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Evaluation of serum vitamin B12 and D, iron, ferritin, folate, calcium, phosphorus and magnesium levels in children in palliative care clinic: a single-center cross-sectional study

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Abstract

Background Pediatric palliative care (PPC) patients are at an elevated risk of malnutrition. Nutritional inadequacy can also cause micronutrient deficiencies. These factors can lead to weight loss, stunted growth, and poor quality of life. Despite the prevalence of these issues, limited research exists in the micronutrient status of PPC patients. The purpose of this study was to determine the vitamin B12 and D, iron, ferritin, folate, calcium, phosphorus, and magnesium levels of PPC patients to contribute to a better understanding of their micronutrient needs as well as the appropriate management of diet and treatment approaches.

Methods This was a single-center observational cross-sectional retrospective study. This study evaluated the levels of vitamin B12, 25-hydroxyvitamin D, iron, ferritin, folate, calcium, phosphorus, and magnesium in PPC patients. The patients were classified according to the Chronic Complex Conditions (CCC) v2 and then compared.

Results A total of 3,144 micronutrient data points were collected from 822 hospitalizations of 364 patients. At least one micronutrient deficiency was identified in 96.9% of the patients. The most prevalent deficiencies were observed for iron, calcium, and phosphate. In addition, 25-hydroxyvitamin D deficiency was observed in one-third of patients. Calcium, magnesium, phosphorus, folate, and 25-hydroxyvitamin D were negatively correlated with age.

Conclusion The results of this study indicate that micronutrient deficiencies are highly prevalent in PPC patients. These findings have the potential to contribute to improvements in the nutritional and therapeutic management of patients.

Keywords Pediatric, Palliative care, Micronutrient, Deficiency, Malnutrition

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Background

Palliative care is a multidisciplinary health service that aims to improve the quality of life of children with chronic, complex, progressive, and life-threatening disorders while efficiently managing symptoms [1]. Children under this care are highly susceptible to malnutrition [2]. And also, nutritional deficiencies may result in weight loss, growth retardation, and reduced quality of life [3–6].

Micronutrients, which include nutritional elements such as vitamins and minerals, are essential for maintaining the normal functionality of the body. At least half of children under the age of five are affected by micronutrient deficiencies [7]. To the best of our knowledge, there is limited research on the micronutrient status of PPC patients. We hypothesize that a significant proportion of PPC patients suffer from micronutrient deficiencies, which negatively impact their clinical outcomes. For instance, malnutrition and micronutrient deficiencies have been reported in most children with cerebral palsy (CP) [8, 9]. A study conducted on pediatric oncology patients revealed that micronutrient abnormalities were present in 74% of the patients. Selenium deficiency has been demonstrated to have a negative impact on clinical outcomes [10].

In contrast to the recommended nutritional intake and expert opinions for healthy children, there is a lack of evidence-based recommendations for micronutrient requirements in children with critical, chronic, and complex illnesses [11]. In the context of PPC, if nutritional history indicates inadequate nutritional intake and/or malnutrition, potential micronutrient deficiencies that may have systemic effects need to be investigated [3].

In addition to medical treatment, nutritional and micronutrient support may be important therapeutic approaches for improving the quality of life of patients monitored at PPC clinics. This approach may play an important role in the effects of chronic diseases and nutrition on metabolism, the course of acute disease, and the frequency of hospital admissions.

The objective of this study was to contribute to a more comprehensive understanding of the micronutrient needs of PPC patients. Therefore, the study aimed to determine micronutrient levels and contribute to the development of more effective strategies for managing nutrition and treatment during hospitalization and follow-up.

Methods

Design

This was an observational, cross-sectional, retrospective study performed at a single center in Türkiye. The study was conducted at the Pediatric Palliative Care Clinic of Dr. Behçet Uz Children's Hospital between November 2018 and September 2023.

This study was reported in accordance with the STROBE statement [12] (see Appendix 1). The study was registered on ClinicalTrials.gov (Protocol ID: PPC Micronutrient, Clinical Trial Number: NCT06146452), Registration Date: 11/19/2023).

Settings and participants

The participants were selected based on the following inclusion criteria: (1) age between one month and 18 years, (2) admission to the Pediatric Palliative Care Clinic, and (3) consent to participate in the study. Patients hospitalized for off-label reasons without chronic, complex, progressive, or life-threatening diseases were excluded. Data other than the first value were excluded from values examined more than once during the same hospitalization of the same patient (seen more than once within a year or for posttreatment control purposes). Patients with conditions such as infection, intoxication, blood transfusion, or parenteral micronutrient intake that could change micronutrient levels were excluded.

The following data of the patients were collected: age, sex, primary diagnosis, and micronutrient levels (vitamin B12, 25-hydroxyvitamin D, iron, ferritin, folate, calcium, phosphorus, and magnesium).

The main diagnoses were classified using the Chronic Complex Conditions (CCC) v2, which includes 11 categories (neurologic and neuromuscular, cardiovascular, respiratory, renal and urologic, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic defect, prematurity/neonatal, malignancy, and miscellaneous not elsewhere classified) [13].

