



Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study



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ABSTRACT

Adults with phenylketonuria (PKU) may experience neurologic and psychiatric disorders, including intellectual disability, anxiety, depression, and neurocognitive dysfunction. Identifying the prevalence and prevalence ratios of these conditions will inform clinical treatment. This nested, case-controlled study used International Classification of Diseases, Ninth Revision (ICD-9) codes from the MarketScan® insurance claims databases from 2006 to 2012 and healthcare claims data for US-based employer and government-sponsored health plans. Prevalence and prevalence ratio calculations of neuropsychiatric comorbidities for adults (≥ 20 years old) with PKU were compared with two groups [diabetes mellitus (DM) and general population (GP)] matched by age, gender, geographic location, and insurance type. Age cohorts (i.e., 20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years, and a combined subset of 20–39) were used to stratify data. The PKU cohort experienced significantly higher rates of several comorbid neurologic, psychiatric and developmental conditions. Compared to GP, PKU was associated with significantly higher prevalence for numerous neuropsychiatric conditions, most notably for intellectual disability (PR = 7.9, 95% CI: 6.4–9.9), autism spectrum disorder (PR = 6.1, 95% CI: 3.6–10.4), Tourette/tic disorders (PR = 5.4, 95% CI: 2.1–14.1), and eating disorders (4.0, 95% CI: 3.2–5.0). Rates of fatigue/malaise, epilepsy/convulsions, sleep disturbance, personality disorders, phobias, psychosis, and migraines among those with PKU exceeded rates for the GP but were comparable to those with DM, with significantly lower rates of concomitant disorders occurring in younger, compared to older, adults with PKU. Lifelong monitoring and treatment of co-occurring neuropsychiatric conditions are important for effective PKU management.

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1. Introduction

Phenylketonuria (PKU) is an inherited deficiency in the phenylalanine hydroxylase (PAH) enzyme caused by one of >950 gene variants [1]. These variants can result in a mildly, moderately, or severely defective PAH enzyme with subsequent benign, slightly elevated, or severely elevated blood phenylalanine (Phe), respectively. Newborn screening for PKU was initiated in the 1960's in the U.S. after the development

of an assay to detect blood Phe [2]. Since then, newborn screening and early initiation of treatment with a Phe-restricted diet and Phe-free medical foods have successfully ameliorated or prevented severe neurological and neurocognitive impairments [3–4].

Phenylalanine is an essential amino acid that is present in most natural protein foods. Dietary treatment recommendations for PKU are designed to promote physical growth and normal neurocognitive development [5]. Even with Phe-restrictive dietary recommendations for all age groups, evidence suggests that PKU management with diet alone has resulted in sub-optimal outcomes, including deficits in neurocognitive and psychosocial metrics, quality of life measures, nutritional deficits, and brain pathology [6]. Current treatment guidelines, based upon available clinical research, indicate that individuals with PKU should maintain lifelong metabolic control with blood Phe levels between 120 and 360 $\mu\text{mol/L}$, which is typically achieved by strict adherence to a Phe-restricted diet and dietary supplementation with Phe-free amino acid fortified medical foods [7–9].

Abbreviations: PKU, Phenylketonuria; PAH, Phenylalanine hydroxylase; Phe, Phenylalanine; DM, Diabetes Mellitus; GP, General population; OCD, Obsessive Compulsive Disorder; GMC, General Medical Condition; ADD/ADHD, Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder; PR, Prevalence ratio; ICD-9, International Classification of Diseases, Ninth Revision.

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Maintaining a Phe-restricted diet that ensures blood Phe levels within recommended guidelines represents a significant burden on quality of life, and adherence is a major medical problem [10]. With limited therapeutic alternatives, many adults with PKU are not adherent to dietary treatment and their blood Phe exceeds the recommended range. For example, Walter et al. found that a majority of adolescents and young adults were not adherent with recommendations for the monitoring and control of blood Phe [11] and, in a recent survey, Brown et al. reported that more than half (51.7%) of respondents were having difficulty managing their PKU, including the maintenance of a Phe-restricted diet [12]. In addition, Berry et al. estimated that 71% of adults with PKU in the US between the ages of 19 and 45 years, who were diagnosed by newborn screen, are not actively treated by a metabolic clinic [13]. This lack of clinical follow-up is presumed to be an interaction of multiple factors and may, in part, reflect the impact of the continuing evolution of treatment practices and guidelines since the initiation of newborn screening. Difficulties accessing metabolic centers and/or lack of insurance coverage also likely contribute to the nonadherence of treatment recommendations. The National PKU Alliance, a patient and caregiver organization focused on supporting the management of PKU, may help to improve lifelong care of these individuals [12].

High blood Phe leads to both acute and chronic neuropsychiatric symptoms [7–9]. Impairment in psychiatric, behavioral, and neurocognitive function often reflect the timing, duration, and intensity of Phe exposure in addition to the emotional burden of having a chronic disorder [14–19]. Because newborn screening was not implemented before the early-to-mid 1960's, majority of adults with PKU > 55 years of age reflect 'late diagnosed' individuals who did not have the opportunity for early diagnosis. In addition, because treatment targets have tightened over the proceeding decades, younger aged cohorts (e.g., individuals with PKU < 40 years of age) would more likely be expected to have maintained treatment for life, had increased opportunity for continuous treatment, and, subsequently, may have less comorbidity compared to older cohorts (e.g., individuals with PKU ≥ 40 years old). Indeed, studies published in the last 15 years of individuals with PKU, who were clinically managed from birth, have demonstrated intellectual abilities predominantly in the normal range [20–21]. However, even with continuous clinical management, neuropsychological, psychosocial, academic, and/or neuropsychiatric impairments have been observed in clinically treated cohorts [22–24].

