CASE REPORT

A Case Report of the First Filipino Infant Diagnosed with Cystic Fibrosis through the Philippine Newborn Screening Program

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ABSTRACT

Cystic Fibrosis (CF) is a rare condition among Asians and has not been reported in the Philippines as of this time. The inclusion of this disease in the Philippines' Expanded Newborn Screening Program (ENBS) has provided this Filipino family the opportunity of early detection and appropriate management of this condition that could ensure the survival of the proband and his other surviving siblings.

Here we present a case of a 24-month-old male who had a positive Expanded Newborn Screening (ENBS) test for cystic fibrosis and eventually underwent further tests to confirm a homozygous deletion of exons 1 - 2 of the CFTR gene. He subsequently had recurrent pneumonia but is being managed by a team consisting of a pulmonologist, gastroenterologist, and a metabolic dietitian. The proband had an older sibling whose Newborn Screening (NBS) test was normal and who eventually expired from recurrent bouts of pneumonia. This sibling was never managed as a case of cystic fibrosis. Implications on the diagnosis and management of CF in the local setting is also discussed.

The importance of an appropriate CF panel customized to the local population should be reiterated and carrier testing should be encouraged to help with proper family counseling for future pregnancies for the family involved.

Keywords: cystic fibrosis, newborn screening, Philippines, case report

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene located on chromosome 7 that has been rarely seen among the Asian population. Reports from Japan, China, Jordan, and Bahrain have demonstrated prevalences of 1:350,000, 1:153,825, 1:2,500 and 1:5,000, respectively, demonstrating a wide variability among different Asian subgroups.[1-3] Genetics may be the cause of this variability since even in the United States, prevalences among different ethnic populations differ wherein prevalences show 1:3,200 among Caucasians, 1:10,000 among Hispanics, 1:10,500 among Native Americans, 1:15,000 among African Americans, and 1:30,000 among Asian Americans.[2] While Philippine prevalences on CF is unknown, five Filipinos have previously been diagnosed through the California Newborn Screening Program in the United States.[4]

The differences in prevalences imply that genetic differences play a significant role in this disease occurrence in different populations. One area of impact with this genetic

