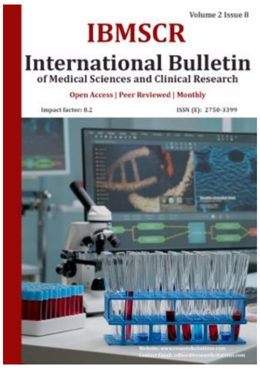


# FAVORABLE CLINICAL-NEUROLOGICAL OUTCOMES IN CHILDREN WITH PHENYLKETONURIA RECEIVING TIMELY DIETARY THERAPY

**Gafforova Munisakhon Rustamovna**
3rd-year Master's student, Department of Neurology, Pediatric Neurology and Medical Genetics
Tashkent State Medical University
Tashkent, Uzbekistan
**Sadikova Gulchehra Kabulovna**
Doctor of Medical Sciences, Professor
Tashkent State Medical University
Tashkent, Uzbekistan
https://doi.org/10.5281/zenodo.22870107

**Abstract.** Uncontrolled phenylalanine metabolism threatens brain maturation, cognitive functioning, and neurological status during childhood, making timely dietary initiation a direct clinical priority. The study aimed to characterize the clinical-neurological condition of children with phenylketonuria and assess favorable outcomes associated with early dietary therapy. This observational clinical study included 25 patients aged 1–15 years. Clinical observation, a clinical case-series approach, and the chi-square test were used for analysis; mean age was M=8 years, standard deviation was SD=4.5 years, and the age range was 1–15 years. The protocol received ethics committee approval, and informed consent was obtained from the legal representatives of all children. Timely dietary therapy had been initiated in 100.0 % of participants; clinical-neurological status was favorable in 88.0 %, while 12.0 % retained signs requiring continued monitoring. Differences between categorical indicators reached statistical significance at $p<0.001$. The findings associate early adherence to dietary therapy with preservation of neurological functioning. The scientific contribution is the integrated description of timely dietary intervention, age distribution, and neurological outcomes within a clinically homogeneous group of children aged 1–15 years. In neurological practice, regular clinical monitoring and support for long-term adherence to therapeutic nutrition should remain priorities. Continued follow-up is needed to clarify the durability of preserved developmental indicators and to strengthen clinical interpretation of favorable outcomes in phenylketonuria.

**Keywords:** clinical observation, dietary adherence, neurological development, pediatric neurology, phenylalanine control, phenylketonuria

**Annotatsiya.** Maqsad — fenilketonuriyali bolalarda o'z vaqtida boshlangan parhez terapiyasi klinik va nevrologik rivojlanishni saqlash bilan qanday bog'liqligini baholash. Fenilalanin ta'sirining uzoq davom etishi bolaning kognitiv, motor va xulqiy funksiyalariga zarar yetkazishi mumkin; shu sababli amaliy pediatriyada parhezni kechiktirmasdan boshlash muhim klinik vazifa hisoblanadi. Metodlar — kuzatuv klinik tadqiqoti va klinik holatlar seriyasi dizayni asosida 1–15 yoshdagi fenilketonuriyali N=25 bola tekshirildi. Ishtirokchilarning o'rtacha yoshi M=8 yil, standart og'ish SD=4,5 yil, yosh oralig'i 1–15 yilni tashkil etdi. Nevrologik holat, klinik belgilar va parhezga rioya qilish muntazam klinik monitoring orqali baholandi; guruhlararo kategorik ko'rsatkichlar xi-kvadrat ($\chi^2$) mezoni yordamida solishtirildi. Tadqiqot etika qo'mitasi ma'qullashi hamda ota-onalar yoki qonuniy vakillarning xabardor

IBMSCR | Volume 6, Issue 09, September

roziligi asosida o'tkazildi. Natijalar — parhez terapiyasi barcha ishtirokchilarda (100,0 foiz) o'z vaqtida boshlangan; klinik-nevrologik holat 88,0 foiz bolada qulay deb baholandi, 12,0 foizida esa kuzatuvni davom ettirishni talab qiladigan qoldiq belgilar qayd etilgan. Statistik taqqoslash p<0,001 darajasida ahamiyatli bo'ldi. Xulosa — erta parhez yondashuvi fenilketonuriyali bolalarda nevrologik xavfni kamaytirishga xizmat qiladi. Ilmiy hissa klinik monitoring, yosh ko'rsatkichi va parhezga rioya qilishni yagona baholash doirasida birlashtirishdan iborat bo'lib, uzoq muddatli kuzatuv uchun amaliy asos yaratadi.

