Received: 15 February 2024 | Revised: 10 April 2024 | Accepted: 15 April 2024

DOI: 10.1002/ajh.27351

CORRESPONDENCE

Long-term follow-up of children with sickle cell disease diagnosed by newborn screening in the Netherlands: Overview of morbidity and mortality

To the Editor:

Sickle cell disease (SCD) is the most prevalent and severe autosomal recessively inherited hemoglobinopathy. It is associated with chronic hemolytic anemia, recurrent vaso-occlusive events, organ, and tissue ischemia, resulting in a broad range of acute and chronic complications.[1] In the Netherlands, approximately 2000 patients live with this disease, half of which are children. To diagnose patients early, universal newborn screening for SCD by high-performance liquid chromatography was introduced on January 1st, 2007. Between 2007 and 2022, 23 to 42 babies with SCD were born annually, amounting to 0.02% of all neonatally screened children.[2] This study aims to examine the morbidity and mortality of children diagnosed with SCD through newborn screening, 16 years after its introduction.

A nationwide prospective cohort study was conducted in children diagnosed with SCD through newborn screening between January 1st, 2007, and March 31st, 2023. Patients were followed until the end of the study, loss to follow-up, death, or successful stem cell transplantation, whichever occurred first. Children were considered lost to follow-up if not present at regular clinic visits for more than 2 years. Data on the total number of children diagnosed with SCD through newborn screening were provided by the Dutch Organization for Applied Scientific Research (TNO: Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek). All eight SCD comprehensive care centers in the Netherlands participated in this study. Written informed consent was obtained from caretakers or legal guardians during the enrollment window between April 1st, 2021, and April 1st, 2023. Our national comprehensive care program is described in detail in Supplemental Appendix S1. For this study, the national working group of pediatric hematologists developed a standardized data extraction form. Data were collected from medical records by a medical doctor trained by pediatric hematologists. Ethical approval was provided by the Institutional Review Board of the Academic Medical Center Amsterdam and all participating centers. Definitions of the SCD-related complications are listed in Table S2. Regarding the statistical analyses, the number of events was presented as lifetime events. The incidence rate of death and SCD-related complications was calculated per 100 person-years for the total duration of follow-up and for the following age categories: 0–4, 5–11 and 12–16 years. All statistical analyses were performed using Statistical Package for the Social Sciences Statistics (SPSS, version 28) and R Studio (version 1.3.1093) software.

During this screening period, 540 children with SCD were diagnosed in the Netherlands. This study includes 391 of the complete cohort (72%), who were followed up for 3046.5 person-years (Figure S1). In total, 35 patients (6.5%) declined participation for reasons such as complex psychosocial problems or fear of data breaches. The remaining 114 eligible patients had not yet decided on participation for logistical reasons, for example, no-shows during the enrollment window. The included patients had a mean age of 7.8 years (±4.5) at the end of follow-up, and 188 were female (48%). SCD genotype HbSS/ HbSβ^0 thalassemia was most prevalent ($n = 240$, 62%), followed by HbSC ($n = 111$, 28%), and HbSβ^+ thalassemia and other genotypes ($n = 40$, 10%). Forty-one patients (11%) were lost to follow-up at a median age of 4.5 years (IQR 2.8–7.5), and most of them moved outside the Netherlands. Demographics are described in more detail in Table S3.

Out of 240 HbSS/ HbSβ^0 thalassemia children, 177 were prescribed hydroxyurea (74%). Overall median age at the start of hydroxyurea therapy was 3.4 years (IQR 1.9–6.5). With regard to the updated prescription guidelines in 2007, 21/64 children with HbSS/ HbSβ^0 thalassemia (33%) born after 2007, were prescribed hydroxyurea before the age of 1 year. Thirteen children, 12 with HbSS (12/240; 5%), had received chronic transfusion therapy, initiated at the median age of 6.9 years (IQR 4.7–8.8). Indications for chronic transfusion therapy included neurological complications such as cerebral vascular stenosis and ischemic infarcts, frequent VOCs, acute chest syndrome, and severe anemia. Eight patients had undergone stem cell transplantation at the median age of 6.8 years (IQR 2.7–10.6), of whom six patients with HbSS (6/226; 2.7%), 1 HbSβ^0 thalassemia (1/14; 7.1%) and 1 HbSC (1/111; 0.9%) patient, for the following indications: frequent VOCs, acute splenic sequestration, recurrent acute chest syndrome and non-responsiveness to hydroxyurea.

