64 F with hypocalcemia of unclear etiology

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Endorama
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I do not have any relevant financial relationships with any commercial interests.

HPI

64 F with recently diagnosed primary CNS lymphoma s/p craniotomy and resection who was noted to have hypocalcemia.

Patient had multiple falls at home and presented to an OSH ER. Head CT showed 3.7 cm mass. She was started on dexamethasone and taken for craniotomy and resection. She was transferred to U of C for further management.

Calcium since admission had decreased from 7.3 → 5.5

More HPI

- Patient notes that she has been on calcium 1000 mg daily since her 20s. She is not sure why she is on this.

She has never been on calcitriol. She denies surgery or radiation in the head & neck. She denies a previous diagnosis of hypoparathyroidism.

- + occasional cramping/stiffening of the hands. Denies seizures
- Denies kidney stones or fractures.

Extended History

PMH: DM2, schizophrenia, hypothyroidism, HTN

Meds: Metformin, levothyroxine, seroquel, losartan

Received dexamethasone x 2 weeks prior to transfer

Social hx: Non-smoker, no alcohol

Family hx: “I don’t know…my mother, father, and sister are all dead.”

Allergies: none

Physical Exam

T 36.3, BP 1 kg (217 LB), BMI 42.4

Gen: No ac

HEENT: Se

CV: RRR, n

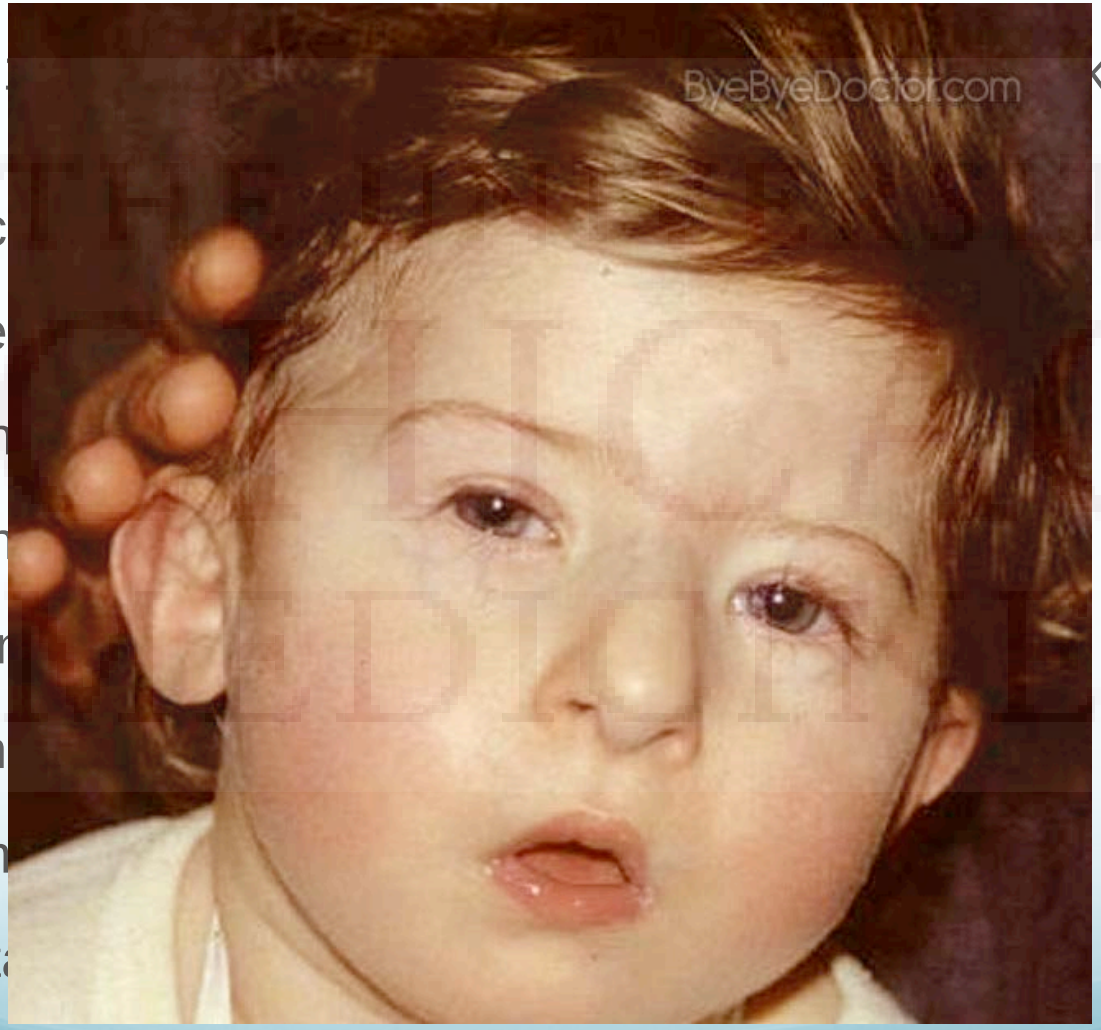
Abd: Soft, n

MSK: Movi

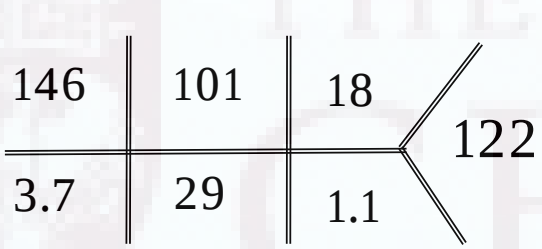
Neuro: Sen

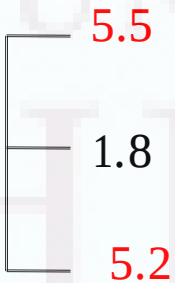
Skin: Warm

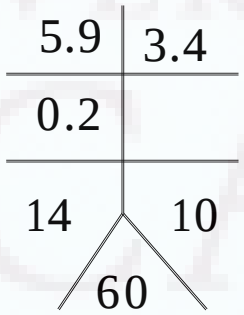
Psych: Agit

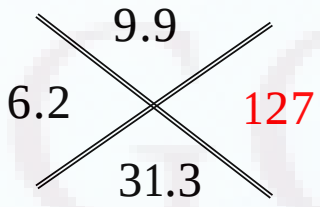


Labs









PTH 16

Ionized Ca 2.45 (L)

25-OH Vitamin D pending

Is this steroid effect?

An aside: What is the effect of glucocorticoids on calcium/Vitamin D metabolism?

Not as simple as I thought!

Glucocorticoids and calcium

- 12 young, normal subjects were studied before and after a 14 day administration of prednisone 20 mg daily

Hahn et al. Effects of short term glucocorticoid administration on intestinal calcium absorption and circulating Vitamin D metabolite concentration in man. JCEM 1981;52(111).

Glucocorticoids and Calcium

Intestinal Ca absorption was reduced from 60.9% at baseline to 42.2% at 14 days

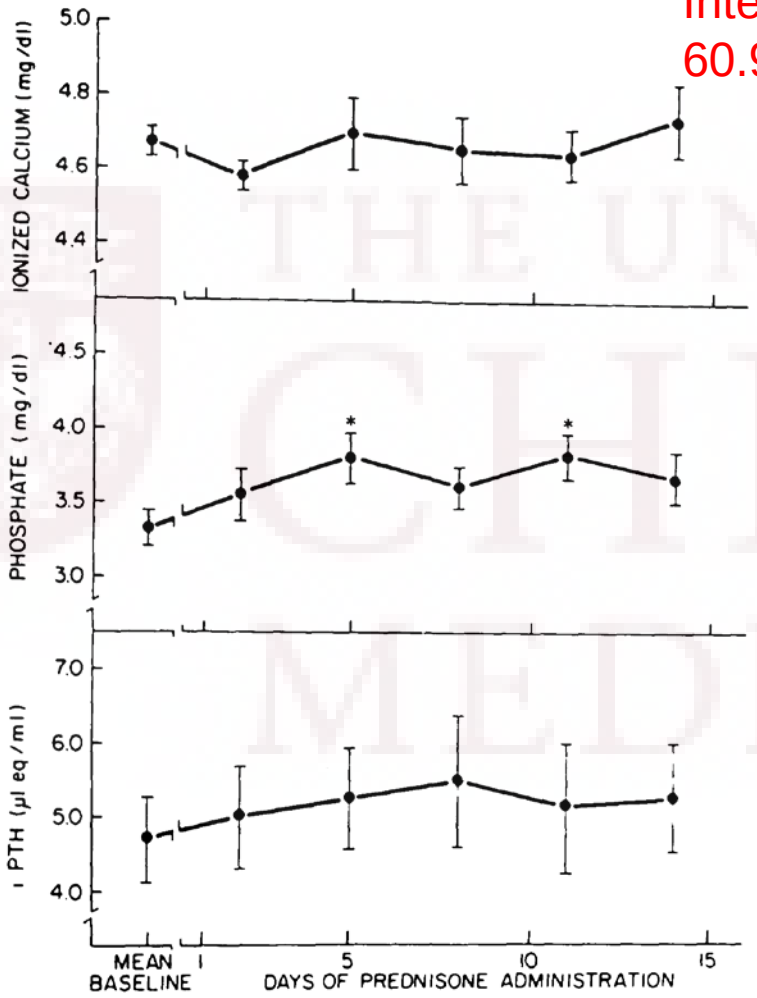
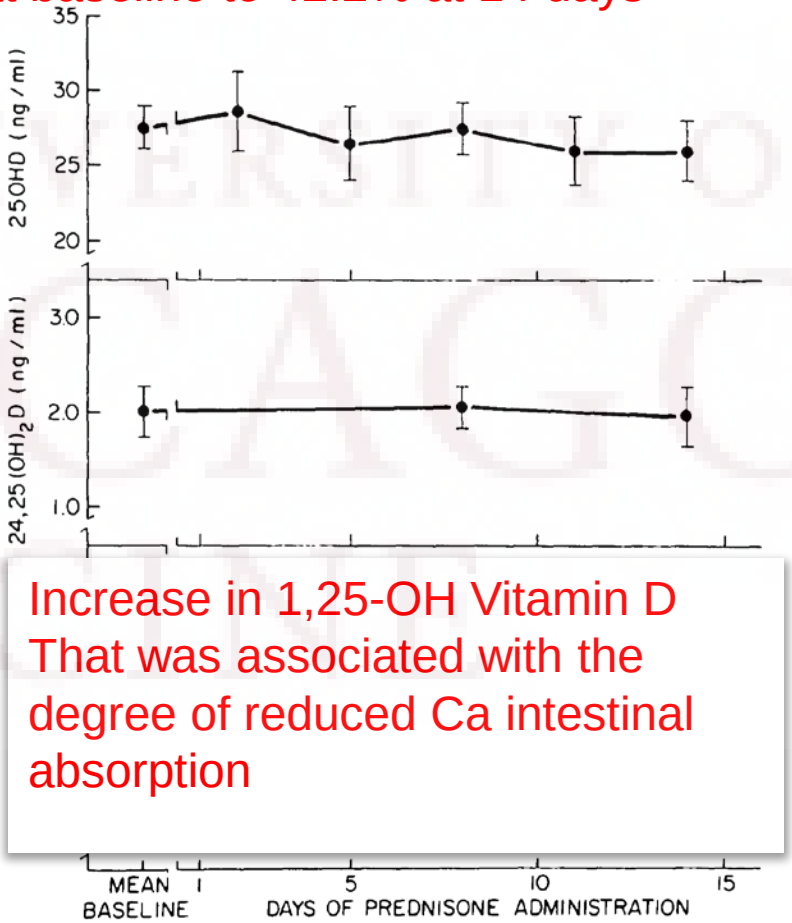


