Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency in Pangasinan utilizing Newborn Screening: A Multicenter Study

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Background:

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is the most common known human enzymopathy, inherited as an X-linked recessive disorder that primarily affects males. Most people with G6PD deficiency are asymptomatic, while others manifest with neonatal jaundice and hemolytic anemia which are usually triggered by an exogenous agent.

Objective:

To determine the prevalence and geographic distribution of glucose-6-phosphatase deficiency in Pangasinan through newborn screening.

Methods:

This is a retrospective descriptive study of the G6PD deficiency cases in Pangasinan. Records of newborn screening results of twelve key hospitals in March 2008 were included. The demographic data such as the town address, sex, date of birth and date of sample collection was noted. The outcome variables include the number of G6PD deficiency cases in Pangasinan, the number of male and female cases and the G6PD enzyme levels. Descriptive statistics was used and mean values were compared using the Student's t-test and statistical package SPSS 13.0 for Windows.

Results:

A total of 4,823 newborn screening results were reviewed and 300 cases were positive for G6PD deficiency. However, only 246 cases were deemed evaluable. Fifty-four cases were excluded because of incomplete data. The prevalence rate of G6PD deficiency in Pangasinan is 6.2%. comparable to the prevalence rate of the disease in the Philippines. Central Pangasinan has the majority of cases with 74% cases. The prevalence among male infants is 3.59%, similar to the incidence among male Filipinos which is 3.9%. The male: female ratio of the disease in Pangasinan is 2.4:1.

Conclusion:

Pangasinan has a prevalence rate of G6PD deficiency that is comparable within the Philippines and the worldwide prevalence of the disease. G6PD screening is recommended in the newborn period to diagnose the disease and if positive, screening of all members of the family should be done.

Key words: G6PD deficiency, newborn screening

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Introduction

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is the most common known human enzymopathy. Inherited as an X-linked recessive disorder that primarily affects men, G-6-PD deficiency affects approximately 400 million people worldwide. [1] It is also fully expressed in homozygous females and variably expressed in heterozygous males. Most people with G6PD deficiency are asymptomatic while others manifest with neonatal jaundice and hemolytic anemia which are usually triggered by an exogenous agent.

G6PD deficiency has been shown to confer protection against severe, life-threatening malaria . [2] Other studies have been done to show that G6PD also affects other diseases. One such study by Chao YC et al.[3] demonstrates higher infection of monocytes in G6PD patients with the dengue virus, which may be important in increasing epidemiological transmission and perhaps with the potential to develop more severe cases pathogenetically. A study by Iranpour R et al [4] studied the prevalence of G6PD deficiency in relation to neonatal jaundice. Although only a small percentage of the subjects in the study had G6PD deficiency, all deficient neonates have no evidence of other factors known to cause hyperbilirubinemia. Early detection of the deficiency was recommended to reduce the risk of severe hyperbilirubinemia and exchange transfusion. A study by Bernaudin, et al [5] showed that G6PD deficiency, absence of alpha-thalassemia and hemolytic rate at baseline are significant independent risk factors for abnormally high cerebral vasculopathy in patients with sickle cell anemia.

G6PD deficiency is most common in Africa, Southeast Asia, Middle East and some areas of the Mediterranean, with prevalence rates ranging from 5%-25%.[6] G6PD deficiency is thought to occur in approximately 50% of Kurdish males, 30% of Sardinia males, and 13% of Saudi males. It occurs in less than 1% of North Americans, but in 11-14% of African-American males.[7] In the Philippines, earlier studies on G6PD deficiency have shown prevalence rates of 4.5% to 25.7% [8], mirroring the worldwide prevalence rate. In fact, Segel cited the Filipinos as one of the ethnic groups with a significant incidence of the disease and should be tested for the defect.[9] A local study by Dubongco[10] showed the incidence of G6PD deficiency at St. Luke's Medical Center as 2.09%. Another local study by Padilla, Silao, Taku, Kaoru,and Masafumi (2003)[8] reveals an incidence of the disease among male Filipinos at 3.9%. The World Health Organization recommends screening all newborns in populations with a prevalence of 3 to 5 percent or more in males.[11]

Greece is one of the Mediterranean countries cited with a high prevalence rate of G6PD deficiency. Northern Greece has a much higher prevalence rate compared with the general Greek population.[12] Another study by Joško[13] showed a higher prevalence of G6PD deficiency in Komiza, a town in Dalmatia which is south of Croatia than the

general population of the region.

