Neurocognitive Surveillance in Children With Phenylketonuria: From Phenylalanine Control to Everyday Function

Mervat Abdallah Hesham [1], Khaled Mohamed Salah [1], Hayam Mohamed Elsayed Elgohary [2] , Elham Magdy Hassan [3] , Ahmed Hesham Sedek Refay [1]

1 Department of Pediatrics, Faculty of Medicine, Zagazig University, Zagazig, Egypt

2 Department of Psychiatry, Faculty of Medicine, Zagazig University, Zagazig, Egypt

3 Department of Phoniatrics-Otolaryngology Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding author: **Ahmed Hesham Sedek Refay**

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

ABSTRACT

Background: Early-treated phenylketonuria (PKU) prevents severe intellectual disability, but subtle neurocognitive and psychosocial difficulties can persist. Aim: To review neurocognitive surveillance in children with PKU and its relation to longitudinal metabolic control. Methods: Narrative review of peer-reviewed literature and current guidance. Results: The most consistently vulnerable domains are executive function, attention, processing speed, working memory, and school-related functioning. Mean blood phenylalanine and its variability provide complementary information, although neither predicts an individual child's outcome in isolation. Developmentally timed assessment, dietetic review, school liaison, and mental-health enquiry improve recognition of functionally important difficulties. Conclusion: Pediatric PKU follow-up should integrate serial metabolic data with age-appropriate neurodevelopmental assessment and practical support for families.

Keywords: phenylketonuria; neurocognition; executive function; phenylalanine; pediatric metabolism

INTRODUCTION

Phenylketonuria (PKU) has changed from a cause of profound preventable intellectual disability into a lifelong disorder in which many children reach mainstream education and adult independence. Newborn screening and early phenylalanine (Phe)-lowering treatment are responsible for this transformation. Nevertheless, early treatment does not erase all neurologic vulnerability. Subtle inefficiency in executive function, sustained attention, processing speed, working memory, and emotional regulation may emerge despite an apparently satisfactory global intelligence quotient. A pediatric follow-up programme therefore needs to evaluate the child rather than the Phe value alone. [1,3,4]

AIM OF THE REVIEW

To synthesize evidence on neurocognitive monitoring in childhood PKU and translate it into a practical, developmentally informed follow-up approach.

METHODS

This narrative review was prepared from peer-reviewed articles indexed in PubMed and related biomedical databases, together with contemporary international guidance. Literature addressing phenylalanine hydroxylase deficiency, childhood neurodevelopment, nutrition, pharmacotherapy, genotype-phenotype relationships, and clinical follow-up was prioritized.

THE NEUROBIOLOGICAL BASIS OF RESIDUAL VULNERABILITY

Phe is transported across the blood-brain barrier by the large neutral amino-acid transporter. When circulating concentrations are high, Phe competes with tyrosine and tryptophan and may reduce cerebral availability of

precursors needed for dopamine and serotonin synthesis. High cerebral Phe may also interfere with protein synthesis, myelin maintenance, and energy-dependent neuronal processes. These mechanisms offer a biologically coherent explanation for why frontostriatal functions can be affected even when major neurologic disability has been prevented. [3,15,18]

Neuroimaging and neuropsychological studies support this model but should not be interpreted as proof that every individual deficit is caused by a single contemporaneous Phe result. White-matter changes have been described in early-treated PKU, while altered prefrontal connectivity may relate to tasks requiring planning, inhibition, and working-memory updating. The functional significance differs among patients; structural findings and cognitive scores are not interchangeable clinical endpoints. [15,16,17]

The developmental timing of exposure matters. Infancy and early childhood are periods of rapid synaptogenesis and myelination, whereas school years and adolescence place increasing demands on speed, organization, flexible thinking, and independent treatment behaviour. A child may therefore appear clinically well in early life and encounter difficulties only when academic and self-management demands increase. [1,4,25]

WHAT EARLY TREATMENT ACHIEVES - AND WHAT IT DOES NOT

Prompt treatment after newborn screening prevents the classical untreated phenotype of severe intellectual disability, epilepsy, microcephaly, and major behavioural disturbance. This benefit is unequivocal and is the central public-health justification for newborn screening. In treated cohorts, however, mean group IQ may lie within the normal range while distributional analyses still identify a greater proportion of children with low-average performance or specific domain weaknesses than among peers. [2,3,12]