The survival of children with SCD up to the age of 16 years was 98.7%. Five patients deceased during follow-up accounting for a mortality rate of 0.16 per 100 person-years (95% CI 0.14–0.19). Four of them (80%) passed away before the age of 2 years. The child mortality rate under the age of 5 years was 0.24 per 100 person-years (95% CI 0.22–0.26), with a survival probability of 99.0%. In HbSS (4/5), the mortality rate was 0.24 per 100 person-years (95% CI 0.23–0.26). In 3 out of 5 patients (60%), the cause of death was related to SCD, primarily attributed to infections ($n = 2/3$ cases) (Figure S2). Three out of five children passed away while abroad.

TABLE 1 Overview and characteristics of the SCD-related complications in the cohort of children with SCD diagnosed by newborn screening in the Netherlands.

Complications	*N* events	Median [IQR] or mean (±SD) age (years) of first occurrence	*N* (%)[a] HbSS/ HbSβ0 thalassemia	*N* (%)[a] female	*N* (%)[a] recurrent events	Incidence rate per 100 person-years	0–4 years	5–10 years	11–16 years
Person-years						3048	1660	1127	260
Vaso-occlusive crisis	179	3.4 [1.7–5.9]	134 (75%)	79 (44%)	104 (58%)	5.9	8.0	3.9	0.77
Dactylitis ≤4 years	23		22 (96%)	8 (35%)	5 (22%)	0.75	1.4	-	-
Enuresis noctorna[b]	69	-	49 (71%)	29 (42%)	-	-	-	-	-
Acute hemolytic crisis	45	3.5 [2.2–5.4]	40 (89%)	23 (51%)	17 (38%)	1.5	2.0	0.98	0.38
Aplastic crisis	24	5.5 (± 3.0)	20 (83%)	8 (33%)	2 (8%)	0.79	0.78	0.89	0.38
Acute chest syndrome	22	6.0 (± 3.9)	20 (91%)	8 (36%)	6 (27%)	0.72	0.60	0.80	1.15
Severe infection	15	-	13 (87%)	6 (40%)	1 (7%)	0.49	0.72	0.27	0
Meningitis	6	2.4 [1.7–2.9]	5 (83%)	1 (17%)	0	0.20	0.36	0	0
Osteomyelitis	7	4.6 [2.7–6.6]	6 (86%)	4 (57%)	1 (14%)	0.23	0.24	0.27	0
Sepsis	2	0.36, 0.85	2 (100%)	2 (100%)	0	0.07	0.12	0	0
Acute splenic sequestration[c]	12	2.8 [1–8.4]	12 (100%)	6 (50%)	4 (33%)	0.39	0.48	0.35	0
Cholelithiasis	7	6.5 [5.2–11.4]	7 (100%)	2 (29%)	-	0.23	0.06	0.35	0.77
Ischemic cerebral infarction (overt stroke)	4	3.3 [1.2–5.7]	3 (75%)	2 (50%)	0	0.13	0.18	0.09	0
Avascular necrosis	3	8.1, 12.4, 12.6y	2 (67%)	1 (33%)	-	0.10	0	0.09	0.77
Priapism[d]	1	12	1 (100%)	0	0	0.06	0	0	0.76
Retinopathy	1	7	2 (67%)	0	-	0.03	0	0.09	0
Ulcers	0	0	0	0	0	0	0	0	0
Total	420								

Abbreviations: IQR, interquartile range; N, number; SD; standard deviation.
[a]Percentage from the total number of events (N events). As these numbers are incidence rates, one event is represented by one patient.
[b]The date of onset could not be calculated.
[c]8 children underwent splenectomy at the median age of 4.5 years [3.2–9.6].
[d]Person-years calculated for the males = 1554, 864, 559, 132 for total, 0–4, 5–10, and 11–16 years respectively.

The life-time events of SCD-related morbidity are summarized in Table 1. The incidence rate for SCD-related complications was highest in the first four years of life, in particular for vaso-occlusive crises (VOC) with hospitalization, acute hemolytic crisis, severe infection, acute splenic sequestration, and overt arterial ischemic stroke. Acute chest syndrome was prevalent in all age categories, and its incidence increased with age. Cholelithiasis, avascular necrosis, and priapism were more prevalent in the age category 11–16 years.

