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EFFECTS OF HYPERPHENYLALANINEMIA ON BRAIN METABOLISM AND NEURODEVELOPMENT IN PHENYLKETONURIA: A SYSTEMATIC REVIEW

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ABSTRACT
Hyperphenylalaninemia, or increased blood phenylalanine levels, is the outcome of phenylketonuria (PKU), an inherited metabolic condition caused by a deficiency of the enzyme phenylalanine hydroxylase. Elevated phenylalanine concentrations still have an impact on brain development and cognitive function, despite the fact that neonatal screening and nutritional treatment have greatly improved outcomes. The consequences of hyperphenylalaninemia on brain metabolism and neurodevelopment in PKU patients are investigated in this systematic study. Recent research indicates that too much phenylalanine affects neurotransmitter production, changes energy metabolism, interferes with myelination and neural maturation, and interferes with the transport of large neutral amino acids over the blood-brain barrier. This review highlights the relationship between long-term metabolic control and neurological outcomes and emphasizes the importance of early diagnosis in reducing the adverse effects of hyperphenylalaninemia on the brain.

Keywords:
Cognitive function, brain metabolism, neurodevelopment, phenylketonuria, myelination

I. INTRODUCTION

Mutations in the phenylalanine hydroxylase (PAH) gene are the main cause of phenylketonuria (PKU), one of the most prevalent hereditary disorders of amino acid metabolism. Phenylalanine builds up in the blood and tissues as a result of this enzyme's deficit, which stops phenylalanine from being normally converted to tyrosine. Hyperphenylalaninemia, or elevated phenylalanine levels, is harmful to the central nervous system, and if ignored, can cause serious neurological problems.

Hyperphenylalaninemia is very dangerous for the developing brain. Elevated levels of phenylalanine can reduce the availability of precursors needed for the synthesis of neurotransmitters like dopamine and serotonin by obstructing the transport of other important amino acids into the brain. Additionally, aberrant myelination, altered energy metabolism, delayed neuronal maturation, and anatomical abnormalities in the brain have all been linked to excess phenylalanine. These alterations lead to decreased neuropsychological functioning, behavioural issues, learning problems, and cognitive impairment. Despite early treatment, many individuals with phenylketonuria (PKU) continue to experience cognitive and neurodevelopmental challenges. This systematic review summarizes current evidence on how elevated phenylalanine levels affect brain metabolism and neurodevelopment in individuals with PKU.

II. OBJECTIVES

The objectives of this systematic review are: (1) To describe how elevated phenylalanine levels affect brain metabolism in phenylketonuria (PKU). (2) To examine the effects of hyperphenylalaninemia on neurodevelopment, cognition, and neurological outcomes. (3) To identify research gaps and future directions on brain metabolism and neurodevelopment in PKU.

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III. METHODOLOGY

This study employed a systematic literature review to evaluate the effects of hyperphenylalaninemia on brain metabolism and neurodevelopment in individuals with phenylketonuria (PKU). A structured and comprehensive approach was used to identify, evaluate, and synthesize existing studies regarding the neurological consequences of elevated phenylalanine levels, including their impact on neurotransmitter synthesis, brain metabolism, cognitive function, and neurodevelopment. The review followed a systematic process to ensure the reliability, transparency, and accuracy of the findings.

❖ Data Sources

The primary sources for this systematic review consisted of peer-reviewed journal articles, review papers, clinical guidelines, and book chapters retrieved from major scientific databases, including PubMed Central (PMC), PubMed/NCBI Bookshelf, Wiley Online Library, ScienceDirect, Frontiers in Genetics, Frontiers in Pediatrics, MDPI (Nutrients), and ResearchGate. Additional literature was identified through manual searches of the reference lists of selected studies to ensure comprehensive coverage of relevant publications.

The literature search included studies published from 2021 to 2025, encompassing landmark studies, clinical investigations, systematic reviews, and recent advances in understanding the effects of hyperphenylalaninemia on brain metabolism and neurodevelopment in phenylketonuria.

