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Vitamin D intoxication with hypercalcemia and acute kidney injury

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Abstract

Background: Vitamin D intoxication in children mostly results from accidental overdosage. The resulting hypercalcemia can lead to hypercalciuria, nephrocalcinosis and acute kidney injury (AKI). Prognostic factors for kidney involvement are still barely known.

Methods and Case: We report the case of a 13-month-old girl with vitamin D intoxication due to accidental overdosage with a subsequent 25(OH)D-level of 661 ng/ml (N<100). Severe hypercalcemia (3.73 mmol/l, N2.25 – 2.75) and AKI (pRIFLE stage 3) with tubulointerstitial nephritis, nephrocalcinosis, and renal anemia were present. Low-calcium diet, hydration, forced diuresis and two doses of bisphosphonates (neridronate) were necessary to treat severe hypercalcemia. Serum calcium normalized within 12 days, normalization of 25(OH)D-level took 7 months. Nephrocalcinosis was still present after 7 months. We performed a literature research using Pubmed to analyse cases with vitamin D intoxication and renal involvement in children.

Results: We identified 46 cases of vitamin D intoxication in children with a medium age of 12.6 -1.0 months. The average vitamin D level was 497 ng/ml. In 45 of 46 cases hypercalcemia was reported with a mean serum ± calcium level of 4.07 mmol/l. Hypercalcemia normalized within 7.3 days in most cases. Nephrocalcinosis was present in 12 of 38 children examined by sonography. 8/13 children had a reduced eGFR at presentation (mean 72 ±32 ml/min/1.73m2). We were able to identify hypercalcemia as a positive predictor for the development of nephrocalcinosis in the reported cases with a cut-off value of 4.37 mmol/l.

Conclusions: Vitamin D intoxication can cause severe hypercalcemia, nephrocalcinosis and AKI. The level of hypercalcemia at initial presentation is a prognostic factor for the development of nephrocalcinosis in children.

Keywords: Vitamin-D-intoxication; Nephrocalcinosis; Hypercalcemia; Acute kidney injury.

Introduction

Vitamin D intoxication is rare but potentially life-threatening and can result in renal long-term consequences [1]. Main cause of vitamin D-intoxication is an accidental overdosage of prescribed medication or an incorrect use of over-the-counter supplements [2]. Rarely it is caused by genetic disorders of the vitamin D metabolism or by the excessive production of the vitamin D metabolite 1,25-$(OH)_2$D in granulomatous disorders, in idiopathic infantile hypercalcemia or in lymphomas [3]. 25(OH)D is produced in the liver from its precursor metabolite cholecalciferol, which is either a product from endogenous 7-dehydroxycholesterin or exogenous administered as vitamin D3 supplement or via nutrition [4]. The renal 1α-hydroxylase converts 25(OH)D to its active form 1,25-(OH)2D, which is regulated by a negative feedback by 1,25-(OH)2D, calcium, phos-

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phorus, fibroblast growth factor 23 (FGF-23) and activated by parathyroid hormone (PTH) [4]. Elevated 25(OH)D levels persist for several months as it is lipophilic and can be stored in adipose tissue [2, 5]. Laboratory findings in vitamin D intoxication are elevated 25(OH)D concentrations (> 150 ng/ml), severe hypercalcemia, hypercalciuria and a low or undetectable PTH [3,6]. Clinical symptoms of vitamin D intoxication include polyuria and polydipsia due to hypercalciuria, cardiovascular symptoms such as QT-shortening or ST segment elevation, neurological manifestations such as apathy, confusion and drowsiness or gastrointestinal symptoms e.g. vomiting, abdominal pain and failure to thrive [3,7-9]. Hypercalciuria and urinary supersaturation of calcium induces intra- and extratubular accumulation of calcium salts in the kidney leading to AKI with tubulointerstitial nephritis and nephrocalcinosis [10]. The deposition of calcium salts and crystals at the tubulointerstitium may induce tubular necroptosis, a programmed cell death driven by activation of immune cells and pro-inflammatory cytokines, thereby aggravating renal failure [11].

