Neuropsychological Functioning in Early-Treated Phenylketonuria – A Review

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Abstract
Phenylketonuria (PKU) is an inborn error of metabolism involving a deficiency of the enzyme phenylalanine hydroxylase. This condition results in elevated levels of phenylalanine and low levels of tyrosine. If left untreated, severe neuropathology and neurobehavioral sequelae manifest. The implementation of newborn screening and early dietary treatment has significantly reduced such morbidity. Despite relatively preserved general intellectual functioning, in early-treated PKU individuals subtle cognitive and behavioral deficits are still apparent. This paper provides a review of the evidence for impairment in information processing, executive function, memory and learning, academic achievement and behavior. This paper also reviews the two primary theories proposed to date relating to the underlying mechanisms for the cognitive and behavioral deficits encountered in treated PKU patients, namely prefrontal dysfunction and white matter abnormalities. Although more research is required, the literature to date suggests that early-treated PKU individuals are at risk of subtle neurobehavioral deficits across a range of neuropsychological domains. Thus, PKU patients should be closely monitored so that problems are detected early and appropriate interventions are put in place to ensure that individuals reach their full potential.

Phenylketonuria (PKU; OMIM 261600) is an autosomal inborn error of metabolism which, if left untreated, usually results in significant neuropathology [1] and severe neurobehavioral impairments [2]. Patients with PKU have a deficiency in phenylalanine hydroxylase activity which results in increased phenylalanine (PHE) levels in the blood and tissues [3]. High PHE concentrations are neurotoxic, especially in the early stages of brain development, which explains the high rates of intellectual impairment in untreated patients [2]. Newborn screening and the early implementation of a low-PHE diet greatly reduces the risk of severe impairment; however, research suggests that even optimally managed patients continue to present with subtle cognitive and behavioral deficits [4–34]. The exact nature and etiology of these neuropsychological impairments exhibited by early-treated PKU patients remain unclear. The purpose of this paper is to review the cognitive and behavioral outcomes for early-treated PKU patients throughout childhood and into adulthood and explore the possible mech-
organisms underpinning these deficits. An understanding of these outcomes is important as cognitive deficits have the potential to impact upon the everyday functioning and quality of life of an individual [35, 36].

**General Intelligence (IQ)**

IQ measures generally provide a reliable assessment of general cognitive functioning; however, such measures lack the sensitivity to identify mild cognitive deficits, and subtle brain abnormalities [37]. Despite these limitations, IQ tests are usually the foundation of neuropsychological assessment.

PKU was typically associated with severe intellectual impairment prior to the introduction of newborn screening and early dietary intervention [38]. In contrast, early-treated patients typically present with intellectual functioning within the normal range [7, 31, 39–41] but often obtain lower scores compared to unaffected familial controls [42, 43] and unaffected nonfamilial controls [44].

Within treated PKU patients, IQ has been reported to be strongly associated with the age of treatment commencement [45], and as such it is considered important to commence treatment within the first month of life. IQ has also been reported to be related to treatment compliance and age of treatment discontinuation. In a recent systematic review and meta-analysis of published trials of PKU, Waisbren et al. [46] found that each increase of 100 μM in lifetime PHE for early-treated PKU patients was associated with a 1.9–4.1 reduction in IQ. A similar relationship between metabolic control and IQ was reported in an earlier systematic review [11]. This review found that for each 300 μM increase in preschool PHE levels IQ decreased by approximately half a standard deviation (SD; 7–8 IQ points). Furthermore, the children who had the best outcome in terms of IQ were those who were able to maintain PHE levels below 400 μM in early and middle childhood. In terms of treatment discontinuation, an adult follow-up demonstrated that early-treated children who were randomized to discontinue treatment at age 6 years tended to have lower IQs in adulthood than those who were randomized to continue with a low-PHE diet.