Laboratory analysis

All biomarkers were evaluated in serum samples. The reference ranges for micronutrient levels were based on laboratory reference values used in the hospital [14–16]. The normal calcium level was determined to be 9–11 mg/dL for patients aged < 3 years, 8.8–10.8 mg/dL for patients aged 3–12 years, and 8.4–10.2 mg/dL for patients aged 13–18 years. The normal level of magnesium was determined to be 1.7–2.3 mg/dL. The normal levels of phosphorus were determined to be 4.8–8.4 mg/dL for patients aged < 1 year, 4.3–6.8 mg/dL for patients aged 1–5 years, 4.1–5.9 mg/dL for patients aged 6–12 years, 3.5–6.2 mg/dL for patients aged 13–16 years in boys and 3.2–5.5 mg/dL for patients aged 13–16 years in girls, and 2.9-5.0 mg/dL for patients aged 16 years and older. Vitamin B12 level < 200 pg/mL was determined as deficiency and 200–300 pg/mL was determined as insufficiency. High vitamin B12 levels were determined to be > 1576 pg/mL for patients aged < 1 year, > 1613 pg/mL for patients aged 1–8 years, > 1125 pg/mL for patients aged 9–14 years and > 888 pg/mL for patients aged > 15 years. Folate levels were classified as deficiency for ≤ 3.9

ng/mL, indeterminate for 4.0-5.8 ng/mL, and normal for 5.9–26.8 ng/mL. The normal levels of ferritin were determined to be 50–200 ng/mL for the first 6 months, 7-140 ng/mL for patients aged 6 months to 5 years, 14–79 ng/mL for patients aged 6–14 years, 6–67 ng/mL for patients aged 15–18 years in girls, 13–83 ng/mL for patients aged 15–16 years in boys, and 11–172 ng/mL in boys aged > 16 years. The normal levels of iron were determined to be 65–175 µg/dL for patients aged < 6 months, 50–120 µg/dL for patients aged 6 months to 14 years, and 50–175 µg/dL for patients aged ≥ 15 years. The 25-hydroxyvitamin D level was classified as deficiency for < 12 ng/mL, insufficiency for 12–20 ng/mL, normal for 20–60 ng/mL, and elevated for > 60 ng/mL.

The term "multiple micronutrient abnormalities" was used to describe cases where more than one micronutrient abnormality (deficiency, insufficiency or elevation) was identified in the same patient through the results of diagnostic tests.

Sample size

To the best of our knowledge, our study was the first to evaluate micronutrient status in PPC patients, so there was no reference study. The sample size was calculated as 249 (hypothesized frequency: 50%, population size: 700, confidence limits: 5%, confidence level: 95%). The G*Power program was used to determine the sample size [17].

Statistical analysis

The distribution of the data was checked using histograms, Q-Q plots, and the Kolmogorov-Smirnov test. To eliminate the effect of extreme outliers in the data, extreme outliers were removed using the "*25th percentile – 3*Interquartile range (IQR)*" and "*75th percentile + 3*IQR*".

Quantitative variables (age, micronutrient levels) were expressed as median and IQR (25th −75th percentiles) in non-normal distribution, and mean and standard deviation (SD), and minimum-maximum (min-max) in normal distribution. Categorical variables (sex and diagnosis) were expressed as numbers and percentages and compared using the chi-square test or Fisher's exact test. If a significant difference was identified between the groups following the comparison, the group or groups from which the difference originated were evaluated by post hoc analysis using the Tukey and Bonferroni tests. For numerical data comparisons between paired groups, the Student's t-test or the Mann–Whitney U test was used. The relationship between two numerical variables was evaluated using Pearson or Spearman correlation tests.

The data were analyzed, and data visualization was performed using Jamovi (Jamovi project 2023, Sydney, Australia, version 2.3) and the Statistical Package for Social Sciences (SPSS®, IBM, Chicago, USA, v.24.0).

All analyses were conducted using two-tailed tests with a significance level of 0.05.

Results

A total of 400 patients were hospitalized in the PPC clinic, and 364 (91%) had at least one micronutrient evaluated in 822 different hospitalizations (mean: 2.25, SD: 2.11, min-max = 1–17). A total of 56.3% (n = 205) of the patients were male, with a median age of 44.9 (IQR: 15.5-112.4) months. The primary diagnoses of the patients were *neurologic and neuromuscular* in 59.6% (n = 217), *metabolic* in 11.3% (n = 41), *other congenital or genetic defect* in 9.3% (n = 34), and *prematurity/neonatal* in 9.3% (n = 34).

In total, 24,866 micronutrients were included in the analysis. Following the exclusion of 35 extreme outliers (25-hydroxyvitamin D n = 3, iron n = 4, ferritin n = 10, vitamin B12 n = 12, and phosphate n = 6) and exclusions, 3144 micronutrient data were analyzed.

At least one micronutrient deficiency was present in 96.9% of the patients (n = 353). The micronutrient levels according to the CCC groups are presented in the Table 1.

