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White matter pathology in phenylketonuria ☆

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ABSTRACT

Early-treated phenylketonuria (PKU) is associated with a range of neuropsychological impairments. Proposed mechanisms for these impairments include dopamine depletion and white matter pathology. Neuroimaging studies demonstrate high-signal intensity in the periventricular white matter in most PKU patients, which can extend into subcortical and frontal regions in more severe cases. A review of histopathology and neuroimaging studies reveals that diffuse white matter pathology in untreated PKU patients is likely to reflect hypomyelination (lack of myelin formation), while in early-treated patients white matter abnormalities observed on magnetic resonance imaging (MRI) is likely to reflect intramyelinic edema. Research demonstrates that this pathology is associated with metabolic control and may be reversed with adherence to a strict low-phenylalanine (Phe) diet. While the functional significance of white matter pathology in PKU is not certain, there is some evidence that these abnormalities are associated with functional impairments when the pathology extends into subcortical and frontal regions.

Introduction

Phenylketonuria (PKU[1]; OMIM 261600 and 261630) is an inborn error of metabolism associated with diffuse brain pathology. The consequences are usually severe when this metabolic condition is left untreated; however, white matter pathology is common even in early diagnosed and treated individuals. PKU appears to principally affect cortical and subcortical white matter, although there is emerging evidence that this condition also influences cortical development, in particular dendritic growth and dendritic spine density [1]. Little is known about the cortical changes related to early-treated PKU in humans as dendritic abnormalities are not easily detectable with current neuroimaging paradigms. However, some recent studies have reported volumetric reductions in gray matter structures including the motor cortex, thalamus, and hippocampus [2,3]. In contrast, considerable human research has examined how PKU impacts white matter development, and this literature will be the focus of this review.

Histopathology

While human histopathology studies are limited to small numbers of selective samples of different ages, these studies can provide important insights into the specific neuropathology associated with PKU. The brains of untreated PKU patients generally show impaired myelination, reflected by pallor of the white matter on myelin stains [1,4]. Astrocystic gliosis is usually present in these affected white matter tracts [5]. In animal models of PKU, studies have demonstrated that oligodendrocytes (i.e., cells that assemble and maintain myelin) fail to form myelin in response to high-phenylalanine (Phe) levels [6]. For example, rats placed on a hyperphenylalanemia diet display increased turnover of myelin components and inhibited myelin synthesis [7], which is similar to the disturbed myelin metabolism observed in a mouse mutant deficient of phenylalanine hydroxylase (PAH; EC 1.14.16.1) [8]. Given that elevated Phe is a symptom of untreated or poorly treated PKU, the impaired myelination observed in these individuals is probably due to a toxic effect of high-Phe levels on oligodendroglia [4].

In utero the fetus with PKU of a mother heterozygous of PKU does not experience the elevated Phe levels associated with this metabolic disorder, and brain development up to birth is thought to proceed normally. After birth, Phe levels rise quickly and from this point forward are considered neurotoxic for subsequent brain development. This view is consistent with the location of white matter

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[1] *Abbreviations used:* PKU, phenylketonuria; Phe, phenylalanine; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; VEP, visual evoked potentials; SEP, somatosensory evoked potentials; DTI, diffusion tensor imaging; CSF, cerebrospinal fluid; ADC, apparent diffusion coefficient; MW, myelin water; FA, fractional anisotropy; BBB, blood–brain barrier; IQ, intelligence quotient.

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lesions in untreated PKU, which generally occur in regions in which myelination occurs postnatally [4,6]. As a consequence, it has been proposed that oligodendrocytes in regions that myelinate post-birth (e.g., optic tract, corpus callosum, subcortical white matter, and periventricular white matter) are vulnerable to high-Phe levels post-birth, while oligodendrocytes associated with white matter tracts that myelinate pre-birth (e.g., internal capsule and brainstem) are resistant to elevated Phe levels post-birth [4]. If this is the case, one would expect that offspring from untreated or poorly treated maternal PKU pregnancies would show myelination abnormalities in the internal capsule, brainstem, and other early myelinating tracts. However, to date, there is limited supporting evidence. A neuroimaging study reported no myelination abnormalities in offspring without PKU, although significant changes to the corpus callosum were observed [9]. Further, an autopsy report on an infant whose mother had poorly controlled maternal PKU and died at 4 months of age revealed age-appropriate myelination in early myelinating tracts including the brainstem, spinal cord, and cerebellum, but myelination was delayed in tracts that commence myelination late in the third trimester, such as the optic radiation [10].

