Claims-Based Analysis of Homocysteine Testing, Elevated Homocysteine Levels, and Homocystinuria Diagnosis in the United States

Marcia Sellos-Moura[1], Frank Glavin[1], David Lapidus[2], Patrick T. Horn[1], Kristin Evans[3], Liisa Palmer[3]

[1]Orphan Technologies, 430 Bedford Street, Suite 195, Lexington, MA 02420, USA; [2]LapidusData Inc., 321 NE 4th St, Oklahoma City, OK 73104, USA; [3]IBM Watson Health, 7700 Old Georgetown Rd, Bethesda, MD 20814, USA

Background

- Classical homocystinuria (HCU) is a rare inherited (genetic) disorder in which the body is unable to process the toxic compound homocysteine (tHCY), which is involved in several important metabolic processes. It is caused by mutations in the cystathionine beta synthase (CBS) gene.[1]
- At least 1 in 200,000–335,000 people worldwide, and 1 in 100,000-200,000 in the United States, are estimated to have HCU.[2,3,4]
- 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. [5,6] Newborn screening typically tests for HCU by an indirect method: the concentration of methionine (a precursor to tHcy) is measured, rather than tHcy itself. As a result, newborn screening often produces false negatives.[7]
- Adults not diagnosed with HCU during childhood are frequently misdiagnosed because abnormally high tHcy levels (hyperhomocysteinemia) can indicate other medical conditions in addition to homocystinuria including vitamin deficiencies, and increased risk of heart attack or stroke,[5] making definitive diagnosis of HCU difficult.

Objectives

- To examine incidence of tHcy testing and intermediate to severe tHcy levels (>30 µmoles/L)[8], which are suggestive of classical HCU.
- To estimate the prevalence of patients who have tHcy levels >30 in the United States population.

Methods

Data Source

- This study utilized patient-level de-identified US administrative claims in the IBM MarketScan® Lab Database from January 1, 2006 through March 31, 2016.
- The IBM MarketScan® Lab Database provides a full longitudinal view of a patient's medical claims history across the care continuum, providing information on diagnoses, procedures, lab tests, medications, and healthcare costs. The Lab Database contains results for tests of blood, serum, plasma, urine, and other specimens, including those for tHcy levels.

Patient Selection and Study Design:

- Individuals with a lab test result for tHcy, identified by LOINC code 13965-9 (Homocysteine in serum or plasma [moles/volume]), between January 1, 2006 and March 31, 2016 were selected.
- Of those who had a test result, the proportion who had a tHcy test result >30 µmoles/L were classified as having an intermediate to severely elevated tHcy test.
- The proportion of patients with the following selected diagnoses prior to having a tHcy test result >30 µmoles/L were identified using International Classification of Diseases (ICD-9 and ICD-10) codes: hypertension, hyperlipidemia, hypothyroidism, vitamin D deficiency and chronic renal disease.
- The proportion of patients with a diagnosis of HCU among those who had a tHcy test result >30 µmoles/L was also calculated.
- The proportion of patients who were prescribed selected medications within 2 weeks after a tHcy test result >30 µmoles/L were identified using drug therapeutic classes. The medication classes included antihypertensives, lipid-lowering drugs, anxiolytics/antidepressants, thyroid hormone and vitamin D supplements.

Analysis

- The incidence (per 1000 person-years) of patients having a tHcy test was calculated, as well as the incidence (per 1000 person-years) of patients having a test result with tHcy level >30 µmoles/L.
- The point prevalence of patients with a history of tHcy level >30 µmoles/L was estimated for the United States poulation on 4/1/2016 using United States Census Bureau population estimates.

Results

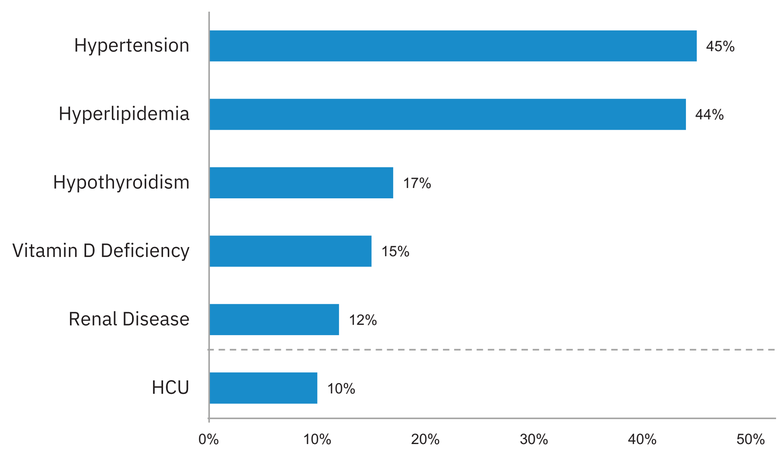
Patient Population and tHcy Test Results

- 1.9 million patients were enrolled in the Lab Database throughout 4/1/15-3/31/16 (the most recent year of available data), providing the denominator for the prevalence of tHcy-tested patients.
  - Of the 1.9 million patients, 15,012 (0.8%) had a tHcy test result between 1/1/2006 and 3/31/2016. The mean tHcy test result was 10.8 µmoles/L (SD 15.1 µmoles/L).
  - Of the 15,012 patients with a tHcy test result since 2006, 223 (1.5%) had tHcy >30 µmoles/L (mean 96.0 µmoles/L [SD 174.1 µmoles/L], median 39.9 µmoles/L).