❖ Inclusions and Exclusions

To ensure the relevance and quality of the studies included in this systematic review, specific inclusion and exclusion criteria were established based on the relevance to the effects of hyperphenylalaninemia on brain metabolism and neurodevelopment in phenylketonuria (PKU).

❖ Inclusions Criteria

Studies were included in the review if they met the following criteria:

- ➢ Investigated the effects of hyperphenylalaninemia in individuals with phenylketonuria.
- ➢ Reported findings related to brain metabolism, neurotransmitter synthesis, cognitive function, neurodevelopment, or neurological outcomes.
- ➢ Included clinical studies, observational studies, experimental research, systematic reviews, or evidence-based clinical guidelines.
- ➢ Published in peer-reviewed scientific journals.
- ➢ Written in English with accessible full-text articles.

❖ Exclusion Criteria

Studies were excluded if they met any of the following criteria:

- ➢ Did not specifically address hyperphenylalaninemia or phenylketonuria.
- ➢ Focused solely on genetic mutations or biochemical findings without discussing brain metabolism or neurodevelopment.
- ➢ Conference abstracts, editorials, opinion papers, letters, or publications lacking sufficient original scientific evidence.
- ➢ Duplicate publications or overlapping datasets, in which case the most comprehensive study was retained.
- ➢ Non-English publications or studies with inaccessible full-text articles.

❖ Search Results

The systematic search identified relevant studies investigating the effects of hyperphenylalaninemia on brain metabolism and neurodevelopment in individuals with phenylketonuria (PKU). After applying the predefined inclusion and exclusion criteria, the selected studies were included in the final review for qualitative synthesis. 15 studies provided comprehensive evidence on how elevated phenylalanine levels disrupt brain metabolism through

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impaired neurotransmitter synthesis, altered cerebral energy metabolism, and white matter abnormalities, ultimately affecting cognitive function and neurodevelopment.

The included studies comprised clinical investigations, observational studies, systematic reviews, and experimental research involving pediatric and adult patients with PKU. Each study was evaluated based on its methodological quality, relevance to the research objectives, and contribution to understanding the mechanisms by which hyperphenylalaninemia influences brain function and neurodevelopment.

❖ **Data Extraction**

Data were extracted systematically from each eligible study using a standardized data collection format to ensure consistency and accuracy. The extracted information included the author(s), year of publication, study design, study population, phenylalanine levels, neurological and neurodevelopmental outcomes, alterations in brain metabolism, cognitive findings, treatment approaches, and key conclusions. Information regarding neurotransmitter synthesis, white matter abnormalities, cerebral metabolism, and long-term neurological outcomes was also documented whenever available.

❖ **Statistical Analysis**

The selected studies were analyzed using a qualitative narrative synthesis. Findings from the included literature were compared and synthesized to identify consistent evidence regarding the effects of hyperphenylalaninemia on brain metabolism and neurodevelopment in phenylketonuria. Particular emphasis was placed on alterations in neurotransmitter production, cerebral energy metabolism, white matter integrity, cognitive function, and developmental outcomes. The effectiveness of current treatment strategies, including dietary phenylalanine restriction, sapropterin, pegvaliase, large neutral amino acid supplementation, and emerging gene therapies, was also evaluated to determine their role in preserving neurological function and improving long-term neurodevelopmental outcomes.

IV. RESULTS AND DISCUSSION

A total of 15 studies met the inclusion criteria and were analyzed qualitatively. These studies included clinical investigations, observational studies, systematic reviews, and experimental research on patients with PKU (children, adolescents, and adults), as well as broader reviews on PKU pathophysiology and treatment.

Most studies focused on:

- How high phenylalanine (Phe) levels affect brain metabolism (neurotransmitters, myelin, white matter).
- The relationship between blood Phe and cognitive or neuropsychological outcomes (IQ, attention, executive functions).
- The effectiveness of current and emerging treatments (diet, sapropterin, pegvaliase, LNAA, and gene-based therapies).

Table 1. General characteristics of key studies on hyperphenylalaninemia, brain metabolism, and neurodevelopment in PKU.

