Highly abnormal thermotests in familial dysautonomia suggest increased cardiac autonomic risk

Max J Hilz, Edwin H Kolodny, Irene Neuner, Brigitte Stemper, Felicia B Axelrod

Abstract

Objective—Patients with familial dysautonomia have an increased risk of sudden death. In some patients with familial dysautonomia, sympathetic cardiac dysfunction is indicated by prolongation of corrected QT (QTc) interval, especially during stress tests. As many patients do not tolerate physical stress, additional indices are needed to predict autonomic risk. In familial dysautonomia there is a reduction of both sympathetic neurons and peripheral small nerve fibres which mediate temperature perception. Consequently, quantitative thermal perception test results might correlate with QTc values. If this assumption is correct, quantitative thermotesting could contribute to predicting increased autonomic risk.

Methods—To test this hypothesis, QTc intervals were determined in 12 male and eight female patients with familial dysautonomia, aged 10 to 41 years (mean 21.7 (SD 10.1) years), in supine and erect positions and postexercise and correlated with warm and cold perception thresholds assessed at six body sites using a Thermodex.

Results—Due to orthostatic presyncope, six patients were unable to undergo erect and postexercise QTc interval assessment. The QTc interval was prolonged (>440 ms) in two patients when supine and in two additional patients when erect and postexercise. Supine QTc intervals correlated significantly with thermal threshold values at the six body sites and with the number of sites with abnormal thermal perception (Spearman’s rank correlation p<0.05). Abnormal Thermodex results were more frequent in the four patients with QTc prolongation and the six patients with intolerance to stress tests.

Conclusion—The results suggest that impaired thermal perception correlates with cardiac sympathetic dysfunction in patients with familial dysautonomia. Thus thermodexing may provide an alternative, albeit indirect, means of assessing sympathetic dysfunction in autonomic disorders.

Keywords: familial dysautonomia; QTc interval; quantitative thermal testing

Cardiovascular instability is a prominent manifestation of familial dysautonomia, an autosomal recessive disorder affecting development and survival of sensory, sympathetic, and some parasympathetic neurons. Both hypertensive crises and orthostatic hypotension without compensatory tachycardia can occur. Failure of sympathetic activation with retention of parasympathetic system activity in patients with familial dysautonomia may be one of the major causes of death in this population. Survival analysis disclosed that 40% of these patients have either an unexplained death in their sleep or a sudden daytime cardiorespiratory arrest. To date, there are no indices to identify which patients with familial dysautonomia are at risk of sudden death. Common tests used to assess cardiac autonomic function, such as the Valsalva manoeuvre, deep metronomic breathing, or sustained handgrip test, often cannot be applied to patients with familial dysautonomia. Because of impaired coordination and abnormal breathing pattern, many patients are unable to pace their breathing, perform a Valsalva strain correctly, or sustain the handgrip without simultaneous breathholding. By contrast, measurements of ECG indices such as the corrected QT interval (QTc) are easily performed even in patients with poor cooperation.

Based on reports that prolongation of the QTc may be a potential marker for patients at risk for arrhythmia and sudden death, Glickstein et al studied this index in patients with familial dysautonomia and noted that a significant number of patients had a prolonged QTc, greater than 440 ms. Most patients with familial dysautonomia had normal QTc intervals at rest, but with the challenge of head upright tilt or exercise, by contrast with controls, a significant number of patients with familial dysautonomia had QTc prolongation. However, eight of 54 patients participating in that study did not tolerate the tilt or exercise tests. In these patients, QTc assessment is of limited use and additional non-invasive indices are required to evaluate autonomic risk.

As well as sympathetic dysfunction, patients with familial dysautonomia manifest impaired temperature perception, which is due to a decreased number of small nerve fibres. The degree of dysfunction of Aδ and C fibres is easily assessed by quantitative thermal threshold testing. Non-invasive psychophysical assessment of warm and cold perception thresholds has proved useful in the diagnosis of small fibre neuropathies of various
Definitions: perceiving five of the stimuli applied for each threshold determination. Exception of repeated stimuli. No patient presented with hyperaesthesia. Incomplete perception was hypoaesthesia, dysaesthesia, or paradoxical sensation, and patients with absent or incomplete perception were discarded from the study. The initial diagnosis of familial dysautonomia was established by Dr F B Axelrod, director of the Familial Dysautonomia Treatment and Evaluation Center, New York University, New York, NY, USA. Among the criteria used to establish the diagnosis of familial dysautonomia were Jewish Ashkenazi extraction, delayed development, failure to thrive, episodic fevers, decreased pain and temperature perception, absent deep tendon reflexes, absence of overflow tears, absence of fungiform papillae of the tongue, decreased corneal reflex, increased sweating, postural hypotension and skin blotching and hypertensive crises with stress, and absent axon flare response after intradermal histamine injection.

