Case Report

Infantile Osteopetrosis with a CLCN7 Variant: An Educational Case Highlighting Integrated Diagnosis and Variant Interpretation

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Keywords

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Abstract

Background: Infantile osteopetrosis is a rare inherited disorder caused by defective osteoclast-mediated bone resorption, resulting in increased bone density and marrow failure. The CLCN7 gene encodes a chloride channel essential for osteoclast acidification.

Case Presentation: A 4-month-old male presented with failure to thrive, pallor, hepatosplenomegaly, and recurrent infections. Examination revealed frontal bossing and hypotonia. Laboratory evaluation showed anemia and persistent hypocalcemia (6.8 mg/dL; reference 8.5–10.5 mg/dL). Skeletal survey demonstrated diffuse osteosclerosis with a characteristic “bone-within-bone” appearance. Differential diagnoses, including storage disorders and leukemia, were excluded. Clinical exome sequencing identified a homozygous CLCN7 missense variant, c.613G>A (p.Gly205Arg), classified as a variant of uncertain significance (VUS) based on ACMG/AMP criteria (PM2, PP3).

Conclusion: Diagnosis in this case was primarily clinico-radiological, with genetic findings providing supportive evidence. This report presents an educational case emphasizing the importance of integrated clinical, radiological, and laboratory evaluation, and highlights the challenges in interpreting variants of uncertain significance in clinical practice.

Background

Osteopetrosis comprises a group of inherited disorders characterized by defective osteoclastic bone resorption, resulting in increased bone density and impaired marrow function. Infantile autosomal recessive osteopetrosis represents the most severe form and typically presents early in life with anemia, hepatosplenomegaly, and skeletal abnormalities [1]. The CLCN7 gene, located on chromosome 16p13.3, encodes a chloride channel expressed in osteoclasts. This channel functions in conjunction with vacuolar H^+-ATPase to maintain an acidic microenvironment within the resorption lacuna, which is essential for bone mineral dissolution. Mutations in CLCN7 disrupt this process, leading to impaired bone resorption and progressive osteosclerosis [2]. This report is presented as an educational case highlighting the role of integrated diagnosis and the complexities of genetic variant interpretation

Case Presentation

A 4-month-old male infant presented with failure to thrive, pallor, hepatosplenomegaly, and recurrent infections. Birth history was unremarkable. On examination, the child had frontal bossing and generalized hypotonia (Figure 1 and 2).

Laboratory Evaluation

Complete blood count revealed anemia with preserved leukocyte counts. Serum calcium levels were persistently low (6.8 mg/dL; reference range: 8.5–10.5 mg/dL).
Further biochemical evaluation demonstrated elevated parathyroid hormone (PTH: 136 pg/mL), low-normal vitamin D levels (21 ng/mL), and mildly elevated alkaline phosphatase (ALP: 365 IU/L).

Table 1: Key Laboratory Findings and Interpretation in Infantile Osteopetrosis.

Parameter	Value	Reference Range	Interpretation
Hemoglobin	7.2 g/dL	10.5-13.5	Anemia from marrow encroachment
Albumin-corrected Ca	6.8 mg/dL	8.5-10.5	Hypocalcemia (impaired resorption)
PTH	136 pg/mL	15-65	Secondary hyperparathyroidism
25-OH Vitamin D	21 ng/mL	30-100	Low-normal (not primary cause)
ALP	365 IU/L	100-350	Elevated bone turnover
WBC	6660	Cells/ Cu mm	Rules out leukemia

The observed hypocalcemia, in conjunction with elevated PTH, is consistent with secondary hyperparathyroidism resulting from impaired osteoclastic bone resorption. Reduced calcium mobilization from bone leads to compensatory PTH elevation, while ALP elevation reflects increased bone turnover activity. These findings support the underlying pathophysiology of osteopetrosis.

Radiological Findings

Skeletal survey demonstrated diffuse osteosclerosis with classical metaphyseal "bone-within-bone" appearance and generalized increase in bone density, strongly suggestive of osteopetrosis.

Differential Diagnosis

Initial differentials included storage disorders (e.g., Gaucher disease) and hematological malignancy. These were excluded based on normal β-glucocerebrosidase enzyme assay, absence of abnormal cells on peripheral smear, and lack of organ-specific biochemical abnormalities, in conjunction with characteristic radiological findings.