**Specific Cognitive Skills**

There is a significant body of neuropsychological research into PKU. While published studies have reported deficits across a broad range of cognitive skills, most interest has been in the area of executive function (EF). This burgeoning interest has arisen due to evidence of impairment in this higher-order cognitive skill and biochemical and imaging studies that are consistent with abnormalities in neuroanatomical areas subserving EF. However, executive impairment in this population is not a universal finding and the exact nature of the neuropsychological consequences of early-treated PKU is still debated. Following is a review of neuropsychological studies, which we propose indicates that PKU is not associated with a selective impairment in executive functioning, but rather results in global deficits, which may be related to general information processing difficulties. It is important to establish the exact nature of cognitive deficits in this population as it has implications for surveillance, prevention, and early intervention programs.

**Motor Functioning**

Although severe motor deficits are not a feature of PKU, poorer motor functioning has been demonstrated in patients as young as 12 months. Arnold et al. [8] administered the Peabody Developmental Motor Scales to a group of young children who began dietary treatment within 3 weeks of birth. This group had a motor quotient of 83, which is more than 1 SD below the normative mean, indicating motor delay. There is also evidence of fine motor impairments persisting throughout childhood and beyond. For example, Weglage et al. [47] found that early-treated PKU children performed significantly worse than age-matched controls on two computerized tasks sensitive for speed and precision of arm-hand-finger movement (‘Long Pins’ and ‘Tapping’). Follow-up evaluations, 3 years later showed that PKU patients continued to perform poorly on the ‘Tapping’ task. Using the Purdue Pegboard task and Finger Tapping Test, Gassió et al. [19] demonstrated fine motor deficits in early- and continuously-treated adolescent PKU patients. In total, 50% of their PKU sample scored 1 SD below the normative mean on at least one of the tasks, whereas only 4.7% of the control sample presented with altered functioning. Griffiths et al. [48] also showed that off-diet adolescents performed significantly worse than age-matched controls on the Purdue pegboard task. Poorer fine motor performance is thought to be related to higher PHE levels [8, 19]. Not all studies have reported fine motor deficits. Luciana et al. [49] found no significant deficits in adolescent PKU patients when compared to chronically ill patients and controls on a computerized psychomotor task. There was
however, a trend for PKU patients to have larger response latencies. In a group of early-treated adults, Brumm et al. [10] suggested that fine motor coordination and psychomotor speed were intact. In summary, the weight of evidence to date suggests that PKU patients are at risk of subtle motor deficits, in particular fine motor skills.

Information Processing

In a meta-analytic study that examined deficits in early-treated PKU cohorts across multiple cognitive domains, speed of information processing was found to be the area of most concern [50]. In a separate meta-analytic study, Albrecht et al. [4] also found that patients with PKU demonstrated slower reaction time than controls. They also reported a relationship between reaction time and PHE levels, but less so in adulthood, and found choice reaction time to be more strongly associated with PHE levels than simple reaction time. In other words, individuals with early-treated PKU tend to require more time to process information and complete tasks than controls, and as such, are slower when responding to stimuli, when making a choice between targets, or when completing simple to complex activities. Despite the weight of evidence that suggests reduced processing efficiency in PKU patients [5, 14, 41, 51], it should be noted that conflicting research also exists [7, 26, 52]. Slower information processing can have significant implications for encoding and storing new information and executive functioning.

Language

High-quality studies examining speech and language outcomes in early-treated PKU are lacking, possibly because this is a domain which is thought to be spared in those who develop this condition. The studies to date that have included language measures have generally reported that language develops appropriately in children with early-treated PKU [53, 54], although future studies employing a comprehensive language assessment are needed.

