Idiopatyczna hiperkalcemia niemowląt – czy nadal idiopatyczna ?

WARSZAWSKI
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Helena Ziółkowska

Katedra i Klinika Pediatrii i Nefrologii

Warszawskiego Uniwersytetu Medycznego

XII Ogólnopolska Konferencja Polskiego Towarzystwa Nefrologii Dziecięcej

Lublin 23-25 maja 2013

Hiperkalcemia – Ca w surowicy > 2,65 mmol/l (10,6 mg/dl; 5,3 mEq/l)

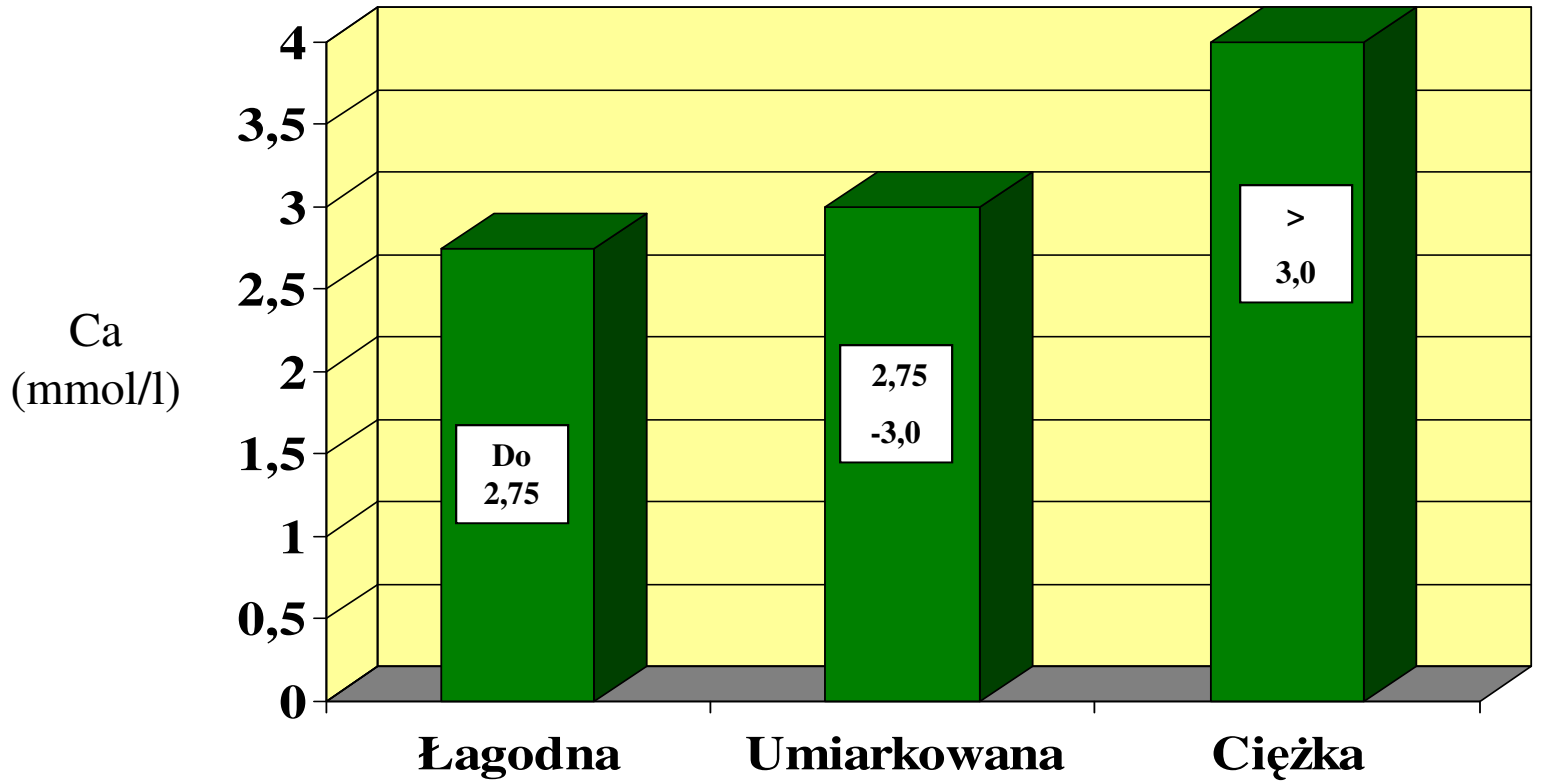


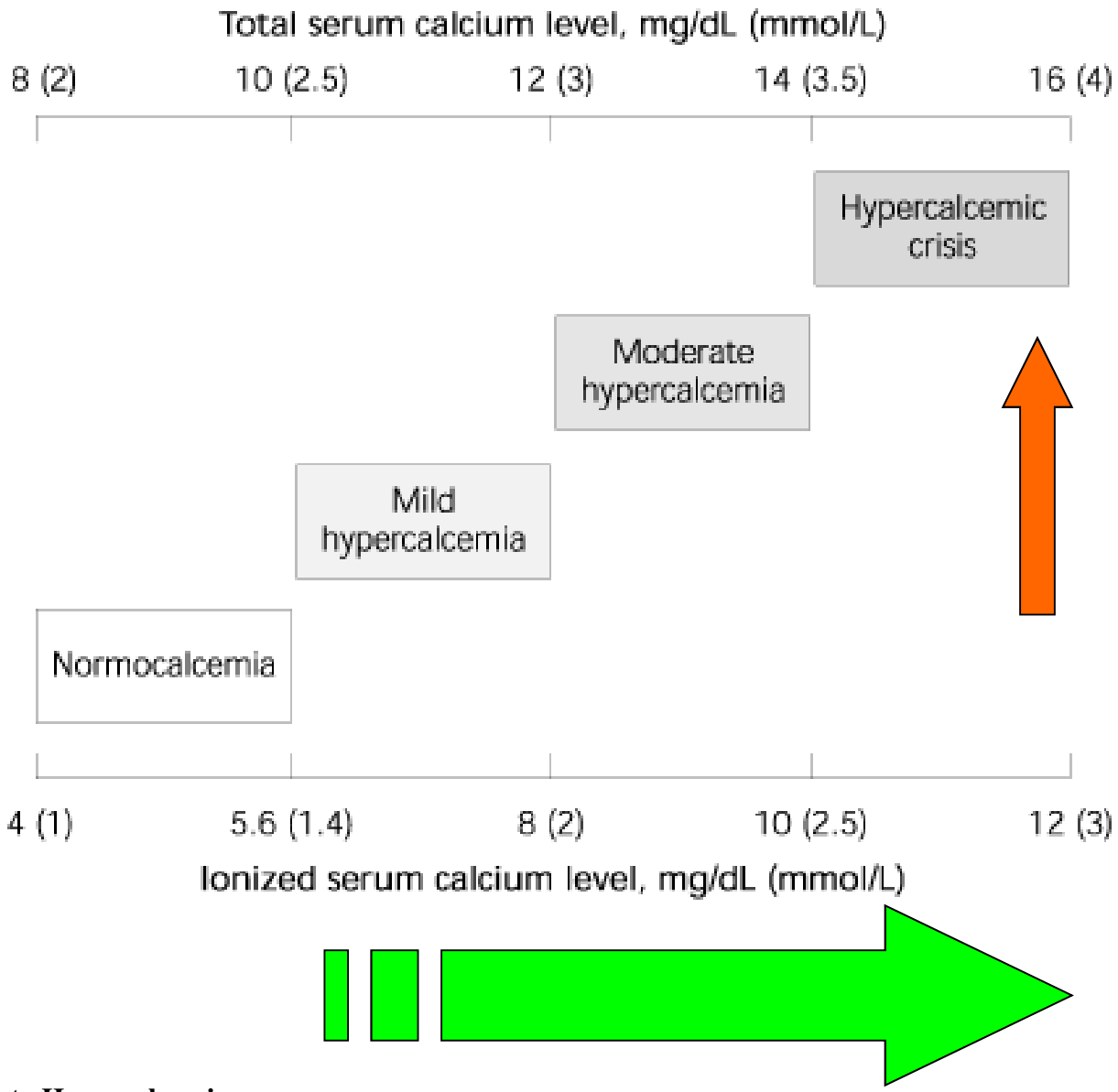
Table 1 Representative normal values for age for concentrations of serum total calcium

	Age (years)	Serum total calcium (mg/dl)
Infants	0–0.25	8.8–11.3
	1–5	9.4–10.8
Children	6–12	9.4–10.3
Men	20	9.1–10.2
	50	8.9–10.0
	70	8.8–9.9
Women	20	8.8–10.0
	50	8.8–10.0
	70	8.8–10.0

Portale AA. Blood calcium, phosphorus, and magnesium. In: Favus MJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 4th ed. Philadelphia, USA: Lippincott, Williams, & Wilkins; 1999. p. 116.

