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Infrared thermal analysis and individual differences in skin temperature asymmetry in Rett syndrome

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Abstract

Purpose—We aimed to evaluate the feasibility of using a portable infrared thermal camera (IRTC) to quantify the degree of thermal dysregulation (cold hands/feet) and test for naturally occurring within-patient skin temperature asymmetry in Rett syndrome.

Procedures—Infrared thermal images were acquired passively from 15 patients (mean age = 13.7 years, range 4 – 47) with clinical diagnoses of Rett. Images were acquired using a FLIR T400 IRTC (still images recorded at 5hz, resolution of 320x240 pixels, thermal sensitivity=.05° C; capture session lasted approximately 3 min). The IRTC was orthogonal to the body part (hands, feet) and positioned approximately 1 m from the skin's surface.

Main Findings—There were large intra-individual left/right differences in temperature. Seven (47%) and eight (53%) patients had statistically significant ($p < 0.05$) left/right asymmetries between hands (M diff = 0.87°C, sd = 1.21) and feet (M diff = 1.73°C, sd = 3.03), respectively. Coders were reliable (intra-class correlations 0.97–0.99) on temperatures and selection of anatomical regions of interest.

Conclusions—The degree of thermal asymmetry may reflect prolonged activity of the sympathetic nervous system and individual differences in sympathetic regulation. As clinical trials emerge and endpoints are considered, portable IRTC may provide one non-invasive means of evaluating changes in sympathetic regulation.

In the general population, there is remarkable contralateral skin surface-temperature symmetry.¹ Disruptions to this symmetry may be a practical biomarker for vascular instability and related autonomic dysfunction. Discolored skin, red feet, red hands, and related temperature anomalies are repeatedly reported in clinical descriptions of Rett syndrome [RTT] ('cold hands/feet' are supporting RTT diagnostic criteria). The impaired

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control of skin temperature, although documented, has not been systematically investigated and remains poorly understood in RTT. In one early study, atypical thermal profiles of four girls with RTT were documented.² Of note, one of the four girls had inadvertently undergone a unilateral (left lumbar) sympathectomy during scoliosis surgery. Two consequences from this ‘natural experiment’ seemed to follow: On the affected limb side (the side of the unilateral sympathectomy with presumably some degree of sympathetic tone reduction secondary to the sympathectomy), there appeared to be increased warmth and physical growth of the limb and foot. On the unaffected side, the temperature of the leg was reduced by as much as 3°C, the leg and foot was smaller, and the inference was that distal wasting in addition to observed skin temperature differences may have reflected increased sympathetic tone. Since this observation, there have been no further investigations into skin temperature and RTT.

Infrared thermography is a non-invasive tool that may be useful for characterizing the autonomic and sympathetic function of patients and has been applied to a variety of conditions in which thermal regulation is a clinical problem with suspected sympathetic involvement in various patient populations including stroke³ and complex regional pain syndrome.⁴ Applications to individuals with severe and profound developmental disability have been infrequent. In a cold-stress challenge paradigm, Suzuki et al⁵ used infrared thermography with a sample of children and young adults with severe motor and intellectual disabilities and found impaired skin vasomotor responsivity. Although the specificity of the findings were unclear, the study provided a clear example of the use of infrared thermography coupled with a temperature-stress challenge protocol for non-verbal individuals with severe motor impairments. Svedberg et al⁶ took a different approach by characterizing and comparing basal distal (hand, feet) skin temperature using infrared thermography across pre-school children with and without neurologic impairment including healthy controls and children with cerebral or spinal cord damage. Non-ambulatory children with cerebral damage (cerebral palsy) were observed to have significantly lower average skin temperatures than children without disabilities as well as ambulatory children with cerebral damage.

Given the limited nature of any objective investigation of cold extremities in RTT, the goal of this preliminary study was (1) to evaluate the feasibility of using portable infrared thermal cameras (IRTC) in the field to quantify the clinical peripheral symptoms of RTT specific to thermal dysregulation (cold hands/feet) and (2) test for the presence of within-patient skin temperature asymmetry in a clinical sample of girls and women with RTT.

Methods

Following IRB approval through the University of Minnesota and Gillette Children’s Specialty Care and informed consent, infrared thermal images were acquired passively from a convenience sample 15 patients (mean age = 14.5, range 4–47) with clinical diagnoses of RTT (Table 1). Images were acquired in field-based settings (regional fund raiser mtg.) using a FLIR T400 IRT camera (still images were recorded at 5hz, at a resolution of 320x240 pixels, thermal sensitivity=.05° C). Image capture sessions lasted approximately 3 min. The IRT camera was orthogonal to the body part and positioned approximately 1 m

from the skin's surface. Points on the skin at predefined locations were coded for temperature on each limb (N = 17 for hands, 7 for feet). The specific number of points coded varied across participants due to spasticity/hand movements (mean = 13.7 hands; 6.7 feet). If a point of interest was not visible then that point of interest was not included in the measurement of the contralateral limb to insure comparability between the right and left sides. No participant was missing more 5 measurements per hand or two measurements per foot. Coders were reliable (intra-class correlations 0.97–0.99) on temperatures and selection of anatomical regions of interest (i.e., two independent coders recorded the temperature of approximately 30% randomly selected regions of interest with very high levels of agreement). All patients had had greater than 20 min to acclimatize to their surroundings. Hands and feet were arranged to fit within the camera frame, hands were placed on a foam covered metal plate with a 1 cm square grid with fingers spread as far as the participant would allow without withdrawing them from the plate. Feet were kept in natural positions on wheelchair with shins and lower leg exposed. To the best of our knowledge, no participants were engaged in any form of strenuous physical activity prior to imaging.