Author & Year	Title	Location / Setting	Sample / Source	Main Findings / Key Results
Rovelli & Longo, 2023	Phenylketonuria and the brain	International review (Mol Genet Metab)	Narrative/systematic review of PKU across lifespan	High phenylalanine is toxic to the brain; timing and duration of exposure determine severity (from microcephaly and severe disability to executive and mood problems). Early and

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				continuous Phe control is key to protecting brain development.
Pilotto et al., 2021	Phenylalanine Effects on Brain Function in Adult Phenylketonuria	Italy, neurology clinics	19 adults with PKU; cross-sectional clinical, neuropsychological, imaging study	Higher plasma Phe is strongly linked to failed neuropsych tests, neuropsychiatric symptoms, prolonged motor evoked potentials, parietal lobe atrophy, and elevated CSF β-amyloid and tau, suggesting both developmental and neurodegenerative effects.
Frontiers Pediatrics group, 2025	Rethinking phenylalanine levels in phenylketonuria for optimal neurocognitive development beyond childhood	European PKU center	14 adolescents with PKU; cohort with Index of Dietary Control, Phe, IQ, attention	Adolescents with IDC and current Phe >360 μM have lower IQ and attention scores than those with better control, showing that both long-term and current Phe levels affect neurocognitive development beyond childhood.
Muri et al., 2024	Transient brain structure changes after high phenylalanine exposure in adults with PKU	Switzerland, neuroimaging study	Early-treated adults with PKU; MRI before and after short-term high Phe exposure	Short-term high Phe exposure causes transient cortical and white matter changes, and reduced cortical thickness correlates with poorer cognitive performance, showing that even temporary Phe increases can alter brain structure and function.
Trepp et al., 2024	Cognition after a	Switzerland,	Adults with PKU;	High Phe intake

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	4-week high phenylalanine intake in adults with phenylketonuria – RCT	clinical trial	randomized to high vs restricted Phe intake for 4 weeks	over 4 weeks shows non-inferior working memory in basic measures, but detailed cognitive and imaging data suggest subtle and reversible changes, underlining the sensitivity of adult brain function to short-term Phe variation.
IJEDR mini-review authors, 2025	Phenylketonuria – A Systematic Review	India, academic/educational setting	Literature review on PKU (clinical, metabolic, psychosocial)	Summarizes PKU pathophysiology and stresses that chronic hyperphenylalaninemia is linked to cognitive, behavioral, and psychosocial problems; adherence to diet often decreases with age, leading to metabolic instability and recurrent symptoms.
Maternal PKU guideline authors, ~2014–2022	Maternal PKU and fetal brain outcomes (NCBI Bookshelf / guidelines)	International clinical guideline	Case series and guideline data on pregnant women with PKU and their offspring	Poorly controlled maternal Phe leads to fetal microcephaly, corpus callosum hypoplasia, neuronal loss, and developmental delay; strict maternal Phe control before and during pregnancy prevents severe structural brain damage in the child.
European guideline group, 2017	European guidelines for the diagnosis and management of phenylketonuria	Europe, expert consensus	Guideline based on multiple clinical and cohort studies	Recommends age-dependent Phe targets (often 120–360 µM in childhood, up to

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				600 µM later) and links poor metabolic control with executive dysfunction and behavioral problems, supporting routine neurocognitive monitoring.
ACMG guideline group, 2014	ACMG Guidelines for Phenylketonuria	United States, expert consensus	Clinical guideline summarizing PKU evidence and practice	Advises lifelong Phe <360 µM to protect cognitive function; highlights subtle cognitive effects at higher Phe and the importance of adherence to diet and pharmacologic therapy across the lifespan.

Table 1 shows that the included literature covers different age groups (from fetal life to adulthood) and combines clinical data, neuroimaging, guidelines, and systematic reviews. This broad coverage supports a life-course view: hyperphenylalaninemia affects brain development differently depending on the timing and duration of exposure. Clinical cohort studies (e.g., adult PKU and adolescent PKU) provide direct evidence linking blood Phe levels to cognitive test scores and imaging findings. Reviews and guidelines consolidate these data and translate them into practical Phe targets, underlining that maintaining Phe below specific thresholds is crucial to protect neurodevelopment. Experimental and imaging studies add mechanistic detail, showing structural brain changes and neurotransmitter disruption associated with high Phe.