Studies of adult outcomes associated with early-treated PKU have identified increased rates of symptoms and impairment related to mood, anxiety, hyperactivity/inattention, and executive functioning [24–29]. Burton et al. found that 53% of adults with PKU screened positive for the presence of clinically significant psychiatric symptoms [30]. Unlike the general population and other studies of chronic illness, the age of individuals with PKU is positively correlated with the presence and intensity of psychiatric symptoms [16]. Even with early treatment, PKU in adulthood has also been associated with recurrent headaches, neurological signs, seizures, and tremor, to a greater degree in those with a history of early discontinuation of treatment [31–35]. More contemporary studies have reported modest rates of seizures and/or tremor in this population [36–37].

The purpose of the current study is to investigate the prevalence and prevalence ratios (PR) of neuropsychiatric disorders in a large, population-based sample of adults with PKU. This study uses an insurance claims database to: (1) measure the prevalence of neuropsychiatric disorders in adults with PKU and (2) determine the PRs of these conditions when compared to matched cohorts within the general population (GP) and adults with diabetes mellitus (DM). DM is a chronic disorder that also includes dietary intake restrictions and frequent blood monitoring for routine management.

2. Methods

This retrospective cohort study used three MarketScan® Research Databases which provided healthcare claims data for US-based

employer and government-sponsored health plans for the years 2006 to 2012. These databases did not include claims for uninsured individuals. Diagnoses were based on the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification (CM) Codes. During this timeframe, ICD-9-CM was the official system of assigning codes to diagnoses associated with hospital utilization in the United States (<http://www.cdc.gov/nchs/icd/icd9cm.htm>). Individuals were identified using at least 1 PKU claim in the years 1995 to 2012. To be included in this study, individuals in the database must have been ≥20 years of age in 2006 to prevent inclusion of presumptive positive individuals who may have been miscoded during the newborn screening period and reflect diagnostic codes used during adulthood.

Adults with PKU (ICD-9 code 270.1) were matched for age, gender, geographic region (Northeast, Midwest, South, West) and insurance type (commercial, Medicare, Medicaid) to both diabetes mellitus (DM) and general population (GP) cohorts, achieving approximately 1:2 and 1:6 ratios, respectively. Patients with DM were identified with at least one claim of ICD-9 code 250 and all related 250 sub codes (Diabetes Mellitus Type 1 or Type 2) and zero concomitant claims of PKU. The GP cohort was drawn from the complete data set, excluding claims of PKU. These groups were stratified by age (i.e., 20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years). The combined subset of 20–39 year olds was analyzed to provide evaluation of outcomes of an adult cohort most likely to have had PKU diagnosed at birth through newborn screening, early-initiation of dietary treatment, and increased likelihood of having had the opportunity for "early and continuous treatment" rather than merely "early treatment" for PKU [38].

2.1. Statistical analyses

Patients with an ICD-9 diagnostic code 270.1 (Phenylketonuria - PKU) in the MarketScan® Research Databases were included in the PKU cohort analysis. Only adjudicated data up to and including 2012 were included. A prevalence ratio (PR) was used to compare comorbidity prevalence between the PKU, DM, and GP cohorts. Because the PR across age cohorts did not follow a normal distribution, corresponding 95% confidence intervals (CI) for each PR were based on the natural log of each comparison. Statistical differences for prevalence rates among and between age groups were determined by Chi-square analysis. An alpha level of 0.05 was assumed for all statistical tests.

2.2. Prevalence of neuropsychiatric disorders

Neuropsychiatric diagnoses were assessed by ICD-9 codes (Supplemental File 1) on database claims for study cohorts and included attention-deficit hyperactivity disorder (ADD/ADHD), alcohol dependency, anxiety, autism spectrum disorder, bipolar disorder, depression, eating disorder, epilepsy and convulsion, fatigue and malaise, intellectual disability, migraine and headache, movement disorders, Parkinson's, tremor, obsessive-compulsive disorder (OCD), pain disorder, personality disorder, and Tourette syndrome/tic disorder among others. Disorders included in the study were pre-defined by the authors based on PKU comorbidities reported in the medical literature and clinical experience. The corresponding ICD-9 codes for each disorder were defined by at least 2 experts familiar with ICD-9 coding for neuropsychiatric diagnoses.

2.3. Sensitivity analyses and estimation of error

To include as many individual records as possible, data were analyzed without restricting total enrollment time in the database. A sensitivity analysis was then performed for individuals with no minimum enrollment time in the database and those with a minimum of six, twelve, and eighteen months of total enrollment time in the database. In addition, an analysis of the individuals meeting all inclusion criteria with 2 or more PKU diagnosis codes (270.1) in the database between 1995 and 2012 were evaluated.

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