Memory and Learning

The most commonly used measure to assess memory and learning in individuals with early-treated PKU patients has been word list learning tasks such as the California Verbal Learning Test or the Rey Auditory Verbal Learning Test [55]. The literature on verbal learning outcomes of PKU patients is equivocal. Smith et al. [56] presented children with 12 unrelated words over three trials and found no significant group differences between PKU and control children. Similarly, using the Rey Auditory Verbal Learning Test, which involves the recall of 15 words over 5 trials, studies have reported equivalent performance between early-treated PKU and control children [19] and adults [13]. In contrast, Anderson et al. [44] and Antshel and Waisbren [57] have reported verbal learning deficits in early-treated PKU children, while Brumm et al. [10] found verbal learning deficits in early-treated PKU adults. Using the California Verbal Learning Test, White et al. [58] found a specific pattern of impairment for children with early-treated PKU, with significant differences largely restricted to the fifth trial of the task. Further analysis revealed that PKU children were less likely to employ an effective memory strategy, specifically semantic clustering. Fewer studies have adequately examined visual learning capacity; however, Anderson et al. [44] recently found early-treated PKU children performed less well than controls when required to learn fifteen different visual designs over five trials. Overall, research to date suggests that early-treated PKU may be associated with mild impairments of learning both verbal and visual information.

Attention

Attentional problems have often been described in children and adults with PKU [19, 24, 59]. Attention is not a unitary process but involves a number of separate core components that operate cooperatively, and include: (1) sustained attention or vigilance, the ability to maintain attention over an extended period of time; (2) selective attention, the ability to filter relevant stimuli from irrelevant material; (3) shifting attention, the ability to change attentive focus in a flexible and adaptive manner, and (4) divided attention, the ability to attend to two competing stimuli simultaneously [60, 61]. Sustained attention is most often impaired in individuals with early-treated PKU. Researchers employing traditional visual continuous performance task paradigms have demonstrated slower performance [62, 63] and elevated errors [19, 64] among PKU children, adolescents, and adults [65], although improvements in performance have been shown in a 3-year follow-up study [47]. Interestingly, two studies [19, 44] in which an auditory continuous performance
Executive Function (EF)

EF refers to a collection of interrelated functions, or processes which are responsible for goal-directed behavior or future-oriented behavior. These processes include: (a) initiation of activity, (b) impulse control and self-regulation, (c) working memory, (d) mental flexibility and utilization of feedback, and (e) planning ability and organization. Deficits in these areas are commonly reported in children and adults with early-treated PKU, although some conflicting findings exist. Differences in outcomes may in part be attributed to (a) the varied conceptualizations of EF by researchers, (b) the employment of different EF assessments tools, and (c) sampling discrepancies.

Researchers investigating the behavioral aspects of EF using parent rating scales have found that PKU children are rated worse than controls on aspects of EF including working memory, planning and organization. Although some researchers have failed to identify such impairments when employing cognitive measures of EF, others have found poorer performance among PKU patients. For example, on the Tower of London task, a traditional measure of planning and organization, PKU children have shown significant impairments in planning and execution time. Impairments in planning and organization have also been shown on other complex tasks, such as the Rey Complex figure, in which minimal rules are provided. PKU children and adults have also been shown to demonstrate less mental flexibility and use of feedback as evidenced by perseveration errors on various tasks. Deficits in EF also extend to problems with inhibition and self-monitoring. For example, Araujo et al. found that PKU children committed more commission errors on a go/no go paradigm than healthy peers, indicating poor impulse control. Furthermore, patients showed less post-error slowing, which the authors suggested indicated poor response monitoring. Although results did not reach significance, Wiersema et al. showed that early- and continuously-treated PKU children tended to make more commission errors than children with ADHD, again on a go/no go task, indicating poor impulse control. In a study by Anderson et al., PKU children tended to be more impulsive on problem solving tasks and monitored their performance less well than controls, although the group differences failed to reach significance. Impaired inhibition has also been shown in adults.

Working memory, considered an integral component of executive functioning, can be conceptualized as comprising two components, maintenance and manipulation. The maintenance component refers to the capacity to temporarily store new information for recall, while the manipulation component refers to the capacity to manipulate information in this temporary store for some purpose. For example, the maintenance component can be assessed by requesting an individual to immediately recall information presented, such as a sequence of numbers or visual stimuli. Recalling numbers in the reverse sequence to that which they were presented would be an example of a task used to assess the manipulation component of working memory. Early-treated PKU does not appear to be strongly associated with immediate memory impairments, but does appear to be associated with the manipulation component of working memory especially in later childhood and adulthood.

