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Autonomic Nervous System Dysregulation in Monozygous Twins With Nephropathic Cystinosis

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Kidney Int Rep (2018) **3,** 1489–1496; https://doi.org/10.1016/j.ekir.2018.07.019

INTRODUCTION

Nephropathic cystinosis (NC) (OMIM 219800) is a rare, autosomal recessive disorder due to one of many possible mutations in the cystinosin (CTNS) gene that creates a functional defect in the lysosomal membrane exporter protein, CTNS. It is commonly diagnosed in infancy due to a presentation that includes failure to thrive, glycosuria, and severe renal Fanconi syndrome; NC generally leads to chronic kidney disease (CKD).

NC results in failure of cystine efflux from cell lysosomes and often cystine crystal accumulation.[1–4] If NC is not addressed and treated, kidney failure develops in the mid to late childhood years (or earlier, depending on the specific mutation), and many extrarenal organs are affected as well. Additional actions of CTNS have been proposed for other cell functions, including regulation of mammalian target of rapamycin complex-1 (mTORC1),[5] and in the absence of CTNS, these actions may contribute to the disease pathogenesis via impaired chaperone-mediated autophagy, accumulation of autophagosomal markers, increased mitophagy, and increased cellular apoptosis.[6,7] The only Food and Drug Administration–approved pharmacotherapy, cysteamine bitartrate, targets the metabolic defect and reduces cystine substrate depletion (as measured in leukocytes), and is believed to represent tissue lysosomsal organ depletion, which is not easily measured. A cystine level <1 nmol$^{1/2}$ cystine per milligram cell protein is categorized as being consistent with cystine depletion[8–10] in a mixed white blood cell preparation. With strict adherence to achieve optimal substrate depletion, it is believed that end-stage kidney failure that requires dialysis or transplantation is delayed but generally not ultimately prevented, and the average age of kidney transplantation simply advances to later adolescence or young adulthood from the childhood years.[11] Even with good control of the biomarker, it appears that many extrarenal problems develop as the patient with NC ages. Such extrarenal complications become more pronounced and extensive over time. Some of the clinically observed early extrarenal complications include altered skin and/or heat sensations, temperature regulation, heat intolerance, and reduced sweating (seen most commonly in those with a 57-kb CTNS deletion), which suggests that lysosomal cystine accumulation alone is most likely not responsible for the entirety of the metabolic derangements of cystinosis.[1,12] It has recently been noted that there is also inactivation or alteration of the upstream transient receptor potential vanilloid 1 (TRPV1) gene in CTNS$^{-/-}$ mice that harbor the 57-kb deletion; there may also be a resulting dysregulation in sympathetic nervous system activity in response to heat exposure.[13] Thus, a concern for body temperature regulation in patients with NC may be a realistic matter to evaluate.

To further explore temperature regulation, we examined a pair of identical female adolescent twins with NC 6 years after kidney transplantation (from a single deceased donor). The twins underwent clinical

testing to determine whether they exhibited autonomic dysregulation, a heretofore unstudied issue that might be relevant in NC, and to document thermoregulation dysfunction.

CASE PRESENTATION

Case 1

Monozygotic female adolescent twins, aged 16 years old, were originally diagnosed in infancy with NC and found to have a 57-kb deletion of the CTNS gene, the most frequent cause of NC in Western populations. They were on cysteamine bitartrate (cystagon-immediate release) since diagnosis. Each was currently prescribed Procysbi (cysteamine-delayed release [DR]) 675 mg every 12 hours. In addition, each twin was prescribed cysteamine hydrochloride (0.44%) eye drops due to cystine crystal accumulation in the lens and cornea.

Both twins were transplanted 6 years previously with kidneys from a single deceased donor source. Since that time, both twins experienced several episodes of transplant rejection, whereas twin 1 also developed Epstein-Barr virus positive posttransplant proliferative disorder. Table 1 includes clinical and medication data on the patients at the time of autonomic testing. As shown in Table 1, twin 2 exhibited a diastolic blood pressure (DBP) that exceeded the threshold for sex and height and had DBP readings 20% higher than those of twin 1.

