Autonomic function in Friedreich’s ataxia

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Abstract
Autonomic function studies were performed on 15 patients with Friedreich’s ataxia, and the results compared with those of 76 healthy subjects. There was an increase in resting supine heart rate, attributed to cardiac abnormalities. Other tests of sympathetic and parasympathetic function were normal. The normal autonomic function studies are consistent with the pathological findings of degeneration predominantly of large diameter myelinated fibres with sparing of small myelinated and unmyelinated fibres.

Some studies have suggested that there is increased vasomotor tone and increased plasma catecholamine levels in Friedreich’s ataxia and it has been postulated that the increase in catecholamine release may contribute to the development of hypertrophic cardiomyopathy. This study was carried out to determine whether or not there was evidence of autonomic dysfunction in the condition.

Materials and methods
Subjects
Patients Fifteen patients with Friedreich’s ataxia (FA) who presented over a two year period for initial evaluation or follow up were investigated. There were six males and nine females whose ages ranged from 11 to 53 years (median, 25 years). They fulfilled the diagnostic criteria described by Harding. None of the patients had any symptoms of autonomic dysfunction.

Control subjects Autonomic function studies were performed on 76 healthy subjects (32 males, 44 females) whose ages ranged from five to 85 years (median, 35 years.) None of the control subjects or FA patients had hypertension, ischaemic heart disease, chronic obstructive airways disease or evidence of central nervous system disease. None was taking medications known to have any effect on the cardiovascular or nervous systems.

Autonomic function studies Both invasive and noninvasive tests of autonomic function were used in the study. The following tests were performed using continuous heart period monitoring and noninvasive blood pressure assessment in most cases. Intra-arterial blood pressure measurement was used in some patients.

Detailed descriptions of these studies have been published.

A) Noninvasive Tests
1 Valsalva ratio
2 Heart rate variation with respiration
   a) Sinus arrhythmia
   b) Expiratory: Inspiratory ratio (E:I ratio)
3 Heart rate response to standing (30:15 ratio)
4 Cardiovascular changes with tilting
   a) Systolic blood pressure
   b) Diastolic blood pressure
   c) Heart rate
5 Change in diastolic blood pressure with isometric exercise
6 Plasma noradrenaline studies
   a) Supine plasma noradrenaline levels
   b) Percentage increase in plasma noradrenaline after tilting
7 Sweat test

B) Studies using intra-arterial blood pressure recording
1 Valsalva manoeuvre
2 Baroreceptor sensitivity

Informed consent was obtained from each patient and the protocol for the investigations of autonomic function was approved by the Medical Ethics Committee of the University of Sydney.

Statistical Analysis
Data from the control subjects were examined for skewness and outliers. Where necessary, transformation to natural logarithms was used. Comparison of the least squares fitted models was made before deciding whether to make no adjustment, a linear adjustment or a quadratic adjustment for age.

To test for heterogeneity of mean values between the FA patients and the control subjects, analysis of covariance was used to control for the effect of age when a linear effect of age was observed. The two sample t test was used where no age effect was observed. Where evidence of nonlinearity was found the quadratic models were compared and a 3 degrees of freedom F test performed. The raw data were used in constructing graphs. Where natural logarithms were used to determine regression equations, normal
Pathways for Hemodynamic Changes in Friedreich's Ataxia

**Results**

Control subjects

Results of investigations in the control subjects have been published previously. A significant relationship with age was observed with the Valsalva ratio, sinus arrhythmia, E:I ratio, 30:15 ratio, resting heart rate, change in heart rate with tilting, supine plasma noradrenaline levels and baroreceptor sensitivity. Except for resting heart rate and supine plasma noradrenaline levels, a linear decrease with increasing age was observed. For supine plasma noradrenaline levels a linear increase with increasing age was observed. With resting heart rate significant evidence of nonlinearity was found and a quadratic adjustment for age was made.

No significant relationship with age was detected in the other autonomic tests. Except for baroreceptor sensitivity there was no significant difference between males and females in the tests of autonomic function.

Friedreich's ataxia patients

Noninvasive tests The results of the tests of autonomic function in control subjects and FA patients are summarised in the table. After controlling for the effect of age the mean of the supine resting heart rates of the FA patients was significantly higher than that of the control subjects. There was no significant difference between the mean values of the FA patients and the control subjects in the remaining autonomic tests. A sweat test was performed on only one patient and was normal.