Common Comorbid Conditions and Prescriptions for Patients with tHcy >30 µmoles/L

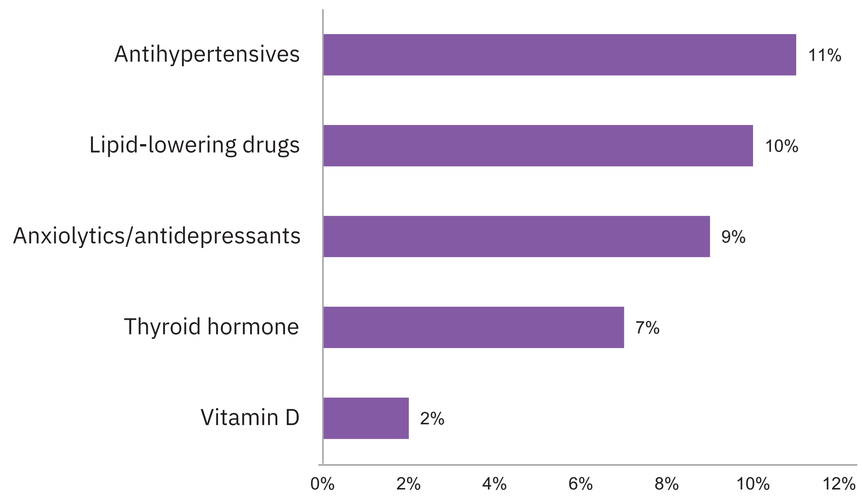
- Of patients with a tHcy test result >30 µmoles/L, 45% were diagnosed with hypertension, 44% hyperlipidemia, 17% hypothyroidism, 15% vitamin D deficiency and 12% renal disease prior to their tHcy test result (Figure 1).
- Only 10% (22) of patients with a tHcy test result >30 µmoles/L were diagnosed with HCU anytime during their enrollment in the database (Figure 1).
- Within 2 weeks after their tHcy >30 result, 11% of patients filled ≥1 prescription for antihypertensives, 10% lipid-lowering drugs, 9% anxiolytics or antidepressants, 7% thyroid hormone, and 2% vitamin D (Figure 2).

Figure 1. Common Diagnoses* in Patients with a tHcy Test Result >30 µmoles/L



* Comorbid condition diagnoses were assessed prior to tHcy testing; HCU diagnosis was at any point in their claims history.

Figure 2. Common Medications Prescribed* for Patients with a tHcy Test Result >30 µmoles/L

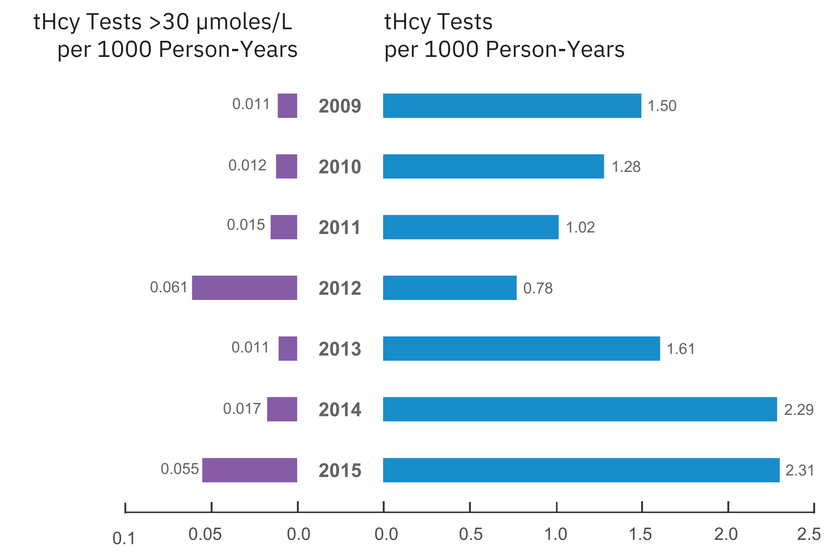


* Prescriptions were assessed within 2 weeks after the tHcy test

Annual Incidence of tHcy Testing and Projected Prevalence of tHcy >30 µmoles/L

- Annual incidence of any tHcy test result was 0.8–2.3 (mean 1.5) tests/1000 person-years in 2009–2015 (Figure 3) (required at least 3 years of enrollment with no prior tHcy test, so incidence was not calculated for 2006-2008; 2016 was not included since only data through 3/31/2016 were available).
- Among patients confirmed to have no recent tHcy test result >30 µmoles/L, the annual incidence of a tHcy result >30 µmoles/L was 0.01-0.06 (mean 0.03)/1000 person-years (Figure 3).

Figure 3. Incidence of a tHcy Test and tHcy Results >30 µmoles/L, 2009-2015



- Estimated point prevalence of patients with a history of tHcy level >30 µmoles/L in the U.S. on 4/1/2016 was 0.012% (38,634 patients) (95% CI ~0.010%– 0.014%; 33,562–43,706 patients).

Limitations

- This study was limited to only those individuals with commercial health coverage or private Medicare supplemental coverage. Results of this analysis may not be generalizable to individuals with other insurance or without health insurance coverage.
- The data in this study was limited to data found in administrative claims, which may be subject to data coding limitations and data entry error. There is also potential for misclassification of diagnoses or other study outcomes, based on the limitations of claims data.
- The analysis was conducted during a specific study time period. Any temporal changes or differences outside of that time window were not captured in this study.

Conclusions

- This study is one of the first to estimate the incidence of patients having tHcy testing and having tHcy levels in the range of classical HCU in the U.S.
- Of patients with lab values indicative of classical HCU, only 10% had a diagnosis of HCU.
- Over 38,000 patients in the U.S. are estimated to have a history of tHcy levels >30 µmoles/L.
- Such patients warrant further evaluation for the etiology of their hyperhomocysteinemia, including screening for classical HCU.

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