FIG. 1. Plasma ionized calcium and serum phosphate and iPTH concentrations during baseline and prednisone administration periods. Values represent the mean ± SEM of determinations in 12 subjects. *, Significantly different from baseline values ($P < 0.02$).



Increase in 1,25-OH Vitamin D That was associated with the degree of reduced Ca intestinal absorption

FIG. 2. Serum 25OHD, 24,25-$(OH)_2$D, and 1,25-$(OH)_2$D concentrations during baseline and prednisone administration periods. Values represent the mean ± SEM of determinations in 12 subjects. *, Significantly different from baseline values ($P < 0.02$).

Acute PTH Response

11 hospitalized patients with “mild illnesses” who had recovered were dosed with 100 mg of hydrocortisone over 5 min then given 100 mg of hydrocortisone over 4 hours.

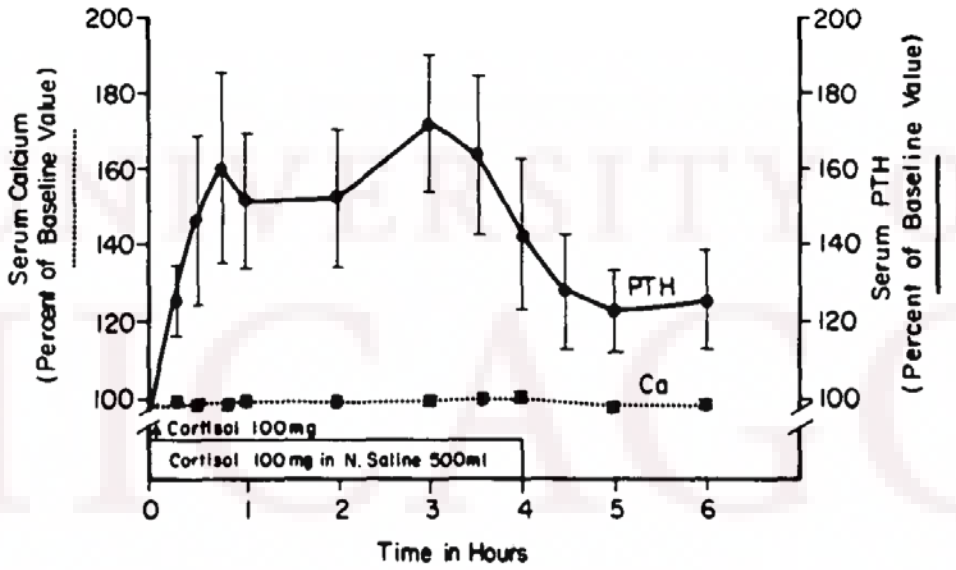


FIG. 2. Effect of cortisol infusion on serial serum Ca and PTH concentrations during the following 6 hr. Values (mean ± SE) at each time period are expressed as percent of the baseline pre-infusion values (designated as 100%). Difference in PTH value from baseline: ¼ hr: $p < 0.05$; 1, 2, 3, 3½ hr: $p < 0.02$; other times: not significant.

Fucik et al. Effect of glucocorticoids on function of the parathyroid glands in man. JCEM 1975;40:152.