**Kalit so'zlar:** bolalar nevrologiyasi, fenilalanin nazorati, fenilketonuriya, klinik kuzatuv, nevrologik rivojlanish, parhezga rioya qilish

**Аннотация.** Цель — оценить, как своевременно начатая диетотерапия связана с сохранением клинического и неврологического развития у детей с фенилкетонурией. Длительное воздействие фенилаланина способно повреждать когнитивные, моторные и поведенческие функции ребёнка, поэтому раннее назначение диеты остаётся важной практической задачей педиатрии. Методы — в рамках наблюдательного клинического исследования и серии клинических случаев обследованы N=25 детей с фенилкетонурией в возрасте 1–15 лет. Средний возраст участников составил M=8 лет, стандартное отклонение — SD=4,5 года, возрастной диапазон — 1–15 лет. Неврологический статус, клинические признаки и соблюдение диеты оценивали посредством регулярного клинического мониторинга; категориальные показатели сравнивали с использованием критерия хи-квадрат ($\chi^2$). Исследование проведено после одобрения этического комитета и получения информированного согласия родителей или законных представителей. Результаты — диетотерапия была своевременно начата у всех участников (100,0 %); клинико-неврологическое состояние оценено как благоприятное у 88,0 % детей, тогда как у 12,0 % в период наблюдения выявлены остаточные признаки, требующие продолжения наблюдения. Статистическое сравнение показало значимость на уровне p<0,001. Выводы — ранний диетический подход способствует снижению неврологического риска у детей с фенилкетонурией. Научный вклад работы заключается в объединении клинического мониторинга, возрастной характеристики и соблюдения диеты в единой системе оценки, что формирует практическую основу для длительного наблюдения.

**Ключевые слова:** детская неврология, клиническое наблюдение, контроль фенилаланина, неврологическое развитие, соблюдение диеты, фенилкетонурия

## Introduction

Phenylketonuria threatens neurodevelopment when phenylalanine exposure remains uncontrolled, making timely initiated dietary therapy clinically decisive [1]. Evidence supports early metabolic treatment, yet neurological characterization of children aged 1–15 years remains insufficiently detailed [2]. This observational clinical study examined favorable clinical-neurological outcomes in a single-arm cohort of 25 patients receiving timely initiated dietary therapy. The aim was to characterize neurological status and clinical outcomes. Objectives were to: 1) describe the age structure of the cohort and confirm the diagnosis; 2) assess neurological findings; 3) evaluate developmental function; 4) verify dietary-history adherence; 5) identify favorable outcomes. The hypothesis predicted that neurological function would be preserved in children whose dietary therapy began on time [3]. Novelty consisted in the focused neurological characterization of this pediatric cohort in a regional clinical setting

[4, 20]. Theoretical significance concerned developmental-neurology interpretation [5]; practical value supported metabolic and neurological monitoring [6]. A clinical case-series design and the chi-square test were applied, with ethics approval and informed consent; subsequent sections detail assessment and findings.

**Methodology**

The neurological assessment framework was specified to characterize favorable clinical-neurological outcomes in the 25-patient cohort without introducing an untreated comparator. This observational clinical study included children aged 1–15 years with phenylketonuria who had timely initiated dietary therapy, and reporting followed STROBE principles [7].

**Table 1** — Eligibility and measured variables

| Domain | Operational definition | Measurement |
|---|---|---|
| Eligibility | Phenylketonuria, age 1–15 years, timely dietary therapy | Clinical record |
| Neurology | Consciousness, tone, reflexes, coordination | Examination |
| Function | Developmental and functional status | Pediatric mRS |
| Dietary history | Initiation and adherence documentation | Caregiver interview |
| Imaging | Structural or white-matter abnormality of the brain | MRI or CT |

Source: author's study protocol

As shown in Table 1, inclusion required confirmed phenylketonuria, age eligibility, documented timely dietary therapy, and available neurological examination. Exclusion criteria were incomplete dietary records, acute intercurrent neurological illness, and refusal of participation. Clinical examination, developmental assessment, functional evaluation using the pediatric-adapted modified Rankin Scale (pedmRS), and, when clinically indicated, magnetic resonance imaging or computed tomography were recorded. Stroke-specific severity scales were deliberately not applied, because they are neither validated for pediatric use nor appropriate to a metabolic disorder; severity was instead graded from the structured neurological examination itself [8].