Laboratory findings (biochemical characteristics) for both twins are shown in Table 2. Creatinine, blood urea nitrogen, and cystatin C levels were consistent with the CKD stage of each twin. Both patients also had blood drawn for measurement of their leukocyte cystine levels, which were obtained at the time of their regular laboratory tests. Those results were 1.65 and 1.90 $nmol^{1/2}$ cystine per milligram per protein for twins 1 and 2, respectively. Because the twins exhibited leukocyte cystine levels >1 $nmol^{1/2}$ cystine per milligram per protein, it indicated they had not achieved an optimal degree of substrate depletion for cystinosis patients on cysteamine therapy. This was due to incomplete adherence with their cysteamine bitartrate therapy. Table 3 lists a summary on cystinosis.

Both twins frequently described issues with heat intolerance and photophobia secondary to corneal cystine crystal deposition, but they demonstrated consistently normal clinical neurological examination findings. We decided to complete further testing of the twins to evaluate heat intolerance and possible associated autonomic dysfunction as opposed to what may simply be avoidance of light exposure on sunny days.

Table 1. Characteristics and medications of female monozygotic twins with nephropathic cystinosis

Characteristics	Twin 1	Twin 2
Age (yrs)	16	
Race	W	
Ethnicity	H	
Wt. (kg)	43.6	46.0
Ht. (cm)	152.3	154.8
BMI percentile (for age and sex) (kg/m^2)	25th	40th
Resting BP (mm Hg)	118/70	123/84
Measured GFR (ml/min per 1.73 m^2)	59.3	70.0
CKD stage	3a	2
Tacrolimus level (ng/ml)	5.5	4.5
Medications, Dose, Frequency		
Procysbi (cysteamine DR)	675 mg q 12 h	
Cysteamine HCL (0.44%)	1 gtt. OU q h while awake	
Amlodipine	10 mg/d	
Cardura	4 mg/d	—
Lisinopril	10 mg/d	
Drisdol	50,000 IU/ q 14 d	—
Cellcept	500 mg BID	
Tacrolimus	3 mg BID	2 mg BID
Synthroid	137 μg/d	125 μg/d
Mg oxide	400 mg BID	
Bactrim 400-80	40 mg 3×/wk	

BID, twice a day; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DR, delayed release; GFR, glomerular filtration rate by plasma clearance of iohexol; gtt, drops; H, Hispanic; HCL, hydrochloride; Ht., height; IU, international units; Mg, magnesium; OU, both eyes; q, every; W, white; Wt., weight.

Clinical Testing

During the period before testing, a directly measured glomerular filtration rate was completed on each twin using a plasma clearance of iohexol procedure.[14] The twins then underwent 3 clinical procedures at the Center for Autonomic Medicine in Pediatrics at Ann & Robert H. Lurie Children's Hospital of Chicago (Chicago, IL). Those procedures included the head-up tilt (HUT) test to assess baroreceptor function, a thermoregulatory sweat test (TST) to measure sudomotor function, and the quantitative sweat response test (QSWEAT), which is a sudomotor axon reflex test in which responses of the local axon reflex of sweat glands to iontophoresed acetylcholine are quantitated.[15] The use of the TST and QSWEAT procedures on patients are considered to be the gold standard for clinical evaluation, because they demonstrated a 90% sensitivity for detection of small fiber neuropathy.[16]

The HUT determines whether orthostatic (in)tolerance can be demonstrated and evaluates the interrelationship of breathing, heart rate (HR), and BP while the patient transitions from a supine to an upright position and then returns to the supine position. Simply stated, a patient lays on a tilt table in a supine

Table 2. Laboratory results

Results Conventional units (SI Units)								
Twin #	**Cr**	**BUN**	**Cystatin C**	**Alb**	**Phos**	**Na**	**K**	**Glucose**
1	1.08 (95.47)	15 (5.35)	(1.25)	4.5 (45)	3.7 (1.20)	136 (136)	4.0 (4.0)	98 (5.44)
2	0.81 (71.60)	13 (4.64)	(1.09)	4.9 (49)	3.8 (1.23)	137 (137)	4.2 (4.2)	94 (5.22)
Normal reference range	0.25–1.14 mg/dl	5.0–18.0 mg/dl	0.5–1.3 mg/l (1–17 yr)	3.6–4.7 g/dl	3.0–4.8 mg/dl	134–146 mEq/l	3.7–5.7 mEq/l	60–110 mg/dl
SI units normal Reference Range	22.1–100.78 mmol/l	1.78–6.43 mmol/l	0.50–1.30 mg/l	36.0–47.0 g/l	0.97–1.55 mmol/l	134–146 mmol/l	3.7–5.7 mmol/l	3.33–6.11 mmol/l

Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; K, potassium; Na, sodium; Phos, phosphorus (inorganic); SI, Standard international.

horizontal position for 10 to 20 minutes while baseline measurements are taken. Then, a HUT to 70° is done with measurements collected thereafter for 10 minutes. Following this, a tilt-down to a supine horizontal position occurs and is sustained for 2 minutes of additional measurements.