Calcium

The calcium levels of 364 patients were evaluated on average 2.23 times (SD: 2.08; min-max: 1–17). The median calcium level was 9.3 mg/dL (IQR: 8.8–9.8). There were 187 patients (23.0%) with hypocalcemia and twenty-one patients (2.6%) with hypercalcemia. A significant difference was observed between the calcium levels and the diagnosis groups ($\chi^2(10) = 46.0$, $p < 0.001$). Post hoc analysis revealed that hypercalcemia was more prevalent in the malignancy group than in the normocalcemia group ($p = 0.001$). In addition, hypercalcemia was more common in the prematurity/neonatal group than in the hypocalcemia and normocalcemia groups ($p < 0.001$ and $p = 0.034$, respectively). Hypocalcemia was observed in all tests in the renal and urological groups (100.0%, n = 7) and in 50.0% (n = 2) of the patients in the malignancy group. There was no significant difference between the calcium levels and sex ($p = 0.227$). A negative correlation was observed between age and the calcium level (r_s (1) = -0.344, $p < 0.001$) (Fig. 1).

Magnesium

A total of 360 patients underwent magnesium level evaluation on average 2.18 times (SD: 2.03; min-max: 1–16). The median magnesium level was 2.14 (IQR: 1.95–2.31) mg/dL. A total of fifty-three patients (6.7%) exhibited hypomagnesemia, while 204 patients (25.6%) exhibited hypermagnesemia. There was a significant difference

Table 1 Micronutrient levels according to CCC v2

CCC	Calcium, Median (IQR) (mg/dL)	Magnesium, Median (IQR) (mg/dL)	Phosphate, Median (IQR) (mg/dL)	25(OH)D, Median (IQR) (pg/mL)
Neurologic and Neuromuscular	9.2 (8.7–9.7)	2.11 (1.92–2.29)	4.2 (3.5–4.9)	25.86 (17.11–34.12)
Cardiovascular	9.4 (9-10.1)	2.25 (2.09–2.4)	4.7 (4.4–5.2)	49.7 (42.8-54.35)
Respiratory	10.0 (9.5–10.3)	2.25 (2.04–2.34)	5.07 (4.2–5.95)	22.15 (12.45–33.35)
Renal and Urologic	7.7 (6.3–7.9)	1.87 (1.52–2.12)	5.7 (5.21–7.38)	49.35 (26.4–72.3)
Gastrointestinal	9.6 (9.2–9.8)	2.12 (1.96–2.23)	5.07 (4.73–6.22)	21.4 (21.3-59.94)
Hematologic or immunologic	9.6 (9.3–10.5)	2.3 (2.24–2.39)	5.5 (5.19–5.62)	49.36 (-)
Metabolic	9.4 (8.9–9.7)	2.16 (1.96–2.32)	4.33 (3.75–4.93)	23.8 (17-32.8)
Other CGD	9.2 (8.4–9.9)	2.11 (1.97–2.37)	4.44 (3.69–5.12)	20.62 (13.5-35.06)
Malignancy	8.7 (8.0-9.6)	1.8 (1.55–2.02)	4.15 (2.65–5.65)	-
Premature and Neonatal	9.5 (9.0-10.1)	2.22 (2.03–2.34)	4.64 (4.0-5.5)	30.38 (21.9–39.7)
Mis., not elsewhere classified	9.9 (9.0-10.3)	1.83 (1.68–2.3)	5.18 (4.3–6.15)	20.11 (-)
Total	9.3 (8.8–9.8)	2.14 (1.95–2.31)	4.38 (3.6–5.06)	26.35 (18.09–35.08)
CCC	**Ferritin, Median (IQR) (mg/dL)**	**Iron, Median (IQR) (mg/dL)**	**Folate, Median (IQR) (mg/dL)**	**Vitamin B12, Median (IQR) (pg/mL)**
Neurologic and neuromuscular	76.9 (36.4-158.2)	54.2 (34.2–74.4)	9.4 (6.2-13.97)	719 (515–980)
Cardiovascular	213.7 (-)	77.6 (-)	16.1 (14.7–17.6)	694 (467–1227)
Respiratory	171.3 (51.3-291.4)	41.6 (33.3–87.2)	12.7 (10.5–14)	614.5 (525-858.5)
Renal and urologic	-	-	3.3 (-)	920.5 (852–989)
Gastrointestinal	185.1 (139.4-652.5)	37.6 (31.2–44.0)	20.9 (16.6–25.3)	1111.5 (1052–1171)
Hematologic or immunologic	38.2 (23.8–52.6)	41.8 (40.5–43.2)	19.9 (16.3–23.6)	521 (475–1067)
Metabolic	190.6 (42.4-331.2)	62.2 (37.65–94.4)	9.3 (5.5–13.0)	737 (575–1022)
Other CGD	188.7 (56.7-344.4)	52 (33.4–83.0)	9.6 (4.9–13.8)	871.5 (625.5-1143.5)
Malignancy	-	-	-	-
Premature and neonatal	241.0 (83.7-477.5)	69.6 (49.2-101.5)	16.2 (12.8–17.7)	879 (687–1342)
Mis., not elsewhere classified	49.2 (-)	-	-	628 (-)
Total	85.0 (40.9-252.9)	52.3 (34.5–81.5)	10.9 (6.4–15.0)	739 (545–1066)