Urinary Calcium excretion is increased as well

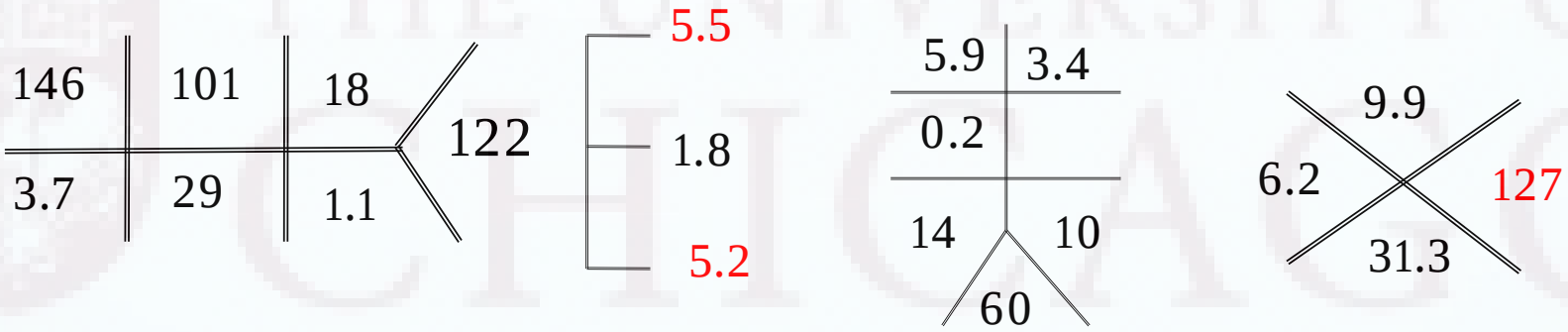
Table I. Indices of urinary calcium excretion in glucocorticoid-treated asthmatics and matched asthmatic control subjects (n = 15)

	Control	Glucocorticoid	p
Ca_t, m*M*	2.46 ± 0.02 (2.36 − 2.60)	2.47 ± 0.02 (2.33 − 2.63)	NS
Ca_i m*M*	1.26 ± 0.01 (1.20 − 1.30)	1.25 ± 0.01 (1.20 − 1.30)	NS
uCa/Cr (molar ratio)	0.25 ± 0.03 (0.12 − 0.51)	0.56 ± 0.09 (0.13 − 0.89)	< 0.005
Ca_E, mmol/LGF	0.022 ± 0.003 (0.010 − 0.046	0.051 ± 0.008 (0.009 − 0.111)	< 0.005
TmCa, m*M*	1.86 ± 0.03 (1.64 − 2.03)	1.63 ± 0.06 (1.31 − 1.97)	< 0.005
uNa/Cr (molar ratio)	13.8 ± 1.6 (3.5 − 27.7)	16.6 ± 2.0 (1.39 − 32)	NS
Serum creatinine, m*M*	0.087 ± 0.004 (0.05 − 0.12)	0.092 ± 0.004 (0.07 − 0.11)	NS

Ca_t = Total serum calcium, Ca_i = serum ionized calcium, uCa/Cr = urine calcium/creatinine ratio, Ca_E = urine calcium excretion per litre of glomerular filtrate, TmCa = tubular maximum for calcium reabsorption, uNa/Cr = urine sodium/creatinine ratio. All samples were taken in the fasting state. Data are means ± SEM and the range of values in each group is shown in parentheses.

Reid et al. Evidence of decreased tubular reabsorption of calcium in glucocorticoid treated asthmatics. Hormone Res 1987;27:200-04.

Back to the case!



PTH 34

Ionized Ca 2.45 (L)

25-OH Vitamin D 25

Epic Everywhere Calcium level (3 years ago): 7.5

Diagnosis and workup?

