Comparison of the Estimated Prevalence of Diagnosed Homocystinuria and Phenylketonuria in the United States

Marcia Sellos-Moura, Frank Glavin, David Lapidus, Patrick T. Horn, Kristin Evans, Carolyn R. Lew, Debra E. Irwin

Background

- Classical homocystinuria (HCU) is a rare inherited (genetic) disorder in which the body is unable to process the toxic compound homocysteine (HCY), which is involved in several important metabolic processes. HCU is caused by mutations in the cystathionine beta synthase (CBS) gene.
- At least 1 in 200,000–335,000 people worldwide, and 1 in 100,000 to 200,000 in the United States, are estimated to have homocystinuria (HCU).  
- However, these prevalence estimates are widely believed to be an underestimate of the prevalence of HCU. Several studies have estimated the birth prevalence of HCU to be much higher.  
- Newborn screening (NBS) typically tests for HCU by an indirect method: the concentration of methionine (a precursor to HCY) is measured rather than HCY itself, and NBS often produces false negatives. HCU may be undiagnosed at birth due to NBS that is inadequately sensitive. Moreover, NBS for HCU has been underutilized in the newborn period, which is involved in several important metabolic processes.

Methods

- Data Source
  - This study utilized patient-level de-identified US administrative claims in the IBM MarketScan® Commercial and Medicare Supplemental Database from January 1, 2010 through December 31, 2016.
- Patient Selection and Study Design
  - Enrolled patients had an HCU diagnosis or a PKU diagnosis between January 1, 2010 and December 31, 2016, were identified in the MarketScan® database using the following criteria:
    - HCU cohort – Unique patients with:
      - At least 1 non-diagnostic claim with International Classification of Diseases, 10th revision (ICD-10) code E70.1 (homocystinuria) between January 1, 2010 and December 31, 2016.
      - Each patient's entire available data history during the study was included in the analysis, including ICD-9 diagnoses predating the ICD-10 system.
    - PKU cohort – Unique patients with:
      - At least 1 non-diagnostic claim with ICD-9 code 270.1 (phenylketonuria) or ICD-10 code E70.0 (classical phenylketonuria) between January 1, 2010 and December 31, 2016.
- The first diagnosis of HCU or PKU observed during the study time period was set as the index date.
- Note that the patient population represents a population with prevalent disease. Patients may have been diagnosed prior to the beginning of the study time period.
- Demographics were captured on the index date.

Results

- Patient Population Characteristics
  - A total of 6,613 and 5,120 patients met inclusion criteria for HCU and PKU (Figure 1). The average age of HCU patients (55.5 years) was 38 years older than that for PKU patients (17.5 years). Both cohorts were slightly over 50% female, were primarily residing in urban areas, and the majority were covered by EPO/PPO plans (Table 1).

Objectives

- To estimate the prevalence of diagnosed HCU in the United States (U.S.) population across age groups compared with that of diagnosed PKU in similar age groups.

Table 1. Demographic Characteristics at First Recorded Diagnosis in Study Period

<table>
<thead>
<tr>
<th>Age Group</th>
<th>HCU (N=6,613)</th>
<th>PKU (N=5,120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>411 (6.2%)</td>
<td>27 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-5</td>
<td>32 (0.5%)</td>
<td>11 (0.2%)</td>
<td>0.008</td>
</tr>
<tr>
<td>6-12</td>
<td>165 (2.5%)</td>
<td>23 (0.4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>13-17</td>
<td>335 (5.1%)</td>
<td>53 (1.0%)</td>
<td>0.008</td>
</tr>
<tr>
<td>&gt;18</td>
<td>5,902 (89.8%)</td>
<td>4,831 (94.9%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 2. MarketScan Prevalence of HCU and PKU Per 1000 Study Population, 1/1/2010 - 12/31/2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>HCU Per 1000</th>
<th>PKU Per 1000</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0.11</td>
<td>0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-14</td>
<td>0.09</td>
<td>0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15+</td>
<td>0.06</td>
<td>0.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions

- While HCU and PKU are both inherited metabolic disorders, the observed prevalence in the United States showed a dramatically different age distribution.
- As expected, the highest proportion of diagnosed PKU patients was observed in the youngest age group (ages 0–11 years), likely due to infants being diagnosed through universal newborn screening.
- Conversely, the prevalence per 1000 HCU cases among the younger age group was dramatically lower than among older persons, implying that HCU patients are not diagnosed primarily at birth or during early childhood, even though HCU is a lifelong genetic disease.
- This suggests that newborn screening fails to capture the vast majority of HCU cases, with patients diagnosed late in life, including adulthood, when they present with symptoms or comorbid conditions indicative of HCU.

References

4. The newborn screen for PKU utilizes a direct method, and the majority of PKU patients are diagnosed at birth.
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