Galactosemia among Positive-screened Patients who Underwent Lactose Challenge: A Review of Records of the Newborn Screening Program

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ABSTRACT

Background. Newborns screened positive for Galactosemia through Expanded Newborn Screening (ENBS) with borderline levels undergo lactose challenge that requires interruption of breastfeeding temporarily then shifting to soy-based formula.

Objective. To determine the percentage of Classical Galactosemia (CGal), Non-classical Galactosemia (NCGal), probable mild variant form, and negative Galactosemia among newborns screened positive for Galactosemia who underwent lactose challenge.

Methods. This is a retrospective study. NBS records were reviewed and data were collected from January 2015 to December 2020.

Results. Out of the 117 newborns screened positive for Galactosemia, 58 underwent lactose challenge. Majority were male, term with a birth weight of 2500-4000g and received a final disposition in 4-6 months. Fifteen patients underwent 1-week lactose challenge wherein six reached a resolution on first challenge. Majority, 35 (60.3%) were negative for Galactosemia, six (10.3%) probable mild variant Galactosemia, three (5.2%) NCGal, and no CGal were observed. Fourteen suspected cases (24.1%) are pending final disposition.

Conclusion. This study describes the demographics of newborns flagged for Galactosemia who underwent lactose challenge. A 1-week lactose challenge may be recommended to further detect patients who are negative for Galactosemia.

Keywords: galactosemia, ENBS, lactose challenge

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INTRODUCTION

Newborn screening (NBS) programs are established with the goal to reduce associated morbidity and mortality by early identification of heritable inborn errors of metabolism coupled with timely treatment and management.[1] The NBS represented the first population-based genetic testing and screening program in the public health system.[2] In the Philippines, it was introduced in June 1996 and was enacted through Republic Act 9288 (Newborn Screening Act of 2004). By 2014, Expanded Newborn Screening (ENBS) was implemented with the inclusion of more than 20 disorders detectable by tandem mass spectrometry to the basic NBS panel of disorders whose list include congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), phenylketonuria (PKU), glucose-6-phosphate dehydrogenase (G6PD) deficiency, Galactosemia (GAL), and maple syrup

urine disease (MSUD).[3,4] Unlike most newborn screening tests that quantify small molecules, NBS for Galactosemia is based on an assay quantifying the activity of galactose-1P uridyltransferase (GALT) enzyme and the total galactose (galactose + galactose-1P) or TGAL. TGAL can be elevated in those who have the condition especially if they have consumed lactose containing milk.[5] If flagged positive for Galactosemia, they may be shifted from a lactose-containing milk to a soy-based milk or elemental formula until follow-up testing can be completed.

GAL is an inborn error of carbohydrate metabolism characterized by the inability to convert galactose to glucose which was first described in 1980 by von Reuss while Leloir's discovery of the pathway of galactose catabolism in the 1940s and 1950s enabled other scientists to link the disease to a specific enzymatic step in the pathway (Figure 1).[6-8]

In the Leloir pathway, there are three galactose-metabolizing enzymes namely galactokinase (GALK), galactose-1-phoshate uridyltransferase (GALT), and uridine diphosphate (UDP)-galactose 4-epimerase (GALE). When any of these enzymes is deficient or absent, it leads to accumulation of galactose, thereby diagnosed with the condition, Galactosemia. Three inborn errors of galactose metabolism are known: CGal (type I) resulting from complete or partial deficiency of the GALT enzyme. Clinical manifestations include feeding problems, failure to thrive, hepatocellular damage, bleeding, and sepsis in untreated infants, while cataracts are seen in 10% of cases. GALE (type II) deficiency can present with a very rare profound deficiency resembling classical Galactosemia. The more common partial deficiency is benign. GALK (type III) deficiency presents primarily as cataracts in untreated patients.[7-9]