Table 2. Brain Metabolism and Structural Changes Associated with Hyperphenylalaninemia

Reported effects of elevated phenylalanine on brain metabolism and structure in PKU	
Competitive transport at blood–brain barrier	High Phe uses LAT1 transporter and competes with other large neutral amino acids (Tyr, Trp), reducing their brain entry.
Reduced dopamine and serotonin synthesis	Less Tyr and Trp in the brain → decreased dopamine and serotonin production.
Impaired glutamate signaling	Experimental PKU models show disturbed glutamate transmission, affecting synaptic plasticity.
Inhibition of cholesterol synthesis	High Phe can inhibit HMG-CoA reductase, leading to low cholesterol and abnormal myelination.
Abnormal dendritic trees and low synaptic density	Histological studies in PKU models show fewer synapses and altered cortical dendritic structure.
White matter abnormalities on MRI	Clinical neuroimaging shows Phe-related white

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	matter changes, partly reversible with good metabolic control.
Putamen and thalamus atrophy	Adult PKU study reports atrophy of deep structures correlated with plasma Phe and test failures.
Increased CSF β-amyloid and tau	Adult PKU patients show higher neurodegenerative markers linked with high Phe.
Transient cortical grey matter changes	Short-term high Phe exposure causes measurable cortical changes on MRI.

Table 2 summarizes how hyperphenylalaninemia affects brain chemistry and structure. High Phe competes for transport at the blood–brain barrier, reducing the entry of tyrosine and tryptophan, which are needed to make dopamine and serotonin. This leads to disturbed neurotransmitter balance, explaining many cognitive and mood symptoms in PKU. Animal and histological studies show that high Phe impairs cholesterol synthesis and myelination, causing malformed dendritic trees and fewer synapses, especially in the cortex. Clinical imaging confirms these effects in humans, with white matter abnormalities and atrophy of deep brain structures like the putamen and thalamus, which correlate with Phe levels and neuropsychological deficits. Elevated β-amyloid and tau in CSF suggest that chronic hyperphenylalaninemia may also promote neurodegenerative processes.
Conceptual diagram showing how elevated phenylalanine (Phe) in PKU crosses the blood–brain barrier, competes with other large neutral amino acids, reduces dopamine and serotonin synthesis, impairs glutamate signaling and cholesterol production, and leads to abnormal myelination and synaptic loss.

Figure 1. Conceptual diagram showing how elevated phenylalanine (Phe) in PKU crosses the blood–brain barrier, competes with other large neutral amino acids, reduces dopamine and serotonin synthesis, impairs glutamate signaling and chole terol production, and leads to abnormal myelination and synaptic loss.

