ORIGINAL ARTICLE

Acceptance, Knowledge, and Experiences of Pediatric Hematologists in the Philippines on Newborn Screening for Hemoglobinopathies

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ABSTRACT

Background. Hemoglobinopathies as a group is one of the most common conditions confirmed through the newborn screening (NBS) program of the Philippines. This led to the increased participation of pediatric hematologists in the NBS program.

Objective. The aim of the study was to assess newborn screening acceptance and knowledge of pediatric hematologists using an online questionnaire.

Method. Members of the Philippine Society of Pediatric Hematology (PSPH), who are practicing pediatric hematologists in the Philippines, were invited to answer an online questionnaire.

Results. Sixty members of the PSPH (65.2%) answered the survey. All the respondents are familiar with the newborn screening program. Fifty-seven respondents (95 %) have already managed a case of hemoglobinopathy identified through the newborn screening program. Differences in the approach to management and level of confidence with diagnostic test result interpretation have been noted. General themes of their concerns include being unaware of the protocol, concerns on delays in confirmatory tests, request for guidelines on follow-up, and incongruence of results with clinical picture.

Conclusion. The information collected may be used to develop strategies to better equip our pediatric hematologists and assist the PSPH standardize management protocols for hemoglobinopathies.

Keywords: hemoglobinopathies, newborn screening, pediatric hematologists

INTRODUCTION

Newborn screening (NBS) in the Philippines began as a project in 1996 to determine the prevalence of some endocrinologic and metabolic disorders and has later become integrated with the Philippine public health delivery system.[1,2] In 2004, the newborn screening, which at that time had six disorders included in the panel, was institutionalized through the Newborn Screening Act of 2004 or Republic Act 9288 (RA 9288). This has, since then, been considered to be one of the more successful programs of the Department of Health (DOH). In 2014, an administrative order from DOH provided guidelines for implementing expanded NBS (ENBS) which screens for more than 28 conditions, including hemoglobinopathies. In 2018, full insurance coverage of the ENBS was implemented.[3] This milestone allowed more cases of hemoglobinopathies to be detected.

Hemoglobinopathies are the most common monogenic diseases and recognized to be a global health problem.

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Overall, around seven percent of the world's population are carriers. The value of adding this group of disorders in the newborn screening panel is early identification of disease and intervention altering the natural history of the condition before significant morbidity and mortality occurs.[4]

Hemoglobinopathies are characterized by either structural variants in the alpha (α)-globin and beta (β)-globin genes or quantitative differences in α- or β-globin chain production, which can have severe clinical significance.[5] Sickle cell disease (SCD), for example, refers to a hemoglobinopathy caused by structural variations in the β-globin chain. On the other hand, decreased amounts of α- or β-globin chains results in α- or β-thalassemia, respectively. Thalassemia, the most common human monogenic disease, has a high prevalence in Asian populations. While β-thalassemias, in general, are clinically more significant, α-thalassemias, with its variable phenotype, have a higher overall frequency. The most severe phenotype, β-thalassemia major, can result from any one of several causes including the complete absence of β-globin chains (β^0-thalassemia) and co-inheritance of a β-thalassemia mutation and a common variant in Asians, hemoglobin (Hb)E (interacting HbE/β-thalassemia). In infancy, this results to hemolytic anemia, poor growth, and skeletal abnormalities. The clinical severity of α-thalassemia is directly related to the type and number of α-globin gene mutations involved. Patients with one or two α-gene deletions or mutations are asymptomatic while deletion or inactivation of three α-globin genes results in Hemoglobin H (HbH) disease and deletion of all four α-genes results in Hb Bart's hydrops fetalis which is usually fatal. HbH disease is usually characterized by hemolytic anemia and is more severe in those with Hb Constant Spring, another fairly common mutation in Asian population. Those affected with hemoglobinopathies are usually asymptomatic at birth.[6] Like SCD, thalassemias can be detected through NBS and related confirmatory studies, and early diagnosis and treatment has been shown to significantly improve health outcomes.[6, 7]

High-Performance Liquid Chromatography (HPLC), Capillary Electrophoresis (CE), and DNA/molecular testing are some of the diagnostic tests, both screening and confirmatory, a pediatric hematologist sees in cases of hemoglobinopathies. HPLC is the preferred screening method to make a presumptive diagnosis of a clinically significant hemoglobin disorder primarily because of its high sensitivity and specificity.[4,8] CE, on the other hand, is a method which can separate and quantitate Hb A2, Hb E, Hb F, Hb H and Hb Bart's, which are important parameters required for the diagnosis of thalassemias and hemoglobinopathies.[9] In addition, molecular confirmation can be done to determine the specific genotype.

