the children newly diagnosed as having SCD is missed by the neonatal screening programme as they were born abroad.
- ▶ It appears that comprehensive medical care is not available to all children with SCD as approximately 60% of the children newly diagnosed as having SCD are not reported by paediatricians.

infections with encapsulated bacteria in 7–10% of the cases.^{6–8} With daily prophylactic penicillin administration and immunisation, the risk of serious infections is markedly reduced.⁷ Children with SCD benefit from neonatal screening because this enables administration of these preventive measures before they have any symptoms. It is recommended that children with SCD receive care by specialised paediatricians and periodic evaluation by a multidisciplinary team in a comprehensive care setting.^{9–12} Therefore, all children diagnosed as having SCD by neonatal screening are referred to a paediatric haematologist. As the screening programme 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 not benefit from the screening programme, and diagnosis will be delayed to the moment that they become symptomatic.

The aim of the present study was to estimate the prevalence of paediatric SCD, the number of children newly diagnosed as having SCD in The Netherlands per year and the proportion of children with diagnoses through neonatal screening. 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 children newly diagnosed as having SCD (age <18 years) with SCD, we first tracked the children in whom the diagnosis was already established at 1 January 2003. Second, we estimated the number of children newly diagnosed as having SCD in the 4 years after January 2003.

Estimate of the prevalence of SCD in children <18 years in 2003

The estimate of the prevalence of SCD in children in The Netherlands at 1 January 2003 was based on two national data sources: a survey among paediatric practices and a query in laboratory databases. In March 2004, all 107 Dutch paediatric practices (including eight university hospitals) were requested to supply information on the SCD patients (<18 years of age) who were under their care in January 2003. Data from non-responding practices 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 eight university hospitals) that perform haemoglobinopathy testing (by high-performance liquid chromatography or haemoglobin electrophoresis). For all patients born after 1 January 1985 (<18 years of age in January 2003) with Hb S >40%, the following data were collected: initials, date of birth, postal code of home address, date of the test and final diagnosis. If results of more than one diagnostic test were 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 1 January 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.

Estimate of children newly diagnosed as having SCD (incidence) in the period 1 January 2003 to 1 January 2007

This estimate was also based on two sources: 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 patients newly diagnosed as having SCD by sending a monthly electronic surveillance card to all Dutch paediatric practices.¹³ The following data were collected: initials, date of birth, date of diagnosis, final diagnosis and the country of birth of mother and child. Children diagnosed as having SCD after 1 January 2003 were used to validate the estimate 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} This method estimates the total number of cases in a population (n) based on 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 paediatric practices were the first source, and the laboratory databases were the second source.

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 prevalence of children with SCD in 2003 and the number of newly diagnosed cases in the next years 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:

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 survey)

$$\hat{n} = \frac{c_1 c_2}{m},$$

and the second (laboratory databases) sources, respectively, and m is the number of children diagnosed as having SCD identified in both sources (matches).

The following formula was then used to calculate the SD for \hat{n} :

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

$$\text{SD} = \sqrt{c_1 c_2 (c_1 - m)(c_2 - m) / m^3}.$$

distribution.

RESULTS

Prevalence of children with SCD in 2003

The survey among paediatric practices had a response rate of 91% and identified 258 children (aged <18 years) with SCD living in The Netherlands on 1 January 2003. The majority of these children originated from West Africa (48%) or Surinam/Dutch Antilles (31%).

For the laboratories, the response rate was 100% among the laboratories of the university hospitals ($n=8$) and the national referral laboratory and 40% ($n=12$) for laboratories of local hospitals. Non-responding laboratories were all situated in areas where prevalence is known to be very low.

The laboratory survey identified 190 cases, with 79 cases overlapping the paediatric practices survey. The estimate for prevalence of SCD in children living in The Netherlands on 1 January 2003 was 621 (95% CI 532 to 709) based on these datasets (table 1). Paediatricians reported 258 (41%) of these cases.

Children newly diagnosed as having SCD 2003–2007

The response rate of the DPSU was 95%. Between 2003 and 2007, the total number of patients newly diagnosed as having SCD was 120 with an annual range of 21–41 children.

