Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 10: 1–6

DOI: 10.1177/2050313X211068562
journals.sagepub.com/home/sco
SAGE

Hypercalcemia associated with dysgerminoma and elevation of calcitriol: A case report and review of the literature

Natsuko Hara[1], Hirotsugu Suwanai[1], Hironori Abe[1], Fumiyoshi Yakou[1], Takuya Ishikawa[1], Munehiro Urayama[1], Takeshi Nagai[2], Toshitaka Nagao[2], Jumpei Shikuma[1], Takashi Miwa[1], Ryo Suzuki[1] and Masato Odawara[1]

Abstract

We report on the case of a patient with dysgerminoma, a rare germ cell tumor, which showed hypercalcemia with an elevation of 1α,25-dihydroxycholecalciferol (calcitriol). A 27-year-old nulliparous woman presented with hypercalcemia during the examination of a right ovarian tumor with an elevation of calcitriol, lactate dehydrogenase, and alkaline phosphatase. Fractional excretion of calcium was elevated, and intact parathyroid hormone was suppressed. After undergoing right salpingo-oophorectomy, the patient's serum calcium and calcitriol returned to the normal range within a week. A literature search was conducted on the topic by reviewing databases for dysgerminoma showing hypercalcemia. We identified 14 patients from the literature and performed a pooled analysis, including the results of our case. However, most cases lack data that can help investigate the potential association between parathyroid hormone, parathyroid hormone-related protein, calcitriol, and phosphorus in hypercalcemia. Thus, more case reports that include additional information are required to fully elucidate the mechanism of hypercalcemia associated with dysgerminoma.

Keywords

Dysgerminoma, hypercalcemia, calcitriol

Date received: 6 July 2021; accepted: 2 December 2021

Introduction

Hypercalcemia accounts for approximately 0.6% of all acute hospitalizations, and malignancy is its primary cause (45%).[1] Ovarian germ cell tumors have an incidence of 20%–25% of all ovarian neoplasms, but less than 5% are malignant.[2,3] Of these, 32.8% correspond to germinoma, a female analog of seminoma.[4] Thus, dysgerminoma is a rare disease and accounts for only around 2% of all malignant ovarian neoplasms.[5] Some case reports of hypercalcemia due to dysgerminoma have been reported. Here, we report one case that was experienced at our facility, and a review of the association between dysgerminoma and hypercalcemia with an elevation of 1α,25-dihydroxycholecalciferol (calcitriol).

Case presentation

A 27-year-old nulliparous woman presented to the gynecology department with a complaint of lower abdominal pain that had persisted for 2 weeks. A massive tumor was found in the patient's ovary. The patient was referred for hypercalcemia, which was revealed during the examination of the tumor. She had no symptoms of nausea, vomiting, change in mental status, loss of appetite, or polyuria. She had no past medical histories or any family history of illness. The computed tomography scan revealed a right solid ovarian mass measuring $12.3 \times 11.8 \times 11.0\,cm^3$ without evidence of metastases (Figure 1(a)). Magnetic resonance imaging showed a heterogeneous mass that did not appear

[1]Department of Diabetes, Metabolism, Endocrinology, Rheumatology and Collagen Diseases, Tokyo Medical University, Tokyo, Japan
[2]Department of Pathology, Tokyo Medical University, Tokyo, Japan

Corresponding Author:
Hirotsugu Suwanai, Department of Diabetes, Metabolism, Endocrinology, Rheumatology and Collagen Diseases, Tokyo Medical University, 6-7-1 Nishishinjyuku, Shinjyuku-ku, Tokyo 160-0023, Japan.
Email: suwanai-h@umin.ac.jp

