THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

“28 Year Old Male With Neurofibromatosis Type 1”

Dr. Darji does not have any relevant financial relationships with any commercial interests.

ENDORAMA:
28 Year Old Male With Neurofibromatosis Type 1

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January 3rd, 2019

Objectives

- Review the clinical features of neurofibromatosis type 1 (NF1)
- Review the clinical features of osteogenesis imperfecta
- Discuss the bone abnormalities seen in patients with NF1 and review treatment options

Chief Complaint

28 year old Caucasian male presents with osteoporosis and history of multiple fractures

HPI

- Presents to Bone Clinic for follow up for osteoporosis
  - Hx of neurofibromatosis type 1 (NF1), diagnosed at 5 months based on café au lait spots
  - Hx of osteogenesis imperfecta type 1, diagnosed at 4 years old by skin biopsy
  - Multiple fractures in the past
  - Previously on Fosamax
  - On calcium and vitamin D supplementation

Osteoporosis History

- History of nine fractures during childhood and adolescence
  - Right femur fracture in 10/2007 after a fall
  - Right mid-fibula fracture in 1/2008 after falling when using his crutches
  - Left wrist fracture in 5/2015 after a fall
- No fractures since 2015
  - Pt has been exercising, working on balance and avoiding falls
- Previously on Fosamax 2008-2011
  - Stopped after improvement in bone density
- BMDs have been stable

Review of Systems

- Constitutional: No fever, chills, activity change, fatigue
- HEENT: No hearing loss. No congestion, sore throat, neck pain
- Resp: No cough, shortness of breath
- CV: No CP, palpitations, LE edema.
- GI: No abdominal pain, n/v, d/c or blood in stool.
- MSK: No myalgias.
- Skin: **+neurofibromas**
- Neuro: No dizziness, seizures, syncope, or headaches.
- Endo: No heat/cold intolerance. No hair/skin changes noted.
- Heme: No adenopathy
- Psych: No anxiety or depression.

Additional history

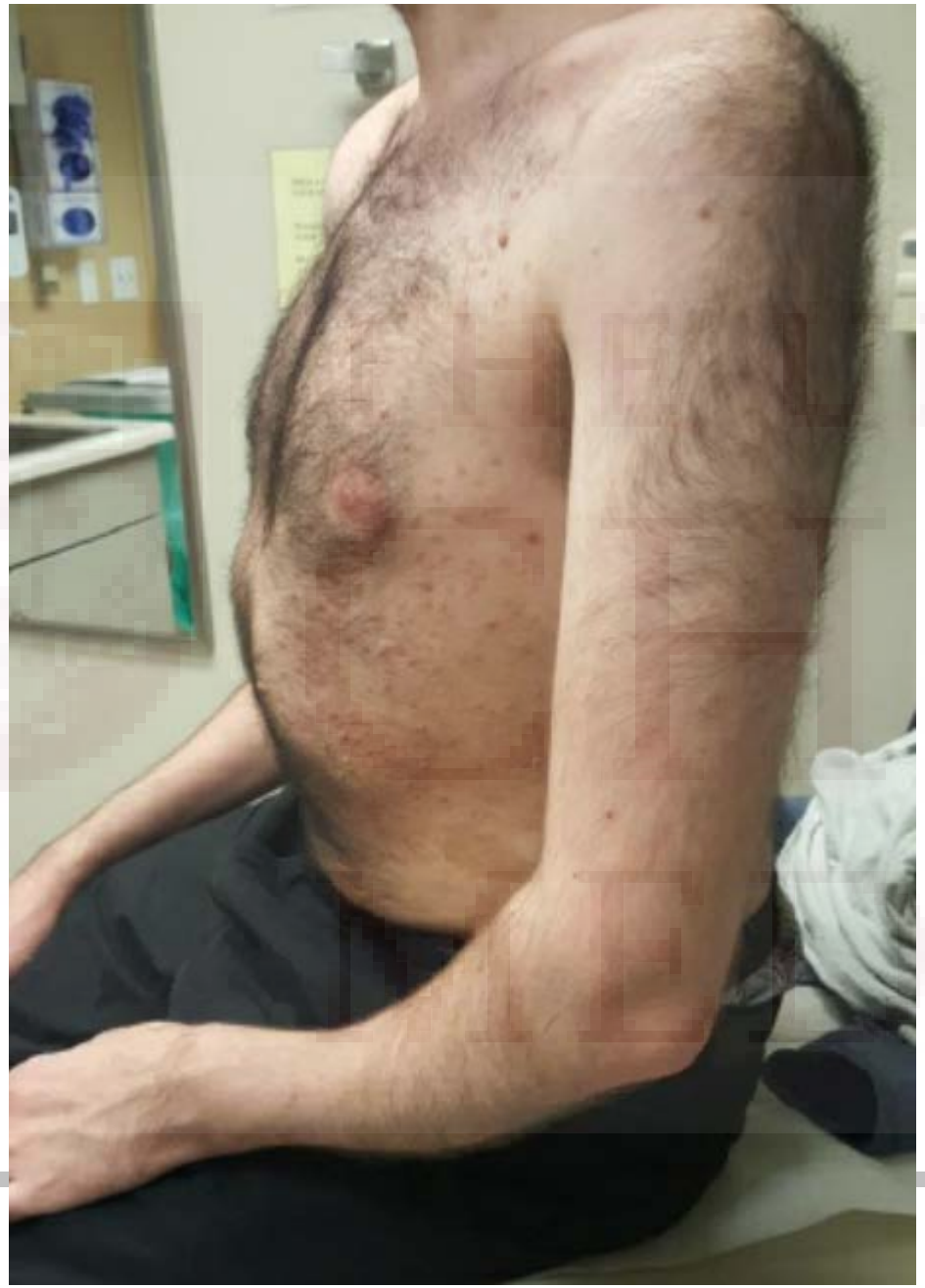
- Past Medical History: neurofibromatosis type 1, osteogenesis imperfecta type 1, osteoporosis, distal aqueductal stenosis
- Past Surgical History: surgical repair of right femur fracture and left humeral fracture, Endoscopic third ventriculostomy and reservoir placement
- Family History: no family hx of osteoporosis, NF1, OI
- Social History: works as accountant, denies tobacco, alcohol, and illicit drugs

