Clinical case

Hypochloremia and hyponatremia as the initial presentation of cystic fibrosis in three adults

Hypochlorémie et hyponatrémie révélatrices d’une mucoviscidose : à propos de trois cas adultes

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Résumé
La mucoviscidose provient de mutations du gène cystic fibrosis transmembrane conductance regulator (CFTR). Le diagnostic est effectué le plus souvent chez le nourrisson ou l’enfant devant des atteintes respiratoires ou digestives. Des troubles hydro-électrolytiques inauguraux sont classiques dans l’enfance, mais n’ont été rapportés à ce jour que chez trois adultes. Nous décrivons ici trois nouveaux cas d’adultes ayant présenté comme premiers signes de mucoviscidose une hypochlorémie et une hyponatrémie de déplétion après avoir été exposés à la chaleur. Chez une patiente, l’hyponatrémie a été compliquée de convulsions. Les deux autres patients, deux frères, étaient porteurs de la mutation c.4434insA de l’exon 24 qui n’a pas été décrite à ce jour. Une déshydratation aiguë est très rarement la première manifestation de mucoviscidose chez l’adulte, mais peut engager le pronostic vital. Une forme modérée de mucoviscidose doit donc être évoquée en présence d’une déshydratation extracellulaire avec hyponatrémie et hypochlorémie chez un adulte, même en l’absence de signe accompagnateur.

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Mots clés: Mucoviscidose ; CFTR ; Hyponatrémie ; Hypochlorémie ; Alcalose métabolique

Abstract
Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Most diagnoses of CF are made during infancy or childhood, and are based on respiratory or digestive involvement. Initial extracellular dehydration leading to the diagnosis of CF is usual in infants but has only exceptionally been reported in adults. We describe three new adult cases of CF initially presenting with depletive hyponatremia and hypochlorremia following exposure to heat. At first consultation, these patients had no symptoms suggestive of CF. One patient presented with a seizure induced by hyponatremia. The two other patients were siblings carrying a novel c.4434insA mutation in exon 24 of CFTR. Acute dehydration is a very rare initial manifestation of CF but may be life-threatening. The possibility of CF should not be ignored in cases of depletive hyponatremia, hypochloremia or hypokalemic metabolic alkalosis, even in otherwise healthy patients.

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Keywords: Cystic fibrosis; CFTR; Hyponatremia; Hypochloremia; Metabolic alkalosis

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1. Introduction

Cystic fibrosis (CF), the most common life-threatening autosomal recessive disorder in Caucasians, is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, chromosome 7 [1]. Respiratory and digestive complications often lead to the diagnosis of CF during childhood. Salt loss through abundant perspiration causes depleitive hyponatremia, hypochloremia, and hypokalemic metabolic alkalosis in CF patients. An initial CF presentation with extracellular dehydration is usual during infancy [2] but is extremely rare in adults, with very few cases reported to date [3–7]. We describe three adult cases of CF initially presenting with extracellular dehydration associated with hyponatremia and hypochloremia.

2. Results

2.1. Family 1

A 21-year-old man was admitted in July 1994 for asthenia, paresthesia, and vomiting. He had recently taken up a job as a metalworker. He had no medical history or record of medication use. The results of physical examination were normal. Laboratory analyses revealed hyponatremia, hypokalemic and hypochloremic alkalosis, and renal failure (Patient 1, Table 1). These problems resolved rapidly with intravenous isotonic saline infusion and potassium chloride supplementation. The electrolytic disorders were attributed to the vomiting.

The patient was readmitted in July 1995 with similar symptoms. He had changed jobs and was then working as a cook in a restaurant where he was professionally exposed to high ambient temperatures. He was not on any medication. Laboratory analyses revealed electrolytic disorders associated with metabolic alkalosis and adaptive alveolar hypoventilation (Table 1). The patient was treated as in July 1994 and recovered rapidly. Adrenal insufficiency was ruled out and excessive sweating in a hot working environment was assumed to have triggered his symptoms.

In 2006, the patient underwent exploration for infertility. Obstructive azoospermia with absence of the vas deferens suggested a diagnosis of CF. Sweat test by quantitative pilocarpine iontophoresis revealed a chloride concentration of 94 mmol/L. In 2000, a heterozygous F508del mutation was observed in 2003 (Table 1). The electrolyte balance was restored by abundant water intake. Both of them denied further symptoms.