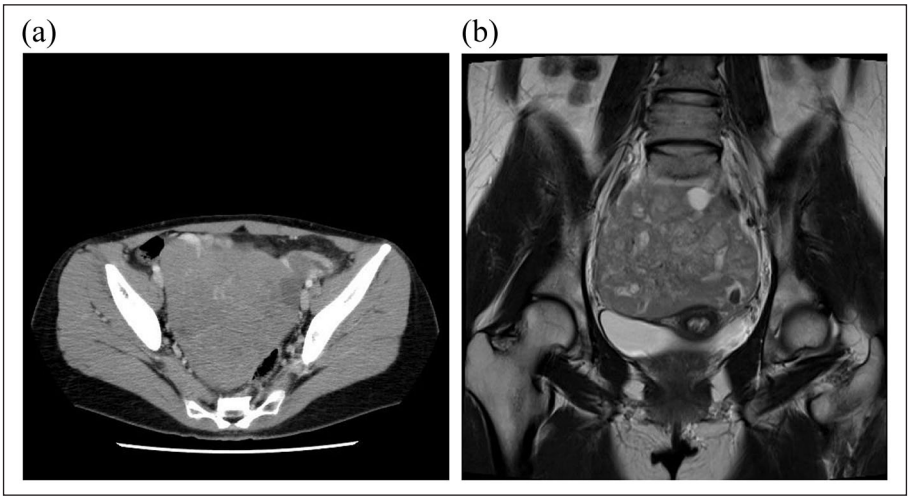

Figure 1. Imaging findings. (a) Computed tomography scan of abdomen. A large mass of approximately 12 cm occupies the pelvic cavity. Although the mass comprised mainly solid components, partially cystic components are also present. (b) Magnetic resonance imaging T2-weighted image shows a heterogeneous mass with no fat component.

to contain fat tissue (Figure 1(b)). Laboratory data showed the following (Table 1): serum calcium—13.3 mg/dL (normal range: 8.2–10.2); albumin—4.4 g/dL (3.9–4.9); phosphorous—3.7 mg/dL (2.5–4.7); magnesium—2.2 mg/dL (1.8–2.7); lactate dehydrogenase (LDH)—1411 U/L (70–120); alkaline phosphatase (ALP)—399 U/L (104–338); parathyroid hormone (PTH)—6 pg/mL (10–65); PTH-related protein (PTHrP) ⩽ 1.0 pmol/L (< 1.1); calcitriol—96.9 pg/mL (20–60); 25 (OH) vitamin D—15.2 ng/mL (< 20); fractional excretion of calcium (FeCa)—3.51%; fractional excretion of phosphate (FeP)—25.1%; blood urea nitrogen (BUN)—16.6 ng/dL (0.4–0.8); creatinine—0.93 mg/dL (0.4–0.8); CA125—49.1 U/mL (< 35); and alpha fetoprotein (AFP)—1.9 ng/mL (< 10.0). The serum calcium level increased rapidly, while the symptoms of hypercalcemia (nausea and loss of appetite) occurred in parallel. Hypercalcemia was treated by saline diuresis and calcitonin, but medical treatments only had a marginal effect. The patient underwent a right salpingo-oophorectomy with the removal of the right ovarian tumor. The right ovary measured $13 \times 12.5 \times 6.5\,cm^3$ (Figure 2(a)). Histology findings revealed large and rounded homogeneous tumor cells with prominent nucleoli and abundant cytoplasm. Infiltration of small lymphocytes, which are typical dysgerminoma features, was also observed, and the tumor cells did not transgress the capsule (Figure 2(b)). The cytology of the ascitic fluid showed no tumor cells, and there was no evidence of metastasis. As a consequence of the findings, the patient was diagnosed with stage pT1aNxM0 (UICC, 2009) and stage Ia (FIGO, 2014). On the first postoperative day, the level of serum calcium decreased to within the normal range without any medical treatment (Figure 3). Likewise, calcitriol was corrected within a week after the surgery. The following data were collected a week after the surgery: serum

Table 1. Laboratory data at first visit.

