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Psychosocial aspects of PKU: Hidden disabilities – A review ☆

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ABSTRACT

Phenylketonuria (PKU) is an inborn error of metabolism, and its detrimental effects on neurocognitive functioning have been well studied. Early detection and treatment of PKU prevent the severe consequences of this disorder. However, even early- and well-treated patients experience hidden disabilities, including subtle deficits in executive functioning, mild reductions in mental processing speed, social difficulties, and emotional problems that may remain unnoticed for years. Poor executive function (EF) may impact treatment adherence and may lead to psychosocial deficits that are not always visible. These psychosocial aspects include social difficulties and psychosocial problems, such as forming interpersonal relationships, achieving autonomy, attaining educational goals, and having healthy emotional development. Studies report EF deficits in children and adults with early-treated PKU, which contribute significantly to the hidden disabilities in this population. In adults, hidden disabilities affect job performance and social relationships as a result of residual attention deficits, poor EF (e.g., planning, organizing), and reduced processing speed. An indirect relationship also exists between quality of life and EF impairment. In the absence of overt psychiatric symptoms, low level depressive or anxious symptom may be present. The interaction between the neurocognitive deficits and psychiatric symptoms puts this population of patients at significant risk for experiencing hidden disability. PKU is a disorder in which a less than optimal psychosocial outcome arises from the cumulative impact of relatively mild symptoms. The key to reducing risks associated with PKU is metabolic control throughout life.

Introduction

Phenylketonuria (PKU; OMIM 261600 and 261630),[1] an inborn error of metabolism, leads to clearly recognized symptoms of phenylalanine (Phe) toxicity, including mental retardation, seizures, skin abnormalities, self-abuse, and psychiatric problems [1]. Early detection and treatment of PKU prevent the most obvious and severe consequences of this disorder. Individuals with PKU do not appear sick and often do not feel the effects of poor metabolic control. However, even early- and well-treated patients experience hidden disabilities, such as subtle deficits in executive function (EF), mild reductions in mental processing speed, social difficulties, and emotional problems that may remain unnoticed for years [2,3]. Women with PKU who become pregnant appear and feel healthy but risk bearing children with microcephaly, growth retardation, developmental delay, and congenital heart disease [4]. Most studies in PKU focus on the association between blood Phe levels and neuropsychological functioning. However, an equally important risk in PKU may be the cumulative impact of its hidden disabilities.

Metabolism of Phe and mechanisms of pathogenesis in PKU

In PKU, the metabolic block in the breakdown of Phe to tyrosine results from insufficient activity of the phenylalanine hydroxylase (PAH; EC 1.14.16.1) enzyme. Without dietary or other therapeutic intervention, plasma Phe levels become elevated and yield neurotoxic effects, including severe mental retardation and structural brain abnormalities [5]. Two hypotheses have been advanced to explain the underlying mechanisms generating the cognitive and neurological deficits encountered in PKU despite treatment. One hypothesis suggests that the decrease in tyrosine concentrations plays a role in the development of the clinical phenotype [6–8]. An alternate explanation suggests that it is the hypomyelination which occurs in selective areas of the cortex that leads to the

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[1] *Abbreviations used:* PKU, phenylketonuria; PAH, phenylalanine hydroxylase; Phe, phenylalanine; QoL, quality of life; EF, executive function; HRQoL, health-related quality of life; CoL, course of life.

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cognitive deficits seen in PKU [9,10]. Whatever the underlying cause, the impact on psychosocial development remains significant. Adjustments required to cope with the neuropsychological deficits and the restrictions necessary for adequate treatment of PKU impose a burden on the affected individual and family. Comorbid conditions, including depression and anxiety associated with PKU, place further barriers on maintaining appropriate interpersonal relationships and a satisfying quality of life (QoL). Recognition of these "hidden" disabilities in PKU is the first step in developing interventions for improved outcomes in this disorder.