The Philippines, being one of the Southeast Asian countries with a high prevalence rate of G6PD deficiency, is a fertile ground for studies related to G6PD. One such area of study is to determine if there is a geographical distribution of G6PD within the country, similar to the ones conducted in Greece and Croatia. Free newborn screening are available in certain rural health units in the Philippines. [15] However, no study has been made to document the prevalence rate of G6PD in Pangasinan. The Newborn Screening Center in the National Institutes of Health, Manila definitely has all the data from all over the country but a particular study aimed specifically at documenting and comparing the prevalence rates of G6PD deficiency in the different regions has not been made.

Objectives:

General Objective:

To document the prevalence rate of G6PD deficiency by newborn screening in Pangasinan

Specific Objectives:

1. To determine the number of G6PD deficiency cases in Pangasinan by newborn screening.
2. To determine the prevalence of G6PD Deficiency on the basis of:

A. geographical distribution in Pangasinan

B. gender distribution and ratio

3. To compare the G6PD enzyme levels based on gender.

Significance of the Study

The five heritable conditions included in the Newborn Screening Program are G6PD Deficiency, Congenital Hypothyroidism, Phenylketonuria, Galactosemia and Congenital Adrenal Hyperplasia. The importance of detecting these five disorders was recognized when their prevalence in the Philippines were established. Eventually, a law was passed to implement the newborn screening system. Republic Act No. 9288 or The Newborn Screening Act of 2004 [14] was enacted to institutionalize a national newborn screening system that is comprehensive, integrative and sustainable, with the objective of ensuring that every newborn has access to newborn screening for certain heritable conditions that can result in mental retardation, serious health complications or death if left undetected and untreated. G6PD deficiency is the most common human enzyme deficiency in the world. Knowledge of its prevalence in the province can help attain local awareness, align and allocate health resources for its prevention and treatment.

Glossary

Glucose-6-phosphate dehydrogenase(G6PD) - a cytosolic enzyme in the pentose phosphate pathway , a metabolic pathway that supplies reducing energy to cells (such as erythrocytes) by maintaining the level of the co-enzyme nicotinamide adenine dinucleotide phosphate (NADPH)

Glucose-6-phosphate dehydrogenase deficiency (G6PD Deficiency)- an X-linked recessive hereditary disease characterized by abnormally low levels of glucose-6-phosphate dehydrogenase (abbreviated G6PD or G6PDH), especially important in red blood cell metabolism. Individuals with the disease may exhibit nonimmune hemolytic anemia in response to a number of causes, most commonly infection or exposure to certain medications or chemicals.

Materials and Methods

This is a retrospective descriptive study of the G6PD deficiency cases in Pangasinan. Twelve key hospitals in Pangasinan were included in the study. Only the results of samples collected from September 2004 to March 2008 were included. The newborn screening results were manually tallied and the G6PD deficiency positive cases were entered into the study. G6PD enzyme levels were noted as well as demographic data such as the town address, sex, date of birth and date of sample collection. The outcome variables include the number of G6PD deficiency cases in Pangasinan, the number of male and female cases and the G6PD enzyme levels.

Descriptive statistics was used. Mean values were compared using the Student's t-test with data analysis using the statistical package SPSS 13.0 for Windows.

Limitations of The Study

The study results were limited to the data gathered from the twelve hospitals which were chosen because of the availability of the newborn screening test as part of their services. Moreover, majority of the hospitals were taken from Dagupan City where newborn screening is commonly available. Another limitation of the study was the number of inclusive years from which the results were taken, which was of 5 years. An initial review of the results was done and it was noted that starting September 2004, the G6PD enzyme levels were included in the results. Prior to that, only the words "NORMAL" and "DEFICIENT" appear on the results.