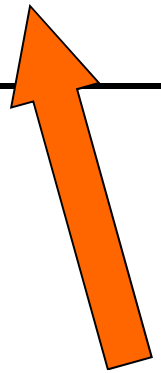
Objawy hiperkalcemii:

- Brak łaknienia
- Zaparcia
- Zahamowanie przyrostu masy ciała
- Poliuria
- Odwodnienie
- Ostra niewydolność nerek
- Nadciśnienie tętnicze
- Obrzęk mózgu



A Practical Approach to Hypercalcemia
MARY F. CARROLL, M.D., DAVID S. SCHADE, M.D., *Am Fam Physician.* 2003 May 1;67(9):1959-1966

1951	Fanconi G. Chronic disorders of calcium and phosphate metabolism in children. Schweiz Med. Wochenschr 1951;81:908-913
1952	Lightwood R. Idiopathic hypercalcemia with failure to thrive: nephrocalcinosis. Proc R Soc Med. 1952;45:401
1953	Lightwood R, Stapleton T. Idiopathic hypercalcemia in infants. Lancet 1953; 265(6779):255-256
1956	British Paediatric Association. Hypercalcaemia in infants and vitamin D BMJ 1956;2:149

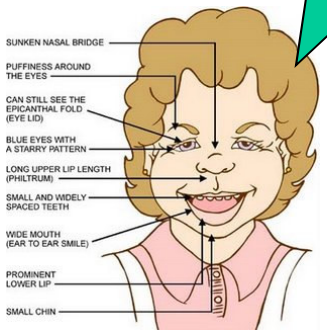


1956- British Paediatric Association. Hypercalcaemia in infants and vitamin D. BMJ 2:149

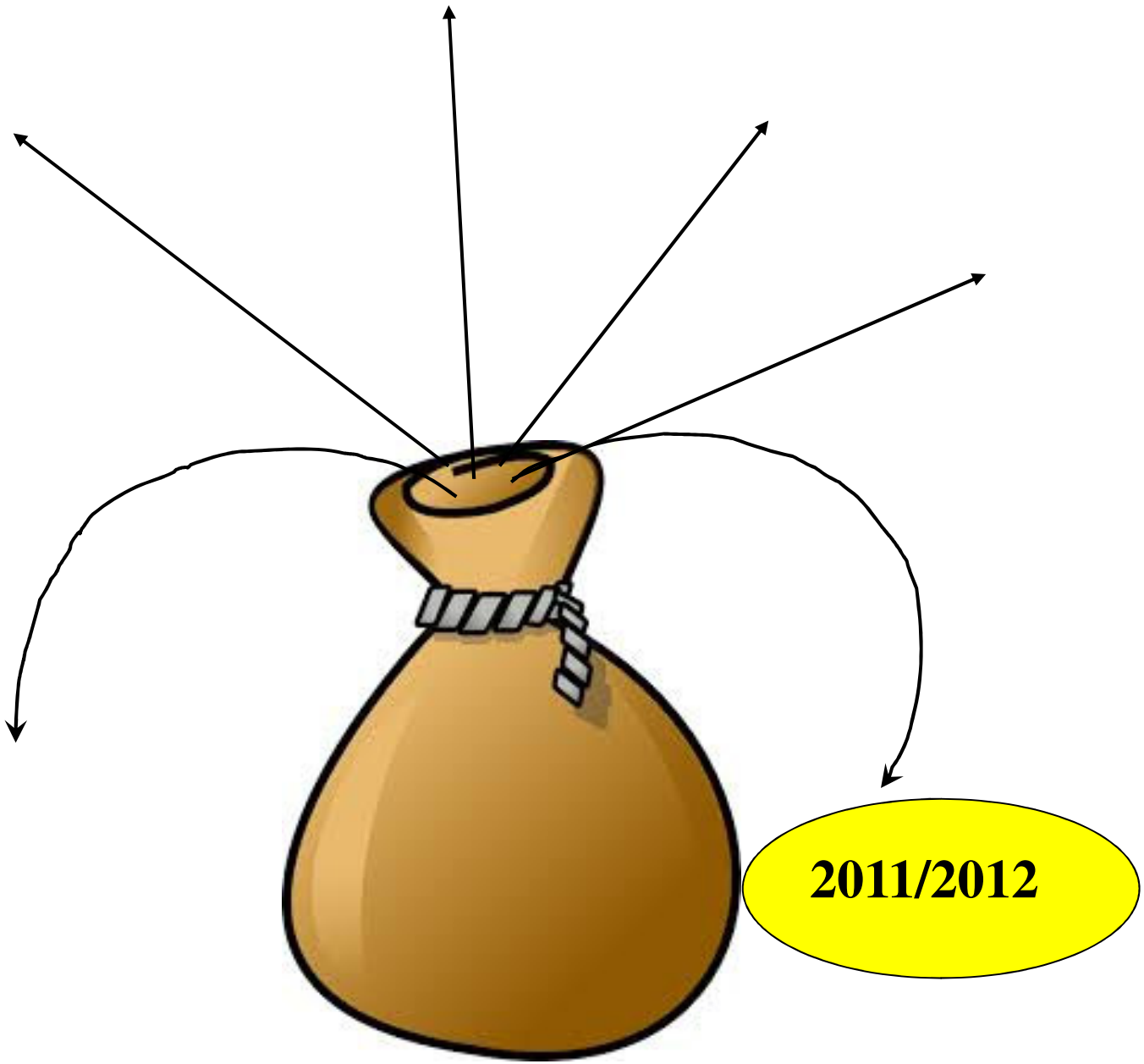
200 przypadków w ciągu 2 lat

Williams JC, Barrat-Boyes BG, Lowe JB Supravalvular aortic stenosis. Circulation 1961;24:1311-1318

Beuren AJ, Apitz J, Harmjanz D. Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. Circulation 1962;26:1235-1240



Idiopatyczna hiperkalcemia niemowląt (Lightwooda)


2011/2012

Przyczyny hiperkalcemii u niemowląt (wg częstości występowania)

1. **Samoistna hiperkalcemia niemowląt (tzw. łagodna hiperkalcemia typu Lightwooda)**
2. **Zespół Williamsa**
3. **Zatrucie witaminą D**
4. **Martwica tkanki tłuszczowej noworodka**
5. **Przejściowa nadczynność przytarczyc noworodka matki z niedoczynnością przytarczyc**
6. **Wrodzona nadczynność przytarczyc**

Pronicka E, Rowińska E, Kulczycka H. Pediatria Polska 2/1996

Hiperkalcemia

Wywiad + badanie fizykalne

Witamina D w ostatnim miesiącu

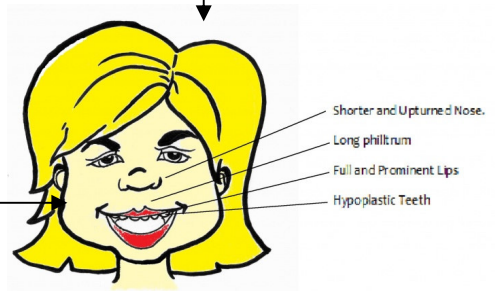
Charakterystyczne cechy fenotypowe + zmiany naczyniowe

