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Case Report

Pseudo-Bartter syndrome: A CFTR-related disorder?

Noelia Rodriguez Mier [a,b,*], Virginie Antoons [c], Senne Cuyx [a,b], Anabela Santo Ramalho [b], Mieke Boon [a,b], Marijke Proesmans [a,b], Djalila Mekahli [c,d], François Vermeulen [a,b]

[a] Department of Pediatrics, Pediatric Pulmonology, University Hospital of Leuven, Leuven, Belgium
[b] Department of Development and Regeneration, Woman and Child Unit, CF Research Lab, KU Leuven, Leuven, Belgium
[c] Department of Pediatrics, Pediatric Nephrology, University Hospital of Leuven, Leuven, Belgium
[d] Department of Cellular and Molecular Medicine, PKD research group, KU Leuven, Leuven, Belgium

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ABSTRACT

This case report presents a 14-month-old boy with a history of cystic fibrosis (CF) carrier status, diagnosed following a positive newborn screening for CF (CF-NBS), who developed symptoms suggestive of Pseudo-Bartter syndrome (PBS). Despite initial evaluations not meeting CF diagnostic criteria, subsequent investigations revealed an intermediate sweat chloride concentration, a second CFTR mutation, and CFTR dysfunction through rectal organoid morphology analysis (ROMA) consistent with CFTR-related disorder (CFTR-RD). This case raises important considerations regarding the diagnosis and management of CFTR-RD. PBS can be considered as a rare presentation of CFTR-RD and can occur in children with sweat chloride below the CF range. Functional testing of CFTR by ROMA enabled a more accurate diagnosis. Despite the negative work-up after CF-NBS, this infant developed CFTR-RD, but this should not be considered as a screen failure. Follow-up of children with CFTR-RD at a CF centre is preferred, because of the risk of developing CF.

A 14-month-old boy presented with a two-week history of anorexia and vomiting following a recent summer vacation in Italy. His medical history is relevant for a false positive CF newborn screening (CF-NBS). At birth, his first tier immunoreactive trypsinogen (IRT) level was 88 ng/mL (> p99 of 59 ng/mL), and a single *F508del* variant was detected with the limited 12 *CFTR* variants panel followed by a normal sweat chloride concentration (SCC) of 25.6 mmol/L. Information about CF carriership was provided and no further follow-up was scheduled at our CF centre. At a later age, progressive failure to thrive was attributed to a cow's milk protein allergy, with weight and height dropping from the 90th percentile (z-score = 1.5) at birth to respectively below the 3rd percentile (z-score = -2.8) and to the 6th percentile (z-score = -1.6) at 14 months.

At presentation, clinical examination was unremarkable beyond the low weight and height. Blood biochemistry revealed severe metabolic alkalosis with a pH of 7.58 and a bicarbonate level of 48.9 mmol/L. Partial respiratory compensation was observed with a pCO2 level of 51.9 mmHg. Additionally, hypokalemia (2.35 mmol/L), hypochloremia (75 mmol/L), and hyponatremia (133 mmol/L) were present.

These findings were consistent with (pseudo-)Bartter syndrome. A nephrological evaluation ruled out known kidney causes as indicated by a very low fractional excretion of sodium and chloride (<1%). After correcting the ion disturbances, a repeat sweat test showed an SCC of 34.6 mmol/L, in the intermediate range. *CFTR* sequencing identified an *N1303I* (c.3908A>T) variant *in trans* with the known *F508del* variant. Although not listed in CFTR2, it has been reported in the CFTR-France database in 10 individuals: 7 with congenital bilateral absence of the vas deferens and 3 with CF Screen Positive Inconclusive Diagnosis (CFSPID). SCC was in the CF range in 5 out of 10 patients, intermediate in 2 and not reported in the remaining 3 patients.

Based on the clinical presentation, SCC, and genetics, the patient did not meet the diagnostic criteria for CF. Further investigation of CFTR function through rectal organoid morphology analysis (ROMA)[1] revealed clear CFTR dysfunction (circularity index = 0.578, intensity ratio = 1.138) **(**Fig. 1**A and B)**. Stimulation of CFTR with forskolin alone caused major organoid swelling, compatible with high residual function **(**Fig. 1**C)**. The swelling was slightly increased by the CFTR modulators tezacaftor and ivacaftor, without further increase with the addition of elexacaftor.