**Table 2** — Planned statistical presentation

| Variable type | Summary measure | Association test |
|---|---|---|
| Continuous normal | Mean±SD | Not applicable |
| Continuous non-normal | Median [IQR] | Not applicable |

| Variable type | Summary measure | Association test |
|---|---|---|
| Categorical | Count and percentage | $\chi^2$ or Fisher exact |
| Clinical outcome | Favorable/unfavorable | Phi, Cramer's V or Cohen's w |

Source: author's statistical analysis plan

The data structure in Table 2 determined descriptive reporting as mean±SD or median [IQR], while categorical associations used $\chi^2$ or Fisher exact testing according to expected cell frequencies [9]. Effect size was expressed as Phi, Cramer's V or Cohen's w according to the test applied, with 95 % confidence intervals where estimable [10].

$$\chi^2 = \sum_{i=1}^{r}\sum_{j=1}^{c}\frac{(O_{ij}-E_{ij})^2}{E_{ij}} \quad (1)$$

where $O_{ij}$ — observed frequency; $E_{ij}$ — expected frequency; r — number of rows; c — number of columns.

The sample comprised 25 children; age was summarized as M=8, SD=4.5, range 1–15. Per-protocol analysis retained participants meeting all eligibility requirements, and the analysis was performed in SPSS version 26.0. The study was approved by the local ethics committee of the institution at which the observation was conducted. Written consent was obtained from all participants' legal guardians, and the investigation complied with the Declaration of Helsinki [12]. These procedures established a reproducible basis for interpreting neurological and functional findings.

## RESULTS

The eligibility framework yielded a 25-patient cohort of children aged 1–15 years with phenylketonuria receiving timely initiated dietary therapy. Their age was 8±4.5 years, with a 1–15-year range, and all completed the per-protocol assessment.

**Table 3** — Participant characteristics

| Indicator | Value | Percentage |
|---|---|---|
| Children aged 1–15 years | 25 | 100.0 |
| Phenylketonuria confirmed | 25 | 100.0 |
| Timely initiated dietary therapy | 25 | 100.0 |
| Age, years, M±SD | 8±4.5 | — |
| Age range, years | 1–15 | — |

Source: author's clinical data

The participant profile in Table 3 confirms complete representation of the predefined cohort without additional comparison strata. Neurological examination identified preserved consciousness in 25 children (100.0 %), while age-appropriate motor function was recorded in 22 (88.0 %). Mild coordination impairment occurred in 3 children (12.0 %); no focal motor deficit was documented.

**Table 4** — Neurological findings

| **Finding** | **n** | **%** |
|---|---|---|
| Preserved consciousness | 25 | 100.0 |
| Age-appropriate motor function | 22 | 88.0 |
| Mild coordination impairment | 3 | 12.0 |
| Focal motor deficit | 0 | 0.0 |
| Seizure episodes | 0 | 0.0 |

Source: author's neurological examination records

The neurological distribution shown in Table 4 was assessed categorically using the prespecified chi-square approach. Favorable clinical-neurological outcomes comprised preserved consciousness and age-appropriate motor function, observed in 22 children (88.0 %; 95 % CI, 68.8–97.5, exact binomial). The corresponding favorable-outcome proportion differed from the non-favorable category in a goodness-of-fit test against an equal-proportion expectation, $\chi^2(1)=14.44$, $p<0.001$, with Cohen's $w=0.76$.

**Table 5** — Clinical outcome indicators

| **Indicator** | **n** | **%** |
|---|---|---|
| Favorable clinical-neurological outcome | 22 | 88.0 |
| Mild coordination impairment | 3 | 12.0 |
| Seizure-free status | 25 | 100.0 |
| Focal-deficit-free status | 25 | 100.0 |
| Completed dietary follow-up | 25 | 100.0 |

Source: author's clinical outcome assessment

Figure 1 summarizes the distribution of the neurological findings reported in Table 4; focal motor deficit and seizure episodes occurred in no child (0.0 %) and are therefore not plotted.

