Prerenal azotemia from excessive sweating in an adult with a cystic fibrosis gene mutation

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ABSTRACT

We present the case of a 58-year-old male with chronic kidney disease who was admitted to the hospital multiple times with extracellular fluid volume depletion and prerenal azotemia. Some episodes were associated with gastrointestinal fluid losses and others with profuse diaphoresis in the absence of gastrointestinal fluid losses. At the age of 57 years, a common cystic fibrosis transmembrane conductance regulator protein mutation and a family history of cystic fibrosis were documented. We hypothesize that the abnormal cystic fibrosis transmembrane conductance regulator resulted in repeated bouts of excessive sweating, extracellular fluid volume depletion, and acute renal failure. This case is unique because of the prolonged period of time over which multiple documented episodes of prerenal acute renal failure occurred and because of the onset of the episodes in adulthood.

Key words: Acute renal failure, prerenal azotemia, extracellular fluid volume depletion, cystic fibrosis, cystic fibrosis transmembrane conductance regulator protein

Introduction

Cystic fibrosis (CF), one of the most common inherited diseases in the Caucasian population, usually presents with persistent pulmonary infections, pancreatic insufficiency, and elevated sweat chloride levels. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) protein, which is expressed in all exocrine tissues. We present a case of an adult male with chronic kidney disease (CKD) and a family history of CF who came to our attention due to multiple episodes of acute renal failure (ARF) from extracellular fluid volume (ECFV) depletion related to profuse diaphoresis or diarrhea. During the diagnostic work-up, he was found to have mutation in the *CFTR* gene. Review of the literature demonstrated that the spectrum of severity of CF is wide and that CF predisposes to volume depletion and ARF in children. Our case suggests that adults with certain CFTR mutations may present with mild and atypical forms of CF, such as prerenal ARF due to volume depletion.

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Case Report

A white male who was born in 1950 had nonprogressive CKD [serum creatinine concentration (S-Cr) 1.5-2.0 mg/dL] since 1994. In 1996, he had a transient episode of increased azotemia (to 4.2 mg/dL) of unknown etiology. Multiple additional episodes of ARF occurred between 2004 and 2008; he was admitted to our hospital 8 times during this period [Figure 1]. ARF appeared to be prerenal from ECFV depletion, since the patient presented with hypotension and orthostasis, and the increases in azotemia resolved rapidly (2-3 days) with intravenous crystalloid infusion alone. The highest serum creatinine and blood urea nitrogen were 7.9 and 158 mg/dL, respectively, without need for dialysis. Episodes of ECFV depletion with ARF occurred some of the time from diarrhea (February 2005, December 2005, December 2006) and some of the time from excessive sweating in the absence of diarrhea (December 2004, August 2005, October 2007). In January 2005, he was admitted with

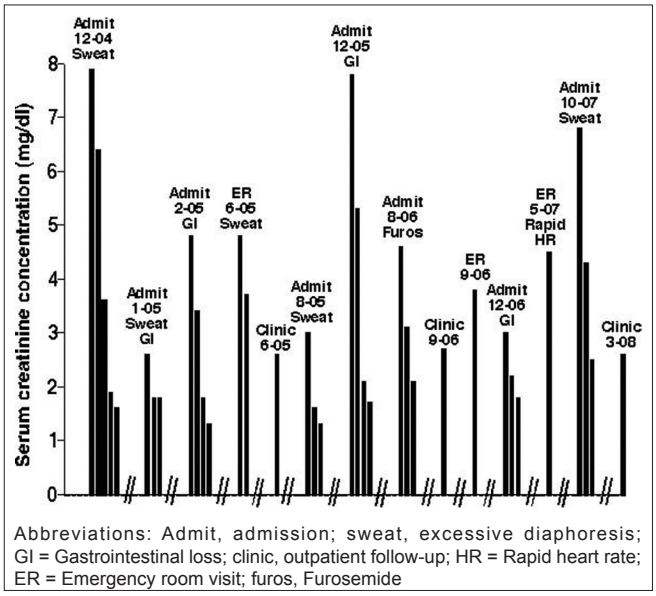

Figure 1: Episodes of ARF from 2004 through 2008. The x-axis represents time, and the double slash (//) represents gaps in time. Each bar signifies the S-Cr value from a single day, and adjacent bars signify S-Cr values on consecutive days. In addition to the 35 S-Cr values represented by the bars, 32 baseline S-Cr values, ranging from 1.5 to 2.0 mg/dL, have been documented in the 2004-2008 period but are not represented on the figure for the sake of clarity

both diarrhea and profuse diaphoresis. Another admission in August 2006 was felt to have resulted from overdiuresis from furosemide, which he took for several months for congestive heart failure symptoms. Two colonoscopies revealed ischemic colitis. Figure 1 also shows 6 outpatient episodes of elevated S-Cr (clinic, emergency room visits), but the lack of laboratory data does not allow us to determine the nature of the ARF.