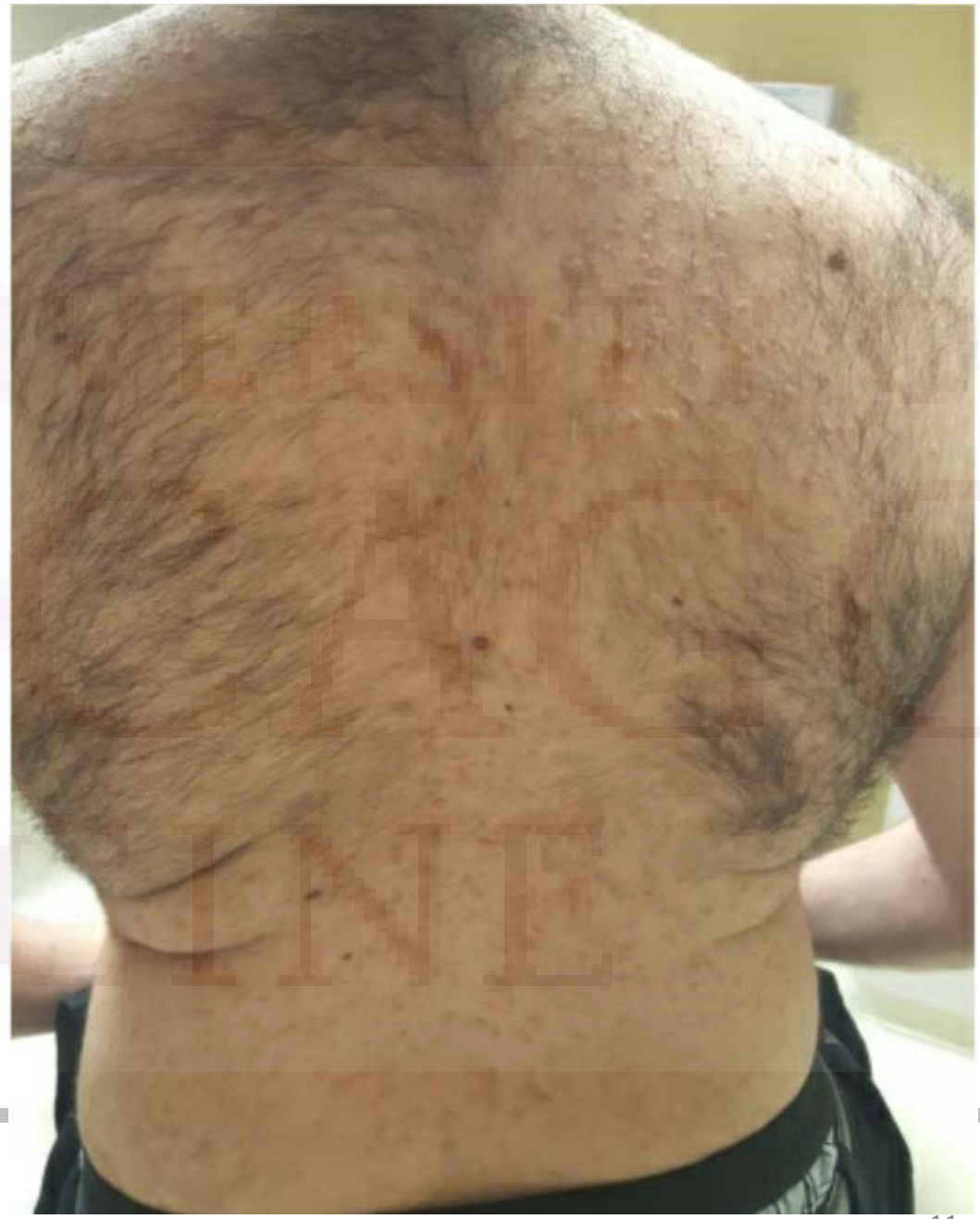
Additional history

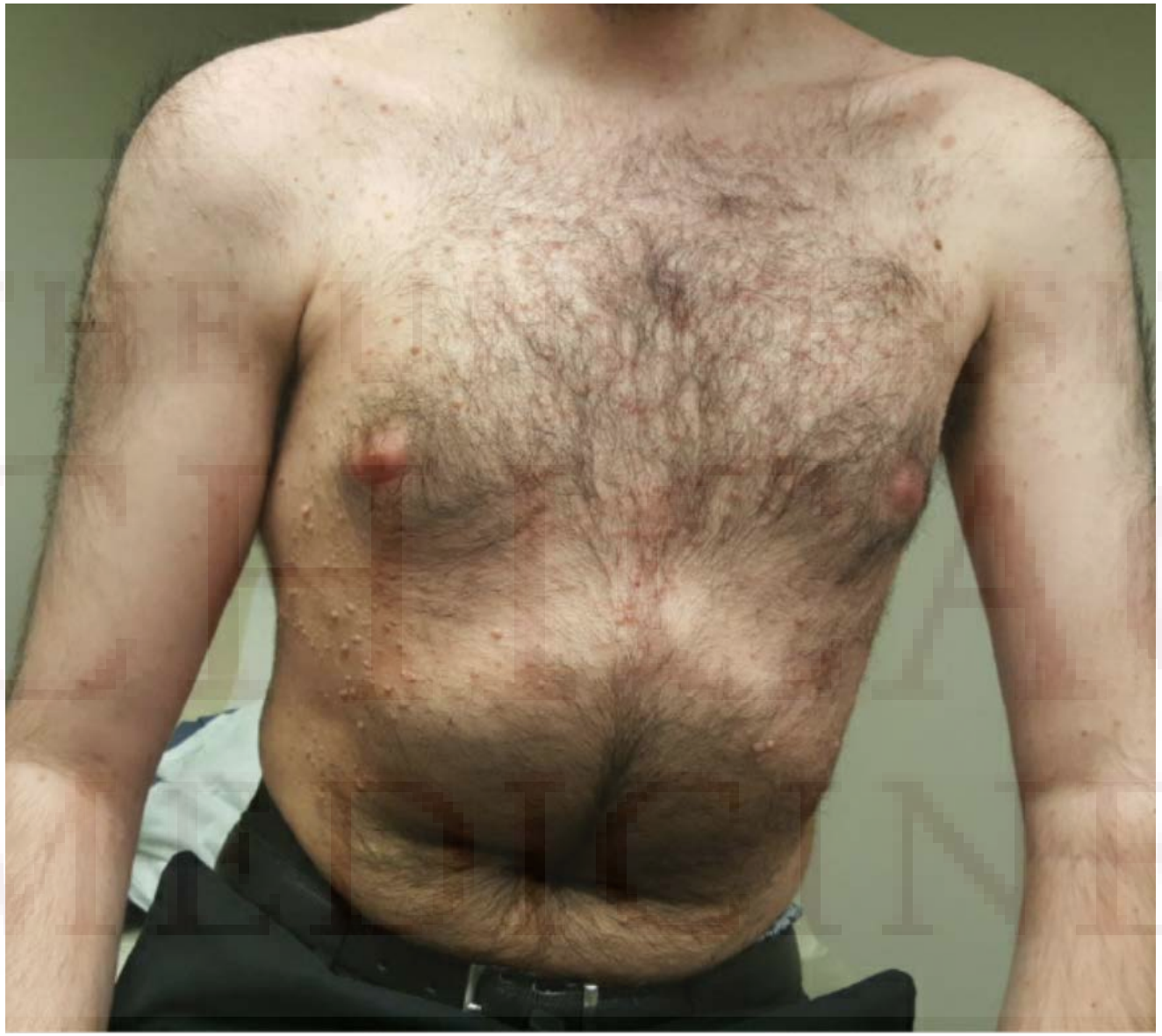
- Meds: vitamin D3 2000 IU daily, calcium carbonate 500mg BID
- Allergies: NKDA

Physical Exam

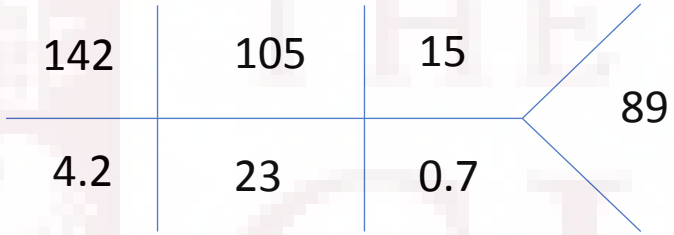
- Vitals: 74 kg, BMI 22, Temp 97.4, HR 89, RR 17, BP 123/71, SpO2 100%
- General: No apparent distress. Appears stated age.
- HEENT: **macrocephaly**; No pharyngeal erythema. PERRL, EOMI.
- Neck: No neck tenderness. No thyroid nodules appreciated.
- Cardiovascular: regular rate and rhythm. No peripheral edema.
- Pulmonary/Chest: clear to auscultation bilaterally.
- Gastrointestinal: soft, non-tender, non-distended. No rebound or guarding.
- Musculoskeletal: **left arm deformity, left upper arm atrophy, scoliosis, impaired balance**
