



Psychiatric symptoms and disorders in phenylketonuria[☆]

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ABSTRACT

Psychological and psychiatric problems are well documented across the lifespan of individuals with early-treated phenylketonuria (PKU). Early-treated children and adolescents tend to display attentional problems, school problems, lower achievement motivation, decreased social competence, decreased autonomy, and low-self-esteem. As they enter adulthood, early-treated individuals may carry forward low self-esteem and lack of autonomy but also tend to develop depressed mood, generalized anxiety, phobias, decreased positive emotions, social maturity deficits, and social isolation. The correlation between level of metabolic control and severity of symptoms suggests a biological basis of psychiatric dysfunction. Additionally, psychosocial factors such as the burden of living with a chronic illness may contribute to psychological and psychiatric outcomes in PKU. The lack of a PKU-specific psychiatric phenotype combined with the observation that not everyone with PKU is affected highlights the complexity of the problem. More research on psychiatric and psychological outcomes in PKU is required. Of particular importance is the routine monitoring of emotional, behavioral, and psychosocial symptoms in individuals with this metabolic disorder. Longitudinal studies are required to evaluate the impact of new and emerging therapies on psychiatric and psychosocial functioning in PKU. Unidentified or untreated emotional and behavioral symptoms may have a significant, lifelong impact on the quality of life and social status of patients.

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Background

Phenylketonuria (PKU; OMIM 261600 and 261630),¹ an inherited disorder of amino acid metabolism, provides insights into the biochemical and psychosocial etiology of psychiatric disorders. In PKU, mutations in the phenylalanine hydroxylase (PAH; EC 1.14.16.1) gene prevent the breakdown of phenylalanine (Phe) into tyrosine [1]. Phe is one of the essential amino acids found in all protein. Its metabolite, tyrosine, is a precursor of dopamine and other important neurotransmitters in the brain.

Blood Phe levels vary in individuals with PKU depending on the severity of metabolic disruption and the amount of dietary Phe ingested. Increased concentrations of Phe have a neurotoxic effect, contributing to the structural brain damage, severe mental retardation, and psychiatric disturbances present in untreated patients with PKU [2–6]. Early identification of PKU through newborn

screening and prompt initiation of treatment with a Phe-restricted diet have prevented the most severe consequences of this disorder. However, psychiatric disorders, behavioral problems, and cognitive deficits commonly occur [7].

From a biological standpoint, elevations in Phe probably do not directly cause psychiatric symptoms. Instead, there are three likely mechanisms through which elevated Phe indirectly affects brain function, including myelin abnormalities, disruption of amino acid transport across the blood–brain barrier, and reductions in neurotransmitters [8].

In terms of myelin abnormalities, excess Phe may inhibit myelin development [1]. Recent magnetic resonance imaging (MRI) studies document an association between high Phe levels and reduced myelin [9]. Although the mechanism by which Phe affects myelin is not clear, myelination is delayed in untreated or poorly treated children with PKU, and dysmyelination occurs in adults who discontinue the Phe-restricted diet [10].

Turning to disrupted transport across the blood–brain barrier, Phe shares a common transport system with several other essential amino acids. When blood Phe is elevated, normal amounts of other amino acids, such as tyrosine and tryptophan, fail to reach the brain [11]. Tyrosine and tryptophan are precursors of neurotransmitters such as dopamine and serotonin, respectively, which are consequently reduced in the brain [12–14].

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¹ *Abbreviations used:* PKU, phenylketonuria; Phe, phenylalanine; PAH, phenylalanine hydroxylase; MRI, magnetic resonance imaging; IQ, intelligence quotient; ADHD, attention-deficit/hyperactivity disorder.

Dopamine has been a particular focus in PKU research, and levels of this neurotransmitter are reduced in the cerebrospinal fluid of people with PKU [1]. It should be kept in mind, however, that dopaminergic pathways do not operate in isolation. Although the complex interactions among neurotransmitter systems are not fully understood, dopamine, norepinephrine, and serotonin are all involved in regulating mood, emotion, and cognition [15].

