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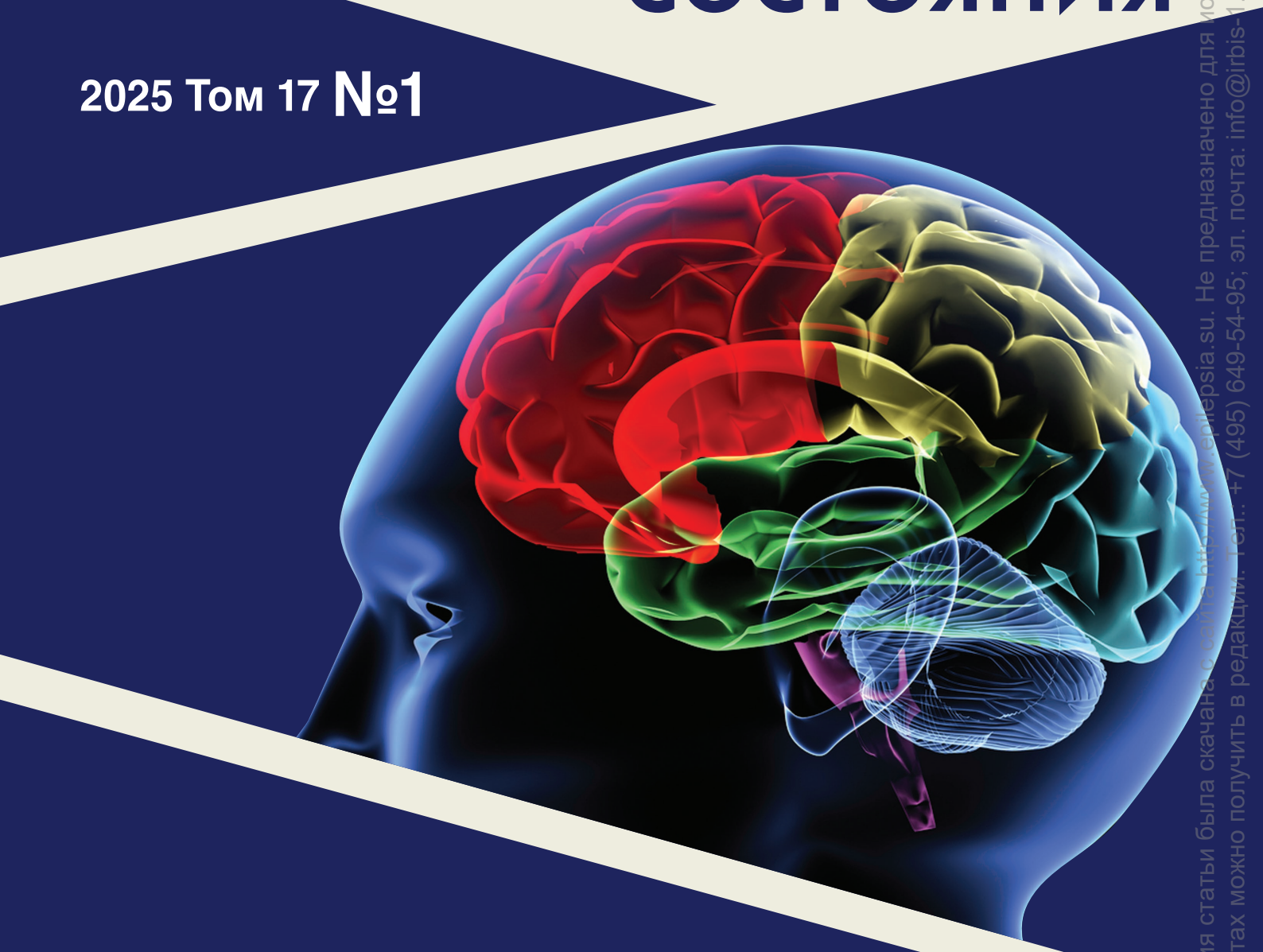

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Cow's milk in infant diet is a risk factor for hypocalcemic seizures

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ABSTRACT

Background. Seizures are common in infants due to the inherent sensitivity of the developing brain to various insults, with metabolic alterations being a ordinary cause. Among these, hypocalcemia is a prevalent factor. Early diagnosis of hypocalcemic seizures is essential as the management and prognosis differ from other seizure causes.