During the TST, the core body temperature is increased slowly to 1 °C higher than at prewarming (baseline) or a patient reaches a core temperature of 38 °C (whichever is greater). To prepare for the procedure, sweat-indicator powder is applied to the patient's anterior surface while lying supine on a bed. The patient is then rolled into the chamber, and it is sealed shut, while continuous surveillance and collection of all physiological measurements of the patient, chamber, and temperatures occurs. The ambient temperature is slowly increased with an average ramp rate of 5.0 °C/hour and with a relative humidity range of 35% to 45%.

Finally, for the QSWEAT, the patient is placed in a supine horizontal position. Once situated, 4 quarter-sized capsules of acetylcholine are topically applied on the forearm, proximal and distal leg, and foot. An imperceivable 2-mA current is delivered over a 5-minute period, followed by a 5-minute recovery, which results in an accurate quantitation of sweat produced in small areas of the skin.

Testing Results

Figures 1a to d represent the continuous HR and BP recordings of twin 1 (Figure 1a and b) and twin 2 (Figure 1c and d) during the HUT over the 10-second transition from a supine horizontal position to a 70° upright tilt. As seen in Figure 1a, the HR of twin 1 exhibited a compensatory increase to a maximum of 110 beats/min at 6.9 minutes into the HUT and remained at this level until she was returned to a horizontal and/or supine position. This was a change of 52 beats/min. In Figure 1b, a systolic BP (SBP) decline of 29.8 mm Hg can be seen at 0.3 minutes into the HUT. The BP of twin 1 recovered quickly to pre-HUT levels and remained stable thereafter throughout the 10-minute HUT. Conversely, for twin 2, HR increased by 45 to 120 beats/min and a 30-mm Hg SBP drop occurred when transitioned from a supine position to a 70° HUT (Figure 1c and d). In addition, the HR and SBP remained at these levels throughout the HUT until the twin returned to the supine position. Thus, both twins exhibited orthostatic tachycardia during HUT that was maintained until returning to the supine horizontal body position, which indicated a greater than average response compared with normative data.

For the TST, the baseline (pre-TST) for twin 1 and twin 2 are shown in Figure 2a and 2c, respectively, whereas postwarming period results for each twin are found in Figure 2b and 2d, respectively. By referencing the temperature scale shown between Figure 2a and 2b and Figure 2c and 2d, the images clearly demonstrate both twins with cold hands and feet before warming (Figure 2a and 2c). Conversely, in post-TST images, both twins displayed symmetric warming of their

Table 3. Teaching points

(i) Cystinosis results from a functional defect in the lysosomal-membrane exporter protein, cystinosin (CTNS), thereby resulting in failure of cystine efflux from cell lysosomes. When untreated, cystine crystals result and are deposited throughout the body, including in the cornea, retina, and most organs.
(ii) Nephropathic cystinosis (NC) is often diagnosed in infancy due to the development of severe renal Fanconi syndrome with failure to thrive. Chronic electrolyte replacement is essential.
(iii) Cystine accumulation is measured in leukocytes with a cystine level < 1 nmol$^{1/2}$ cystine per milligram cell protein categorized as being consistent with optimal cystine depletion.
(iv) Cysteamine bitartrate is the only Food and Drug Administration–approved therapy for cystinosis and is available in immediate and delayed release formulations.
(v) In NC, the 57-kb deletion has been associated with transient receptor potential vanilloid 1 (TRPV1) gene functional impairment.
(vi) Long-term extra renal manifestations of NC are frequently observed and include cognitive impairment and/or delays, altered skin and/or heat sensations, abnormal temperature regulation, heat intolerance, reduced sweating, and myopathy, the latter of which may eventually contribute to respiratory failure, all suggestive of autonomic nervous system dysfunction pertinent to thermoregulation.