> 10 000 j/d

< 10 000 j/d

Zatrucie witaminą D

- **Idiopatyczna hiperkalcemia Lightwooda**
- Zespół Williamsa
- Inne przyczyny



delecja w chromosomie 7

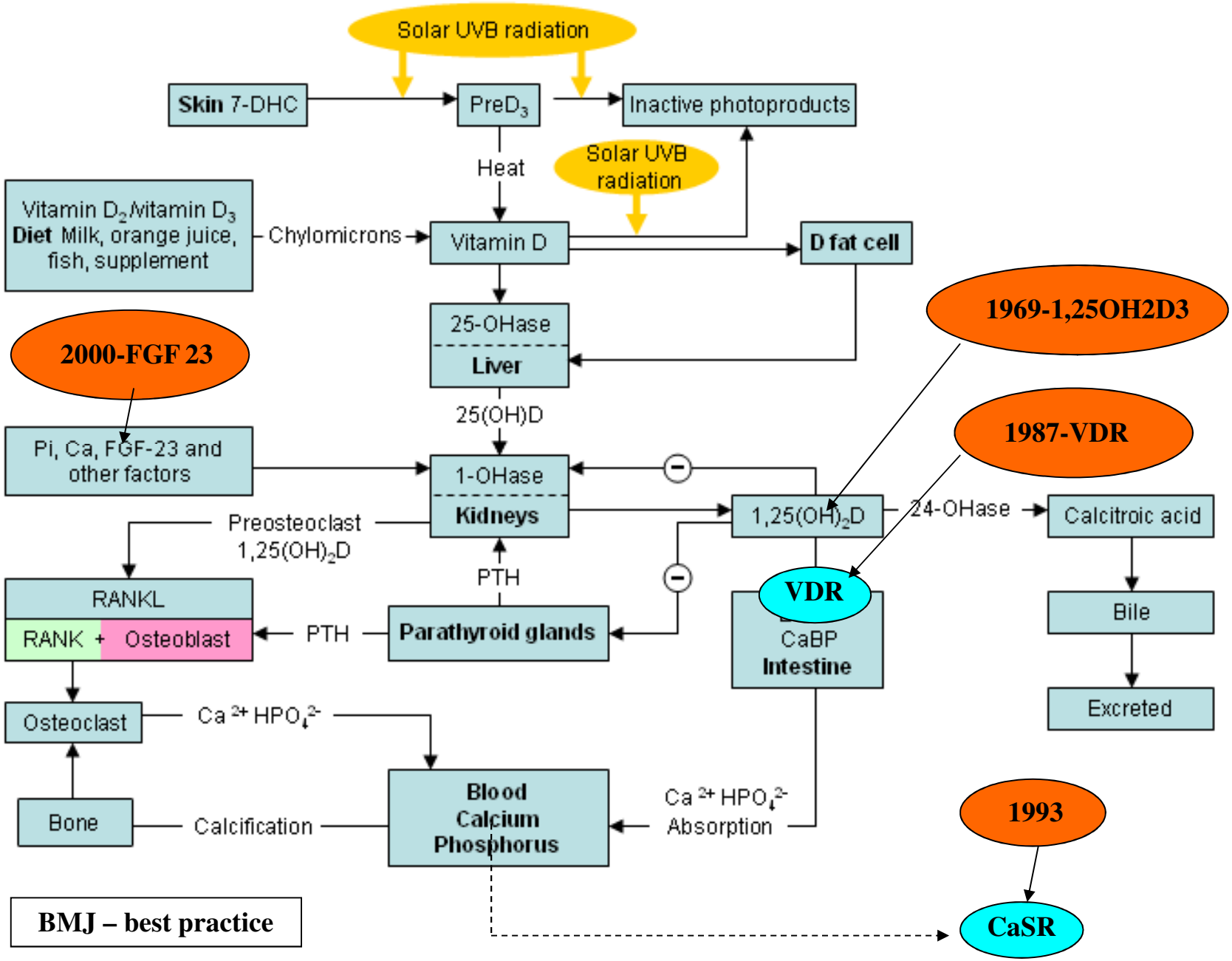

Solar UVB radiation
Skin 7-DHC
PreD3
Inactive photoproducts
Heat
Solar UVB radiation
Vitamin D2/Vitamin D3
Diet Milk, orange juice, fish, supplement
Chylomicrons
Vitamin D
D fat cell
1969-1,25OH2D3
2000-FGF 23
25-OHase
Liver
25(OH)D
1987-VDR
Pi, Ca, FGF-23 and other factors
1-OHase
Kidneys
1,25(OH)2D
24-OHase
Calcitroic acid
Preosteoclast
1,25(OH)2D
PTH
VDR
RANKL
RANK + Osteoblast
PTH
Parathyroid glands
CaBP
Intestine
Bile
Excreted
Osteoclast
Ca 2+ HPO4 2-
Blood
Calcium
Phosphorus
Ca 2+ HPO4 2-
Absorption
1993
Bone
Calcification
CaSR
BMJ – best practice

Table 2 Differential diagnosis of hypercalcemia in neonates and infants (up to 2 years of age)

Iatrogenic
Phosphate depletion
Premature infants on human milk or standard formula
Parenteral nutrition
Hyperparathyroidism
Congenital parathyroid hyperplasia
Maternal hypoparathyroidism
Inactivating mutations in Ca^{2+}-sensing receptor gene
Familial hypocalciuric hypercalcemia (familial benign hypercalcemia)
Neonatal severe hyperparathyroidism
Jansen's metaphyseal chondrodysplasia
Persistent PTHrP
Hypervitaminosis D
Subcutaneous fat necrosis
Williams syndrome/idiopathic infantile hypercalcemia
Other inborn metabolic disorders
Blue diaper syndrome
Lactase deficiency
Disaccharide intolerance
Bartter syndrome
Hypophosphatasia
IMAGe
Down syndrome
Severe congenital hypothyroidism
Maternal hypercalcemia
Vitamin A intoxication

PTHrP, parathyroid hormone-related peptide.

Hypercalcemia in children and adolescents
Steven A. Lietman[a], Emily L. Germain-Lee[b] and Michael A. Levine[c]
Current Opinion in Pediatrics 2010, 22:508–515

Table 3 Laboratory values in differential diagnosis of hypercalcemia

	Serum calcium	Serum phosphorus	Fractional excretion of calcium	PTH	PTHrP	25(OH)D	1,25(OH)2D
Familial hypocalciuric hypercalcemia	↑	N or ↓	< 0.01	N or ↑	↓	N	↑
NSHPT	↑↑↑	↓	<0.01	↑↑	↓	N or ↓	↑
Subcutaneous fat necrosis	↑	↑	↑	↓	↓	N	↑↑
Williams syndrome	↑	↑	↑	↓	↓	N	N or ↑
Primary hyperparathyroidism	↑	↓	>0.01	↑	↓	N	↑
Humoral malignancy	↑↑	↓	↑	↓	↑↑	N	N or ↑
Osteolytic malignancy	↑↑	↑	↑↑	↓	↓	N	↓
Granulomatous disease	↑	↑	↑↑	↓	↓	N	↑↑
Vitamin D intoxication	↑	↑	↑↑	↓	↓	↑↑	N or ↓
Immobilization	↑	↑	↑↑	↓	↓	N	↓

N, normal; NSHPT, neonatal severe hyperparathyroidism; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide.

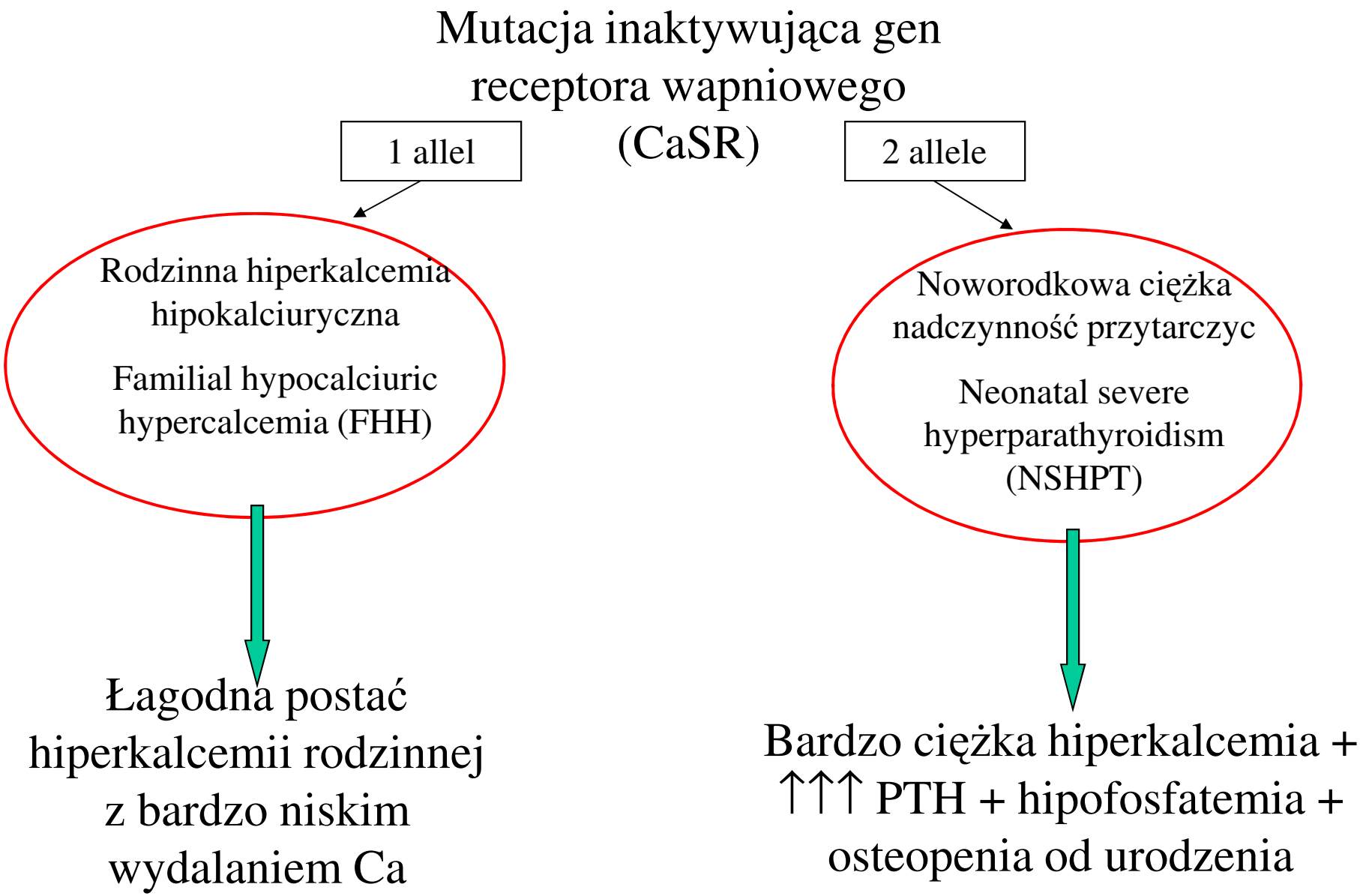
Idiopatyczna hiperkalcemia niemowlat	↑	↑	↑↑	↓	↓	**N lub ↑**	**N lub ↑**

Hypercalcemia in children and adolescents

Steven A. Lietman[a], Emily L. Germain-Lee[b] and Michael A. Levine[c]

Current Opinion in Pediatrics 2010, 22:508–515

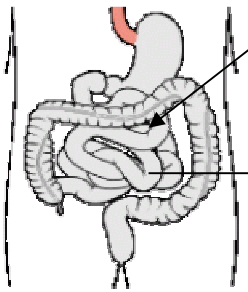
$$Fe_{Ca} = (U_{Ca} \times S_{kr}) : (S_{Ca} \times U_{kr})$$


Mutacja inaktywująca gen receptora wapniowego (CaSR)
1 allel
2 allele
Rodzinna hiperkalcemia hipokalciuryczna
Familial hypocalciuric hypercalcemia (FHH)
Noworodkowa ciężka nadczynność przytarczyc
Neonatal severe hyperparathyroidism (NSHPT)
Łagodna postać hiperkalcemii rodzinnej z bardzo niskim wydalaniem Ca
Bardzo ciężka hiperkalcemia + ↑↑↑ PTH + hipofosfatemia + osteopenia od urodzenia