After confirming CFTR dysfunction in the sweat gland (intermediate SCC) and in the intestinal tract (ROMA in the CF range), along with the presence of one clinical manifestation and two *CFTR* mutations, one of

* Corresponding author.
E-mail address: noelia.rodriguezmier@uzleuven.be (N. Rodriguez Mier).

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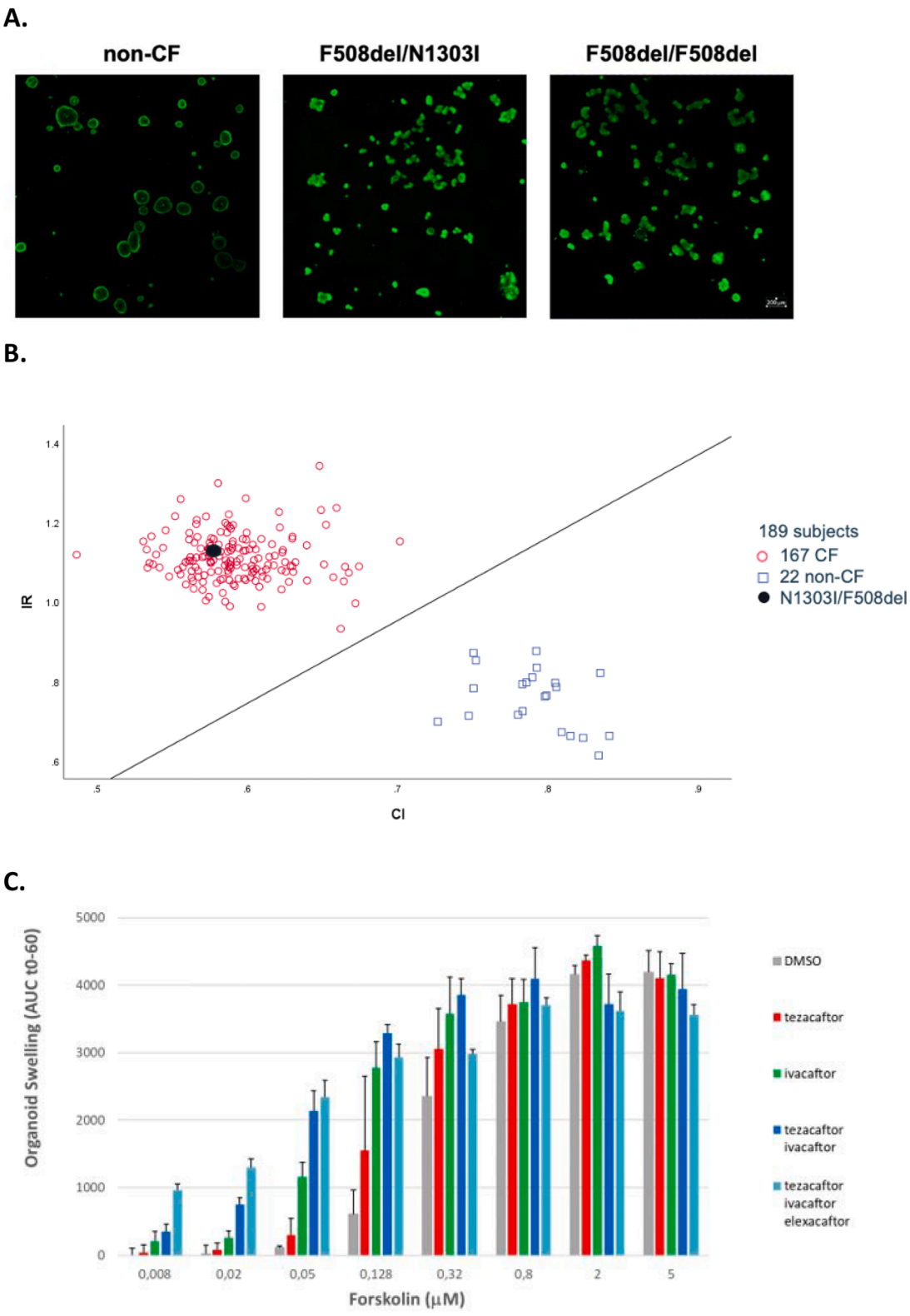