Diagnosis of a specific hemoglobinopathy will guide physicians to the specific management plan. For the α-thalassemias, 1 and 2 gene deletions/mutations do not require treatment. Iron supplements are also contraindicated except in definite cases of iron deficiency. For HbH disease, management depends on the severity of the presentation. Folic acid supplementation is required. For Hb Bart's syndrome, in utero and post-natal transfusions are required. Stem-cell transplantation may also be performed. For beta thalassemia major, curative treatment via hematopoietic stem-cell transplantation and supportive treatment specifically lifelong regular transfusions combined with effective iron removal are part of the management plan.[10] Other hemoglobin variant specific management has also been reported.

After more than 5 years of screening, hemoglobinopathies now ranks among the most screened condition in the newborn screening panel. This is despite it being screened starting only in 2014 when the ENBS was introduced, which is 18 years and 16 years after CH and G6PD deficiency were initially started to be screened, respectively. In addition, traits were not included in the count. The prevalence of hemoglobinopathies based on the Philippine ENB is 1 in 1,560.[11] Along with this increase ascertainment of cases, the demand for quality healthcare for babies with hemoglobinopathies followed. Involvement of specialists, specifically pediatric hematologists, is highly needed. Hence, their participation in the program is essential. In this study, it was aimed to assess newborn screening acceptance and knowledge of pediatric hematologists using an online questionnaire. This is to identify gaps and provide recommendations in order to improve the NBS program for hemoglobinopathies.

METHODS

This is a cross-sectional study which was conducted among pediatric hematologists in the Philippines. Purposive sampling design was utilized, selecting specifically the Pediatric hematologists of the Philippines. All practicing pediatric hematologists in the Philippines were included in the study. The 95 members of the Philippine Society of Pediatric Hematology, excluding the primary author, were invited to participate. The aims and ethical considerations of this study was explained prior to participation, and written consent to participate in the survey. Ethical approval for the study was obtained from the Ethics Research Board of the University of the Philippines.

The online questionnaire involved questions on demographics, knowledge on the NBS program, and experience on patients from the NBS program being referred for management. Submitted survey questionnaires will be collated and analyzed.

Descriptive statistics was used to describe the study variables. Frequency, percentage, and mean scores will be used to report the descriptive analysis. For open ended questions, the answers were grouped into general themes and were summarized in a table.

RESULTS

There was a total of 60 respondents. Table 1 shows the characteristics of the respondents of the survey. Most of them were in the 51-60 years age group (41.5 % of respondent). Majority of them were in Luzon (76.7%). Ten were in the Visayas (16.7%) and 4 (6.7%) in Mindanao. Most of them finished their training in pediatric hematology in one of the five training institutions for this program in the country.

Table 1. Characteristics of survey respondents

Characteristic	N= 60 (65%)
***Age** (years)*	
30-40	12
41-50	18
51-60	27
>61	3
Years in Practice	
< 5 years	13
6-10 years	12
11-15 years	10
16-20 years	18
>21 years	7
Place of Practice	
Luzon (Metro Manila)	46 (27)
Visayas	10
Mindanao	4
Medical School	
Cebu Institute of Medicine	5
Davao Medical Center	1
De La Salle University	2
Far Eastern University	14
Our Lady of Fatima University	1
Manila Central University	2
Mindanao State University	1
Pamantasan ng Lungsod ng Maynila	2
Remedios Trinidad Romualdez Medical Foundation	1
St. Louis University	2
University of the East Ramon Magsaysay Memorial	6
Center	4
University of the Philippines	13
University of Santo Tomas	1
University of the Visayas	4
West Visayas State University	1
Xavier University	
Pediatric Hematology Training	11
Fe Del Mundo (Children's Medical Center	28
Philippines) Philippine Children's Medical Center	
Philippine General Hospital	12
University of Santo Tomas	7
Hospital Abroad	2

Acceptance of the NBS for hemoglobinopathies were assessed via the participants awareness of the NBS program for hemoglobinopathies and their acknowledgment of the need for screening of hemoglobinopathies. All of the respondents were familiar with the newborn screening program in the Philippines and acknowledged the need. All of them were aware that hemoglobinopathies are included in the NBS panel.