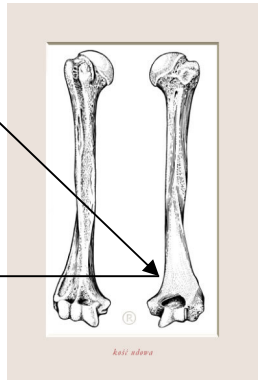
Hipofosfatemia

↓ FGF 23

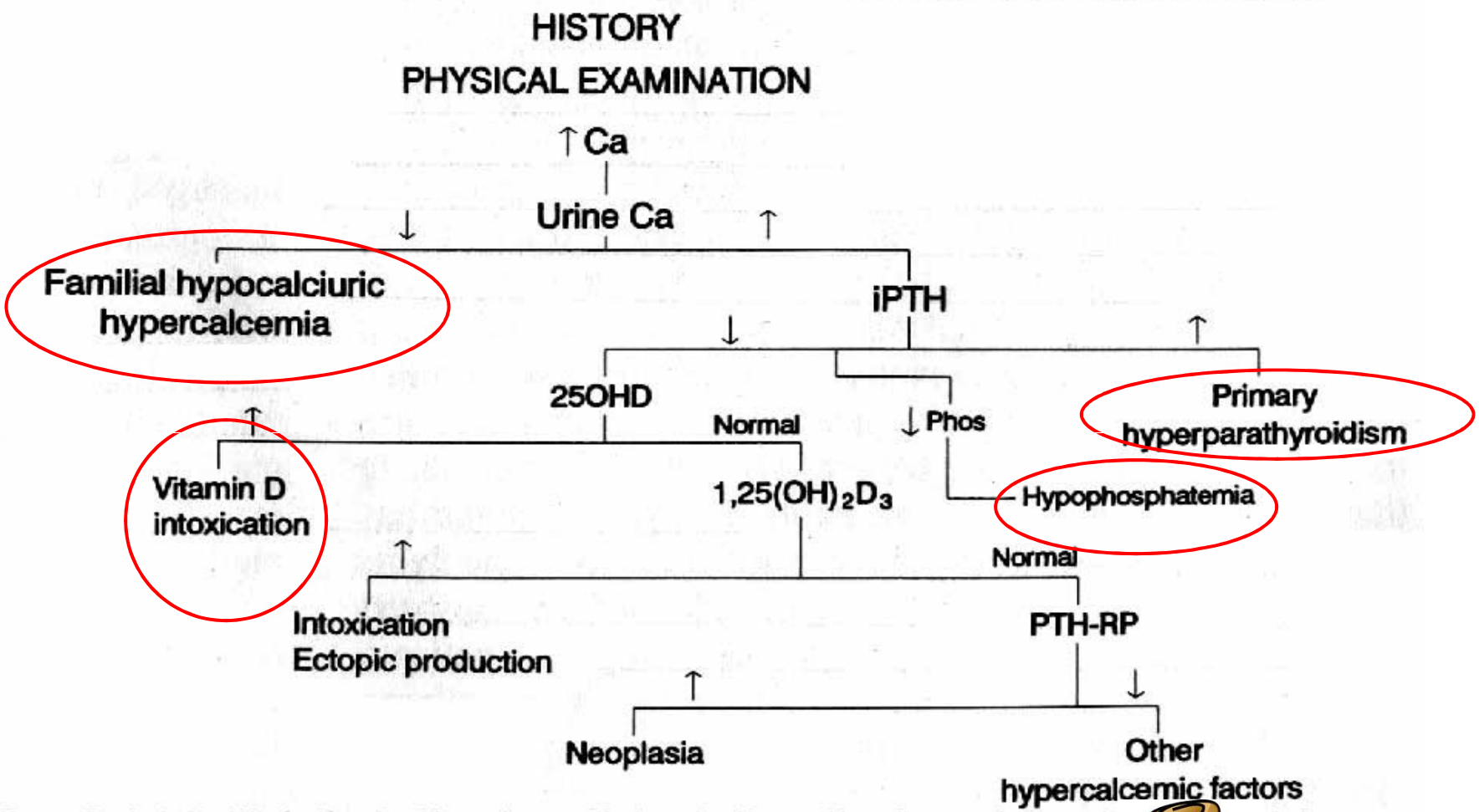
↑ 1,25 OH_2D_3



Ca



Evaluation of hypercalcemia.



From Rudolph AM (ed): Pediatrics, 20th ed. Norwalk, Conneticut, A] & Lange.

idiopatyczna hiperkalcemia niemowląt

Table 1 Clinical and biochemical parameters at presentation (*Cr* creatinine, *FTT* failure to thrive, *UTI* urinary tract infection, *RR* reference range)

Patient no.	Age	Clinical features	Ultrasound findings	Serum calcium level (RR 2.15-2.60 mmol/l)	Random Ca/Cr ratio (mmol/mmol)[a]	PTH (RR 1-7 pmol/l)
1	8 months	FTT	Nephrocalcinosis	3.3	3.8	0.3
2	3 months	FTT	Normal	2.95	2.4	Not done
3	1 month	Premature	Nephrocalcinosis	2.89	6.7	0.6
4	3 months	Pelvicalyceal dilation	Nephrocalcinosis	2.81	3.7	0.3
5	3 months	UTI	Nephrocalcinosis	3.04	3.8	2.4
6	3 months	FTT, poor feeding	Nephrocalcinosis	3.07	2.17	0.8
7	7 months	Haematuria	Calculus	2.64	1.6	2.1
8	2 months	Family history	Normal	2.85	5.9	2.8
9	1 month	Prematurity	Nephrocalcinosis; calculi	4	1.6	0.4
10	3 months	Family history	Normal	2.9	2.0	1.7
11	14months	UTI	Calculus	2.68	2.5	<0.5

[a] Normal range <1 year, <2.2 mmol/mmol; 1–3 years, <1.5 mmol/mmol; 3–5 years, <1.1 mmol/mmol; >5 years, <0.7 mmol/mmol [21]

Long-term follow-up of patients with idiopathic infantile hypercalcaemia

Jianping Huang · David Coman · Steven J. McTaggart · John R. Burke

Pediatr Nephrol (2006) 21:1676–1680

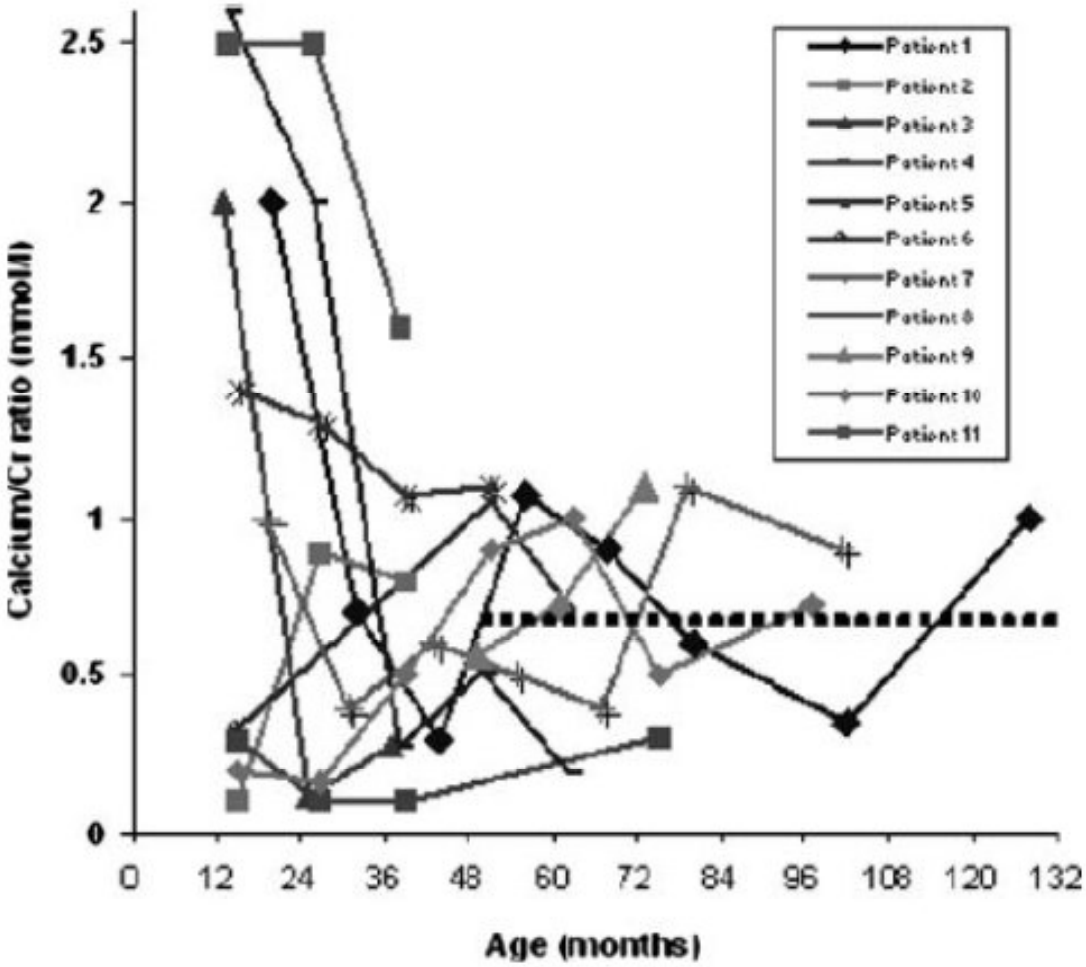


Fig. 2 Long-term follow-up of urine calcium excretion in patients with IIH. Initial calcium/creatinine ratios are not shown (*area under the dashed line* represents normal range)

Long-term follow-up of patients with idiopathic infantile hypercalcaemia

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AMERICAN ACADEMY OF PEDIATRICS

COMMITTEE ON NUTRITION

THE RELATION BETWEEN INFANTILE HYPERCALCEMIA AND VITAMIN D—PUBLIC HEALTH IMPLICATIONS IN NORTH AMERICA

PEDIATRICS, Vol. 40, No. 6, December 1967

TABLE I

INCIDENCE OF INFANTILE HYPERCALCEMIA (ALL FORMS) IN GREAT BRITAIN[9]

Survey	*Period*	*Months*	*Reported Cases*	*Cases per Month*
1	1953 to 1955 1957 to 1958*	30	216	7.2
2	1959	12	82	6.8
3	1960 to 1961	17	50	3.0

day.[21] It was, therefore, proposed that hypersensitivity to the vitamin,[22] a defect in cholesterol metabolism,[23] or defective removal of vitamin D[24,25] were other possibilities to be considered in the etiology.