Treatment

The primary treatment of this condition is to reduce the levels of Phe in the blood, thus limiting Phe accumulation in the tissues and minimizing neurotoxic effects seen in patients with elevated blood levels of this amino acid. This is accomplished through lifelong dietary restriction of Phe and supplementation with a formula containing all required amino acids excluding Phe. Treatment begins in the neonatal period after confirmation of the diagnosis, with initiation of frequent monitoring of plasma Phe levels and making necessary diet and formula adjustments. Adherence to the diet and formula recommendations is particularly important during the critical period of brain development in early childhood years, but it also remains necessary through adulthood [2,11]. This presents significant challenges when patients reach adolescence and move toward independence. In addition, the lack of immediate physiological feedback about Phe levels sometimes contributes to poor decision-making with regard to treatment adherence.

Psychosocial functioning

The detrimental effects on neurocognitive functioning have been well studied [2,12–17], but the interaction between these neurocognitive sequelae and psychosocial functioning have also been explored, albeit to a lesser degree.

Children with PKU

Despite strict adherence to the Phe-restricted diet and regular ingestion of the formula, neuropsychological abnormalities occur in children and adolescents with PKU [2,3]. Early-treated PKU is associated with intellectual performance within the average range but lower than the general population [2,12,13]. A recent meta-analysis involving 43 studies showed a 1.8–3.8 point reduction in intelligence quotient (IQ) for each 100 μmol/L increase in lifetime blood Phe level [16]. And Burgard [17] concluded from a review of longitudinal studies of intelligence of early-treated patients with PKU that IQ development is stable after age 10.

Many studies have reported EF deficits in children and adults with early-treated PKU [2,18–21]. EFs are a group of interrelated cognitive and behavioral skills responsible for goal-directed activity, including attention, short-term memory, planning, organization, behavioral inhibition, and social interaction [18]. These EF deficits contribute significantly to hidden disabilities in children and adolescents with PKU [18–21].

Inattention and behavioral difficulties are detrimental to self-esteem and emotional development. Planning, organization, and impulse control (behavioral inhibition) are required for achieving metabolic control in PKU. Counting grams of Phe, remembering Phe intake, maintaining supplies, inhibiting impulsive food choices, and planning menus all require robust EF. Without good EF, a vicious cycle ensues whereby a person fails to resist disallowed foods or forgets to drink the special formula, which leads to elevated Phe levels and further impairs EF. In other populations, EF impairments have been correlated with deficits in social relationships and communication skills [22,23]. An indirect relationship has been noted between QoL and EF impairment [24].

Slower processing speed, another hallmark in PKU [19], contributes to difficulties in comprehension, ability to complete tasks, and school performance. Gassió and coworkers [12] assessed school performance in a group of 26 early- and continuously-treated PKU patients, as compared to 21 age- and sex-matched controls. PKU patients had significantly more school problems (defined by students needing tutoring, repeating a class, or discontinuing their studies before completing secondary school). In another study teachers reported that 33% of students with PKU had more problems than their classmates in concentration, spelling rules, and mathematics [25]. Stemerdink and colleagues [26] reported in a study of 30 adolescents with PKU and 23 controls that patients were more hyperactive and their school performance was lower than control subjects. Zeman et al. [27] reported that among 67 people with PKU, 7 completed their studies in a special school. Thus, subtle or hidden factors such as IQ loss [12–17], EF deficit [18–21], and reduced processing speed [28] put the child at risk for poor academic performance.

A number of studies have addressed the health-related quality of life (HRQoL) of individuals with PKU. HRQoL was assessed in a cohort of 37 Swiss patients aged 3–18 years with early-treated PKU [29]. The majority of dimensions of QoL in PKU children did not differ significantly from reference values.