The therapy for vitamin D intoxication includes elimination of exogenous vitamin D supply, calcium reduced diet and forced diuresis [12]. Further options are the administration of prednisolone or bisphosphonates (BS) [13,14]. So far, there is only limited data about the efficiency and long-term course of the different treatment strategies. Here, we report a 7-month follow-up of a child with severe vitamin D intoxication treated with BS and give a systematic overview of the literature of published cases with vitamin D intoxication in children including treatment regimes.

Case report

A 13-month-old girl diagnosed with failure to thrive was admitted to a peripheral hospital for further evaluation. The patient presented with pallor, loss of appetite and mild developmental regression. A maximum creatinine of 1.65 mg/dl (N <0,3) and sonographic hyperechogenic kidneys were found. With the suspicion of unexplained chronic kidney disease, the patient was transferred to our hospital after 4 days of treatment with intravenous fluid administration. The medical history was unremarkable for previous illnesses. Upon presentation an inadequate weight gain with 7.1 kg (1st percentile) and a height of 72 cm (3rd percentile) was evident after normal thrive in the first 6 months of life (weight 22th percentile, height 41. percentile). There were no signs of infection. Laboratory blood testing (**Figure 1A**) showed acute renal injury (AKI) (creatinine 1.2 mg/dl; cystatin c 1.79 mg/l; urea 38 mg/dl). AKI was classified as pRIFLE stage 3 (eGFR 33 ml/min/1.73m², N 105+12; cystatin C GFR 48 ml/min/1.73m², N 92+12). Additional findings were severe hypercalcemia (3.73 mmol/l, protein-corrected), anemia (hemoglobin 9.2 g/dl, normochromic, normocytic) and a very low parathyroid hormone (10.1 pg/ml). Urine testing showed hallmarks of tubulointerstitial nephritis with tubular proteinuria (alpha-1-microglobulin/creatinine quotient 20 mg/g, N<14), decreased tubular phosphate reabsorption (63%, N>80%) and decreased water reabsorption (93.2%, N>98.5). There was also an increased fractional sodium (4.82%, N<1) and chloride excretion (6.52%, N<1). An increased calcium-creatinine quotient was initially not detectable. The renal sonography showed enlarged and hyperechogenic kidneys (**Figure 1B**). There was no evidence of detritus or kidney stones. As the laboratory values were suggestive for vitamin D intoxication, the supplements administered were analyzed. The daily vitamin D dosage was found to be far above the recommended norm of 500 IU daily. Due to a 10-fold higher concentration of over-thecounter suspension, the patient received 20.000 IU per day for more than 8 weeks. The patient's entire vitamin D intake for the first 13 months of life was thus eight times higher than the recommended intake. The 25(OH)D level was markedly increased to 661 ng/ml (N 20-100) and the vitamin D-1,25 was 575 ng/l (N 25-154). A calcium-reduced diet and forced diuresis with intravenous fluid substitution combined with furosemide (maximum 7 mg/kg/d) were started (**Figure 1C**). Bisphosphonates (neridronate 2 mg/kg/d) were given on day 2 and 3. For renal anemia and iron deficiency additional subcutaneous administration of erythropoietin and iron supplementation were necessary. Furthermore, the patient developed arterial hypertension, which was treated with amlodipine. Normal creatinine levels were achieved on day 7, normal cystatin C concentrations on day 90, and normocalcemia on day 12 after therapy initiation. The patient was discharged on day 23. Vitamin D levels normalized 7 months after diagnosis. However, the kidneys were still hyperechogenic at that timepoint.

Methods and Statistical Analysis

We performed a literature research at PubMed using the key words "pediatric", "vitamin D intoxication", and "bisphosphonate" and identified 46 pediatric cases from 10 single case reports or case series published in the years 2011 – 2021 [1-3,7-9,12-21]. We selected case reports with reported vitamin D, PTH, and serum calcium concentrations. We calculated the eGFR in ml/min/1.73m² using the Schwartz formula [22]. In cases without height documentation, an age and sex adapted height of the 50th percentile was used to calculate the eGFR [23]. In 38 of the 46 cases, where both serum calcium and nephrocalcinosis were reported, binary logistic regression was performed using SPSS v28 to assess the predictive capacity of serum calcium on the development of nephrocalcinosis.

