Phenylketonuria (PKU) is an inborn error of metabolism in which phenylalanine, an essential amino acid, builds up due to a deficiency of phenylalanine hydroxylase. The presentation is largely neurological in its impact, although it arises from elevations of liver enzymes. The degree of neurological impact is related to how early and consistent treatment is offered, which mainly involves dietary restrictions. If untreated, the neuropathological effects can be quite severe (Huttenlocher, 2000). However, evidence suggests that even with rigid treatment, neurocognitive residuals and behavioral impairments may be seen (Brumm et al., 2004; Channon, German, Cassina, & Lee, 2004). Given the need and importance of early intervention, routine blood panels drawn in the first 48 hours following birth today include screening for PKU.

NEUROPATHOLOGY/PATHOPHYSIOLOGY

PKU arises from a defect in the phenylalanine hydroxylase activity, which converts phenylalanine to tyrosine (Scriver, Kaufman, Eisensmith, & Woo, 1995). Neurologically, this process is crucial for the biosynthesis of various neurotransmitters and to prevent buildup of phenylalanine, which has a neurotoxic effect when presenting in excess in the system (Pietz, 1998). Consequently, the degree of buildup is directly related to the amount of neurological compromise evidenced on MRI (Thompson et al., 1993). In this instance, MRI findings were also related to the time since dietary treatment had been withdrawn.

In untreated infants, microcephaly commonly develops. With advances in neonatal screening, this has become rare. Still, white matter alterations are often noted presenting as spongiosis, gliosis, and delays in myelination (Thompson et al., 1993). This is due to oligodendrocytes being particularly sensitive to the neurotoxic effects of elevated phenylalanine (Dyer, 1999). Cortical neurons may be smaller than normal and in fewer numbers with fewer Nissl granules, and there are often depleted numbers of dendritic spines (Cordero et al., 1983). Cerebral lipid and proteolipid levels may be low (Lew et al., 1989).

Although early treatment reduces the neurological impact of PKU, it does not offset the effects entirely. White matter abnormalities, with greatest prominence in posterior periventricular regions, are still commonly reported in individuals who received early intervention (Pietz, Kreis et al., 1996). The degree of white matter lesions has been consistently linked with phenylalanine levels throughout life (Pietz, Kreis et al., 1996).

Dopamine, norepinephrine, and serotonin depletions have been consistently reported in relation to
PKU, even when early treatment was offered (Burlina et al., 2000; Paans et al., 1996). This has been associated with an interference of elevated phenylalanine levels in the transportation of tyrosine and tryptophan at the blood–brain barrier (Momma, Aoyagi, Rapoport, & Smith, 1987).

**NEUROPSYCHOLOGICAL/CLINICAL PRESENTATION**

As suggested, PKU is largely neurological in its impact. In regard to the clinical manifestations of PKU, a latency effect is often noted, with developmental delays sometimes not becoming evident until after the first year of life. However, myoclonic seizures in untreated individuals may emerge as early as 4 months of age (Gascon, Ozand, & Cohen, 2007). Furthermore, some delays, such as when an infant sits up on its own, crawls, walks, and says first words, may also be noted sooner. Again, these above features are most noted in untreated individuals. Pitt and Danks (1991) in their review of a cohort of individuals never treated, found that 25% had seizures, 50% were profoundly mentally retarded, and the other half were severely to moderately mentally retarded.

In regard to neuropsychological functioning, executive deficits are potentially the most common features of PKU. Deficits in attention, both selective and sustained (Huijbregts, de Sonneville, Licht, van Sprounsen et al., 2002) as well as shifting attention (Huijbregts, de Sonneville, Licht, Sergeant & van Sprounsen, 2002) have been reported. In addition, planning and conceptual reasoning (Leuzzi et al., 2004), inhibition (Huijbregts, de Sonneville, Licht, Sergeant et al., 2002), and working memory (White, Nortz, Mandernach, Huntington, & Steiner, 2002) have all been reported although not consistently found across research (e.g., Feldmann, Denecke, Pietsch, Grenzlebach, & Weglage, 2002). Processing speed and reaction times are also commonly impacted (Huijbregts, de Sonneville, Licht, van Sprounsen et al., 2002). Similarly, retrieval-based memory deficits have been reported (Brumm et al., 2004) as have deficits in immediate memory (Smith, Kilm, & Hanley, 2000; White, Nortz, Mandernach, Huntington, & Steiner, 2001). To a lesser extent, language deficits have been reported (Brumm et al., 2004), but these findings have been inconsistently described in the literature.

Learning difficulties are common (Anderson et al., 2004) and may increase in identification as children age, as executive functions are relied on more in their academics. Disabilities in reading and mathematics are reported at far greater rates than seen in the normal population. In comparison, reading deficits are reported more frequently than deficits in mathematics. For example, Azen et al. (1991) found correlations between phenylalanine levels and performance in intelligence, reading, and spelling performance but not mathematics. In their study, behavior deficits were also linked with phenylalanine. In fact, individuals with PKU demonstrate greater risks for behavioral and psychiatric manifestations (Pietz 1998) including attention deficit hyperactivity disorder and oppositional defiant disorder among others.

**DIAGNOSIS**

PKU is diagnosed through blood tests nowadays completed within 48 hours of birth. Elevation is indicated by levels greater than 1 µM (i.e., >120 µM) and a blood phenylalanine/tyrosine ratio higher than 2 (Gascon et al., 2007). Beyond urinalysis, MRI and CT of the brain are useful in evaluating neurological correlates, with particular attention placed on white matter tracts. EEG may be useful in cases that go undiagnosed for some time as seizures rates are high. This would be unusual in industrialized countries that check for PKU following birth but may be relevant in those coming from other countries that do not have such neonatal practices. Finally, neuropsychological testing should be used in all cases to
determine the nature and extent of neurocognitive deficits given cognitive dysfunction has been found even in well-controlled and early interventions. Particular attention may be placed on executive functions and reaction speed, although comprehensive evaluation is recommended as variable impact of other domains can be observed.

TREATMENT

The primary treatment for PKU following diagnosis is implementation of a controlled diet to reduce phenylalanine intake. This will involve a very low protein diet and use of a phenylalanine-free supplement containing amino acids, minerals, vitamins, and trace elements (Pietz, 1998). For example, aspartame, an artificial sweetener, should be avoided as intestinal hydrolysis liberates phenylalanine (Gascon et al., 2007). The dietary restrictions can be adjusted based on age and severity of the metabolic defect, which is determined through the aforementioned laboratory tests. There are suggestions that as children age, restrictions can be lessened (Azen et al., 1991; Smith, 1994) although this is debated.

When neurological deficits arise, interventions and treatment are consistent with those commonly implemented to counteract such features. Special education services may be required for learning difficulties. Cognitive training may be implemented to teach individuals to better compensate for deficits and to improve functionality.

Bibliography


https://search.credoreference.com/content/topic/phenylketonuria