Dyer [4] argues that white matter pathology in untreated PKU is a developmental process whereby elevated Phe levels stall the myelination process, resulting in severe hypomyelination. Mild and transient involvement of white matter tracts that myelinate post-birth has been suggested also in early-treated PKU patients. However, in early-treated patients myelination is thought to proceed normally, or close to normal, and the lesions are likely to reflect demyelination or dysmyelination. In other words, white matter lesions in untreated PKU is likely to be due to reduced myelin formation, while lesions in well-controlled patients is considered a function of loss or impairment of previously assembled myelin [4].

In the lack of neuropathological confirmation, this attractive model can be explored in light of the data collected in vivo in PKU patients by magnetic resonance imaging (MRI) examination and neurophysiological and clinical studies.

Structural MRI

Probably the first report of white matter abnormality in treated PKU patients using conventional MRI was in 1989 [11]. This case report described two young adults displaying neurological deterioration (years after diet discontinuation) who on T_2 weighted images exhibited increased signal intensity in periventricular white matter.

This report was followed by a series of studies published in the early 1990s, which investigated neuroanatomical changes in treated PKU patients using structural MRI. An influential paper was published in the *Lancet* by Thompson et al. [12]. This case series described seven treated patients who displayed neurological deterioration in adolescence or early adulthood. Six of these patients underwent MRI and all were identified as having white matter abnormalities on T_2 weighted images, specifically high-signal intensity in periventricular white matter. While the size and distribution of these high-signal intensity changes varied between subjects, it was more common in posterior temporal and occipital white matter. The abnormal high-signal areas were thought to indicate "increased water content and/or an alteration in the macromolecular environment of water" in the cerebral white matter. Thompson et al. [12] also described one young adult who had serial MRI scans at age 23, 24, and 25 (two scans, with a repeat scan taken after resumption of treatment). The white matter abnormalities observed on brain scans at 23 and 24 years of age were similar, and during this period this patient remained stable. Between 24 and 25 years of age this patient showed marked clinical deterioration, which interestingly coincided with "striking MRI changes". A follow-up assessment was undertaken 2 months after resuming a strict low-Phe diet, neurological symptoms improved, and the severity of white matter changes diminished.

At roughly the same time Pearsen et al. [13] published the findings of an MRI study involving 17 PKU patients (age range: 9–35 years), nine of which were early-treated and six of these were still following a low-Phe diet. All but one of these patients had "symmetric high-signal intensity in the periventricular white matter of the posterior cerebral hemispheres, with extension into the frontal lobes in advanced cases only". No white matter abnormalities were identified in other brain regions and the basal ganglia appeared unaffected in all cases; however, mild cortical atrophy was seen in eight patients.

The findings of these early reports have been replicated in larger and more representative samples, and also in quite young and well-controlled children [14–26]. The largest cohort study using MRI scanned 77 adolescent and adult PKU patients (recruitment rate of 78%), with suitable images obtained for 74 cases [18]. The majority of the participants ($n = 70$) were early-treated (treatment commenced within 2 months), and most discontinued treatment at age 14 years. Some degree of white matter abnormality was observed in 71 (of 74) scans, with one normal scan and two with "equivocal changes". The MRI abnormalities were less severe for younger participants who were still on treatment in comparison to those who were off treatment.

In summary, the prevalence for white matter abnormalities is high [18,24], with most early-treated patients exhibiting at least mild high-signal intensity in the periventricular white matter [15,18,23]. The prevalence of the white matter abnormalities tends to be higher and more severe in older children [15,18], those who are off treatment [15,18,24], or those with high-Phe levels [15,17,18,22–24,27]. Further studies have also demonstrated that in more severe cases the white matter abnormalities can extend into subcortical regions [15–17,24], posterior limb of the internal capsule into the cerebral peduncles [17], brain stem [22], and cerebellum [22].

A major limitation of these studies is the reliance on qualitative measurements of pathology. Furthermore, the imaging sequences vary across studies, as do the protocols for assessing the presence and severity of white matter abnormalities. Finally, the majority of subjects examined by a number of these published studies (see Table 1) were in their second decade of life or older and longitudinal studies are still lacking. So, as the information based on structural studies is concerned, the age of the onset and the *natural* outcome of MRI white matter abnormalities remain to be explored. In spite of these constraints, the picture emerging from the literature of the last 20 years is striking, showing that over 90% of all PKU patients suffer from white matter abnormalities (Table 1), which were not associated with obvious neurological alterations.