A nomenclature of the genetic hypergalactosemia was classified as follows: 1.) Galactokinase deficiency secondary to pathogenic variants in GALK, 2.) Epimerase deficiency Galactosemia secondary to pathogenic variants in GALE. These two deficiencies were regarded in the Philippines as NCGal, and 3.) Galactose-1-phosphate uridyltransferase deficiency secondary to pathogenic variants in GALT sub-classified as: 3a.) Classic Galactosemia (CGal) with severe GALT enzyme deficiency having absent or barely detectable activity in erythrocytes and liver, 3b.) Clinical variant Galactosemia with 1%-10% residual GALT enzyme activity in erythrocytes and/or liver, and 3c.) Biochemical variant Galactosemia with 15%-33% residual GALT enzyme activity in erythrocytes which includes the Duarte biochemical variant.[10] Total blood galactose assessment is suitable for mass screening, but it carries high false-positive and false-negative results.[11] In the Philippines, TGAL and the GALT activity are tested in DBS. It is considered CGal if the results have no GALT activity detected and with highly elevated TGAL. For NCGal, there is positive GALT activity but with elevated TGAL since the enzymes that can be possibly deficient are GALE and GALK. Lastly, for probable mild variant form, these are newborns who have no GALT activity detected on assay but with normal levels of TGAL. They can be the biochemical variant Galactosemia that includes the Duarte variant wherein there is still residual GALT enzyme activity but cannot be detected on DBS. Negative Galactosemia is defined as newborns screened positive for Galactosemia on initial ENBS but turned out to have normal TGAL and with GALT activity after the lactose challenge (Table 1). For those infants diagnosed with GAL, the recommended intervention is continued and

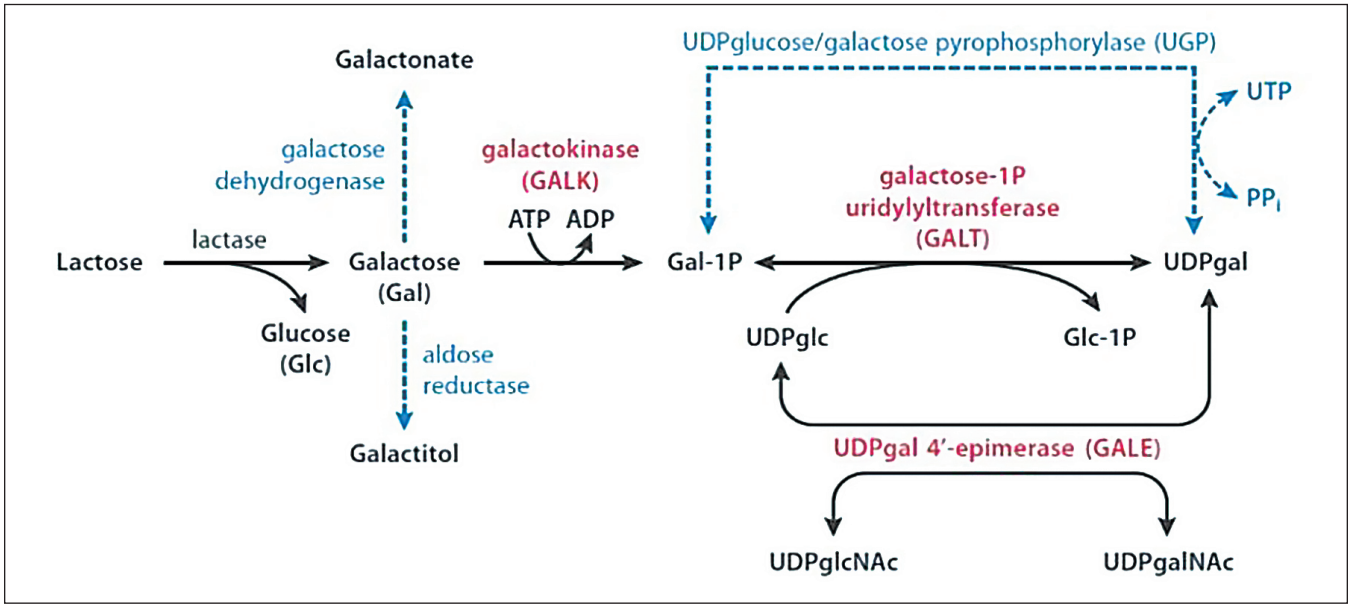

Figure 1. Major reactions of galactose metabolism. The three enzymes of the Leloir Pathway (GALK, GALT, and GALE) are presented in red font.