**aetiologies.**

Correlations between impaired thermal perception and autonomic dysfunction have been described in diabetic, uremic, and alcoholic neuropathies. We hypothesised that a similar correlation exists in familial dysautonomia, as there is neuropathological analogy of sympathetic ganglia reduction and a decrease in peripheral small nerve fibres. Analogy between thermotest results and QTc values would justify substitution of Thermotesting for QTc assessment in patients intolerant to stress tests. In this study, we therefore, compared QTc intervals of patients with familial dysautonomia with their warm and cold perception thresholds determined at various body sites and to the number of body sites showing abnormal thermal perception.

**Material and methods**

**PATIENT SELECTION**

Twenty patients with familial dysautonomia participated in the study. Informed consent was obtained according to the declaration of Helsinki, with a parent signing for patients less than 21 years of age. Twelve patients were male and eight were female. They ranged in age from 10 to 41 years (mean 21.7 (SD 10.1) years). All were ambulatory patients followed up annually at the dysautonomia centre. None of the subjects was taking medication known to modify the QT interval and all had normal ionised serum calcium determinations on the day of the cardiac study. The initial diagnosis of familial dysautonomia was established by Dr F B Axelrod, director of the Familial Dysautonomia Treatment and Evaluation Center, New York University, New York, NY, USA. Among the criteria used to establish the diagnosis of familial dysautonomia were Jewish Ashkenazi extraction, delayed development, failure to thrive, episodic fevers, decreased pain and temperature perception, absent deep tendon reflexes, absence of overflow tears, absence of fungiform papillae of the tongue, decreased corneal reflex, increased sweating, postural hypotension and skin blotching and hypertensive crises with stress, and absent axon flare response after intradermal histamine injection.

**THERMOTEST ASSESSMENT**

Warm and cold perception thresholds were psychophysically determined with a Somedic Thermostat™ (Somedic, Stockholm, Sweden), a modification of the “Marsstock” device. The thermodes operate on the Peltier principle applying continuously increasing ramp-like temperature stimuli to the tested skin area at a temperature change rate of 1°C/s. Simultaneously, a thermocouple attached to the stimulating surface continuously registers instantaneous temperature changes within 0.1°C. Data are digitally displayed on a monitor and stored on hard disk. Thermal stimuli are generated at randomised 4 s to 10 s intervals (Senselab™, Somedic, Sweden) with preset stimulation limits, a minimum of 5°C and a maximum of 45°C. Thermal stimulation started from a baseline of 32°C. Once the subject signals stimulus perception, the temperature returns to baseline.

Warm and cold perception thresholds were determined by the “method of limits”, which is comparable with the determination of hearing thresholds by means of a Békésy audiometer. Warm or cold stimuli are steadily increased until the subject indicates stimulus perception by pressing a button. This ends stimulation and reverses the thermode temperature to the

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**Table 1 Warm and cold perception thresholds in 20 patients with familial dysautonomia and 90 controls at six different body sites**

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients (n=20) (mean (SD))</th>
<th>Controls (n=90) (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold threshold:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theness</td>
<td>14.0 (8.4)</td>
<td>1.9 (0.8)</td>
</tr>
<tr>
<td>Arm</td>
<td>13.8 (10.2)</td>
<td>1.3 (0.8)</td>
</tr>
<tr>
<td>Cheek</td>
<td>10.2 (7.5)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Calf</td>
<td>14.0 (9.8)</td>
<td>2.8 (1.9)</td>
</tr>
<tr>
<td>Foot</td>
<td>15.3 (10.3)</td>
<td>2.9 (1.6)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>12.0 (8.2)</td>
<td>1.4 (0.7)</td>
</tr>
<tr>
<td>Warm threshold:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theness</td>
<td>8.3 (3.3)</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>Arm</td>
<td>8.1 (4.0)</td>
<td>2.2 (1.5)</td>
</tr>
<tr>
<td>Cheek</td>
<td>6.6 (4.4)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>Calf</td>
<td>9.3 (4.0)</td>
<td>3.5 (2.2)</td>
</tr>
<tr>
<td>Foot</td>
<td>8.5 (4.4)</td>
<td>3.0 (1.9)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>6.9 (3.6)</td>
<td>1.8 (1.0)</td>
</tr>
</tbody>
</table>

In patients with familial dysautonomia all thresholds were significantly higher than in the control group (Mann-Whitney U test, p<0.005).

