Negative Sweat Chloride Testing in the Setting of a Positive Newborn Screen and *CFTR* Compound Heterozygosity

Lucille De Maria,[a] Marion Marlinge,[a,b] Melisande Baravalle,[c] Jean-Christophe Dubus,[c] and Julien Fromonot [a,b,*]

[a]Laboratory of Biochemistry, Timone University Hospital, AP-HM, Marseille, France; [b]Centre for Nutrition and Cardiovascular Disease (C2VN), INSERM, INRAE, Aix Marseille University, Marseille, France; [c]Pediatric Pulmonology Department, Timone University Hospital, Marseille, France.

* Address correspondence to this author at: Laboratory of Biochemistry, Hôpital de la Timone, 264 Rue Saint-Pierre, 13385 Marseille Cedex 5, Provence-Alpes-Côte d'Azur, France. E-mail julien.fromonot@univ-amu.fr.

CASE DESCRIPTION

A 14-month-old female of European descent was referred to our hospital due to inconclusive sweat chloride tests (STs) and a previous positive newborn screening (NBS) for cystic fibrosis (CF).

The patient was born at full-term as the firstborn in a family with no history of genetic diseases. On her third day of life, NBS showed high immunoreactive trypsinogen levels (triplicate average: 109 ng/mL) above the reference level (99.5th percentile: 65 ng/mL). Molecular testing for the 29 recommended *CFTR* variants by the French NBS program was performed on a dried blood spot using the Elucigene® CF30V2 kit (Gen-Probe Inc.). She was found to carry the common *CFTR* heterozygous pathogenic variant: NM_000492.4:c.1521_1523del, (p.Phe508del; p.F508del). Since birth, she had been experiencing infant asthma, which was treated with fluticasone propionate or salmeterol aerosol. However, she did not present with the gastrointestinal phenotype including meconium ileus or diarrhea with steatorrhea. At 1 month of age, she underwent the first ST which was performed in accordance with the management guidelines (coulometric method, ChloroChek®, ELITechGroup Inc.). Results showed a chloride concentration within the intermediate range (44 mmol/L, reference level <30 mmol/L). The test was repeated after 1 week because of the initial result and this second ST was negative (chloride concentration: 29 mmol/L). Accordingly, further tests were not conducted at this point.

At 14 months of age, new examinations were performed as her parents wanted to have a second child. The patient's medical history included persistent ear, nose, and throat obstructions with chronic cough leading to exertional dyspnea, nocturnal snoring with apnea, and 2 hospitalizations due to respiratory complications (COVID-19–induced asthma and viral retrocardiac pneumonia). Expanded analyses for 50 *CFTR* variants (Elucigene CF-EU2v1 kit) revealed compound heterozygosity for 2 pathogenic variants in trans: c.1521_1523del (p.F508del) inherited from her mother and c.3454G>C (p.D1152H) inherited from her father. Despite the combination of these pathogenic variants, the third ST was still negative (chloride concentration: 23 mmol/L), and the patient's fecal elastase level over 800 µg/g (reference level >200 µg/g) confirmed exocrine pancreatic sufficiency.

At this stage, the diagnosis remained unclear because of the discrepancies between the ST results and the *CFTR* genotype. She was then hospitalized for the third time because of a viral-induced respiratory congestion with wet cough for 10 days. The respiratory congestion was associated with bacterial superinfection (*Streptococcus pneumoniae* and *Moraxella catarrhalis*) and mild diffuse bronchial thickening on chest radiography.

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QUESTIONS TO CONSIDER	
1.	Why is sweat chloride testing required in a child with a positive NBS result of hypertrypsinemia?
2.	What important information was obtained through expanded *CFTR* genotyping?
3.	What are the factors that should be considered to obtain a conclusive diagnosis of CF?
4.	What are the potential causes of persistent negative sweat chloride results?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the October 2024 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/70/10 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

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