Sickle cell trait newborn screen results: disclosure and management

Margaret Lilley¹ · Stephanie Hoang¹ · Pamela Blumenschein¹ · Ann-Marie Peturson² · Iveta Sosova¹ · Lauren Macneil¹ · Ross Ridsdale¹ · Susan Christian¹

Received: 3 September 2020 / Accepted: 19 October 2020 / Published online: 26 October 2020
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Abstract

This study aims to evaluate the notification process of sickle cell trait (SCT) identified by newborn screening in Alberta. On April 1, 2019, Alberta began newborn screening for sickle cell disease (SCD) and elected to report sickle cell trait (SCT). For 1 year, healthcare providers (HCPs) were sent a questionnaire which addressed the perceived importance of disclosing the SCT results, whether HCPs felt competent in disclosing the result, knowledge of available resources, and comfort with coordinating and interpreting testing for the newborn's parents. As a control, we collected data from HCPs receiving positive cystic fibrosis (CF) newborn screen results. A total of 107 out of 203 SCT questionnaires were returned and 41 of 66 CF questionnaires were returned. Respondents felt it was important that the results be shared with families (98% and 100%, respectively). Most respondents felt competent (SCT: 95%; CF: 85%), and willing to disclose the result to the family (SCT: 92%; CF: 88%). Fewer respondents were comfortable interpreting the results (SCT: 70%; CF: 51%), and willing to arrange parental testing (SCT: 61%; CF: 59%). Family practitioners were significantly more willing to arrange SCT parental testing (88%) compared to pediatricians (40%) (OR = 5.3; CI 1.9, 15.4; $p < 0.001$). HCP comments revealed two themes: referral to another HCP for follow-up and identification of the primary HCP. Results support this disclosure process, and HCPs felt comfortable following up with SCT newborn screen results. The study identified challenges such as pediatricians being less comfortable ordering parental testing and the ordering HCP not always being the primary care provider.

Introduction

Newborn screening plays a critical role in the lives of infants. As of April 1, 2019, all newborns in Alberta, Canada, are offered screening for 21 treatable disorders, including sickle cell disease (SCD). SCD is a group of hereditary conditions caused by abnormalities of the beta-globin subunit of hemoglobin that leads to sickling of red blood cells when in the deoxygenated state. Sickle cell anemia (SCA), one of the SCDs, is an autosomal recessive disorder that occurs when an individual is homozygous for a specific variant of the beta-globin gene. Carriers of this allele have an abnormal biochemical profile that can be identified by newborn screening. These individuals are known as sickle cell trait (SCT) carriers

and are largely asymptomatic for the classical presentations of SCD; however, they are known to have an increased risk of health complications (renal medullary cancer, hematuria, exertional rhabdomyolysis, and exercise-related sudden death) making identification of these carriers important (Goldsmith et al. 2012; Tantawy 2014; Tsaras et al. 2009). Furthermore, identifying newborns with SCT can have reproductive implications for both the newborn's parents and eventually the child themselves.

Prior to the addition of SCD to the newborn screening panel, a multidisciplinary working group was formed to determine the disclosure policy and process for SCT. The working group reviewed the literature and policies from other programs that include SCD in their newborn screening. Both opt-in and universal disclosure models have been reported in North America (Hayeems et al. 2017; Mandl et al. 2002; Parker et al. 2007; Shuchman 2014). After consideration of four models including opt-in, opt-out, universal disclosure, and universal non-disclosure, Alberta Health authorities chose to implement a universal disclosure policy for SCT. Therefore SCT results are included in the final newborn screen result.