**Table 2 Frequency of impaired warm and cold perception in 20 patients with familial dysautonomia tested at six different body sites**

<table>
<thead>
<tr>
<th>Site of cold stimulation:</th>
<th>Pathological hypoaesthesia (n=20)</th>
<th>Thermal anoaesthesia (n=20)</th>
<th>Incomplete perception (n=20)</th>
<th>Complete perception (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Calf</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Theness</td>
<td>17</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Forearm</td>
<td>20</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Shoulder</td>
<td>18</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cheek</td>
<td>17</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of warm stimulation:</th>
<th>Pathological hypoaesthesia (n=20)</th>
<th>Thermal anoaesthesia (n=20)</th>
<th>Incomplete perception (n=20)</th>
<th>Complete perception (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td>14</td>
<td>5</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Calf</td>
<td>16</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Theness</td>
<td>20</td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Forearm</td>
<td>19</td>
<td>8</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Shoulder</td>
<td>18</td>
<td>9</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Cheek</td>
<td>17</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

The number of patients with pathological thresholds represents the sum of patients with thermal hypoaesthesia, dysesthesia, or paradoxical sensation, and patients with absent or incomplete perception of repeated stimuli. No patient presented with hyperaesthesia. Incomplete perception was defined as perceptions of five of the stimuli applied for each threshold determination.
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inducing drowsiness and biasing cooperation. 

medication with central nervous testing, we established that no patient was tak-

doxtical sensations or dysaesthesias. Before 

warms or cold stimuli, or if they reported para-

mean normative values by more than 2 SD, if 

considered abnormal if thresholds exceeded 

23.7 (10.6) years). Thermal perception was 

aged 10 to 42 years (52 male, 38 female; mean 

related data established in 90 healthy controls 

mode was used at the cheek and thenar. 

× 2.5 cm thermodewas used for testing at the shoulder, 

calf, and foot. A 1.5 cm × 2.5 cm thermodewas used fortesting at the shoulder, 

innervated by the sural nerve. A 2.5 cm × 5.0 cm thermode was used for testing at the shoulder, 

forearm, calf, and foot. A 1.5 cm × 2.5 cm ther-

mode was used at the cheek, and thenar. 

Thresholds were determined at six body sites: at the cheek, at the shoulder 1.5–2.5 cm above 

the midpoint of the scapular spine, at the distal 

volar forearm 3 cm proximal to the wrist, at the 

thenar, at the distal medial calf 4–5 cm above 

the medial malleolus in the L4 dermatome, and 

at the lateral dorsum of the foot in the area 

innervated by the sural nerve. A 2.5 cm × 5.0 cm thermode was used for testing at the shoulder, 

forearm, calf, and foot. A 1.5 cm × 2.5 cm ther-

mode was used at the cheek, and thenar. 

Thresholds were compared with normative age 

related data established in 90 healthy controls 

aged 10 to 42 years (52 male, 38 female; mean 

23.7 (10.6) years). Thermal perception was 

considered abnormal if thresholds exceeded 

mean normative values by more than 2 SD, if 

patients did not perceive all of the five repeated 

warm or cold stimuli, or if they reported para-

doxical sensations or dysaesthesias. Before 

testing, we established that no patient was taking 

medication with central nervous effects 

inducing drowsiness and biasing cooperation. 

With a temperature change rate of 1°C/s and 

a 0.1–0.2°C accuracy of the Thermodest, a 

reaction time of 0.1–0.2 s is sufficient for 

threshold assessment. To familiarise the study 

participants with the task of quickly responding 

to a stimulus, and to ensure adequate reaction 

time, we performed a simple test which had 

previously proved useful in children.13 The 

participants were instructed to tap on the 

examiner’s knee as quickly as possible after the 

examiner had touched their own knee. A stop-

watch was used to assure that reaction time did 

ever exceed 0.1 s. 

To correlate QTc intervals with the severity 

of thermal perception dysfunction, QTc values 

were not only compared to warm and cold 

thresholds at the six body sites, but also to the 

number of abnormal perception sites found in 

each patient. The level of significance was set 

at p<0.05. Data were analysed by a commercially 

available statistical program (SYSTAT, Evan-

ston, IL, USA).