Although many studies suggest a primary neurobiological explanation for psychological and psychiatric problems in patients with PKU, psychosocial factors cannot be ignored. Dietary therapy is highly restrictive, necessitates close monitoring by parents, and highlights how children with PKU differ from peers. Stress associated with this chronic disorder and the burden of the restrictive diet likely play roles in the increase in psychiatric symptoms among patients with PKU [16–21].

Psychiatric and psychological functioning in untreated PKU

The psychiatric and psychological functioning of individuals with untreated PKU has been studied since the disease was initially described by Fölling in 1934. Fölling characterized patients as anxious, shy, angry, prone to temper tantrums, irritated, unsociable, and catatonic [22]. Patients with untreated PKU were known to demonstrate severe behavioral disturbances including psychotic, autistic, and aggressive disorders [23]. These individuals are among the most difficult patients to manage in institutions for the intellectually disabled, displaying self-mutilation, aggression, impulsivity, and psychosis [24].

Psychiatric and psychological functioning in children with early-treated PKU

With the introduction of newborn screening in 1963 and widespread initiation of dietary treatment, the severe psychiatric disturbances associated with untreated PKU were eliminated. Pediatric studies enhanced understanding of the impact of diet discontinuation on the developing brain and psychiatric functioning. Not surprisingly, the effects of dietary discontinuation became evident not only in cognitive functioning, but also in emotional and behavioral adjustment.

Among early-treated children with PKU, diet discontinuation and higher blood Phe levels were associated with a higher incidence of behavior problems [25–27]. For boys, an excess of behavioral deviance was documented even when intelligence quotient (IQ) was taken into account, whereas for girls it was restricted to those with IQs <70 [25]. Findings from the United States PKU Collaborative Study identified increased behavior problems related to early discontinuation of dietary treatment [28]. Smith et al. [26], in a collaborative study from the United Kingdom, studied 544 8-year-old children with early-treated PKU. Compared to controls, subjects with poor metabolic control (blood Phe >600 $\mu\text{mol/L}$) were 2.5 times more likely to show deviant behavior while patients with good metabolic control (blood Phe <600 $\mu\text{mol/L}$) were 1.5 times more likely to exhibit these problems. Similar results appeared in reports from the German Collaborative Study in which children with early-treated PKU were twice as likely to show moderately severe psychiatric disturbance compared to a normative 13-year-old control group ($n = 191$) [19].

Studies in children who had discontinued or relaxed the diet exhibited a range of specific deficits. Realmuto et al. [29] evaluated 13 early-treated children with normal IQ. Six (46%) met criteria for attention deficit disorder. Other DSM-III diagnoses included adjustment disorder with depressed mood, encopresis, oppositional defiant disorder, and phobias. Burgard et al. [19] also noted that the 13-year-old adolescents with PKU in the German Collaborative Study were significantly more likely to demonstrate distract-

ibility compared to controls. Stimulant use to treat attention deficit disorder was noted in 26% of children with PKU followed at one clinic [30], although response to medication was not reported. In other studies, children with PKU exhibited delayed social competence, difficulties with peers, and a tendency to be more solitary [19,31–33]. Additional characteristics noted by parents in describing their adolescents with PKU included less autonomy, greater dependency, low self-regard in terms of scholastic ability and health, low achievement motivation, low frustration tolerance, less extroversion and impulsiveness, and a tendency to be serious [34].

Children who continued treatment fared better. Weglage et al. [16] studied 58 10-year-old patients who were treated early and maintained on diet. These patients did not show a higher risk for emotional and behavioral maladjustment compared to healthy controls [16]. Sullivan [35] compared early- and continuously-treated patients with PKU aged 14–25 years with age-matched and chronically ill peers. Although no significant differences were found between groups in terms of psychiatric disorders, emotional symptoms, or self-concept, 40% of the PKU group and 50% of the chronically ill group reported that they had sought help for psychological concerns compared to none of the peer controls. These services included individual and family treatment as well as psychiatric evaluations that were not a component of routine illness-related evaluations or participation in research projects.

Landolt et al. [36] investigated quality of life in children and adolescents with early- and continuously-treated PKU. Children with PKU were as psychologically well-adjusted as controls; however, they showed less positive emotions. Parents characterized their children as less joyful, happy, and confident. Patients with higher Phe levels during the first year of life were reported to have more problems in emotional functioning than their counterparts with better metabolic control.