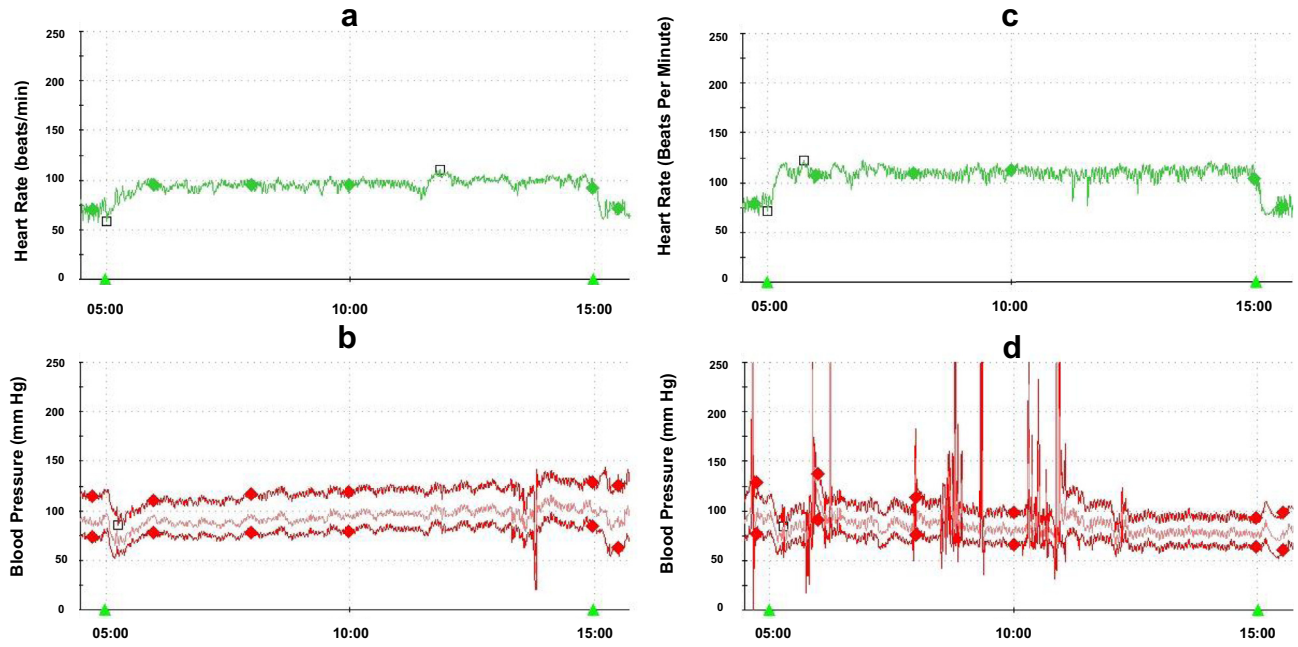

Figure 1. Head up-tilt (HUT) of twins 1 and 2 for continuous heart rate (a,c) and blood pressure recordings (b,d).

hands but their feet remained slightly cooler compared with other body regions (Figure 2b and 2d).

Postwarming images of twin 1 (Figure 3a) and twin 2 (Figure 3b) are shown with patchy regions of anhidrosis (in yellow) compared with the purple areas of sweat indicator powder, which demonstrated the regions where sweating occurred. Twin 1 had 53% anhidrosis but preserved sweating on the upper