While the Phe levels in the 12 months preceding the study were not associated with QoL and psychologic adjustments, mean blood Phe concentrations in the first year of life were found to be significantly predictive of psychological adjustment and some dimensions of QoL. Patients with higher Phe values during this period experienced more problems in cognitive and emotional functioning and were less well-adjusted psychologically than those with better biochemical control. Compared to parents with healthy children, parents in this Swiss study [29] reported their children to be less joyful, happy, and confident. However, psychological adjustment was shown to be better than in the healthy reference group, suggesting that these patients were at least as well-adjusted as healthy controls.

Adolescents and adults with PKU

Education and employment

Simon and colleagues [4] in Germany found few differences in the level of education achieved and the distribution of highest professional qualifications between young adults with PKU and control groups. However, more than half of the female patients had not completed vocational training as compared to one-third in the general population. These results are confirmed by the study of Bosch et al. [30] in the Netherlands, who reported that a higher percentage of PKU patients had attended special education classes in primary school, though the highest level of education attained was comparable in the two groups. Also, in the study by Schmidt and colleagues [15] in England, the educational and career status of the 51 adult subjects with PKU appeared not to differ from the general population even though in this cohort the diet had been relaxed since age 10.

While these studies suggest adequate achievement, neuropsychological testing in adults reveals reduced processing speed [2,28,31,32], which can result in slower processing of auditory information. These individuals may then appear inattentive or unintelligent. Residual attention deficits and poor EF in adulthood also affect job performance and social relationships.

Psychiatric disorders

The overall rate of psychiatric disorders in individuals with PKU as compared to controls has not been shown to differ significantly [33]. However, the pattern of disturbances was different, with PKU subjects demonstrating increased internalizing disorders such as depression, anxiety, and decreased externalizing disorders including hyperactivity or antisocial behavior. Depressive disorders as per ICD10 classification were more prevalent in female than male PKU subjects. PKU subjects demonstrate an approximately 50% increased risk of showing moderate or severe symptoms [33,34]. There was a positive correlation between occurrence of psychiatric symptoms and IQ and between occurrence of psychiatric symptoms and biochemical control up to age 12. These findings are consistent with the concept of hidden disability, as these individuals may not present with overt psychiatric symptoms yet they may experience chronic low level depressive or anxious symptoms.

In many chronic illnesses, exacerbations of symptoms or cognitive decline can lead to "treatment fatigue" [35]. In patients with PKU, the challenges that contribute to this fatigue include maintaining a lifelong restrictive diet, the need for frequent monitoring of Phe levels, and regular hospital visits. Stress related to continued cognitive and emotional difficulties further challenges the individual, often resulting in poor adherence to treatment and exacerbation of symptoms [2]. Studies suggest that by adulthood, fewer than 20% of individuals with PKU maintain metabolic control [29].

Course of life

Individuals with PKU whose diets and health have been closely monitored throughout life may be more dependent on their parents and they may have fewer opportunities to participate in peer and school-based activities. This may inhibit the achievement of developmental tasks [30]. Seeking out contacts outside the family and reaching other developmental milestones that move the individual toward independence are of paramount importance to adjustment to adulthood [36,37]. There might be obstacles to this course of life (CoL) process [4]. CoL was evaluated in the study by Bosch and colleagues [30]. The CoL questionnaire is a Dutch measurement instrument used to assess achievement of developmental milestones. It was previously developed to assess CoL in young adults 18–30 years of age, who had grown up with a chronic or life-threatening disease as compared to an age-matched group of controls [38]. The study utilized three scales including (1) development of autonomy; (2) psychosexual development; (3) social development. The study also added measures of sociodemographic outcome such as living situation, education, and employment. As with the results of the HRQoL questionnaires, those for CoL were comparable for PKU patients and controls.

Interpersonal relationships

Weglage and coworkers [39] revealed that adolescents with PKU reported restrictions both in their social lives and their emotional development, and mothers of these patients reported upbringing that was overprotective and restrictive. Within the family, lower levels of cohesion were reported relative to controls [23]. Patients, particularly those in the adolescent years, revealed psychosocial problems [39,40]. Simon and colleagues [4] reported a tendency for lower or delayed levels of autonomy among PKU patients, with a large percentage still living with their parents. Adults with PKU had a lower rate of forming normal adult relationships than normal controls, with a higher percentage of being unmarried (82% vs. 55%). Fewer had children (12% vs. 47%). The majority of the unmarried patients were not in a stable relationship and among males the proportion was 95%.