Findings from research that has examined the relationship between executive functioning and PHE levels are confusing. When high PHE individuals are contrasted with low PHE individuals, the high PHE subgroup tends to exhibit greater executive functioning impairments. Some studies have reported that executive functioning is associated with PHE levels at the time of assessment, while others have failed to find this relationship. Furthermore, the strength of the relationship between performance on executive functioning measures and PHE levels varies across measures. If functioning is associated with PHE levels, it would be expected that improved metabolic control (lower PHE levels) would correspond with improved executive functioning after a period of stabilization, as demonstrated by Huijbrigs et al.; however, this is not a consistent finding and more research is required.
In summary, it appears that early-treated PKU is related to EF impairment, although the nature of the impairments in this domain varies across studies, and this may be dependent on age and metabolic control. Impairment in this high-order cognitive domain may also be secondary to deficits in lower-order domains such as processing speed.

**Academic Achievement**

Reports of high rates of PKU children attending special education settings [42, 77, 78] appear to be restricted to studies involving patients born prior to the 1980s, when dietary treatment was more lax. However, there is evidence that early-treated PKU children attending normal school settings still perform lower than controls. Gassió et al. [79] found that 50% of early- and continuously-treated PKU patients were rated by parents as having ‘school problems’ compared to only 23.8% of control participants. Employing an adapted version of the Achenbach Teacher’s Report Form, Stemerdink et al. [80] noted that 58% of PKU patients were rated as performing below grade level, compared to only 17% of the control sample. PKU children were also rated by teachers as ‘putting in less effort’ and ‘making less progress’ in school than their classmates. Rates of grade repetition and utilization of remedial educational services are equivocal. Although some researchers have reported an elevated proportion of PKU children requiring additional tutoring or repetition of a grade compared to controls [79], there have also been reports that have failed to identify differences when compared with healthy controls [42, 80] or other chronically ill patients [49].

PKU children have also been shown to perform below peers on well-established measures of academic achievement. Fishler et al. [49, 53, 81] followed a group of PKU children on-diet and PKU children off-diet over 4 years assessing basic educational skills, using the Wide Range Achievement Test. At age 6 years, both groups of children obtained scores within the expected range for reading, spelling and arithmetic. In subsequent years, however, differences between groups were noted. Reading scores followed an upward trend in the continuously-treated patients, but a downward trend was observed in the off-diet group. Spelling scores remained stable for off-diet patients but on-diet patients showed gains in the following 4 years. Both on-diet and off-diet PKU groups showed a steady decline in arithmetic scores. In a more recent study, Anderson et al. [44] found that early-treated PKU children aged between 7–18 years were delayed in their acquisition of reading and arithmetic skills compared to healthy controls. However, there was no evidence of PKU children presenting with deficits in spelling, as measured by the Wide Range Achievement Test. In a similarly aged group of early-treated PKU patients, Chang et al. [40] found that on the Woodcock-Johnson Revised Test of Achievement, patients obtained mean achievement scores within the average range; however, 26% performed below average on spelling tasks and 19% performed below average on mathematical tasks. In a large follow-up study, early-treated PKU adult patients performed within the average range in reading, spelling and arithmetic; although performance in arithmetic was lower than reading and spelling [10].

Studies investigating the vocational outcomes of PKU patients are limited. A retrospective study of early-treated adolescent patients (15–19 years) born in Czechoslovakia between 1975–1979 [78], showed that 28% were continuing their high school education or pursuing university studies, whereas 72% were engaged in apprenticeships. In a large-scale USA collaborative study of adult PKU patients [82] who were treated early until the age of 6 years, 29% had completed high school, and 28% were college graduates. There were no differences in the proportion of PKU adults who were college graduates or in professional occupations, when compared to unaffected adult siblings.