Laboratory value	Reference range	RResult
White blood cell count (/μL)	2700–8800	3600
Red blood cell count (/μL)	$3.7–5.4 \times 10^6$	4.02×10^6
Hemoglobin (g/dL)	11.0–17.0	12.3
Hematocrit (%)	34.0–49.0	35
Platelet count (/μL)	$140.0–340.0 \times 10^3$	179.0×10^3
Aspartate aminotransferase (IU/L)	8–38	40
Alanine aminotransferase (IU/L)	4–44	12
LDH (IU/L)	106–211	1411
Total protein (g/dL)	6.6–8.2	7.2
Albumin (g/dL)	3.9–4.9	4.4
Total bilirubin (mg/dL)	0.2–1.2	0.43
Urea nitrogen (mg/dL)	2.5–6.3	16.6
Sodium (mEq/L)	138–148	139
Potassium (mEq/L)	3.6–5.2	4.3
Chlorine (mEq/L)	98–108	104
Calcium (mg/dL)	8.2–10.2	13.3
Magnesium (mg/dL)	1.8–2.7	2.02
Phosphate (mg/dL)	2.5–4.7	3.7
Creatinine (mg/dL)	0.4–0.8	0.93
Estimate glomerular filtration rate (mL/min/1.73 m^2)	–	60.3
Intact PTH (pg/mL)	10–65	6
PTHrP (pmol/L)	< 1.1	⩽ 1.0
Calcitriol (pg/mL)	20–60	96.9
25(OH) vitamin D (ng/mL)	> 20	15.2
FeCa (%)	–	3.51
FeP (%)	–	25.1

PTH: parathyroid hormone; PTHrP: parathyroid-related protein; FeP: fractional excretion of phosphate; FeCa: fractional excretion of calcium; LDH: lactate dehydrogenase.

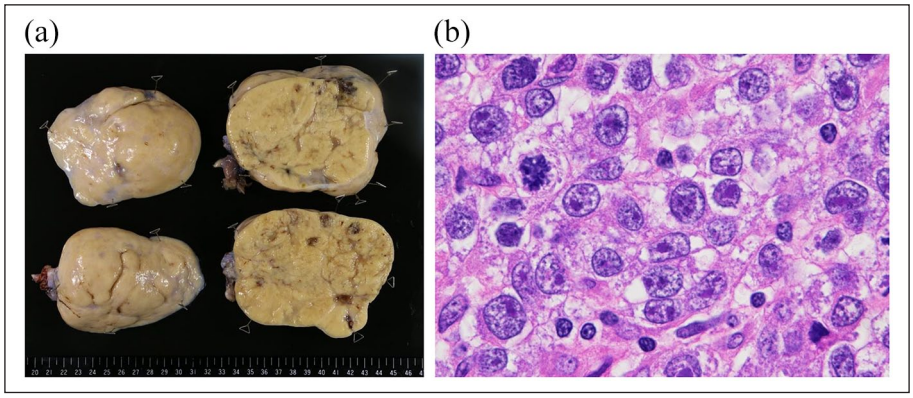

Figure 2. Pathological findings. (a) The right ovary measured 13 × 12.5 × 6.5 cm^3. (b) Large and rounded homogeneous tumor cells with prominent nucleoli and abundant cytoplasm, and infiltration of small lymphocytes can be observed.

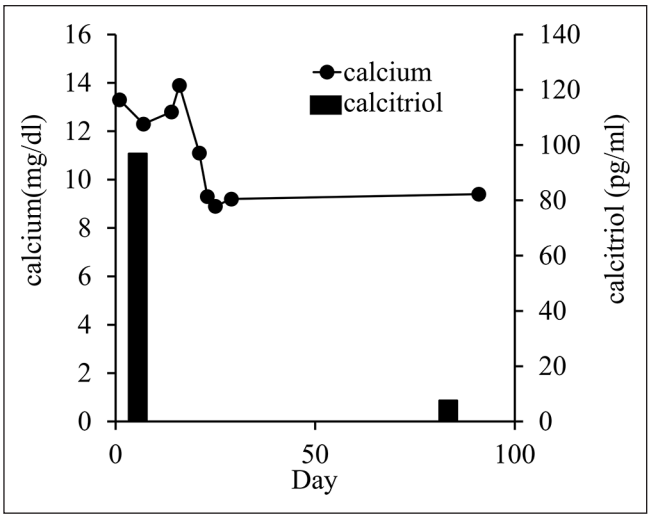

Figure 3. Data for calcium and calcitriol before and after therapy. Though medical treatment only had a marginal effect, the level of serum calcium immediately decreased to levels within the normal range after surgical treatment.

calcium—9.2 mg/dL; albumin—3.7 g/dL; phosphorous—3.5 mg/dL; magnesium—1.9 mg/dL; LDH—356 U/L; ALP—197 U/L; intact PTH—28 pg/mL; PTHrP ≤ 1.0 pmol/L; calcitriol—7.6 pg/mL; 25 (OH) vitamin D—9.1 ng/mL; FeCa—1.2%; FeP—13.6%; BUN—10.9 ng/dL; and creatinine, 0.73 mg/dL. However, 3 months after diagnosis, her calcium level remained normal, and there was no evidence of recurrence.