Thirty-two of the patients newly diagnosed as having SCD (27%) were born outside The Netherlands. Five of them were diagnosed before, in their country of origin; the other 27 children were diagnosed in The Netherlands for the first time. The laboratory survey identified 173 cases, including 58 cases that had been reported by the paediatricians. According to the capture–recapture method, an estimated 358 (95% CI 303 to 413) children had been newly diagnosed as having SCD in The Netherlands between 2003 and 2007 (mean 94/year; 95% CI 61 to 127) (table 1). Paediatricians reported only 120 cases (34%).

Original article

Table 1 Estimates of the total number and children newly diagnosed as having sickle cell disease using capture–recapture method in The Netherlands

Group	Paediatricians (n)	Laboratories (n)	Both (n)	Estimated number (n (95% CI))	Proportion of patients reported by paediatricians (%)	Incidence/prevalence (95% CI)
Cases <18 years on 1 January 2003	258	190	79	621 (532 to 709)	41	Prevalence 1: 5152 (4513 to 6015)
Newly diagnosed cases (2003–2007)	120	173	58	358 (303 to 413)	34	Incidence 1: 2011 (1743 to 2376)

Incidence, annual newly diagnosed cases per live births.

DISCUSSION

This study demonstrates that the estimated number of children with SCD in The Netherlands is much higher than expected. The total number of children with SCD in 2003 is estimated to be 621, and the annual number of children newly diagnosed as having SCD between 2003 and 2007 is 94. The prevalence is five times higher than estimates that were made a decade before but is in agreement with previous estimations from a national enquiry performed in 2002.^{16 17} This may be explained by the effect of demographic changes and by underestimation in previous studies that used a single data source.¹⁶

In the present study, the number of affected children is estimated by the capture–recapture method based on two independent sources. The paediatric practices are the first source, and the laboratory databases are the second source. As laboratory tests are ordered by a variety of physicians, these sources are considered to be independent. The response rate of laboratories in high prevalence areas was 100%, whereas the response rate of laboratories in low prevalence areas was 40%. In the situation that the true prevalence in these latter areas is higher, this may have led to some underestimation of the true prevalence of SCD in the present study.

The number of cases identified by the paediatricians (258 and 120, respectively) is less than half of the estimated number of total and newly diagnosed children with SCD (621 and 358, respectively). This difference cannot be explained completely by underreporting of paediatricians. Children that were transient visitors to The Netherlands may account for a small proportion of the difference. However, as the majority of children stay in The Netherlands, these data suggest 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 specialised comprehensive care setting is necessary to ensure good quality care.^{9–12}

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 healthcare system, special efforts are needed to ensure that these children have sufficient access to the healthcare system.

Immigrants that arrive in The Netherlands from regions with a high prevalence of SCD are not systematically screened for these disorders. Our study demonstrates that immigrant children constitute one-third (27%) of the newly diagnosed SCD patients in The Netherlands. These children are at high risk of life-threatening complications before SCD is diagnosed. They do not enjoy the benefits of neonatal screening as children born in The Netherlands do. As this introduces disparities in healthcare, the initiation of other screening programmes should be considered (eg, directed at children

that are adopted or children of immigrant families). These data may convince policy makers to include haemoglobinopathy screening to the health screening package which is offered to immigrants.

The results of the present study demonstrate that not all children with SCD are under the care of a paediatrician. Following the introduction of neonatal screening for SCD in January 2007, the National Institute for Public Health and the Environment (RIVM) started an information campaign to inform general practitioners and general paediatricians about the care for patients with SCD. Information was distributed by leaflets, DVDs and internet, and regional information meetings were organised. Furthermore, there have been publications in the national scientific journals. Hopefully, this campaign will increase the awareness among physicians and eventually result in referral of these children to specialised paediatricians in comprehensive care centres for SCD.

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 programme, clinicians need to remain alert for yet-undiagnosed children presenting with symptoms that may suggest SCD.⁴

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Competing interests None.

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