Results

Values for QTc were prolonged in four of the 

20 patients. The QTc was prolonged in two 

patients when supine. A third patient develop-

ed prolongation when erect and a fourth 

postexercise.

Supine QTc intervals ranged from 387 ms to 

467 ms (mean 417 (SD 18.7) ms), erect QTc 

intervals ranged from 395 ms to 483 ms (mean 

417.2 (SD 21.3) ms) and postexercise QTc 

intervals from 398 ms to 465 ms (mean 417.7 

(SD 21.8) ms). However, an erect QTc interval 
could only be determined in 15 patients and a 

postexercise QTc interval in 14 patients. One 

patient could not stand or exercise because of 

bilateral Charcot knee joints. Presyncope 
symptoms developed in four patients when 

they assumed the erect position and in a fifth 

patient after exercise.

All participants had a reaction time <0.1 s in 

the test preceeding thermal threshold assess-

ment. Thermal stimulation was abnormal in all 

patients, but were more impaired in patients 

with prolonged QTc than in those with normal 

QTc values, and even worse in the six patients 

intolerant to standing or exercise. In all 

patients, thermal thresholds at the six tested 
sites were higher than in the control group 

(Mann-Whitney U test: p<0.005). There was 

no consistent pattern of impaired thermal sen-

sation (tables 1 and 2). The degree of threshold 

increase varied from one body site to the other, 

and the number of abnormal perception sites 

differed from one patient to another. The 

frequency of abnormal sensitivity was highest at 

the thenar and the distal volar forearm. At 

these sites, either cold or warm sensation was 

altered in all 20 patients. The site with the lowest 

frequency of abnormal results was the feet. Here, thresholds were abnormal in 

75% of the patients.

In the 20 patients, perception of the five 

stimuli applied for threshold averaging at each 

of the six tested sites was incomplete in 15% of 

the warm and in 13.3% of the cold threshold 

determinations. Moreover, the individual vari-

ability of the five repeated stimuli was signifi-

antly higher in patients than in controls. At the 

different sites, variability of warm and cold 

perception was twofold to 14-fold higher in 

patients than in controls—that is, the threshold 

reproducibility was significantly lower in pa-

tients than in controls (Mann-Whitney U test 

p<0.005).

In the four patients with prolonged QTc 

intervals, warm and cold perception was abnor-

mal at all of the six tested sites apart from one 

patient with normal warm perception at the 

foot. By contrast, patients with normal QTc 

intervals showed normal warm perception at 

15.6% of the tested sites and normal cold 

perception at 17.7% of the sites. Similarly, in 

the six patients with familial dysautonomia
intolerant of standing or exercise, warm and cold perception was abnormal at all tested sites whereas the 14 other patients with familial dysautonomia had normal perception for warmth at 19% of the sites and for cold at 20.2% of the sites. Moreover, the six patients presented with warm anaesthesia at 33.3% of the sites compared with warm anaesthesia at 36.1% of the sites and cold sites. Moreover, the six patients had highly abnormal Thermotest results showing that the major pathological process in familial dysautonomia is one of insufficient nerve fibre development rather than postnatal degeneration. As the failure of small nerve fibre development varies individually, the pattern of thermal perception also varies from one patient to another and might affect the distribution of small fibre dysfunction varies individually and does not follow a rather predictable pattern as seen in dying-back neuropathies. Thermal perception was more often impaired at the upper than the lower limbs. However, some patients had highly abnormal Thermotest results suggesting that they had pronounced impairment of both autonomic function and thermal perception.

Discussion

The cause of increased frequency of sudden death in the familial dysautonomia population has not been elucidated. Postmortem examination has never disclosed cardiac abnormalities. As familial dysautonomia is a disorder that primarily affects small fibre development and function, it is likely that sympathetic cardiac conduction as well as thermal sensory function are impaired to a similar extent. The degree to which patients are affected varies considerably. To date, no one has developed a clinical means of assessing severity of disease or method of predicting patients at increased risk of sudden death. Prolongation of the QTc interval is considered an indicator of cardiac risk, and orthostatic presyncope indicates autonomic dysregulation. Our study shows that highly abnormal Thermotest results may be a predictor of increased cardiac autonomic risk. Thermostest results correlated with supine QTc interval values in all 20 patients, but coefficients of correlation varied between 0.43 and 0.71. However, patients with prolongation of the QTc interval and especially patients intolerant of standing and exercise had Thermostest results significantly more abnormal than those of the patients with normal supine, posttilt, or postexercise QTc intervals. Three of our patients had a cardiac arrest within 12 months. One of these patients had a prolonged supine QTc interval and the other two developed presyncope with physical stress. All three patients had highly abnormal Thermotest results suggesting that they had pronounced impairment of both autonomic function and thermal perception.