Objective: To investigate the prevalence and associated risk factors of hypocalcemic seizures in children aged 1 month to 2 years.

Material and methods. This prospective observational study was conducted over 18 months in a tertiary care teaching hospital, following institutional ethics committee approval. All children in the specified age group presenting with seizures were enrolled and given standard care. Demographic and relevant risk factor details were recorded in a pre-designed proforma. Children with hypocalcemia underwent further testing for vitamin D, parathormone, alkaline phosphatase, and magnesium blood levels. Based on a previous study, a sample size of 225 was calculated to achieve a power of 80% and a confidence interval of 95%, with a marginal error rate of 0.06.

Results. Of the 225 children enrolled (53.7% boys), the most common type of seizures was simple febrile seizures (46.2%). The prevalence of hypocalcemic seizures was 3.6% (8 cases). Significant factors associated with hypocalcemic seizures included age and the administration of cow's milk before 1-year age. All children with hypocalcemic seizures had vitamin D deficiency, with a mean vitamin D level of 7.77 ng/dl, and elevated alkaline phosphatase levels (mean 841.8 U/l).

Conclusion. Hypocalcemic seizures should be considered in the evaluation of seizures in children, particularly in young infants and when cow's milk is introduced before 1-year age.

KEYWORDS

hypocalcemia, seizures, cow's milk, infants

For citation

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Коровье молоко в рационе младенцев – фактор риска развития гипокальциемических приступов

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РЕЗЮМЕ

Актуальность. Из-за врожденной чувствительности развивающегося мозга к различным повреждениям у младенцев нередко наблюдаются судороги, причиной которых часто служат метаболические изменения. Среди них распространенным фактором является гипокальциемия. Большое значение имеет ранняя диагностика гипокальциемических приступов, поскольку их ведение и прогноз отличаются от таковых при других вариантах судорог.

Цель: изучить распространенность гипокальциемических приступов и связанные с ними факторы риска у детей в возрасте от 1 мес до 2 лет.

Материал и методы. Проспективное наблюдательное исследование проводилось в течение 18 мес в высокоспециализированной клинической больнице после одобрения местного этического комитета. Все дети в указанной возрастной

группе, у которых наблюдались приступы, были включены в исследование и получили стандартную медицинскую помощь. Демографические данные и соответствующие факторы риска были внесены в ранее разработанную карту пациента. Дети с гипокальциемией прошли дополнительное тестирование с измерением уровней витамина D, паратгормона, щелочной фосфатазы и магния в крови. На основе предыдущего исследования был определен размер группы в 225 человек для достижения мощности 80% и доверительного интервала 95% с предельной частотой ошибок 0,06.

Результаты. Из 225 включенных в исследование детей (53,7% мальчиков) наиболее распространенным типом приступов были простые фебрильные (46,2%). Распространенность гипокальциемических приступов составила 3,6% (8 случаев). Значимые факторы, связанные с гипокальциемическими приступами, включали возраст пациента и употребление коровьего молока до достижения возраста 1 года. У всех детей с гипокальциемическими приступами обнаружен дефицит витамина D (средний уровень 7,77 нг/дл) и повышенное содержание щелочной фосфатазы (средний уровень 841,8 ед/л).

Заключение. Гипокальциемические приступы следует учитывать при оценке судорог у детей, особенно у младенцев и при употреблении коровьего молока до достижения ими возраста 1 года.

КЛЮЧЕВЫЕ СЛОВА

гипокальциемия, приступы, коровье молоко, младенцы

Для цитирования

Арункартик К., Тасма Сантанакришнан А. Коровье молоко в рационе младенцев – фактор риска развития гипокальциемических судорог. *Эпилепсия и пароксизмальные состояния.* 2025; 17 (1): 48–53 (на англ. яз.). https://doi.org/10.17749/2077-8333/epi.par.con.2025.198.

INTRODUCTION / ВВЕДЕНИЕ

Seizures are common in infants, owing to inherent sensitivity of the developing brain to various insults [1]. The metabolic status alteration is one of the common cause of seizures [2]. Among the metabolic causes, hypocalcemia is one of the frequent causes [3]. Early diagnosis of hypocalcemic seizures is essential, because the management and prognostication is different from other causes of seizures [4].