Results

We analyzed 46 pediatric cases with vitamin D intoxication from 10 single case reports or case series published in the years 2011 – 2021 (**Figure 2A**) [1-3,7-9,12]. Reasons for vitamin D intoxication in the studied cases included high doses prescribed by physicians, manufacturing errors in dietary supplements, self-medication with over-the-counter supplements, enriched fish oil, or accidental overdose (**Table 1**). Median age at presentation was 12.6 months ± 1.0 months (**Figure 2A**). Renal function parameters were documented in 13 of 46 cases with a mean GFR of 72.1 ± 32 ml/min/1.73m² (Figure 2A). Eight of these 13 children presented with a reduced eGFR defined as an eGFR lower than 1 standard deviation from

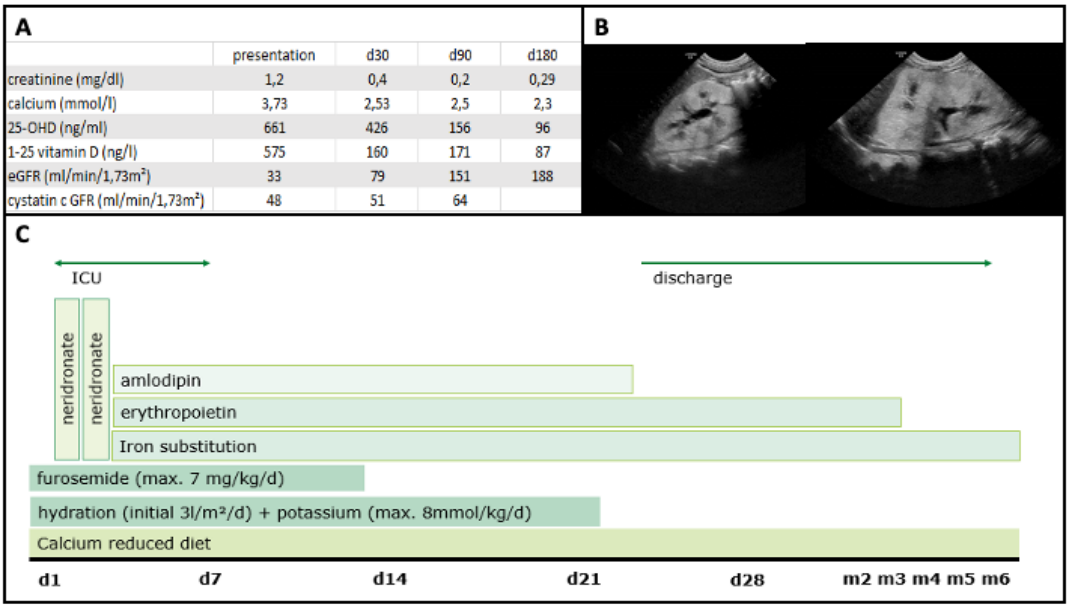

Figure 1: *(A) Laboratory of our patient at presentation, day 30, day 90 and day 180. (B) sonographic hyperechogenic kidneys of our patient. (C) patient´s treatment plan. D: day; m: month; ICU: intensive care unit.*

