Association of 5-HIAA and Mortality in Neuroendocrine Tumor Patients: A Systematic Review and Meta-Analysis

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Presented at the NANETS Annual Multidisciplinary NET Disease Symposium, October 4-6, 2018, Seattle, WA

Background

• Excessive secretion of serotonin by neuroendocrine tumors (NET) has been associated with tumor burden, fibrosis, and intermediate outcomes such as development of carcinoid heart disease (CaHD) and progression of CaHD1,2

• There is a lack of studies clearly defining the relationship between 5-hydroxyindoleacetic acid (5-HIAA), a marker of serotonin, and long-term outcomes such as mortality in patients with NETs3,4

We conducted a systematic review and meta-analysis to investigate the association between 5-HIAA and all-cause mortality in NET patients

Methods

• A systematic literature search was performed for studies published in English between 2007-2017 and indexed in PubMed, Embase, or secondary sources

• Clinical and observational studies in patients with NETs reporting 24-hour urinary 5-HIAA (mg/24 h) and mortality were included

• Mortality was converted to rates per person-years (number of patients by months of study follow-up, divided by 12) and log-transformed to normalize the data

• A restricted maximum likelihood (REML) meta-regression model, which controls for study size and dispersion, was used to estimate the relationship between 5-HIAA and 1-year mortality

Systematic Literature Review

• 1,715 records were screened, 307 of which underwent full-text review

• 36 studies reporting urinary 5-HIAA and mortality were assessed for eligibility in the meta-analysis, of which 12 studies (with 14 treatment arms) were included (Figure 1)

• The 12 included studies reported results for 755 NET patients contributing 3,442 person-years (Table 1)

Conclusions

• In NET patients, elevated 5-HIAA levels are predictive of all-cause mortality within 1 year

• Reducing serotonin may lead to better long-term outcomes for NET patients

References


Disclosures

This study was funded by Lexicon Pharmaceuticals, Inc.
Vijay N. Joish, MD, is an employee of Lexicon Pharmaceuticals, Inc.
Sandip Shah, PhD, and Helen (Dong) Shao, PhD, are employees of MKTXS who received funding from Lexicon Pharmaceuticals, Inc. for this work.
Jerome Zacks, MD, has received research support from Lexicon Pharmaceuticals, Inc.

5-HIAA and Mortality

• Mean 5-HIAA across all studies was 149.2 mg/24 h (range, 4.0 to 358.0; Table 1); the reference range is 2 to 7 mg/24 h5

Mean 5-HIAA was 43.4 mg/24 h in studies not reporting CS or CaHD specifically; 161.0 mg/24 h in CS patients, and 199.2 mg/24h in CaHD patients

• The overall annual mortality rate was 13% (95% CI, 9% to 20%) across studies from the random effects model (Figure 2)

Overall mortality was 5.6% in studies not reporting CS or CaHD specifically; 8.2% in CS patients, and 27.8% in CaHD patients

Meta-Regression Analysis: 5-HIAA and Mortality

• For every 10-unit increase in 5-HIAA, the meta-regression model yielded an 11.8% (95% CI, 8.96 to 17.0) increase in 1-year mortality (Figure 3)

Results

• This association remained significant after controlling for underlying subgroup conditions (NET only, CS, CaHD; P = 0.007)

Conclusion

• In NET patients, elevated 5-HIAA levels are predictive of all-cause mortality within 1 year

• Reducing serotonin may lead to better long-term outcomes for NET patients

Table 1. Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>NET Type</th>
<th>CS</th>
<th>CaHD</th>
<th>Negative</th>
<th>5-HIAA (mg/24 h)</th>
<th>Mortality Rate</th>
<th>Follow-Up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>USA</td>
<td>NET</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>20.0</td>
<td>14.0</td>
<td>12</td>
</tr>
<tr>
<td>Study 2</td>
<td>USA</td>
<td>NET</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100.0</td>
<td>20.0</td>
<td>18</td>
</tr>
</tbody>
</table>

Figure 1. PRISMA

Figure 2. Forest

Figure 3. Model

Full ePoster
Table 1. Studies
Figure 1. PRISMA
Figure 2. Forest
Figure 3. Model
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Figure 1. PRISMA flow diagram of screened and included studies

- Records identified through database search (n = 1,362)
- Additional records identified through other sources (n = 353)
- Records after duplicates removed (n = 1,587)
- Screening records excluded, with reasons (n = 1,286)
  - Publication type (n = 529)
  - Patient population (n = 383)
  - Outcomes (n = 309)
  - Not retrievable (n = 59)
- Full-text articles assessed for eligibility (n = 307)
- Full-text articles excluded, with reasons (n = 271)
  - Patient population (n = 106)
  - Not retrievable (n = 71)
  - Outcomes (n = 66)
  - Publication type (n = 28)
- Studies included in qualitative synthesis (n = 30)
- Studies included in quantitative analysis (n = 12)

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References of Included Studies


Table 1. Study population and clinical characteristics contributing to the analysis