Discussion

Two researchers searched the electronic database PubMed (1990 to May 2019) independently with the Medical Subject Headings terms "dysgerminoma" and "hypercalcemia." The selected papers, which included case reports of hypercalcemia due to dysgerminoma, were evaluated. Ultimately, 13 papers, including 14 cases, matched our criteria and are summarized below as a literature review.

In total, we found 14 cases in addition to the current case that met our eligibility criteria (Table 2). All cases developed in patients less than 30 years of age, and abdominal pain, nausea, and loss of appetite were observed in seven, seven, and six cases, respectively. In five patients, where calcitriol was measured before surgery, the values were higher than the standard values in all cases and intact PTH values were suppressed except in one case. Furthermore, in these five cases, the PTHrP values were only elevated in one case. Phosphorus was also detected in two cases, including our case, and was not elevated in any of the other cases. In 10 cases that described phosphorus, 2 cases had high levels; in 1 case, it was low; and in the other cases, phosphorus was within the reference range. Intact PTH was described for 11 cases; in 10 cases, it was below the standard value and in 1 case, it was high. In six cases where PTHrP was measured, the values were elevated in two cases. In addition, seven cases were diagnosed as stage III or higher.

In our study, the major symptoms of dysgerminoma were abdominal pain, nausea, and loss of appetite. The calcitriol values were higher than standard in five cases where the values were measured before surgery and the values decreased to normal level soon after the surgeries. In four cases, intact PTH values were suppressed and PTHrP values were not elevated.

In our case, we measured calcium, calcitriol, intact PTH, PTHrP, and phosphorus before and after the surgery. We saw a significant decrease in calcium and calcitriol after resection of the tumor in our case and in other cases where calcitriol was measured. These results strongly suggest that the cause of hypercalcemia was the oversecretion of calcitriol, which is one of the major mechanisms of cancer-associated hypercalcemia. It is conceivable that ovarian tumors secrete calcitriol ectopically, or that the tumors have an abnormal expression of 1α-hydroxylase. Previous reports have indicated that lymphomas secrete calcitriol ectopically, while some reports suggest that calcitriol secreting tumors lead to hypercalcemia in dysgerminoma.[6,11,19] Furthermore, some studies report that 1α-hydroxylase is focally expressed in dysgerminoma tumor cells.[9,11] Consequently, it has been

Table 2. Review of reported cases and our case.

Author, year (Citation)	Age (years)	Symptoms	Ca (mg/dL)	P (mg/dL)	Int-PTH (pg/mL)	PTHrP (pmol/L)	Calcitriol (pg/mL)	Treatment for hypercalcemia pre-operation	Treatment for dysgerminoma	Mechanism of hypercalcemia
Our case	27	Nausea, loss of appetite, abdominal pain	13.3	3.70	6	⩽1.0	96.9	Hydration, calcitonin	RSO	Elevated calcitriol
Hosseini et al. (2019)[6]	12	Bone pain	13.39	N	112	0.122	175.4	Hydration, pamidronate, calcitonin, glucocorticoids	LSO	Elevated calcitriol, elevated PTHrP
Hosseini et al. (2019)[6]	16	Nausea, loss of appetite, abdominal pain, lethargy	11.18	N	5	N	87.9	Hydration	RSO, OE, PW	Unspecified
Nourani et al. (2013)[7]	9	Constipation	14.5	3.20	8	<2.1	N	Hydration, furosemide	LSO	Unspecified
Jawaid et al. (2011)[8]	10	Abdominal pain, lethargy	15.11	N	N	N	N	Hydration, bisphosphonate therapy	BSO, OE, resection of tumor	Unspecified
Wald et al. (2009)[9]	13	Nausea, loss of appetite, abdominal pain, frequent urination	14.9	N	N	N	19	Hydration, furosemide	LSO, left PPAL	Unspecified
Matthew et al. (2006)[10]	16	Loss of appetite, fatigue	15.4	3.58	8	<0.3	N	Hydration, furosemide	LSO, PLB	Unspecified
Evens et al. (2004)[11]	18	N.P.	15.9	1.80	11.3	0.3	71	Intravenous pamidronate therapy	N	Elevated calcitriol
Radhakrishna et al.(2001)[12]	26	Nausea, constipation, abdominal pain	16.39	3.22	8.487	N	N	Hydration, furosemide	BSO, IOE, PPAL	Unspecified
Okoye et al. (2001)[13]	14	Nausea, loss of appetite, constipation, abdominal pain	15.03	3.38	5	N	N	Hydration, furosemide, pamidronate, calcitonin	LSO	Unspecified
Allbery et al. (1998)[14]	13	Loss of appetite	12.9	N	185.3	N	198	Pamidronate, calcitonin	Surgical tumor debulking	Elevated calcitriol, elevated PTH
Inoue et al. (1995)[15]	18	N.P.	14.4	3.80	N	258.9	N	N	RSO, OE, PPL, removal of IAWM	Elevated PTHrP
Fleischhacker et al.(1994)[16]	19	Thirst, frequent urination	12.2	3.70	2	N	N	N	RSO, OE, RPPLD, two cycles of VAC	Unspecified
Bakri et al. (1993)[17]	25	Loss of appetite, abdominal pain, frequent urination	15.5	6.10	656.33	N	N	Hydration diuresis	Exploratory laparotomy	Unspecified
Giebel et al. (1992)[18]	16	Nausea, thirst, lethargy, frequent urination	15.2	2.90	N	N	N	Hydration	TAH, BSO, PLD	Unspecified