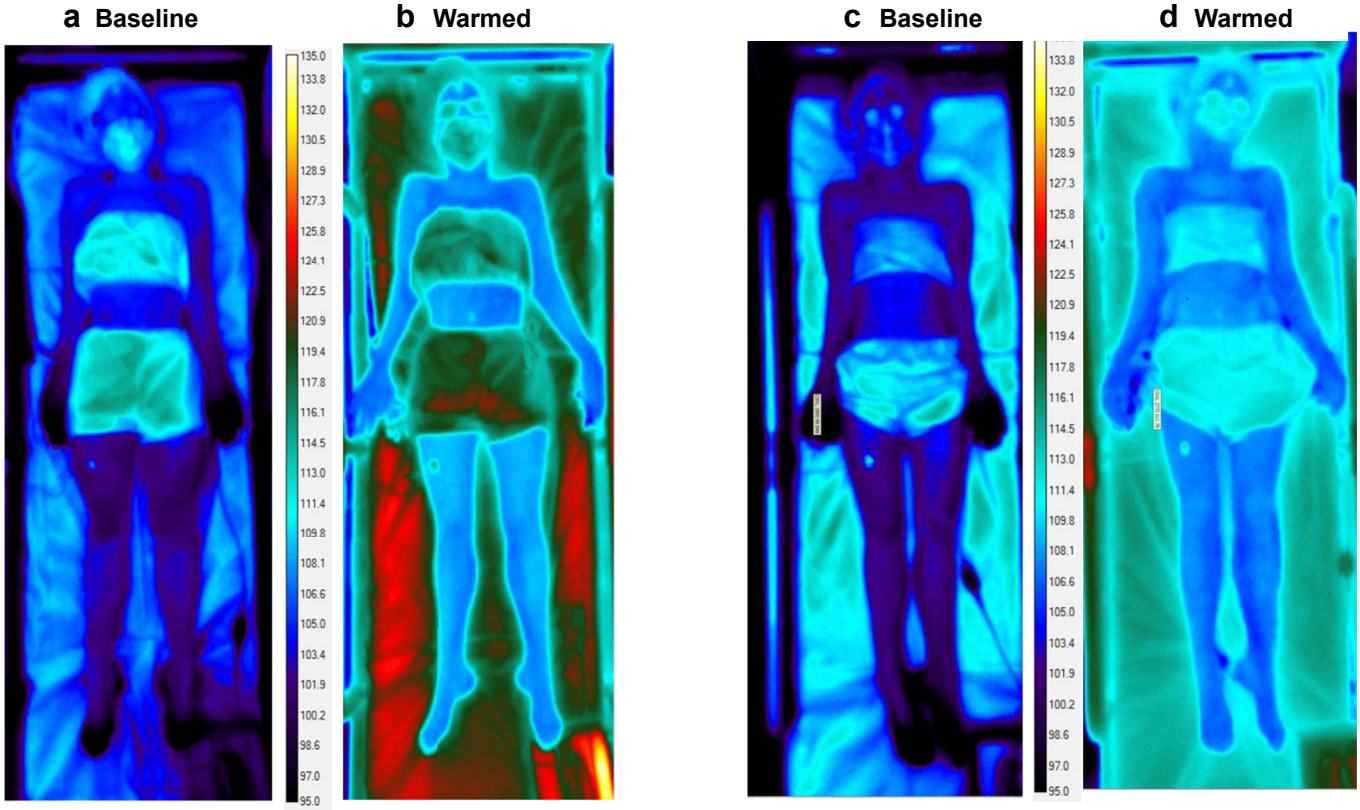

Figure 2. Thermoregulatory sweat test baseline and warmed (post) test twin 1 (a,b) and twin 2 (c,d), respectively. A temperature-color gauge is centered between each baseline and the warmed figure with values shown in degrees Fahrenheit.

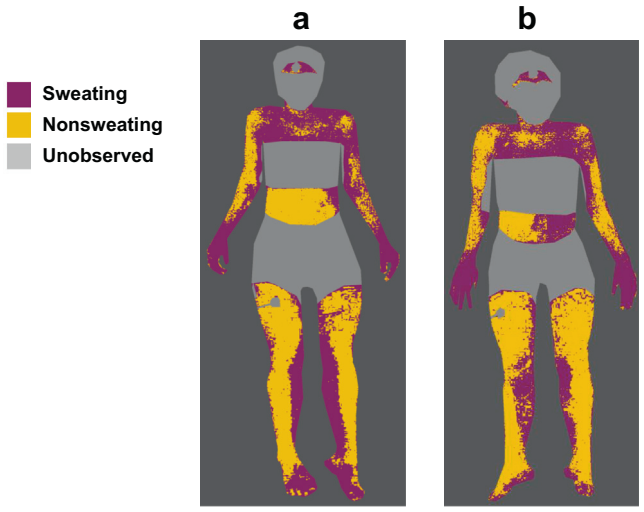

Figure 3. Diaphoresis patterns of twin 1 (a) and twin 2 (b) at the completion of the thermoregulatory sweat test (TST).

trunk, left abdomen, both hands, and medial legs, whereas twin 2 exhibited 50% anhidrosis and residual sweating of the upper trunk, bilateral hands, and medial legs.

QSWEAT results of twin 1 are shown with sweat rates of the forearm (25−50th percentile) (Figure 4a); proximal (Figure 4b) and distal leg sweat rates were each <10th percentile (abnormal for sex and age) (Figure 4c), and the foot was between the 10th to 25th percentile (Figure 4d). In addition, these abnormalities were categorized as a "latency of the sweat response" of the forearm, distal leg, and foot, as well as a "lack of recovery" of the proximal leg. Results for twin 2 showed a similar sweat response latency of the proximal leg (Figure 5b). Otherwise, twin 2 exhibited normal sweat volumes and rates for her age as seen for the forearm (10th−25th percentile) (Figure 5a), proximal leg (25th percentile) (Figure 5b), distal leg (25th percentile) (Figure 5c), and foot (50−80th percentile) (Figure 5d).