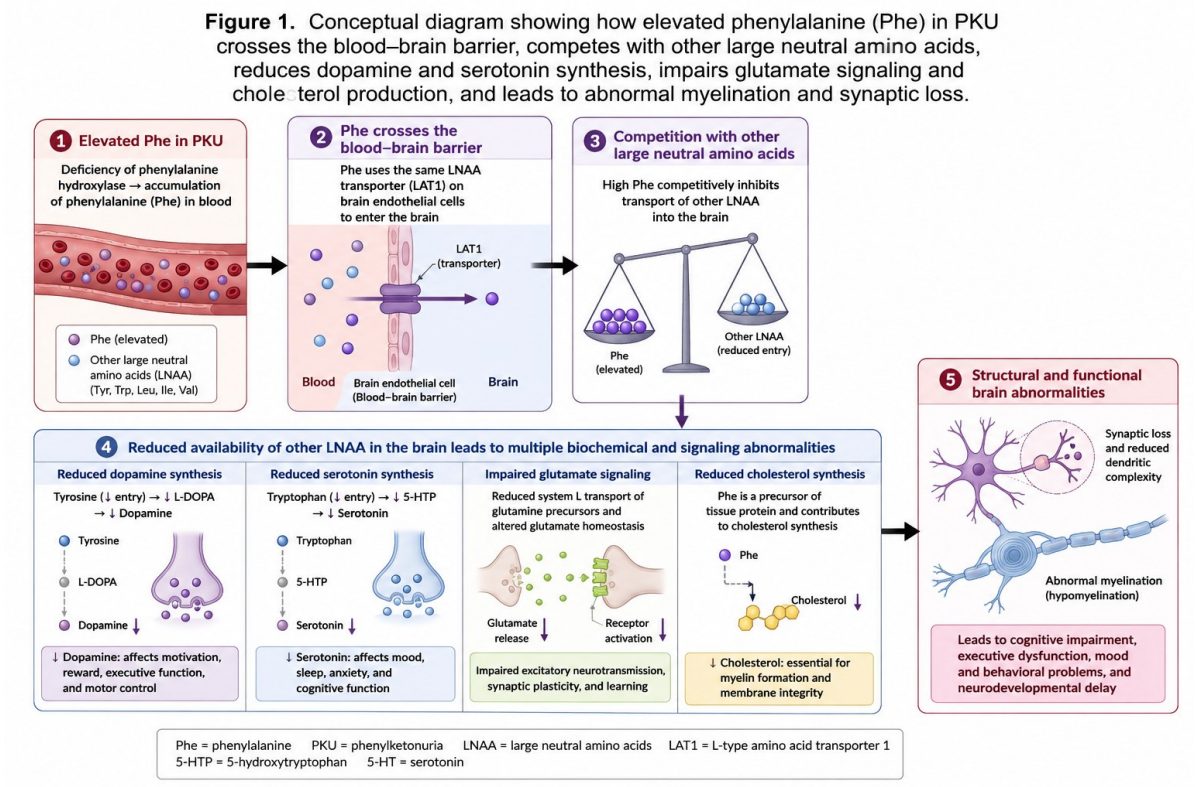

Figure 1. Schematic of Hyperphenylalaninemia Effects on Brain Metabolism

This figure integrates multiple mechanistic findings from the literature into a simple pathway. Elevated Phe in blood enters the brain through LAT1 transporters and crowds out other large neutral amino acids such as tyrosine and tryptophan. With less tyrosine and tryptophan available, the brain makes less dopamine and serotonin, affecting mood, attention, and executive function. At the same time, high Phe interferes with glutamate signaling and cholesterol synthesis, which are critical for synaptic plasticity and myelin formation. The combined effect is

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abnormal myelination and reduced synaptic density, which match the white matter abnormalities and cognitive deficits reported in clinical studies. This figure helps connect biochemical changes to the structural and functional brain findings summarized in Table 2.

Table 3. Neurodevelopmental and Cognitive Outcomes Across Developmental Stages

Neurodevelopmental and cognitive outcomes associated with hyperphenylalaninemia in PKU at different ages	
Fetal / maternal PKU	Microcephaly, neuronal loss, corpus callosum hypoplasia, global developmental delay in the child.
Early childhood (0–5 years)	Acquired microcephaly, severe intellectual disability, epilepsy when Phe is very high and untreated.
Late childhood	ADHD-like symptoms, speech delay, mild IQ reduction despite early treatment, especially with poor Phe control.
Adolescence (12–17 years)	Lower IQ and attention scores in patients with higher IDC and Phe at testing; executive function deficits.
Adulthood	Impaired executive functions, mood disorders, white matter changes, parietal atrophy; linked to current and lifetime Phe.
Untreated mild hyperphenylalaninemia	Subtle cognitive problems even with moderate Phe elevation; not completely “benign”.