CCC v2: Chronic Complex Conditions version 2 (Feudtner et al., 2014), IQR: Interquartile range, Mis: Miscellaneous, CGD: Congenital or Genetic Defect, 25(OH)D: 25-Hydroxyvitamin D

in the magnesium levels between the diagnosis groups ($\chi^2(10)=26.8$, $p=0.003$). According to the post hoc analysis, hypomagnesemia was more frequent than normomagnesemia and hypermagnesemia in the renal & urological group ($p=0.001$ and $p=0.020$, respectively), and hypomagnesemia was more frequent than normomagnesemia in the malignancy group ($p=0.004$). Hypomagnesemia was present in 50.0% ($n=2$) of patients in the malignancy group and 42.9% ($n=3$) of those in the renal and urological group. There was no significant difference between magnesium levels and sex ($p=0.942$). A negative correlation was observed between age and magnesium levels (r_s (1) = -0.301, $p<0.001$) (Fig. 1).

Phosphate

A mean of 2.19 (SD: 2.05; min-max: 1–17) levels were evaluated in 360 patients. The median phosphate level was 4.38 (IQR: 3.6–5.06) mg/dL. There were 146 (18.3%) patients with hypophosphatemia and 70 (8.8%) patients with hyperphosphatemia. There was no significant difference between the phosphate levels and sex ($p=0.077$). However, there was a significant difference between the phosphate levels and diagnosis groups ($\chi^2(10)=48.8$, $p<0.001$). Post hoc analysis revealed that the frequency of hypophosphatemia was greater than that of hyperphosphatemia in the neurological group ($p=0.02$). In contrast, hyperphosphatemia was more frequent than hypophosphatemia and normophosphatemia in the respiratory group ($p=0.001$ and $p<0.001$, respectively). Furthermore, hyperphosphatemia was more frequent than normophosphatemia in the hematological and immunological groups ($p=0.039$). Hypophosphatemia was present in 25.0% ($n=1$) of those in the malignancy diagnosis group and 20.8% ($n=100$) of those in neurological and neuromuscular diagnosis group. There was a negative correlation between age and phosphorus level (r_s (1) = −0.371, $p<0.001$) (Fig. 2).

Vitamin B12

A total of 157 patients underwent evaluation of vitamin B12 levels, with an average of 1.17 assessments (SD: 0.53; min-max: 1–4). The median vitamin B12 level was 739 (IQR: 545–1066) pg/mL. Two tests (1.1%) demonstrated deficiency, six tests (3.2%) indicated insufficiency, and forty-five tests (24.3%) exhibited elevation. There was no significant difference between B12 levels and diagnosis