Genetic Analysis

Clinical exome sequencing performed at MedGenome Laboratories identified a homozygous missense variant in CLCN7: c.613G>A (p.Gly205Arg) (transcript ENST00000382745.9).
The variant was absent (or extremely rare) in population databases such as gnomAD and has not been definitively reported in ClinVar. In silico prediction tools (SIFT, PolyPhen-2, MutationTaster) suggest a deleterious effect on protein function.
Based on ACMG/AMP criteria (PM2, PP3), the variant was classified as a variant of uncertain significance (VUS). Parental testing could not be performed due to logistical constraints, limiting segregation analysis.
Copy number variation analysis was not performed as part of this assay. The sequencing achieved standard clinical exome coverage with adequate read depth for variant detection in coding regions of CLCN7; however, limitations inherent to exome sequencing, including inability to detect deep intronic variants and structural rearrangements, must be considered.

Figure 1: Clinical image showing mild bilateral proptosis,microcephaly and pallor.

To
The Editor-in-Chief
The Electronic Journal of the International Federation of Clinical Chemistry and Laboratory Medicine (eJIFCC)

Subject: Parental Consent for Use of Child's Photograph and clinical details in Manuscript Submission

Dear Editor,

I, the undersigned, am the parent/legal guardian of **Master Kavi Darshan**, who is featured in the manuscript entitled **"Infantile Osteopetrosis with a CLCN7 Variant: An Educational Case Highlighting Integrated Diagnosis and Variant Interpretation"** submitted for consideration for publication in the *Electronic Journal of the International Federation of Clinical Chemistry and Laboratory Medicine (eJIFCC)*.

I hereby give my full consent for the inclusion and publication of my child's **photograph** and information in the above-mentioned article. I understand that the image may appear in print and/or electronic formats of the journal and that it may be accessible to the general public.

I confirm that:

- I have been informed about the purpose of including the photograph and understand that it will be used for academic and educational purposes.
- I have been assured that no identifying information other than the image itself will be disclosed.
- I understand that the image may be used in perpetuity as part of the published record and may not be withdrawn after publication.

I hereby authorize the *Electronic Journal of the International Federation of Clinical Chemistry and Laboratory Medicine* to use this photograph and clinical details in connection with the publication of the aforementioned article.