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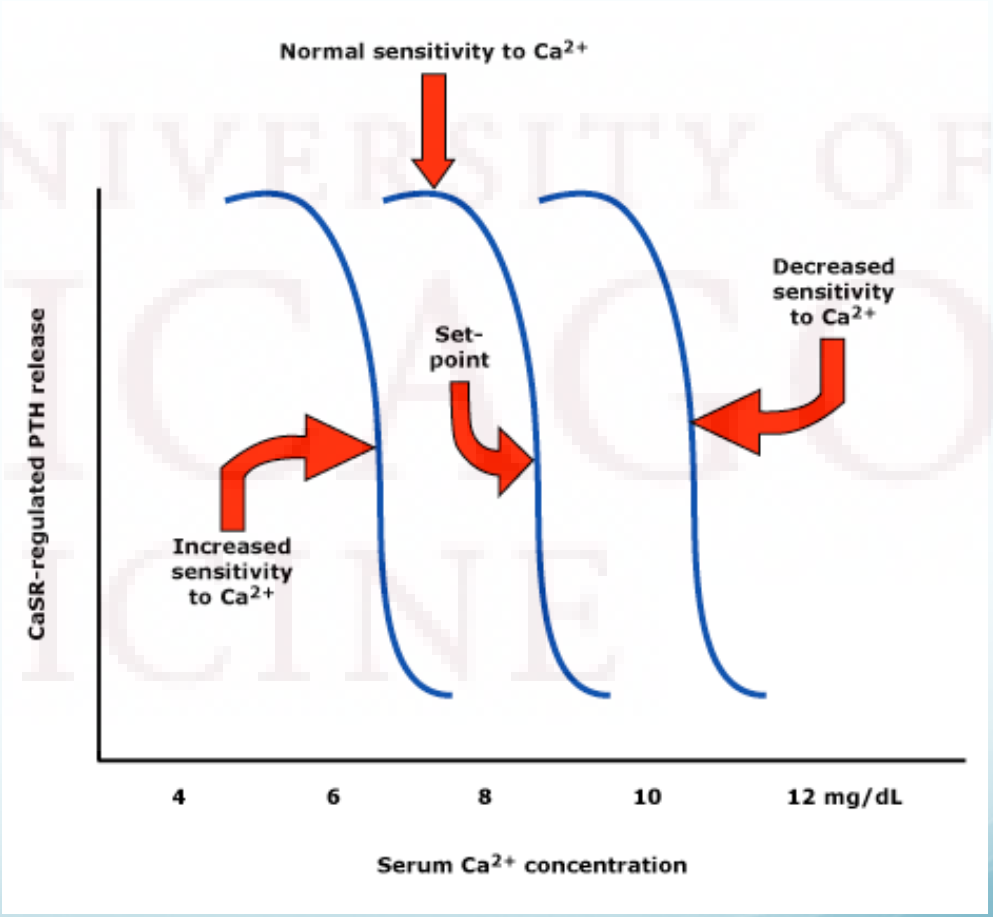
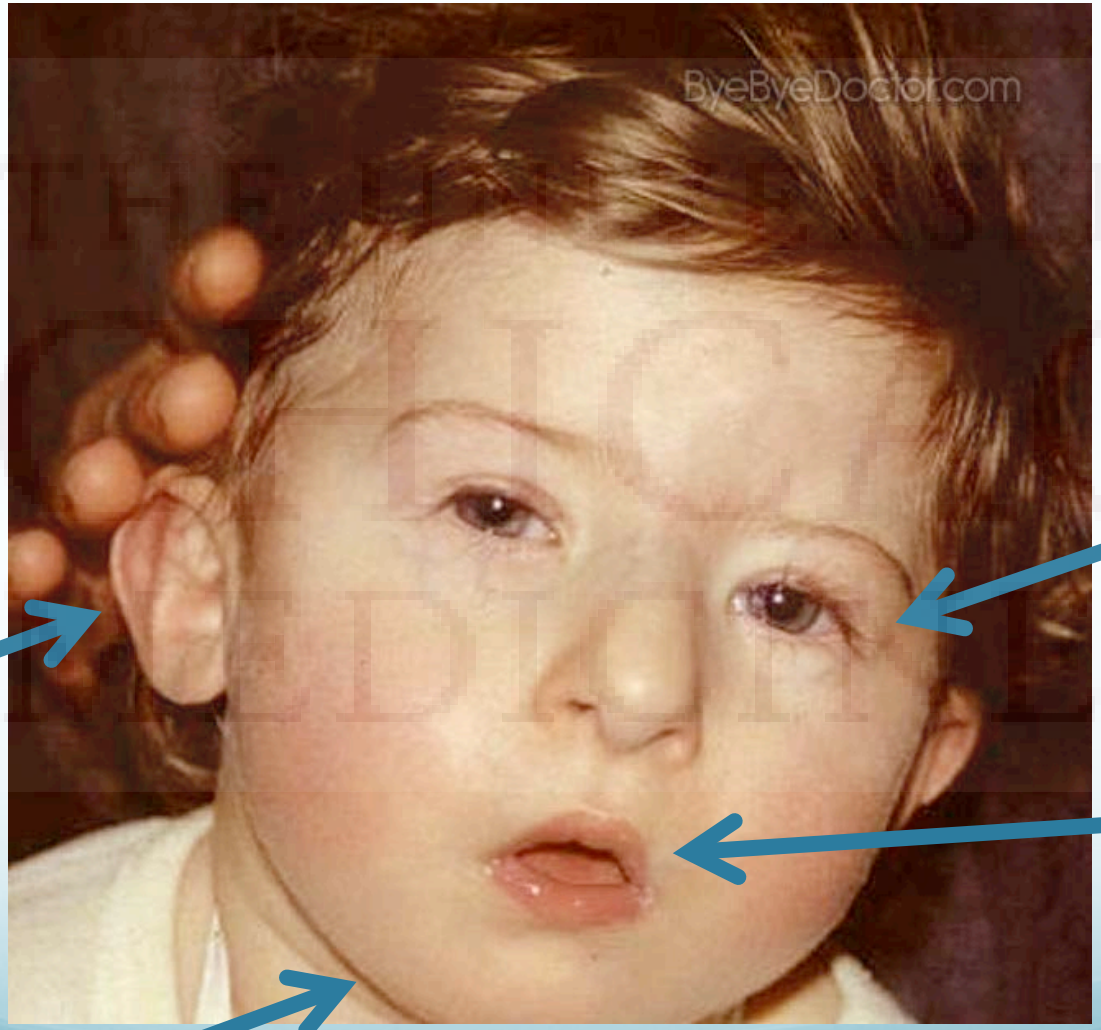
Etiology of hypoparathyroidism?