PTH: parathyroid hormone; LSO: left salpingo-oophorectomy; RSO: right salpingo-oophorectomy; BSO: bilateral salpingo-oophorectomy; OE: omentectomy; IOE: infracolic omentectomy; PW: peritoneal washing; PPAL: pelvic and paraaortic lymphadenectomy; PPL: partial paraaortic lymphadenectomy; RPPLD: right pelvic and paraaortic lymph node dissection; PLD: paraaortic lymph node dissection; IAWM: intraabdominal wall mass; PLB: pelvic lymph node biopsy; TAH: total abdominal hysterectomy; VAC: vincristine, actinomycin D and cyclophosphamide.

suspected that 1α-hydroxylase, which is expressed excessively in tumor cells, is the primary cause of hypercalcemia. However, there are some contradictions between this hypothesis and our literature review. First, there was one case wherein the PTH value was elevated when the calcitriol value was higher than the reference range. Second, there was one case in which both calcitriol and PTHrP were elevated. Finally, the phosphorus values were not high in the cases where calcitriol and calcium were elevated. Excessive active vitamin D3 leads to increased absorption of calcium and phosphorus from the intestine, while serum calcium and serum phosphorus also increase to high levels and, as a result, PTH is suppressed. Since PTHrP is known to cause humoral hypercalcemia in malignancy, we cannot conclude from our literature review that the elevation of calcitriol is the cause for hypercalcemia in dysgerminoma.

The estimated yearly prevalence of hypercalcemia for all cancer is from 1.46% to 2.74%. The most common cancers where this occurs are lung cancer, multiple myeloma, and renal cell carcinoma.[20] Whereas it is quite infrequent among ovarian tumors, hypercalcemia could cause severe symptoms due to neurocognitive dysfunction, volume depletion, and renal failure. Therefore, it is important to suspect the possibility of hypercalcemia in malignant tumors according to the age-appropriate range of serum calcium.[21]

Conclusion

In our case, laboratory data suggested that the cause of hypercalcemia was the oversecretion of calcitriol. To ascertain the mechanism of hypercalcemia with dysgerminoma, we conducted a literature search on 14 cases that matched our criteria. However, most cases lack data that can help investigate the potential association between PTH, PTHrP, calcitriol, and phosphorus in hypercalcemia. Thus, more case reports that include additional information are required to fully elucidate the mechanism of hypercalcemia associated with dysgerminoma.

Acknowledgements

The authors thank the patient for giving consent to publish this case report.