Global IQ is useful but incomplete. A child can obtain an average composite score while taking longer to complete work, losing track of multistep instructions, or struggling with tasks that require rapid switching between rules. Such difficulties are especially relevant to classroom functioning and may be missed by a brief clinic encounter. The systematic review of early and continuously treated children consistently identified executive functions, attention, and processing speed as domains deserving targeted assessment. [4,6]

Interpretation must remain cautious because neurocognitive studies vary in age, test instruments, target Phe ranges, and handling of social and educational confounders. Associations are often stronger at group level than in an individual child. A low score should trigger a broad assessment of learning opportunity, sleep, mood, sensory function, developmental conditions, and metabolic history rather than an automatic attribution to PKU alone. [4,10,14]

MEAN PHE, VARIABILITY, AND THE METABOLIC HISTORY

The relation between Phe exposure and cognition is best understood as cumulative rather than episodic. Meta-analytic evidence has shown an inverse relation between blood Phe and IQ in early-treated PKU, particularly during childhood. The observed effect sizes do not allow clinicians to predict one child's score from one laboratory value, but they reinforce the rationale for maintaining concentrations within the age-appropriate treatment range over time. [5,12]

Variability is a complementary marker. Wide oscillations can occur when natural protein intake, medical foods, illness, growth, or adherence are inconsistent. Earlier work associated instability of Phe with cognitive outcome, and newer longitudinal data continue to examine fluctuation alongside average exposure. Serial home dried-blood-spot results, interpreted with diet and treatment context, are more informative than isolated outpatient values. [7,8,9]

The Phe:tyrosine relationship may offer additional metabolic context because tyrosine becomes conditionally limited in PAH deficiency. It should not be used as a stand-alone cognitive biomarker. Instead, an elevated Phe result should prompt a practical review of prescribed protein substitute, timing of intake, natural protein distribution, access to low-protein foods, intercurrent illness, and barriers reported by the family. [1,22]

A DEVELOPMENTALLY INFORMED SURVEILLANCE MODEL

Follow-up should be organized around developmental transitions. During infancy, surveillance emphasizes treatment initiation, feeding, growth, parental capability, and early developmental milestones. In preschool years, language, adaptive behaviour, emerging attention, and school readiness become increasingly informative. School-aged children require particular attention to reading, mathematics, organization, processing speed, peer participation, and fatigue, whereas adolescence requires assessment of executive self-management and emotional wellbeing. [1,2]

Routine developmental surveillance is not equivalent to repeated full psychometry for every child at every visit. The intensity of formal testing should be guided by age, previous results, metabolic history, school concerns, and family observations. A planned baseline before school entry, reassessment during major educational transitions, and earlier referral when functional concerns arise is more defensible than either neglecting cognition or testing indiscriminately. [1,4]

Reports from teachers and parents add essential ecological information. Difficulties with homework duration, initiation, completion, time awareness, handwriting speed, or coping with simultaneous instructions may be clinically meaningful even if a standard IQ score remains average. The clinician should ask targeted functional questions and obtain school information with family consent. [4,11]

CHOOSING AND INTERPRETING COGNITIVE MEASURES

A broad cognitive test provides a useful framework but should be supplemented when indicated. Measures of working memory, processing speed, sustained attention, executive function, academic attainment, adaptive behaviour, and emotional symptoms answer different clinical questions. Test selection should be age appropriate, culturally and linguistically valid, and administered by clinicians experienced in pediatric neurodevelopment. [4,20]

Serial scores need contextual interpretation. Small numerical differences can reflect practice effects, fatigue, motivation, test version, language, or measurement error. A clinically important decline is more persuasive when it is consistent across domains or accompanied by school and family reports. Conversely, a stable score should not be interpreted as evidence that treatment burden or mental-health needs are absent. [4,24]

The goal is not to label every difference as impairment. Neurocognitive assessment should identify modifiable supports: classroom accommodations, reduced time pressure, organizational coaching, neuropsychology referral, speech and language support, or treatment adjustments that make metabolic control more achievable. [1,4]

