CASE REPORT

Oman Medical Journal [2021], Vol. 36, No. 2: e243

A Novel Cystic Fibrosis Gene Mutation C.4242+1G>C in an Omani Patient: A Case Report

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ARTICLE INFO

Article history:
Received: 23 December 2019
Accepted: 9 March 2020

Online:
DOI 10.5001/omj.2021.28

Keywords:
Infant, Newborn; CFTR protein, human; Cystic Fibrosis Transmembrane Conductance Regulator; Cystic Fibrosis; Genetic Testing; Mutation.

ABSTRACT

Cystic fibrosis (CF) is a genetic disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that affects multisystems in the body, particularly the lungs and digestive system. We report a case of an Omani newborn who presented with meconium ileus and high suspicion of CF. Thus, full *CFTR* gene sequencing was performed, which revealed a homozygous unreported C.4242+1G>C novel gene mutation. Both parents were found to be heterozygous for this mutation. This case sheds light on the importance of the extensive genetic testing of typical CF cases in the absence of family history or during neonatal presentations, especially when the sweat test cannot be performed and the diagnosis can be challenging.

Cystic fibrosis (CF) is a common inherited genetic disease. It is inherited as an autosomal recessive trait, occurring in 1 per 3500 newborns.[1] CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.[2] This gene is located on the long arm of human chromosome 7 at the q31.2 locus with 27 exons [Figure 1].

It is coding for chloride ion channel that is important in creating sweat, saliva, and digestive enzymes and maintaining the mucus layer of the airways and digestive tract. The location of CFTR protein, which is found in several organs, determines which symptoms of CF occur. The organs typically involved are the skin, pancreas, and lungs. There are several mutations in the *CFTR* gene, and different mutations cause different defects in the CFTR protein, with variation in the severity of the disease ranging from poor lung function and pancreatic exocrine insufficiency to chronic lung bacterial colonization, recurrent chest infections, malnutrition, failure to thrive, and liver disease with high morbidity and mortality.[3]

The *CFTR* gene was first identified in 1989, and over 1500 CFTR mutations have been reported to date.[2]

The most common mutation worldwide is delta F508 (ΔF508), which accounts for two-thirds (66–70%) of cases and almost 90% of cases in the Western population.[4]

Unfortunately, reports in the Arab populations are limited. So, determining the exact prevalence of CF in Middle East countries, especially Arabic countries, remains difficult, and the incidence also appears to be low because of underdiagnosis or low rates of reported cases.

In the Arab population, the incidence ranges between 1 in 2560 and 1 in 15 876.[1–3] And, the Δ F508del and p.S549R mutation with some other native Arab mutations are common mutations.[2,4,5]

There are six common mutations of CF in Oman: p.S549R, ΔF508, 3120+1G>A, L578delTA, p.A357T, and 3849+10kbC->T. From these mutations, the p.S549R is the most common with a frequency of 65.2%, followed by the ΔF508 with a frequency of 13%.[6]

In this case report, we report a case of an Omani newborn baby with meconium ileus, who was found to be homozygous for C.4242+1G>C, a novel *CFTR* gene mutation.

CASE REPORT

A full-term female neonate was admitted to the special care baby unit of Sohar Hospital, Sohar, Oman, following normal spontaneous vaginal

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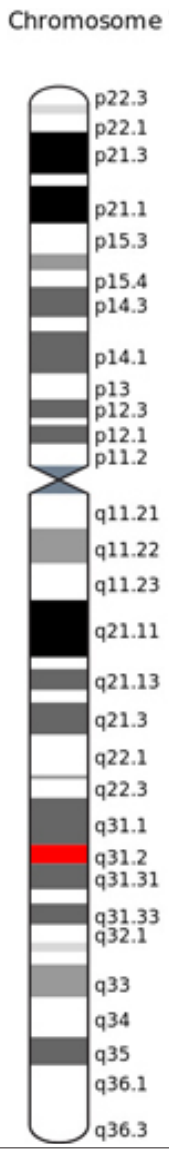

Figure 1: CFTR gene on the long arm of chromosome 7 at q31.2 locus.

delivery with a normal Apgar score. The mother's pregnancy was uncomplicated apart from an abnormal antenatal scan of the fetus, which showed dilated bowel loops with hyperechogenic walls and no peristalsis seen.

The neonate's birth weight was 2.57 kg (between 10th and 50th centile). On physical examination, she did not have any dysmorphic features but had mild abdominal distension. She was admitted for observation and further evaluation. Within a few hours of admission, she showed considerable abdominal distension without passage of meconium, and on examination, she has a patent rectum. An abdominal X-ray showed significant dilatation of the stomach and a loop of small bowel with no air seen in the large bowel. Small bowel obstruction was suspected and thus an urgent referral was made to pediatric surgery. An upper gastrointestinal tract study showed persistent dilated small bowel loops, suggesting intestinal obstruction. Therefore, she underwent an urgent laparotomy and was found to have dilated ileal loops with very sticky meconium. These findings were inconsistent with the diagnosis of meconium ileus. So, CF was highly suspected, and the baby was evaluated for CF.