It is clear that the recommended allowance of 400 I.U. vitamin D per day amply provides for the total vitamin D requirements of normal infants, children, and pregnant women. From the standpoint of preventing rickets, there is no reason for the normal individual to ingest more than this total amount. From the standpoint of avoiding hypercalcemia in the population at large, there is no compelling necessity for physicians or public health authorities to strive for lower overall intakes.

Pediatr Nephrol (1997) 11: 2–6

Pediatric Nephrology

Original article

Persistent hypercalciuria and elevated 25-hydroxyvitamin D_3 in children with infantile hypercalcaemia

Ewa Pronicka[1], Elżbieta Rowińska[1], Hanna Kulczycka[1], Jacek Łukaszkiewicz[2], Roman Lorenc[2], and Roman Janas[3]

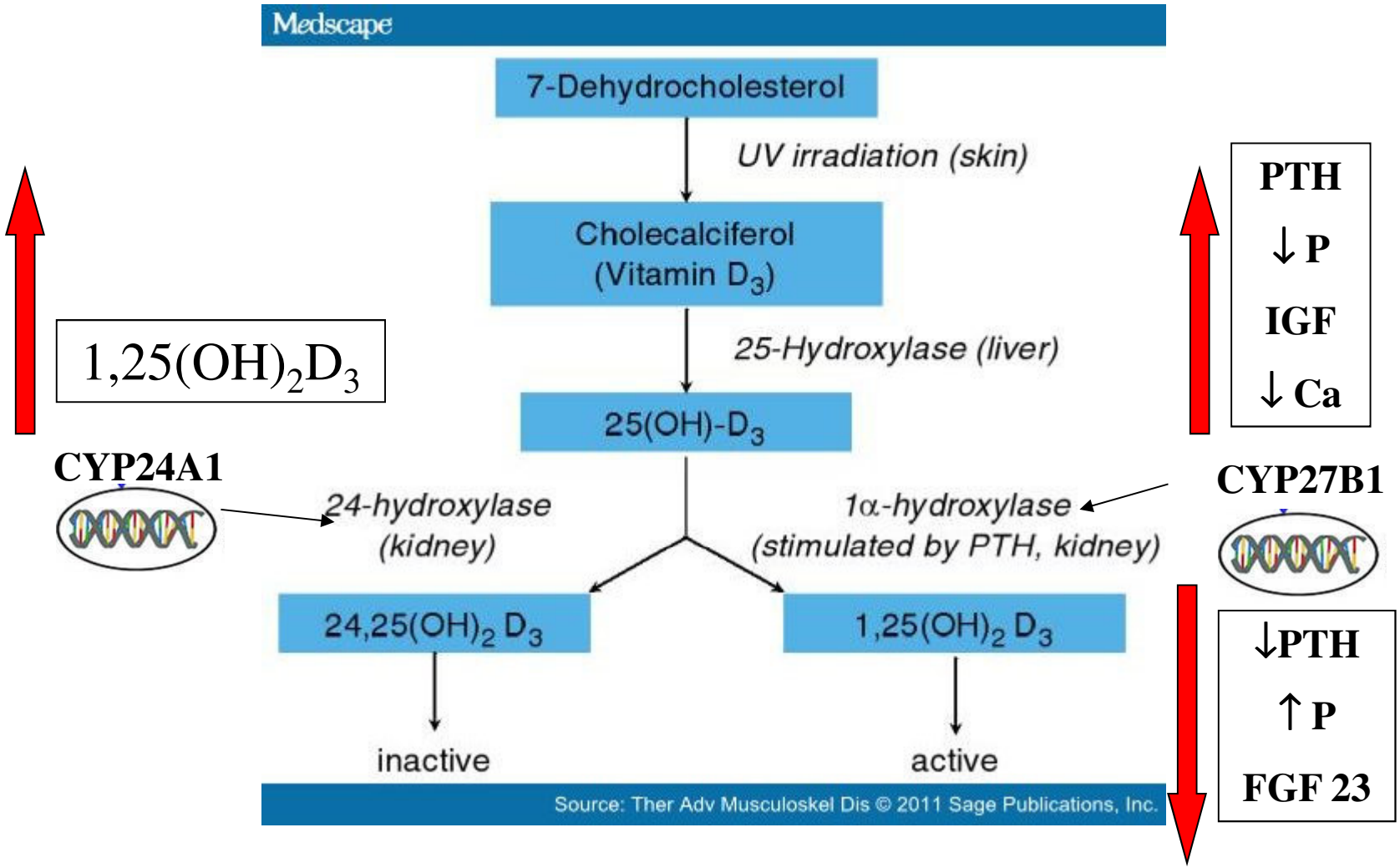
[1] Department of Metabolic Diseases, The Children's Memorial Health Institute, Warsaw, Poland
[2] Department of Biochemistry and Experimental Medicine, The Children's Memorial Health Institute, Warsaw, Poland
[3] Department of Nuclear Medicine, The Children's Memorial Health Institute, Warsaw, Poland

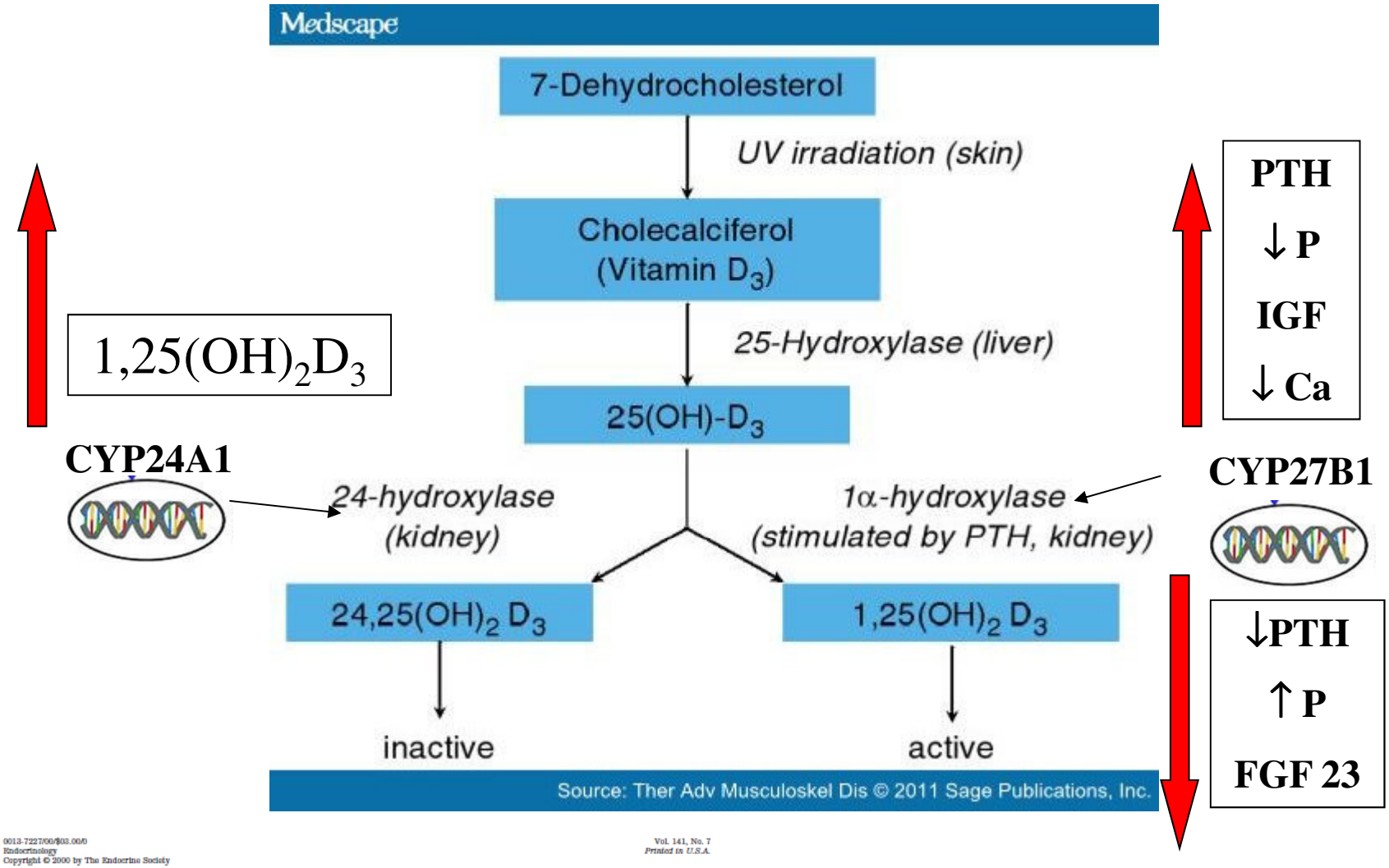
Received September 22, 1995; received in revised form May 3, 1996; accepted May 7, 1996