DIET, NUTRITION, AND COGNITIVE HEALTH

Dietary therapy remains central to pediatric PKU. Restriction of natural protein is coupled with Phe-free or low-Phe protein substitutes, low-protein foods, and individualized Phe prescription. Adequacy of total protein, energy, vitamins, minerals, essential fatty acids, and micronutrients is relevant to normal growth and development. Restriction without robust nutritional replacement is not an acceptable form of metabolic management. [1,22]

Adherence is not simply a matter of family motivation. Taste and convenience of protein substitutes, food availability, school routines, family finances, social eating, and adolescent autonomy all shape the daily feasibility of treatment. Prospective dietary work shows that prescribed special low-protein foods and medical nutrition products make material contributions to energy and macronutrient intake. [22,23]

Dietetic review should therefore explore the pattern of treatment rather than only a calculated allowance. Missed or poorly distributed protein substitute, unplanned fasting, restrictive eating, excessive reliance on low-quality discretionary foods, and conflict around meals can each affect metabolic control and wellbeing. Collaborative problem-solving is more likely to sustain care than blame. [1,23]

PHARMACOLOGIC AND ADJUNCTIVE OPTIONS

For patients with demonstrated responsiveness, sapropterin can increase residual PAH activity and may improve Phe tolerance or lower blood Phe. Its cognitive value is mediated primarily through improved metabolic control and possibly through reducing the burden of diet. Response must be documented with a structured trial and ongoing biochemical monitoring; a prescription alone is not evidence of benefit. [1,2]

A pediatric study reported improvement in caregiver-rated attention and executive-function symptoms after sapropterin in responsive children and adolescents, but these findings should be interpreted with the limits of observational symptom measures. Treatment selection remains individualized, combining biochemical response, dietary impact, tolerability, adherence, and family priorities. [21]

Newer enzyme-substitution therapy has transformed management for some adults with difficult control, but current experience and regulatory indications are largely adult-focused. Pediatric teams should remain aware of evolving options while avoiding premature extrapolation of adult protocols to children. [2,22]

MENTAL HEALTH, FAMILY LIFE, AND ADOLESCENCE

Cognition, behaviour, and mental health overlap. Anxiety, low mood, irritability, and perceived stigma can reduce attention and executive efficiency, while executive difficulties can undermine dietary routines and increase family conflict. Psychiatric symptoms have been described across the PKU lifespan, supporting routine but sensitive inquiry rather than referral only after a crisis. [18,19]

Adolescence is a predictable period of risk because responsibility shifts from parent to patient while peer influences and academic demands increase. Transition planning should start early, teach the meaning of laboratory results and treatment choices, and include the family in a gradual transfer of tasks. It should also prepare girls for lifelong metabolic care before pregnancy, while maintaining equivalent support for boys and young men. [1,25]

Families benefit from a consistent multidisciplinary team including a metabolic pediatrician, dietitian, psychologist or neuropsychologist when required, social support, and links to school. This model treats neurocognitive health as a shared outcome of biochemical, nutritional, educational, and psychosocial care. [1,2]

PRACTICAL CLINICAL RESPONSE TO A CONCERN

When a child with PKU develops declining academic performance or new behavioural concerns, the first step is to define the problem precisely: onset, setting, functional impact, developmental history, and the child's own explanation. The second is to review longitudinal Phe data and diet records rather than focusing only on the latest sample. A nutrition review, screening for mood and sleep problems, hearing or vision difficulties, and liaison with school often identify several actionable contributors. [1,4]

If concerns persist, formal neuropsychological assessment should generate practical recommendations rather than merely a diagnostic label. The metabolic plan can then be refined alongside educational support. Repeating assessment after intervention can be useful when the same tools and adequate interval are used, but clinical function remains the most meaningful outcome. [4,20]

This approach avoids two errors: dismissing concerns because the child was diagnosed early, and overinterpreting every school difficulty as direct evidence of Phe toxicity. Both errors reduce the chance of timely, helpful care. [4,14]