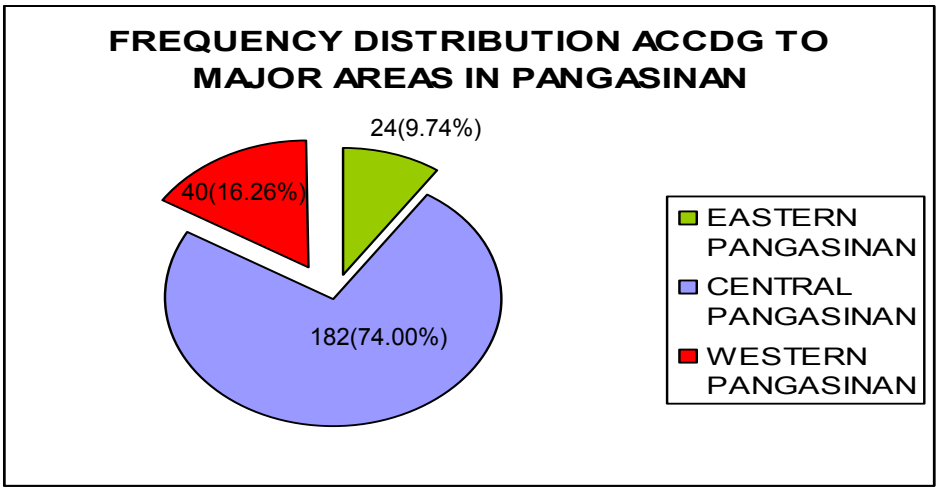
Results

A total of 4,823 newborn screening test results were reviewed. There were only 246 cases deemed evaluable out of 300 due to incomplete data entry for fifty-four cases. The prevalence rate of G6PD deficiency in Pangasinan computed was 6.2%.This is within the range of the national prevalence rate of the disease.

Figure 1 shows that Central Pangasinan has the majority of cases as compared to Western and Eastern Pangasinan with 74% cases coming from this area of the province.

Figure 1. Distribution of Cases Among the 3 Major Areas in Pangasinan

When subdivided into the province's six districts (Appendix II), the fourth district has the most number of cases (Figure 2).



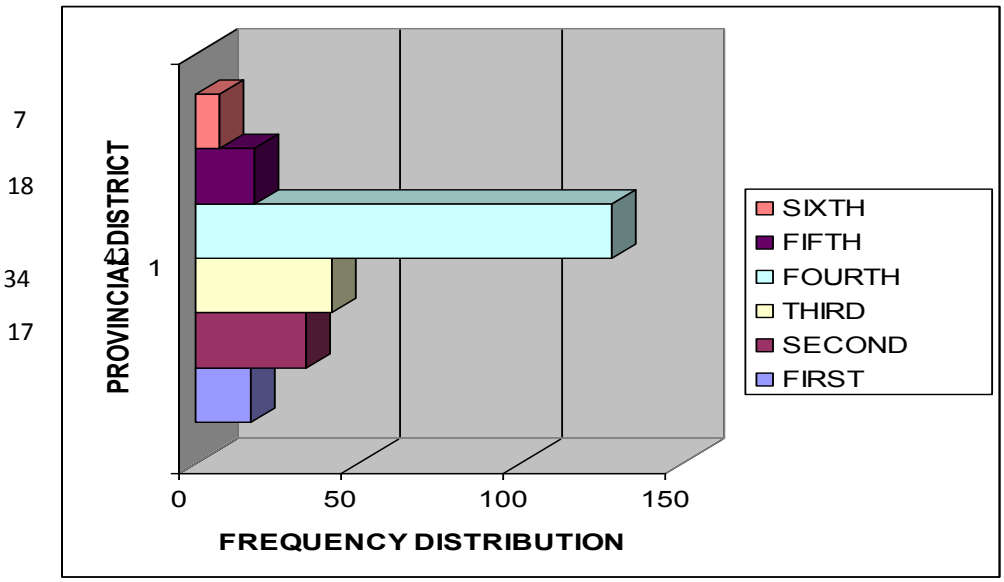


Figure 2: G6PD Deficiency Distribution Among The 6 Provincial Districts

Dagupan City, which is part of both the fourth district and central Pangasinan, has the highest number of G6PD deficient infants representing 25.20 % of the cases which may be due to accessibility of the hospitals and test availability.

The prevalence among male infants is 3.59%, similar to the incidence among male Filipinos which is 3.9%. Male: female ratio of the disease in Pangasinan is 2.4:1 as shown in the figure below.

Table1. Distribution of cases with G6PD based on gender

Gender	No. of Cases	Percentage
Male	173	70.3
Female	73	29.70

The mean G6PD deficient enzyme levels by newborn screening in the male and female infants were found to be 1.0254±0.30716 units/gram Hb & 1.2247±0.32136 units/gram Hb respectively.

