“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

Monika Darji
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

<table>
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<tr>
<th>Anion gap 14</th>
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<th>15</th>
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<tr>
<td>Ca 9.7</td>
<td>89</td>
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<tr>
<td>4.2</td>
<td>23</td>
<td>0.7</td>
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<tr>
<td>23</td>
<td>0.7</td>
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<table>
<thead>
<tr>
<th>Total protein</th>
<th>7.3</th>
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<tbody>
<tr>
<td>Albumin</td>
<td>4.4</td>
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<tr>
<td>Total bilirubin</td>
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<tr>
<th>Alkaline phosphatase</th>
<th>71</th>
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<tr>
<td>ALT</td>
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<tr>
<td>AST</td>
<td>15</td>
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<table>
<thead>
<tr>
<th>25-OH vitamin D</th>
<th>36</th>
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<tr>
<td>PTH</td>
<td>28</td>
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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
## Diagnosis

### NIH diagnostic criteria for neurofibromatosis type 1

Two or more of the following clinical features must be present:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
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<tr>
<td>Two or more neurofibromas of any type or one plexiform neurofibroma</td>
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<tr>
<td>Freckling in the axillary or inguinal regions</td>
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<td>Optic glioma</td>
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<td>Two or more iris hamartoma (Lisch nodules)</td>
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<td>Distinctive bony lesion, such as sphenoid dysplasia, or medullary narrowing and cortical thickening of the long bone cortex with or without pseudoarthrosis</td>
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<tr>
<td>A first-degree relative (parent, sibling, or offspring) with NF1 based on the above criteria</td>
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</table>

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
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 $-1.38 \pm 1.05$, [95% CI $-1.62; -1.13$], $p<.001$
  • Mean femoral neck z-score was $-0.77 \pm 0.87$ [95% CI $-1.0; -0.5$]
  • Mean trochanteric BMD z-score was $-0.73 \pm 0.94$ [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

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<thead>
<tr>
<th></th>
<th>PTH (pg/ml)</th>
<th>25 OH-Vit D (ng/ml)</th>
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<tbody>
<tr>
<td>NF1 (n=70)</td>
<td>55 ± 18.3</td>
<td>21.8 ± 12.3</td>
</tr>
<tr>
<td>SN (n=60)</td>
<td>32.3 ± 15.3</td>
<td>32.9 ± 16.5</td>
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**P** NS 0.01 versus NS
<table>
<thead>
<tr>
<th></th>
<th>Z-score L1–L4</th>
<th>BMD L1–L4 (g/cm²)</th>
<th>Z-score FN</th>
<th>BMD FN (g/cm²)</th>
</tr>
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<tbody>
<tr>
<td>NF1</td>
<td>-0.909 ± 0.6</td>
<td>0.935 ± 0.13</td>
<td>-0.892 ± 0.7</td>
<td>0.765 ± 0.09</td>
</tr>
<tr>
<td>(n.70)</td>
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<tr>
<td>SN</td>
<td>0.032 ± 0.3</td>
<td>1.110 ± 0.17</td>
<td>-0.297 ± 0.2</td>
<td>0.839 ± 0.12</td>
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<td>(n.60)</td>
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<tr>
<td>P</td>
<td>0.003 versus NS</td>
<td>&lt;0.001 versus NS</td>
<td>0.005 versus NS</td>
<td>0.02 versus NS</td>
</tr>
<tr>
<td>NS</td>
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Petramala et al, 2012

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<th>BMD L1–L4 (g/cm²)</th>
<th>Z-score FN</th>
<th>BMD FN (g/cm²)</th>
<th>P</th>
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<tr>
<td><strong>NF1 pre</strong></td>
<td>-0.909 ± 0.6</td>
<td>0.935 ± 0.13</td>
<td>-0.892 ± 0.7</td>
<td>0.765 ± 0.09</td>
<td>NS</td>
<td>55 ± 18.3</td>
<td>21.8 ± 12.3</td>
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<td>(n=42)</td>
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<tr>
<td><strong>NF1 post</strong></td>
<td>-0.857 ± 0.5</td>
<td>0.997 ± 0.19</td>
<td>-0.865 ± 0.3</td>
<td>0.812 ± 0.18</td>
<td>NS</td>
<td>40.5 ± 12.3</td>
<td>35 ± 13</td>
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<tr>
<td>(n=42)</td>
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**P** NS NS NS 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
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- Uptodate, Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis. 2018
- Uptodate, Neurofibromatosis type 1 (NF1): Management and prognosis. 2018
- Uptodate, Osteogenesis imperfecta: Clinical features and diagnosis. 2018
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