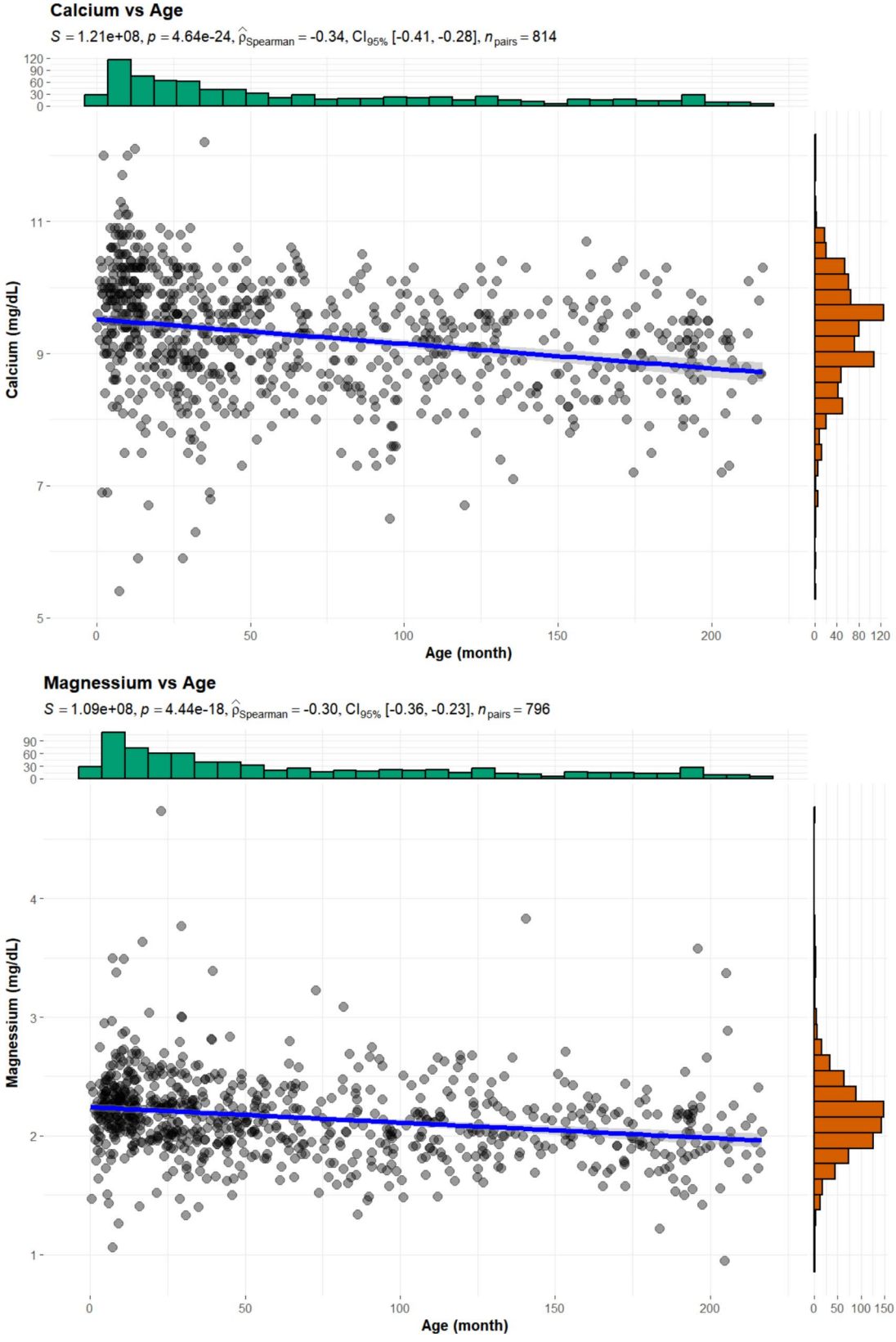

Fig. 1 Scatter plot of calcium and magnesium levels by age. Each dot represents a single data point. Shading around the fitline represents 95% confidence interval. The top (green) histograms are for age and the right (orange) histograms are for micronutrient levels