Table 1. Different types of Galactosemia with their corresponding GALT enzyme activity and metabolite interpretation

Types	GALT enzyme activity	TGAL metabolites (NV: <1.5 for <28 days & <0.5 for >28 days)
Negative	+	Normal
CGal	-	Elevated
NCGal	+	Elevated
Variant form	-	Normal

lifelong dietary restriction of galactose. However, for those who receive a normal follow-up testing result, the galactose restriction is lifted.[5,10,12]

When results are inconclusive wherein the elevated level of TGAL are borderline defined as values that are exact or near the border of the cut off values, the Metabolic team recommends lactose challenge wherein suspected cases are temporarily shifted to a lactose-containing milk for a period (5 days, 1 week, 2 weeks or 1 month) and repeat determination is done. After the lactose challenge, suspected cases are placed back again on lactose-free or soy-based formula while awaiting the results. The next steps could be to repeat the challenge or provide a final disposition. A final disposition can be given whether the screened positive GAL newborns are CGAL, NCGAL, probable mild variant form, or negative Galactosemia (Figure 2).

Those undergoing lactose challenge require interruption of breastfeeding temporarily which can affect the mother-baby bonding. Parents may also be anxious while awaiting the final diagnosis of their infants. No studies have been made regarding the profile of newborns who underwent a lactose challenge nor the optimal length of time to do one. This seeks to determine the profile and outcome among those who initially screened positive for GAL that underwent lactose challenge. The findings of the study will provide guidance in improving our procedures in the initial management plans for patients who screened positive for Galactosemia.