Table 2. Biochemical findings (mean ± SD) during the normocalcaemic phase of idiopathic infantile hypercalcaemia (group 1), in reference group (2) and Williams group (3)

	Group 1 (n = 17)	Group 2 (n = 10)	Group 3 (n = 10)
Serum			
Phosphate (mmol/l)	1.64 ±0.20	1.69 ±0.13	1.63 ±0.26
Alkaline phosphatase (units/l)	443.1±77.6	473.7±183.9	289.2±90.5
25(OH)vitamin D_3 (ng/ml)	41.1 ±26.3*[1], *[2]	19.1 ±10.2	10.6 ±7.0
1,25$(OH)_2$vitamin D_3 (pg/ml)	61.2 ±25.6*[3], *[4]	37.6 ±10.5	38.8 ±16.6
	51.2 ±20.6	39.4 ±15.8	43.4 ±14.8
PTH (ng/ml)	0.45 ±0.12	0.42 ±0.11	0.54 ±0.12
Calcitonin (ng/ml)	9.1 ±2.6	8.8 ±4.0	12.3 ±4.8
Osmolality (mosmol/l)	292.0±5.1	292.5±5.5	295.9±6.0
Urine			
Creatinine clearance (ml/min per 1.73 m^2)	107 ±50	92 ±50	109 ±46
$TmPO_4$/GFR (mmol/l)	1.43 ±0.21	1.41 ±0.18	1.46 ±0.26
Cyclic AMP (µmol/kg per 24 h)	77.5 ±50.1	93.1 ±36.7	62.1 ±23.8
Osmolality during short water deprivation (mosmol/l)	723 ±188	834 ±142	847 ±193

PTH, Parathormone; $TmPO_4$/GFR, Tubular threshold of phosphate/glomerular filtration rate
*[1]P <0.05 group 1 vs. 2; *[2]P <0.01 group 1 vs. 3; *[3]P <0.05 group 1 vs. 2; *[4]P <0.05 group 1 vs. 2 + 3


Medscape
7-Dehydrocholesterol
UV irradiation (skin)
Cholecalciferol
(Vitamin D3)
25-Hydroxylase (liver)
25(OH)-D3
1,25(OH)2D3
CYP24A1
24-hydroxylase
(kidney)
1α-hydroxylase
(stimulated by PTH, kidney)
CYP27B1
24,25(OH)2 D3
1,25(OH)2 D3
inactive
active
PTH
↓P
IGF
↓Ca
↓PTH
↑P
FGF 23
Source: Ther Adv Musculoskel Dis © 2011 Sage Publications, Inc.



0013-7227/00/$03.00/0
Endocrinology
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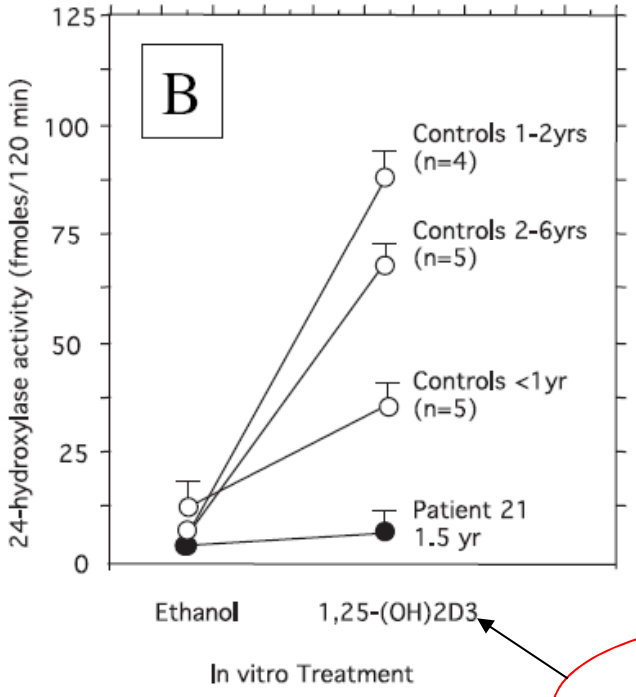
Deficient Mineralization of Intramembranous Bone in Vitamin D-24-Hydroxylase-Ablated Mice Is Due to Elevated 1,25-Dihydroxyvitamin D and Not to the Absence of 24,25-Dihydroxyvitamin D*

RENÉ ST-ARNAUD†, ALICE ARABIAN, ROSE TRAVERS, FRANK BARLETTA, MIHALI RAVAL-PANDYA, KELLI CHAPIN, JOS DEPOVERE, CHANTAL MATHIEU, SYLVIA CHRISTAKOS, MARIE B. DEMAY, AND FRANCIS H. GLORIEUX

Infantile Hypercalcemia and Hypercalciuria: New Insights into a Vitamin D-Dependent Mechanism and Response to Ketoconazole Treatment

Minh Nguyen, PhD, Henri Boutignon, MD, Eric Mallet, MD, PhD, Agnes Linglart, MD, PhD, Huguette Guillozo, Frederic Jehan, PhD, and Michele Garabedian, MD, PhD

(J Pediatr 2010;157:296-302)



10 nM $1,25(OH)_2D_3$

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutations in *CYP24A1* and Idiopathic Infantile Hypercalcemia

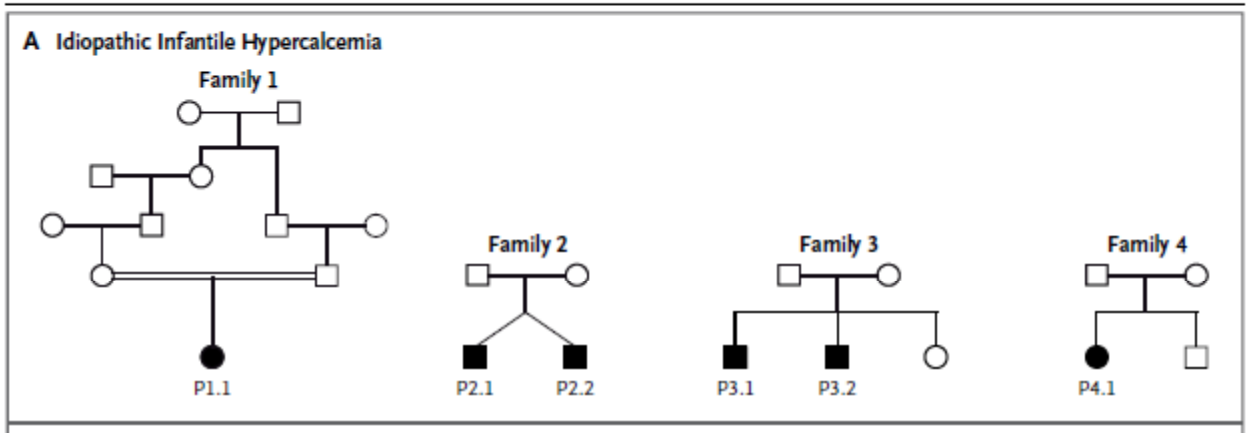
Karl P. Schlingmann, M.D., Martin Kaufmann, Ph.D., Stefanie Weber, M.D., Andrew Irwin, B.Sc., Caroline Goos, Ulrike John, M.D., Joachim Misselwitz, M.D., Günter Klaus, M.D., Eberhard Kuwertz-Bröking, M.D., Henry Fehrenbach, M.D., Anne M. Wingen, M.D., Tülay Güran, M.D., Joost G. Hoenderop, Ph.D., René J. Bindels, Ph.D., David E. Prosser, Ph.D., Glenville Jones, Ph.D., and Martin Konrad, M.D.

N ENGL J MED 365;5 NEJM.ORG AUGUST 4, 2011

Genetic Defect in *CYP24A1*, the Vitamin D 24-Hydroxylase Gene, in a Patient with Severe Infantile Hypercalcemia

Andrew Dauber, Thutrang T. Nguyen, Etienne Sochett, David E. C. Cole, Ronald Horst, Steven A. Abrams, Thomas O. Carpenter, and Joel N. Hirschhorn