- Neurological: Alert & oriented, **proximal muscle weakness**
- Skin: **Cafe au-lait macules on left arm, cutaneous neurofibromas on chest and back**





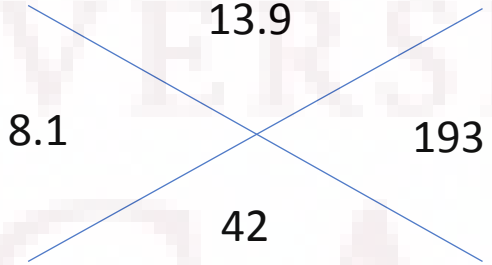


Labs



Ca 9.7

Anion gap 14



Total protein	7.3	Alkaline phosphatase	71	25-OH vitamin D	36
Albumin	4.4	ALT	18	PTH	28
Total bilirubin	0.8	AST	15		

BMD

- BMD on 2/18/08:
  - The spinal BMD of 0.591 g/cm2, 6.30 standard deviations (SDs) below bone mass estimated for a young man of his age and body build
  - The femoral neck BMD of 0.474 g/cm2
- BMD on 11/15/18:
  - The L1-L4 spinal BMD of 0.910 g/cm2 with a T-score of -2.6 and a Z-score of -2.5.
  - The total hip BMD is 0.686 g/cm2 with a T-score of -2.9 and a Z-score of -2.8.
  - Stable BMD compared to 2016