Psychiatric and psychological functioning in adults with early-treated PKU

Concerns regarding emotional well-being in early-treated adults with PKU who had discontinued treatment in middle childhood first appeared in professional journals in the 1990s. Ris et al. [37,38] studied 25 early-treated adult patients. Although patients with PKU were indistinguishable from sibling controls on most psychosocial outcome measures, 20% reported significant psychiatric symptoms on the SCL-90-R [37,40], a widely used self-report symptom checklist. Obsessive-compulsive symptoms, psychoticism, and interpersonal sensitivity were the most frequently reported symptoms [37]. In another study, responses on the Minnesota Multiphasic Personality Inventory (MMPI) from 28 women with PKU corroborated these findings. The 12 women who were either late-treated (treatment initiated after 90 days) or who had terminated dietary treatment for at least 5 years (the extended exposure group) were compared to 16 women who were early- and continuously-treated. Results indicated that the 12 women who were late-treated or off-diet showed significantly greater psychopathology than women who remained on diet. The pattern of scores was consistent with a tendency toward elevations on scales related to thought and mood disorders. The group also had significantly higher scores on social introversion. A significantly greater proportion (75%) of the late-treated or off-diet group had a clinical elevation on one or more scales compared to the on-diet cohort (19%). Although not actively psychotic, the late-treated or off-diet group had difficulties interpreting social and emotional cues in others and was prone to feelings of alienation, depression, and social isolation [41].

Investigators from the German Collaborative Study [20] identified depressive symptoms as the most frequently described psychiatric disturbance associated with PKU in adults. Data from 35 adult

patients with early-treated PKU were compared with 181 of the 18-year-old control patients who had been investigated in the context of an epidemiological study. The overall rate of psychiatric disorders was 25.7% in patients with PKU and 16.1% in the control group. Patients with PKU demonstrated an increased incidence of internalizing disorders, but a decreased incidence of externalizing disorders. Symptoms were primarily in the depressive category and more frequent in women (8 of 18 females and 1 of 17 males). MRI evaluations in 26 of the 35 patients revealed white matter abnormalities of varying severity. No correlation was found between the severity and pattern of psychiatric disturbances and white matter abnormalities. However, a restrictive, controlling style of parenting was a risk factor for the development of psychiatric symptoms.

Anxiety-related disorders comprise the second most frequently reported psychiatric complication in PKU. Koch et al. [42] reported a higher frequency of phobias and panic attacks, in addition to a higher frequency of depression, in adults with PKU. These problems were reported in 41% of those individuals who were off-diet and in 22% of those who continued on dietary treatment. Patients who maintained Phe-restricted diets into adolescence reported reduced rates of these problems compared to adults who terminated treatment in early childhood. Brumm et al. [7] studied 24 adults with early-treated PKU. Two patients performed in the moderate/severe range for depression and two other patients scored in the moderate range for anxiety, representing 17% of the sample. None of these individuals received treatment for their depression or anxiety. In another study, panic attacks and agoraphobia were diagnosed in five adults. The two who successfully returned to a Phe-restricted diet experienced significant improvement in symptoms [43].

A recent study by Simon et al. [44] suggested that psychiatric symptoms influence social behavior and quality of life for individuals with PKU. While 25% of the general population lived with their parents, 48% of the male and 46% of the female patients with PKU (ages 17–38) did so. A higher percentage of patients were unmarried compared with the aged-matched control population (82% vs. 55%). Among unmarried males with PKU, 95% were not in a steady relationship. Only 9% of the female and 18% of the male patients with PKU had children, compared to 50% of the general population [44].

Limitations and future directions

Investigations examining psychiatric and psychological functioning in individuals with PKU often included heterogeneous samples, owing to the variation in the Phe levels of participants and their treatment histories (i.e., age at which dietary treatment was implemented, duration of treatment, and quality of Phe control). Studies on adults with PKU have generally been based on small samples of compliant patients, which limit statistical power to detect subtle effects and raise the concern of inclusion bias. Longitudinal data are meager, preventing a developmental perspective of psychiatric symptoms.