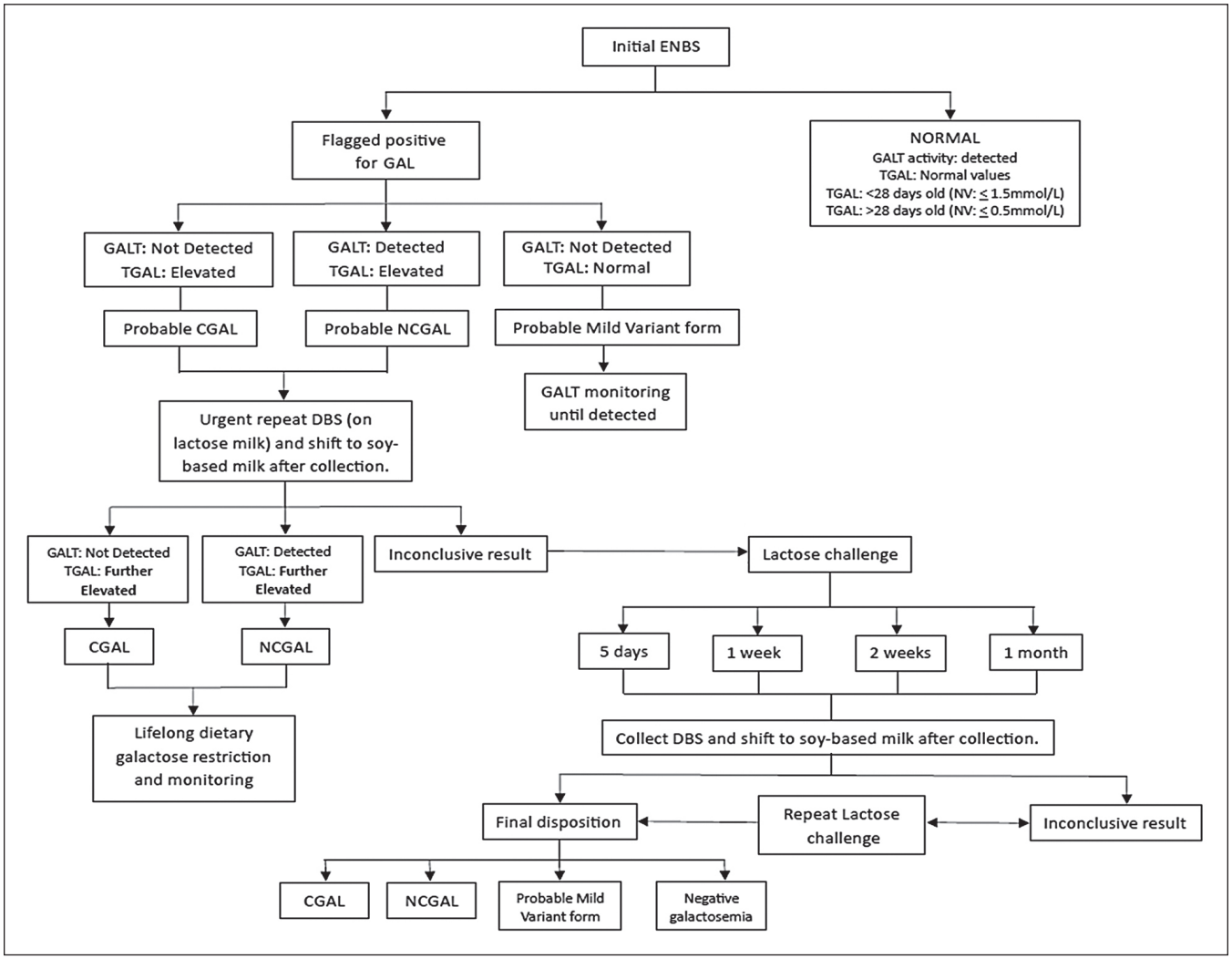

Figure 2. Process of screened positive newborns for Galactosemia.

MATERIALS AND METHODS

This is a retrospective study which involved collection of information of newborns screened positive for Galactosemia who underwent lactose challenge from January 2015 to December 2020. They were automatically referred and followed up by Genetics service of Philippine General Hospital (PGH). These Newborn Screening Centers (NSCs) are the NSC Northern Luzon (NSC-NL), NSC Central Luzon (NSC-CL), NSC- Southern Luzon (NSC-SL), and NSC National Institutes of Health (NSC-NIH).

Due to low incidence of Galactosemia, total enumeration was applied and all Galactosemia-screened newborns who underwent lactose challenge referred to the Metabolic team of PGH-Genetics were included in the study and in the data analysis. The following data were collected: socio-demographic information, results of the NBS, date of collection, age at referral, age at final disposition, status on recall, and the outcome. Statistical analyses in this study were conducted using Statistical Package for Social Sciences (SPSS) version 28. Descriptive statistics using frequency, percentages, measures of central tendency, and variability were employed. This study was approved by the UP-Manila Research Ethics Board [UPMREB code 2021-154-01].

RESULTS

Data from a total of 117 newborns who screened positive for Galactosemia and referred to the Genetics service from January 2015-December 2020 were submitted by the various NSCs of Luzon. Out of the 117 patients, 58 of them underwent lactose challenge and the demographic profile of these patients are listed in Table 2.

There were no reported CGal and only three (5.2%) were NCGal, six (10.3%) with probable mild variant form of Galactosemia and majority, 35 (60.3%) were Negative Galactosemia while 14 (24.1%) still has pending outcomes.

As shown in Table 3, patients with a birthweight of <2000 gm, 20% (7/35) were Negative Galactosemia. For patients with birthweight of 2000-2499 gm, one (33.3%) was NCGal and three (38.6%) were Negative Galactosemia. Among patients with birthweight of 2500-4000 gm, 25 (71.4%) were Negative Galactosemia, six (100%) were probable mild variant Galactosemia and two (66.7%) were NCGal. On the other hand, for preterm patients who underwent lactose challenge, four (11.4%) were Negative for Galactosemia; for term, there are three (100%) who were NCGal, six (100%) probable mild variant Galactosemia and 29 (82.9%) who were Negative Galactosemia. For post term patients, two (2%) were Negative for Galactosemia.