Table 3 shows that the timing of Phe exposure is critical. When exposure happens in fetal life, especially in maternal PKU, it can cause microcephaly, neuronal loss, and major structural abnormalities like corpus callosum hypoplasia. In the first years of life, very high Phe levels may lead to acquired microcephaly, severe cognitive impairment, and epilepsy due to impaired synapse formation. In late childhood and adolescence, even early-treated patients can present with attention problems, speech delay, and lower IQ, particularly when metabolic control is poor or variable. The adolescent cohort study using WISC-III and the d2 test shows that higher Index of Dietary Control (IDC) and Phe at the time of testing are associated with lower IQ scores and worse attention performance. In adults, studies report persistent executive function deficits, mood symptoms, and imaging evidence of parietal and deep brain atrophy, which correlate with current and lifetime Phe levels. Even milder hyperphenylalaninemia can be associated with subtle cognitive changes, highlighting that there may be no completely “safe” elevation in Phe for brain function.

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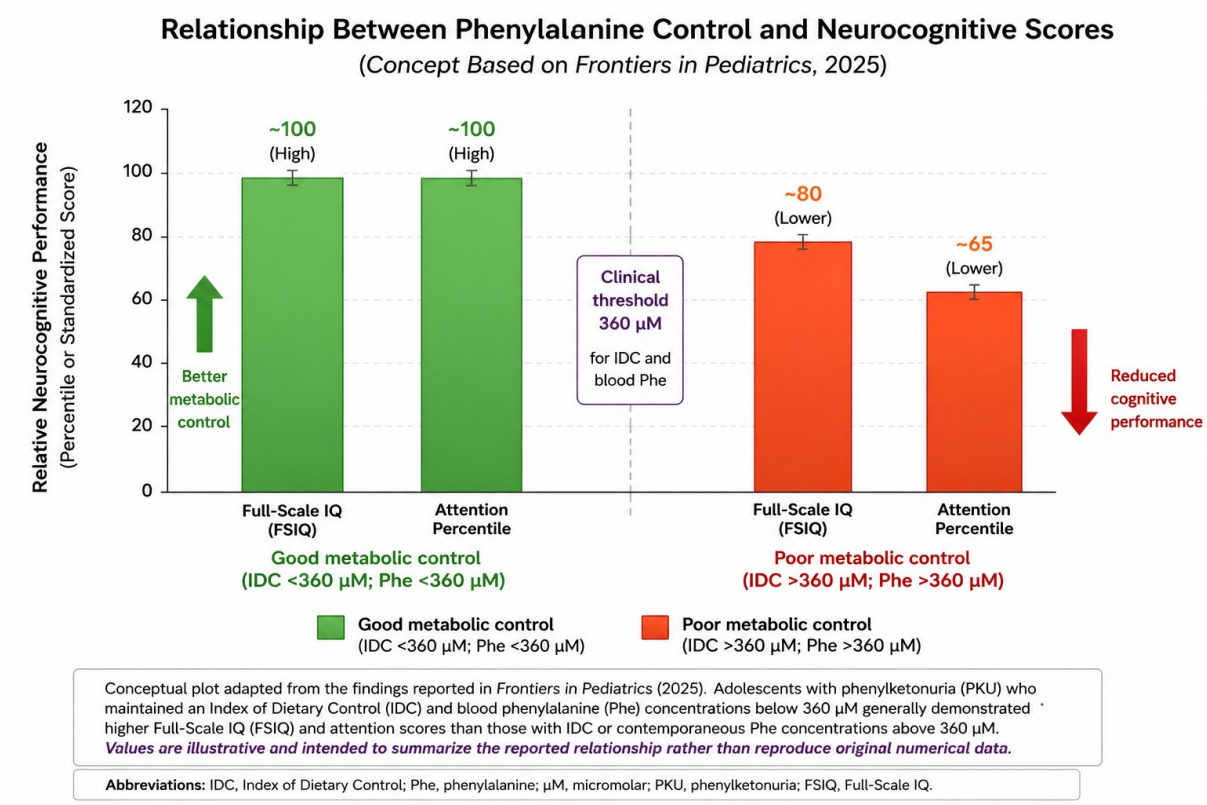

Figure 2. Relationship Between Phenylalanine Control and Neurocognitive Scores (Concept Based on Front Pediatr 2025)