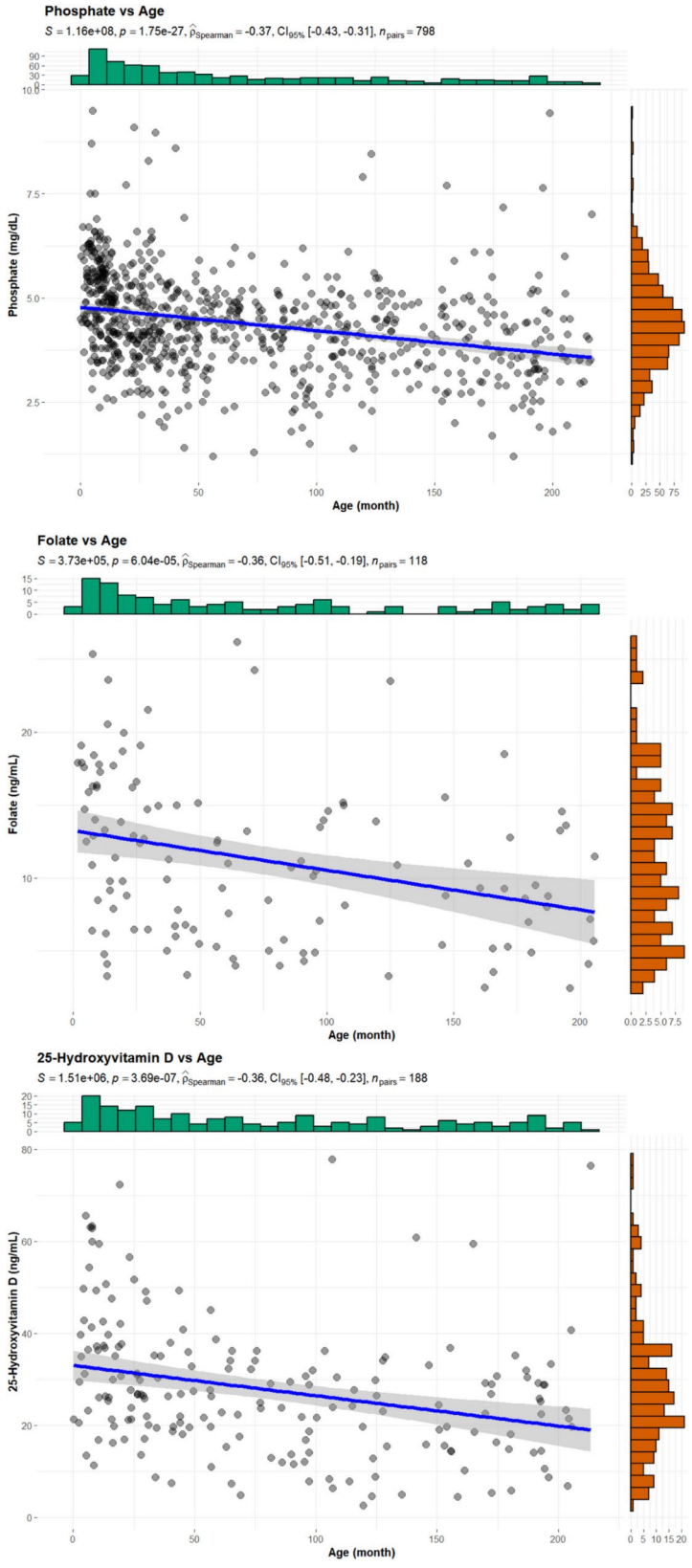

Fig. 2 Scatter plot of phosphorus, folate and 25-Hydroxyvitamin D levels by age. Each dot represents a single data point. Shading around the fitline represents 95% confidence interval. The top (green) histograms are for age and the right (orange) histograms are for micronutrient levels

groups or sexes ($\chi^2(10)=10.1$, $p=0.337$ and $p=0.778$, respectively). Vitamin B12 deficiency and insufficiency were present only in the neurologic and neuromuscular groups ($n=2$, 1.7%; $n=6$, 5.0%, respectively). There was no significant correlation between age and vitamin B12 levels (r_s (1) = -0.120, $p=0.103$).

Folate

A total of 108 patients underwent evaluation of their folate levels, with an average of 1.09 assessments (SD: 0.32; min-max: 1–4) per patient. The median folate level was 10.9 (IQR: 6.4–15.0) ng/mL. Six (5.1%) tests yielded results indicating deficiency, while 19 (16.1%) tests yielded indeterminate results. There was no significant difference between folate levels and sex ($p=0.409$). However, there was a significant difference between the folate levels and diagnosis groups ($\chi^2(10)=21.0$, $p=0.007$). Folate deficiency was present in the only evaluated patient in the renal and urological group (100%, $n=1$), 6.3% ($n=1$) in the metabolic group, and 5.4% ($n=4$) in the neurological and neuromuscular group. Indeterminate folate levels were present in 33.3% ($n=2$) of patients in the other congenital or genetic defects group and in 18.9% ($n=14$) of patients in the neurologic and neuromuscular group. There was a significant correlation between age and folate levels (r_s (1) = -0.361, $p<0.001$) (Fig. 2).

Ferritin

A total of 105 patients underwent evaluation of their ferritin levels, with an average of 1.15 assessments (SD: 0.41, min-max: 1–3) per patient. The median ferritin level was 85.0 (IQR: 40.9-252.9) ng/mL. Of the tests, 7.4% ($n=9$) were low and 54.1% ($n=66$) were high. There was no significant difference between ferritin levels and the diagnosis groups or sex ($\chi^2(10)=12.7$, $p=0.112$ and $p=0.091$, respectively). Low ferritin levels were present in 14.3% ($n=2$) of the metabolic diagnosis group and 8.9% ($n=7$) of the neurologic and neuromuscular group. There was no significant correlation between age and ferritin levels (r_s (1) = -0.004, $p=0.968$).

Iron

A total of 109 patients underwent iron level evaluation on average 1.12 times (SD: 0.36, min-max=1–3) per patient. The median iron level was 52.3 (IQR: 34.5–81.5) µg/dL. Iron levels were found to be low in 58 (47.2%) and high in 4 (3.3%) tests. There were no significant differences between the iron levels and diagnosis groups and sex ($\chi^2(10)=3.7$, $p=0.816$ and $p=0.050$, respectively). Low iron was present in 100% ($n=2$ each) of the gastrointestinal and hematologic/immunologic diagnosis groups, 66.7% ($n=2$) of the respiratory group, and 46.8% ($n=37$) of the neurologic and neuromuscular group. There was no significant correlation between age and iron level (r_s (1) = -0.152, $p=0.094$).

25-Hydroxyvitamin D

A total of 154 patients underwent evaluation of their 25-hydroxyvitamin D levels, with an average of 1.22 assessments per patient (SD: 0.52, min-max: 1–4). The median 25-hydroxyvitamin D level was 26.35 (IQR: 18.09–35.08) ng/mL. In total, 23 tests (12.2%) revealed a deficiency, 37 tests (19.6%) indicated insufficiency, and 15 tests (8%) showed an elevation. There was no significant difference between 25-hydroxyvitamin D levels and sex or diagnosis groups ($p=0.975$ and $\chi^2(10)=13.7$, $p=0.132$, respectively). 25-Hydroxyvitamin D deficiency was present in 25.0% ($n=1$) of the patients in the respiratory group and 16.7% ($n=3$) of those in the other congenital or genetic defects group. 25-hydroxyvitamin D insufficiency was present in 31.6% ($n=6$) of the metabolic group, 27.8% ($n=6$) of those in the other congenital or genetic defects group, and 25.0% ($n=1$) of the respiratory group. A negative correlation was observed between 25-hydroxyvitamin D levels and age (r_s (1) = -0.361, $p<0.001$) (Fig. 2).