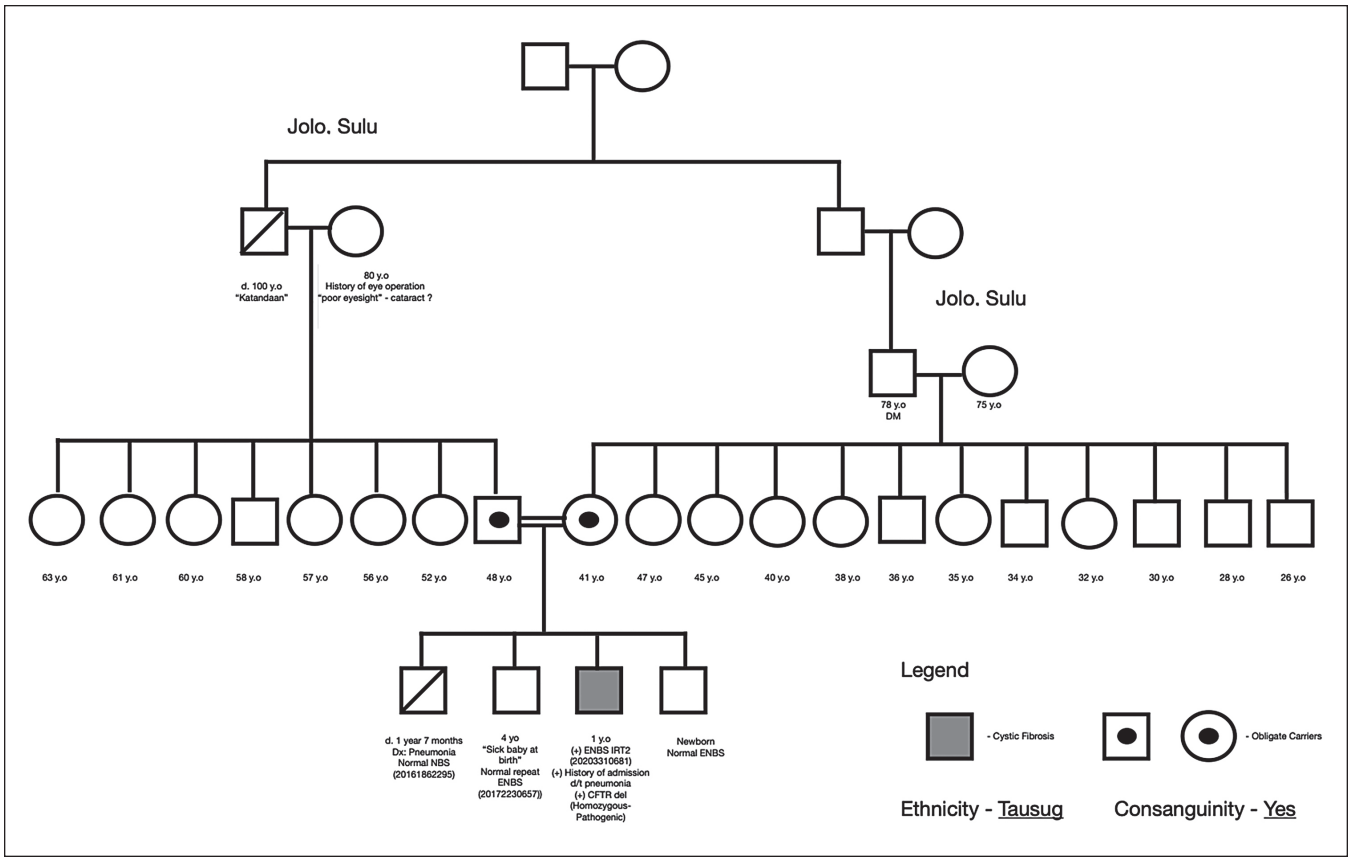

Figure 1. Pedigree of our proband illustrating consanguineous relationship of the parents, as prepared by a Genetic Counsellor and Consultant Geneticist from the Newborn Screening Center Mindanao.

variability is in its clinical presentation and course. A study was done comparing Asian and non-Asian populations living in the UK where it was shown that Asian girls had significantly lower mean forced expiratory volume - 1 second (FEV1) z-scores, forced vital capacity (FVC) z-scores, and had a first isolation of *Pseudomonas aeruginosa* significantly later in life as compared to their non-Asian counterparts. The most common gene mutation seen in CF, the F508del, is seen in 51% of non-Asians as compared to only 20% of the Asian CF patients. Moreover, these mutations were more commonly seen to be heterozygous among the Asian group as compared to non-Asians.[5] Therefore, the importance of genotypic characteristics among different populations should be emphasized and further explored. Another major impact of variable prevalences is the capacity of one population to diagnose CF. In areas with low prevalences such as the Philippines, a low index of suspicion may cause delayed or missed diagnoses thus negatively impacting the management of these cases.

The Philippine Newborn Screening Program (NBS) was initiated as a research project in 1996 and later mandated to law in 2004. It started out screening for five conditions: congenital hypothyroidism, galactosemia, phenylketonuria, congenital adrenal hyperplasia, and homocystinuria. Two years later, glucose-6-dehydrogenase deficiency was included.[6] While the Expanded Newborn Screening (ENBS) included Cystic Fibrosis in 2014 which was supposed to be nationally implemented, it was implemented in Zamboanga City only in 2018 because the Newborn Center for Mindanao was advised to consume the previous supply of NBS kits first before using the new ones. Here, the first genetically and clinically diagnosed case of cystic fibrosis in the Philippines diagnosed through the Newborn Screening Program is presented and implications on the diagnosis and management of CF in the local setting is discussed.

CASE PRESENTATION

The proband is a 24-month-old Filipino male of Tausug ethnicity and a product of a consanguineous marriage between first degree cousins, one generation removed wherein the father of the proband is the first cousin of the proband's maternal grandfather as demonstrated in Figure 1. He is the third of four boys, with the eldest born in 2016 but already deceased at 19 months after experiencing recurrent, almost monthly episodes of pneumonia since his neonatal period. This sibling had a normal newborn screening result that did not include testing for CF at that time. The second-

born sibling, born in 2017, is currently 4 years old and was described to be a sick baby at birth but had an unremarkable medical history thereafter. His repeat Expanded Newborn Screening test was normal. The proband's mother recently gave birth to the youngest male sibling who had normal ENBS results. Family medical history with regards previous generations did not show recurrent pneumonia, gastrointestinal diseases, infertility, or hypertension.

The proband's prenatal history was uneventful. He was delivered with thick meconium staining from a then 41-year-old G3P3 (3002) mother with a birth weight of 2.7 kgs at 37 - 38 weeks age of gestation by Ballard scoring via normal vaginal delivery. He was purely breastfed and there was no meconium ileus. Serial newborn screening immunoreactive trypsinogen (IRT) were done on days 2, 22, 31 and 62 of life with results of 92 µg/L, 73.9 µg/L, 80.4 µg/L and 73.4 µg/L, respectively (cut-off value <73 µg/L). The patient was then enrolled to the Philippine CF DNA Study led by a local geneticist. Through this inclusion, further testing was done with confirmatory molecular testing.