2.2. Family 2

During the August 2003 heat wave, a 30-year-old woman was admitted for mental disorder following an initial seizure. She had given birth 40 days earlier. She had been suffering from asthenia, weight loss, headache, excessive perspiration, and intense thirst for 2 weeks, and more recently from abdominal pain. She had no past medical history. On admission, she suffered a second seizure followed by prolonged coma requiring artificial ventilation. She was apyrexial, and physical examination was normal with no focal neurological deficit. The results of initial laboratory analyses revealed severe hyponatremia, hypochloremia, and renal failure. An arterial blood gas test performed under artificial ventilation detected respiratory alkalosis with a shunt effect (Patient 3, Table 1). Hypoxemia was thought to be secondary to microbial inhalation during convulsions. The results of cerebral computed tomography scans and cerebrospinal fluid analyses were normal, and plasma screening for toxic compounds was negative. The patient received intravenous isotonic fluids, with sodium and potassium chloride, and hydrocortisone hemisuccinate because adrenal insufficiency was suspected. She recovered rapidly. *Pseudomonas aeruginosa* pneumopathy was diagnosed a few days later. Adrenal insufficiency was ruled out. Convulsions were attributed to severe depleitive hyponatremia with no identified cause.

In June 2005, the patient was readmitted for asthenia and vomiting. Her eyes were sunken and her skin wrinkled. Laboratory analyses revealed biological anomalies similar to those observed in 2003 (Table 1). The electrolyte balance was restored by treatment, but was again disrupted 3 weeks later (Table 1). The patient reported abundant sweating, which forced her to change clothes frequently, with episodes of thirst, headache, nausea, and vomiting.

Since her sister had been investigated for CF, sweat tests were performed, and revealed chloride concentrations of 136 and 118 mmol/L. In 2000, a heterozygous F508del mutation was demonstrated by PCR and non-denaturing polyacrylamide gel electrophoresis of amplification products showed a c.1653-1655delCTT (F508del) mutation in exon 10 of the CFTR gene. All exons were analyzed by PCR, denaturing HPLC and sequencing. He carried a c.4434insA mutation in exon 24 resulting in a premature stop codon (p.K1461X). The c.4434insA mutation was inherited from his mother.

He reported no previous symptom suggesting CF. Investigations revealed a mild CF phenotype with borderline stool fat content, functional hypoglycemia without diabetes mellitus, chronic sinusitis secondary to nasal polyps, and slight upper lobes bronchiectasis inducing cough and sputum in the effort with normal pulmonary function.

During the August 2003 heat wave in Europe, his brother was admitted to the emergency department for deep asthenia, muscle cramps, and abdominal pain. He was 24 years old and worked as a waiter. He had no medical history or record of medication use. The results of physical examination were normal. Laboratory analyses revealed hypochloremia, hyponatremia, renal failure, and metabolic alkalosis (Patient 2, Table 1). Intravenous rehydration and electrolyte supplementation rapidly resolved these disorders. Adrenal insufficiency was excluded. Like his elder brother, he carried F508del and c.4434insA mutations, and had bilateral absence of the vas deferens. No previous health problem might have suggested CF. Similar findings were made in a third brother who presented without any other symptoms suggestive of CF, except for bouts of asthenia induced by warm weather that were resolved by abundant water intake. Both of them denied further investigations.
electrophoresis of amplification products. In 2003, a fresh analysis of all exons of \textit{CFTR} by PCR, denaturing high performance liquid chromatography (HPLC), and sequencing revealed the c.3849+40A>G sequence variation of the other allele in intron 19. The c.3849+40A>G intronic variation was inherited from her mother and the c.1653-1655delCTT (F508del) mutation from her father.

The patient’s body mass index was 32.0 kg/m²; her pancreatic function was sufficient but she had asymptomatic diffuse bronchiectasis with a slight pulmonary restriction. She had no history of sinusitis. She reported no symptom previous to the seizure that might have suggested CF.

Her dizygote twin sister had a history of diffuse bronchiectasis with recurrent bronchopulmonary infections since the age of 20 years. Sweat tests revealed chloride concentrations of 109 and 136 mmol/L. She carried the same \textit{CFTR} alleles as her sister. She had exocrine pancreatic insufficiency and nasal polyps with recurrent sinusitis. However, she reported no heat-induced exhaustion and no electrolytic disorders.

3. Discussion

We describe three white Caucasian adults originating from Western France in whom electrolytic disorders occurred after exposure to heat, as an initial manifestation of CF. Data from the patient registry of the US Cystic Fibrosis Foundation showed that in 2002, 9.9% of diagnoses of CF were made in adults, in most cases on the basis of respiratory symptoms [8]. To date, CF with initial electrolytic disorders has been reported in few adult patients [3–7]. Three men were working in a warm environment when they experienced dehydration and muscle cramps. Two of them carried F508del and c.482G>A (R117H) \textit{CFTR} mutations [3,6], and one of them was a compound heterozygote with F508del and c.2789+2insA mutations [4]. All patients suffered from hypochloremia, elevated CO₂ levels, renal failure, and less constantly hyponatremia and hypokalemia. They had mild CF, and two of them suffered from azoospermia. CF may thus be revealed by heat exhaustion as reported in the army personnel [5].