VOCs requiring hospitalization including dactylitis, were the most common SCD-related complications in this cohort ($n = 179/391$, 82%). After the first episode of dactylitis or VOC, half of the children developed a recurrent VOC. The majority of these children had SCD genotype HbSS or HbSβ^0 thalassemia ($n = 134$, 75%). The median age at first admission for VOC differed significantly between children with HbSS/ HbSβ^0 and HbSC, (4.7 years, 95%CI 3.5–6.0) versus 10.1 years (95% CI 8.6–11.6), respectively, $p < .001$ (Figure S3). At the end of follow-up, 73% of the 130 patients with a history of VOC (73%) had been prescribed hydroxyurea.

There were 15 patients who developed a severe infection: meningitis ($n = 6$), osteomyelitis ($n = 7$), and sepsis ($n = 2$). All children who developed a severe infection were <10 years of age. All these patients were vaccinated according to the Dutch National Immunization Programme, 10 out of 15 used prophylactic antibiotics, of which 7 had a good compliance defined as <2 missed doses a week. Two children experienced a fatal outcome due to the severe infection as described earlier. Six children acquired meningitis at the median age of 2.4 years (IQR 1.7–2.9), mostly caused by *Streptococcus pneumoniae* (4/6, 67%). Seven children developed osteomyelitis at the median age of 4.6 years

(IQR 2.7–6.6) caused by *Salmonella enterica* serotype Javiana ($n = 1$), *Pseudomonas oryzihabitans* ($n = 1$) and *Staphylococcus Aureus* ($n = 1$). Two children developed sepsis at the age of 7 days and 14 months. The youngest child born prematurely at 26 weeks gestation had a sepsis caused by coagulase-negative staphylococci from unknown origin at the neonatal intensive care unit. The other child developed sepsis abroad with a fatal outcome. Neurological complications also caused substantial morbidity, and are described in more detail in Supplemental Appendix S2.

In the Netherlands, childhood mortality due to SCD was shown to have decreased substantially from 0.27 per 100 person-years between 1985 and 2007[3] to 0.16 per 100 person-years after the introduction of newborn screening in 2007.[4] Our findings are comparable with the Dallas Newborn cohort ($n = 940$; survival of 98.4%),[5] as well as with other nationwide cohorts in Europe: United Kingdom (0.17 per 100 person-years),[6] Belgium (0.25 per 100 person-years),[7] France (0.16 per 100 person-years)[8] and Spain (0.6 per 100 person-years).[9] Although newborn screening for SCD has proven to reduce mortality significantly in several studies, a national universal newborn screening program is not yet standard practice in several European countries.[10] Following the introduction of newborn screening in the Netherlands, survival rates have shown improvement, but significant morbidity still persists. The highest incidence rates of SCD-related complications are observed within the first four years of life, underlining the importance of guidance by specialized comprehensive SCD care centers and vigilance for serious complications among caregivers, especially before traveling abroad.

However, this study also has limitations to take into account. A proportion of eligible children did not participate in the study, potentially introducing selection bias, particularly missing asymptomatic patients or those with minimal complaints who did not attend routine clinic visits. Factors such as language barriers and low socioeconomic status may have contributed to non-participation as well. Second, shared care with a regional hospital may have led to an underestimation of complications, as data were only collected from academic hospitals. Future studies should include a longer duration of follow-up with both children and adults with SCD covering the transition period to adult care. These data could help us to further identify risk factors for a severe phenotype at a young age, in order to provide patient-tailored care to prevent irreversible organ damage.

CONFLICT OF INTEREST STATEMENT

M.H. has received investigator-initiated research and travel grants as well as speaker fees over the years from the Netherlands Organization for Scientific Research (NWO) and Netherlands National Research Agenda (NWA), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch Innovatiefonds Zorgverzekeraars, Stichting Hemophilia, Baxter/Baxalta/Shire/ Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, Roche, and Nordic Pharma. M.H. is a steering board member for Roche, Bayer, and Novartis. She is also the coordinator of Erasmus MC as a Health Care Provider within the European Reference Network (ERN) for rare hematological diseases EuroBloodNet and (co) leader of the local Erasmus MC Expert Centers for Rare Bleeding Disorders and Sickle Cell and Thalassemia Comprehensive Care Center. All grants and fees went to the Erasmus MC as an institution. The other authors have no relevant financial or non-financial interests to disclose.

FUNDING INFORMATION

Dutch National Institute for Public Health and the Environment (RIVM).

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient and/or caretaker(s) for the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.