J Clin Endocrinol Metab, February 2012, 97(2):E268–E274



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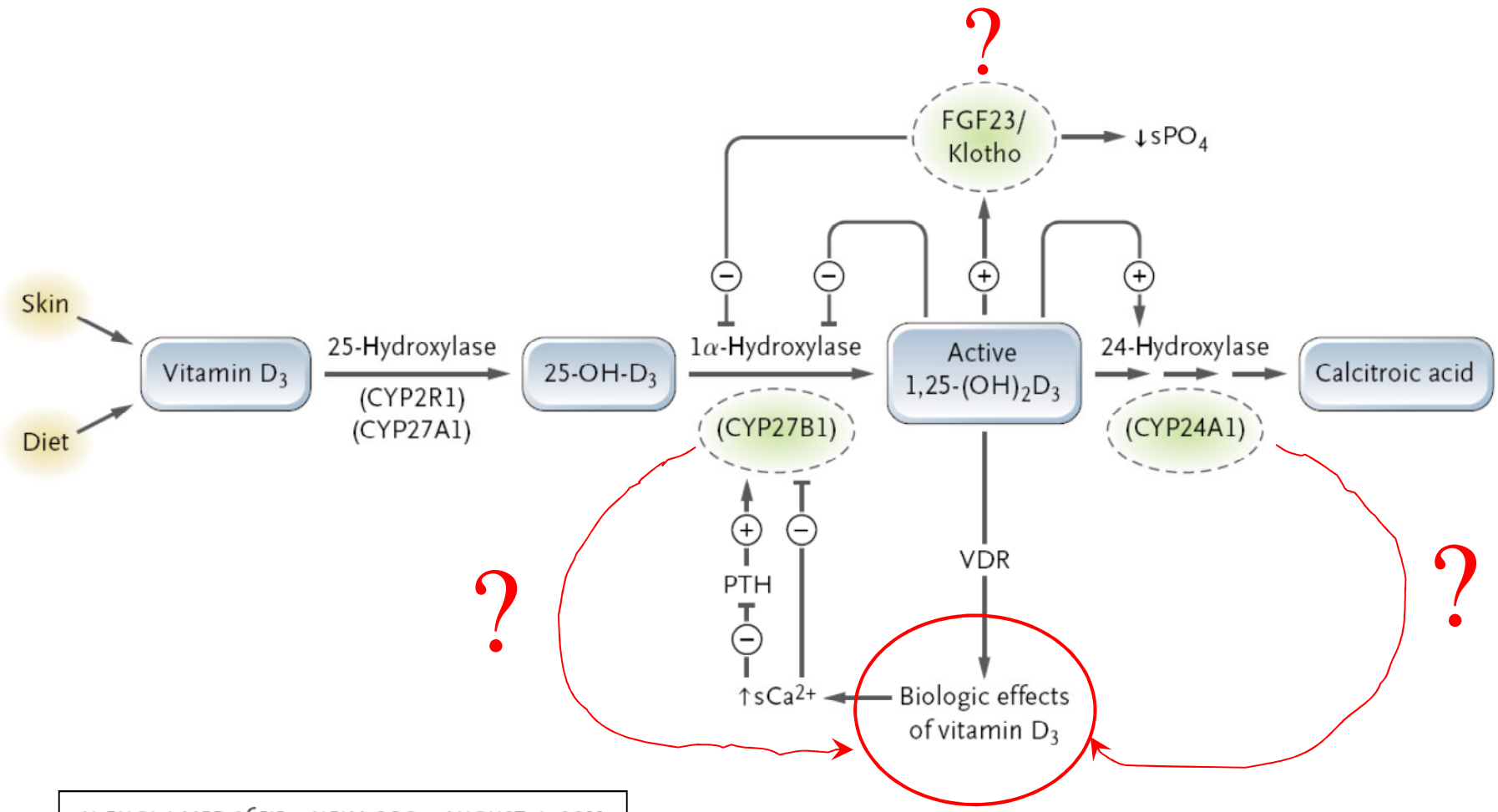

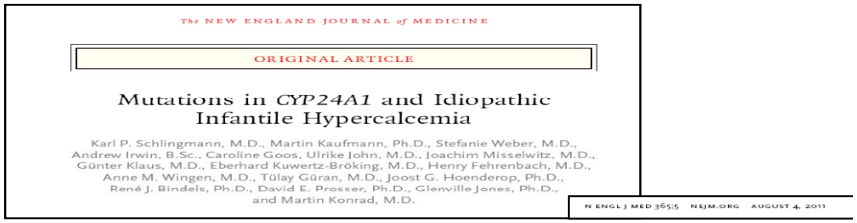

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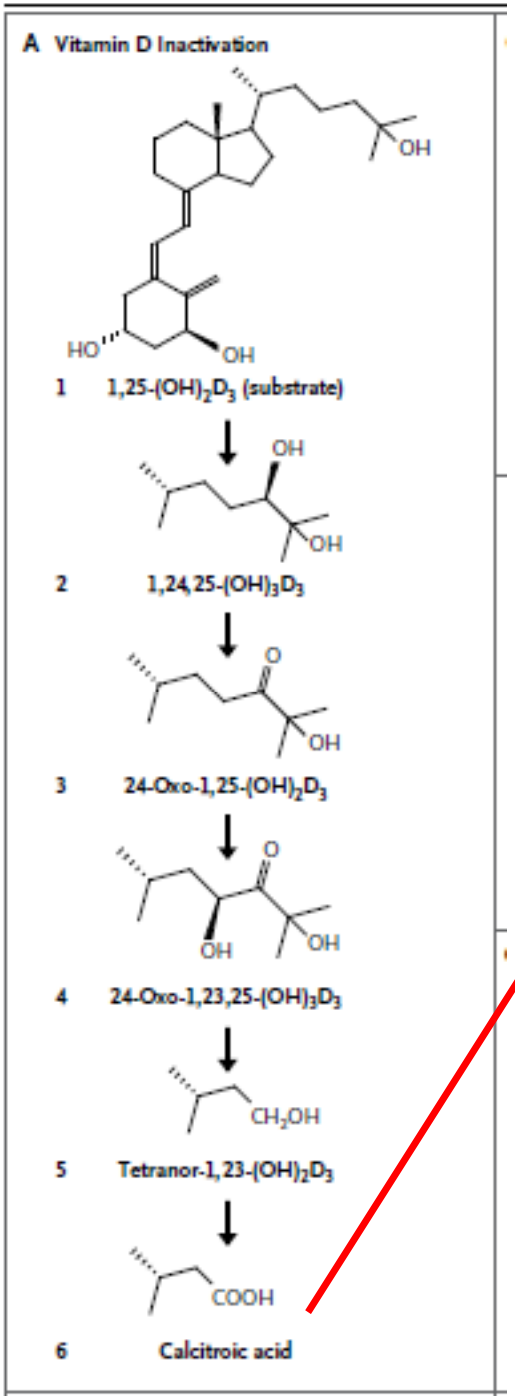
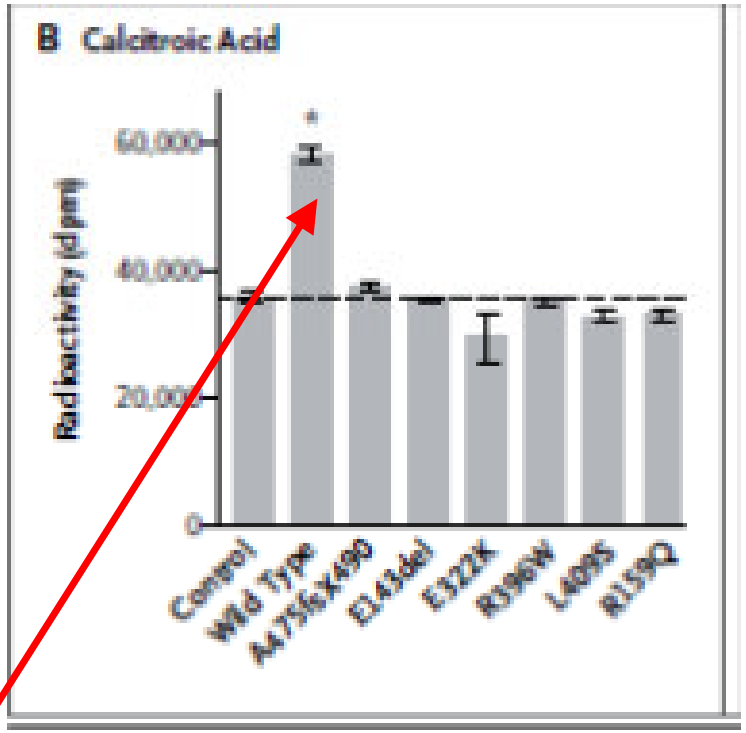
Table 1. Characteristics of the Patients.*

Variable	Idiopathic Infantile Hypercalcemia			
	Patient 1.1	Patient 2.1	Patient 2.2	Patient 3.1
Clinical data				
Age at presentation	6 mo	6 mo	Asymptomatic; diagnosis during family workup	8 mo
Vitamin D prophylaxis	500 IU per day	500 IU per day	500 IU per day	500 IU per day
Time between bolus and symptoms	NA	NA	NA	NA
Clinical symptoms				
Weight loss or failure to thrive	Yes	Yes	No	Yes
Polyuria or dehydration	Yes	No	No	Yes
Muscular hypotonia or lethargy	Yes	No	No	Yes
Hypercalciuria or nephrocalcinosis	Yes	Yes	Yes	Yes
Laboratory findings†				
At initial presentation				
Serum calcium (mmol/liter)	4.0	4.2	3.7	4.3
Serum intact parathyroid hormone (pg/ml)	<1.0	5	4	<1.0
Serum whole parathyroid hormone (pg/ml)	NA	NA	NA	NA
25-hydroxyvitamin D_3 (ng/ml)	50	27	27	64
1,25-dihydroxyvitamin D_3 (pg/ml)	65	57	43	79
At last follow-up				
Duration of follow-up (yr)	10	2	2	7
Serum calcium (mmol/liter)	2.7	2.7	2.6	2.3
Serum intact parathyroid hormone (pg/ml)	8	11	14	5.2
25-hydroxyvitamin D_3 (ng/ml)	7	21	17	33
1,25-dihydroxyvitamin D_3 (pg/ml)	37	65	68	34
***CYP24A1* mutation**	A475fsX490 homozygote	E143del and E151X	E143del and E151X	L409S and R396W