- Surgical destruction or radiation
- Autoimmune
- Infiltration (Hemochromatosis, granulomas, metastatic cancer)
- Hypomagnesemia
- Genetic mutations
  - DiGeorge Syndrome or 22q11.2 mutations
  - Autosomal dominant hypocalcemia – Activating mutation of the CaSR

Autosomal Dominant Hypocalcemia

- Serum Ca usually 6-8, may not be diagnosed until adulthood
- Normal or only slightly low PTH
- High or high normal urinary calcium excretion (particularly compared to what may be expected)
- Recurrent nephrolithiasis, particularly when Ca treatment is started
- No previously normal Ca levels
- Low serum Mag (sometimes)





Not clear in this picture but was in our patient: amblyopia

Almond Shaped eyes

Low set ears

Small mouth/upper lip

Small jaw

22q11.2 deletions

- One in 3900-9700 births
- Variable clinical presentations has led to confusing nomenclature – genetic defect vs. clinical syndromes [DiGeorge Syndrome, velocardiofacial syndrome, some patients with CHARGE syndrome (coloboma, heart, atresia, retardation of growth, genitourinary problems, ear abnormalities)]

Patients with 22q11.2 deletions have variable clinical presentations!

	Frequency of finding
Cardiac anomalies	49–83%
Tetralogy of Fallot	17–22%
Interrupted aortic arch	14–15%
Ventriculoseptal defect	13–14%
Truncus arteriosus	7–9%
Hypocalcaemia	17–60%
Growth hormone deficiency	4%
Palatal anomalies	69–100%
Cleft palate	9–11%
Submucous cleft palate	5–16%
Velopharyngeal insufficiency	27–92%
Bifid uvula	5%
Renal anomalies	36–37%
Absent or dysplastic	17%
Obstruction	10%
Reflux	4%
Ophthalmological abnormalities	7–70%
Tortuous retinal vessels	58%
Posterior embryotoxon (anterior segment dysgenesis)	69%
Neurological	8%
Cerebral atrophy	1%
Cerebellar hypoplasia	0·4%
Dental	
Delayed eruption, enamel hypoplasia	2·5%
Skeletal abnormalities	17–19%
Cervical spine anomalies	40–50%
Vertebral anomalies	19%
Lower limb anomalies	15%
Speech delay	79–84%
Developmental delay in infancy	75%
Developmental delay in childhood	45%
Behaviour or psychiatric problems	9–50%
Attention deficit hyperactivity disorder	25%
Schizophrenia	6–30%

Data were taken from references 16, 18, 112–114, 131–136.

Table 1: **Clinical findings in patients with chromosome 22q11.2 deletion syndrome**

Kobrynski LJ and Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet 2007;370:1443-52.

22q11.2 deletions

- Most patients with 22q11 have mild defects in T-cell numbers and are *not* clinically immunodeficient
- Approximately 1% have complete absence of thymic tissue and have profound immunodeficiency
- Some criteria have used reduced numbers of CD3+ T cells to help define DiGeorge

Diagnosis	Criteria
Definitive	Reduced CD3+ T Cells (<500) and 2 of the following: 1. Conotruncal cardiac defect 2. Hypocalcemia of greater than 3 weeks' duration that requires therapy 3. Deletion of chromosome 22q11.2
Probable	Reduced CD3+ T cells (<1500) and deletion of chromosome 22q11.2
Possible	Reduced CD3+ (<1500) and at least one of the following: 1. Cardiac defect 2. Hypocalcemia of greater than 3 weeks' duration that requires therapy 3. Dysmorphic facies or palatal abnormalities

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Conley ME, Notarangelo LD, Etzioni A. Clin Immunol 1999; 93:190.

Other conditions associated with 22q11 deletion syndromes

- Hypoparathyroidism present in ~50%
- Congenital heart disease
- Psychiatric disorders (including schizophrenia)
- Cognitive impairment (90%)
- Autoimmune disorders
- Platelet disorders (thrombocytopenia, large platelets on smear)

Thrombocytopenia

- Most patients with 22q11 deletion are heterozygous for GPIb gene, similar to Bernard Soulier Syndrome
- Patients have thrombocytopenia with large platelet size
- In general, patients (like ours) do not manifest an increased tendency to bleed
- Has been suggested that it could be used as an indicator of 22q11 diagnosis

Machado Rosa et al. Hematological abnormalities and 22q11.2 deletion syndrome. Rev Bras Hematol Hemoter 2011;33(2);151-54.

Recommendations?

- We recommended FISH for 22q11.2 deletion, lymphocyte panel to look for immune deficiencies, Echo to look for cardiac abnormalities
- IV calcium then Calcium 1000 mg TID + calcitriol 0.5 mcg daily

Imaging and Labs

PET Findings

- Assymetric atrophy of the left submandibular gland
- Narrowing of the anterior portion of the trachea at the level of the aortic arch suggestive of tracheomalacia
- Small water attenuation cystic lesion present superior to the right atrial appendable compatible with pericardial cyst
- Two colonic lesions
- *Left sacral insufficiency fracture*

Echo – could not exclude PFO/ASD but otherwise no abnormalities c/w 22q11.2

CD3 cells: 1179 (Reference Range: 828-2328)

FISH Results

RESULTS: arr 22q11.21(18,916,842-21,800,797)x1

IMPRESSION: Abnormal female microarray analysis

Whole genome microarray analysis detected an approximately 3 Mb single copy loss of chromosome 22q11.21 including the DiGeorge Syndrome region. This result is consistent with a clinical diagnosis of DiGeorge Syndrome. If warranted, Fluorescence in situ hybridization (FISH) testing of family members could be considered.