PROCESSING SPEED AND ATTENTION

Processing speed is one of the most reproducible areas of weakness in early-treated PKU. It affects the amount of time needed to read, write, copy information, complete calculations, and respond under classroom time limits. A child may understand the lesson but still appear inattentive or underachieving when tasks are rapid. This distinction is important because support such as extended time, written instructions, and reduced copying demands may be

more helpful than repeating content alone. [29,31]

Attention in PKU should be assessed clinically before it is labelled as attention-deficit/hyperactivity disorder. Inattention can reflect executive inefficiency, anxiety, sleep disturbance, learning problems, treatment burden, or a separate neurodevelopmental condition. A structured history across home and school, together with formal assessment when needed, avoids both under-recognition and inappropriate diagnostic certainty. [32,33]

SCHOOL PARTICIPATION AND LEARNING

School performance is a functional outcome that families readily recognize. Review should include attendance, homework duration, need for supervision, reading fluency, mathematics, written output, and teacher concerns. Comparing a child only with a population IQ average can miss the gap between potential and day-to-day performance. Early dialogue with educators allows modest accommodations to be introduced before repeated failure affects confidence. [30,34]

Educational support is not a sign that metabolic treatment has failed. It is a parallel component of comprehensive care. A written neuropsychology recommendation can specify practical measures such as shorter task blocks, checking understanding of multistep instructions, organizational aids, and alternative ways to demonstrate learning. The family should remain central to decisions about disclosure of PKU at school. [4,32]

INFLAMMATION, ILLNESS, AND CATABOLISM

Intercurrent illness, fever, poor intake, vomiting, and fasting may increase blood Phe through catabolism. Families need a simple sick-day plan that emphasizes continued protein substitute when tolerated, sufficient energy and fluids, early contact with the metabolic team, and appropriate monitoring. Recurrent illness-related excursions should not be interpreted as ordinary non-adherence; they require anticipatory planning. [1,50]

The clinical team should also examine whether difficult Phe control follows recognizable patterns such as school holidays, travel, supply interruption, growth spurts, or family stress. A short timeline that combines Phe results, diet changes, and life events often converts an apparently unexplained laboratory pattern into a solvable problem. [1,46]

GROWTH, BODY COMPOSITION, AND BONE HEALTH

Normal linear growth and appropriate weight gain are basic markers that the nutritional prescription is sufficient, but they do not capture all nutritional risk. Highly restricted food choices, low physical activity, and reliance on processed low-protein products can influence diet quality. Regular anthropometry and dietetic review should be routine, with laboratory evaluation guided by the clinical picture and local standards. [22,40]

Bone health has received attention in PKU, although the mechanisms are multifactorial and evidence is heterogeneous. Adequate protein substitute, micronutrient intake, vitamin D status when indicated, weight-bearing activity, and attention to puberty are sensible components of pediatric follow-up. This wider health view prevents neurocognitive care from becoming disconnected from general child health. [44,45]

HOW TO SUPPORT ADHERENCE

Adherence improves when families are invited to describe the barriers they actually face. Common issues include late delivery of medical foods, dislike of a product, competing school routines, financial pressure, limited kitchen time, and adolescent reluctance to appear different. Non-judgmental questions lead to more accurate information and make it possible to agree on one or two realistic changes before the next visit. [46,47]

The best plan is often the simplest plan that preserves metabolic safety. Written schedules, pre-measured portions, school letters, telehealth contact, and peer support can reduce daily workload. Adherence should be considered a property of the treatment system as well as of the individual child. [1,47]

LIFELONG PERSPECTIVE

Childhood follow-up should prepare families for the fact that PKU treatment continues through adult life. Adult studies show that cognitive and psychiatric symptoms may become more evident after years of relaxed control, while some patients report benefit after re-engaging with treatment. These findings strengthen the case for supportive transition rather than a message that childhood success means cure. [14,43,49]

EARLY YEARS: BUILDING A SAFE DEVELOPMENTAL BASE

The first years of life are the period in which the family learns to turn a biochemical prescription into ordinary daily care. Parents need repeated demonstration of blood-spot collection, formula preparation, protein-substitute timing, food introduction, and action during illness. Information is best given in small practical steps, because a new diagnosis can overwhelm even highly engaged caregivers. Regular contact also allows the team to detect feeding problems, parental distress, and supply interruptions before they affect metabolic control. [1]