Knowledge of the NBS for hemoglobinopathies was assessed through questions on what specific hemoglobinopathies that they know to be included in the NBS, as well as through their own assessment of their own knowledge on the diagnosis and management of hemoglobinopathies. Figure 1 shows the hemoglobinopathies the respondents know to be included in the expanded newborn screening panel. Hemoglobin H disease, hemoglobin E disease, and beta thalassemia major were the top three hemoglobin disorders the respondents know to be included in the NBS panel.

Knowledge on the diagnostics was noted through their confidence in the interpretation of diagnostic test results for hemoglobinopathies (Table 2) namely HPLC, CE, genotyping or molecular testing. Majority of the respondents are slightly confident. Twenty-eight respondents (46.7%) are not familiar with the algorithm for NBS of hemoglobinopathies. With regards to management, majority of the respondents are highly confident (45%) and slightly confident (43.3%) in managing patients with hemoglobinopathies. Despite this, 93.3% still thought that they need additional training/ workshop on newborn screening, diagnosis, and management of hemoglobinopathies. Of the 60 respondents, 55% attended comprehensive lectures, workshops, or training programs on hemoglobinopathies in the past.

Experiences of pediatric hematologists on case diagnosis of hemoglobinopathies were identified. Fifty-seven respondents (95 %) had already managed a case of hemoglobinopathy from the NBS program. For those who already managed a case of hemoglobinopathy from the NBS program, 59.6% answered that they sometimes receive patients with confirmatory tests already. Thirteen (22.8%) received patients already with confirmatory tests. Eight (14%) received patients even before the hemoglobinopathy was confirmed. Some received patients awaiting confirmatory test results. Forty-two (73.7 %) sometimes order additional diagnostic tests upon consult, primarily CBC. Fourteen (24.6%) always request for additional diagnostic tests.

Table 2. Level of confidence in the interpretation of diagnostic test results and management of hemoglobinopathies

Area	Highly confident	Slightly confident	Neither confident nor unconfident	Not very confident	Not at all confident
Managing a patient with hemoglobinopathy	27 (45%)	26 (43.3%)	7 (11.7%)	-	-
Interpretation of High-performance liquid chromatography (HPLC) results	4 (6.7%)	33 (55%)	15 (25%)	5 (8.3%)	3 (5%)
Interpretation of Capillary Electrophoresis (CE) results	9 (15%)	37 (61.7%)	10 (16.7%)	4 (6.7%)	-
Interpretation of genotyping or molecular testing results	2 (3.3%)	26 (43.3%)	17 (28.3%)	12 (20%)	3 (5%)

Experiences on case management of hemoglobinopathies among pediatric hematologists also vary. Thirty-five (61.4%) answered they immediately prescribe a medication, primarily folic acid, upon seeing a patient with hemoglobinopathy for the first time. One or two give vitamin B complex and low dose iron for purely breastfed especially for non-transfusion requiring patients. For those who do not automatically give medication (38.6%), they check first if it is truly indicated, sometimes observes first and checks the complete blood count. If the patient is asymptomatic after the initial consult, follow-up schedule is after 1 month in 6 respondents (10.5%), after 3 months in 27 respondents (47.4%), after 6 months in 17 (29.8%), after 1 year in 3 (5.3%). Four (7%) answered the follow- up schedule will depend upon the type of hemoglobinopathy.

Table 3 summarizes the concerns raised by the pediatric hematologists regarding newborn screening of hemoglobinopathies. General themes include being unaware of the protocol, concerns on delays in confirmatory tests, request for guidelines on follow-up, and incongruence of results with clinical picture.