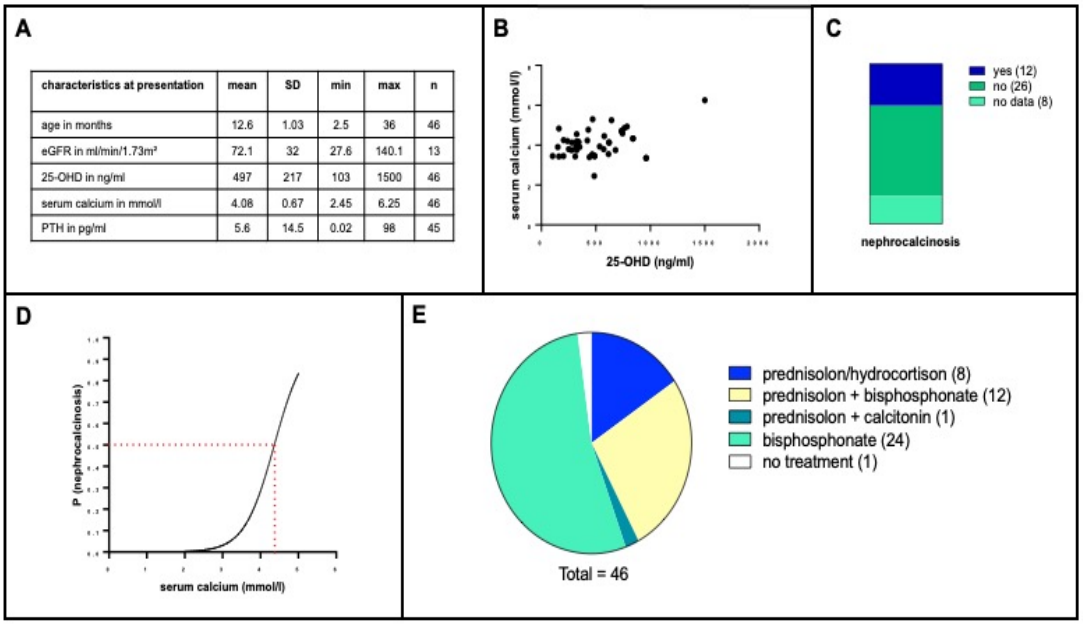

Figure 2: *(A) Clinical and laboratory characteristics of reported cases (n = 46). Max: maximum, min: minimum, SD: standard deviation. (B) Presence of nephrocalcinosis in pediatric cases of vitamin D intoxication. In 12 of 46 children nephrocalcinosis (NC) was detected, 26 patients did not show any signs of NC and in the remaining 8 cases no kidney sonography was reported. (C) 25-(OH)D (ng/ml) levels do not correlate with serum calcium levels of reported cases. (D) Serum calcium level predict nephrocalcinosis. The cut-off serum calcium level to predict nephrocalcinosis in more than 50% is 4.37 mmol/l with an overall classification accuracy of 78.9 %. (E) Distribution of applied treatment regimes. A total of 46 pediatric cases with vitamin D intoxication was analyzed.*

the age specific references values according to KDIGO 2012 Guideline24. Measured 25(OH)D levels revealed a high variability with a mean 25(OH)D level of 497 ± 217 ng/ml (N <150) (**Figure 2A**). Hypercalcemia was present in 45 of 46 cases with a mean serum calcium level of 4.08 ± 0.6 mmol/l (N 2.2-2.7) (**Figure 2A**). The measured PTH values showed high variability with a mean of 5.6 + 14.5 pg/ml (N 13-65) (**Figure 2A**). No significant correlation was found between 25(OH)D levels and serum calcium levels (**Figure 2B**). Sonography of the kidneys was performed in 38 of 46 cases, which revealed the presence of nephrocalcinosis in 12 cases (**Figure 2C**). The binary logistic regression model identified hypercalcemia as a positive predictor to develop nephrocalcinosis (**Figure 2D**). The model was valid and with a Cohen's coefficient of 0.22 the effect size can be classified as medium. Odds ratio to develop nephrocalcinosis is 1.286 for every 0.1 mmol/l increase in serum calcium. The cut-off serum calcium level to predict nephrocalcinosis in more than 50% is 4.37 mmol/l with an overall classification accuracy of 78.9 %. (**Figure 2D**). Fortyfive of 46 patients received i.v.-hydration and diuretics. Forty of 46 patients received a calcium-reduced diet. In all 46 cases the supportive therapy was not sufficient to control the hypercalcemia. Hence, further therapy was needed. With 80 % of all patients included in this analysis, the vast majority received bisphosphonates (**Figure 2E**). The two active ingredients prescribed were pamidronate and alendronate. Eight of 46 children were treated with cor-

tisone only, of which 7 patients got prednisolone and one received hydrocortisone. Twelve patients were treated with the combination of prednisolone and bisphosphonate. Only one patient got calcitonin and prednisolone (**Figure 2E**).