Table 2. Mean Enzyme Levels of G6PD According to Sex

SEX	Number of G6PD deficient infants	G6PD Enzyme Level	
		Mean	Standard
Male	173	1.0254	0.30716
Female	73	1.2247	0.32136

Discussion

The distribution of G6PD deficiency varies significantly among different geographic regions and different population groups. The prevalence of the disease is high in Asia.[6] The Philippines is one of the countries in Southeast Asia that has a high prevalence of the disease.

The Philippines has been reported to have a prevalence rate of G6PD Deficiency of 4.5% to 25.7%[8], reflective of the worldwide prevalence rate. The wide range indicates that the different regions of the country may have significant differences in prevalence rate. The differences could be due to the endemicity of malaria in certain regions of the country and to the members of the population of Mediterranean descent. It is known that Africa and the Mediterranean basin are high-risk areas for the infectious disease malaria. Studies have shown evidence that the parasite that causes this disease does not survive well in G6PD-deficient cells. So the deficiency may have developed as a protection against malaria.

Pangasinan has a prevalence rate near the lower limit of the range of the country's reported values. This suggests on the basis of epidemiologic relations that that malaria is not prevalent in the province and the nil chance of any Mediterranean genetic racial relationship of the people. The different towns and cities in Central Pangasinan are urbanized and have greater accessibility to hospitals with newborn screening services. This does not preclude the people of probably being more aware of new ways to safeguard their health thus the availment. Clustering of the cases in Central Pangasinan may be due accessibility, availability, and greater knowledge on screening services.

The study also shows a higher geographical prevalence of G6PD deficiency in Dagupan City which is the province's chief commercial area. This result confirms that the people in the city avail of the newborn screening test but it may not necessarily reflect an accurate geographical prevalence because a significant number of infants from other towns of the province were not screened for G6PD deficiency.

G6PD deficiency is a recessive sex-linked trait thus males are predominantly affected. Males have only one copy of the G6PD gene, but females have two copies. Recessive genes are masked in the presence of a gene that encodes normal G6PD. Accordingly, females with one copy of the gene for G6PD deficiency are usually normal, while males with one copy have the trait. Being an X-linked disorder, the disease would generally be thought to affect only males. However, some carrier females have been reported to show symptoms due to lyonization which is a random inactivation of an X-chromosome in certain cells creating a population of G6PD deficient erythrocytes coexisting with normal cells.[16] A study by Iranpour et al revealed a 3.2% incidence of the disease in Iranian newborns, with a male: female ratio of 5.5:1. [17] The male:female ratio in Pangasinan is 2.4:1 showing a higher prevalence among Pangasinense female infants in contrast to Iranian female newborns.

The mean enzyme levels of both male and female cases are classified as severe enzyme deficiency levels (<2.92 U/gHb).[18] However, the enzyme levels gathered in this study are from the newborn screening. The results of confirmatory tests are not included in the study, which may differ from the enzyme levels reported here. However, it can be conferred that the severe enzyme deficiency levels by newborn screening increases the possibility of a G6PD deficient patient by confirmatory test. A preliminary study done by Reclos et al. showed a high percentage of partially deficient females that are missed during neonatal screening. [19] The screening test done in the said study used a cut-off of 2.1 units/gm Hb. The newborn screening test of the National Institutes of Health employs a cut off of 8.4 units/g Hb, well above the value recommended by the study which is 6.4 units/g Hb.

Conclusion

Pangasinan has a prevalence rate of G6PD deficiency that is comparable with the worldwide prevalence of the disease. G6PD screening is recommended in the newborn period to diagnose the disease and if positive, screening of all members of the family should be done. Males are more affected than females but the male:female ratio in the province shows that Pangasinense females have a greater tendency to have the disease than females. It is recommended to look into the next prevalence rate studies based on 2009 – 2013 data.