Developmental review in infancy should include motor progress, early communication, social reciprocity, feeding skills, sleep, and family interaction. These domains are not measured by Phe alone. When a concern is identified, early-intervention referral should be made promptly; waiting for a formal school-age cognitive test loses valuable developmental time. A child can receive developmental support while metabolic assessment continues in parallel. [2]

LANGUAGE, COMMUNICATION, AND SOCIAL FUNCTION

Language is a central route to learning and self-regulation. A child with limited vocabulary, reduced verbal fluency, or difficulty following complex sentences may later appear inattentive in the classroom. Screening language at routine developmental stages and listening carefully to parental concern are simple clinical practices. Where the home language differs from the assessment language, interpretation should involve professionals familiar with bilingual development. [4]

Social difficulties should be explored with the same care as test scores. Children may avoid shared meals, worry about being different, or become reluctant to explain their diet to friends and teachers. These experiences can affect confidence, participation, and adherence. Peer-support opportunities and age-appropriate education can make the condition more manageable without making it the child's entire identity. [18]

THE CLINICAL VALUE OF LONGITUDINAL RECORDS

A useful PKU record shows trends clearly: dates and values of Phe and tyrosine, prescribed and reported natural protein, protein-substitute type and dose, illness episodes, treatment changes, growth, and key developmental or school events. The purpose is not surveillance for blame. It is to allow the family and clinician to identify the most likely explanation for a change and judge whether an intervention has worked. [1]

Graphing values can be particularly helpful for adolescents. It makes the relation between routines and results visible and supports shared decision-making. However, numbers should be discussed in a calm, non-punitive way. A result outside target is clinical information, not a moral judgement, and should lead to curiosity about causes and support needs. [46]

SLEEP, FATIGUE, AND DAILY PERFORMANCE

Fatigue can magnify executive and attention difficulties. Sleep duration, sleep timing, snoring, restless sleep, caffeine use in adolescents, and screen use should be part of a broad review when school performance falls. These factors are common in all children and can coexist with PKU-related neurocognitive vulnerability. Addressing them may improve function even when Phe control is unchanged. [4]

Similarly, headaches, gastrointestinal symptoms, restrictive eating, and low activity can interfere with concentration

and adherence. The pediatric metabolic visit should retain the breadth of general pediatrics. A child with PKU still needs assessment of ordinary conditions rather than every new symptom being attributed to metabolism. [1]

COMMUNICATING RISK WITHOUT FEAR

Families deserve honest explanation that good treatment reduces risk substantially but cannot guarantee identical outcomes in every child. Overstating risk may create anxiety and treatment conflict; understating it may reduce engagement with follow-up. The most helpful language explains what the team can monitor, what actions are available, and why long-term consistency is worthwhile. [1]

Children should receive gradually increasing information about PKU in terms they can understand. Explaining why they take protein substitute, why blood spots are needed, and how to ask for help at school supports autonomy. Education should be revisited as the child matures rather than delivered once at diagnosis. [25]

INTEGRATING THE EVIDENCE INTO PRACTICE

No single cognitive task, metabolic index, or treatment decision defines the outcome of childhood PKU. The strongest practical approach combines early and sustained Phe control, adequate nutrition, developmental surveillance, targeted formal assessment, and attention to family feasibility. This integrated model reflects the evidence better than a narrow focus on a single clinic laboratory value. [1]

The outcome that matters most is whether the child can learn, participate, develop relationships, and move toward independent self-care. Clinical teams should make space for these questions at every stage of follow-up. Doing so preserves the major success of newborn screening while responding to the less visible challenges that remain. [2]

FAMILY-CENTRED DECISION MAKING

Treatment targets are important, but the route used to achieve them should be agreed with the family. At each visit, the clinician can ask which part of care is hardest now, what has worked since the last visit, and what one change would make the next month easier. This approach respects the family's expertise in daily care and produces plans that are more likely to be followed. It also allows the team to identify when a seemingly minor obstacle, such as school access to a protein substitute or a delayed delivery, is having a major effect on control. [1]