Multiple micronutrient abnormalities

Multiple micronutrient deficiencies were found in 140 different tests of 109 patients (17.3%). Five deficiencies were found in 4 patients, four in 11 patients, three in 29 patients (30 tests), and two in 65 patients (95 tests). The micronutrient deficiencies most frequently observed together were hypocalcemia and hypophosphatemia (61 tests). This was followed by hypocalcemia-25-hydroxyvitamin D deficiency (36 tests) and hypocalcemia-hypomagnesemia (26 tests). Among patients exhibiting multiple micronutrient deficiencies, 66.42% were in the neurological and neuromuscular group. This was followed by other congenital or genetic defects group with 10.7% and metabolic group with 9.28%.

The most frequently observed association of elevated micronutrient levels was hypermagnesemia-hyperphosphatemia (29 tests). This was followed by hypermagnesemia-high ferritin levels (25 tests) and hypermagnesemia-high vitamin B12 levels (16 tests).

Discussion

A retrospective evaluation of the levels of micronutrients in PPC patients was conducted. The results of this study demonstrated that 96.9% of PPC patients exhibited at least one micronutrient deficiency. The most significant finding was the prevalence of vitamin D deficiency, which was identified in one-third of the patients. Moreover, the most prevalent micronutrient deficiencies were determined to be iron, calcium, and phosphorus. No significant correlation was detected between micronutrient levels and sex. Conversely, calcium, magnesium,

phosphorus, folate, and vitamin D levels negatively correlated with age.

In our study, we found hypocalcemia in 23% of test. Hypocalcemia has been the subject of studies in children who are critically ill [18, 19]. Escobedo-Monge et al. reported that hypocalcemia was seen in pediatric patients with a history of chronic disease, and Chidomere et al. reported that it was seen in children with CP [20, 21]. However, in a study by Carman et al., no significant differences were observed in calcium levels between patients with CP and a control group [22]. Although the study populations were defined as having chronic diseases (malnutrition, syndromes, encephalopathies, kidney disease, or disorders), it is not possible to compare them with chronic complex diseases and PPC patients since the diagnostic distribution of their patients was not mentioned in these studies. Nevertheless, hypocalcemia observed in our study may have been due to vitamin D deficiency. The fact that our patient profile was composed of bedridden and palliative care patients with low exposure to the sun and living indoors at all times may explain the observed vitamin D deficiency and associated hypocalcemia.

In the same study, Carman et al. reported that children with CP exhibited low levels of zinc, vitamin A, phosphorus, and manganese [22]. In another study conducted on patients with CP, 14.5% of patients exhibited phosphorus deficiency [23]. In accordance with the findings of previous studies, our investigation revealed hypophosphatemia in 18.3% of patients.

In our PPC clinic, 59.6% of patients had neurologic and neuromuscular diagnoses. In studies conducted in children with chronic neurologic diseases similar to our study group, vitamin D deficiency was 12.6–76.9%, while vitamin D insufficiency was 15.7–61.0% [8, 21, 24–28]. A study of pediatric cancer patients revealed that vitamin D deficiency was prevalent both at baseline (64%) and during treatment (33–50%) [29]. One-third of the patients had low vitamin D levels. In addition, our study revealed a negative correlation between vitamin D levels and age, which is in contrast with the findings of Le Roy et al. [28]. Several factors contribute to the risk of vitamin D deficiency in PPC patients. These include low exposure to sunlight, nutritional difficulties, and polypharmacy, particularly for antiepileptics, which are commonly found in children with CP [30]. It may be posited that the low levels of 25-hydroxyvitamin D observed were due to a combination of facilitating factors. While this may appear to be a simple observation, it serves as a valuable reminder for clinicians working in this field regarding vitamin D supplementation. Concurrently, vitamin D is important for PPC patients because of its capacity to prevent a multitude of complications commonly observed in these patients, including fractures and susceptibility to infection.

In studies conducted on children with CP, magnesium levels were lower than those in the control group [23, 31]. Hypomagnesemia was reported in 45% and hypermagnesemia in 12% of patients with a history of chronic disease [20]. In their study, Carman et al. there was no significant difference between the magnesium levels of patients with CP and those of the control group [22]. Contrary to our initial expectations, our study revealed a greater rate of hypermagnesemia than hypomagnesemia in PPC patients. However, further research is required to substantiate these findings, which represent the highest rates reported in the literature.

The vitamin B12 deficiency observed in our patient was lower than that observed in other studies (1.1%) [8, 23, 32]. In addition, along with iron parameters, vitamin B12 was the only vitamin that did not correlate with age. In a study conducted in pediatric patients with malignancy, vitamin B12 deficiency was observed in 6% of patients at diagnosis and in 5% of patients at 18 months [10]. Due to the limited number of patients with malignant diseases included in our study, vitamin B12 levels were not evaluated. In a separate study, elevated vitamin B12 levels were observed in 32% of the patients with CP [23]. Elevated vitamin B12 levels were found to be 4.1 times greater in individuals aged 2–50 years with neurodevelopmental disorders than in controls [33]. Although low vitamin B12 levels may cause neurological problems, the mechanism of high vitamin B12 levels in patients with neurological problems (CP, muscular dystrophy etc.) is not fully understood [33]. However, it has been reported that high oxidative stress and hypoxia may cause high vitamin B12 levels [34, 35].