Discussion

Vitamin D intoxication can lead to severe renal complications such as AKI and long-lasting nephrocalcinosis [2]. In recent years, the number of affected pediatric patients seems to have increased with the growing use of vitamin D supplementation [3,8,14]. Infants are at highest risk since they are exposed to daily supplementation [3]. Here, we analyzed 46 published cases of vitamin D intoxication showing that the mean age of the patients was 12.6 months. The presented 13-month-old girl belongs to this most affected age group of hypervitaminosis D. Very recently, Lin et al. presented 44 patients with vitamin D intoxication with a mean age of 17.5 months [25]. Hence, especially in infants with hypercalcemia, vitamin D intoxication should be considered as a relevant differential diagnosis. The level of 25(OH)D in our patient was 661 ng/ml (N <150), which was higher than the mean 25(OH)D level of 497 ng/ml in our 46 reviewed cases with vitamin D intoxication. Lin et al. reported a mean 25(OH)D level of 124 ng/ml, which was much lower than the levels reported in our reviewed cases. A possible explanation could be the fact that only 45.5% of the included children in their study met the criteria for hypervitaminosis [25]. Our analysis of 46 cases with vitamin D intoxication showed no significant correlation between the measured 25(OH)D levels and the serum calcium concentration. These findings are consistent with data from older case series and meta-analyses [2,14]. Polymorphisms in genes that regulate vitamin D metabolism may explain the lack of correlation. Genome-wide association studies showed that single nucleotide polymorphisms (SNPs) of the vitamin D binding protein and of proteins that regulate the synthesis or hydroxylation of 25(OH)D have an impact on the 25(OH)D levels [26-28].

AKI caused by hypercalciuria and nephrocalcinosis was present in 62% (8 of 13 children) of our reviewed cases. These eight children had a reduced eGFR at presentation. By contrast, Lin et al. reported AKI in only 9% (4 of 44 children) with a mean serum creatinine of 0.5 mg/dl [25]. This difference could be explained by a more severe vitamin D intoxication with 1.5-fold higher mean serum calcium levels in our reviewed cases (4.08 mmol/l) compared to the study of Lin et al. (2.57 mmol/l) [25]. In our patient with AKI (pRIFLE stage 3) the eGFR was only 33 ml/min/1.73m2 at presentation and recovered slowly over time. The AKI following vitamin D intoxication was caused by tubulointerstitial nephritis with tubular proteinuria (alpha-1microglobulin/creatinine quotient 20 mg/g, N<14), loss of sodiumchloride, glucosuria as well as a decreased concentration capacity (water reabsorption 93.2%, N>98.5). This tubulointerstitial nephritis may be caused by toxic effects of calcium salts and crystals, which form in the tubular lumen due to supersaturation of calcium [10]. Calcium crystals in the kidney not only cause kidney injury by obstructing the tubular lumen, but also elicit a variety of cytotoxic effects on renal tubular cells by triggering inflammation [11]. They can activate transmembrane surface receptors, which mediate necroptosis in renal tubular cells, a regulated form of necrosis and necroinflammation [11]. The process of self-amplifying necroinflammation might be the explanation for the time gap between normalization of serum calcium levels and kidney function. In our patient, normocalcemia was achieved on day 12 after therapy initiation, whereas it took 90 days until normalization of cystatin C concentrations, demonstrating that acute kidney injury was still ongoing.

Our analysis of 46 published cases showed that 38 children were checked by renal sonography, which revealed nephrocalcinosis in 31%. This is in line with the very recent study of Lin et al. showing that nephrocalcinosis was present in 32% children with hypervitaminosis D (14 of 44 patients) [25]. Unfortunately, no conclusion could be drawn about the course of nephrocalcinosis after normalization of serum calcium. This is due to lack of data in the analyzed case reports and studies. In our patient, nephrocalcinosis was still present 7 months after normalization of serum calcium levels. One case report still showed calcified spots in the renal tissue after one year, while the published data by Lin et al. showed persistent nephrocalcinosis over 5 years of follow-up [19,25], underlining the importance of kidney monitoring in patients with vitamin D intoxication.