DISCUSSION

The possibility that autonomic nervous system dysfunction may occur in NC and be a mechanism responsible for some of the extrarenal manifestations of cystinosis has not been explored in a comprehensive manner. We showed, for the first time using state-of-the-art technology, an overt autonomic dysregulation of thermoregulatory responses in identical twins with NC several years post-transplantation. With respect to the HUT test, both twins clearly exhibited an exaggerated response with a significant drop in SBP, a compensatory escalation in HR, and maintained orthostatic tachycardia during the procedure. However, a normal respiratory rate and level of consciousness were maintained throughout the procedure. These findings were consistent with either autonomic dysregulation or modest to severe hypovolemia, the latter of which was not likely because of 1-l consumption of water before testing, and was not observed or suspected during repetitive physical examinations or by careful history.

Individuals with dysfunctional thermoregulation, including sweating abnormalities, are at high risk for heat intolerance and stress. Previous research showed that NC patients homozygous for a 57-kb fragment deletion exhibited transient receptor potential vanilloid 1 (TRPV1) gene functional impairment. This gene lies upstream to the CTNS gene region, is part of the 57-kb deletion, encodes for the protein, TRPV1, expressed in the primary sensory neurons, and is activated by heat and various chemical compounds, including capsaicin.[17] Recent evidence suggests that TRPV1 is an important factor in thermoregulation in normal environmental conditions.[13] In a rodent model, TRPV1 blockade resulted in pronounced tail skin vasoconstriction and escalating thermogenesis, which suggested that TRPV1 controls both metabolic heat production and compensatory vasodilation.[18] Consistent with this, NC patients exhibit a reduced localized response to capsaicin, a TRPV1 activator, whereas no vasodilatation or chemical irritability was displayed in areas of skin capsaicin exposure. Cystinosis patients who exhibit a higher threshold for detecting a hot stimulus also demonstrate a deficient sensory perception of exposure to a heat source.[17] In addition, a marked hyperthermic response is attenuated by pharmacological TRPV1 blockade.[19] This should be of great concern for NC patients who exhibit the homozygous 57-kb gene deletion, as was shown in our patients.[17] The twins differed somewhat in their response to the TST and QSWEAT, with 1 having quite abnormal results and the other showing mildly abnormal results (Figure 3).

In a different group of individuals with small fiber neuropathy but without NC, an absence of sweating occurred within the same body regions in which chronic unexplained cutaneous sensory symptoms were experienced.[19] Those symptoms included tingling, burning, itching, and numbness, which are described by many NC patients, which suggests that the mechanism might be secondary to the dysfunction of the heat receptor lost with the 57-kb deletion.

Both twins exhibited a significant amount of anhidrosis in segmental distribution patterns; twin 1 also displayed a delayed onset of sweat output upon

