Neuropsychiatric comorbidities in adolescents with PKU in the United States

Karly S. Louie[1], Kristin Lindstrom[2], Shikha Shaji[3], Bharath Kumar Vedantham[4], Barbara Burton[5]

[1]BioMarin UK Ltd, London, UK; [2]BioMarin Pharmaceutical Inc, Novato, CA, USA; [3]Definitive Healthcare, Bengaluru, Karnataka, India; [4]Definitive Healthcare, Framingham, MA, USA; [5]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Introduction

- PKU is a rare genetic disorder caused by deficiency of the PAH enzyme, which prevents the body from breaking down the amino acid phenylalanine (Phe). This PAH deficiency results in elevated levels of Phe in the blood[1]
- The mainstay of PKU treatment is dietary restriction of Phe, with the aim of achieving guideline-recommended Phe levels (≤360 µmol/L for life [US guidelines];[2] or 120–360 µmol/L in those aged <12 years and during pregnancy and 120–600 µmol/L in those aged ≥12 years [European guidelines][1])
  - However, research suggests that many individuals fail to achieve recommended Phe levels with dietary management alone, particularly in adolescence and adulthood[3]
- High Phe levels are associated with increased prevalence of neuropsychiatric comorbidities in adults with PKU,[1,2,4] but the burden of neuropsychiatric comorbidities in adolescence has not been well described

Objective

- The aim of this analysis was to evaluate the prevalence of neuropsychiatric comorbidities in adolescents with PKU compared with non-PKU controls in the US

Methods

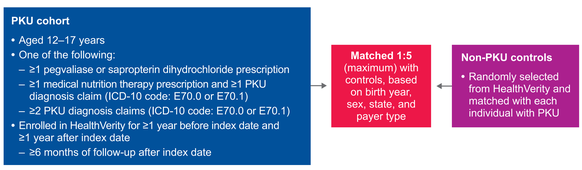
Study design

- This was a retrospective, observational cohort study of adolescents aged 12–17 years with PKU (the PKU cohort) compared with non-PKU controls in the US. The study used electronic health records, alongside medical claims data from the HealthVerity database (**Figure 1**)
- Study period: May 24, 2017 to Mar 31, 2023

Data source

- HealthVerity is a de-identified dataset comprising medical and pharmacy claims compiled from >75 data providers covering >330 million individuals in the US[5]
- Demographics and clinical history, as defined by ICD codes for neuropsychiatric comorbidities,[6] were analyzed

Figure 1. Study cohorts



- Index period: May 24, 2018 to Sep 30, 2022
- Index date:
  - PKU cohort: date of first medical claim for PKU (individuals with no record of treatment) or first treatment prescription (i.e. pegvaliase, sapropterin dihydrochloride, or first medical nutrition therapy) recorded during the index period
  - Non-PKU controls: date of first medical record within the study period

Statistical analysis

- Prevalence of neuropsychiatric comorbidities (defined using ICD codes, as described by Bilder et al.[6]) was estimated during the 12-month baseline period before the index date and throughout follow-up until individuals reached aged 17 years (inclusive) within the study period
  - **Prevalence rate:** (number of individuals with neuropsychiatric symptom[s]) / (population at risk)
- Prevalence ratios were reported to compare differences between the PKU cohort and non-PKU controls
  - **Prevalence ratio:** (prevalence rate of PKU cohort) / (prevalence rate of non-PKU controls)
- Age- and sex-adjusted prevalence was analyzed (**Figure 2**)
  - Individuals were grouped by age and sex:
    - Group 1: Males (12–14 years)
    - Group 2: Males (15–17 years)
    - Group 3: Females (12–14 years)
    - Group 4: Females (15–17 years)
  - **Age- and sex-adjusted prevalence rate:** sum of adjusted prevalence rate for each group, estimated per 100,000 individuals
    - **Age- and sex-adjusted prevalence rate (Group X):** [(number of individuals with neuropsychiatric symptom[s] in Group X) / (total number of individuals in Group X)] × (proportion of individuals in Group X)
  - **Age- and sex-adjusted prevalence ratio:** (adjusted prevalence rate of PKU cohort) / (adjusted prevalence rate of non-PKU controls)

Results

Characteristics of individuals

- Between May 24, 2018 and Mar 31, 2023, 672 adolescents with PKU (the PKU cohort) were matched with 2,512 non-PKU controls (**Table 1**)

Neuropsychiatric comorbidities

- The most common (>5%) neuropsychiatric comorbidities in the PKU cohort (age- and sex-adjusted) from baseline until the age of 17 years were ADD/ADHD, anxiety, migraine and headache, depression, fatigue and malaise, intellectual disability, and autism/ASD (**Figure 2**)
- Neuropsychiatric comorbidities for which the age- and sex-adjusted prevalence ratio was >1.5 were intellectual disability, Tourette syndrome/tic disorder, epilepsy and convulsion, movement disorder, tremor, autism/ASD, ADD/ADHD, and OCD (**Figure 3**)