Table 1
Cumulative data on structural white matter MRI abnormality in PKU without neurological deterioration.

Patients	312
Age range (years)	0.9–49
</> 11 years, *n*	23/172 (available data for 195/312)
PKU (Phe > 600 μM), *n*	300
Hphe (Phe < 600 μM), *n*	12
Early/late detected, *n*	254/58
On/off diet, *n*	107/205
Cognitive functioning (normal/abnormal), *n*	96/59 (available data for 165/312)
MRI white matter pathology (normal/abnormal), *n*	22 (7%)/290 (93%)

Data summarize patients reported in Refs. [13,14,16–26]. Numbers should be accepted with prudence, considering that it is not totally possible to rule out repeated enrollment of the same patient in more than one paper.

Regression of white matter abnormalities

The regression in MRI-defined white matter abnormalities observed in a patient by Thompson et al. [12] has also been described by others [17,28,29]. Bick et al. [17] noted less severe white matter pathology in two of three patients who returned to a strict low-Phe diet in just 3 months, however, these improvements diminished for both patients when treatment was again discontinued. In this study, the improvement in MRI changes appeared related to the maintenance of good metabolic control. This view is consistent with the lack of improvement on MRI showed by the third patient, who returned to treatment but continued to record relatively high-Phe levels.

While these case reports provided hope that MRI-defined abnormalities in PKU are reversal, more empirical evidence for this view was provided by an landmark study by Cleary et al. [28]. This study involved serial MRI scans in 41 patients (aged 14–49 years) who following a baseline scan either (1) returned to a strict low-Phe diet with amino acid supplementation aiming for Phe levels less than 400 μmol/L ($n = 5$), (2) started a low-protein diet with amino acid supplementation aiming for Phe levels less than 900 μmol/L ($n = 21$) or (3) made no dietary changes ($n = 15$). The follow-up MRI scans, which were conducted after 3–12 months of intervention, revealed regression in white matter abnormalities in all five patients who returned to a strict treatment regime. In contrast, some reversal of MRI changes was observed in 5 of 21 patients who returned to a low-protein diet and in 4 of 15 patients who made no dietary change. All these patients who showed reduction in white matter changes but one had a lower Phe level at the second scan. Regression of white matter abnormalities was significantly associated with blood Phe levels, in particular blood Phe level at the time of the follow-up scan. Further inspection of the data indicated that improvement in white matter score was primarily observed in those participants who were able to reduce their blood Phe to less than 900 μmol/L. Unfortunately, the clinical correlations (if any) of the different outcomes of MRI white matter alterations were not explored in this study.

The duration of strict metabolic control needed to significantly reduce white matter abnormalities is not known, but it is clear that reversal of these changes does not occur rapidly [30] and a minimum of 2 months may be needed [28].

Metabolic control

Evidence that the severity of white matter pathology can be reduced with a return to a strict low-Phe diet and good metabolic control (i.e., blood Phe < 400 μmol/L) implies that the evolution of this lesion is linked to poor metabolic control. While most studies have found that the severity of abnormalities is related to blood Phe levels [15,17,18,22–25,27,31], this is not a universal finding [13,16]. The approach for determining the role of metabolic control in MRI-defined white matter changes has varied greatly. Most studies have correlated white matter abnormalities with concurrent blood Phe, but other parameters of metabolic control examined include previous 6 months Phe, previous 12 months Phe, and lifetime Phe. These parameters are usually associated with age, given that treatment guidelines alter according to age. Thus, untangling the independent effects of age and metabolic control on the development of white matter pathology is difficult.

Early reports that MRI-defined white matter changes are not related to metabolic control were based on small sample studies ($n = 15$ [13] and $n = 9$ [16]). These studies did not describe in detail the analyses conducted, but it appears that qualitative rating of diet history was the basis of the analyses rather than Phe level. Larger cohort studies and those that have examined the relationship between severity of white matter and blood Phe have tended to report a positive finding, such that high-Phe levels are generally associated with more severe white matter pathology [15,17,18,22,24,25]. In an early report examining the issue of metabolic control, Thompson et al. [24] found that severity of white matter pathology was greater in those patients who were off treatment, especially those off treatment for greater than 2 years, patients who had blood Phe levels in excess of 1200 μmol/L, and patients older than 11 years. They reported that MRI abnormalities were either absent or minimal in young children who were still on a strict diet and with concurrent blood Phe less than 700 μmol/L [24]. More in-depth analyses were conducted by Cleary et al. [18] in their large cohort study including concurrent Phe, maximum Phe, mean lifetime Phe, mean Phe in the first 4 years, and mean Phe in the last 5 years. Of these metabolic control parameters concurrent Phe correlated most strongly with MRI score ($r^2 = 0.34$). Mean lifetime Phe ($r^2 = 0.14$) and mean PHE in the last 5 years ($r^2 = 0.16$) were also moderate predictors of white matter abnormalities. Consistent with these findings, mean MRI scores were significantly higher (abnormal) in patients older than 14 years and off treatment when compared to younger patients who were still on treatment.