The early introduction of cow's milk into an infant's diet before the age of 1 year is a dietary risk factor of hypocalcemic seizures. Studies have demonstrated that cow's milk consumption correlates with an increased risk of hypocalcemia due it's impact on the calcium-phosphorus ratio and parathyroid hormone [5, 6]. The data on prevalence of hypocalcemic seizures are limited [7].

The current study hypothesizes that early introduction of cow's milk significantly contributes to the risk of hypocalcemic seizures in children.

Objective: To investigate the prevalence and associated risk factors of hypocalcemic seizures in children aged 1 month to 2 years.

MATERIAL AND METHODS / МАТЕРИАЛ И МЕТОДЫ

Study design / Дизайн исследования

This 18-month prospective observational study was carried out in a tertiary care teaching hospital after institutional ethics committee approval. All children in the age group of 1 month to 2 years, presenting with seizures were enrolled in the study. Children previously enrolled in the study who were re-admitted during the study period were planned to be excluded. The study participants received standard care of seizures. The demographic details and the relevant risk factor details were entered in a pre-designed proforma.

Laboratory tests / Лабораторные тесты

The study participants with hypocalcemia were further tested for vitamin D, parathormone, alkaline phosphatase and magnesium levels. The serum calcium was measured using Arsenezo method. The serum magnesium was measured using Xylidyl method. The serum vitamin D and serum intact parathormone levels were measured using electro chemiluminescence method. The serum phosphorus was measured by phosphomolybdate method. The alkaline phosphatase level was estimated by para-nitrophenylphosphate and AMP-buffer[1] methods.

Hypocalcemia was defined as serum calcium level less than 8 mg/dl [8]. Serum vitamin D levels less than 20 ng/dl was defined as vitamin D deficiency [9]. Hypomagnesemia was defined as serum magnesium level less than 1.5 mg/dl [8].

Statistical analysis / Статистический анализ

Based on a previous study [10], with assumed prevalence of 30% of hypocalcemic seizures, a minimum sample size of 225 subjects was calculated at a power of 80%, confidence interval level of 95%, and marginal error rate of 0.06. Data were entered into Microsoft Excel database (Microsoft, USA) software. The statistical analysis was performed using SPSS Version 26 (IBM, USA). The categorical variables were expressed as frequency and percentage. The continuous variables were expressed as mean and standard deviation. The association between variables was tested using χ^2 test or Fischer's exact test. A p-value of less than 0.05 was taken as significant.

[1] 2-amino-2-methyl-1-propanol for buffer solutions.

RESULTS / РЕЗУЛЬТАТЫ

The prevalence of hypocalcemic seizures / Распространенность гипокальциемических приступов

A total of 225 children (121 (53.7%) boys, 104 (46.3%) girls) were enrolled in the study. The most common type of seizures was simple febrile seizures (n=104, 46.2%). The prevalence of hypocalcemic seizures comprised 3.6% (n=8). The other causes are shown in **Table 1**.

Association between demographic and other factors / Связь между демографическими и другими факторами

The association between demographic and other factors are shown in **Table 2**. The age and cow's milk administration

Table 1. The various causes of seizures in the study participants (n=225), n (%)

Таблица 1. Различные причины приступов у участников исследования (n=225), n (%)

Diagnosis / Диагноз	Number of children / Количество детей
Hypocalcemic seizures / Гипокальциемические приступы	**8 (3.6)**
Simple febrile seizures / Простые фебрильные приступы	104 (46.2)
Unprovoked seizures / Неспровоцированные приступы	35 (15.6)
Complex febrile seizures / Сложные фебрильные приступы	25 (11.1)
Seizure disorder / Судорожное расстройство	19 (8.4)
Camphor induced seizures / Приступы, вызванные камфарой	16 (7.1)
Fever provoked seizures / Приступы, вызванные лихорадкой	5 (2.2)
Febrile status epilepticus / Фебрильный эпилептический статус	4 (1.8)
Breakthrough seizures / Прорывные приступы	3 (1.3)
Hypoxic seizures / Гипоксические приступы	2 (0.9)
DPT-induced seizure / Приступы, вызванные АКДС	1 (0.4)
Pyridoxine dependent seizure / Пиридоксин-зависимые приступы	1 (0.4)
Tumour induced seizure / Приступы, вызванные опухолью	1 (0.4)
Hyponatremic seizure / Гипонатриемические приступы	1 (0.4)