Out of the 58 patients who had lactose challenge, 27 of them had more than one lactose challenge to reach a disposition. Their demographic profile as shown in Table 4 are as follows: Thirteen (48.1%) were males and 14 (51.9%) were females. Four (14.8%) had birthweight of <2000 gm, three (11.1%) weighed 2000-2499 gm, and 20 (74.1%) weighed 2500-4000 gm. There were two (7.4%) preterm and post term, respectively while 23 (85.2%) were term. Only five (18.5%) were sick and 22 (81.5%) were well on recall.

For the years 2015-2016 shown in Table 5, there are two (66.7%) NCGal, one (16.7%) Probable Mild Variant Galactosemia, and five (14.3%) Negative Galactosemia. For 2017-2018, one (33.3%) was NCGal, one (16.7%) Probable Mild Variant Galactosemia and 13 (37.1%) Negative Galactosemia. For 2019-2020, there are four (66.7%)

Table 2. Demographic and Clinical Profile of Patients Screened positive for Galactosemia who underwent lactose challenge (N=58)

Demographics and Clinical Profile	Frequency (N)	Percentage (%)
Gender		
Male	32	55.2
Female	26	44.8
Birthweight		
<2000 gm	7	12.1
2000-2499 gm	5	8.6
2500-4000 gm	46	79.3
Maturity		
Preterm	4	6.9
Term	52	89.7
Post Term	2	3.4
Age when Initial ENBS was done		
Immediately after 24th hour	11	19.0
48th-72nd hour	26	44.8
>3 days – 7 days	10	17.2
8-30 days	8	13.8
>31 days	3	5.2
Age at Initial Referral		
within 7 Days	6	10.3
8-14 Days	20	34.5
15-30 Days	9	15.5
31-60 Days	14	24.1
>61 Days	9	15.5
Age at Final Disposition		
Within 1 Month (30 Days)	8	13.8
Within 2-3 Months (31-60 Days)	20	34.5
Within 4-6 Months (61-180 Days)	26	44.8
Within 7-10 Months (181-330 Days)	3	5.2
More than 11 Months (> 330 Days)	1	1.7
Status on Recall		
Well	50	86.2
Sick	8	13.8
Deceased	0	0.0
Outcome		
Classical Galactosemia	0	0.0
Non-classical Galactosemia	3	5.2
Probable Mild Variant Galactosemia	6	10.3
Negative Galactosemia	35	60.3
Suspected cases with no final disposition yet	14	24.1

Table 3. Outcomes of Screened Positive Patients for Galactosemia who Underwent Lactose Challenge according to Birthweight and Maturity

Demographics	Outcome			
	Classical Galactosemia, N (%)	Non-classical Galactosemia, N (%)	Probable Mild Variant Galactosemia, N (%)	Negative Galactosemia, N (%)
Birthweight				
<2000 gm	0 (0.0)	0 (0.0)	0 (0.0)	7 (20.0)
2000-2499 gm	0 (0.0)	1 (33.3)	0 (0.0)	3 (38.6)
2500-4000 gm	0 (0.0)	2 (66.7)	6 (100)	25 (71.4)
Total	0	3	6	35
Maturity				
Preterm	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.4)
Term	0 (0.0)	3 (100)	6 (100)	29 (82.9)
Post Term	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)
Total	0	3	6	35

**14 patients still with no final disposition*

Probable Mild Variant Galactosemia and 17 (35%) Negative Galactosemia.

Based on Table 6, there are a total of 17 patients who reached a disposition after the first lactose challenge. Of the 58 patients, 17 (29.3%) underwent one trial of lactose challenge, 15 (25.8%) underwent two challenges, 10 (17.2%) underwent three while two (3.5%) underwent four rounds of lactose challenge. Fourteen remain to have no outcomes at the time of the study.