Summary parameters for metabolic control (i.e., lifetime Phe) have generally been calculated by averaging Phe values; however, means should only be used when the distribution is normally distributed, and this is not always the case. In a younger cohort, Anderson et al. [31] examined this relationship between metabolic control and severity of white matter abnormalities but utilized median values rather than means to represent lifetime Phe, early Phe (first 6 months), and recent Phe (previous 12 months). Consistent with previous reports, lifetime Phe ($r^2 = 0.36$) and concurrent Phe ($r^2 = 0.45$) were strong predictors of white matter abnormalities, but median Phe level over the previous 12 months was even more predictive ($r^2 = 0.61$). Children with moderate to severe MRI changes had a mean concurrent Phe of 786 μmol/L and mean lifetime Phe of 542 μmol/L, which was significantly higher than those children with no or mild white matter pathology.

A reliance on blood Phe levels is a limitation of the above studies. In the mid-1990s studies using magnetic resonance spectroscopy (MRS) emerged. MRS is used to measure the concentration of different metabolites in tissue and has enabled brain Phe levels to be estimated [32–40]. In early-treated PKU patients, blood and brain Phe levels generally correlate highly [19,32,35,38], although there is some data to suggest that this linear relationship deviates at higher Phe levels [19,36,37,41]. Furthermore, inter-individual variability has been reported, with some patients exhibiting significant variability between blood and brain Phe levels [32,33,36,37,39,41,42]. For example, Moats et al. [42] describes four PKU patients who, despite exhibiting high-historic Phe levels, recorded low-brain Phe levels and normal intellectual functioning. It has been speculated that this inter-individual variability may explain the different clinical outcomes observed between patients despite very similar metabolic control; in some cases individual treatment recommendations may be warranted [40]. Brain Phe has been related to white matter abnormalities, with Rupp et al. [38] reporting a moderate association similar to that for concurrent blood Phe.

Neurophysiological evidence of white matter alteration

White matter integrity can be reliably explored by neurophysiological techniques, which are useful in detecting a possible impairment of nervous potential generation and conduction—a frequent finding in demyelinating diseases. Lou et al. [21] found normal visual evoked potentials (VEP) in 14 PKU subjects with a wide spectrum of white matter involvement. Cleary et al. [18] recorded VEP and somatosensory evoked potentials (SEP), central motor

conducting time, and peripheral motor nerve conduction velocity in a subgroup of PKU patients enrolled for their neuroradiological study. Despite some peripheral and/or central conduction alterations detected in a few subjects, the authors did not identify a pattern of neurophysiological alteration consistent with white matter abnormalities and concluded that there was no convincing evidence of major neurophysiological abnormality in PKU subjects with white matter abnormality.

However, VEP abnormalities in a high percentage of PKU adolescents and young adults with variable white matter involvement have been reported in other studies [43,44]. In 22 of 27 PKU patients aged 14–31 years, Jones et al. [43] found alterations of both latency (21/22) and amplitude (14/22) of VEP P100 peak associated with moderate to severe (score 3–5) white matter alterations in 20 of 22 patients (concurrent blood Phe 430–2010 μmol/L). In contrast, VEP were normal in eight of nine PKU patients younger than 14 (concurrent Phe level 348–1166 μmol/L) who showed minimal white matter involvement (in the only abnormal subject of this group, a pattern of retrochiasmal visual pathway involvement was associated with a higher white matter severity score and concurrent blood Phe level 1320 μmol/L). Level of blood Phe higher than 1200 μmol/L was associated with a higher probability of VEP abnormalities, while VEP latency was not significantly correlated with white matter score, despite a general trend of VEP alterations to occur in the patients with most severe involvement of white matter.