✉ Margaret Lilley
Margaret.Lilley@albertaprecisionlabs.ca

¹ Newborn Screening Laboratory, Alberta Precision Laboratories, 4B2.04 WMC, University of Alberta Hospital, 8440 112 St., Edmonton, Alberta T6G 2H7, Canada

² University of Alberta, Edmonton, Alberta, Canada

Presently, there is limited data on the comfort and attitudes of healthcare providers (HCPs) related to the notification and follow-up care of infants identified as carrying SCT, particularly in a Canadian context. The objective of this study was to assess the self-perceived competence and comfort HCPs have in regard to disclosure of SCT screen results, organization of follow-up testing, interpretation of diagnostic test results, and knowledge of available specialists and resources. To allow for comparison to an established newborn screening notification process, data was also collected from HCPs receiving positive cystic fibrosis (CF) newborn screen results.

Methods

Notification process for SCT newborn screen results

SCT results are included in the final newborn screen result. HCPs are faxed a SCT notification letter indicating that a newborn in their care was found to have SCT together with a one-page information sheet. The information sheet provides background information including implications for family members and directs providers to an Alberta-specific practice guideline for SCT identified by newborn screening (<https://actt.albertadoctors.org/CPGs/Pages/Sickle-Cell-Trait.aspx>). This resource provides a detailed follow-up algorithm, frequently asked questions, and contact information for specialty clinics. All other positive screens are verbally disclosed to the responsible HCP by a genetic counselor, and additional support is provided by specialty clinics.

Notification process for CF newborn screen results

Newborn screening for CF was implemented in Alberta in 2007. There are three types of positive newborn screen results for CF, including an inconclusive result for infants with an abnormal immunoreactive trypsinogen (IRT) measurement and a single pathogenic variant identified by molecular genetic testing. Results are phoned to the ordering HCP by a genetic counselor who explains the result and recommends referral to a cystic fibrosis clinic for clinical assessment and sweat chloride testing. In addition, a preliminary result and a one-page information sheet are faxed to the HCP. Inconclusive CF newborn screen results were chosen as a control group as the disclosure process is well-established. The majority (> 90%) of these infants will have a normal sweat chloride values and will therefore be diagnosed as CF carriers, and therefore was felt to be most similar to SCT in the context of newborn screening.

Participants and procedures

Between April 1, 2019, and March 31, 2020, a questionnaire was faxed to order HCPs in Alberta receiving a SCT notification letter or an inconclusive CF newborn screen result. HCPs could receive both SCT and CF questionnaires if they had patients with positive screen results for each disorder during the study period.

Questionnaire

The questionnaire included 8 questions and took about 5 min to complete. Most questions were in a multiple-choice format, with one matrix question that included a 4-point Likert scale (1 = strongly disagree to 4 = strongly agree) to indicate agreement with the statements regarding handling SCT or inconclusive CF newborn screen results. Demographic data and HCPs' comfort with the notification, testing, and follow-up process for either SCT or CF were collected. A space for additional comments was included at the end of the questionnaire. Questionnaires not returned were followed up with a faxed reminder and a copy of the questionnaire. Each HCP completed only one questionnaire for each disorder regardless of the number of SCT or CF newborn screen results they received. Ethics approval was obtained through the University of Alberta Health Ethics Research Board (Pro00089510).

Data analysis

The questionnaire was created and managed using the REDCap electronic data capture tool hosted at the University of Alberta (Harris et al. 2009). Data is mostly descriptive in nature. Responses are categorized as agreed (agreed and strongly agreed) or disagreed (disagreed or strongly disagreed). Continuous variables are presented as means with standard deviations. Categorical variables are presented as counts with percentages. Where appropriate, chi-squared analysis or Fisher's exact test was used to evaluate the relationship between demographic data and outcome data. The Stata Statistical Software: Release 13 (College Station, TX: StataCorp LP) was used for statistical analysis. Comments were reviewed by 2 independent reviewers and themes were identified.