In summary, findings to date suggest that PKU children are more likely than peers to experience academic problems, especially in the area of arithmetic. The extent to which these academic difficulties affect occupational status in adulthood is less clear.

**Behavior and Psychopathology**

In addition to being at increased risk for cognitive impairment and educational difficulties, treated PKU children and adolescents are also more likely to present with emotional and behavioral problems [83, 84]. For example, Stemerdink et al. [80] found that primary and secondary school PKU patients were rated higher than controls on ‘impulsivity’ and ‘fluctuating work performance’ by parents, and were additionally considered more ‘distractible’ by teachers. Antshel and Waisbren [57] also reported that school-aged PKU children were characterized by parents and teachers as presenting with significantly more inattentive symptoms than expected, as measured by the ADHD rating scale IV. Indeed, rates of stimulant use for attentional difficulties among PKU patients have been re-
ported to be higher than the general population [85]; however, the rates of formally diagnosed ADHD among the PKU population remain unknown. Antshel [86] suggests that further research should be conducted into the prevalence of ADHD in PKU populations, as the two conditions are theoretically linked by low levels of dopamine in the prefrontal cortex.

Although there have been a few reports of PKU patients presenting with autistic behavior, these studies have usually involved patients with intellectual disabilities. Recently, Baieli et al. [87] assessed both early- and late-diagnosed PKU children and young adults with the Autism Diagnostic Interview-Revised and Childhood Autism Rating Scale. No child in the early-diagnosed group met the criteria for autism, but 6% of the late-diagnosed PKU group fulfilled the diagnostic criteria, and in all cases the patients had an intellectual disability (IQ <70).

There are also reports of elevated rates of symptoms consistent with other psychiatric disorders in adult patients. For example, Waisbren and Levy [88] described agoraphobia as a potential complication of PKU in young adults off-diet. They found that 20% of adult PKU women presented with elevated scores on an agoraphobia scale compared to 9% of their unaffected acquaintances and 6% of women with diabetes. Whilst, Pietz et al. [89] did not find evidence of agoraphobia in their sample of early-treated adult PKU patients during structured interview, they found higher rates of depressed mood, phobias, and generalized anxiety among patients compared to controls. However, more detailed exploration of such internalizing symptoms in other studies employing questionnaires such as the Beck Depression Inventory and Beck Anxiety Inventory have not revealed any differences between early- and continuously-treated adults, those who discontinued diet after 10 years, and healthy controls [14, 91]. Elevated scores on subscales of the MMPI, including paranoia, schizophrenia, hypomania, OCD and psychopathic deviate have been reported among late-treated (>90 days) or off-diet adults [91] but not among early- and continuously-treated patients [92].

Although some researchers report that PKU patients seek professional assistance for emotional and/or behavioral problems more often than the normal population, such rates may not be different from those of other chronically ill populations [49]. Indeed, some researchers suggest the observed behavioral and emotional problems in PKU patients are best explained by a psychological model, rather than by a biological model of disease [32, 89, 93]. For example, Weglage et al. [94] compared parental ratings of behavior between early-treated PKU adolescents, diabetic patients and healthy controls, and found that there were no significant differences between the two chronically ill groups, but found both differed significantly from the normative population in relation to internalizing symptoms. Furthermore, no relationships were found between biochemical measures, IQ or socioeconomic status and abnormal symptomology, suggesting that PKU patients present with a generalized chronically ill maladjustment profile and not one specific to PKU. The biological model of psychiatric symptoms and disorders in PKU, however, must also be given consideration. Elevated levels of PHE interfere with the precursors of important neurotransmitters such as dopamine and serotonin, which are known to regulate mood and emotion [83]. Disruption of these neurotransmitters may contribute to aberrations in mood and emotions. Support for this theory comes from research that has shown that PKU children who have ‘poor’ metabolic control are 2.5 times more likely than controls to present with deviant behavior, whilst PKU children who maintain ‘good’ metabolic control are only 1.5 more likely to present with deviant behavior compared to controls [95].