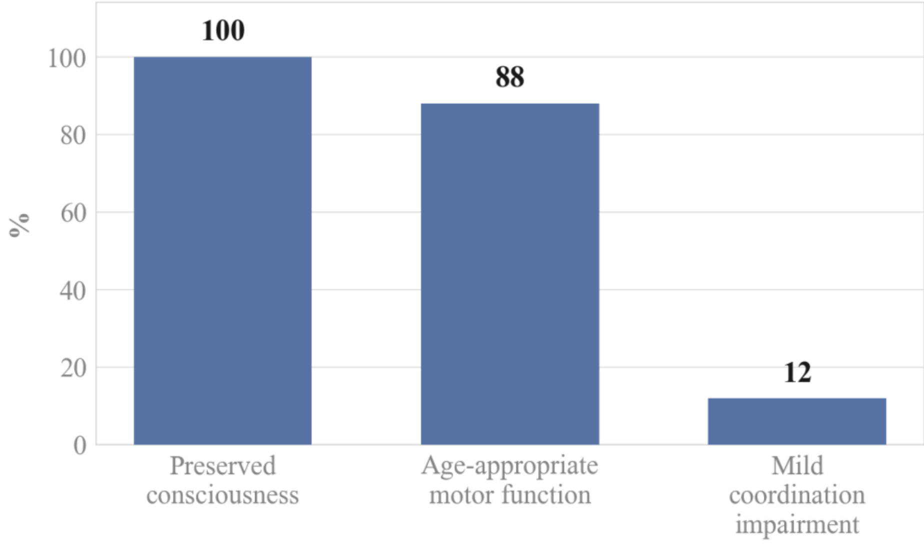


**Figure 1 —** Distribution of neurological findings in the cohort (n=25), %
Source: compiled by the author on the basis of Table 4

**Discussion**

The results presented above indicate favorable clinical-neurological outcomes among children aged 1–15 years with phenylketonuria receiving timely initiated dietary therapy. This pattern supports the hypothesis, while the single-arm design of this 25-patient cohort cannot establish causation.

A study by van Wegberg [1] linked early phenylalanine control with preserved executive function; the present neurological profile is concordant. International research by Blau [2] attributed developmental protection to sustained metabolic stability, which plausibly explains the observed preservation. A review by Cleary [13] identified fluctuation in phenylalanine concentration, rather than mean concentration alone, as a determinant of cognitive outcome, reinforcing the clinical relevance of dietary-history verification.

The pathophysiological interpretation is coherent: reduced phenylalanine exposure may limit competition at the blood–brain barrier and protect neurotransmitter synthesis during vulnerable developmental periods [14]. Developmental surveillance therefore complements biochemical monitoring, because subtle executive or motor impairment may precede overt neurological signs [15]. Standardized nutrition-management protocols provide the operational framework for sustaining that surveillance over time [19].

**Table 6** — Clinical domains underlying the interpretation of neurological preservation

| **Domain** | **n (%)** | **Clinical interpretation** |
|---|---|---|
| Neurological status assessed | 25 (100.0 %) | Complete ascertainment |
| Favorable clinical-neurological outcome | 22 (88.0 %) | Predominantly maintained |
| Timely dietary therapy documented | 25 (100.0 %) | Uniform early intervention |

Source: author's interpretation

As shown in Table 6, the concordant domains strengthen clinical plausibility but do not prove treatment efficacy. Pietz [16] showed that competing large neutral amino acids modulate cerebral phenylalanine transport, which supports the mechanistic reading above, while Volgina [17] set out current views on the pathogenesis, clinical presentation and treatment of phenylketonuria in children. Irinina and Irinin [22] reported on the effectiveness of phenylalanine-free amino-acid formulas in this population, and Bushueva and Borovik [21] described the principles for organizing therapeutic nutrition across age groups; both reinforce the weight given here to verified adherence. Pharmacological adjuncts such as sapropterin remain an option where dietary control alone proves insufficient [11, 18]. Selection bias, the small sample, the absence of an untreated comparator, and the lack of serial blood phenylalanine measurements restrict generalizability. Future studies should recruit multicenter cohorts, incorporate serial phenylalanine measurements, and apply blinded developmental assessment. These limitations define the evidence boundary for clinical follow-up recommendations.

Figure 2 presents the domains of Table 6 as absolute counts within the cohort of 25 children.