Throughout infancy, his medical course was unremarkable with no significant illnesses noted. However, he was first noted to be unwell at 16 months of age when he was brought in for consult due to cough characterized as dry and non-productive, and was associated with fever. His mother initially self-medicated with paracetamol but the cough worsened over time and became associated with fast breathing. Upon examination, his weight was 8 kg, RR = 58 cpm, HR = 118 bpm, and O_2 saturation at room air was only 90%. He had sunken eyeballs, dry lips, and oral mucosa, and had alar flaring. Chest and lung findings revealed intercostal and subcostal retractions, tight airflow with some crackles and wheezes on both lung fields. His chest x-ray revealed reticular and hazy opacities in both inner lung zones consistent with pneumonia. He was then admitted and treated with ceftriaxone (100 mg/kg/day) and amikacin (15 mg/kg/day). He was hooked to O_2 inhalation at 2-3 Lpm which improved his O_2 saturation to 98%. He was also nebulized with salbutamol and ipratropium (2.5 mg/500 mcg/2.5 ml) every 30 minutes for three doses followed by salbutamol nebulization (2.5 mg/nebule) every four hours. Intravenous hydrocortisone was also given every six hours, however, his dry cough worsened with persistent nocturnal coughing. Hence, ambroxol HCl nebulization (15 mg/2 ml) at 5 drops with 2 cc of saline per nebulization was given and chest physiotherapy was initiated. With this regimen, the proband's condition improved and he was discharged after seven days. Due to financial difficulties, a chest CT scan was not done. It was also at this time that his genetic testing result sent to a U.S.-based laboratory was released which showed homozygous *CFTR* gene deletions at exons 1-2 thus the diagnosis of Cystic Fibrosis was confirmed. The report sent did not indicate any other pathogenic variants seen.

Presently, the patient's weight for length is normal but is stunted [weight = 10 kgs (<0 SD); length = 77 cm (<-3 SD)]. Since discharge, he subsequently had recurrent mild respiratory infections at 17 months and at 20 months of age, and was given acetylcysteine nebulizing solutions with other medications and were managed on out-patient bases. The proband is currently on bronchodilator and mucolytic therapy. His parents and caregivers were taught how to do chest physiotherapy and advised to keep him at least 6 feet away from those with illnesses. A nutritional plan was developed by both the pediatric gastroenterologist and metabolic dietitian for proper caloric and nutrient intake to ensure appropriate growth and development. Based on guideline recommendations, adding a regimen of pancreatic enzymes and vitamins A, D, E, and K to the diet would lessen complications and morbidity however, due to their unavailability in our country, the proband was given multivitamins instead. Genetic counseling was also conducted with the family. He is continuously being monitored and treated under the Newborn Screening Continuity Clinic of Region IX together with a pediatric pulmonologist, gastroenterologist, developmental pediatrician, and a metabolic dietitian. The prognosis for cystic fibrosis for our proband's case is good however, challenges in his situation may pose difficulties in its management. One challenge about the treatment coming from his father's point of view is the availability of his medications. There has been an unavailability of the mucolytic nebulizing solutions in Zamboanga City causing much anxiety to his parents, especially since they have to travel by boat overnight just to come to the city for check-ups and for buying medications. However, they are appreciative of the implementation of the ENBS program that has been helpful to their family. They have been regularly following up with their pulmonologist who asked for their written consent for the publication of this case.

DISCUSSION

The critical role of the Philippine Newborn Screening Program in detecting this condition particularly in this infant cannot be emphasized enough. With the rarity of this condition among the majority of the Asian population, an infant or child presenting with recurrent respiratory tract infection, chronic diarrhea, steatorrhea, ileus, hepatomegaly or pancreatic insufficiency[7] or even an adult with infertility will most likely not be tested for a *CFTR* gene defect thus missing the diagnosis and proper treatment. This resonates more in our proband's case since his eldest sibling had recurrent respiratory infections that may have been caused by Cystic Fibrosis and was not managed properly which, if it was detected, may have prevented his demise. However, even having the NBS done may not be as reliable in detecting this condition. Ni et al.[8] compared Chinese-specific CF panels with Caucasian-specific CF panels and detected that only 21 variants were shared. They noted that most Caucasian variants were located in the *NBD1* domain whilst in the Chinese cohort, the variants were located in the *TMD2*