Results

During the 1-year study period, 51,268 infants were screened, resulting in 390 SCT newborn screen results being reported to 203 HCPs. Of these HCPs, 110 returned the questionnaire. One respondent only completed demographic information and was therefore excluded from analysis. The response rate

for the SCT questionnaire was therefore 54% ($n = 109/203$). In addition, 71 inconclusive CF newborn screen results were called out to 66 HCPs. Forty-one HCPs returned the CF questionnaire for a response rate of 62% ($n = 41/66$). Demographic data for non-respondents was obtained from the College of Physicians and Surgeons of Alberta or the College of Midwives of Alberta websites and did not differ significantly from HCPs that returned the questionnaire. There were significant differences between SCT respondents and CF respondents with regard to gender and location of practice. SCT respondents were significantly more likely to be female (OR: 2.6; CI: 1.2, 5.8; $p = 0.01$) and less likely to practice in a small-sized city compared to CF responders (OR: 0.1 CI: 0.01, 0.3; $p < 0.001$) (Table 1).

HCP responses to both the SCT and CF questionnaires are summarized in Table 2. The vast majority of respondents to both questionnaires indicated that this information was important to share with the family (SCT: 105/107, 98%; CF: 41/41, 100%) and that they would be disclosing the results to the family themselves (SCT: 100/109, 92%; CF: 36/41, 88%). In general, HCPs felt competent disclosing the newborn screen result (SCT: 102/107, 95%; CF: 35/41, 85%), and knowledgeable about where to find information on the conditions (SCT: 94/106, 88%; CF: 37/41, 90%). Most HCPs knew where to refer a newborn if they presented with clinical symptoms of SCT (95/106, 90%), and where to refer newborns with

a positive CF newborn screen for diagnostic testing (37/41, 90%).

Approximately 60% of HCPs were willing to arrange follow-up testing for the parents of newborns who received a positive newborn screen for SCT or CF. Overall, HCPs felt more comfortable interpreting parents' hematology studies (70%) compared to genetic studies (51%) (OR: 2.1; CI: 0.9, 4.8; $p = 0.045$) and referring parents if they were both found to be carriers for the condition based on hematological studies (75%) compared to genetics studies (58%) (OR: 2.1; CI: 0.9, 4.9; $p = 0.047$). A significant difference was noted between the willingness of family physicians (39/50, 78%) compared to pediatricians (14/37, 38%), to order follow-up parental testing for a SCT newborn screen result (OR: 5.8; CI 2.1, 16.7; $p = 0.0001$). The same relationship was not statistically significant for family practitioners (15/24, 63%) compared to pediatricians (7/14, 50%) when managing CF newborn screen results (OR: 1.67, CI 0.36, 7.72; $p = 0.45$).

Themes identified after reviewing the comments provided by respondents are described in Table 3. The most common comments reflected that follow-up care would be managed by another provider. Consistent with this, a number of respondents raised concerns with not being the primary care provider for the newborn and parental testing being outside their scope of practice. Other themes included the diagnosis already being known in the family, finding the provided information sheet helpful, and having previous experience with SCT.

Table 1 Respondents' and non-respondents' demographic data

Demographics	SCT respondents	SCT non-respondents	CF respondents	CF non-respondents
Gender				
Male	31 (29%)	34 (35%)	21 (53%)	10 (40%)
Female	77 (71%)	62 (65%)	19 (48%)	15 (60%)
Type of HCP				
Family practitioner	53 (49%)	42 (44%)	24 (59%)	11 (44%)
Pediatrician	38 (35%)	33 (34%)	14 (34%)	10 (40%)
Neonatologist	7 (6%)	13 (14%)	1 (2%)	3 (12%)
Midwife	10 (9%)	6 (6%)	1 (2%)	1 (4%)
Other	1 (OBGYN) (1%)	2 (2%)	1 (NP) (2%)	0 (0%)
Location of practice				
Greater Edmonton area	41 (38%)	33 (34%)	10 (24%)	9 (36%)
Greater Calgary area	50 (46%)	47 (49%)	10 (24%)	8 (32%)
Medium-sized city (pop. 30,000–150,000)	15 (14%)	9 (9%)	10 (24%)	2 (8%)
Small-sized city/town or rural (pop. < 30,000)	3 (3%)	7 (7%)	11 (27%)	6 (24%)
Years of practice				
0–5 years	25 (23%)	Not available	10 (24%)	Not available
6–10 years	17 (16%)		5 (12%)	
10–15 years	16 (15%)		4 (10%)	
> 15 years	52 (47%)		22 (54%)	

