LRRK1-Related Osteosclerotic Metaphyseal Dysplasia: A Three Case Series

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Background & Significance

- Osteosclerotic metaphyseal dysplasia (OSMD) is an ultra-rare skeletal dysplasia associated with pathogenic variants in *leucine-rich repeat kinase 1* (LRRK1)
- LRRK1 regulates osteoclast function
- Phenotypic findings in OSMD typically include progressive osteosclerosis, metaphyseal abnormalities, low-trauma fractures, growth impairment, and variable skeletal complications[6,7]:
  - Osteosclerosis of metaphyses
  - Diaphyseal lucency
  - Osteosclerosis of the vertebral bodies, ribs, pelvis, and skull
- Some cases presented with:
  - Short stature[2]
  - Erlenmeyer flask deformity[5]
  - Osteonecrosis of the jaw[3]
  - Mild facial dysmorphism[3]
  - Developmental delay[4]
  - Optic nerve atrophy[1]
  - "Sandwich vertebrae" and platyspondyly[5]
- As of 2023, there are 13 cases of OSMD in the literature, with only 8 being molecularly confirmed
- The phenotypic spectrum, natural history, and long-term clinical outcomes of LRRK1-related OSMD remain incompletely defined



Figure 1. Skeletal involvement of OSMD

Case Descriptions

- Proband 1 is a 9-year-old girl with a history of idiopathic thrombocytopenic purpura (ITP) and autism. Exome sequencing incidentally found biallelic likely-pathogenic variants in *LRRK1*. Radiographs were then obtained which showed metaphyseal sclerosis. Her most significant complication is bone pain. DEXA scan was unremarkable. CBC indicated low platelets during flares of ITP. Genetic variant: p.(Q484*) and p.(W1086*).

- Proband 2 is a 6-year-old boy with a history of pyogenic granulomas and asthma. Chest x-ray in the setting of status asthmaticus incidentally showed osteosclerosis of proximal humeri and ribs. His most significant complications are rapidly increasing bone mineral density and bone pain crises. Most recent DEXA scan showed Z score of +9.1 in the left hip, +14.3 in the left femoral neck, and -0.3 in the left forearm. CBC indicated mildly low hemoglobin and hematocrit. Panel testing showed biallelic *LRRK1* variants. Genetic variant: p.(G1589*) and p.(R1943*).

- Proband 3 is the 8-year-old sister of proband 2 with a history of Grave's Disease. Radiographs of the knee for trauma showed increased density of metaphyseal bands at age 5. DEXA was unremarkable. CBC has occasionally indicated low hematocrit. She does not have the symptom of bone pain. Familial variant testing showed biallelic *LRRK1* variants. Genetic variant: p.(G1589*) and p.(R1943*).

Feature	Metaphyseal Osteosclerosis	Vertebral Endplate/Body Sclerosis	Pathologic Fractures	Optic Involvement	Short Stature
Frequency	11/11	8/8	7/10	4/5	5/11
This Study	3/3	1/3	0/3 (bone pain 2/3)	0/3	1/3

Table 1. Frequencies of several features of OSMD as reported in the literature references. Frequencies are reported as the number of patients with the feature out of the number of patients that were evaluated for the feature.[1,2,3,4,5,6,7]

Discussion

- These three individuals from two unrelated families with LRRK1-related OSMD broaden the known phenotype of this rare disorder.

- While most reported cases presented with pathologic fractures, these individuals were diagnosed through incidental findings.

- This study expands the spectrum of recognized clinical and imaging findings, including novel presentation of the idiopathic thrombocytopenia purpura. Additional cases are needed to determine whether this represents a phenotypic expansion or a coincidental comorbidity.

Imaging



Figure 2. X-ray images of proband 1. Images illustrate sclerosis of vertebrae and long bones in the hand and leg.



Figure 3. X-ray images of proband 2. Images illustrate Erlenmeyer flask deformity of the femur and sclerosis of the long bones of the leg.



Figure 4. X-ray images of proband 3. Image illustrates sclerosis of long bones of the leg.

References

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