<table>
<thead>
<tr>
<th>Study*</th>
<th>Study Population (N)</th>
<th>Follow-Up (months)</th>
<th>Person-years</th>
<th>Deaths, n</th>
<th>Mean 5-HIAA (mg/24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernheim 2008</td>
<td>265</td>
<td>72</td>
<td>1,590</td>
<td>199</td>
<td>183.0</td>
</tr>
<tr>
<td>Bhattacharyya 2011</td>
<td>22</td>
<td>12</td>
<td>22</td>
<td>11</td>
<td>150.0</td>
</tr>
<tr>
<td>Bhattacharyya 2013</td>
<td>12</td>
<td>8.5</td>
<td>9</td>
<td>6</td>
<td>139.8</td>
</tr>
<tr>
<td>Castillo 2008</td>
<td>11</td>
<td>21</td>
<td>19</td>
<td>2</td>
<td>251.0</td>
</tr>
<tr>
<td>Chambers 2008</td>
<td>46</td>
<td>72</td>
<td>276</td>
<td>14</td>
<td>60.7</td>
</tr>
<tr>
<td>Edwards 2016</td>
<td>47</td>
<td>7</td>
<td>27</td>
<td>18</td>
<td>168.0</td>
</tr>
<tr>
<td>Khan 2011</td>
<td>69</td>
<td>72</td>
<td>414</td>
<td>19</td>
<td>71.0</td>
</tr>
<tr>
<td>Komoda 2011</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>157.5</td>
</tr>
<tr>
<td>Mansencal 2010</td>
<td>30</td>
<td>27</td>
<td>67</td>
<td>13</td>
<td>358.0</td>
</tr>
<tr>
<td>Mansencal 2010</td>
<td>56</td>
<td>27</td>
<td>126</td>
<td>22</td>
<td>251.0</td>
</tr>
<tr>
<td>Mokhles 2012</td>
<td>22</td>
<td>28</td>
<td>51</td>
<td>9</td>
<td>186.0</td>
</tr>
<tr>
<td>Nykjaer 2007</td>
<td>15</td>
<td>72</td>
<td>90</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Nykjaer 2007</td>
<td>41</td>
<td>72</td>
<td>246</td>
<td>13</td>
<td>32.5</td>
</tr>
<tr>
<td>Sward 2009</td>
<td>107</td>
<td>56</td>
<td>499</td>
<td>42</td>
<td>76.5</td>
</tr>
</tbody>
</table>

*Some studies included specific subgroups of NET patients, for example with CS or CaHD.

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**Figure 2.** Forest plot of mortality rate from each study

<table>
<thead>
<tr>
<th>Study*</th>
<th>Population (N)</th>
<th>Deaths</th>
<th>Person-years</th>
<th>Mortality Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Komoda 2011</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>100% (85 to 100)</td>
</tr>
<tr>
<td>Bhattacharyya 2013</td>
<td>12</td>
<td>6</td>
<td>9</td>
<td>67% (35 to 92)</td>
</tr>
<tr>
<td>Edwards 2016</td>
<td>47</td>
<td>18</td>
<td>27</td>
<td>67% (48 to 83)</td>
</tr>
<tr>
<td>Bhattacharyya 2011</td>
<td>22</td>
<td>11</td>
<td>22</td>
<td>50% (30 to 70)</td>
</tr>
<tr>
<td>Mansencal 2010</td>
<td>30</td>
<td>13</td>
<td>67</td>
<td>19% (11 to 30)</td>
</tr>
<tr>
<td>Mokhles 2012</td>
<td>22</td>
<td>9</td>
<td>51</td>
<td>18% (9 to 29)</td>
</tr>
<tr>
<td>Mansencal 2010</td>
<td>56</td>
<td>22</td>
<td>126</td>
<td>17% (11 to 25)</td>
</tr>
<tr>
<td>Bernheim 2008</td>
<td>265</td>
<td>199</td>
<td>1,590</td>
<td>13% (11 to 14)</td>
</tr>
<tr>
<td>Castillo 2008</td>
<td>11</td>
<td>2</td>
<td>19</td>
<td>11% (1 to 28)</td>
</tr>
<tr>
<td>Sward 2009</td>
<td>107</td>
<td>42</td>
<td>499</td>
<td>8% (6 to 11)</td>
</tr>
<tr>
<td>Chambers 2008</td>
<td>46</td>
<td>14</td>
<td>276</td>
<td>5% (3 to 8)</td>
</tr>
<tr>
<td>Nykjaer 2007</td>
<td>41</td>
<td>13</td>
<td>246</td>
<td>5% (3 to 7)</td>
</tr>
<tr>
<td>Khan 2011</td>
<td>69</td>
<td>19</td>
<td>414</td>
<td>5% (3 to 7)</td>
</tr>
<tr>
<td>Nykjaer 2007</td>
<td>15</td>
<td>2</td>
<td>90</td>
<td>2% (0 to 6)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>3,442</td>
<td>20</td>
<td>40</td>
<td>13% (9 to 20)</td>
</tr>
</tbody>
</table>

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Figure 3. Meta-regression of urinary 5-HIAA and 1-year mortality