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Case report

Five cases of missed cystic fibrosis heterozygous mutations identified after a positive newborn screen on a sibling

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ABSTRACT

In Michigan (MI), NBS for CF was started in October 2007 using the IRT/DNA protocol. In 2016, a component of the Hologic molecular test kit used by the MI NBS lab was recalled (40 CF mutation 2nd tier test). This recall had a major impact on states using the Hologic test kits in their NBS programs. Michigan specimens were sent to another state's NBS Lab for 2nd tier testing using the Luminex 60 mutation test kit until the Luminex kit could be procured and validated in MI. In this report, we present five cases born during this time period. These cases were initially reported out as having normal NBS results for CF but had heterozygous F508 del (c.1521_1523delCTT) mutations later identified. Of the five cases, one was diagnosed with CF (Case1), one with CF related metabolic syndrome (CRMS), and the other three were carriers.

Abbreviations

CF	Cystic Fibrosis
NBS	Newborn screening
IRT	Immunoreactive trypsinogen
CDC	Centers for Disease Control and Prevention
CFF	CF Foundation
MI	Michigan
CRMS	CF CFTR-related metabolic syndrome
MDHHS	Michigan Department of Health and Human Services (MDHHS)
PCP	Primary care physician
PI	Pancreatic insufficiency
MSSA	Methicillin Sensitive Staphylococcus aureus

; CF NBS, Cystic Fibrosis Newborn Screen.

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CT	Computed tomography
BMI	Body Mass Index

1. Introduction

Cystic Fibrosis (CF) is the second most common life shortening, inherited disease, after; sickle cell disease [1]. Numerous reports have shown that early CF diagnosis led to; reduction in pulmonary complications [2], improved nutritional status, cognition, and improved; overall survival [3]. As a result, in 2004, the Centers for Disease Control and Prevention (CDC), and; CF Foundation (CFF) recommended adding CF to the newborn screening (NBS) panel [4]. In Michigan (MI), NBS for CF was started in October 2007 using the IRT/DNA protocol. The IRT cutoff value is a floating ≥96% ile daily.

In 2016, a component of the Hologic molecular test kit used by the MI NBS lab was recalled(40 CF mutation 2nd tier test). This recall had a major impact on states using the Hologic test kits in their NBS programs. Michigan specimens were sent to another state's NBS Lab for 2nd tier testing using the Luminex 60 mutation test kit until the Luminex kit could be procured and validated in MI.

In this report, we present five cases born during this time period. These cases were initially reported out as having normal NBS results for CF but had heterozygous F508 del (c.1521_1523delCTT) mutations later identified. Of the five cases, one was diagnosed with CF (Case1), one with CF related metabolic syndrome (CRMS), and the other three were carriers. The study was determined as not regulated by the University of Michigan Institutional Review Board.

Case 1: In 12/2019, University of Michigan CF Center alerted the Michigan Department of Health and Human Services (MDHHS) that a three-and-a-half-year-old girl with no mutations identified on NBS was diagnosed with CF, following a younger sibling's abnormal NBS and CF diagnosis. The younger sibling's newborn screen revealed an elevated IRT at 144 ng/ml, and 1 copy of F508del. The sweat chloride concentration was 101 & 103 mmol/L. Sweat testing was performed on the older sibling according to the CFF clinical care guidelines. Her sweat chloride concentration was 100 mmol/L, and she was found to be pancreatic insufficient (PI). Her IRT on NBS was elevated at 373 ng/ml, but no mutations were identified by the out of state lab performing the second-tier testing. Per the MI NBS algorithm, the patient's primary care physician (PCP) was notified that she had a very high IRT (99.8%ile) and to watch for any CF related symptoms. She was asymptomatic until age of 33 months when she started having productive cough. She was seen several times by her PCP and was diagnosed with mild persistent asthma. In addition, PI symptoms started with slow weight gain and frequent greasy bowel movements. Following the CF diagnosis, the NBS sample was retrieved, re-ran using the Luminex 60 mutation panel, and heterozygous F508del was identified. The second mutation for both sibling was 2184insA (p.Gln685ThrfsX4, c.2052dupA, or c.2052_2053insA). She has been admitted three times thus far for CF pulmonary exacerbations. Chest computed tomography (CT) scan was performed during her second admission which revealed mild bronchiectasis. Her CF throat cultures have been growing Methicillin Sensitive Staphylococcus aureus (MSSA). The delayed diagnosis resulted in lung damage as the need for repeat admissions for treatment of CF pulmonary disease. Compared to her sister, her lung damage is significant. At the time of diagnosis, parents were upset about the delay in the diagnosis and counselling by our social worker and psychologist were done.