Conclusions

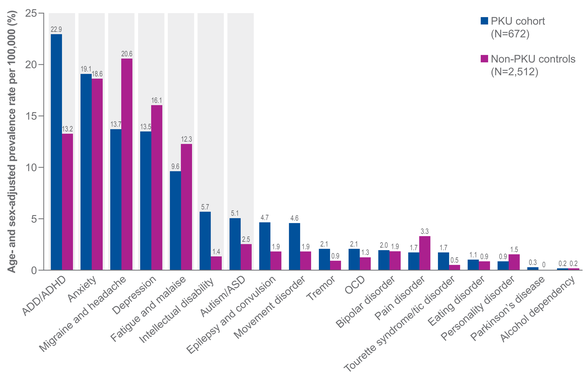
- This US cohort study of adolescents with PKU found that many of the neuropsychiatric symptoms previously described in adults are also prevalent during adolescence
  - These conditions are likely to worsen in adulthood unless Phe levels are effectively controlled
- Some neuropsychiatric comorbidities, including intellectual disability, Tourette syndrome/tic disorder, and ADD/ADHD, were more prevalent in the PKU cohort relative to non-PKU controls
  - Notably, rates of intellectual disability were four times higher in the PKU cohort compared with non-PKU controls
- These findings underscore the critical importance of maintaining control of Phe levels throughout childhood and adolescence to minimize the burden of neuropsychiatric comorbidities
- Similar data from a Swedish cohort are being presented at this meeting
  - Wed Sep 3, 11:00–12:30; session theme: PKU 1; session name: oral presentation 3; presenter: Karly S. Louie

Table 1. Demographics and characteristics of individuals

Demographic/characteristic, n (%)	PKU cohort (N=672)	Non-PKU controls (N=2,512)
Age		
12–14 years	376 (56.0)	1,580 (62.9)
15–17 years	296 (44.0)	932 (37.1)
Sex		
Male	362 (53.9)	1,345 (53.5)
Female	310 (46.1)	1,167 (46.5)
Age and sex group		
Group 1: Males (12–14 years)	197 (29.3)	810 (32.2)
Group 2: Females (12–14 years)	179 (26.6)	770 (30.7)
Group 3: Males (15–17 years)	165 (24.6)	535 (21.3)
Group 4: Females (15–17 years)	131 (19.5)	397 (15.8)
Treatment		
Sapropterin dihydrochloride ± medical nutrition therapy	257 (38.2)	N/A
Medical nutrition therapy only	171 (25.4)	N/A
Pegvaliase	15 (2.2)	N/A
No record of treatment	229 (34.1)	N/A

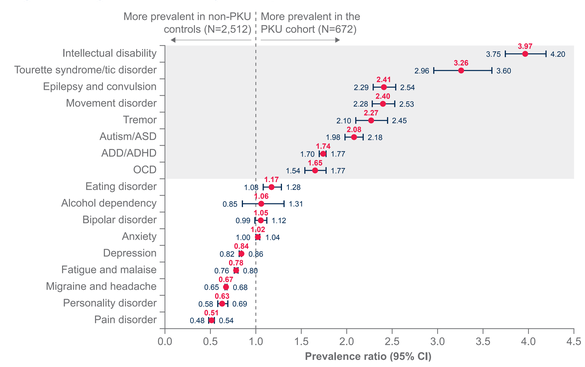
Percentages may not total 100% due to rounding

Figure 2. Age- and sex-adjusted prevalence rate per 100,000 individuals



Gray shading indicates neuropsychiatric comorbidities for which the age- and sex-adjusted prevalence rate was >5% for the PKU cohort

Figure 3. Age- and sex-adjusted prevalence ratio



Gray shading indicates neuropsychiatric comorbidities for which the age- and sex-adjusted prevalence ratio was >1.5. Note there is no adjusted prevalence ratio for Parkinson's disease

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Disclosures

Karly S. Louie is an employee of, and holds stock or stock options in, BioMarin UK Ltd. **Kristin Lindstrom** is an employee of, and holds stock or stock options in, BioMarin Pharmaceutical Inc. **Barbara Burton** has received consulting payments from Agios Pharmaceuticals, Alltrna, Applied Therapeutics, Aro Biotherapeutics, BioMarin, Chiesi, Horizon Therapeutics, JCR Pharmaceuticals, Maze Therapeutics, Moderna, Orchard Therapeutics, Passage Bio, Sanofi, Takeda, Travere Therapeutics, Ultragenyx, and uniQure, and has participated as a clinical trial investigator for BioMarin, Denali Therapeutics, Homology Medicines, JCR Pharmaceuticals, Sangamo Therapeutics, Takeda, and Ultragenyx. **Shikha Shaji** and **Bharath Kumar Vedantham** have no conflicts of interest to declare.

Abbreviations

ADD, attention-deficit disorder; **ADHD**, attention-deficit/hyperactivity disorder; **ASD**, autism spectrum disorder; **CI**, confidence interval; **ICD**, International Classification of Diseases; **N/A**, not applicable; **OCD**, obsessive-compulsive disorder; **PAH**, phenylalanine hydroxylase; **Phe**, phenylalanine; **PKU**, phenylketonuria.

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