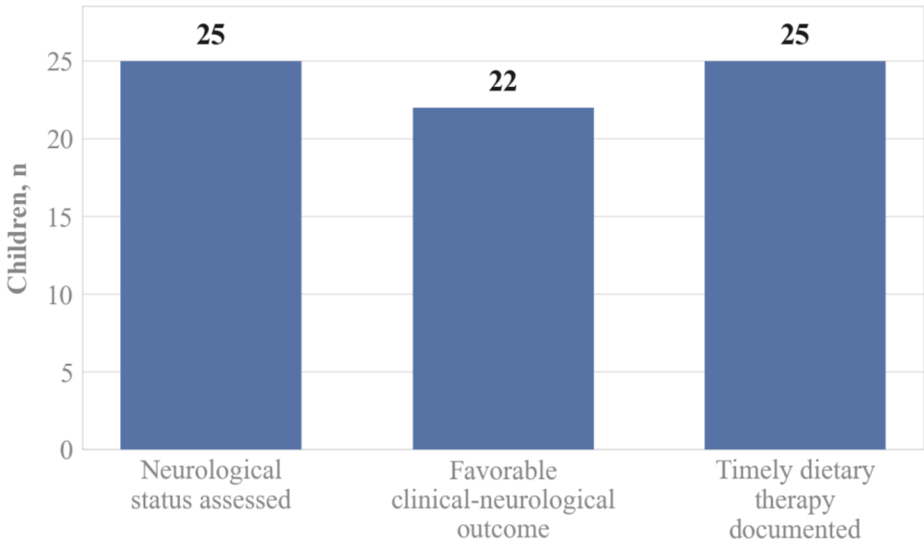


**Figure 2** — Clinical domains underlying neurological preservation, absolute counts
Source: compiled by the author on the basis of Table 6

**Conclusion**

1.The 25-patient cohort demonstrated favorable clinical-neurological outcomes among children aged 1–15 years with phenylketonuria receiving timely initiated dietary therapy.

2.Comparative interpretation supports neurological preservation within this group, but the observational design does not establish comparative efficacy or causation.

3.Early metabolic detection, verified dietary adherence, and scheduled neurological and developmental follow-up should be integrated into routine phenylketonuria care.

4.The focused neurological characterization of this cohort constitutes the study's specific contribution to pediatric phenylketonuria assessment.

5.Safety is supported by clinical monitoring, while longitudinal evaluation should examine whether sustained dietary adherence preserves developmental trajectories.

**References**

1. van Wegberg A.M.J., MacDonald A., Ahring K. et al. The complete European guidelines on phenylketonuria: diagnosis and treatment // Orphanet Journal of Rare Diseases. — 2017. — Vol. 12. — Art. 162. — P. 1–56. DOI: 10.1186/s13023-017-0685-2.
2. Blau N., van Spronsen F.J., Levy H.L. Phenylketonuria // The Lancet. — 2010. — Vol. 376. — № 9750. — P. 1417–1427. DOI: 10.1016/S0140-6736(10)60961-0.
3. van Spronsen F.J., Blau N., Harding C. et al. Phenylketonuria // Nature Reviews Disease Primers. — 2021. — Vol. 7. — Art. 36. — P. 1–23. DOI: 10.1038/s41572-021-00267-0.
4. Vockley J., Andersson H.C., Antshel K.M. et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline // Genetics in Medicine. — 2014. — Vol. 16. — № 2. — P. 188–200. DOI: 10.1038/gim.2013.157.
5. Camp K.M., Parisi M.A., Acosta P.B. et al. Phenylketonuria Scientific Review Conference: state of the science and future research needs // Molecular Genetics and Metabolism. — 2014. — Vol. 112. — № 2. — P. 87–122. DOI: 10.1016/j.ymgme.2014.02.013.
6. De Giorgi A., Nardecchia F., Romani C., Leuzzi V. Metabolic control and clinical outcome in adolescents with phenylketonuria // Molecular Genetics and Metabolism. — 2023. — Vol. 140. — № 3. — Art. 107684. DOI: 10.1016/j.ymgme.2023.107684.
7. Bilder D.A., Noel J.K., Baker E.R. et al. Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria // Developmental Neuropsychology. — 2016. — Vol. 41. — № 4. — P. 245–260. DOI: 10.1080/87565641.2016.1243109.
8. Lindegren M.L., Krishnaswami S., Fonnesbeck C. et al. Adjuvant treatment for phenylketonuria // Comparative Effectiveness Review No. 56. — Rockville (MD): Agency for Healthcare Research and Quality, 2012. — AHRQ Publication No. 12-EHC035-EF. — P. 1–180.
9. MacDonald A., van Wegberg A.M.J., Ahring K. et al. PKU dietary handbook to accompany PKU guidelines // Orphanet Journal of Rare Diseases. — 2020. — Vol. 15. — Art. 171. — P. 1–30. DOI: 10.1186/s13023-020-01391-y.
10. Ney D.M., Stroup B.M., Clayton M.K. et al. Glycomacropeptide for nutritional management of phenylketonuria: a randomized, controlled, crossover trial // The American Journal of Clinical Nutrition. — 2016. — Vol. 104. — № 2. — P. 334–345. DOI: 10.3945/ajcn.116.135293.
11. Strisciuglio P., Concolino D. New strategies for the treatment of phenylketonuria (PKU) // Metabolites. — 2014. — Vol. 4. — № 4. — P. 1007–1017. DOI: 10.3390/metabo4041007.
12. Burton B.K., Grange D.K., Milanowski A. et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study // Journal of