Following that diagnosis, MDHHS retrieved all specimens tested by the out of state NBS Lab in 2016 and the second-tier screen was repeated. Four additional specimens that had been reported out as having no mutations were identified as heterozygous F508del mutation. MDHHS created an updated NBS results mailer with an explanation letter was sent to PCPs. All 4 children had sweat tests done, and results are below.

Case 2: The patient was a 3 year, 10 months old male. His IRT was 97 ng/ml. He had no respiratory symptoms but had malodorous and oily stools suspicious for PI. The sweat chloride concentration was intermediate at 48 and 44 mmol/L. The fecal elastase concentration was >500 mcg/g and throat culture grew normal flora. Repeat sweat chloride test revealed an intermediate concentration of 35 and 33 mmol/L. Full gene sequencing revealed F508del plus G1069R. G1069R (p.Gly1069Arg).

This combination has varying consequences. He was diagnosed with CRMS and has been followed by one of the CF centers in MI.

Case 3: The patient was 3 years, 9 months old female. She was asymptomatic. Her IRT concentration was 64 ng/ml and genotype re-assessment revealed F508del heterozygous mutation. Sweat chloride concentration was normal at 21 and 25 mmol/L. She was found to be a CF carrier.

Cases 4 and 5: The patients were 3.5 and 4 years old when seen at the CF center. Their sweat chloride concentration was 21 and 30 mmol/L respectively. They had no respiratory or GI symptoms, and their weights and BMIs were within normal limits. Both were CF carriers.

2. Discussion

Since the implementation of NBS in the US, most new diagnoses of CF are identified through NBS.

Early detection of CF provides the opportunity to improve outcomes by initiating, monitoring and treatments in the pre-symptomatic period [5]. Several studies have supported the benefits of early diagnosis and intervention to improve lung function, nutritional outcomes, and overall health [2]. In addition, delay in diagnosing CF can lead to further anxiety and stress to patients' families and their pediatricians. Although these cases were reported out with no mutations identified, it is crucial to maintain a high index of suspicion for CF in patients who exhibit classical symptoms, even in the setting of a negative newborn screen. False negative results can result from the newborn screen, with one article describing the many possible causes of false negative results that can occur after newborn screening for CF [6]. Another study estimated the number of false negative CF newborn screens/year as high as 70 tests a

year, with 37 of the cases from states that uses IRT/IRT algorithm (which account for only 18% of the newborns) and 33 cases that uses IRT/DNA algorithm (the remaining 82% of U.S. newborns) [7]. Several other reports also reported false negative CF newborn screening tests as well [8,9].

The first case had an IRT above 99.8%ile and as per MI NBS protocol, a letter was sent to the PCP to monitor for any CF related symptoms and refer the child to a CF center if symptoms developed. Since the PCP didn't refer the patient when she started developing symptoms, an addition to the protocol was made to include a letter to be sent to the family as well to monitor for any CF symptoms since the delay in the diagnosis of the first case has led to worsening respiratory symptoms, several hospitalizations, and poor weight gain. It is important to emphasize that following the CF care guidelines was crucial in diagnosing the first case and identifying the error in detecting the other cases.

Declaration of competing interest

The authors have nothing to declare.

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