Serum calcium levels above 3.5 mmol/l are known to cause further organ damage, but there is very limited data about risk factors and long-term consequences of renal involvement [1]. Here, we were able to identify a cut-off serum calcium level of 4.37 mmol/l to predict the development of nephrocalcinosis. When reaching this calcium level, the estimated risk for nephrocalcinosis is above 50 %. Nevertheless, in our patient a maximum serum calcium level of 3.73 mmol/l was sufficient to cause nephrocalcinosis. Our findings imply that patients with vitamin D intoxication should have routine check-up for renal involvement including sonography and renal function parameters for at least several years. Further prognostic factors for nephrocalcinosis following vitamin D intoxication are low body weight <10.25 kg and height <78.5 cm. In particular the body surface area (BSA) <0.475 m^2 is a significant prognostic predictor of nephrocalcinosis, emphasizing the need for renal check-ups in the very small and young infants with hypervitaminosis D [25]. The basic management of vitamin D intoxication includes vitamin D restriction, calcium reduced diet and forced diuresis [12]. A case series from 1948 showed that it takes up to 1 year to achieve normocalcemia when only those two treatment options were available [29]. Hence, almost every case requires further medication. The most common drugs used in our analysis were bisphosphonates such as pamidronate 20/46, alendronate 4/46 and prednisolone 8/46 or a combination of both 12/46. Retrospective studies revealed a significant superior effectiveness of bisphosphonates towards prednisolone regarding the management of hypercalcemia. Time to normalization of serum calcium and relapses of hypercalcemia are lower when bisphosphonates are used [1,12,14]. In our case report, we used two shots of neridronate and achieved normocalcemia on day 12. No side effects were observed, and no major complications of bisphosphonates were reported in the reviewed cases. We summarize that severe hypercalcemia due to vitamin D intoxication should be treated with bisphosphonates, as it is well tolerated and the most efficient medication to treat hypercalcemia.

Conclusion

Every child with severe vitamin D intoxication and hypercalcemia should be checked for renal complications including assessment of renal function parameters und renal sonogra-

phy. Beyond the basic therapeutic management consisting of vitamin D restriction and forced diuresis, the administration of bisphosphonates should be considered. Administration of bisphosphonate in children is safe and the most effective treatment for hypercalcemia in vitamin D intoxication.

Conflict of interest:

The authors declare no conflict of interest.

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References

1. Sezer RG, Guran T, Paketçi C, Seren LP, Bozaykut A, Bereket A. Comparison of oral alendronate versus prednisolone in treatment of infants with vitamin D intoxication. Acta Paediatr 2012; 101(3): e122-5. [DOI: 10.1111/j.1651-2227.2011.02497.x].

2. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD. Vitamin D supplementation and risk of toxicity in pediatrics: a review of current literature. J Clin Endocrinol Metab 2014; 99(4): 113241. [DOI: 10.1210/jc.2013-3655].

3. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Płudowski P, Jones G. Vitamin D Toxicity-A Clinical Perspective. Front Endocrinol (Lausanne) 2018; 9: 550. [DOI: 10.3389/fendo.2018.00550].

4. de Paula FJ, Rosen CJ. Vitamin D safety and requirements. Arch Biochem Biophys 2012; 523(1): 64-72. [DOI: 10.1016/j.abb.2011.12.002].

5. Shroff R, Knott C, Rees L. The virtues of vitamin D--but how much is too much? Pediatric nephrology (Berlin, Germany) 2010; 25(9): 1607-20. [DOI: 10.1007/s00467-010-1499-9].

6. Tebben PJ, Singh RJ, Kumar R. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment. Endocr Rev 2016; 37(5): 521-547. [DOI: 10.1210/er.2016-1070].

7. Tripty N, Tushar J, Sunil J. Vitamin D Intoxication Presenting as Subacute Encephalopathy-A Case Report. Child Neurol Open 2021; 8: 2329048x211008075. [DOI: 10.1177/2329048x211008075].

8. Galior K, Grebe S, Singh R. Development of Vitamin D Toxicity from Overcorrection of Vitamin D Deficiency: A Review of Case Reports. Nutrients 2018; 10(8). [DOI: 10.3390/nu10080953].

9. Ozkan B, Hatun S, Bereket A. Vitamin D intoxication. Turk J Pediatr 2012; 54(2): 93-8.

10. Habbig S, Beck BB, Hoppe B. Nephrocalcinosis and urolithiasis in children. Kidney Int 2011; 80(12): 1278-91. [DOI: 10.1038/ki.2011.336].

11. Mulay SR, Desai J, Kumar SV, et al. Cytotoxicity of crystals involves RIPK3-MLKL-mediated necroptosis. Nat Commun 2016; 7: 10274. [DOI: 10.1038/ncomms10274].