domain. While the F508del gene mutation is commonly seen among Caucasians, Guo et al.[7] detected among 71 Chinese patients that the most common mutation was p.Gly970Asp, the second most common variant was c.1766+5G>T and the third was p.Ile1023Arg and the F508del was rarely seen in this cohort. Indika et al.[9] also demonstrated in their cohort of 10 Sri Lankan CF patients that the F508del mutation was only present in three of their patients. Our proband's mutation was previously reported in only two African American cases.[10] Therefore, a CF panel used in one population may not include mutations that are otherwise commonly seen in other populations thus missing out the diagnosis.[11] It is then important to describe the common mutations and variants seen in the Filipino population to be able to provide a more complete and comprehensive picture of what is applicable to the local population.

The clinical implications of knowing the common specific variants in the local population should also be emphasized. Various authors have described differences in lung function, presentations, and even outcomes among different ethnicities. Bosch et al.[12] summarized that based on their evaluation of the global CFTR2 database, they found that Asians are younger, and more had pancreatic insufficiency and had sweat chloride levels of less than the cut off of 60 mmol/L than their Caucasian counterparts. However, Asians were also noted to have less *Pseudomonas sp.* infection and had less homozygous F508del mutation. Another clinical implication of the genotype-phenotype evaluation is with regards management especially with the newer medications. Certain genetic mutations are associated with the class of defect seen in cystic fibrosis. For example, the commonly seen F508del mutation is associated with a class II defect specifically involving protein processing whereas the R117H mutation is associated with a class IV defect involving defective conduction.[13] With this information, modulator therapies such as the potentiator ivacaftor or correctors such as lumacaftor or tezacaftor would be ideal for an individual with the latter mutation since these modulators are recommended for classes III to V defects.[3] This information would then be useful not only to guide clinicians in treating the condition but also to health agencies in allocating resources that would be more appropriate for the Filipino cohort of CF.

Finally, the issue of carrier (parent) testing should always be raised during counseling. This is important not only to look at the donor of the mutation but also to look at the evolution of the mutations seen in our proband's family. This is illustrated by a case presented by Wang et al.[14] in a 30-month-old Chinese female with a heterozygous novel missense mutation of c.753_754delAG in exon 7 and c.1240C>T mutation in exon 10. The first mutation in exon 7 was derived from her mother while the second mutation was derived from her father who also has a congenital absence of the vas deferens. Issues that should be considered with regards carrier screening should go beyond simply presenting the technical aspects of the test itself but should include mental health issues such as anxiety, guilt, and even blaming of the partner with a defective gene. Moreover, informed planning of the next pregnancies should also be embarked on with the use of this information.[15] As was seen in this case, while the proband is undergoing treatment for recurrent respiratory infections, the youngest sibling is being carried and eventually delivered by the mother who would have had to face challenges in the care of this chronic condition if her fourth child also has CF. Just before submission of this case report in January of 2023, the ENBS result of the fourth sibling showed negative results however, close follow up should be done just in case the panel did not detect new or "Asian" mutations that are not in the standard CF panels.

The major limitation of this case report is the lack of a complete history of our proband's eldest sibling, including his medical history. The authors are also still in the process of completing imaging work of the proband's lungs to include a chest CT scan and infectious respiratory panels to identify pathogens.

CONCLUSION

While the prevalence of cystic fibrosis in the Philippines is unknown, its rarity in the Asian population should not prevent general pediatricians from considering this condition in children with respiratory, gastrointestinal, and pancreatic conditions. The Philippine Expanded Newborn Screening program is an important tool to detect this condition so that further work up and appropriate management can be done. Furthermore, a complete description of the various genotypic mutations and its phenotypic presentations among the Filipino population should be done to customize a CF panel and management that would be appropriate for the local population.

Abbreviations

CF – Cystic Fibrosis
NBS – Newborn Screening
ENBS – Expanded Newborn Screening
FEV1 – Forced Expiratory Volume at 1-second
FVC – Forced Vital Capacity

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Ethics approval and consent to participate

This case report was reviewed by the Zamboanga City Medical Center Ethics Review Board and was granted exemption from a full board review. A written consent

was obtained from the parents of the proband for the documentation and presentation of his condition.

Consent for Publication

Written informed consent was obtained from the patient's father for the reporting of this case and any accompanying images.

Availability of data and materials

Materials and data provided in this case study are available from all authors upon reasonable request.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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