Other relevant medical history included hypertension, congestive heart failure, psoriasis, diabetes mellitus, and pneumonia. Relevant chronic medications have included prednisone 10 mg, benazepril, doxazosin, simvastatin, and mesalamine. He has a family history of CF - 2 nephews (homozygous for F508del) and possibly a brother (died at 1 year of age). Review of systems revealed occasional thick yellow sputum, chronic dyspnea, polyarthralgias with nonsteroidal anti-inflammatory drug use, and sticky, oily, floating stools, which reminded the patient's wife of the stools in the diapers of his nephews with CF. He denied hemoptysis, fever, and night sweats.

Physical examination revealed a body mass index 24.8, blood pressure 130/60 mmHg, respirations 20/min, heart rate 80/min, and afebrile. He was a well-nourished, well-developed male without sinus tenderness, nasal polyps, or digital clubbing. The rest of the physical exam was otherwise normal except for a psoriatic rash at the hairline and arthritic change in the hands.

Renal ultrasound in 2007 revealed the right kidney 8.2 cm in length and the left kidney 9.8 cm in length, with poor corticomedullary differentiation, thinned cortex, and no hydronephrosis. Proteinuria measured twice by urine protein-to-creatinine ratio was minimal (0.15 and 0.2 g/g). Two elective sweat chloride tests, performed when the patient was euvolemic and not in ARF, were 42 and 43 mmol/L (normal less than 40 mmol/L, positive greater than 60 mmol/L). A full genetic analysis (Ambry Genetics), which screens for more than 1400 known CFTR mutations, revealed F508del/unknown with the *7T/9T* allele for exon 9. Chest radiograph and computed tomography revealed pleural calcifications, but neither interstitial disease nor bronchiectasis was noted. Fecal elastase was 206 μg/g of stool (normal > 200 μg/g). Blood levels of fat-soluble vitamins, performed to screen for pancreatic malabsorption, showed mild vitamin D deficiency [total 25-hydroxy vitamin D 16 ng/dL (25-80 ng/mL)] and normal vitamin A and E levels.

Discussion

The cause of this patient's CKD is not completely clear. Although he had an extended history of diabetes mellitus, his CKD most likely resulted from nonsteroidal anti-inflammatory agents that he took for chronic psoriatic arthritis. Lack of proteinuria and small kidney lengths are more consistent with a tubulointerstitial process such as analgesic nephropathy and less consistent with diabetic glomerulosclerosis. In addition, renal vasoconstriction in response to decreased cardiac output from diastolic dysfunction may also have contributed to the chronic reduction in glomerular filtration rate.

The patient developed at least 8 episodes of prerenal ARF from ECFV depletion for which he was hospitalized over a 4-year period. It is likely that the outpatient episodes of increased S-Cr constitute additional bouts of ARF from ECFV depletion, but laboratory data are too scant to confirm these. The very rapid restoration of glomerular filtration rate with intravenous crystalloid and the absence of associated events or agents that cause acute tubular injury are strongly consistent with the diagnosis of prerenal azotemia. We suspect that ECFV depletion occurred from gastrointestinal losses in some of the episodes and from severe, salty sweating in other episodes. Historical and laboratory features were suggestive of atypical/mild CF, including symptoms of steatorrhea that resolved with oral pancreatic enzymes, a fecal elastase at the lower limits of normal, excessive/salty sweating, 2 abnormal but non-diagnostic sweat tests, and a common CFTR mutation. On the other hand, he did not have a typical CF phenotype, and we identified only one CFTR mutation associated with CF.

It is possible that the elevated sweat chloride was a laboratory error, but the values were consistent on repeat testing. Certain medical conditions (during ECFV depletion, atopic dermatitis, inherited storage diseases) have been associated with elevated sweat testing results, but these are not relevant for this patient.[1] Sweat test was performed both times electively and when the patient was euvolemic. Also possible but even less likely is an abnormality of the epithelial sodium channel, which can result in abnormal sweat test values and a CF-like presentation;[2] genetics of the epithelial sodium channel were not tested in our patient. We attempted to obtain nasal potential difference testing, but he declined due to financial considerations and to avoid the long travel to the center that performed the assay. A number of clinical factors may have made this patient more susceptible to acute reductions in glomerular filtration rate when he became volume depleted: existing CKD, history of congestive heart failure, the angiotensin converting enzyme inhibitor, and non-steroidal anti-inflammatory drugs.