Thermostest results showed that the distribution of small fibre dysfunction varies individually and does not follow a rather predictable pattern as seen in dying-back neuropathies. Thermal perception was more often impaired at the upper than the lower limbs. However, our Thermostest findings are consistent with various neuropathological studies of sural nerves, dorsal root, and sympathetic ganglia showing that the major pathological process in familial dysautonomia is one of insufficient nerve fibre development rather than postnatal degeneration.
upper limbs equally or more often than the lower limbs.16

Thermotest results are not a direct indicator of autonomic dysfunction, but previous studies of diabetic, uremic, or alcoholic patients describe similarities between dysfunctions of temperature perception and autonomic regulation.19–21 In familial dysautonomia, the finding of such clinical similarities is supported by a similar degree of neuropathological abnormality in peripheral small fibre nerves and sympathetic ganglia. In familial dysautonomia, there is a reduction of unmyelinated sural nerve fibres to 5%–15% of the normal number and of neuron somas in the Gasserian and spinal ganglia to 50% of normal, and neuron somas in cervical and thoracic sympathetic ganglia are reduced to 27–37% of the normal number.22–24 The decrease in peripheral small fibres is clinically reflected by impaired thermal perception,22 24 24 32 and the reduction of cervical and thoracic ganglia accounts for cardiac autonomic dysfunction,15 55 56 which might be recognised clinically by prolonged QTc interval values. In Romano-Ward long QT syndrome, an imbalance of left and right cervicothoracic sympathetic activity is assumed to induce prolongation of the QT interval.15

In patients with familial dysautonomia, determination of QTc intervals provides important information. Abnormal QTc intervals were detected in 20% of our patients. Glickstein et al reported QTc prolongation in 33% of patients with familial dysautonomia with an age distribution similar to our group (mean 24 (8.7) years).25 Limitations of QTc assessment seem to account for the different incidences. Eighty five per cent of patients studied by Glickstein et al could stand and exercise compared with only 70% of our group. We assume that Glickstein et al were able to show a higher incidence of QTc prolongation because more of their patients were able to tolerate stress tests. Stress tests are essential to unveil cardiac conduction abnormalities. In their control group (mean 24.7 (7.6) years), Glickstein et al found no QTc intervals exceeding 440 ms at rest, but one of the controls had a QTc prolongation of 452 ms after standing.25

Several previous studies show the need for stress tests to unmask prolongation of the QTc interval.40 Shimizu et al40 reported normal supine QTc values in five of 11 patients with Romano-Ward syndrome (45.5%). With physical exercise all patients showed prolongation of the QTc interval.40 Gobin et al40 and Sivieri et al41 reported that supine QTc values often fail to disclose diabetic cardiac autonomic neuropathy which had been diagnosed with other cardiovascular function tests such as Valsalva or Ewing manoeuvres. In the study of Gobin et al57% of the patients with cardiac autonomic neuropathy had normal QTc intervals.57 Unfortunately, cardiovascular function tests requiring physical effort might not be tolerated either by patients with familial dysautonomia manifesting presyncope during tilt or stair stepping. From our clinical experience, most patients with familial dysautonomia cannot perform Valsalva manoeuvres or other tests such as a sustained handgrip manoeuvre requiring prolonged and steady coordination and cooperation.

Patients with normal supine QTc intervals but intolerance of stress tests require further evaluation of cardiac risk. Two of our patients who had a cardiac arrest could not undergo QTc stress tests. Therefore, alternative tests supporting the cardiac risk evaluation but requiring only little physical cooperation are desirable.

Thermotesting provides a non-invasive alternative that requires no physical effort. The method of limits14 44 46 used in this study needs only slight patient cooperation; is easy to understand and thus yields highly reproducible results even in preschool children.57 In abundant studies the algorithm has proved useful in quantifying peripheral small fibre dysfunction.14 15 16 19 37 47 48 Verdugo and Ochoa described as many as 36 different combinations of impaired thermal sensation patterns.44

In patients with familial dysautonomia, Thermotesting assesses the most prominent peripheral nerve dysfunction and thus refines the clinical grading of the disease. Thermotesting might also be useful for long term follow up studies. Most importantly, our results show that highly abnormal Thermotest results are an indirect suggestion of advanced cardiac autonomic dysfunction and merit further evaluation of cardiac function

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