Genetic counseling is recommended.

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Conley ME, Notarangelo LD, Etzioni A. Clin Immunol 1999; 93:190.

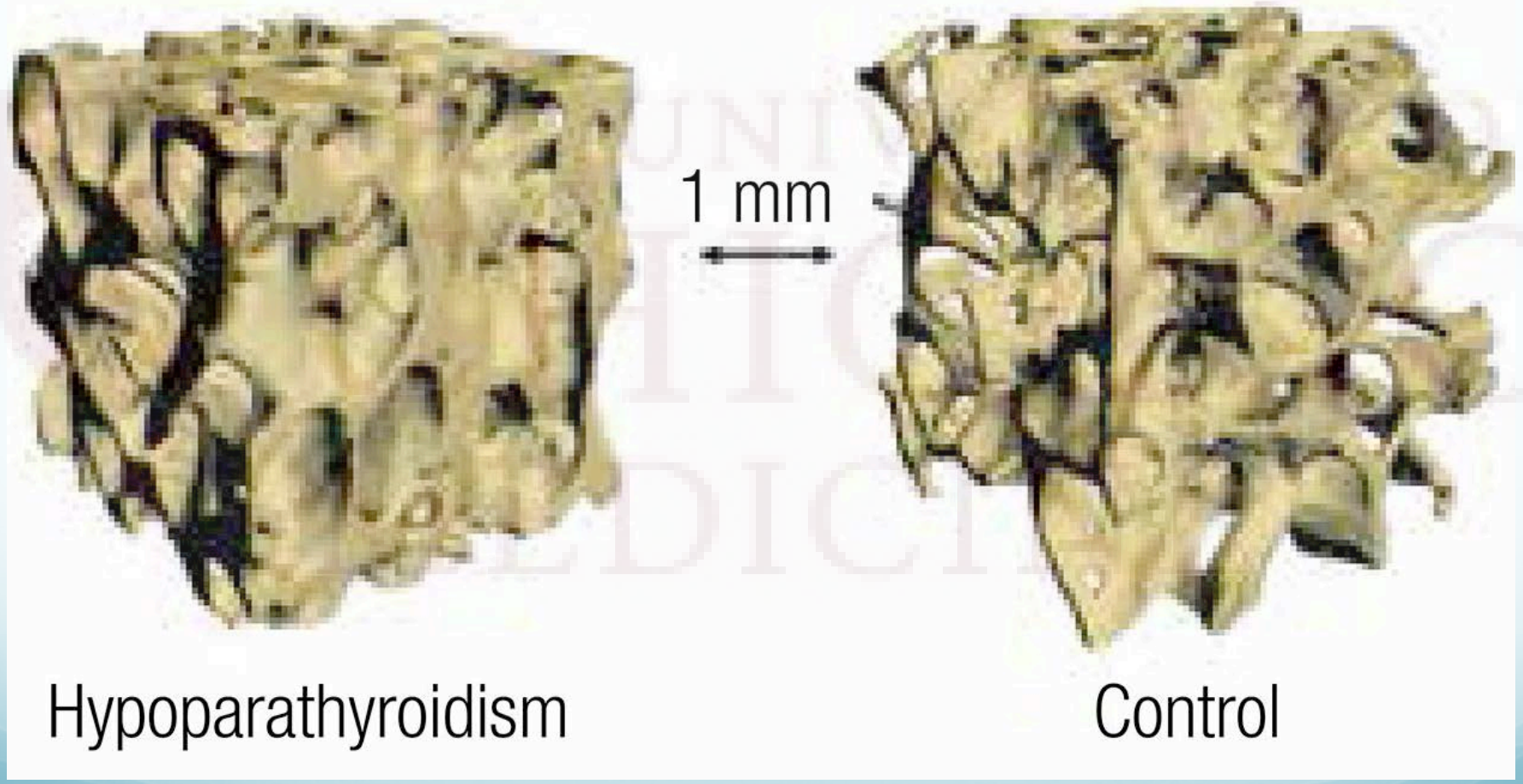
Fractures and hypoparathyroidism

- 180 patients with non-surgical hypoparathyroidism were shown to have similar overall fracture risk as the general population, but higher risk of fractures in the upper extremities (HR 1.93, 95% CI 1.31-2.85)
- Conversely, in 688 patients with postsurgical hypoparathyroidism, overall fx risk was similar but risk of upper extremity fractures was *lower* (HR 0.69, 95% CI 0.49-0.97)

Bottom Line

Long term effects of increased bone mass (likely beneficial) vs. low bone turnover (possibly deleterious to bone quality) on bone strength and fracture risk are unclear

Shoback DM, …., Vokes T et al. Presentation of hypoparathyroidism: etiologies and clinical features. JCEM 2016;101:2300-12.