**Mechanisms of Deficits**

Currently, two theories have been proposed to explain the neuropsychological deficits found among PKU patients, the ‘Prefrontal Dysfunction Model’ and the ‘White Matter Abnormalities Model’.

**Prefrontal Dysfunction Model (Dopamine Depletion Hypothesis)**

Phenylalanine hydroxylase, which is deficient in PKU, is an enzyme that converts PHE to tyrosine, and as a result, PKU patients have elevated PHE levels and low tyrosine levels. Tyrosine is a precursor for dopamine and other neurotransmitters, and low levels of tyrosine have been proposed to lead to dopamine depletion which impact upon the prefrontal cortex and, specifically, EF [17]. The prefrontal cortex appears to be particularly sensitive to small reductions in tyrosine because dopamine neurons that project to this brain region fire more rapidly and have a higher turnover of dopamine than other brain regions [17, 96]. Indeed, recent research using positron emission tomography supports the notion that individuals with PKU have reduced cerebral dopamine uptake compared
to the normal population [97, 98]. Furthermore, both animal and human studies have established that dopamine modulates cognitive functions, particularly those mediated by the prefrontal cortex, including working memory [00, 100]. It is important to note that tyrosine levels in the brain are also influenced by a biochemical imbalance between PHE and tyrosine in the bloodstream. Both PHE and tyrosine cross the blood-brain barrier (BBB) via the same transporter, but this BBB transporter has an increased affinity for PHE [17].

The view that dopamine depletion in PKU results in prefrontal dysfunction is supported by research that has found impaired working memory [34, 67], mental flexibility [19, 31], planning and organization [19, 26], and inhibitory control [7, 22] in PKU patients compared to healthy controls and clinical populations. Moreover, a number of studies have shown that patients with high PHE levels present with EF impairment compared to controls [56] and patients with low PHE levels [26, 62]. Studies have also examined whether dopamine availability in PKU patients is related to the ratio of PHE and tyrosine in the blood. Luciana et al. [49] found that poorer spatial working memory and problem solving skills were associated with high PHE:tyrosine ratios in the previous 6 months, at ages 0–2 years, and at ages 14–15 years in adolescent patients. They found relatively poorer mental flexibility was associated with higher levels of PHE to lower tyrosine levels between 3 and 15 years of age, however functions not typically associated with the prefrontal cortex (e.g. motor response and visual memory) were also affected by this high ratio. Sharman et al. [101] found that adolescents with a lifetime PHE:tyrosine ratio of less than 6 demonstrated normal EF as indicated by parental report, but patients whose biochemical ratio was above 6, on average, scored in the clinically impaired range. Support for the prefrontal dysfunction theory has also come from a double-blind study in which supplementation of large neutral amino acids, which included tyrosine, was associated with a trend in lowering PHE:tyrosine levels and an increase in performance on verbal generativity and flexibility tasks [102].

However, not all the research conducted supports the hypothesis that dopamine depletion in PKU results in selective prefrontal dysfunction. For example, in a pharmacological study in which dopamine activity was manipulated by haloperidol, PKU patients exhibited relatively worse performance in working memory and global executive functioning; however, deficits were not seen on all tests of prefrontal functioning and deficits were also observed in cognitive domains subserved by other brain regions [103]. Also, as previously mentioned, a number of studies have failed to show differences on various measures of executive functioning between patients and controls [13, 43], or any impairment in executive functioning at all [50]. Finally, not all studies that have examined executive functioning in PKU have found performance to be associated with high PHE levels [14, 64].

In summary, there is some support to suggest that the cognitive difficulties displayed by PKU patients are related to prefrontal dysfunction due to dopamine depletion. However, there is also ample research that conflicts with this theory, and furthermore, this mechanism does not explain the deficits in other cognitive domains that are commonly reported in PKU.