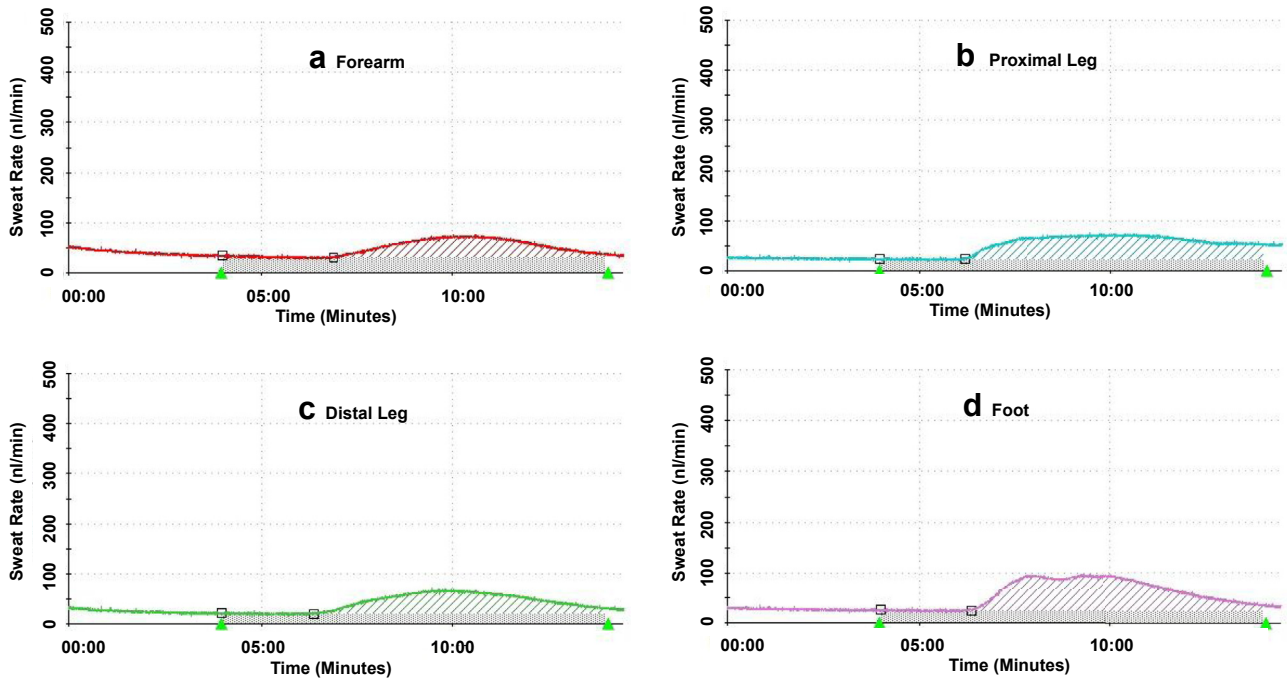

Figure 4. Quantitative sweat rate (nanoliters per minute) of twin 1 for the left forearm (a), proximal leg (b), distal leg (c), and foot (d).

stimulation and showed a lag in time in sweating recovery.[20] These findings suggested postganglionic sudomotor peripheral nerve dysfunction. This pathology directly implicates dysregulation of the autonomic nervous system, because at the time of testing, their hydration status was deemed normal and neither twin was taking antihistamines. However, there have been no clinical findings of peripheral or optic neuropathy or autonomic nervous system dysfunction observed per thorough and repetitive clinical examinations of the twins. Although we were aware of rare tacrolimus side effects associated with some cases of peripheral[21] and optic[22] neuropathy, we were unaware of any influence on the twins specific to the onset of neuropathy or sweating irregularities.

Our findings resulted in a further question of whether sweat gland peripheral nerve innervation and resulting density are altered in NC or whether peripheral nerve function itself is diminished,[23] either of which could result in inefficient core temperature