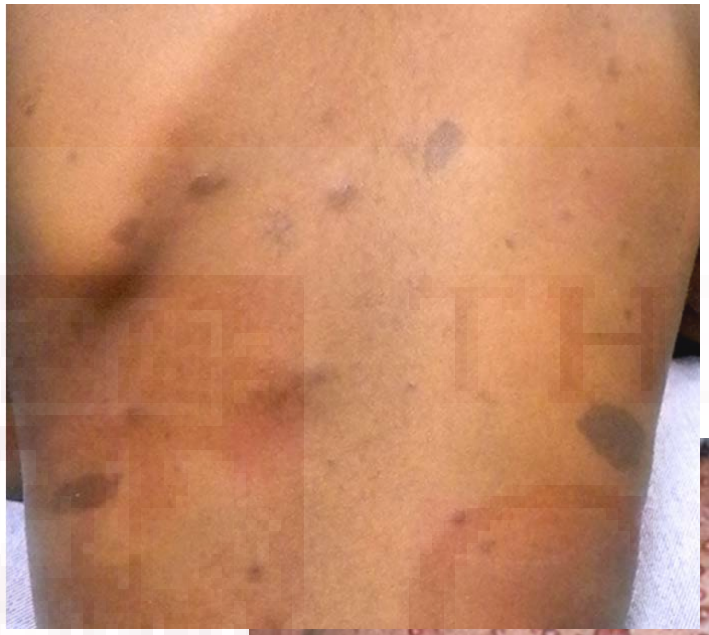
NF1

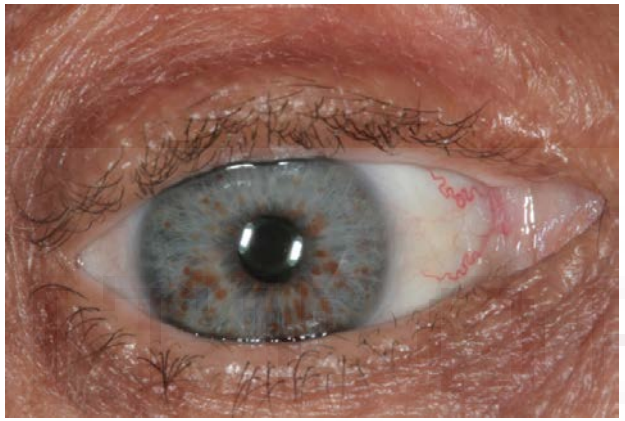
- Also known as von Recklinghausen disease
- Hallmarks are multiple café-au-lait macules and neurofibromas
- Autosomal dominant genetic disorder
- Incidence of approximately 1 in 2600 to 3000 individuals
  - Approximately one-half are familial

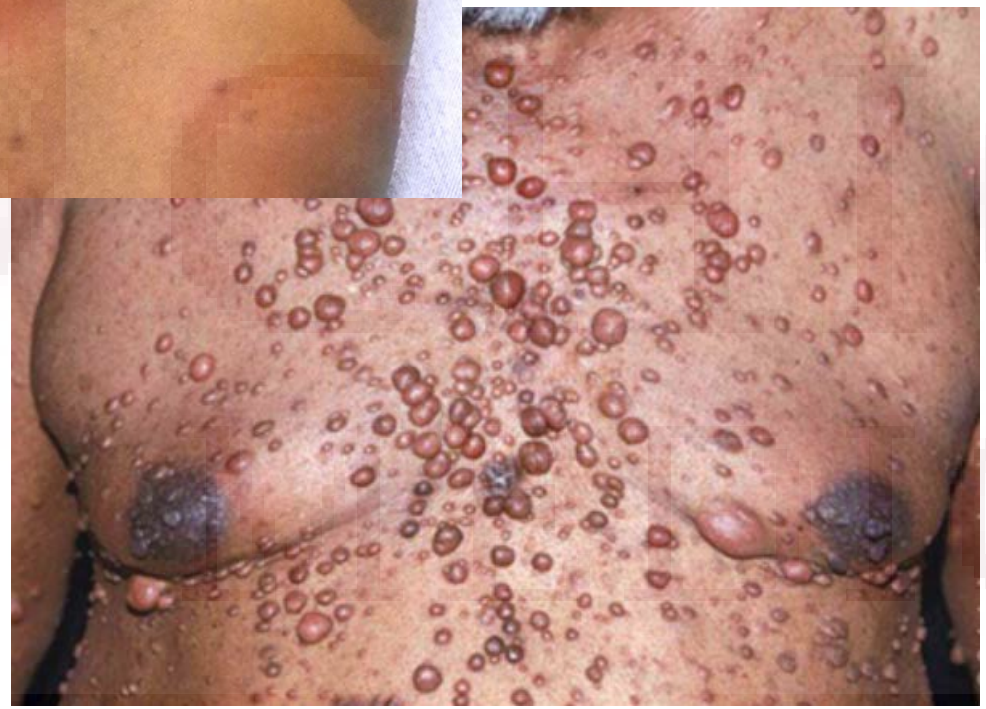
Clinical Manifestations of NF1

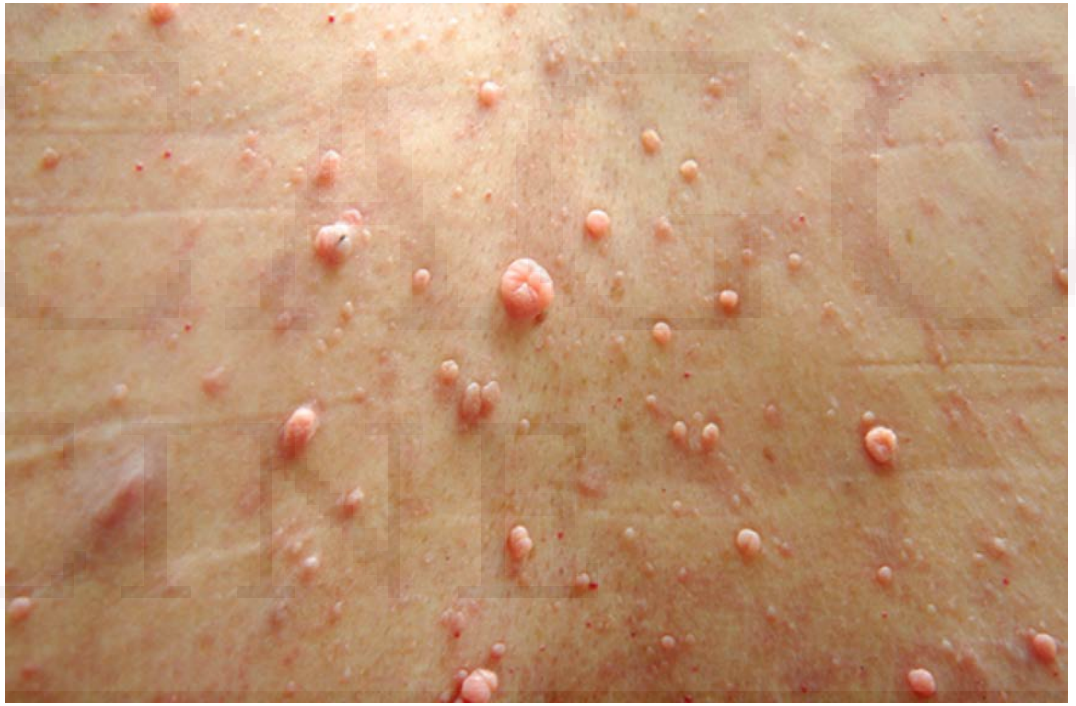
- Café-au-lait macules
- Freckling, especially the axillary and inguinal areas
- Lisch nodules
- Peripheral neurofibromas
- Optic pathway gliomas
- Bone abnormalities
- Soft tissue sarcomas
- Cognitive deficits and learning disabilities
- Macrocephaly
- Seizures
- Peripheral neuropathy
- Hypertension