Mutations in *CYP24A1* and Idiopathic Infantile Hypercalcemia

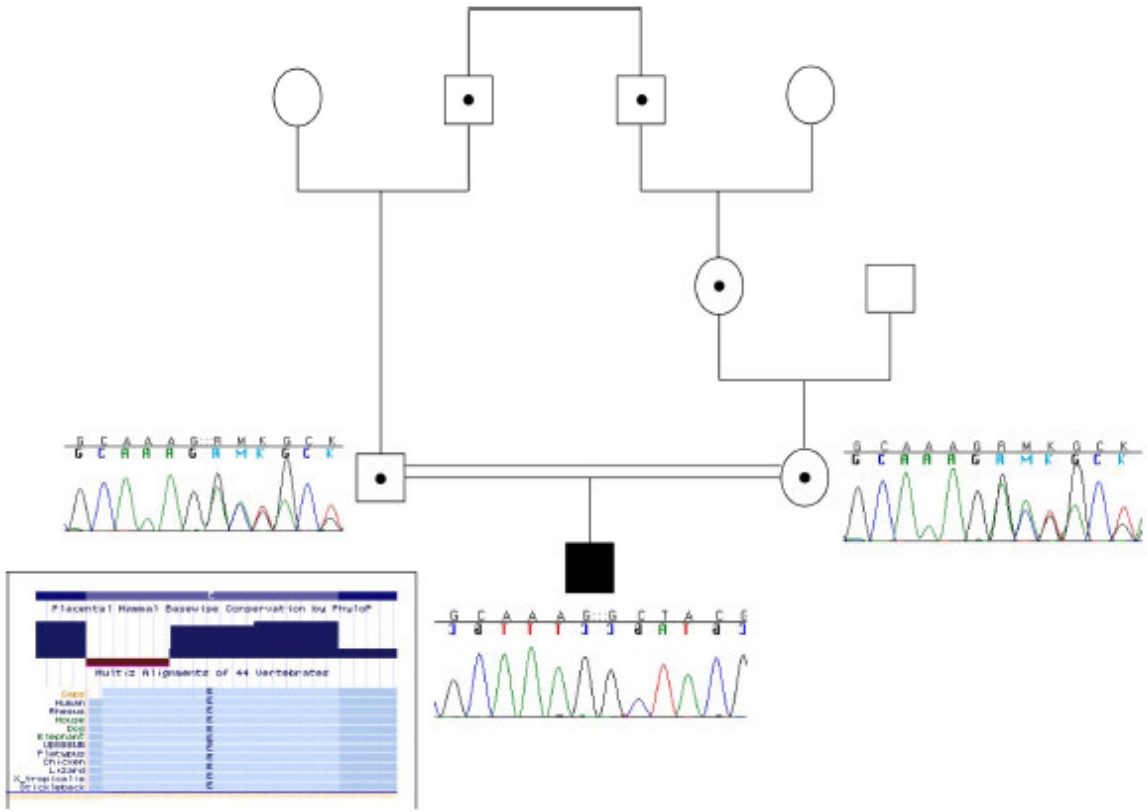
Karl P. Schlingmann, M.D., Martin Kaufmann, Ph.D., Stefanie Weber, M.D., Andrew Irwin, B.Sc., Caroline Goos, Ulrike John, M.D., Joachim Misselwitz, M.D., Günter Klaus, M.D., Eberhard Kuwertz-Bröking, M.D., Henry Fehrenbach, M.D., Anne M. Wingen, M.D., Tülay Güran, M.D., Joost G. Hoenderop, Ph.D., René J. Bindels, Ph.D., David E. Prosser, Ph.D., Glenville Jones, Ph.D., and Martin Konrad, M.D.

N Engl J Med 2011;365:410-21.

Genetic Defect in *CYP24A1*, the Vitamin D 24-Hydroxylase Gene, in a Patient with Severe Infantile Hypercalcemia

Andrew Dauber, Thutrang T. Nguyen, Etienne Sochett, David E. C. Cole, Ronald Horst, Steven A. Abrams, Thomas O. Carpenter, and Joel N. Hirschhorn

J Clin Endocrinol Metab, February 2012, 97(2):E268–E274



Badanie wchłaniania Ca za pomocą wapnia znakowanego izotopem przy stosowaniu różnych diet.

Pacjent wchłaniał 95% Ca z diety nisko-wapniowej i 85% z diety normowapniowej [norma dla wieku 45,6 ± 2,5]

24,25 OH_2D_3 prawie nieoznaczalne przy prawidłowych poziomach 25OHD

Mutacja genu CYP24A1 (dziedziczenie autosomalne recesywne)

Leczenie

- Odstawienie witaminy D
- Nawadnianie
- Glikokortykosteroidy
- Bisfosfoniany
- Kalcytonina

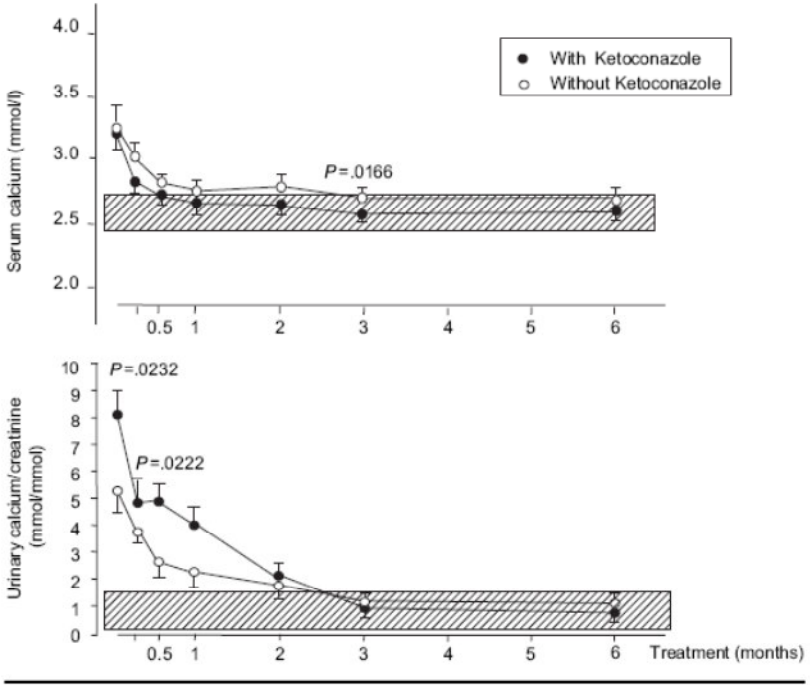
} Sporadycznie

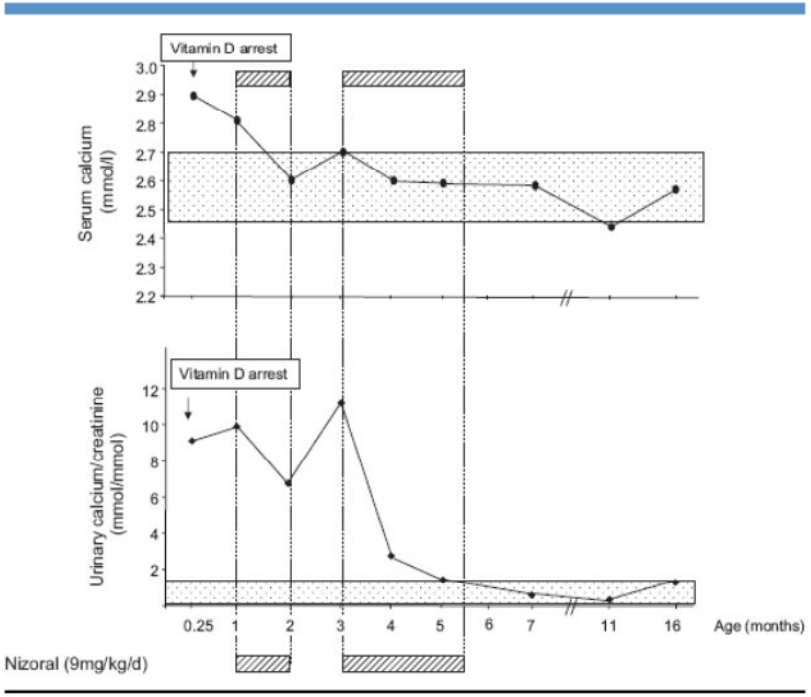
Inhibitor cytochromu P 450 - ketokonazol

Infantile Hypercalcemia and Hypercalciuria: New Insights into a Vitamin D-Dependent Mechanism and Response to Ketoconazole Treatment

Minh Nguyen, PhD, Henri Boutignon, MD, Eric Mallet, MD, PhD, Agnes Linglart, MD, PhD, Huguette Guillozo, Frederic Jehan, PhD, and Michele Garabedian, MD, PhD

(J Pediatr 2010;157:296-302)





20 dzieci z IHN, 10 z nefrokalcynozą otrzymywało ketokonazol 3-9 mg/kg/d, zależnie od ciężkości objawów. Średni czas leczenia 5,4±3,3 m-ca (0,5-12).

TABLE 2. Serum and urinary analytes before and after treatment with ketoconazole

	Urinary Ca (mg per 24 h), (25–300)	PTH (pg/ml), (15–65)	Total serum Ca (mg/dl), (8.9–10.1)	Serum inorganic P (mg/dl), (2.5–4.5)	$1,25(OH)_2D$ (pg/ml), (18–64)
Before	390.5 ± 80.59	7.5 ± 1.68	10.4 ± 0.49	4.1 ± 0.57	79.7 ± 34.49
After	149.5 ± 14.84	22.5 ± 6.36	9.8 ± 0.42	4.1 ± 0.42	59.5 ± 16.2
P value	0.007	NS	NS	NS	NS

Hypercalcemia, Hypercalciuria, and Elevated Calcitriol Concentrations with Autosomal Dominant Transmission Due to *CYP24A1* Mutations: Effects of Ketoconazole Therapy

Peter J. Tebben, Dawn S. Milliner, Ronald L. Horst, Peter C. Harris, Ravinder J. Singh, Yanhong Wu, John W. Foreman, Paul R. Chelminski, and Rajiv Kumar

J Clin Endocrinol Metab, March 2012, 97(3):E423–E427

Idiopatyczna hiperkalcemia niemowląt

– czy nadal idiopatyczna ?