SCT sickle cell trait, CF cystic fibrosis, OBGYN obstetrician/gynecologist, NP nurse practitioner, Pop population

Table 2 Attitudes and comfort level of respondents

Agreement with the following statements	SCT Agree/strongly agree	CF Agree/strongly agree
Result is important to share with the family.	105/107 (98%)	41/41 (100%)
I feel competent to discuss the screen result with the family.	102/107 (95%)	35/41 (85%)
I know where to find information about this condition.	94/106 (88%)	37/41 (90%)
I know where to refer this child if he/she has active clinical symptoms (SCT) or for diagnostic testing (CF)	95/106 (89%)	37/41 (90%)
I am willing to order follow-up testing on the parents of this child.	62/104 (60%)	24/41 (59%)
I know what follow-up testing to consider for the parents of this child.	72/103 (70%)	22/40 (54%)
I understand how to interpret the follow-up testing for the parents of this child.	73/104 (70%)	21/40 (51%)
I know where to refer the parents of this child if they are both carriers.	79/105 (75%)	24/41 (58%)

SCT sickle cell trait, CF cystic fibrosis

Conclusion

Our study supports continuing with a universal disclosure model for SCT identified by newborn screening. Several areas for improvement were highlighted including identification of the most appropriate HCP and additional support for HCPs ordering genetic testing. The Alberta disclosure process provides a model for future newborn screen disorders.

HCPs feel that SCT newborn screen results are important. They are comfortable disclosing the results to families and performing the tasks associated with the newborn screen result. Previous investigations highlighted that certain factors, such as HCPs understanding of the condition and knowledge of follow-up procedures, could impact follow-up care (Collins et al. 2013; Vansenne et al. 2011). A survey of HCPs in Ontario found that the majority of HCPs feel responsible for

caring for families with a positive newborn screen result (Hayeems et al. 2013). Only 46% of those HCPs felt confident in their ability to discuss newborn screen results with parents compared to 95% (SCT) and 85% (CF) of HCPs in our study. The Ontario study evaluated newborn screening in general which HCPs may associate with rare metabolic conditions. The clinical implications, level of urgency, and uncertainty associated with a positive newborn screen result is dependent on the screened condition. Therefore, HCPs' confidence in discussing a positive newborn screen result is likely condition-dependent. SCT and inconclusive CF newborn screen results are associated with less urgency and uncertainty which may explain the higher levels of confidence seen in our study population. Based on the volume of results, an Alberta physician is more likely to receive a SCT newborn screen result than any other screened condition. Therefore, it is important to

Table 3 Themes identified in respondent comments

Theme	n	Examples
1. Follow-up managed by other HCP	16	I contacted their regular family physician who is doing ongoing care. (ID #248)
2. Concern with notification process	10*	
Not the primary care provider	6	In our current system, these results are problematic. We pediatricians see patients once for newborn exam and do NOT do primary care. These results come back to us and we are not following these patients, do not have demographic info/phone # and it is logistically difficult to provide counselling (ID #9).
Scope of practice regarding ordering parental testing	2	I am willing to order but unsure if ordering labs on parents not in my care is in my scope (ID #227). As I am not primary caregiver for parents, I would not want to order their follow up tests, but would refer them to their primary caregiver (ID #86).
Concerns with report	2	Need to make positive SCT result more easy to notice as the [heading on the] report just says "NORMAL" (ID #132).
Unable to reach family	1	Unable to get a hold of family (ID #222)
3. Diagnosis already known in family	5	Mom has known sickle cell trait (ID #142).
4. Information provided was helpful	4	Thank you very much for attaching the health care professional information handout! Very helpful! (ID #26)
5. Experienced with SCT	4	Hemoglobinopathy is prevalent in my population (ID #127).