NF1









Diagnosis

NIH diagnostic criteria for neurofibromatosis type 1

Two or more of the following clinical features must be present:
Six or more café-au-lait macules of more than 5 mm in greatest diameter in prepubertal individuals, and more than 15 mm in greatest diameter in postpubertal individuals
Two or more neurofibromas of any type or one plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
Two or more iris hamartoma (Lisch nodules)
Distinctive bony lesion, such as sphenoid dysplasia, or medullary narrowing and cortical thickening of the long bone cortex with or without pseudoarthrosis
A first-degree relative (parent, sibling, or offspring) with NF1 based on the above criteria

NIH: National Institutes of Health; NF1: neurofibromatosis type 1.

Osteogenesis Imperfecta (OI)

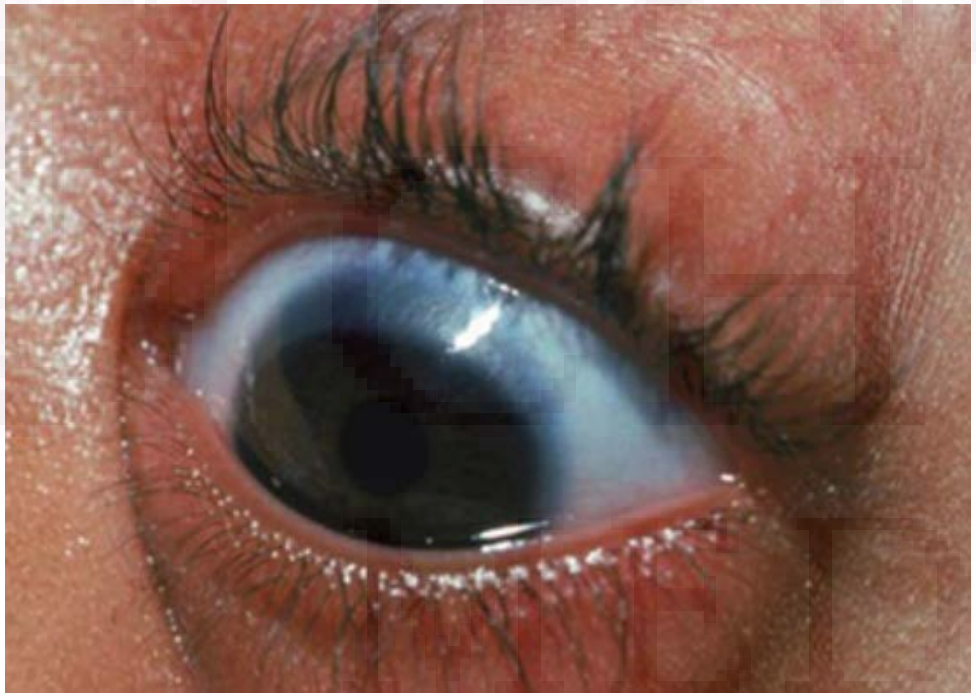
- Inherited connective tissue disorder
- Most commonly caused by mutations in genes encoding the alpha-1 and alpha-2 chains of type I collagen
  - Autosomal dominant mutation in *COL1A1* (located at 17q21.31-q22) or *COL1A2*
- Incidence of OI is approximately 1 per 20,000 births
- Nine subtypes based on genetic, radiographic, and clinical features

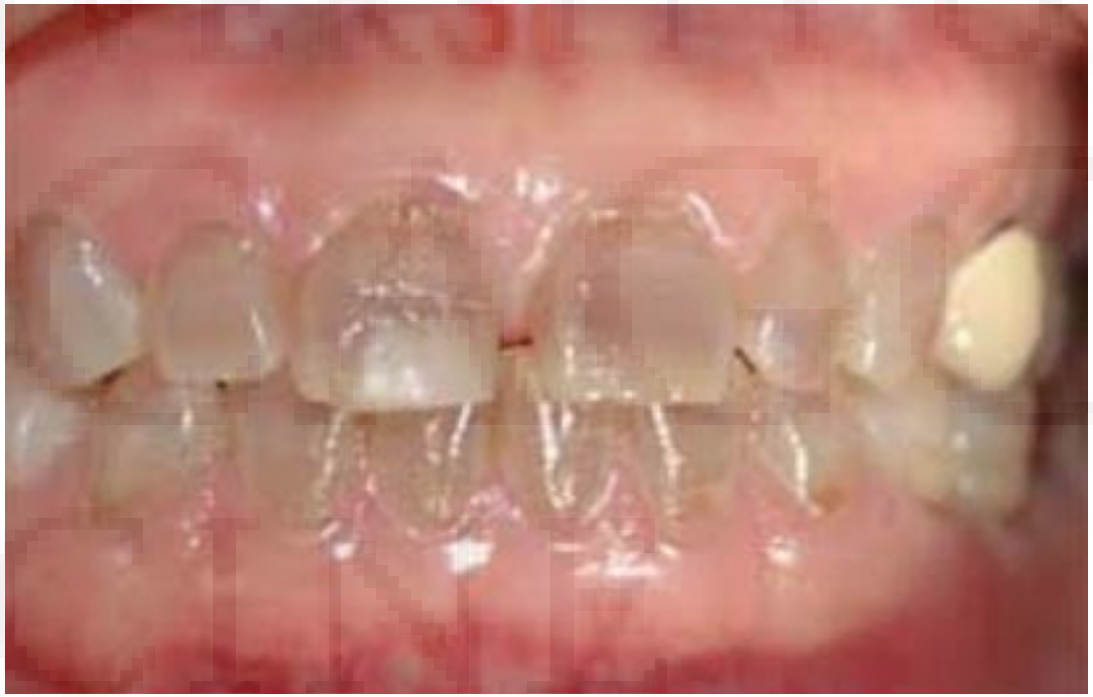
Clinical Manifestations of OI

- Excess or atypical fractures with little or no trauma
- Short stature
- Scoliosis
- Blue sclera
- Hearing loss
- Dentinogenesis imperfecta