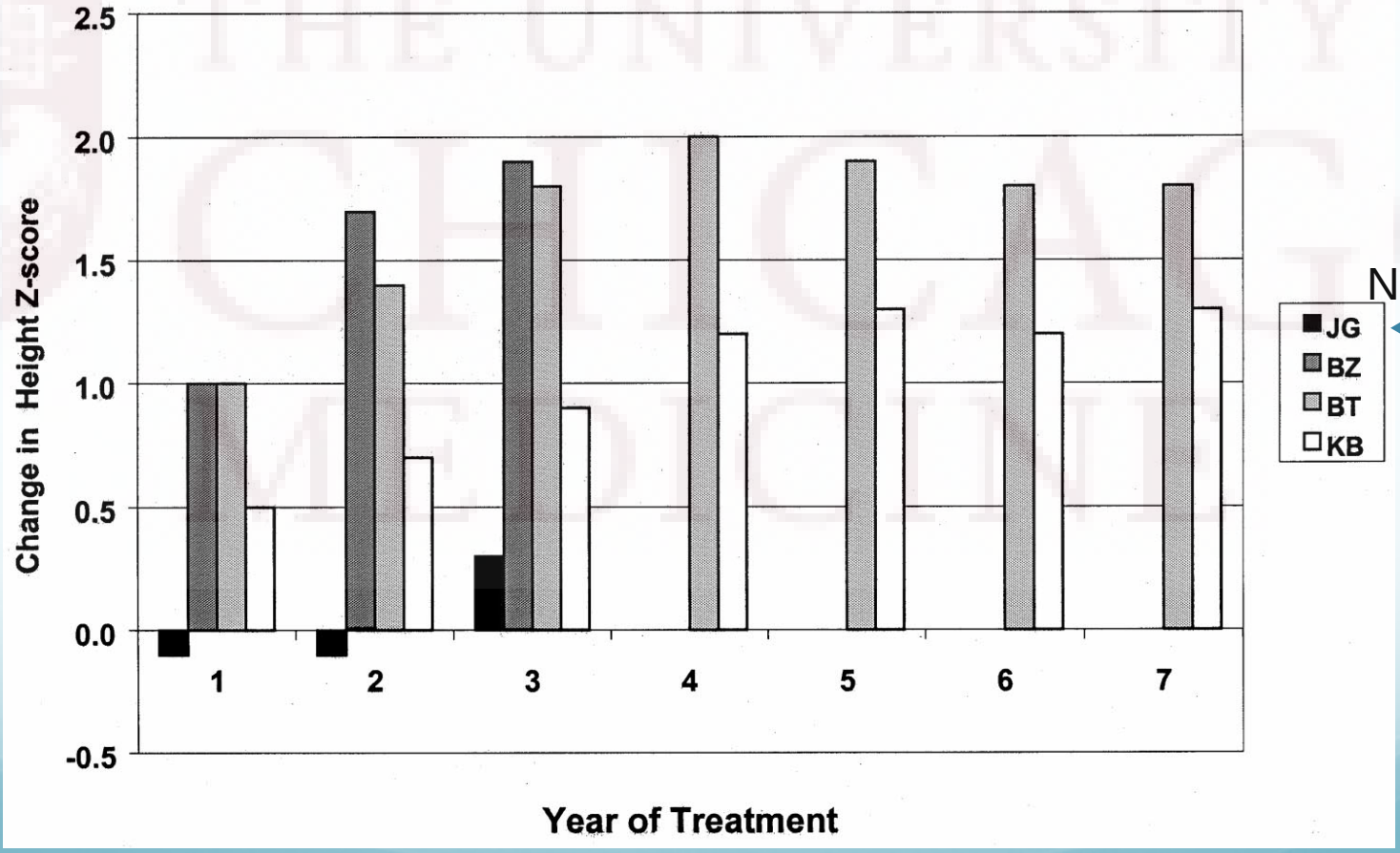

1 mm
Hypoparathyroidism
Control

Malignancy

- In 687 patients with 22q11.2 deletion (mostly pediatric patients), the rate of malignancy was 0.9% (Neuroblastoma, ALL, hepatoblastoma, Wilms tumor, thyroid carcinoma)
- Several case reports of lymphoma, particularly B-cell lymphoma; this is usually in patients with more significant immunodeficiency

McDonald-McGinn et al. Malignancy In Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome/Velocardiofacial Syndrome). American Journal of Medical Genetics 2006;140A:906-9.

Are there other endocrine abnormalities associated with 22q11.2 deletions?



Are there other endocrine abnormalities associated with 22q11.2 deletions?

Thyroid

Hypothyroidism – reported in 1% in the largest series

Hyperthyroidism – Graves' has been reported in 2 case reports

Weinzimer S. Endocrine aspects of the 22q11.2 deletion syndrome. Genetics in Medicine 2001;3(1):19-22.

Follow up

- Once steroids were off, patient able to be weaned to calcium and cholecalciferol supplements alone
  - Calcium 750 mg TID, D3 2,000 IU daily
  - No Calcitriol
- Chose not to follow with Endocrine (despite my urging)
- Patient continues to receive chemotherapy for her lymphoma
- Calcium levels have fluctuated between 7.0-9.0 on inpatient admissions

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References

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