Shared decision making is especially useful when the child becomes old enough to express preferences about food, sampling, medication, and disclosure. The child should be included progressively, with information matched to developmental level. Parents remain essential partners, but the aim is to build skills and confidence rather than create a sudden handover at adolescence. [25]

QUALITY IMPROVEMENT IN THE METABOLIC CLINIC

Metabolic services can improve neurocognitive care by using simple standard processes: recording developmental and school concerns at visits, reviewing Phe trends in a consistent format, documenting dietetic barriers, and specifying who follows up an abnormal result. These steps make it less likely that a functional concern is lost between laboratory review and the next clinic appointment. [1]

Audit can focus on practical indicators such as time from newborn-screen result to treatment, frequency of completed blood monitoring, access to dietetic review, and timely referral for developmental assessment. Such measures do not replace clinical judgement, but they show whether the service is delivering the basic conditions required for good outcomes. [2]

INTERPRETING NEW EVIDENCE

Families may encounter online claims that a single supplement, diet pattern, or technology will remove the need for established treatment. Clinicians should welcome questions while explaining the difference between a plausible

mechanism, a small uncontrolled study, and evidence sufficient to change pediatric practice. This protects children from restrictive or costly interventions that may add burden without benefit. [2]

At the same time, clinicians should avoid therapeutic pessimism. New pharmacologic, nutritional, and digital-support options may offer meaningful benefit for selected patients. The appropriate response is careful evaluation, transparent discussion of uncertainty, and continued monitoring of biochemical and functional outcomes. [21]

CLINICAL TAKE-HOME MESSAGE

The best evidence supports a broad view of outcome in PKU. Blood Phe remains a central treatment marker because it reflects exposure that is relevant to brain health. Yet it is only one part of the child's story. Learning, attention, mental health, nutrition, family functioning, and participation in ordinary childhood activities all deserve routine clinical attention. [1]

A child whose Phe results are within range can still need help; a child whose results are frequently high may still have strengths that should guide support. This balanced approach avoids reducing a complex developing child to a laboratory result and keeps follow-up focused on the real purpose of treatment: the best possible life course. [4]

RESEARCH PRIORITIES

Future pediatric studies should use common definitions of metabolic exposure, include repeated measures of functioning, and report social and educational context. Larger prospective cohorts are needed to clarify which patterns of Phe variability matter most and whether improved biochemical control produces measurable functional benefit in particular subgroups. Digital cognitive tasks and patient-reported outcomes may eventually complement, but should not replace, validated clinician-administered assessment. [4,9,28]

CONCLUSION

Early diagnosis and sustained specialist follow-up remain the foundation of care. The most useful pediatric strategy is proactive, individualized, and family-centred: it connects biochemical monitoring with age-appropriate developmental assessment, dietetic expertise, treatment selection, and timely support at periods when adherence or neurocognitive demands change.