- Type 1 – least severe
  - Fractures tend to involve the long bones of the arms and legs, ribs, and the small bones of the hands and feet
    - Decline after puberty
  - Premature osteoporosis

OI





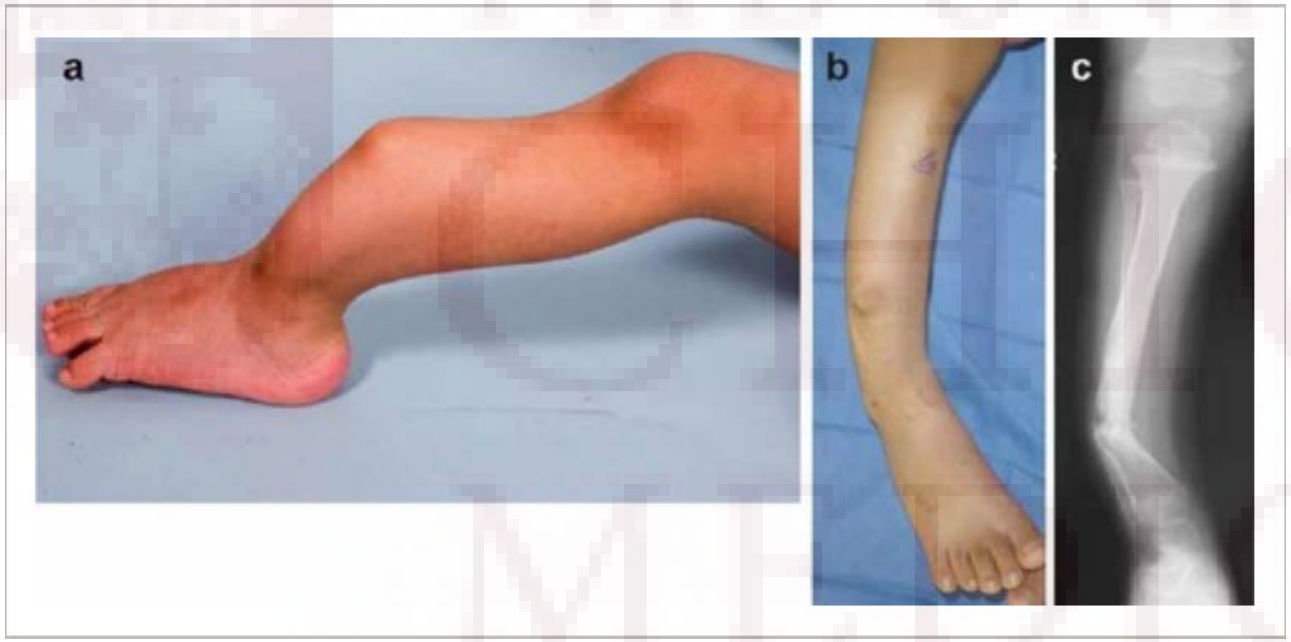
Diagnosis and Treatment

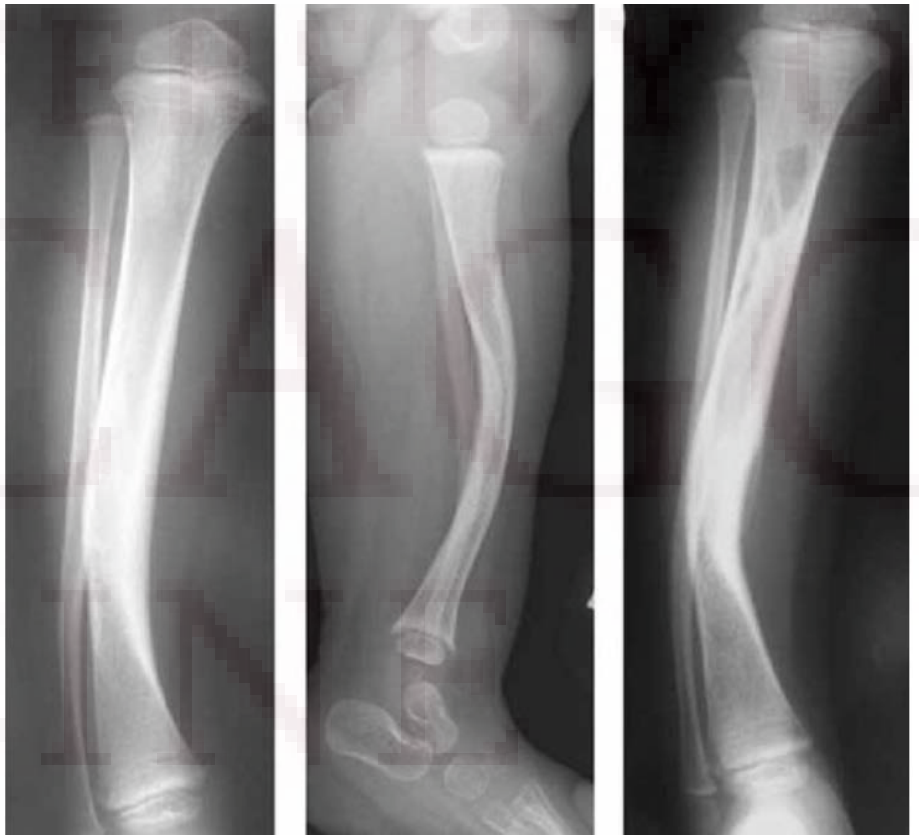
- Based on signs and symptoms, family history, presence of extraskeletal symptoms
- Molecular genetic testing
- Skin biopsy to determine the structure and quantity of type I collagen
- Bisphosphonates are the mainstay of pharmacologic treatment to prevent fractures