Note. *DPT – vaccine against diphtheria, pertussis, and tetanus.*

Примечание. *АКДС – адсорбированная коклюшно-дифтерийно-столбнячная вакцина.*

Table 2. Association between demographic variables and hypocalcemic seizures, n (%)

Таблица 2. Связь между демографическими параметрами и гипокальциемическими приступами, n (%)

Factor / Фактор	Hypocalcemic seizures / Гипокальциемические приступы (n=8)	Non-hypocalcemic seizures / Негипокальциемические приступы (n=217)	p
Age less than 6 months, n (%) / Возраст менее 6 мес, n (%)	6 (75)	16 (7.4)	<0.001
Age, months / Возраст, мес	4.5±3.665	12.85±5.117	<0.001
Serum calcium, mg/dl // Сывороточный кальций, мг/дл	6.2±0.5606	9.682±0.4498	<0.001
Boys, n (%) / Мужской пол, n (%)	5 (62.5)	116 (53.5)	0.728
Presence of fever, n (%) / Наличие лихорадки, n (%)	1 (12.5)	150 (69.1)	0.002
Absence of developmental delay, n (%) / Отсутствие задержки развития, n (%)	8 (100.0)	206 (94.9)	0.665
Generalized seizures, n (%) / Генерализованные приступы, n (%)	8 (100.0)	213 (98.2)	0.864
Gestational diabetes, n (%) / Гестационный диабет, n (%)	0 (0.0)	10 (4.6)	0.691
Preterm birth, n (%) / Преждевременные роды, n (%)	1 (12.5)	21 (9.7)	0.691
Low birth weight, n (%) / Низкий вес при рождении, n (%)	1 (12.5)	28 (12.9)	0.725
Presence of family history of seizures, n (%) / Наличие семейного анамнеза приступов, n (%)	2 (25.0)	29 (13.4)	0.304
Vitamin D supplements not given, n (%) / Отсутствие приема добавок витамина D, n (%)	7 (87.5)	135 (62.2)	0.263
Cows milk administration before 1-year age, n (%) / Применение коровьего молока до возраста 1 года, n (%)	3 (37.5)	10 (4.6)	0.007

before the age of 1 year, was the significant factors associated with hypocalcemic seizures.

Biochemical profile of children with hypocalcemic seizures / Биохимический профиль детей с гипокальциемическими приступами

The biochemical profile of children with hypocalcemic seizures is shown in **Table 3**. All children with hypocalcemic seizures had vitamin D deficiency. The mean vitamin D level was 7.77 ng/dl. The alkaline phosphatase level was elevated in all the children with hypocalcemic seizures. The mean alkaline phosphatase level was 841.8 U/l. Out of the 8 children with hypocalcemic seizures, 7 (87.5%) had elevated parathormone levels. The mean parathormone level was 276.7 pg/dl. The serum magnesium level was low in 1 (12.5%) child with hypocalcemic seizures. The mean magnesium level was 1.7 mg/dl. The serum phosphorus level was normal in all of the 8 children with hypocalcemic seizures.

DISCUSSION / ОБСУЖДЕНИЕ

The prevalence of hypocalcemic seizures in the present study reached 3.6%. In the published studies, there is a wide range in prevalence, from 4.6 to 68.3% [6, 7, 10–13]. The difference in this prevalence rate may be attributed by difference in demography of the study population, study design with differences in inclusion criteria, level of ante-natal care, level of new-born and infant care, exposure to sunlight, and the pattern of complimentary feeding practices.

In our study, the mean age of children with hypocalcemic seizures was 4.5 months. A similar observation has been made in other published studies [14, 15]. The higher metabolic demand for calcium and relative immature calcium homeostasis mechanism in early infants could underlie higher prevalence of hypocalcemic seizures in this age group [16].

All children with hypocalcemic seizures had generalised type of seizures in our study. Similar pattern of generalised type of hypocalcemic seizures has been reported earlier [6, 7]. This is due to the generalised neuro-activation and excitability induced by hypocalcemia [17].

In our study, 87.5% of the children with hypocalcemic seizures received no vitamin D supplementation that agrees with earlier study [13]. This emphasises the fact that vitamin D supplements are essential in infants for various benefits including prevention of hypocalcemic seizures.