Table 4. Demographic and Clinical Profile of Patients Screened Positive for Galactosemia who Underwent Repeated Lactose Challenge. (N=27)

Demographics and Clinical Profile	Frequency (N)	Percentage (%)
Gender		
Male	13	48.1
Female	14	51.9
Birthweight		
<2000 gm	4	14.8
2000-2499 gm	3	11.1
2500-4000 gm	20	74.1
Maturity		
Preterm	2	7.4
Term	23	85.2
Post Term	2	7.4
Status on Recall		
Well	22	81.5
Sick	5	18.5
Deceased	0	0

On the 1st lactose challenge, six patients underwent 1 week and 2-weeks lactose challenge and majority were Negative Galactosemia. Only one (3.8%) patient underwent 1-month lactose challenge and had a Negative Galactosemia.

A total of 15 patients underwent a second repeat lactose challenge and among these, one (5.6%) patient underwent 5 days lactose challenge with Negative Galactosemia outcome. Seven patients underwent a 1-week lactose challenge wherein four (22.2%) were Negative Galactosemia, one (5.6%) Probable Mild Variant Galactosemia and two (11.1%) were Non-classical Galactosemia. Five (27.8%) patients underwent 2-weeks lactose challenge with Negative Galactosemia outcome and two patients underwent 1-month lactose challenge with one (5.6%) Probable Mild Variant Galactosemia and one (5.6%) Negative Galactosemia.

A total of 10 patients underwent a third repeat of lactose challenge and among these, two (20%) had 1-week lactose challenge with Negative Galactosemia outcome. Five patients underwent 2 weeks lactose challenge, of which four (40%) were Negative Galactosemia and one (10%) with outcome of Probable Mild Variant Galactosemia. Three (30%) underwent

Table 5. Outcomes of Screened Positive Patients for Galactosemia who Underwent Lactose Challenge from January 2015 to December 2020

Coverage	Outcome			
	Classical Galactosemia, N (%)	Non-classical Galactosemia, N (%)	Probable Mild Variant Galactosemia, N (%)	Negative Galactosemia, N (%)
2015-2016	0 (0.0)	2 (66.7)	1 (16.7)	5 (14.3)
2017-2018	0 (0.0)	1 (33.3)	1 (16.7)	13 (37.1)
2019-2020	0 (0.0)	0 (0.0)	4 (66.7)	17 (35)
Total	0	3	6	35

**14 patients still with no final disposition*

1 month lactose challenge and with Negative Galactosemia outcome. Lastly, two patients still had fourth lactose challenge and one (25%) was diagnosed as NCGal and one (25%) was diagnosed as Negative Galactosemia. Table 6 also shows that 15 patients with outcomes underwent a 1-week lactose challenge of which six of them already had an outcome on the first lactose challenge; seven had outcomes on the second repeat of lactose challenge and two had outcomes on the third lactose challenge. Sixteen patients with outcomes underwent 2 weeks lactose challenge of which, six had outcomes on the first lactose challenge while five patients had outcomes on the second and third repeat of lactose challenge.

DISCUSSION

The initial ENBS in this study were collected mostly on the 48th to 72nd hour of life and 11 out of the 58 had initial ENBS after the 24th hour of life which is the ideal time for ENBS collection. This shows that there is improved collection and submission of NBS cards however there is still that 5.2 % with delayed implementation and collection. It must be noted that the initial recommended date of collection of NBS samples was at the 49th–72nd hour, but this was changed in 2018 when the new recommendation was to collect DBS immediately after the 24th hour of life. Most of them (20 - 34.5%) were referred to the metabolic team of PGH-Genetics on the 8th to 14th day of life after a second repeat DBS. The NBS program has continuously made recommendations and improvements to address these concerns on collection, monitoring, and transmittal of result. Like most NBS programs, there can be different responses to finding a result outside the reference range.[5]

Out of the 58 newborns who underwent lactose challenge, 35 were negative for Galactosemia, while six were probable mild variant form that needs galactose level monitoring based on set protocol and only three were assessed as NCGal. For variant Galactosemia, some patients have been found to have residual GALT activity and the most common variant form of Galactosemia is Duarte Galactosemia (DG).[5] It is often the cause of hypergalactosemia and is frequently flagged as positive in NBS. A study done by Capistrano-Estrada and Silao (2017) on patients presumed to have variant forms of