A previous study revealed that 67.5% of children with CP had inadequate daily dietary folate intake [36]. Folic acid deficiency has also been reported in 32% of patients with CP [23]. İspiroğlu et al. reported a folate deficiency of 10% in their study of patients who could not feed themselves due to neurological disease [32]. In contrast to the limited number of studies, we found folic acid deficiency in 5.1% and indeterminate in 16.1% of our patients. The reason for this phenomenon remains unknown due to the limitations of the study methodology. It has been hypothesized that nutritional status and micronutrient supplementation may be contributing factors. Further research is needed to confirm these findings.

In this study, iron levels were low in almost half of the patients. However, ferritin levels were low in only 7.4% of the patients. Previous studies have indicated that iron and ferritin levels are lower in children with CP [23, 28, 31, 37, 38]. Furthermore, Le Roy et al. observed a decline in ferritin levels with increasing age, consistent with the results of our study [28]. İspiroğlu et al. reported an iron

deficiency rate of 8% [32]. One study reported that iron deficiency was present in 19% of children receiving long-term enteral nutrition [39]. During our study, we did not assess the nutritional status or anemia status of the patients.

This study highlights the prevalence of micronutrient deficiencies among PPC patients. The findings underscore the necessity for regular monitoring of micronutrient levels in these patients and the importance of addressing deficiencies with appropriate supplements. In particular, vitamin D and calcium deficiencies warrant early diagnosis and treatment, as they can precipitate significant health issues in this patient group. Further research is needed to determine the micronutrient status of patients with PPC and to develop appropriate interventions.

Strengths and limitations

To the best of our knowledge, this study is the first to examine micronutrient levels in PPC patients.

Importantly, micronutrient levels may be misleading in cases of infection or inflammation [40]. Furthermore, antiepileptic drugs may induce micronutrient deficiencies owing to their impact on bone and mineral metabolism [41]. One of the limitations of our study was that all possible confounding factors for micronutrient levels (nutrition, micronutrient usage and metabolic, endocrinological, and infectious conditions) were not evaluated. Although tests performed for infectious conditions were excluded, it would have been beneficial to match them with laboratory and clinical findings and to evaluate and exclude bias and false negatives. In addition, differential diagnosis of low/high levels of micronutrients should have been conducted. For example, we should also have evaluated Methylmalonic Acid (MMA) level for low vitamin B12, CBC with differential and soluble iron transferrin receptors for low iron and ferritin, parathyroid hormone and ionized calcium for blood calcium level (although flawed as well in inflammation/chronic disease) [42, 43]. These additional tests could have provided additional information about micronutrient abnormalities and clarified the complexity. Since our study was retrospective, we were unable to evaluate laboratory problems (how blood samples are collected, transfer methods, the analysis process, the stage of the disease at which they are evaluated, and the timing of the evaluation according to the patient's hospitalization, etc.) that could affect micronutrient levels. Additionally, the inability to evaluate the status of other micronutrients (zinc, vitamin B1, etc.) that could not be studied at our hospital represents another limitation of our study.

Conclusions

This study highlights the prevalence of micronutrient deficiencies among PPC patients and the necessity of regularly monitoring micronutrient levels and administering appropriate supplements to address deficiencies, as these deficiencies can profoundly impact patient health. In particular, deficiencies of critical micronutrients, including vitamin D, calcium, iron, and phosphorus, can result in significant health complications in this patient group. Therefore, early diagnosis and treatment are of paramount importance. Moreover, further investigation of nutritional status and the effects of micronutrient supplements will contribute to improving the overall health status of PPC patients. These findings underscore the significance of micronutrient management in clinical practice and provide a foundation for future research. Identification and management of micronutrient deficiencies should be a fundamental aspect of multidisciplinary care to enhance the quality of life of PPC patients.

Abbreviations

CCC	Chronic Complex Conditions
CP	Cerebral palsy
IQR	Interquartile range
Min-max	Minimum-maximum
PPC	Pediatric Palliative Care
SD	Standard deviation

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

D.O. conceived of the presented idea. D.O. and S.Ç.S devised the project, the main conceptual ideas and proof outline. D.O., B.Ö. and N.H. developed the theory and performed the computations. S.Ç.S. collected and processed the data. D.O and S.Ç.S. analyzed the data. All authors discussed the results and contributed to the final manuscript.

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Data availability

The data sets generated and analyzed during the study are not publicly available due to the absence of permission for data set sharing obtained during the ethics committee approval process, and the absence of a request for permission to share data in the informed consent provided to participants.

Declarations

Ethics approval and consent to participate

Approval was obtained from the University of Health Sciences İzmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital Ethics Committee (09.28.2023/882).

Informed consent was obtained from all participants and/or their legal guardians. All methods were conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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