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Elevated Sweat Chloride Levels Due to Arsenic Toxicity

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To the Editor: Arsenic toxicity is associated with gram-negative bacterial lung infections, bronchiectasis, and diabetes mellitus. The symptoms of arsenic toxicity overlap with those of cystic fibrosis, an autosomal recessive disease that is most common in people of Northern European ancestry. Cystic fibrosis is caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that functions as a chloride channel that regulates fluid transport in the lungs, pancreas, and other organs. The diagnostic test for cystic fibrosis is the sweat test; an elevated sweat chloride level indicates CFTR dysfunction. Recent studies in cell culture show that arsenic causes degradation of CFTR.¹ We report the findings of a study examining the association between arsenic exposure and sweat chloride level in Bangladeshi adults.

Participants in this cross-sectional study were recruited from a roster of previous participants in a case-control study of arsenic-related skin lesions conducted between 2001 and 2003 in Pabna, Bangladesh,² a rural area where the groundwater is contaminated with arsenic. Many of the patients in this study also participated in a follow-up study conducted between 2007 and 2009.³ For the current study, we evaluated 30 participants from the group who had been in the group with lesions and 70 participants who had been controls in the 2001–2003 study. Arsenic levels were measured with the use of ultraviolet visible spectrophotometry.⁴ Fingernails were analyzed by means of inductively coupled plasma-mass spectrometry.⁵ Sweat conductivity was measured with the use of a Sweat-Chek analyzer (Wescor); values for sweat conductivity were converted by the instrument to equivalent levels of sodium chloride and reported in millimoles per liter. For the 54 participants whose sweat

conductivity was 50 mmol per liter or higher, a second sample was obtained and sweat chloride level was measured with the use of a Dimension RxL Max analyzer (Siemens). Sweat was obtained from skin that had not been affected by arsenic-related or other lesions. Pulmonary-function tests were conducted with a SpirHOMEter (Cosmed). DNA from participants whose sweat chloride reached a level that was diagnostic for cystic fibrosis (≥ 60 mmol per liter) underwent *CFTR* full-gene sequencing analysis (sequencing was performed by Ambry Genetics).

None of the 11 participants with sweat chloride levels of 60 mmol per liter or higher had a genetic diagnosis of cystic fibrosis (Table 1). Current arsenic levels in water were higher for the 40 participants with abnormal sweat conductivity (>60 mmol per liter) than for participants with normal or intermediate sweat conductivity (median, 11.9 µg per liter vs. 2.7 µg per liter; *P* = 0.01). The same pattern was seen with current arsenic levels in fingernails (median, 5.64 µg per gram vs. 1.39 µg per gram; *P* = 0.008). Adjusted models revealed no significant confounding according to age, sex, smoking status, or body-mass index. There was no relationship between sweat chloride level and scores on lung-function tests or pulmonary symptoms. Our study shows that elevated sweat chloride levels are found among persons exposed to arsenic in the absence of a genetic diagnosis of cystic fibrosis.

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Table 1

Clinical Characteristics and Laboratory Results for Persons with Elevated Sweat Chloride Levels.*

Participant No.	Age	Male Sex	Smoking Status	History of Skin Lesions	Sweat Conductivity	Sweat Chloride	Arsenic in Drinking Water			Arsenic in Fingernails			FEV ₁	CFTR Sequencing
	yr					mmol/liter	At Enrollment (2001-2003)	At Follow-up (2007-2009)	Currently (2013-2014)	At Enrollment (2001-2003)	At Follow-up (2007-2009)	Currently (2013-2014)		Reportable Variant [†]
								µg/liter			µg/g		%	
1	55	No	Never	No	75	62	431.0	420.0	155.7	14.08	17.83	20.86	97	p.1807 M (c.2421A→G)
2	28	Yes	Current	No	69	63	88.3	–	151.9	9.42	–	12.52	87	p.V456A (c.1367T→C)
3	33	Yes	Previous	No	86	63	24.2	150.0	12.0	4.00	1.30	1.69	85	c.3469-20T→C
4	40	Yes	Never	Yes	98	66	38.6	69.0	8.9	9.85	1.90	3.07	51	c.4243-16A→G
5	30	Yes	Never	Yes	76	68	535.0	43.0	19.4	11.86	11.81	12.99	89	No mutations
6	38	Yes	Current	No	76	69	1.1	–	60.6	9.64	–	11.61	77	12/5T; 10/9T [‡]
7	55	Yes	Current	Yes	74	70	661.0	30.0	0.4	18.28	10.84	26.48	114	No mutations
8	58	Yes	Previous	Yes	58	72	553.0	900.0	1.1	19.42	29.43	12.83	80	No mutations
9	37	Yes	Never	No	83	75	33.0	11.0	1.8	3.47	4.15	4.71	78	No mutations
10	42	Yes	Current	Yes	88	76	697.0	920.0	0.9	24.06	45.19	5.86	54	No mutations
11	65	Yes	Previous	Yes	84	78	839.0	–	15.2	15.72	15.95	11.54	104	No mutations

* FEV₁ denotes forced expiratory volume in 1 second, and dashes indicate that the participant was not evaluated in a 2007-2009 follow-up study.^a

[†] All reported variants were heterozygous. No deletions or duplications were identified.

[‡] Analysis of intron 8 *CFTR* TG-repeat/poly(T) variants revealed that one participant had the indicated genotype; all other participants had the nonreportable sequence 7T/7T poly(T).