REFERENCES

1. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12:162.
2. Smith WE, Berry SA, et al. A 2023 evidence-based clinical guideline of the American College of Medical Genetics and Genomics for the diagnosis and management of phenylalanine hydroxylase deficiency. Genet Med. 2025;27(1):101303.
3. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010;376(9750):1417-1427.
4. Canton M, Le Gall D, Feillet F, Bonnemains C, Roy A. Neuropsychological profile of children with early and continuously treated phenylketonuria: a systematic review and future approaches. J Int Neuropsychol Soc. 2019;25(6):624-643.
5. Fonnesbeck CJ, McPheeters ML, Krishnaswami S, Lindegren ML, Reimschisel T. Estimating the probability of IQ impairment from blood phenylalanine for phenylketonuria patients: a hierarchical meta-analysis. J Inherit Metab Dis. 2013;36(5):757-766.
6. Albrecht J, Garbade SF, Burgard P. Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: a meta-analysis. Neurosci Biobehav Rev. 2009;33(3):414-421.
7. Anastasoaie V, Kurzius L, Forbes P, Waisbren S. Stability of blood phenylalanine levels and IQ in children with phenylketonuria. Mol Genet Metab. 2008;95(1-2):17-20.
8. Hood A, Grange DK, Christ SE, et al. Variability in phenylalanine control predicts IQ and executive abilities in children with phenylketonuria. Mol Genet Metab. 2014;111(4):445-451.
9. Feldmann R, Och U, Beckmann LS, Weglage J, Rutsch F. Children and adolescents with early treated phenylketonuria: cognitive development and fluctuations of blood phenylalanine levels. Int J Environ Res Public Health. 2024;21(4):431.
10. de la Parra A, Garcia MI, Waisbren SE, Cornejo V, Raimann E. Cognitive functioning in mild hyperphenylalaninemia. Mol Genet Metab Rep. 2015;5:72-75.
11. Gassio R, Artuch R, Vilaseca MA, et al. Cognitive functions in classical phenylketonuria and mild hyperphenylalaninemia: experience in a paediatric population. Dev Med Child Neurol. 2005;47(7):443-448.
12. Waisbren SE, Noel K, Fahrbach K, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab. 2007;92(1-2):63-70.
13. Koch R, Burton B, Hoganson G, et al. Phenylketonuria in adulthood: a collaborative study. J Inherit Metab Dis. 2002;25(5):333-346.
14. Palermo L, Geberhiwot T, MacDonald A, et al. Cognitive outcomes in early-treated adults with phenylketonuria: a systematic review. J Inherit Metab Dis. 2017;40(1):3-13.
15. Christ SE, Moffitt AJ, Peck D. Disruption of prefrontal function and connectivity in individuals with phenylketonuria. Mol Genet Metab. 2010;99 Suppl 1:S33-S40.
16. Christ SE, Price MH, Bodner KE, Saville C, Moffitt AJ, Peck D. Morphometric analysis of gray matter integrity in individuals with early-treated phenylketonuria. Mol Genet Metab. 2016;118(1):3-8.