12. Kara C, Çetinkaya S, Gündüz S, Can Yılmaz G, Aycan Z, Aydın M. Efficacy and safety of pamidronate in children with vitamin D intoxication. Pediatr Int 2016; 58(7): 562-8. [DOI: 10.1111/ped.12875].

13. Sagsak E, Savas-Erdeve S, Keskin M, Cetinkaya S, Aycan Z. The use of pamidronate for acute vitamin D intoxication, clinical experience with three cases. J Pediatr Endocrinol Metab 2015; 28(5-6): 709-12. [DOI: 10.1515/jpem-2014-0279].

14. Demir K, Döneray H, Kara C, et al. Comparison of Treatment Regimens in Management of Severe Hypercalcemia Due to Vitamin D Intoxication in Children. J Clin Res Pediatr Endocrinol 2019; 11(2): 140-148. [DOI: 10.4274/jcrpe.galenos.2018.2018.0131].

15. Zhou L, Taylor-Miller T, Zacharin M, Efron D. Extreme hypercalcaemia due to accidental vitamin D intoxication. J Paediatr Child Health 2019; 55(1): 104-106. [DOI: 10.1111/jpc.14127.]

16. Waheed N, Cheema HA, Saeed A, et al. Vitamin D Intoxication In 7-Month-Old Infant With Recommended Daily Intake Of Vitamin D. J Ayub Med Coll Abbottabad 2018; 30(4): S673-s675.

17. Simm PJ, Biggin A, Zacharin MR, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health 2018; 54(3): 223-233. [DOI: 10.1111/jpc.13768].

18. Kara C, Gunindi F, Ustyol A, Aydin M. Vitamin D intoxication due to an erroneously manufactured dietary supplement in seven children. Pediatrics 2014; 133(1): e240-4. [DOI: 10.1542/peds.2013-0711].

19. Conti G, Chirico V, Lacquaniti A, et al. Vitamin D intoxication in two brothers: be careful with dietary supplements. J Pediatr Endocrinol Metab 2014; 27(7-8): 763-7. [DOI: 10.1515/jpem-2013-0220].

20. Ketha H, Wadams H, Lteif A, Singh RJ. Iatrogenic vitamin D toxicity in an infant--a case report and review of literature. J Steroid Biochem Mol Biol 2015; 148: 14-8. [DOI: 10.1016/j.jsbmb.2015.01.022].

21. Bilbao NA. Vitamin D Toxicity in Young Breastfed Infants: Report of 2 Cases. Glob Pediatr Health 2017; 4: 2333794x17731695. [DOI: 10.1177/2333794x17731695].

22. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clinical journal of the American Society of Nephrology : CJASN 2009; 4(11): 1832-43. [DOI: 10.2215/cjn.01640309].

23. Klaus R, Jansson AF, Griese M, Seeman T, Amann K, Lange-Sperandio B. Case Report: Pediatric Renal Sarcoidosis and Prognostic Factors in Reviewed Cases. Frontiers in pediatrics 2021;9:724728. (In eng). DOI: 10.3389/fped.2021.724728.

24. Chapter 1: Definition and classification of CKD. Kidney international supplements 2013; 3(1): 19-62. [DOI: 10.1038/kisup.2012.64].

25. Lin TH, Lu HJ, Lin CH, et al. Nephrocalcinosis in children who received high-dose vitamin D. Pediatr Nephrol 2022. [DOI: 10.1007/s00467-022-05512-6].

26. Jiang X, O'Reilly PF, Aschard H, et al. Genome-wide association study in 79,366 Europeanancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nature communications 2018; 9(1): 260. [DOI: 10.1038/s41467-017-02662-2].

27. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide associa-

tion study. Lancet (London, England) 2010; 376(9736): 180-8. [DOI: 10.1016/s0140-6736(10)60588-0].

28. Sinotte M, Diorio C, Bérubé S, Pollak M, Brisson J. Genetic polymorphisms of the vitamin D binding protein and plasma concentrations of 25-hydroxyvitamin D in premenopausal women. The American journal of clinical nutrition 2009; 89(2): 634-40. [DOI: 10.3945/ajcn.2008.26445].

29. Howard JE, Meyer RJ. Intoxication with vitamin D. The Journal of clinical endocrinology and metabolism 1948; 8(11): 895-910. [DOI: 10.1210/jcem-8-11-895].