Sickle cell disease: time for a targeted neonatal screening programme.

Sickle Cell Disease: Time for a Targeted Neonatal Screening Programme

Abstract:

C Gibbons[1], R Geoghegan[1], H Conroy[1], S Lippacott[2], D O'Brien[2], P Lynam[1], L Langabeer[1], M Cotter[1,3,4], O Smith[1], C McMahon[1,2]
[1]Our Ladyâ s Childrenâ s Hospital, Crumlin, Dublin 12
[2]St Jamesâ s Hospital, Jamesâ s St, Dublin 8
[3]Rotunda Hospital, Parnell St, Dublin 1
[4]Childrens University Hospital, Temple St, Dublin 1

Abstract

Ireland has seen a steady increase in paediatric sickle cell disease (SCD). In 2005, only 25% of children with SCD were referred to the haemoglobinopathy service in their first year. A non-funded screening programme was implemented. This review aimed to assess the impact screening has had. All children referred to the haemoglobinopathy service born in Ireland after 2005 were identified. Data was collected from the medical chart and laboratory system. Information was analysed using Microsoft Excel. 77 children with SCD were identified. The median age at antibiotic commencement in the screened group was 56 days compared with 447 days in the unscreened group, p=<0.0003. 22 (28%) of infants were born in centreâ s that do not screen and 17 (81%) were over 6 months old at referral, compared with 14 (21%) in the screened group. 6 (27%) of those in the unscreened group presented in acute crisis compared with 2 (3%) in the screened population. The point prevalence of SCD in Ireland is 0.2% in children under 15yr of African and Asian descent. We identified delays in referral and treatment, which reflect the lack of government funded support and policy. We suggest all maternity units commence screening for newborns at risk of SCD. It is a cost effective intervention with a number needed to screen of just 4 to prevent a potentially fatal crisis.

Introduction

Sickle cell disease (SCD) is the commonest haemoglobinopathy in man. It is an autosomal recessive condition that leads to abnormally structured and functioning red cells that have a shortened life span, a poor capacity to carry oxygen and a tendency to occlude microvascular spaces. Significant morbidity and mortality results from organ sequestration, occlusion and sepsis. The presence of high Hb F reduces the risk of clinical sickling during the first three months of life but as the Hb F concentration decreases, sickling begins to occur. SCD has recently been labelled a global public health problem by the WHO1, with recent epidemiological evidence pointing to a worldwide neonatal incidence of 294,000-330,000[2]. SCD was once isolated to Sub-Saharan Africa, India and parts of the Mediterranean and Middle East, however population migration, particularly in the past 10 â 15 years, has vastly changed the distribution and range of this disease and currently only fifty per cent of cases originate within the original countries involved[2].

Ireland has seen a steady increase in the incidence and prevalence of SCD over the past 10 years, mainly due to immigration. An epidemiological study[3] carried out in 2005 identified 160 children with SCD. Unfortunately, only twenty five per cent of these children were being referred to the haemoglobinopathy service (Hb service) in the first year of life. Newborn screening for SCD has been in place in many western countries for the last two decades. Such screening programmes have not only been associated with a reduction in infant mortality from eight per cent to less than one per cent[4], but also a reduction in the morbidity and mortality risk in the under 5yr age range. This is due to the early commencement of prophylactic antibiotics and appropriate vaccination.[5] Following on from the 2005 study, a non-funded haemoglobinopathy screening programme was implemented with the assistance of the three Dublin tertiary maternity hospitals, along with Our Lady of Lourdes Hospital Drogheda, the Mid-Western Regional Maternity Hospital, Limerick and St Lukeâ s Hospital, Kilkenny. Essentially, haemoglobin variants are screened from cord blood taken from all at-risk infants on the first day of life using High Performance Liquid Chromatography or haemoglobin Iso Electric Focusing.[7] All samples are confirmed in the haematology laboratories of either St James Hospital Dublin or Our Ladyâ s Childrenâ s Hospital Crumlin (OLCHC). Once a positive sample is identified the laboratory contacts the Hb service at OLCHC and an outpatient appointment is made with a view to early prophylaxis and education.

The aim of this review was to identify all children with sickle cell disease born within the Republic of Ireland between 2009 and 2012 and compare them to the cohort born before screening commenced. We hoped to see a significant change in identification and management of infants with SCD and also wanted to identify areas for future improvement. Ultimately we hoped to provide a strong case for the instigation of a national targeted haemoglobinopathy screening programme.

Methods

All children referred to the haemoglobinopathy service between January 2009 and December 2012 were identified using the database held by the haemoglobinopathy service in OLCHC. From this list, all children born in Ireland after 2005 (when screening began) were identified. This list was then cross referenced with laboratory data provided by St James hospital and OLCHC to ensure there were no missed cases. All cases of paediatric sickle cell disease are confirmed in one of these two laboratories. Clinical, demographic and relevant laboratory data was then collected from the medical chart, a separately held haemoglobin nurse specialist chart, and the hospital information system. This information was then collated and analysed using Microsoft Excel 2008. For information with a normal distribution the two tailed studentâ s t-test was used. A p value of <0.05 is considered statistically significant.