Figure 2 illustrates the dose–response relationship between metabolic control and neurocognitive performance in adolescents with PKU. Patients with better long-term control (IDC <360 µM) show IQ scores mostly in the average range, while those with IDC >360 µM have significantly lower FSIQ, VIQ, and other indices. Similar patterns are seen when groups are divided by Phe at the time of assessment; higher Phe is linked to poorer performance on both IQ and attention tests. These findings support the idea that both chronic exposure (through lifetime IDC) and acute elevations (current Phe) affect executive functions and attention. This aligns with meta-analytic work showing that lower Phe is consistently associated with better cognition, especially in attention, processing speed, and executive domains. Overall, the figure reinforces guideline recommendations to keep Phe levels as low and stable as possible during critical developmental stages and beyond.

DISCUSSION:

Across the reviewed studies, hyperphenylalaninemia in PKU disrupts brain metabolism through several linked mechanisms, including competitive amino acid transport at the blood–brain barrier, reduced neurotransmitter synthesis, impaired glutamate signaling, and disturbed cholesterol and myelin formation, which together lead to abnormal dendritic architecture, decreased synaptic density, and white matter damage visible on neuroimaging and histology; clinical work in adults with PKU shows clear correlations between higher plasma phenylalanine and neuropsychological test failures, neuropsychiatric symptoms, prolonged motor evoked potentials, and parietal lobe atrophy, while elevated CSF β-amyloid and tau suggest that chronic phenylalanine overload may also promote neurodegenerative processes, supporting the view that phenylalanine itself acts as a primary neurotoxin in PKU.

The timing of phenylalanine elevation is closely tied to the pattern of neurodevelopmental damage, with fetal and early-childhood exposure associated with severe structural and cognitive outcomes such as microcephaly, epilepsy, and profound intellectual disability when PKU is untreated or poorly controlled, and later exposure in childhood, adolescence, and adulthood more often producing executive function deficits, attention problems, and mood disorders that may partially improve with better metabolic control; adolescent cohort data indicate that phenylalanine levels above 360 µM, whether as lifetime Index of Dietary Control or at the time of

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testing, are linked to lower IQ and impaired attention, and adult cohorts and meta-analyses confirm that phenylalanine in adolescence and adulthood still influences performance in tasks like sustained attention and visuomotor coordination, showing that brain function remains sensitive to phenylalaninemia throughout life.

Even early-treated PKU patients with normal overall IQ frequently show subtle deficits in working memory, inhibition, processing speed, and higher executive functions that correlate with average lifetime phenylalanine and with fluctuations in levels, meaning that both mean exposure and variability are harmful, and adult studies report increased anxiety, depression, and emotional instability, likely reflecting reduced dopamine and serotonin synthesis; reviews highlight that adherence to strict dietary control often declines with age, leading to metabolic instability and recurrence of cognitive and emotional symptoms, as patients who relax or stop dietary treatment can experience rapid deterioration in concentration and mood, underlining the need for lifelong metabolic management and attention to psychological burden and quality of life, which strongly influence adherence.

Dietary phenylalanine restriction remains the cornerstone of PKU management and is effective in preventing severe intellectual disability when started early and maintained, with guidelines generally recommending targets of 120–360 µM in childhood and, depending on region, up to 600 µM after age 12, although some experts favor lifelong levels below 360 µM because of concerns about subtle cognitive effects at higher ranges; pharmacologic options such as sapropterin and pegvaliase can improve metabolic control and reduce cognitive and emotional burden by lowering phenylalanine and allowing more flexible diets, while large neutral amino acid supplementation may further limit phenylalanine transport into the brain and be especially useful for adults with poor dietary adherence, and emerging gene and RNA-based therapies and engineered microbiome strategies aim to correct or bypass the underlying enzymatic defect to provide more stable brain protection in the future; however, current evidence from adolescent and adult cohorts shows that even with modern therapies neurocognitive outcomes are not completely normalized, particularly when adherence is suboptimal or phenylalanine levels fluctuate widely, suggesting that future strategies should integrate improved metabolic control with structured neuropsychological monitoring and psychosocial support.