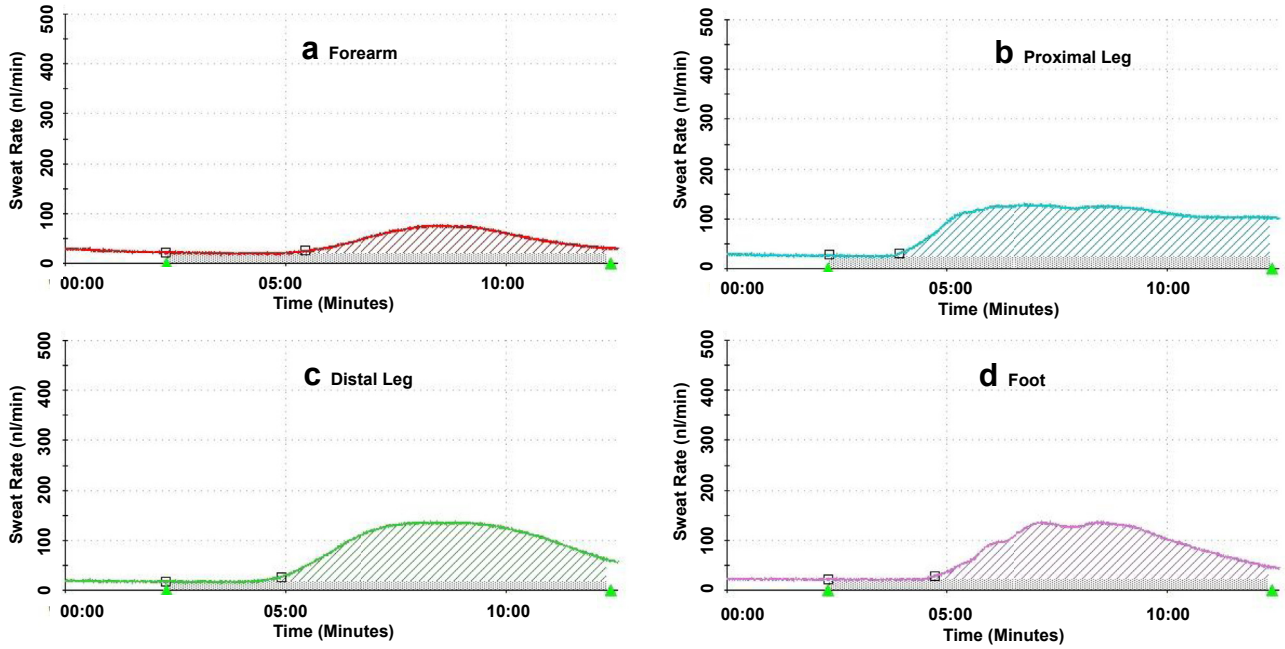

Figure 5. Quantitative sweat rate (nanoliters per minute) of twin 2 for the left forearm (a), proximal leg (b), distal leg (c), and foot (d).

reduction upon heat stress exposure. In clinical practice, NC patients are well known for their complaints regarding hot weather intolerance and avoidance of high temperate environmental exposure.

An important and additional observation during testing was that both twins exhibited a lack of vasodilation (warm up) of the feet at TST procedure completion. These findings were reminiscent of Buntinx's research regarding TRPV1 impairment in NC because the upstream effects of TRPV1 on the sympathetic nervous system are via sensory nerve nociceptive signaling.[13] Thus, in NC, the presence of significant areas of anhidrosis might be reflective of peripheral nerve dysfunction and an inability to efficiently cool the body during heat exposure. Unfortunately, the issue of peripheral nerve dysfunction in NC has never been addressed because the last published testing results on NC patients were published in 1991, at which time sensory nerve conduction studies in the extremities were limited to only examination and measurement of large sensory nerve function.[24] However, since that time, newer methodologies have been developed that can test small sensory nerve function and could potentially provide entirely different findings.[25]

One other consideration is whether TRPV1 dysfunction in NC is related to other formidable pathology that results in end-organ damage and other secondary disease manifestations that occur despite compliance with cystine reduction therapy.[11] One recent report observed autophagy and proteasome dysfunction in thymocytes of TRPV1 knockout mice, which resulted in a pattern of increased cellular apoptosis.[26] In addition, mTORC1 signaling is downregulated in NC and therefore may play a role in the upregulation of abnormal chaperone-mediated autophagy.[6] Therefore, in cystinosis, a lysosomal storage disease, the loss of CTNS leads to lysosomal dysfunction with enlarged and defective mitochondria retained in the lysosomes, as demonstrated in renal proximal tubular epithelial cells.[27] In cystinosis because lysosomal-associated membrane protein 2 receptor (LAMP2A) has been shown to partially mislocalize from lysosomes and undergo an increased lysosomal degradation,[6] the resulting pathological reduction in chaperone-mediated autophagy and its diminished mitochondrial clearance generate reactive oxygen species, as well as an accumulation of autophagosomal markers.[27] Thus, it is also feasible that neurodegeneration and peripheral nerve dysfunction, as well as myopathies[26] might evolve over time in cystinosis as demonstrated in other lysosomal storage diseases, including one that also exhibited a LAMP2 deficiency.[28] Development of these pathologies, which are associated with a number of extrarenal manifestations of NC, including heat intolerance, anhidrosis, peripheral vasoconstriction, and other types of autonomic nervous system dysfunction, are plausible.

CONCLUSIONS

Further detailed examination and testing of NC patients is warranted and should include a directly measured glomerular filtration rate and laboratory findings indicative of hydration status at the time of testing procedures. In addition, research specific to the pathophysiological mechanisms and potential pharmacological therapies for extrarenal manifestations should be addressed in the future. Also, it is important to consider that obtaining therapeutic levels of cystine depletion is not an easy undertaking for the patient. To obtain their therapeutic dosage of cysteamine bitartrate (DR), each twin was required to ingest 9 capsules of Procysbi 75 mg DR every 12 hours for a total of 18 capsules/d, as well as administer eye drops hourly while awake, making consistent compliance with all therapies on a perpetual basis extremely problematic. Yet, even with strict adherence to all medication self-administration, extrarenal manifestations of NC still occur, and at this point in time, we are no closer to determining those specific mechanisms nor therapeutic targets for prevention or treatment.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Our sincere thanks to the staff of the Center for Autonomic Medicine in Pediatrics at Ann & Robert H. Lurie Children's Hospital of Chicago for their professional expertise in the clinical testing of the patients.

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