In our study, 37.5% of the children with hypocalcemic seizures had received cow's milk feeding before the age of 1 year. This rate was 63.4% in a previously reported study [6]. The high phosphorus content in cow's milk leads to hypocalcemia via increased deposition of calcium in bone tissue, hypoparathyroid state, and reduced absorption of calcium from the intestine [18, 19].

In our study, all children with hypocalcemic seizure had hypovitaminosis D. Vitamin D deficiency as the common cause of hypocalcemic seizures has been reported in various studies [20–22]. Vitamin D is an essential component in calcium homeostasis. The deficiency of vitamin D results in reduced absorption of calcium from intestine resulting in hypocalcemia.

In our study, all children with hypocalcemic seizures had elevated alkaline phosphatase and normal phosphorus level. This finding has been observed in previously reported stud-

Table 3. The biochemical profile of children with hypocalcemic seizures

Таблица 3. Биохимический профиль детей с гипокальциемическими приступами

No. / №	Age / Возраст	Calcium, mg/dl // Кальций, мг/дл	Vitamin D, ng/dl // Витамин D, нг/дл	Magnesium, mg/dl // Магний, мг/дл	iPTH, pg/dl // иПТГ, пг/дл	Phosphorus, mg/dl // Фосфор, мг/дл	ALP, U/l // ЩФ, Е/л	Albumin, g/dl // Альбумин, г/дл	Creatinine, mg/dl // Креатинин, мг/дл
1	1 month / 1 мес	6.2	6.5	2.1	421	5.7	1249	4	0.3
2	1 month / 1 мес	6.4	6	1.2	43	5.7	495	3.2	0.2
3	2 months / 2 мес	6.7	14.4	1.8	119	5.2	846	3.2	0.2
4	2 months / 2 мес	6.1	6.6	1.7	221	5.1	593	3.1	0.1
5	5 months / 5 мес	6.6	12.2	2	212	5.9	647	4.4	0.2
6	6 months / 6 мес	6.3	2.8	1.6	481	4.9	1792	3.4	0.2
7	8 months / 8 мес	4.9	3.4	2	321	4.2	715	3.9	0.2
8	11 months / 11 мес	6.4	10.3	1.9	394	5.5	398	3.3	0.2

Note. *iPTH – intact parathyroid hormone; ALP – alkaline phosphatase.*

Примечание. *иПТГ – интактный паратиреоидный гормон; ЩФ – щелочная фосфатаза.*

ies [15, 23]. Phosphate levels were not low as expected in the cases of hypocalcemia and hypovitaminosis D. This may be due to early presentation of vitamin D deficiency, where parathyroid response has not started or late presentation of vitamin D deficiency, where there is resistance to parathyroid hormone [24].

CONCLUSION / ЗАКЛЮЧЕНИЕ

The hypocalcemic seizures should be considered in the evaluation of seizures in infants, particularly in young infants and when there is introduction of cow's milk in infant diet, before the age of 1 year.

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Limitation of the study	**Ограничение исследования**
The ionized calcium levels and corrected calcium levels were not used in the definition for hypocalcemia in this study, which is the limitation	Уровни ионизированного кальция и скорректированные уровни кальция не использовались при определении гипокальциемии в данном исследовании, что является ограничением
Ethics declarations	**Этические аспекты**
The study was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association and was approved by Research Ethics Commission of Sri Ramachandra Institute of Higher Education and Research (CSP-MED/20/JAN/58/05 dated March 13, 2020)	Исследование проводилось в соответствии с принципами Хельсинкской декларации Всемирной медицинской ассоциации и получило одобрение Комиссии по этике научных исследований Института высшего образования и научных исследований Шри Рамачандры (CSP-MED/20/JAN/58/05 от 13.03.2020)
Data sharing	**Раскрытие данных**
Raw data could be provided upon reasonable request to the corresponding author	Первичные данные могут быть предоставлены по обоснованному запросу автору, отвечающему за корреспонденцию
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The statements, opinions, and data contained in this publication were generated by the authors and not by IRBIS Publishing (IRBIS LLC). IRBIS LLC disclaims any responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred in the content	Содержащиеся в этой публикации утверждения, мнения и данные были созданы ее авторами, а не издательством ИРБИС (ООО «ИРБИС»). Издательство снимает с себя ответственность за любой ущерб, нанесенный людям или имуществу в результате использования любых идей, методов, инструкций или препаратов, упомянутых в публикации

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