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References

1. Padilla Carmencita, Silao Catherine Lyn, Shirakawa Taku, Nishiyama Kaoru, and Matsuo Masafumi, *Molecular Basis of Glucose-6-phoshate dehydrogenase deficiency Among Filipinos* Pediatrics International April 1999 41(2): 138-141
2. Public Library of Science "G6PD Deficiency is associated with Significant Protection Against Severe, Life-threatening Malaria" Science Daily March 2007 http://www.sciencedaily.com/releases/2007/03/070313114502.htm
3. Chao Yuan-Chang Chao, Huang Ching-Shan, Lee Chun-Nan, Chang Sui-Yan, King Chuan-Chuen, and Kao Chuan-Liang *Higher Infection of Dengue Virus Serotype 2 in Human Monocytes of Patients with G6PD Deficiency* PLoS ONE February 2008 3 (2): e1557
4. Iranpour R, Akbar MR, and Haghshenas I. *Glucose-6-phosphate dehydrogenase Deficiency in Neonates* Indian Journal of Pediatrics November 2007 70(11): 855-857
5. Bernaudin F, Verlhac S, Chevret S, Torres M, Coic L, and Arnand C. *G6PD Deficiency, Absence of Alphathalssemia and Hemolytic Rate at Baseline are Significant Risk Factors for Abnormally High Cerebral Velocities in Patients with Sickle Cell Anemia* Blood September 4, 2008; DOI 10.1182/blood-2008-03-143891
6. Carter, Suzanne "G6PD Deficiency" Aug 2005 http://www.emedicine.com
7. Chicago Center for Jewish Genetic Disorders "Glucose-6-phosphate Deficiency" Jan 2003 http://www.jewishgeneticscdnter.org/what/shepardi/g6pd.asp
8. Padilla Carmencita , Nishiyama Kaoru, Shirakawa Taku, and Matsuo Masafumi *Screening for Glucose-6 -phosphateDehydrogenase Deficiency Using a Modified Formazan Method: A Pilot Study on Filipino Male Newborns* Pediatrics International Feb 2003 45 (1): 10-15
9. Kliegman Robert M, Behrman Richard E, Jenson Hal B, Stanton Bonita MD, Zitelli Basil J, and Davis Holly W. *Nelson Textbook of Pediatrics 18th ed.* Philadelphia: Saunders Elsevier, 2007.
10. Dubongco, M.A.T. *G6PD Deficiency at St. Luke's Medical Center* Philippine Pediatric Researches 2002 -2005 Abstracts p.81
11. Frank, Jennifer. *Diagnosis and Management of G6PD Deficiency* American Family Physician October 2005 72(7)
12. Ntaois, G. Chatzinikolaou C, Tomos C, Manolopoulos C, Karalazou P, Nikolaidou A, and Alexiou-Daniel S. *Prevalence of Glucose-6-phosphate Dehydrogenase Deficiency in Northern Greece* Internal Medicine Journal March 2008 38(3): 204-206
13. Markić J, Krzelj V, Markotic A, Marusic E, Stricevic L, Zanchi J, et al *High Incidence of Glucose-6-phosphate Dehydrogenase Deficiency in Croatian Island Isolate: Example from Vis Island, Croatia* Croatian Medical Journal Aug 2006 47(4): 566-570
14. Beyond Commitment: A Decade of Saving Lives Newborn Screening Reference Center National Institutes of Health Philippines: 2006 p.16
15. Guillermo, Jemin *Newborn Screening for Infants Urged* PIA Press Release July 24, 2007
16. Leong, Aaron *Is there a Need for Neonatal Screening of glucose-6-phosphate Dehydrogenase Deficiency in Canada?* McGill Journal of Medicine January 2007 10(1): 31-34
17. Iranpour Ramon, Hashemipour Mahin, Talaei Seyed-Mojtaba, Soroshnia Mohsen, and Amini Abasgholi *Newborn Screening for Glucose-6-phosphate Dehydrogenase Deficiency in Isfahan, Iran: A Quantitative Assay* Iranian Journal of Pediatrics 2008 15(2): 62-64
18. Ainoon O, Alawiyah A, Yu YH, Cheong SK, Hamidah NH, Boo NY, Zaleha M. *Semiquantitative Screening Test for G6PD Deficiency Detects Severe Deficiency but Misses a Substantial Portion of Partially-deficient Females* Southeast Asian Journal of Tropical Medicine and Public Health 2003 34(2): 405-414
19. Reclos GJ, Hatzidakis KH, Schulpis KH. *Glucose-6-phosphate dehydrogenase deficiency neonatal screening: preliminary evidence that a high percentage of partially deficient female neonates are missed during routine screening.* Journal of Medical Screening 2000 7(1):46-51