An increase of VEP P100 latencies was also confirmed when the integrative function of visual system was explored by structured stimuli with different spatial frequencies and contrasts [44]. Phe values higher than 900 μmol/L and the patient's age independently affected VEP latency elicited by higher frequency and/or reduced contrast and VEP latency elicited by the lower spatial frequency, respectively. Also in this study the involvement of white matter on MRI, which was found in all patients, was not correlated with severity and patterns of neurophysiological alterations. The picture emerging from these studies shows that while VEP and white matter alterations share a similar linkage with the recent exposure to blood Phe level and the patient's age, they do not appear to be associated with each other and may be representing different pathologic backgrounds [44].

In conclusion, although the pattern of neuroradiological abnormality suggests a demyelinating process in early-treated PKU subjects during their second decade of life and afterwards, neurophysiological studies do not completely support that demyelination is the main pathological background of these alterations.

Advanced MRI sequences

Conventional MRI studies have clearly demonstrated that periventricular white matter pathology is common in early-treated PKU patients, and the severity of pathology is strongly associated with metabolic control. The changes in MRI have been described as elevated water content, edema, and immature or vacuolated myelin [16,18,24]. However, more advanced MRI sequences are necessary to fully understand the etiology of these white matter abnormalities, such as MRS and diffusion tensor imaging (DTI).

While some MRS studies have reported altered spectra in PKU patients [45], others have reported normal concentration of the primary metabolites in a range of regions [17,21,22]. Discrepancies that have been reported include a decrease in choline concentration [46], as well as choline/creatine [45] and inositol/creatine [47] ratios. A more relevant finding is the increased volume of cerebrospinal fluid (CSF)-like water compartment in affected white matter regions [22]. The volume of CSF-like water compartment is significantly less in unaffected white matter regions in comparison to affected regions [22].

More recently DTI has been utilized to assess the nature of the white matter lesions observed on conventional MRI. DTI is an imaging technique that allows the assessment of water diffusion in white matter, enables representation of the architecture of fiber tracts through the analysis of differential tissue anisotropy, and provides information relating to axonal loss and demyelination. Most DTI studies report reduced apparent diffusion coefficients in PKU patients [19,46,48,49]. Phillips et al. [48] reported reduced apparent diffusion coefficient (ADC) in occipital white matter, splenium, genu, frontal white matter, and corona radiate in three PKU patients compared to six healthy volunteers. The authors suggest that the restricted diffusion in PKU patients is unlikely to reflect increased extracellular fluid or demyelination, as these phenomena are more likely to result in increased diffusion [48]. The most likely explanation offered was that the reduced diffusion reflected water within the myelin or increased myelin turnover. While Dezortova et al. [46] also found reduced ADC values in PKU patients, this was specifically in lesioned white matter and not in unaffected white matter. These findings were interpreted to reflect a greater concentration of unbound water molecules in the white matter lesion and alterations to the myelin sheath. More recent DTI studies by Leuzzi et al. [19], Vermathen et al. [49], and Scarabino et al. [50] also report reduced diffusivity in regions exhibiting white matter changes and agree that this is likely to represent increased intracellular water content. Moreover, a reduction of ADC values has also been reported in unaffected (on T_2 images) regions of white matter [49,51]. Similar to hyperintensity on T_2 weighted images, restricted diffusion in the posterior white matter has been reported to be strongly associated with metabolic control over the preceding 12 months ($r^2 = -0.59$), such that higher Phe levels are related to reduced ADC values [52]. A significant, although weaker, relationship was also identified between metabolic control and ADC values in the frontal white matter [52].

The pathologic background associated with the reduced value of ADC and the hypotheses that the ADC alteration could reflect a possible change in myelin content in the brain of patients with PKU were further explored in vivo by MRI [53] or multimodal MR (combined DTI, relaxometry, and MRS) approaches [49]. These studies computed in adult PKU subjects and age-matched controls the fraction of the water contributing to brain water signal trapped between myelin bilayers (*sensu strictu* myelin water [MW]), which is alleged to be a quantitative marker of myelin integrity. MW content was found reduced in lesions and in unaffected tissue of PKU patients [49], while the pool of extracellular water was increased [49,53]. Coupled with ADC reduction, this pattern of alterations suggests a swelling or separation of myelin sheaths with intramyelinic edema and formation of vacuoles [49]. Controversial data are available as the fractional anisotropy (FA), which reflects the integrity of the tridimensional architecture of the myelin fibers, is concerned. FA is found preserved by some studies [19] and altered (with prevalent impairment in longitudinal direction) by others [49].