Bone abnormalities in NF1

- Long bone dysplasia
  - Infants and young children
  - Anterolateral bowing of the tibia -> narrowing of medullary cavity and cortical thickening -> fracture
  - Fractures < 2 years old
- Pseudoarthrosis
  - False joint that occurs when there is nonunion of bone fragments at the site of a long bone fracture
  - Male predominance
- Vertebral defects, nonossifying fibromas, sphenoid wing dysplasia

Long bone dysplasia





Bone abnormalities in NF1

- Short stature
  - Szudek et al. 2000, cross-sectional study with 569 white North American patients with NF1, 13% had a height ≥2 SD below the population mean
  - Virdis et al. 2003 reported 20-30% of adults with NF1 have a height below the 3rd percentile
- Scoliosis
  - Approximately 10-25% of patients with NF1
- Osteoporosis
  - Decreased bone density in patients with NF1
  - Increased risk of fractures

Osteoporosis in NF1

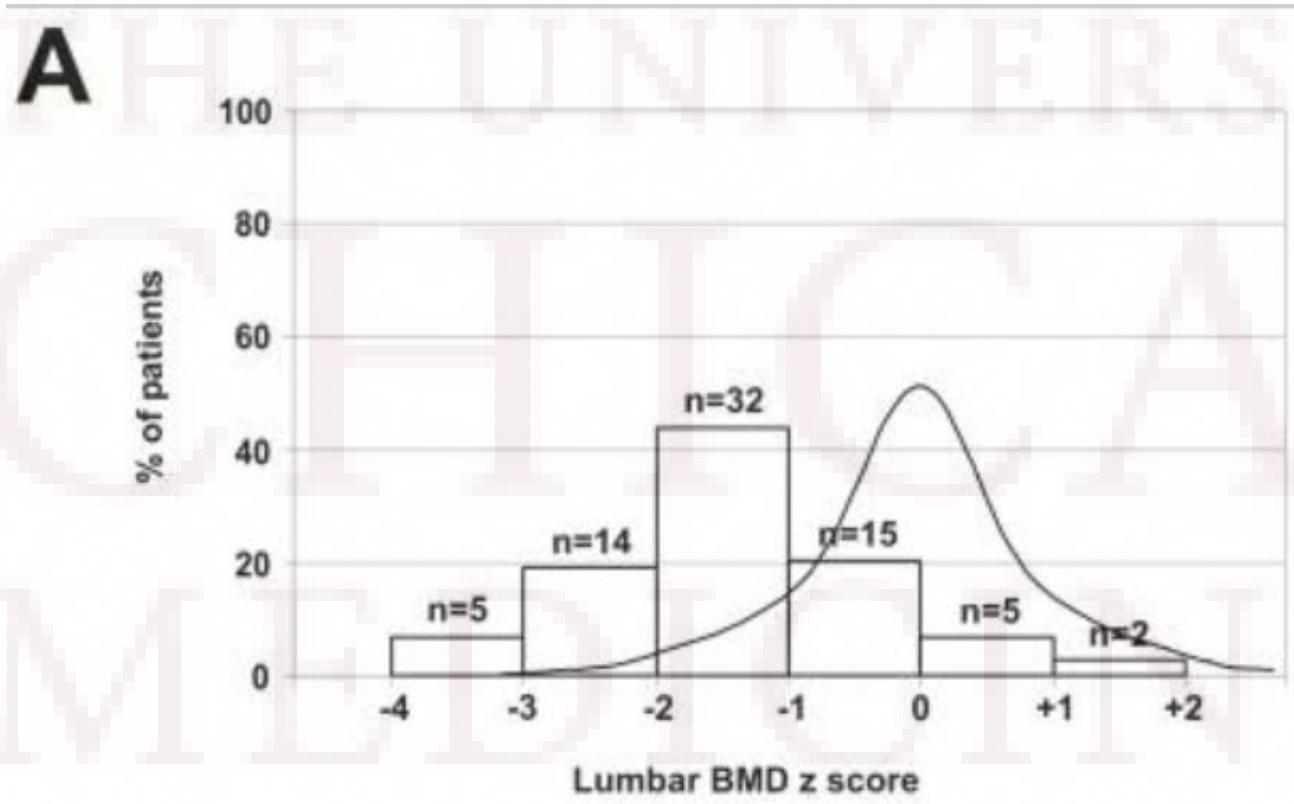
- Decreased BMD in both sexes at an early age has been reported in up to 50% of patients with NF1
  - Challenging to interpret BMDs in children
  - Severity of osteoporosis is unclear
- Increased risk of fractures in patients with NF1
  - Small sample sizes
- Low Vitamin D level in subset of patients with NF1