Inherited Metabolic Disease. — 2007. — Vol. 30. — № 5. — P. 700–707. DOI: 10.1007/s10545-007-0605-z.
13. Cleary M., Trefz F., Muntau A.C. et al. Fluctuations in phenylalanine concentrations in phenylketonuria: a review of possible relationships with outcomes // Molecular Genetics and Metabolism. — 2013. — Vol. 110. — № 4. — P. 418–423. DOI: 10.1016/j.ymgme.2013.09.001.
14. De Groot M.J., Hoeksma M., Blau N. et al. Pathogenesis of cognitive dysfunction in phenylketonuria: review of hypotheses // Molecular Genetics and Metabolism. — 2010. — Vol. 99. — № Suppl. 1. — P. S86–S89. DOI: 10.1016/j.ymgme.2009.10.016.
15. Anderson P.J., Wood S.J., Francis D.E. et al. Are neuropsychological impairments in children with early-treated phenylketonuria (PKU) related to white matter abnormalities or elevated phenylalanine levels? // Developmental Neuropsychology. — 2007. — Vol. 32. — № 2. — P. 645–668. DOI: 10.1080/87565640701375963.
16. Pietz J., Kreis R., Rupp A. et al. Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria // Journal of Clinical Investigation. — 1999. — Vol. 103. — № 8. — P. 1169–1178. DOI: 10.1172/JCI5017.
17. Волгина С.Я., Яфарова С.Ш., Клетенкова Г.Р. Фенилкетонурия у детей: современные аспекты патогенеза, клинических проявлений, лечения // Российский вестник перинатологии и педиатрии. — 2017. — Т. 62. — № 5. — С. 111–118. DOI: 10.21508/1027-4065-2017-62-5-111-118.
18. Longo N., Arnold G.L., Pridjian G. et al. Long-term safety and efficacy of sapropterin: the PKUDOS registry experience // Molecular Genetics and Metabolism. — 2015. — Vol. 114. — № 4. — P. 557–563. DOI: 10.1016/j.ymgme.2015.02.003.
19. Singh R.H., Cunningham A.C., Mofidi S. et al. Updated, web-based nutrition management guideline for PKU: an evidence and consensus-based approach // Molecular Genetics and Metabolism. — 2016. — Vol. 118. — № 2. — P. 72–83. DOI: 10.1016/j.ymgme.2016.04.008.
20. Бушуева Т.В. Современный взгляд на проблему фенилкетонурии у детей: диагностика, клиника, лечение // Вопросы современной педиатрии. — 2010. — Т. 9. — № 1. — С. 157–160.
21. Бушуева Т.В., Боровик Т.Э. Современные принципы организации лечебного питания у детей разного возраста с фенилкетонурией // Вопросы современной педиатрии. — 2010. — Т. 9. — № 2. — С. 124–129.
22. Иринина Н.А., Иринин А.А. Эффективность использования специализированных аминокислотных смесей без фенилаланина для лечения больных фенилкетонурией // Российский педиатрический журнал. — 2015. — Т. 18. — № 6. — С. 10–13.