In conclusion, the cumulative results of neuroradiological and neurophysiological studies in PKU patients support the view of MRI white matter alteration as resulting from a (chronic) intramyelinic edema, which does not result in a demyelinating process or in a relevant derangement of the pattern of MW connectivity.

Functional consequences of PKU-related white matter pathology

Cognitive and motor functions are dependent on both the structural integrity of specific brain regions as well as the tracts connecting these brain structures. The smooth flow of neural impulses is necessary for the brain to operate efficiently so that information can be transmitted throughout the brain and inte-

grated across multiple regions [54]. 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 [54]. 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 [55]. 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 posit, a broad array of neuropsychological difficulties has been reported in the PKU population [31,56–72].

Mild neurologic impairments have been reported in patients with PKU, including increased tremor and fine motor performance [73–75]. This population has also been found to exhibit slow reaction times [22,31,58,65,76,77], perception difficulties [67], compromised interhemispheric transfer [61,64], language problems [57], and memory and learning [31,57,67,68] deficits. However, the domain that has generated most interest in PKU children is attention and executive functioning. For example, deficits in selective and sustained attention [22,66,78,79], working memory [72], inhibitory control [62,65,69], conceptual reasoning [59,68,69], planning ability [59,70], mental flexibility [31,63,66], and organisational strategy [71] have all been reported. The general nature of these impairments is consistent with white matter pathology.

Some researchers have reported selective deficits in prefrontal functions such as executive skills, leading to the premise that cognitive impairment in early-treated PKU patients is a result of mild depletion in dopamine [70]. Dopamine depletion has been observed in early- and continuously-treated patients, and it is thought to occur as a result of insufficient levels of tyrosine crossing the blood–brain barrier (BBB) [80]. The prefrontal cortex is thought to be particularly sensitive to low dopamine, given that it rapidly turns over this neurotransmitter [81–83], and studies have reported an association between prefrontal dysfunction (i.e., working memory) and dopamine depletion [82,84,85]. While a considerable body of evidence supports the dopamine depletion/executive dysfunction theory, conflicting research also exists. For example, (1) some studies have failed to identify executive dysfunction in PKU cohorts [76,86–88], (2) the severity of executive deficits has reported to decrease rather than increase with age possibly reflecting developmental delay [88,89], and (3) a randomized controlled trial of tyrosine supplementation revealed no benefits [90]. The dopamine depletion theory also does not explain the commonly reported deficits in processing speed, interhemispheric transfer, and mild neurologic functions. As a consequence, it has been proposed that the profile of neuropsychological deficits seen in PKU patients may reflect multiple mechanisms including white matter pathology and dopamine depletion [15,31].

Theoretically, it is reasonable to assume that at least some of the difficulties experienced by PKU patients are due to white matter pathology; however, support for this view is limited. In fact, most studies have reported that white matter abnormalities observed on MRI do not correlate significantly with general intelligence (IQ) [13,17,18,22,24,74,91]. Still, it is possible that this relationship is non-linear rather than linear, and that the pathology needs to reach a certain threshold before it begins to compromise functioning [15,31]. This view is supported by a study by Anderson et al. [15], who contrasted the neuropsychological profiles of early-treated PKU children with no white matter abnormalities on MRI ($n = 6$), 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. Thus, it was concluded 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. The weak association between total MRI scores and IQ may also relate to the insensitivity of IQ measures to subtle brain pathology and cognitive functioning [15]. For example, Pietz et al. [22] reported a weak correlation between MRI grade and IQ ($r^2 = -0.03$) yet found a significant relationship between MRI grade and sustained attention ($r^2 = 0.17$) and reaction time (dominant hand: $r^2 = 0.28$; non-dominant hand: $r^2 = 0.22$).

In summary, there is some evidence that white matter pathology in PKU patients is at least partly related to some of the neuropsychological problems exhibited by these individuals. However, deficits associated with white matter pathology may be restricted to those with pathology that extend beyond the posterior periventricular region, and it may affect specific cognitive functions which are not easily detectable on general functional outcome measures.

Conclusions

PKU is associated with diffuse white matter pathology in both treated and untreated patients. In untreated patients this is likely to reflect hypomyelination (lack of myelin formation) while in early-treated patients this pathology is likely to reflect intramyelinic edema. Research demonstrates that this pathology is associated with metabolic control, and as such can be reversed with adherence to a strict low-Phe diet for at least 2 months. There is some debate relating to the functional significance of white matter pathology in PKU; however, it seems that these abnormalities are associated with functional impairments when the pathology extends into subcortical and frontal regions.

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