How to Assess Cardiac Autonomic Dysfunction in Familial Amyloidotic Polyneuropathy? The Association Between Cardiac Abnormalities and Neurological Involvement

M.C. Azevedo Coutinho, N. Cortez Dias, G. Cantinho, I. Conceição, M. Peres, A. Silva, F. Gaspar, E. Conduto, M. De Carvalho, A. Nunes Diogo
University Hospital Santa Maria, Lisbon - Portugal

Purpose

Familial amyloidotic polyneuropathy (FAP) is a hereditary form of amyloidosis caused by a single amino acid mutation in transthyretin (TTRVal30Met) and involves the peripheral and the autonomic nervous system. We sought to determine the association of cardiac dysautonomia with the neurological involvement in FAP.

Methods

- **Neurological Evaluation:**
  - Clinical and Electromyographic (EMG) scores (0-100%; 0=no disability and 100%=maximal disability)

- **Cardiac Evaluation:**
  1. Heart/Mediastinum I\textsubscript{123}-metaiodobenzylguanidine (H/M I\textsubscript{123} MIBG) uptake
  2. Chronotropic Index (CI) and Heart Rate Recovery (HRR) from exercise stress test (Bruce protocol)
  3. Time and frequency domains Heart Rate Variability (HRV) analysis from 24 h Holter monitoring

- **Ambulatory Blood Pressure Monitoring (ABPM)**

The association of the significant autonomic dysfunction parameters with neurological involvement was assessed by multivariate regression analysis, considering as testing class the tertile with highest risk in univariate analysis.

Population

- **Gender:** 92 patients with TTRVal30Met+
  - Male: 63 (69%)
  - Female: 29 (31%)

- **Age:**
  - All patients: 43 ± 14 years
  - Group I: 47 patients with neurological involvement
    - Mean age: 43 ± 14 years
    - EMG Score: 11 ± 6
    - Clinical Score: 12 ± 10
  - Group II: 45 asymptomatic carriers
    - Mean age: 42 ± 13 years

Results

Table 1. Cardiac autonomic function according to neurological involvement

<table>
<thead>
<tr>
<th>Group I (n = 47)</th>
<th>Group II (n = 45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M I\textsubscript{123} - MIBG</td>
<td>1.84 ± 0.38</td>
<td>2.08 ± 0.23</td>
</tr>
</tbody>
</table>

Exercise Stress Test

- Rest HR (bpm): 92 ± 17
- Peak HR (bpm): 140 ± 24
- 1st min recovery HR (bpm): 128 ± 23
- CI: 0.57 ± 0.22
- HRR (bpm): 18 ± 9

Heart Rate Variability

- SDNN (ms): 102 ± 43
- Total Power (ms\textsuperscript{2}): 2201 ± 3330
- LF (ms\textsuperscript{2}): 1002 ± 961
- HF (ms\textsuperscript{2}): 518 ± 1631

Ambulatory Blood Pressure

- Nocturnal systolic BP drop (%): 9 ± 3.4
- 12 ± 6

Table 2. Univariate and multivariate regression analysis for the prediction of neurological disability

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Univariate analysis</th>
<th>Multivariate regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I (n=47)</td>
<td>Group II (n=45)</td>
</tr>
<tr>
<td>MIBG ≤ 1.80</td>
<td>22 (47%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Rest HR ≥ 95</td>
<td>19 (40%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Peak HR ≤ 10</td>
<td>25 (53%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>CI ≤ 0.63</td>
<td>26 (55%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>HRR ≤ 17</td>
<td>24 (51%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>SDNN ≥ 198</td>
<td>23 (49%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>T. Power ≤ 1174</td>
<td>22 (47%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>VLF ≤ 713</td>
<td>23 (49%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>LF ≤ 296</td>
<td>21 (45%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>HF ≤ 237</td>
<td>34 (72%)</td>
<td>27 (60%)</td>
</tr>
<tr>
<td>Dipper ≤ 8.85</td>
<td>21 (45%)</td>
<td>10 (22%)</td>
</tr>
</tbody>
</table>

Figure 1. Accuracy of the autonomic function parameters for predicting neurological involvement, assessed by ROC curve analysis.

Figure 2. H/M I\textsubscript{123} - MIBG, heart rate variability analysis, chronotropic index and heart rate recovery in a 28-ya patient with an EMG score of 0% and a clinical score of 6%

Conclusions

- Symptomatic FAP patients have significant cardiac dysautonomia.
- CI and HRR are the autonomic parameters better associated with the systemic neurological involvement in FAP.
- Therefore these parameters may be very useful to determine the optimal timing for liver transplantation, which is nowadays the only way to control the progression of the disease.

Conflict of interest: none declared