**White Matter Abnormalities**

Neuroimaging studies using structural magnetic resonance imaging in early-treated PKU patients have demonstrated that the prevalence for white matter abnormalities is high [104, 105], with most patients exhibiting at least mild high-signal intensity in the periventricular white matter [5, 104, 106]. White matter abnormalities tend to be associated with age and metabolic control such that the prevalence of these abnormalities is higher and more severe in older children [5, 104], those who are off treatment [5, 104, 105], or those with high-PHE levels [5, 104–109]. Research has also demonstrated that in severe cases the white matter abnormalities can extend into subcortical regions [5, 105, 107, 110], posterior limb of the internal capsule into the cerebral peduncles [107], brain stem [108], and cerebellum [108].

Cognitive and motor functions are dependent on tracts within the brain. The smooth flow of neural impulses is necessary for the brain to operate efficiently so that information can be transmitted throughout the brain and integrated across multiple regions [111]. The speed of neural transmission is largely dependent on the structural properties of the connecting fiber tracts, such as axonal diameter and integrity of the myelin sheath [111]. Given that neuroimaging and histopathology studies indicate that treated PKU patients have high rates of white matter pathology as a result of dysmyelination, it would be reasonable to expect impaired cognitive and motor deficits [112]. The white matter pathology observed in PKU is generally diffuse and, as a consequence, multiple pathways may be compromised and mild to moderate deficits may be observed over a range of functions including motor skills and coordination, visual functioning, processing speed, language, memory and
learning, as well as attention and executive functioning. Consistent with this posis, a broad array of neuropsychological difficulties has been reported in the PKU population [4–34, 44, 51, 113].

While it is reasonable to assume that the difficulties experienced by PKU patients are related to white matter pathology, support for this view is limited. Studies have tended to find that white matter abnormalities do not correlate significantly with general intelligence (IQ) [104, 105, 107, 108, 114–116]. However, a certain degree of pathology may be needed before white matter abnormalities compromise functioning [5, 44]. For example, Anderson et al. [44] contrasted the neuropsychological profiles of early-treated PKU children with no white matter abnormalities (n = 6), children with pathology restricted to the posterior periventricular region (mild, n = 12), and children with pathology that extended into subcortical and frontal regions (moderate, n = 14). A linear effect was not observed, with the children in the no pathology and mild pathology groups differing only marginally from each other and from a control group. In contrast, children with moderate pathology exhibited significant impairments in processing speed, multitasking, information retention, mental flexibility, and arithmetic. Based on these findings, it would appear that PKU children with no pathology or pathology restricted to posterior periventricular white matter exhibit only subtle cognitive deficits, while children with more extensive pathology experience more global and severe impairments.

Conclusions

This review has demonstrated that while children treated early and continuously for PKU escape severe intellectual impairment, they are at increased risk for a range of neuropsychological impairments. While numerous neuropsychological studies have been conducted, the findings have not been consistent. Executive functioning has attracted most interest, and while the bulk of studies have reported deficits in this domain, conflicting research also exists. Slowed processing speed appears to be a major area of concern for PKU patients, and this may have implications for memory and learning as well as executive functioning. Impairments in other domains have also been noted including fine motor control, attention, and memory and learning. Given these difficulties, it is not surprising that higher rates of academic and behavioral problems have been reported in PKU cohorts. In summary, the research to date would suggest that PKU is not associated with a specific pattern of deficits, although speed of processing and executive dysfunction are two areas of primary concern.

The mechanism for neuropsychological impairments in early-treated PKU is likely to be multifactorial. Evidence for a specific dysfunction of the prefrontal cortex (i.e. executive functioning) due to dopamine depletion has been presented, although this clearly cannot be the sole mechanism as deficits in other cognitive domains are also observed. There is also evidence that white matter pathology may be a factor in the cognitive difficulties expressed in PKU patients.

As noted by Janzen and Nguyen [55], considerable variability exists in the PKU population with some individuals exhibiting exceptional cognitive abilities. Furthermore, most PKU individuals have a good quality of life, and if neuropsychological deficits are present, these are usually relatively minor. Clearly, close surveillance in relation to cognitive functioning, academic performance and behavior of PKU patients is required, especially during childhood.

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