In normal conditions, chloride is reabsorbed from the primitive sweat through \textit{CFTR}. This chloride current supports sodium reabsorption through activation of epithelial sodium channels at the apical membrane of duct cells. Thus, the excreted sweat is finally hypotonic. In CF, defective chloride absorption fails to activate the sodium channel, thus leading to sodium sweat loss [9]. When CF patients sweat excessively, they lose a large amount of sodium chloride [9], causing the blood volume to decrease. Blood volume contraction induces secondary hyperaldosteronism and hypokalemic metabolic alkalosis. Renin secretion stimulates angiotensin II production, enhancing proximal renal bicarbonate reabsorption [10]. In the collecting duct, aldosterone promotes bicarbonate reabsorption, and proton and

| Table 1 | Hemodynamics and biochemical data for the three patients on admission. |
|---------|-------------------------------------------------|---------|---------|---------|
| Variable | Family 1                                      | Family 2 |
|         | Patient 1 July 1994                          | Patient 2 August 2003                          | Patient 3 |
|         | SBP mmHg                                      | 110     | 110     | 124     |
|         | DBP mmHg                                      | 60      | 60      | 70      |
| Venous plasma | | 70      | 73      | 82      |
| Na mmol/L                      | 135–145                                      | 126     | 114     | 128     |
| K mmol/L                       | 3.5–5.0                                      | 4.2     | 4.4     | 2.3     |
| Cl mmol/L                      | 95–105                                       | 82      | 56      | 71      |
| CO₂ mmol/L                     | 24–30                                        | 24      | 21      | 31      |
| Protein g/L                    | 65–80                                        | 89      | 106     | 104     |
| Creatinine µmol/L              | 44–120                                       | 110     | 488     | 238     |
| Arterial blood                 |                                              |         |         |         |
| pH                               | 7.37–7.43                                    | 7.51    | 7.49b   | 7.47    |
| PaO₂ mmHg                       | 90–100                                       | 68.0    | 72.0b   | 81      |
| PaCO₂ mmHg                     | 37–43                                        | 51.8    | 25.0b   | 41      |
| HCO₃ mmol/L                    | 25–29                                        | 41.4    | 18.5b   | c       |
| Urine                           |                                              |         |         |         |
| Na mmol/L                       | c                                            | 15      | 18      | 10      |
| K mmol/L                        | c                                            | 80      | 88      | 23      |
| Cl mmol/L                       | c                                            | 8       | 9       | 12      |

Cl: chloride; CO₂: carbon dioxide; DBP: diastolic blood pressure; HCO₃: bicarbonate; K: potassium; Na: sodium; PaCO₂: arterial carbon dioxide pressure; PaO₂: arterial oxygen pressure; pH: potential of hydrogen; SBP: systolic blood pressure.

a Adult reference range of the laboratory.
b On artificial ventilation.
c Not available.
potassium secretion, leading to hypokalemic metabolic alkalosis. The differential diagnoses of CF dehydration, based mainly on urine analysis, are summarized in Table 2 [3,4,6,10–12].

Compared to the severe CFTR alleles, certain mild alleles tend to be associated with significantly lower sweat chloride concentrations [13]. However, neither the CFTR genotype nor sweat chloride levels have been shown to be correlated with the occurrence of dehydration episodes. Indeed, the risk factors for dehydration in CF have not yet been determined. Thus, in case of exposure to heat, any CF patient may experience extracellular dehydration, even a patient with a mild form of the disease or with isolated congenital bilateral absence of the vas deferens. That is why every CF patient should be advised to avoid exposure to heat and should be prescribed sodium chloride supplementation during the warm season.

The c.4434insA mutation in exon 24 (Family 1) has not been reported so far in the CF mutation database [14]. Mutations in the exon 24 of CFTR gene are not routinely screened in France and the c.4434insA mutation was revealed after an extensive analysis of all CFTR exons. This mutation is likely to be pathogenic because it results in a premature stop codon, leading to the formation of a truncated protein (p.K1461X), and it was not found in a panel of more than 500 control chromosomes. Third, it was present in the proband’s sister who was also affected with CF. Similarly to a more distal intronic variation in intron 19 (c.3849+10kbC>T) [18], the c.3849+40A>G intronic variation might create a new splicing site leading to the aberrant insertion of an additional cryptic exon. This intronic variation may also induce an aberrant splicing of succeeding exons, or reduce the efficiency of transcription.

4. Conclusion

Missing the diagnosis of mild forms of CF may lead to life-threatening complications. As a lesson from these observations, although acute dehydration is a rare initial manifestation of the disease, the possibility of CF should not be ignored in cases of depletive hyponatremia, hypochloremia or hypokalemic metabolic alkalosis, even in otherwise healthy patients. Once the diagnosis of CF is established, recurrences of dehydration should be prevented by salt supplementation during the warm season.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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