ARF in CF patients has been reported previously, mostly from acute use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, aminoglycosides, other antibiotics, and cyclosporine,[3-10] but no such association was evident in our patient. Desmazes-Dufeu *et al*. described severe dehydration, ECFV depletion, and functional kidney failure in 6 of 245 adults with established CF during the August 2003 heat wave in France.[11] Fluid resuscitation normalized the blood chemistry values within 48 h in 5 patients, but the sixth patient died of malignant hyperthermia. Ballestero *et al*. described repeated episodes of hyponatremia and ECFV depletion without renal failure as the first presentation of CF in infants in Spain.[12] The authors concluded that CF should be included in the differential diagnosis of unexplained hyponatremic volume depletion, especially in countries where neonatal CF screening is not routinely performed. A report from elsewhere in the Mediterranean region (Cyprus) described ECFV depletion and electrolyte abnormalities as presenting features of CF in children, in contrast to the classic CF abnormalities of pulmonary infection and pancreatic insufficiency.[13] These milder forms of CF were caused by genotypes different from the classic F508del/F508del, such as F508del/unknown (as in our case), L346P/F508del, L346P/1677delTA, F508/W1282K, F508del/W1282X, F508del/621+1G>T, and N1303K/unknown. The authors concluded that milder CF mutations are not recognized in many regions of the world. Interestingly, South Carolina's humid warm climate is not unlike that of the countries mentioned above (France, Spain, Cyprus). For example, Charleston, South Carolina, is located on the Atlantic coast at the geographic latitude of 32 degrees north, while Cyprus is located in the Mediterranean Sea at a latitude of 35 degrees north.

Our patient appears to be the first reported to have a CFTR mutation causing sweating, ECFV depletion, and severe pre-renal ARF, with the mutation detected in adulthood. One other somewhat similar case has been reported: a 36-year-old male found to have CF after he presented twice to medical attention with excessive sweating, fatigue, muscle cramps, hypokalemic metabolic alkalosis, and mild, reversible azotemia, with a maximum S-Cr of 1.6 mg/dL.[14] The existing literature reports clinical scenarios with presentations and natural histories that are different from those of our patient: adults with established CF who developed ECFV depletion and ARF during a heat wave[11] and ECFV depletion and ARF as the first manifestation of CF in infants[12] and children.[13] In addition, we feel that the repeated nature of the ARF episodes and the extended duration and documentation of follow-up are unique and remarkable.

In summary, a 58-year-old male with CKD experienced recurrent and severe episodes of prerenal azotemia from ECFV depletion from profound diaphoresis or diarrhea. During his work-up for his ARF, he was found to have a family history of CF, F508del/unknown CFTR genotype, and abnormal sweat tests. We could not confirm the diagnosis of CF, but we postulate that the underlying CKD and salt and water losses caused by the mutant CFTR contributed to several of his episodes of ARF.

References

1. LeGrys VA, Rosenstein BJ, Doumas BT, Miller WG, D'Orazio P, Eckfeldt GH, *et al*. Sweat testing: sample collection and quantitative analysis; approved guidelines - second edition (NCCLS document C34-A2) 2000;20:30.
2. Sheridan MB, Pfong P, Groman JD, Conrad C, Flume P, Diaz R, *et al*. Mutations in the beta subunit of the epithelial sodium channel in patients with a CD-like syndrome. Hum Molec Genet 2005;14:3483-98.
3. Bald M, Ratjen F, Nikolaizik W, Wingen AM. Ciprofloxacin-induced acute renal failure in a patient with cystic fibrosis. Paediatr Infect Dis J 2001;20:320-1.
4. Bertenshaw C, Watson AR, Lewis S, Smyth A. A survey of acute renal failure in cystic fibrosis patients in the United Kingdom. Thorax 2007;62:541-5.
5. Drew JH, Watson AR, Smyth A. Antibiotics and acute renal failure in children with cystic fibrosis. Paediatr Perinat Drug Ther 2002;5:65-7.
6. Kennedy SE, Henry RL, Rosenberg AR. Antibiotic-related renal failure and cystic fibrosis. J Paediatr Child Health 2005;41:382-3.
7. Kovesi TA, Swartz RB, MacDonald N. Transient renal failure due to simultaneous ibuprofen and aminoglycoside therapy in children with cystic fibrosis. N Eng J Med 1991;338:65-6.
8. Moffrett BS, Rosenstein BJ, Magayzel PJ. Ciprofloxacin-induced renal insufficiency in cystic fibrosis. J Cyst Fibros 2003;2:152-4.

9. Schindler R, Radke C, Paul K, Frei U. Renal problems after lung transplantation of cystic fibrosis patients. Nephrol Dial Transplant 2001;16:1324-8.
10. Stephens SE, Ridgen SPA, Price J. Acute renal failure in cystic fibrosis patients treated with ceftazidine and gentamicine in combination. Arch Dis Child 2001;84:169.
11. Desmazes-Dufeu N, Hubert D, Purgel PR, Kanaan R, Velea V, Dusser D. Severe dehydration and August 2003 heat wave in a cohort of adults with cystic fibrosis. Presse Medicale 2005;34:647-8.
12. Ballestero Y, Hernandex MI, Rojo P, Manzanares J, Nebreda V, Carbajosa H, *et al*. Hyponatremic dehydration as a presentation of cystic fibrosis, Ped Emerg Care 2006;22:725-7.
13. Yiallouros PK, Neocleous V, Zeniou M, Adamidou T, Costi C, Christophi C, *et al*. Cystic fibrosis mutational spectrum and genotypic/phenotypic features in Greek-Cypriots, with emphasis on dehydration as presenting symptom, Clin Genet 2007;71: 290-2.
14. Dave S, Honney S, Raymond JR, Flume PA. An unusual presentation of cystic fibrosis in an adult. Am J Kid Dis 2005;45:41-4.

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