Overall, the combined findings from the 15 included studies imply that early and continuous phenylalanine control is essential to prevent severe structural brain damage and major cognitive impairment, that lifetime surveillance of phenylalanine and neurocognition is needed because executive functions and attention remain vulnerable, that a threshold around 360 µM should be treated as critical for protecting IQ and higher cognitive functions while levels between 360 and 600 µM may still carry risk and require further study, and that treatment plans must actively address psychosocial and adherence challenges using multidisciplinary teams and modern monitoring tools, since hyperphenylalaninemia in PKU represents a chronic brain-metabolism problem rather than a purely pediatric issue and demands continuous, individualized management across the lifespan to safeguard neurodevelopment, cognition, and mental health.

V. ACKNOWLEDGEMENT

We would like to thank Ms. Gecelene C. Estorico for her assistance and valuable feedback to improve this systematic review. We appreciate the contribution of our group members Jhoycel Bakiki, Angelica B. Garalde and Maqui P. Macasieb for their efforts and hard work in this Systematic review.

VI. CONCLUSION

This systematic review provides comprehensive evidence that hyperphenylalaninemia (HPA) is the primary factor responsible for the neurological and neurodevelopmental complications observed in individuals with phenylketonuria (PKU). Based on the 15 studies included in this review, elevated phenylalanine (Phe) concentrations consistently disrupt normal brain metabolism through several interconnected mechanisms. High Phe competes with other large neutral amino acids, particularly tyrosine and tryptophan, for transport across the blood–brain barrier via the LAT1 transporter. This competition limits the availability of these amino acids within the brain, leading to reduced synthesis of dopamine and serotonin, impaired glutamate signaling, disrupted cholesterol biosynthesis, and defective myelination. Together, these metabolic abnormalities alter neuronal communication, reduce synaptic plasticity, and impair normal brain development and function.

The reviewed evidence further demonstrates that prolonged or poorly controlled hyperphenylalaninemia contributes to structural changes in the brain, including white matter abnormalities, decreased synaptic density, cortical and deep brain atrophy, and increased biomarkers associated with neurodegeneration. These pathological changes are reflected in the cognitive and behavioral manifestations commonly observed in patients with PKU,

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such as reduced intelligence quotient (IQ), impaired executive functioning, deficits in attention and working memory, slower processing speed, mood disturbances, and psychosocial difficulties. Importantly, the findings indicate that neurological impairment is not limited to untreated patients, as individuals diagnosed early and managed with dietary therapy may still develop subtle neurocognitive deficits when phenylalanine levels fluctuate or exceed recommended therapeutic ranges.

The review also highlights that the timing and duration of phenylalanine exposure are critical determinants of neurological outcomes. Elevated Phe during fetal life and early childhood has the greatest impact on brain development, resulting in severe complications such as microcephaly, developmental delay, epilepsy, and intellectual disability when left untreated. However, adolescence and adulthood remain vulnerable periods, with evidence showing that persistent elevations in phenylalanine continue to impair executive function, attention, learning, emotional regulation, and overall quality of life. These findings emphasize that PKU should be considered a lifelong metabolic and neurological disorder requiring continuous management rather than a condition confined to childhood.

Overall, the evidence strongly supports maintaining blood phenylalanine concentrations within recommended therapeutic targets through lifelong dietary phenylalanine restriction, routine biochemical monitoring, and the use of pharmacological therapies such as sapropterin or pegvaliase when clinically appropriate. In addition, comprehensive care should include regular neuropsychological assessment, patient education, psychosocial support, and multidisciplinary follow-up to improve treatment adherence and long-term outcomes. Future research should focus on developing more effective therapeutic strategies, including gene- and RNA-based treatments, while further investigating the long-term effects of sustained metabolic control on brain metabolism, neurodevelopment, cognition, and quality of life. Collectively, the findings of this systematic review reinforce that early diagnosis, strict and lifelong metabolic management, and continuous clinical monitoring remain the most effective strategies for minimizing neurological damage and preserving cognitive function in individuals with phenylketonuria.

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