The relationship between metabolic control and psychiatric symptoms needs to be clarified. Depression and anxiety may be egosyntonic in adults with PKU, who have experienced these symptoms for decades [45], necessitating field testing of psychiatric assessment tools. In addition, most studies published to date analyzed Phe data collected retrospectively [17,19,20,26,34,42] and relied primarily on mean and concurrent Phe levels as markers of biochemical control [17–20,26,34,41]. However, Phe variability was found to be a better predictor of long-term intellectual outcome [46]. Arnold et al. [47] also reported an association between increased Phe variation and impaired executive functioning. Phe variability may contribute to psychiatric outcome as well and needs to be studied in this context.

The impact of pharmacologic and other interventions needs to be evaluated. Medications that lower Phe levels without modifying diet permit patients to attain metabolic goals with less sacrifice [48] and create an opportunity to examine the impact of dietary constraints. Despite the increased incidence of depressive and anxious symptoms in individuals with PKU, response to antidepressant and anxiolytic medications in this population has never been evaluated. Studies are needed to determine if lowering blood Phe levels is as effective as psychotropic medication in treating these comorbid conditions. Moreover, the question needs to be asked whether Phe-lowering medication and psychotropic medications work synergistically to improve psychiatric symptoms, executive functioning, treatment adherence, and metabolic control in individuals with PKU.

Conclusions

Children and adults with PKU experience psychiatric symptoms and display disturbed emotional and behavioral functioning. As noted in Table 1, the list of symptoms covers a broad range. A review of the literature demonstrates, however, that the prevalence and severity of problems generally correlates with the timing and degree of exposure to elevated blood Phe levels. Children with poor metabolic control during the early, critical years are most likely to be affected and to exhibit more serious symptoms. Although all individuals with PKU appear to be at risk for attention problems and mood disorders, those who discontinue dietary treatment present with impulsivity and hyperactivity while continuously-treated children are more likely to display inattention and distractibility. Adults are more likely to experience depression and anxiety.

PKU represents an example of the biologic basis of psychiatric dysfunction mediated by psychosocial factors. Dopamine, norepinephrine, and serotonin interact in the central nervous system and all are involved in regulating mood, emotion, and cognition [15]. The prefrontal cortex is implicated in a number of higher cognitive functions as well as processing emotions and regulation of stress responses, and it has been found to be sensitive to even modest reductions in dopamine [49]. Depressive symptoms may result from dysregulation of any or all of these neurotransmitters

Table 1
Psychiatric, emotional, and behavioral manifestations of phenylketonuria.

Untreated individuals	Early-treated children and adolescents	Early-treated adults
<ul style="list-style-type: none"> • Psychotic symptoms • Autistic behaviors • Hyperactivity • Aggression • Anxiety • Depressed mood • Impaired social skills associated with profound intellectual disability • Social withdrawal 	<ul style="list-style-type: none"> • Attentional problems • School problems • Less achievement motivation • Decreased social competence • Decreased autonomy • Low self-esteem 	<ul style="list-style-type: none"> • Depressed mood • Generalized anxiety • Phobias • Decreased positive emotions • Low self-esteem • Social maturity deficits • Social isolation/withdrawal • Lack of autonomy

[15]. Functional brain imaging provides evidence that the dopamine system also plays a role in social anxiety.

The underlying biologic cause of the psychiatric problems associated with PKU can be modified by treatments that are largely dependent on the capacity of the patient (or parent) to adhere to medical recommendations. The capacity to adhere to the dietary regimen reflects psychosocial competence – the skills necessary to plan meals, resist dietary indiscretion, and maintain self-control in the face of peer pressure and feelings of being different. A major challenge in addressing psychiatric problems in PKU is that elevated Phe levels leading to psychiatric symptoms such as depression, anxiety, and attention deficits inhibit the ability of individuals with PKU to follow dietary restrictions, which further exacerbates the symptoms.

The most effective strategy may be to monitor the emotional and behavioral well-being of individuals with PKU so that appropriate interventions can be instituted before psychiatric symptoms and dysfunctional behavior patterns become entrenched and a cycle of elevated Phe levels and worsening symptoms ensues. Longitudinal studies are needed to evaluate the impact of interventions, including new and emerging therapies. Treatment guidelines addressing psychosocial factors that mediate the impact of biologic parameters will increase the probability of good metabolic control and in turn improve quality of life for individuals with PKU.

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