Table 6. Outcomes of 3 Days, 5 Days, 1 Week, 2 Weeks, and 1 Month Lactose Challenge

Lactose Challenge	Outcome				
	Classical Galactosemia, N (%)	Non-classical Galactosemia, N (%)	Probable Mild Variant Galactosemia, N (%)	Negative Galactosemia, N (%)	
1st					1st
3 days	-	-	-	-	-
5 days	-	-	1 (3.8)	3 (11.5)	4
1 week	-	-	0 (0.0)	6 (23.1)	6
2 week	-	-	2 (7.7)	4 (15.4)	6
1 month	-	-	0 (0.0)	1 (3.8)	1
					Total: 17
2nd					2nd
3 days	-	-	-	-	-
5 days	-	0 (0.0)	0 (0.0)	1 (5.6)	1
1 week	-	2 (11.1)	1 (5.6)	4 (22.2)	7
2 week	-	0 (0.0)	0 (0.0)	5 (27.8)	5
1 month	-	0 (0.0)	1 (5.6)	1 (5.6)	2
					Total: 15
3rd					3rd
3 days	-	-	-	-	-
5 days	-	-	-	-	-
1 week	-	-	0 (0.0)	2 (20.0)	2
2 week	-	-	1 (10.0)	4 (40.0)	5
1 month	-	-	0 (0.0)	3 (30.0)	3
					Total: 10
4th					4th
3 days	-	-	-	-	0
5 days	-	-	-	-	0
1 week	-	-	-	-	0
2 week	-	0 (0.0)	-	0 (0.0)	0
1 month	-	1 (25.0)	-	1 (25.0)	2
					Total: 2
Total		3	6	35	

Galactosemia who have normal blood galactose metabolite despite the absence of GALT enzyme activity showed that none of them were Duarte variants.[12] Also of note in our results is the high percentage (60.3%) of cases that were screened positive for Galactosemia but turned out to be negative. In general, concerns are raised on this high false positive cases for Galactosemia, defined as the number of infants screened positive that needs follow-up testing but ultimately are determined not to have Galactosemia or with DG.[10] The magnitude of false positive results generated in NBS programs presents a great challenge in future improvement and attention must be given to improve laboratory tests, use of more specific markers, and better risk communication for families of patients with positive test results.[13] Likewise, for screened Galactosemia newborns, the urgent reporting of an increased TGAL concentration, with or without GALT deficiency, sets off a chain of events like immediate notification of their physicians, and/or metabolic specialists; bringing the newborn in for observation; confirmatory testing; and possible diet change. These events, in false positive screens are often nonproductive, wasteful of medical resources and traumatic for families.[14] There are 14 cases still for final disposition awaiting the galactose monitoring results after lactose challenge and still for relaying of results to the metabolic team. For these cases, some of the difficulties or challenges that may arise are the follow up of the family or that they can be lost to follow up and problems in procuring the soy-based formula then shifting back again to a lactose-containing milk. The clinical profile of the 27 patients who had repeated lactose challenge is shown in Table 4 and no definitive conclusions can be drawn with regard to the profile's contribution to the probability of undergoing a prolonged lactose challenge. These cases may have to be studied closely individually.

Majority of the newborns who are term and with normal birthweight of 2,500-4,000 gm were negative for Galactosemia. It was also noted that there were no preterm and newborns with low birthweight of <2000 gm diagnosed to have true Galactosemia. According to Berry, there are several etiologies of elevated galactose level or secondary hypergalactosemia involving liver dysfunction. The liver is the primary organ responsible for galactose metabolism and elevated plasma galactose can be seen in liver dysfunction even in the presence of normal erythrocyte GALT enzyme activity.[13] In the neonatal period, most especially preterm and newborns with low birthweight, transient liver dysfunction is common, and they may present with jaundice which can be secondary to immature liver function. It occurs in 45-60% of term newborns while for preterm, it occurs in 80%.[15] Transient liver dysfunction causing secondary hypergalactosemia in newborns can be a reason for patients who are screened positive for Galactosemia and on further monitoring with lactose challenge, turned out to be negative. However, this warrants a larger scale study to be conducted on preterm and low birthweight newborns screened positive for Galactosemia. In this 5-year study, the number of patients screened positive for Galactosemia increased from the succeeding years as shown in Table 5 and this may also be attributed to the inclusion of ENBS in the Philippines as a national insurance benefit in 2019 which resulted to an increased newborn population coverage.[4]