DISCUSSION

The role of pediatric hematologists in the care of patients with hemoglobinopathies is essential and cannot be overemphasized. Hematologists practicing in the Philippines, which is included in the thalassemia belt, encounter a lot of these cases. With the ENBS running for five years now, pediatric hematologists are aware of the inclusion of hemoglobinopathies in the panel, however, not all are

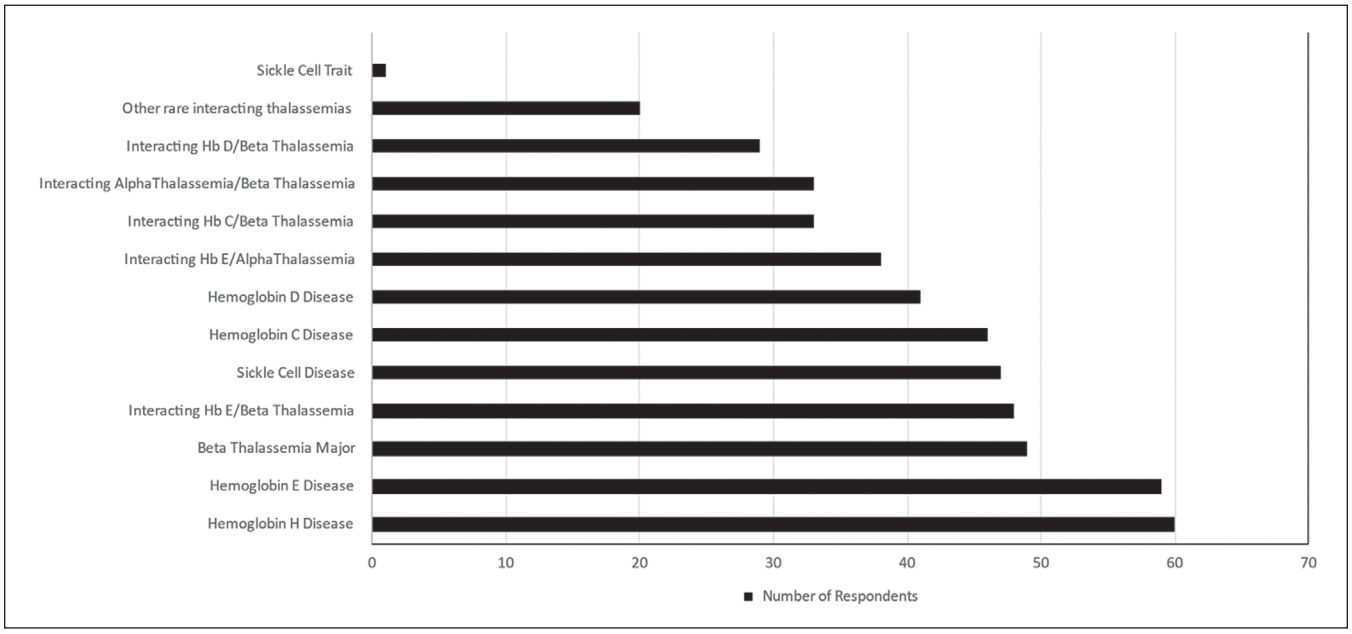

Figure 1. Hemoglobinopathies which the pediatric hematologists know are included in the expanded newborn screening program in the Philippines.

Table 3. Summary of concerns of respondents

General Theme	Specific Concerns
Unaware of the protocol	• There is unawareness that traits are not detected by newborn screening. • There is confusion as to those that proceeds to confirmatory testing and which ones need further confirmatory tests. • There is unawareness as to how patients can avail of the confirmatory tests. • There are suggestions to do DNA testing even for carriers/traits and to those not eligible but willing to pay.
Delays in the confirmatory tests	• There are limited facilities doing the confirmatory tests. • There had been limitations due to the pandemic. • There had been delays in releasing and informing of patients re screening results.
Incongruence of results with clinical picture	• There are false-negative results (normal NBS but with thalassemia).
Need for Guidelines	• There is a need for to formulate evidence-based recommendations for follow-up care of all patients with hemoglobinopathies. • There had been concerns on management of specific hemoglobinopathies.

familiar with what specific conditions are being screened. Most of the respondents are aware of the Hemoglobin H disease, Hemoglobin E disease, Beta Thalassemia Major and Interacting Hemoglobin E/Beta Thalassemia. These are primarily the once encountered in their clinics. In addition, some of the respondents are not aware that the NBS program aims to detect diseases and not traits/carriers.

It is advantageous that the pediatric hematologists are aware of the NBS program for hemoglobinopathies and that they see the value in doing so. Also seeing their concerns with regards to detection of traits and carriers, highlights the direction this group of doctors is heading to. As the program continues, the burden of disease in the country is coming to light. Hence, NBS for hemoglobinopathies will probably evolve and mature.