Results

IRT Surface Temperatures & Asymmetry

The mean foot temp. = 26.5°C (sd = 3.8, range = 22.0–32.7°C) (cf. 28.6 ± 1.5, healthy comparison values, Zaproudina et al, 2008). The mean hand temp. = 29.2°C (sd = 2.76, range = 24.8–32.7) (cf. 29.8 ± 1.8, healthy comparison values, Zaproudina et al, 2008). Individual participant values for corresponding sites/regions of interest (ROI) are presented in Table 2. There were large intra-individual left/right differences in temperature (Figure 1 for representative image). Seven of fifteen girls had statistically significant ($p < 0.05$) left/right asymmetries between hands (M diff = 0.87°C, sd = 1.21, range = 0.05–3.81) and eight of fifteen had statistically significant asymmetries between feet (M diff = 1.73°C, sd = 3.03, range = 0.10–10.70).

Skin Temperature & Clinical Features

We tested whether there were associations between thermal variables (hand and foot temperatures, asymmetries) and selected clinical features. There were no statistically significant associations between asymmetries or extremity temperatures and participant age, ambulatory status, or seizure disorders.

Discussion

Skin temperature is regulated through sympathetic vasomotor control; perturbations presumably reflect disrupted peripheral nerve function. Our results replicate one earlier report of distal hypothermia and asymmetries in RTT. Although autonomic dysregulation is well recognized in RTT, the majority of the work has focused on breathing abnormalities. The observed temperature asymmetries, some over 10°C, suggest more work is needed investigating the relations among distal atrophy, vascular function, and sympathetic tone. The degree of thermal asymmetry may reflect prolonged/excessive activity of the sympathetic nervous system.

Normative skin temp values for extremities are approximately $29.8 \pm 1.8^{\circ}\text{C}$ for hand and $28.6^{\circ}\text{C} \pm 1.5$ for foot.⁷ In this sample, the average foot temperature was approximately 2°C cooler. With respect to hand temperatures and known pediatric values, Svedberg et al published a comparative study with a pediatric sample with and without neurodevelopmental disabilities and associated neurologic impairments.⁶ In comparing their reported temperature values, a few observations are important to note. First, specific to the dorsal hand – the mean healthy pediatric control values were 33.5°C (cf. 29.8°C for adult based⁷, respectively). Second, the mean value for the neurologically impaired pediatric sample (mostly children with cerebral palsy) for the dorsal hand was 32.5°C . It seems, then, based on the published reports to date that (a) children's average dorsal hand temperature is slightly greater than adult, (b) children with and without developmental disabilities were comparable. Both points are in directions opposite from our observations in RTT – the girls in our sample had colder (not warmer) skin temperatures.

Perhaps more important was the observation of naturally occurring temperature asymmetries. The asymmetry noted for one girl in the original case report was described in relation to a post-surgical outcome.² Here we document that there are individual differences and, in some cases, large existing skin temperature asymmetries in RTT that were not secondary to surgery. In other words, skin temperature asymmetries existed that were not related to or following surgical experience.

There were several classes of relevant variables overlooked and not measured in this study limiting the generality of the findings. For future research, co-occurring musculoskeletal conditions associated need to be considered in more detail including contractures, dystonias, and hip subluxation in addition to historical and ongoing interventions for these conditions (surgical, physical therapy, etc.). In addition, there is the possibility that hand preference could be a relevant variable. In a study of 145 2–24 year-old subjects in the Australian RTT database, the authors reported an unexpectedly high percentage of left hand preference (33.6%), while 40.7% had right hand preference and 25.7% no preference.⁹ These results raise the question as to whether hand preference may have been a factor in determining which hand was warmer in the present study. Considered another way, the unexpectedly high percentage of left hand preference in RTT (if confirmed) may reflect the fact that neurological deficits are often greater in the right hand¹⁰, with a consequent lower skin temperature on that side possibly leading to a left hand preference.