*Some respondents noted more than one concern

ensure that Alberta HCPs have sufficient resources and are confident following up on these results.

Some HCPs were not comfortable coordinating parental follow-up testing and referral. A pediatrician or midwife may feel that it is outside of their clinical scope of practice to order follow-up testing on the parents. Since family physicians may care for multiple family members, they may be better suited to receiving SCT newborn screen results. A HCP may be listed as the ordering provider while the infant is in the hospital but may not plan to follow that infant after discharge. Addressing this concern would involve changing the process of identifying the most appropriate HCP. This could occur by changing the way the ordering provider is identified at the time the newborn screen specimen is collected or by adjusting the SCT notification process.

When the SCT and CF survey responses were compared, HCPs were more comfortable ordering and interpreting hematological testing compared to CF genetic testing. HCPs were also more knowledgeable regarding referrals for parents who are carriers of SCD than CF even though disclosure of inconclusive CF newborn screen results has been long-standing and includes a telephone discussion with a genetic counselor. HCP comfort with testing for SCT may be explained by hematological testing being a more familiar test compared to genetic testing which is often seen as esoteric. Routine preconception screening for hemoglobinopathies has been a recommended practice since 2008, whereas such screening for cystic fibrosis is not currently recommended in Canada (Langlois et al. 2008; Wilson et al. 2002). Carroll et al. found that only 32% of family physicians felt confident deciding who should be referred for genetic counseling or testing and that only 16% felt confident discussing the benefits, risks, and limitations of genetic testing with patients (Carroll et al. 2019). In addition, the referral pathways for CF and SCT newborn screen results differ with respect to both roles of the primary care provider and the specialists and referral criteria for the Medical Genetics clinics. For SCT newborn screen results, the primary care provider is responsible for the follow-up of both the newborn and the family. For inconclusive CF screens, the specialist is responsible for the follow-up of the newborn, and it may be unclear who is responsible for the follow-up for the parents. This lack of clarity regarding roles and responsibilities may also contribute to the disorder-specific differences identified. HCPs may benefit from additional supports when ordering genetic testing which may include information sheets or educational videos, providing additional information and clarity about roles and responsibilities. The Medical Genetics clinics in Alberta do not have unified referral criteria with respect to whether both parents must be confirmed carriers of a recessive disorder in order for the referral to be accepted. An alternative service delivery model such as group genetic counseling for these parents could be considered. Although this would serve the patients' needs, it would not improve the HCPs' perceived

competency. As genetic testing becomes more common, increasing HCPs' confidence and competency will be an important aspect of providing care to families.

Overall, our results show that HCPs feel that it is appropriate to report SCT as part of the newborn screen result and that the current notification system is acceptable. HCPs appreciated the information provided to them at the time of SCT notification. This model could be applied to newborn screening for other disorders that incidentally identify carrier status. This is notable as newborn screening will continue to expand and will likely include an increasing number of molecular assays. As newborn screening programs continue to increase the number of conditions they screen for, effective notification processes become progressively important to deal with the large volume of positive results in a timely and cost-effective manner.

Limitations

There are several limitations to our study. First, it is possible that the non-responding HCPs do not feel that SCT newborn screen results are important and are less likely to disclose the results. Second, there was a difference in the gender and location of practice between the CF and SCT respondents. Finally, this study only assessed the HCPs' stated intention to disclose results and arrange follow-up; it does not confirm the completion of these activities.

Areas for further research

Areas for further research include exploring how families were informed of their child's SCT newborn screen result and their satisfaction with the disclosure. The ongoing educational needs of individuals with SCT and their HCPs can be explored as these individuals mature and approach family planning.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Ethics approval was obtained through the University of Alberta Health Ethics Research Board (Pro00089510).

Informed consent Participants were provided with an introductory letter that preceded the survey. Consent was implied by the completion of the survey.

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