Fig. 1. CFTR function analysis A. Rectal organoids of index case (middle). For comparison rectal organoids from a non-CF individual (*left*) and F508del homozygous individual with CF (*right*) are shown. CF organoids have an irregular shape without a visible lumen while non-CF organoids are circular with a non-water-filled central lumen. **B. ROMA (rectal organoid morphology analysis) result.** ROMA clearly discriminates CF from non-CF organoid samples based on the Intensity Ratio (IR) and Circularity Index (CI) of the rectal organoids using a linear discriminant analysis (adapted from Cuyx et al. Thorax 2021). The ROMA indexes of the N1303I/F508del organoids are in the range of CF organoids (*black circle*). **C. FIS assay results on rectal organoids of index case.**

which was of uncertain significance, the patient was diagnosed with Pseudo-Bartter syndrome (PBS) as a CFTR-related disorder (CFTR-RD). After rehydration and salt supplementation, the child's blood electrolytes returned to normal. Oral salt supplementation and tube feeding were continued for 8 months resulting in catch-up growth and weight gain just above the 25th percentile (z-score = -0.6). Ultimately, salt supplementation and tube feeding were discontinued successfully without recurrence of poor weight gain or metabolic alkalosis under a salt-rich diet.

The present case highlights four important issues.

First, CFTR-RD is defined in the latest recommendations as "a clinical condition with evidence of CFTR protein dysfunction that does not meet the diagnostic criteria for CF" [2]. However, there is an ongoing debate surrounding the inclusion of isolated PBS or metabolic alkalosis in the list of CFTR-RD[2]. This question has also been raised in an Italian cohort, where three infants were diagnosed with isolated PBS[3]. Among them, one tested positive at CF-NBS, while all displayed normal or intermediate SCC results. Even after a follow-up period averaging nine years, no additional manifestations of CF were diagnosed.

Secondly, demonstrating CFTR dysfunction is a hard task in infants. Nasal potential difference measurements are not feasible, and intestinal current measurements require considerable experience 'on site'. Therefore, we analyzed the morphology of the rectal organoids. This CFTR assay is not yet fully validated but can be offered more widely, as the rectal biopsy can be sent to a reference lab for further analysis [1].

Thirdly, PBS develops owing to renal or extrarenal chloride loss, leading to hypokalemic alkalosis. The pathophysiology of PBS in people with CF is thought to be primarily driven by salt loss in sweat. In this case, PBS occurred in an infant with only mild SCC elevation. He presented with progressive weight loss and slowing of height growth, most likely as a symptom of chronic salt depletion not adequately counteracted by the normal - low sodium - diet of a toddler and exacerbated by high sweat volumes during a heat wave.

Although it may seem unlikely, PBS has also been described in eight Indian infants with CF with normal/intermediate SCC results[4]. CFTR dysfunction could increase the risk of PBS in dehydrated and even mildly salt-depleted infants, by disturbing the salt homeostasis in the kidney. Renal bicarbonate excretion is indeed dependent on functional CFTR[5].

Pseudo-Bartter syndrome treatment is essentially hydration and electrolyte replacement therapy, with close follow-up of weight gain and of urine and salt electrolytes.

Finally, such exceptional cases have sparked discussions regarding the need for further follow-up after a positive CF-NBS but no CF(SPID) diagnosis. This infant should not be considered as a 'false negative' neonatal screening. The primary aim of neonatal screening is to lower the age at diagnosis in children with CF to allow early treatment and improve prognosis, rather than merely detecting CFTR dysfunction. While the risk of progression to a CFTR-RD following a positive neonatal screening remains uncertain, it is likely to be low. Furthermore, the relevance of a 'pre-symptomatic diagnosis' in CFTR-RD is unclear given the better overall prognosis. However, it may be recommended that screen-positive children with (unexplained) failure to thrive or chronic respiratory symptoms should be evaluated at a CF centre. Further follow-up of children with CFTR-RD at a CF centre is preferred, because of the risk of developing CF symptoms.

In conclusion, PBS can be considered as a rare presentation of CFTR-RD and can occur in children with sweat chloride below the CF range. Functional testing of CFTR by ROMA enabled a more accurate diagnosis. Despite the negative work-up after CF-NBS, this infant developed CFTR-RD, but this should not be considered as a screen failure.

Credit author statement

- Noelia Rodriguez Mier: investigation, data curation, writing – original draft
- Senne Cuyx: formal analysis, data curation, writing – review & editing
- Anabela S. Ramalho: conceptualization, methodology, formal analysis, resources, writing – review & editing, supervision
- Virginie Antoons: investigation, writing – review & editing
- Mieke Boon: writing – review & editing
- Marijke Proesmans: writing – review & editing
- Djalila Mekahli: investigation, writing – review & editing
- François Vermeulen: conceptualization, methodology, investigation, resources, writing – review & editing, supervision

Declaration of competing interest

None to declare.

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