The potential clinical utility of these findings is not clear and remains to be investigated. Although our scores were reliable at a single time point, it needs to be established whether they are reproducible over repeated measurement; thus the reproducibility/stability of temperature difference/change needs to be established over time for RTT, especially in determining the utility of these methods of potential outcome measures following therapeutic interventions. The utilized technology is non-invasive, associated with moderate costs, objective, and quantifiable.⁸ Conversely, the technology can break down and at this point has more research value versus clinical utility. More research will be needed to correlate findings with patient level of functionality and interventions as they become available. Overall, the degree of thermal asymmetry may reflect prolonged activity of the sympathetic nervous system and individual differences in sympathetic regulation. As clinical

trials emerge and endpoints are considered, portable IRTC may provide one non-invasive means of evaluating changes in autonomic regulation.

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Figure 1.

Observed resting-state temperature foot asymmetry ($> 10^{\circ}\text{C}$) in a 12 yr. old non-ambulatory female with RTT [C.943_1140 ins, 198 del]. The asymmetry was not the result of post-surgical intervention and suggests more work is needed investigating the relations among distal atrophy, vascular function, and sympathetic tone. Image acquired using a FLIR T400 IRT camera (still images were recorded at 5hz, at a resolution of 320x240 pixels, thermal sensitivity= $.05^{\circ}\text{C}$; capture session lasted approximately 3 min). The IRT camera was orthogonal to the body part (feet) and positioned approximately 1 m from the skin's surface. The patient had had greater than 20 min to acclimatize to their surroundings. Feet were arranged to fit within the camera frame and were kept in natural positions on wheelchair with shins and lower leg exposed.

Table 1

Summary of participant characteristics and diagnostic status.

Participant	Age	Ambulation Status	Seizures Disorder	RTT Diagnosis	MECP2 Mutation
1	8	Non-ambulatory	Not controlled	Classic	Exon 4 deletion
2	5	Non-ambulatory	Controlled	Classic	R168X c.502C>T
3*	13	Non-ambulatory	Not controlled	Classic	Q262X
4	12	Non-ambulatory	Not controlled	Classic	No mutation identified
5	5	Without assistance	None	Classic	R168X
6	9	Non-ambulatory	Not controlled	Classic	Unknown
7	47	Without assistance	None	Classic	No testing conducted
8	12	Non-ambulatory	Not controlled	Classic	c.943_1140ins6del198
9	7	Non-ambulatory	Controlled	Classic	S49X
10	21	Non-ambulatory	Not controlled	Classic	Unknown
11*	14	With assistance	Controlled	Classic	K144X
12	10	Without assistance	Controlled	Classic	R168X
13	11	Non-ambulatory	Controlled	Classic	879ins37del1371
14	4	Without assistance	None	Classic	R106W
15	27	With assistance	Not controlled	Atypical	No testing conducted

Note:

* denotes history of spinal fusion surgery for scoliosis prior to IRT imaging.

Table 2

Summary of average limb temperatures and right-left asymmetries in degrees Celcius.

Participant	Age	Mean R hand temp (SD)	Mean L hand temp (SD)	Difference hands	Mean R foot temp (SD)	Mean L foot temp (SD)	Difference feet
1	8	31.99 (.75)	31.91 (.90)	0.08	23.49 (.59)	24.44 (.39)	0.96*
2	5	25.62 (1.23)	26.12 (1.35)	0.49*	23.34 (.38)	23.24 (.53)	0.10
3	13	27.44 (1.14)	27.84 (1.09)	0.40*	23.70 (.80)	24.16 (.32)	0.46*
4	12	24.50 (.86)	26.64 (.84)	2.14*	22.84 (.26)	23.03 (.68)	0.19
5	5	32.94 (.53)	33.66 (.49)	0.73*	27.54(2.17)	30.73 (2.61)	3.19*
6	9	24.81 (1.98)	24.77 (1.80)	0.05	28.17 (1.82)	28.00 (1.47)	0.17
7	47	31.29 (1.09)	27.47 (.84)	3.81*	23.36 (1.06)	23.01 (1.25)	0.35
8	12	31.32 (.62)	30.97 (.27)	0.35	34.49 (1.01)	23.79 (1.17)	10.70*
9	7	32.97 (.57)	32.76 (.75)	0.21	33.06 (.40)	32.34 (.80)	0.72*
10	21	28.60 (1.82)	31.92 (1.38)	3.33*	23.33 (.24)	23.11 (.29)	0.22*
11	14	27.315 (.50)	27.485 (.34)	0.17	24.49 (.70)	24.33 (.51)	0.16
12	10	26.37 (.32)	26.49 (.97)	0.12	22.04 (.21)	21.90 (.45)	0.14
13	11	28.12 (.95)	28.63 (.99)	0.51*	29.51 (1.12)	22.79 (.57)	6.73*
14	4	32.67 (.82)	32.39 (.35)	0.31	32.37 (.63)	33.04(2.10)	0.67
15	27	29.29 (1.83)	29.65 (1.57)	0.35	32.63 (.98)	31.46 (.94)	1.17*
Mean (SD)	13.7	29.13 (2.94)	29.36 (2.77)	.83 (1.16)	26.95 (4.42)	25.96 (3.97)	1.73 (3.03)
Median		28.94	29.13	0.35	24.49	24.16	0.46

Note:

* denotes paired t-test p-value <.01.