Elefteriou et al., 2009

Brunetti-Pierri et al. 2008

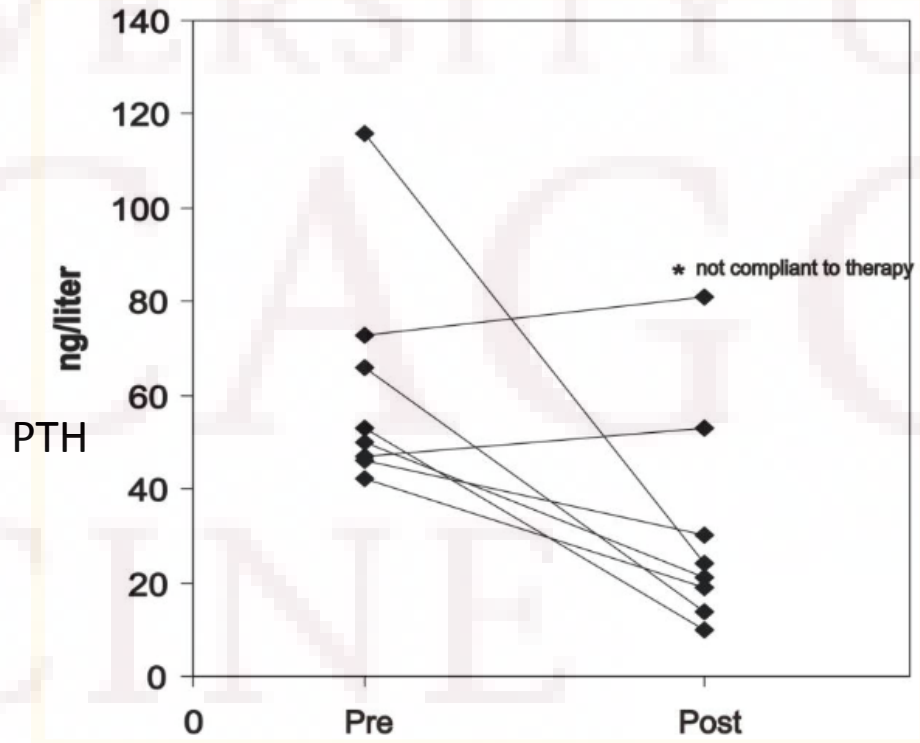
- 73 patients with NF1: 26 males, 47 females, mean age 16.6 years old
- Whole body, lumbar spine, and femoral BMD z-scores were all significantly decreased. The spine was the most severely affected
  - Mean lumbar spine BMD z-score is −1.38 ± 1.05, [95% CI −1.62; −1.13], p<.001
  - Mean femoral neck z-score was −0.77 ± 0.87 [95% CI −1.0; −0.5]
  - Mean trochanteric BMD z-score was −0.73 ± 0.94 [95% CI −0.95; −0.49]
- More than 50% of subjects had at least one regional site in the osteopenic range, and 33% had at least one regional site in the osteoporotic range

Brunetti-Pierri et al. 2008



Brunetti-Pierri et al. 2008

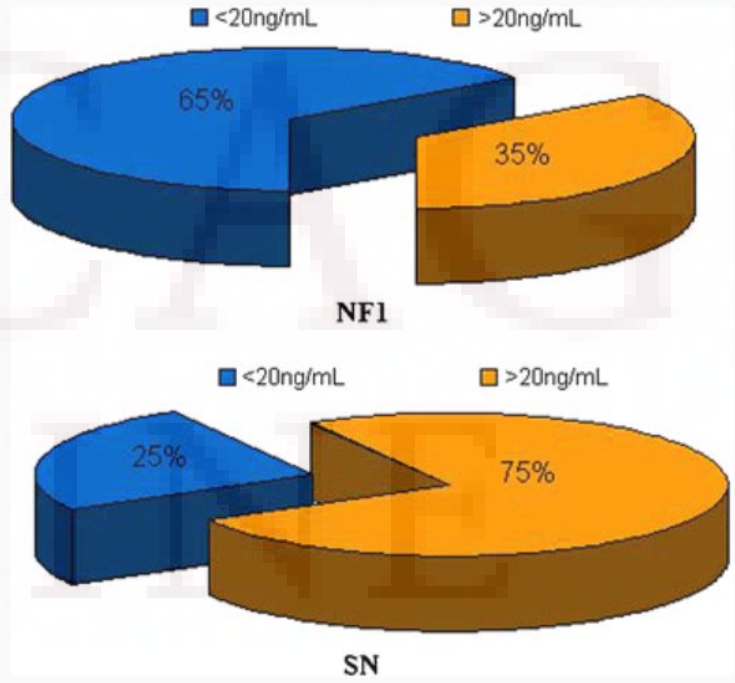
- In a subgroup of 16 subjects from the NF1 with BMD showing osteopenia and osteoporosis (mean lumbar z-score = −2.1, age range 6–38 yrs), PTH was significantly elevated compared to age-matched controls



Petramala et al, 2012

- 70 NF1 patients: 37 men and 33 women, mean age 41.1 years old

	PTH (pg/ml)	25 OH-Vit D (ng/ml)
NF1 (n.70)	55 ± 18.3	21.8 ± 12.3
SN (n.60)	32.3 ± 15.3	32.9 ± 16.5
P	NS	0.01 versus NS



Petramala et al, 2012

	Z-score L1–L4	BMD L1–L4 (g/cm²)	*Z*-score FN	BMD FN (g/cm²)
NF1 (n.70)	−0.909 ± 0.6	0.935 ± 0.13	−0.892 ± 0.7	0.765 ± 0.09
SN (n.60)	0.032 ± 0.3	1.110 ± 0.17	−0.297 ± 0.2	0.839 ± 0.12
P	0.003 versus NS	<0.001 versus NS	0.005 versus NS	0.02 versus NS

Petramala et al, 2012

	Z-score L1–L4	BMD L1–L4 (g/cm²)	*Z*-score FN	BMD FN (g/cm²)
NF1 pre (n.42)	−0.909 ± 0.6	0.935 ± 0.13	−0.892 ± 0.7	0.765 ± 0.09
NF1 post (n.42)	−0.857 ± 0.5	0.997 ± 0.19	−0.865 ± 0.3	0.812 ± 0.18
P	NS	NS	NS	NS

	PTH (pg/ml)	25 OH-Vit D (ng/ml)
NF1 pre (n.42)	55 ± 18.3	21.8 ± 12.3
NF1 post (n.42)	40.5 ± 12.3	35 ± 13
P	NS	<0.01

Treatment

- In children, conservative treatment with calcium and vitamin D supplementation, weight bearing exercise
  - Bisphosphonates – effect on BMD and fracture risk in children with NF1 is unknown
- In adults, treatment is similar to adults without NF1

Our patient

- Osteoporosis associated with NF1 vs osteogenesis imperfecta?

Back to our patient

- Previously on Fosamax 2008-2011
- No new fractures since 2015
- BMDs stable over last several years
- Plan:
  - Continue calcium and vitamin D supplementation
  - Continue weight-bearing and strengthening exercise
  - Fall precautions
  - Monitor BMDs

Objectives

- Review the clinical features of neurofibromatosis type 1 (NF1)
- Review the clinical features of osteogenesis imperfecta
- Discuss the bone abnormalities seen in patients with NF1 and review treatment options

References

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