Since it is not possible to perform sweat test during the neonatal period, immunoreactive trypsinogen screening was done and came high (2954). Along with that, the stool fecal elastase test was also highly suggestive of CF (< 15 µg). So, with this typical presentation of CF and positive neonatal screening test, full CFTR genome sequencing was performed and showed a likely pathogenic homozygous mutation C.4242+1G>C.

This mutation has never been reported before and is likely to be the case to date. Her parents are healthy, consanguineous, and second-degree relatives. She has three healthy siblings. The parents were tested for carrier status, and both were found to be carriers of the heterozygous C.4242+1G>C mutation.

On follow-up, a few months later, the patient was seen in the clinic and she was maintained on nutritional supplements and she was monitored by both gastroenterology and CF teams. To date, she has had no rare respiratory symptoms or infections.

DISCUSSION

Despite a better understanding of CF, diagnosis in the neonatal period remains a challenge because of the difficulty of performing a proper sweat test with reliable results. Usually, the diagnosis of these suspected neonates with CF is delayed until the development of severe respiratory and gastrointestinal complications that could be prevented or minimized by early detection and treatment.

CF is a lethal genetic disorder that affects multiple organ systems, and the incidence rate is steadily increasing.

Worldwide, CF can be diagnosed by many different methods, including newborn screening, sweat test, and genetic test.

The introduction of newborn screening (raised concentration of immunoreactive trypsinogen) helps in early detection and better management of CF.

In 2014, 63.4% of newly diagnosed CF cases were detected by newborn screening, and 66.4% were diagnosed in the first year of life.[7]

Moreover, nowadays, the sweat test is a gold standard test for CF. Still, it does not rule out CF if negative and has limited value in the neonatal period because of unreliable results.

In addition, genetic testing is mostly performed on the most common mutations such as Δ508. Because not all mutations are found on these spot genetic tests, a negative screen does not guarantee that a child will not have CF. Therefore, if a family has a known uncommon mutation, specific screening for that mutation can be performed.

For example, the American College of Medical Genetics recommendation in 2004 for the screening of CF is through a sweat chloride test and a 23-gene mutation panel.[6] However, this recommended 23 genetic panel has different sensitivity based on ethnicity, with the highest sensitivity found in Ashkenazi Jews (94%) and the lowest in Asian Americans (49%).[2,4–6,8,9] Therefore, expanding this panel to include ethnicity-specific mutations can increase the test sensitivity.

Another example, a 64-mutation-panel suggested by Heim et al, increases CF screening sensitivity to 84.1%.[10]

Thus, along with the typical clinical presentation, the genetic sequencing of the *CFTR* gene is the most common diagnostic tool available for CF to avoid misdiagnosis of CF, especially in a situation where the sweat test cannot be performed.

We performed a full CFTR genome sequencing and showed a likely pathogenic homozygous mutation C.4242+1G>C.

The C.4242+1G>C variant found in this patient was not previously described. It consists of an insertion of a C nucleotide before the G, typically positioned at 4242+1.

CONCLUSION

CF is a common genetic disorder. The spectrum presentation of CF is wide and varied. In the neonatal period, the most important clinical manifestation is meconium ileus, and the effective management of a newborn with CF helps improve the overall prognosis later in life. However, the diagnosis of clinically suspected neonates with CF still presents a diagnostic challenge. This case highlights the value of clinical evaluation and the need for extensive genetic investigations for CF diagnosis during the neonatal period.

Disclosure

The authors declared no conflicts of interest. Parental conset obtained.

REFERENCES

1. Hamosh A, FitzSimmons SC, Macek M Jr, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr 1998 Feb;132(2):255-259.
2. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989 Sep;245(4922):1073-1080.
3. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations–correlation with incidence data and application to screening. Hum Mutat 2002 Jun;19(6):575-606.
4. Li H, Wen Q, Li H, Zhao L, Zhang X, Wang J, et al. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) in Chinese patients with congenital bilateral absence of vas deferens. J Cyst Fibros 2012 Jul;11(4):316-323.
5. Al-Kindy H, Ouhtit A, Al-Salmi Q, Al-Bimani M, Al-Nabhani M, et al. Novel mutation in the CFTR gene of cystic fibrosis patients in Oman. J Mol Biomark Diagn 2014;5(168):2.
6. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American college of medical genetics mutation panel. Genet Med 2004 Sep-Oct;6(5):387-391.
7. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: cystic fibrosis foundation consensus report. J Pediatr 2008;153(2):S4-S14.
8. Sugarman EA, Rohlfs EM, Silverman LM, Allitto BA. CFTR mutation distribution among U.S. Hispanic and African American individuals: evaluation in cystic fibrosis patient and carrier screening populations. Genet Med 2004 Sep-Oct;6(5):392-399.
9. Hubert D, Fajac I, Bienvenu T, Desmazes-Dufeu N, Ellaffi M, Dall'Ava-Santucci J, et al. Diagnosis of cystic fibrosis in adults with diffuse bronchiectasis. J Cyst Fibros 2004 Aug;3(3):203.
10. Heim RA, Sugarman EA, Allitto BA. Improved detection of cystic fibrosis mutations in the heterogeneous U.S. Population using an expanded, pan-ethnic mutation panel. Genet Med. 2001;3:168–76.