Author contributions

N.H. gathered information and wrote the manuscript H.S. and H.A. supervised and designed the project; H.A. treated the patient and gathered information; F.Y., T.I., and M.U. analyzed the data and contributed to the discussion of the research; T.N. performed the histological examination of the ovary; J.S., T.M., R.S., and M.O. supervised the treatment and the research. All authors have read and approved the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This study is exempted from ethical approval as this is retrospectively presented for a single patient. Our institution does not require ethical approval for reporting individual cases or case series

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

ORCID iD

Hirotsugu Suwanai https://orcid.org/0000-0001-9102-630X

References

1. Dent DM, Miller JL, Klaff L, et al. The incidence and causes of hypercalcaemia. *Postgrad Med J* 1987; 63: 745–750.
2. Talerman A. Germ cell tumor of the ovary. *Curr Opin Obstet Gynecol* 1997; 9: 44–47.
3. Tewari K, Cappuccini F, Disaia PJ, et al. Malignant germ cell tumors of the ovary. *Obstet Gynecol* 2000; 95: 128–133.
4. Smith HO, Berwick M, Verschraegen CF, et al. Incidence and survival rates for female malignant germ cell tumors. *Obstet Gynecol* 2006; 107(5): 1075–1085.
5. Quirk JT, Natarajan N and Mettlin CJ. Age-specific ovarian cancer incidence rate patterns in the United States. *Gynecol Oncol* 2005; 99(1): 248–250.
6. Hosseini B, Leibl M, Stoffman J, et al. Two cases of hypercalcemia in pediatric ovarian dysgerminoma. *J Obstet Gynaecol Can* 2019; 41(5): 660–665.
7. Nourani M and Manera RB. Pediatric ovarian dysgerminoma presenting with hypercalcemia and chronic constipation: a case report. *J Pediatr Hematol Oncol* 2013; 35(7): e272–e273.
8. Jawaid W, Solari V, Howell L, et al. Excision of extensive metastatic dysgerminoma to control refractory hypercalcaemia in a child at high risk for tumour-lysis syndrome. *J Pediatr Surg* 2011; 46(1): e13–e19.
9. Wald A, Narasimhan S, Nieves-Arriba L, et al. Prolonged hypercalcemia following resection of dysgerminoma: a case report. *Obstet Gynecol Int* 2009; 2009: 956935.
10. Matthew R, Christopher O and Philippa S. Severe malignancy-associated hypercalcemia in dysgerminoma. *Pediatr Blood Cancer* 2006; 47: 621–623.
11. Evans KN, Taylor H, Zehnder D, et al. Increased expression of 25-hydroxyvitamin D-1alpha-hydroxylase in dysgerminomas: a novel form of humoral hypercalcemia of malignancy. *Am J Pathol* 2004; 165(3): 807–813.
12. Radhakrishna S, Haq S, Lofts F, et al. Ovarian dysgerminoma presenting with hypercalcaemia. *BJOG* 2001; 108: 1302–1304.
13. Okoye BO, Harmston C and Buick RG. Dysgerminoma associated with hypercalcemia: a case report. *J Pediatr Surg* 2001; 36: E10.
14. Allbery SM, Swischuk LE and John SD. Hypercalcemia associated with dysgerminoma: case report and imaging findings. *Pediatr Radiol* 1998; 28(3): 183–185.

15. Inoue H, Kikuchi Y, Hirata J, et al. Dysgerminoma of the ovary with hypercalcemia associated with elevated parathyroid hormone-related protein. *Jpn J Clin Oncol* 1995; 25(3): 113–117.
16. Fleischhacker DS and Young RH. Dysgerminoma of the ovary associated with hypercalcemia. *Gynecol Oncol* 1994; 52: 87–90.
17. Bakri YN and Akhtar M. Gonadal dysgerminoma-seminoma associated with severe hypercalcemia. *Acta Obstet Gynecol Scand* 1993; 72(1): 57–59.
18. Giebel SC, Stanhope CR, Malkasian GD Jr, et al. Humoral hypercalcemia associated with a dysgerminoma. *Mayo Clin Proc* 1992; 67(10): 966–968.
19. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; 352: 373–379.
20. Goldner W. Cancer-related hypercalcemia. *J Oncol Pract* 2016; 12: 426–432.
21. Lietman SA, Germain-Lee EL and Levine MA. Hypercalcemia in children and adolescents. *Curr Opin Pediatr* 2010; 22: 508–515.