Intra-arterial heart rate and blood pressure recording

Valsalva manoeuvre The full haemodynamic response to the Valsalva manoeuvre was normal in all eight FA patients (median age 27 years, age range 20–53 years) tested.

Baroreceptor sensitivity After controlling for the effect of age, there was no significant difference between the mean baroreceptor sensitivity of the FA patients and the mean baroreceptor sensitivity of the control subjects.

**Cardiac investigations**

Electrocardiograms and echocardiography were performed on all 15 patients. The electrocardiogram was abnormal in 11 patients; the abnormalities included non-specific ST-T wave changes, T wave inversion, right bundle branch block and left-ventricular hypertrophy. Echocardiography demonstrated abnormalities consistent with left ventricular hypertrophy in six patients.

**Discussion**

The autonomic function studies demonstrated no significant abnormality of sympathetic or parasympathetic function in the patients with Friedreich's ataxia, when compared with control subjects. The only abnormal finding was a significant increase in the resting supine heart rate which can be explained by cardiac abnormalities. No abnormality was demonstrated in the full haemodynamic response to the Valsalva manoeuvre with continuous intra-arterial blood pressure recording in any of the eight patients so tested.

There have been few studies of autonomic function in Friedreich's ataxia. Reports of increased vasomotor tone, manifest by reduced blood flow in the forearm and calf have not been well substantiated.

An increase in free and conjugated plasma catecholamines has been described in a group of patients with the disease and one patient has been reported with paroxysmal dysautonomia, manifested by episodes of headache, sweating, skin rash, tachycardia and hypertension associated with increased plasma and urinary catecholamine levels.

In all our patients, however, supine plasma noradrenaline levels and their increase with tilting to the upright posture were within the normal range. It has been postulated that increased catecholamine release contributes to the development of hypertrophic cardiomyopathy.

Our findings do not confirm this hypothesis.

Conditions affecting small fibres are most

**Tests of autonomic function in control subjects and Friedreich's ataxia patients**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Median Range</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>76</td>
<td>35 5-85</td>
</tr>
<tr>
<td>Sinus arrhythmia</td>
<td>72</td>
<td>35 5-85</td>
</tr>
<tr>
<td>E:I ratio</td>
<td>72</td>
<td>35 5-85</td>
</tr>
<tr>
<td>30:15 ratio</td>
<td>71</td>
<td>36 5-85</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>70</td>
<td>35 5-85</td>
</tr>
<tr>
<td>Cardiovascular changes with tilting</td>
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<tr>
<td>a) Systolic BP (mmHg)</td>
<td>70</td>
<td>35 5-85</td>
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<tr>
<td>b) Diastolic BP (mmHg)</td>
<td>70</td>
<td>35 5-85</td>
</tr>
<tr>
<td>c) Heart rate (beats/min)</td>
<td>70</td>
<td>35 5-85</td>
</tr>
<tr>
<td>Change in diastolic blood pressure with isometric exercise (mmHg)</td>
<td>66</td>
<td>36 13-85</td>
</tr>
<tr>
<td>Supine plasma noradrenaline levels (nmol/L)</td>
<td>55</td>
<td>42 15-85</td>
</tr>
<tr>
<td>% increase in plasma noradrenaline levels with tilting</td>
<td>54</td>
<td>44 15-85</td>
</tr>
<tr>
<td>Baroreceptor sensitivity (mmHg/beat)</td>
<td>21</td>
<td>47 24-82</td>
</tr>
</tbody>
</table>

*The mean resting heart rate of the FA patients was significantly higher than that of the control subjects. There was no significant difference in the other tests of autonomic functions.*
likely to cause autonomic dysfunction since the sympathetic and parasympathetic nerve fibres that participate in cardiovascular control comprise mainly small (2–6 μm) myelinated and unmyelinated fibres. The demonstration of normal autonomic function studies in patients with Friedreich’s ataxia is consistent with the pathological findings of predominantly large diameter fibre degeneration in the peripheral nerves. The peripheral autonomic nervous system does not appear to have been examined in detail in major histopathological studies of Friedreich’s ataxia but where the vagal nuclei and subpericardial autonomic ganglia have been examined no consistent pathological changes have been found. It may be concluded that there is no definite physiological or pathological evidence of autonomic disturbances in Friedreich’s ataxia.

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