Health-related quality of life

Bosch and colleagues [30] evaluated the HRQoL of 32 early- and continuously-treated Dutch PKU patients aged 18–30 years. The results of the HRQoL questionnaires were comparable for PKU patients and controls. In Germany, Simon and colleagues [4] undertook a study to evaluate QoL and described sociodemographic outcomes in 67 adolescents and young adult PKU patients. Again, no significant differences were identified between self-assessed QoL in the patient and control groups. In these studies, QoL was derived from self-reports on generic HRQoL questionnaires administered to subjects with PKU who were all treated early and continuously. A cohort of patients that relaxed or discontinued the diet at an earlier age might report more abnormalities in a QoL study. Cultural effects may play a role in that Dutch guidelines, for treatment are more strict that those in Germany or the United States. Moreover, the generic questionnaires that were used in the studies contain scales evaluating matters like pain symptoms and basic motor symptoms, which are not PKU-related problems.

Discussion

The interaction between the neurocognitive deficits and psychiatric symptoms puts this population of patients at significant risk for experiencing hidden disability. PKU is a disorder in which a less than optimal psychosocial outcome arises from the cumulative impact of relatively mild symptoms. The key to reducing risks associated with PKU is metabolic control throughout life. The challenge of non-adherence remains an obstacle to better health outcomes. Interventions that have been shown to improve adherence in PKU and other disorders include educational, behavioral, and social support strategies.

A. Educational strategies

1. Improve knowledge of the disease and its treatment. The health care provider should involve the patient as a partner in the process, acknowledging the patient's previous illness experiences, in place of an authoritarian approach.
2. Enhance verbal information with written materials (e.g., booklets, pamphlets, videos). A stepwise approach is most effective, taking into account the patient's developmental and intellectual abilities.
3. Assess knowledge through patient interviews.
4. Repeat educational intervention at follow-up and annual visits.
5. Provide information in a brief, organized, and specific manner.
6. Encourage adolescents to ask questions and express their feeling and thoughts about the disease and treatment.

B. Behavioral strategies

1. Listen to the needs of the patient at each visit and try to make adjustments to the treatment regimen to facilitate adherence.
2. Patients can record their dietary intake on calendars or pocket computers, which will increase motivation and responsibility.
3. Provide a reward or incentive for adherence, such as a point system or appraisal by the parent or health care provider.

C. Social support strategies

1. Provide continued supervision while respecting the patient's responsibility and autonomy.
2. Do not speak exclusively to the parent, but rather relate directly to the teenager in a sincere and honest manner. This will cultivate a good relationship with the adolescent where they feel they are being taken seriously, cared about, and listened to.
3. Instead of just discussing the treatment regimen, focus on the adolescent and their concerns to build trust.

4. Permit phone calls, emails, or the Internet as alternate forms of contact that fall within the guidelines of the Health Insurance Portability and Accountability Act.
5. More frequent follow-up visits with the same practitioner facilitates continuity of care, which is a focal point in chronic disease management.
6. Involve the family members to understand and support the child's journey towards independence.
7. Support groups for adolescents provide an outlet for them to share problems and coping mechanisms. Summer camps for children and special retreats for adults with PKU provide opportunities for social support. Some camps integrate children with PKU into normal camps and provide low-protein foods and blood Phe monitoring.
8. A mutual written contract can be signed between the patient and the health care provider, each committing to everything necessary to facilitate adherence with the regimen.

Attention to psychosocial outcomes as well as neuropsychological performance will improve prospects for individuals with PKU to form relationships, have healthy emotional development, and achieve desired educational and professional goals.

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