As also evident in the responses in Table 3, general concerns include lack of awareness of the protocol, delays in confirmatory tests, lack of follow-up guidelines, and incongruence of results with clinical picture. These concerns are important to be noted and be addressed. Education or orientation can be done to increase awareness of the clinicians to the aims and protocols of the program. Discussions on the limitations of the tests may also be done to address concerns on incongruence and lead to investigations on how this can be improved. Concerns on delays may be addressed through proper communication with the NSCs and the confirmatory test laboratories. Guidelines on follow-up are already being developed by the society. Coordinated efforts of the different stakeholders to promote education and awareness of these disorders will also support improvement of the diagnosis and management of these disorders. These concerns will pose challenges in the long run if not addressed. Hence, it is advantageous that these were determined and be addressed for the improvement of the program.

To improve the confidence of respondents in the interpretation of diagnostic test results and management of hemoglobinopathies, a review of fellowship/specialty training program may be done to better equip future pediatric hematologists. For the practicing specialists, focused workshops or trainings may be developed.

With the increasing number of babies screened with hemoglobinopathies, the demand for pediatric hematologists has also increased. The participation and involvement of pediatric hematologists in the newborn screening program is necessary. With this study, gaps may be identified and be addressed towards these specialists' involvement as healthcare providers of our patients with hemoglobinopathies and as advocates of the NBS program. Before NBS for hemoglobinopathies, prevalence is unknown, diagnosis and management are not standardized. With the NBS program, these things were started to be established and improved for the patients. Being in the thalassemia belt, diagnosis and management of this group of conditions is aimed to provide better outcome for the citizenry.

CONCLUSION

Pediatric hematologists play a vital role in the care of patients with hemoglobinopathies. It is important to empower them with knowledge regarding the NBS program and equip them with tools to better care for the patients. Through workshops or trainings, information regarding the NBS protocol, diagnostic test interpretation and management may be done to address concerns raised by the pediatric hematologists.

Ethics Approval

This study was approved the University of the Philippines Manila Research Ethics Board (UPMREB 2021-217-01).

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

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REFERENCES

1. Padilla CD. Newborn screening in the Philippines. Southeast Asian J Trop Med Public Health. 2003; 34(3): 87-88.
2. Padilla CD, Basilio JA, Oliveros YE. Newborn screening. Research to Policy. Acta Medica Philipp. 2009; 43(2): 6-14.
3. Padilla CD, Therrell BL, Panol KAR, Suarez RCN, Reyes MEL, Jomento CM, et al. Philippine Performance Evaluation and Assessment Scheme (PPEAS): Experiences in Newborn Screening System Quality Improvement. Int J Neonatal Screen. 2020; 6:95. DOI: https://doi.org/10.3390/ijns6040095.
4. Michlitsch J, Azimi M, Hoppe C, Walters MC, Lubin B, Lorey F, et al. Newborn Screening for Hemoglobinopathies in California. Pediatr Blood Cancer. 2009; 52:486-490.
5. Therrell BL, Hoppe C, Mann MY, Azimi M, Brants A, Brown SE, et al. Newborn screening for hemoglobinopathies. 1st ed. CLSI guideline NBS08. Wayne, PA: Clinical and Laboratory Standards Institute; 2019. p. 7.
6. Lorey F, Cunningham G, Vichinsky EP, Lubin BH, Witkowska HE, Matsunaga A, et al. Universal newborn screening for Hb H disease in California. Genet Test. 2001; 5:93–100.
7. Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med. 2014 Nov 13;371(20):1908-16.
8. Hoppe CC. Newborn screening for non-sickling hemoglobinopathies. Hematology. 2009:19-25.
9. Sangkitporn S, Sangkitporn SK, Tanjatham S, Suwannakan B, Rithapirom S, Yodtup C, et al. Multicenter validation of fully automated capillary electrophoresis method for diagnosis of thalassemias and hemoglobinopathies in Thailand. Southeast Asian J Trop Med Public Health. 2011; 42(5):1224-32.
10. Kohne E. Hemoglobinopathies: Clinical Manifestations, Diagnosis, and Treatment. Dtsch Arztebl Int. 2011 Aug; 108(31-32): 532–540.
11. Newborn Screening Reference Center, NBS Statistics. [Internet]. 2019 [cited 2021 Sept] Available from: https://www.newbornscreening.ph/images/stories/ResourcesPrevalence/prevalence-2019.pdf.