Cystic Fibrosis mutation W19X in Tunisia: Second case identified

La mutation mucoviscidosique W19X en Tunisie: Deuxième cas identifié

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RÉSUMÉ

La mucoviscidose est une exocrinopathie généralisée à transmission autosomique récessive due à une mutation du gène CFTR. Plus de 1800 mutations ont été identifiées depuis sa découverte en 1989, dont certaines semblent être spécifiques de la population tunisienne. Nous décrivons dans cette étude une patiente atteinte de mucoviscidose. Il s'agit du deuxième cas identifié porteur d'une nouvelle mutation non-sens à l'état homozygote: la W19X. Cette mutation n'a été identifiée que chez des patients d'origine tunisienne, et semble être responsable d'un tableau sévère de mucoviscidose. L'identification d'une telle mutation par notre étude nous permet de mieux définir le spectre de mutation de cette maladie en Tunisie afin d'améliorer le conseil génétique.

Mot clés : mucoviscidose, gène CFTR, patient tunisien, mutation mucoviscidosique, W19X

SUMMARY

Cystic Fibrosis (CF) is a lethal autosomal recessive condition due to a defect at the level of the transmembrane conductance regulator gene which plays a role in cell homeostasis. Numerous mutations have been identified as the cause of this gene defect, with delF508 being one of the most common mutations in Tunisia. This is a case report describing, up to our knowledge, the second case of a patient with CF carrying a rare mutation: W19X. W19X is a nonsense mutation that has been previously identified in only one other Tunisian patient with CF. Since both incidence of this mutation have been described in Tunisia, it seems as if W19X is specific to Tunisian CF patient with significant morbidities. The information provided by this study contributes to defining the molecular spectrum of CF in Tunisia, in the aim of improving genetic testing and prenatal diagnosis.

Key words: cystic fibrosis, Tunisian patient, CFTR mutation, W19X.

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INTRODUCTION

Cystic Fibrosis, one of the most common autosomal recessive severe diseases, is a generalized exocrinopathy affecting serous glands and mucous secretion. In its classic form, it is characterized by a bronchiectasis leading eventually to chronic respiratory failure, and pancreatic exocrine sufficiency causing a generalized malabsorption (1). Its underlying cause is a mutation of a gene located on the long arm of the chromosome 7: the CFTR gene (2). This gene is responsible for the synthesis of the CFTR protein, which regulates the transport of chlorine across the cellular membranes. Therefore, a mutation in the CFTR gene will lead to the absence or a malfunctioning CFTR protein, blocking the passage of chlorine through the cellular membrane (3). Since the discovery of the CFTR gene in 1989, there has been more than 1800 different mutations, which have been classified according to the nature of the molecular lesion and the pathophysiological mechanism involved (4). This classification is the basis for the study of the genotype-phenotype correlations in the expression of this disease (5). There have been seventeen mutations detected on the different exons of the CFTR gene, the most frequent of which was the F508del, followed by three others mutations (G542X, W1282X and N1303K). These latter mutations are known to be common in the Mediterranean area (6).

Aim

This is a case report of a Tunisian patient with a severe case of CF, carrying the W19X mutation, which is believed to have been described only once before in Tunisia.

REPORTED CASE

The patient was a four months old male infant, who was the first born of a healthy couple, of first degree consanguinity from the southern region of Tunisia. There was no particular family history and the pregnancy was uneventful. He was born at 34 weeks, with a birth weight of 2,340kg, by a cesarean section for a suspected acute chorioamnionitis and fetal distress. During his first hour of life, he was hospitalized in the neonatal unit for neonatal respiratory distress, and was treated for duration of one day with oxygen by Hood. At the age of 7 weeks, he developed watery diarrhea without associated fever or other symptoms. At the time of this episode, he was being fed a premature milk preparation, which was replaced by hydrolysates of cows'milk protein. The change of formula was very well tolerated and he showed signs of improvement. At the age of 2 months, he developed an acute bronchiolitis, for which he was treated in an outpatient setting. At 4 months of age, he was admitted to hospital for continuous diarrhea, dyspnea and failure to thrive. His physical exam showed an infant of average general condition, with a weight of 3,650 kg (between -4 and -3 DS) and a height of 58 cm (between -2 and -1 DS). He was hemodynamically stable and had an unremarkable neurological evaluation. However, he had signs of respiratory distress, with evident polypnea and retractions. Upon auscultation, he had bilateral wheezing, but maintained an oxygen saturation of 99% in ambient air. His laboratory tests showed a hypochromic microcytic anemia of 10 g/dL, a hyponatremia of 125 mmol/L, a hypokalemia of 1.74 mmol/L and a respiratory alkalosis on his blood gas. Serum calcium, renal and hepatic markers, as well as urinary electrolytes were normal.

The patient was perfused and his electrolyte disturbances were corrected. He was also placed on oxygen by nasal cannula and received inhaled epinephrine for his respiratory distress.

On the tenth day of his hospitalization, he presented an anal prolapse. An abdominal ultrasound was performed and was unremarkable. His hospital stay was further marked by a worsening of his respiratory distress and the development of a fever on the 15th day of hospitalization. The patient's chest x-ray showed retro and bilateral para-cardiac opacities.

He was then started on a broad-spectrum antibiotic regimen (cefotaxime and vancomycin) and was eventually intubated and ventilated five days later. The patient was declared deceased 20 hours later. The sweat test and the immune deficiency balance could not be performed; however, the molecular biology was positive for the W19X CFTR mutation in a homozygous state.

DISCUSSION

In Tunisia, there has been17 mutations of the CFTR gene identified, some of which appear to be specific to the Tunisian patients (6). To our knowledge, this is the second

case of CF in Tunisia, in which W19X has been isolated. W19X is a nonsense mutation that has been previously identified in only one other Tunisian patient suffering with CF. This first described patient was a two-year female patient, with parents of second degree consanguinity, from the Gabes region (Southern Tunisia). She presented a severe form of the disease and was colonized by Pseudomonas Aeruginosa at an early age, unlike 80% of cystic fibrosis patients who are colonized with this organism at the age of eight (7). The second patient described with this mutation is the case we have just presented. This is a rare mutation that was not reported in two Tunisian studies, including respectively 269 and 68 Tunisian patients with cystic fibrosis (6, 8). In both cases mentioned above, this mutation was relayed to a severe presentation of CF and asignificant morbidity. Since this gene has been only described so far in patients of Tunisian origin, it seems to be specific to the Tunisian population. Regardless of the limited number of studies of the CFTR gene in Tunisia, W19X mutation has been added to the 5 mutations recently identified in the Tunisian population that may be specific to Tunisian patients with CF (8).

The information provided by this case, contributes to defining the spectrum of CF mutations in Tunisia as well as a better understanding of the genotype - phenotype relationship and the influence of the genetic variability on clinical expression in CF patients.

CONCLUSION

This case report, describes the second Tunisian CF patient with a particular mutation in the CFTR gene, that is the W19X mutation. Other than it seeming to be specific to the Tunisian population, our report also shows that patients with this mutation in the homozygous state present a severe form of the disease. The identification of such a mutation enables us to better define the spectrum mutations of CF in Tunisia and therefore refining prenatal diagnosis and screening of healthy carriers.

Conflicts of interests:

None

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