17. Clocksin HE, Hawks ZW, White DA, Christ SE. Inter- and intra-tract analysis of white matter abnormalities in individuals with early-treated phenylketonuria. Mol Genet Metab. 2021;132(1):11-18.
18. Ashe K, Kelso W, Farrand S, et al. Psychiatric and cognitive aspects of phenylketonuria: the limitations of diet and the promise of new treatments. Front Psychiatry. 2019;10:561.
19. Bilder DA, Burton BK, Coon H, et al. Psychiatric symptoms in adults with phenylketonuria. Mol Genet Metab. 2013;108(3):155-160.
20. Duarte CMDA, Piazzon FB, Rocco IS, Mello CBD. Influence of blood phenylalanine level variations on the development of executive functions and social cognition in children with phenylketonuria. J Pediatr (Rio J). 2023;99(5):507-513.
21. Grant ML, Dorenbaum A, Chen E, et al. Neuropsychiatric function improvement in pediatric phenylketonuria after sapropterin treatment. Mol Genet Metab. 2023;139(2):107569.
22. MacDonald A, van Wegberg AMJ, Ahring K, et al. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis. 2020;15:171.
23. Daly A, Evans S, Pinto A, Ashmore C, Rocha JC, MacDonald A. A 3-year longitudinal prospective review examining dietary profile in children with phenylketonuria. Nutrients. 2020;12(10):3153.
24. Cazzorla C, Ceglie G, Leuzzi V, et al. Predictors of intellectual functioning in children with phenylketonuria. Neuropsychology. 2014;28(1):67-77.
25. van Spronsen FJ, van Wegberg AMJ, Ahring K, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017;5(9):743-756.
26. Weglage J, Pietsch M, Feldmann R, et al. Normal clinical outcome in patients with classical phenylketonuria and strict dietary treatment. J Pediatr. 1999;134(6):699-705.
27. Jahja R, van Spronsen FJ, de Sonneville LMJ, et al. Long-term follow-up of cognition and mental health in adult phenylketonuria: a PKU-COBESO study. Behav Genet. 2017;47(5):486-497.
28. Cámara B, Florindo C, de Lima CB, et al. Rethinking phenylalanine levels in phenylketonuria for optimal neurocognitive development beyond childhood. Front Pediatr. 2025;13:1488809.
29. Burgard P. Development of intelligence in early treated phenylketonuria. Eur J Pediatr. 2000;159 Suppl 2:S74-S79.
30. Burgard P, Bremer HJ, Buhrdel P, et al. Rationale for the German recommendations for phenylalanine level control in phenylketonuria 1997. Eur J Pediatr. 1999;158(1):46-54.
31. White DA, Nortz MJ, Mandernach T, Huntington K, Steiner RD. Age-related working memory impairments in children with classical phenylketonuria. J Int Neuropsychol Soc. 2002;8(1):1-11.
32. Huijbregts SCJ, de Sonneville LMJ, Licht R, Sergeant JA, van Spronsen FJ. Inhibition of prepotent responding and attentional flexibility in treated phenylketonuria. Dev Neuropsychol. 2002;22(2):481-499.
33. Antshel KM. ADHD, learning, and academic performance in phenylketonuria. Mol Genet Metab. 2010;99 Suppl 1:S52-S58.
34. Waisbren SE, Hanley W, Levy HL, et al. Outcome at age 4 years in a worldwide collaborative study of children treated for phenylketonuria. JAMA. 1988;259(19):2861-2866.
35. Koch R, Azen C, Friedman EG, Fishler K. Paired comparisons between early treated PKU children and their matched sibling controls on intelligence and school achievement test results at eight years of age. J Inherit Metab Dis. 1984;7(2):86-90.
36. Weglage J, Ullrich K, Pietsch M, et al. Neuropsychological performance and plasma phenylalanine concentrations in treated phenylketonuria patients. Pediatrics. 1997;100(6):E3.
37. Moyle JJ, Fox AM, Arthur M, Bynevelt M, Burnett JR. Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. Neuropsychol Rev. 2007;17(2):91-101.
38. Kemper AR, Brosco JP, Comeau AM, et al. Newborn screening for phenylketonuria: a systematic review of outcomes and evidence. Pediatrics. 2018;141(Suppl 1):S32-S39.
39. Gropper SS, Acosta PB. Effect of simultaneous ingestion of L-amino acids and whole protein on plasma amino acid and growth in phenylketonuria. J Am Coll Nutr. 1991;10(6):528-536.
40. MacLeod EL, Ney DM. Nutritional management of phenylketonuria. Ann Nestle Eng. 2010;68(2):58-69.
41. Rohr FJ, Munier AW, Sullivan DK, et al. The resource mothers study of children with phenylketonuria: influence on feeding and development. Mol Genet Metab. 2005;86 Suppl 1:S59-S65.
42. Jahja R, Huijbregts SCJ, de Sonneville LMJ, et al. Cognitive profile and mental health in adult phenylketonuria: a PKU-COBESO study. Neuropsychology. 2017;31(4):437-447.
43. Trefz FK, van Spronsen FJ, MacDonald A, et al. Management of adult patients with phenylketonuria: a European perspective. Mol Genet Metab. 2019;127(1):1-6.
44. Modan-Moses D, Vered I, Schwartz G, et al. Peak bone mass in patients with phenylketonuria. J Inherit Metab Dis. 2007;30(2):202-208.
45. Demirdas S, Coakley KE, Bisschop PH, et al. Bone health in phenylketonuria: a systematic review and meta-analysis. Orphanet J Rare Dis. 2015;10:17.
46. Jurecki E, Cederbaum S, Kopesky J, et al. Adherence to clinic recommendations among patients with phenylketonuria in the United States. Mol Genet Metab. 2017;120(3):190-197.
47. Bosch AM, Burlina A, Cunningham A, et al. Assessment and management of phenylalanine hydroxylase deficiency in children. Mol Genet Metab. 2021;132(2):89-100.
48. van Vliet D, van Wegberg AMJ, Ahring K, et al. Can untreated PKU patients escape from intellectual disability? A systematic review. Orphanet J Rare Dis. 2018;13:149.
49. Gassio R, Campistol J, Vilaseca MA, Lambruschini N, Cambra FJ, Fuste E. Do adult patients with phenylketonuria improve their cognitive function after restarting a low-phenylalanine diet? Acta Paediatr. 2003;92(12):1474-1476.
50. Moseley KD, Koch R, Moser AB. Lipid status and long-chain polyunsaturated fatty acids in treated phenylketonuria. J Inherit Metab Dis. 2002;25(1):56-64.