Newborns recommended to have lactose challenge will be subjected to interruption of breastfeeding and it may add to financial constraint of the family since the prices of soy-based formula in the Philippines is a bit steep as well as the cost of filter card monitoring. It also depends on whether these newborns will be subjected to repeated lactose challenge or whether there will be an outcome already after just one trial of lactose challenge. In Table 6, a total of 17 patients had an outcome or diagnosis after one lactose challenge, 27 had repeat lactose challenge while the other 14 had no result of the lactose challenge and still with inconclusive diagnosis. Based on the results, both 1-week and 2-weeks lactose challenge with total of six patients each group had outcomes already on the first lactose challenge. For those who underwent a second lactose challenge, most of the patients (7) had outcomes on a 1-week lactose challenge while on the 2-weeks lactose challenge, there were five patients who had outcomes. These results suggest that a 1-week lactose challenge per repeat may be sufficient in reaching an outcome.

The semiquantitative GALT analysis using fluorometric Beutler enzyme spot test is done in our NBS program for Galactosemia screening. It is an effective screening test since it can provide an immediate detection of CGal but also has disadvantages. Exogenous factors like heat and humidity affecting enzymatic measurements in DBS or a relatively low residual GALT enzyme activity due to the Duarte variant can be reasons for the high rate of false positive cases.[16,17] Although there are cut off values for the GALT and TGAL, the result may also be dependent on visual evaluation.[17] With this, some may be overly cautious that results can be reported as borderline values with the thought that there will be a second repeat card to be done to verify the result.

The quantitative GALT assay using Liquid Chromatography-Tandem mass spectrometry (LC-MS/MS) has been developed that can accurately and reliably measure the GALT activity and TGAL providing more conclusive results.[18,19] For some follow up testing programs in the United States and other countries, GALT genotyping is included as part of their diagnostic panel for Galactosemia to increase screening specificity and contributes to low false positive results. The diagnosis of CGal is confirmed by the demonstration of GALT enzyme deficiency and identification of pathogenic variants in the GALT gene.[18] Likewise, for those with elevated TGAL but with normal GALT activity, GALK and GALE enzyme activity can also be determined by the recently developed LC-MS/MS.[17-19] NCGal can be identified using this method which entails a significant improvement for diagnostic testing. In a developing country like the Philippines, this guideline may be possibly adopted but taking

into consideration the limited resources, we still perform galactose monitoring and lactose challenge for these patients.

CONCLUSION

NBS is helpful in the early detection of patients with possible inborn error of metabolism, but some results may be inconclusive during the screening. For Galactosemia, patients may be asked to undergo a lactose challenge and repeat DBS determinations. This study showed that the clinical profile may not be helpful in predicting which patients will undergo a lactose challenge but a 1-week lactose challenge may be the optimal time to reach a disposition for patients. To further lessen the challenges encountered by NBS and the family, quantitative enzyme assay and genotyping may be included in Galactosemia testing.

Recommendations

The study involved newborns screened positive for Galactosemia who underwent lactose challenge and no other studies to date has studied on this population. We therefore recommend conducting a prospective study and this can serve as a reference. The real challenge lies on the problems encountered by the NBS and the family due to several trials of monitoring and high percentage of false positive cases hence research on the psychosocial aspect can also be done. Instead of the semiquantitative analysis done in our NBS, we recommend adopting a quantitative testing and assay of both GALE and GALK enzyme for better detection of true positive cases. For those with inconclusive biochemical testing result, molecular testing can also be considered in the future.

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