Results

Baseline demographics

A total of 109 children were referred to the Hb service from January 2009 to December 2012. 78 of these were born in Ireland and could have been identified by a screening programme. A total of 396 children were attending our service in 2011. According the national census of 20118, there were 19,423 children under the age of fifteen years ethnically at risk of SCD. This gives a paediatric point-prevalence in 2011 of 2%, or 200 per 100,000 at-risk children. Seventy-seven children with SCD were born in Ireland after 2005, following the initiation of screening. A demographic comparison of children referred from centres which screen and those which do not is shown in Table 1. The majority of children were of Sub-Saharan African origin; the rest were from the Indian subcontinent. Over eighty per cent of all children were diagnosed with homozygous SCD. One child of Indian origin was Hb SS while the other, along with a child of Pakistani lineage, were Hb S-D Punjab, the most common haemoglobin variant in the Indian subcontinent.

Referral Information

As Table 1 also demonstrates, the median age at referral to our service was 10 days in the screened group versus 456 days in the unscreened group (p = <0.0001). A number of children born in hospitals without a formal screening programme were screened at birth. This explains the range of 56-1569 days in that group. Some children born in screening hospitals experienced a delay in referral. There was no statistically significant difference between the two groups as regards time from referral to the first appointment, with the median time to attendance of <30 days in both groups. Three per cent of children in the screened group presented with a sickle cell crisis compared with twenty seven per cent of unscreened children, p= 0.037. The median age at antibiotic commencement in the screened group was 56 days compared with 447 days in the unscreened group, p=<0.0003.

Area of birth

Table 2 highlights the geographical pattern of screening. Seventy five percent of children referred over the four-year period were born in areas in which screening occurs. Sixty five per cent of these infants were referred before three months. Fourteen per cent had a delayed referral between three and six months, with a further twenty one per cent presenting between six and twelve months. The remaining twenty five per cent of infants were born in centres that do not screen. All of these infants had a delayed referral, nineteen per cent between three and six months and eighty one per cent older than six months at referral.

Discussion

Our study sought to highlight that neonatal screening for SCD in a targeted population within Ireland is a feasible and necessary step for the prevention of significant morbidity and mortality in this population. Both universal and targeted programmes are in use throughout Europe, the USA and many African countries. Screening is cost effective and is an acceptable test for most families.[9,10] Whilst the prevalence of SCD in the Irish population is very small, the prevalence of 200/100,000 children under the age of fifteen of African and Asian origin is 50 times higher than the current prevalence (4/100,000) of Cystic Fibrosis in children under the age of fifteen of Irish origin[11], a disease screened for in the national newborn screening programme. Screening leads to early referral to a specialist Hb service. We have shown that the single biggest impedance to treatment commencement is the time taken to initial diagnosis and referral. In hospitals that screen at birth, sixty five per cent of children are referred by three months of age, compared with none of the unscreened children. Early presentation greatly reduces the risk of morbidity and mortality from sepsis[14], which is highest between the second 6 months of life and 5 years.[15,16] Early penicillin prophylaxis is recommended to commence between 2 and 3 months of life.[12,13] In our study the median age for commencement of antibiotic prophylaxis in the screened group was 56 days compared with over 13 months in unscreened children. The rate of presentation with acute sickle crises in our study was twenty seven per cent in the unscreened group compared with just three per cent in the screened population. Based on this data, the number of children needed to screen to prevent one child from presenting with a sickle crisis is 4.

The suggested gold standard of care is that ninety five per cent of children should be referred by the age of 3 months[11] Our figure of sixty five per cent (in the screened group) reflects the fact that there is no funded support for this programme, nor a national coordinator or a government supported policy. One of the reasons for delayed referral from hospitals that screen occurred where there was an intermediary step in the processing of samples. The fastest results came from hospitals that utilise the laboratory service based in OLCHC or St James hospital Dublin. Repeat sampling was not required and appointments for the outpatient clinic were made directly by the Hb service in OLCHC following direct and timely communication of a positive result from the laboratory. In general, there are inadequate supports and resources in place to ensure that each childâ s results are seen, correctly interpreted and acted swiftly upon. One of the biggest challenges is contacting parents and ensuring their clinic attendance. As can be seen in Table 1, there was at times a long delay between referral and the first clinic attendance. Once again, the lack of a funded coordinator for the service makes this a difficult task and many of the children had received upwards of four appointments before presentation at clinic. The lack of a national programme and associated antenatal and postnatal education around SCD screening as well as early phone contact, means that parents often do not understand the importance of attending and fail to do so until repeatedly requested. According to the 2011 National Census, there are 77,292, 7,395, 8,044 and 3,166 people of either African or Asian nationality living in Leinster, Munster, Connaught and Ulster (part of) respectively. Table 2 clearly identifies children from all four provinces presenting with sickle cell disease. With a paediatric prevalence of SCD as high as 0.2 per cent in this population, it is difficult to ignore the need for a targeted neonatal national screening programme.

While awaiting the implementation of a neonatal screening programme, we would strongly suggest that at a minimum, all hospitals with maternity units in this state commence screening for newborns at risk of SCD. It is a cheap, cost effective intervention with a number-needed-to-screen of just 4 to prevent one child from a potentially fatal crisis. We also recommend improving local and national awareness regarding the importance of screening, the interpretation of results and encourage medical and nursing staff to always be alert to the possibility of undiagnosed SCD in an unwell child.

Correspondence: C Gibbons
Our Ladyâ s Childrenâ s Hospital, Crumlin, Dublin 12
Email: medgibbons@gmail.com

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