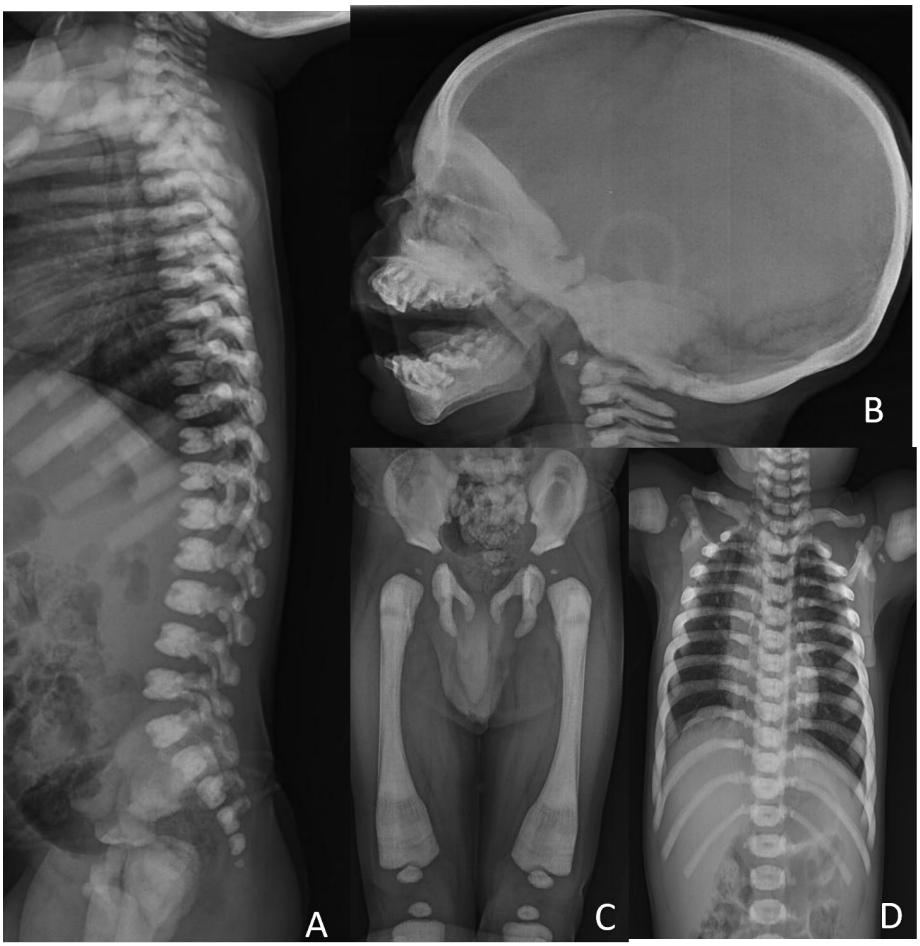
Thanking You,

Yours Sincerely,

Mr.Jagan S

(Father)

Figure 2: (A)DORSO LUMBAR SPINE: Homogenous increased density noted in vertebral bodies. (B) SKULL(LAT VIEW) :



Diffuse sclerosis involving the base of the skull,pituitary fossa,mastoid and cervical vertebra ; Atlanto axial widening present. (C)PELVIS : Squaring of ileum ; Flattened acetbulum ; Increased density of proximal femur ; Flaring of distal femur. (D) CHEST (PA VIEW) Diffuse increased density in the ribs, vertebral column and proximal humerus.

Discussion

Osteopetrosis is characterized by defective osteoclastic activity, leading to impaired bone resorption, skeletal sclerosis, and bone marrow failure. The diagnosis in this case was primarily established based on clinical features and characteristic radiological findings, with genetic analysis providing supportive evidence.

The CLCN7 gene plays a critical role in osteoclast function by facilitating chloride transport necessary for acidification of the resorption lacuna. Mutations disrupt this process, resulting in failure of bone mineral dissolution.[6]

Although the identified variant is classified as a VUS, the strong phenotypic concordance with CLCN7-related osteopetrosis supports a possible contributory role. However, the absence of segregation analysis and functional validation precludes definitive classification.

The variant was classified as a VUS based on ACMG/AMP criteria (PM2, PP3); however, the absence of stronger evidence limits definitive pathogenic classification. Additional criteria that could support reclassification include functional studies demonstrating impaired chloride channel activity (PS3), segregation analysis in affected family members (PP1), or identification of the same variant in unrelated affected individuals (PS4). In the absence of such data, cautious interpretation and clinicoradiological correlation remain essential.

The biochemical profile in this case further supports the diagnosis. Hypocalcemia in osteopetrosis results from defective osteoclastic activity, leading to reduced calcium release from bone. The elevated parathyroid hormone level observed reflects a compensatory response to hypocalcemia (secondary hyperparathyroidism). Mild elevation of alkaline phosphatase indicates ongoing bone remodeling activity, while vitamin D levels were within the low-normal range, excluding primary vitamin D deficiency as a cause of hypocalcemia. These laboratory findings aid in differentiating osteopetrosis from other conditions such as nutritional rickets, storage disorders, and hematological malignancies.[2,3]

From a laboratory medicine perspective, careful interpretation of biochemical parameters is essential. Serum calcium values were albumin-corrected; however, ionized calcium measurement, where available, provides a more accurate assessment of biologically active calcium. Pre-analytical variables such as sample handling and albumin levels may influence total calcium estimation. Analytical considerations, including assay methodology and inter-laboratory variability, should also be acknowledged

Biochemically, osteopetrosis must be differentiated from conditions such as nutritional rickets and hypoparathyroidism. Unlike rickets, where alkaline phosphatase is markedly elevated and hypocalcemia is often associated with elevated parathyroid hormone and low vitamin D, osteopetrosis typically demonstrates hypocalcemia with secondary hyperparathyroidism and only mild to moderate elevation of alkaline phosphatase. In hypoparathyroidism, hypocalcemia is associated with low or inappropriately normal parathyroid hormone levels, helping to distinguish it from osteopetrosis.

Besbas N et Al reported a 26-month-old child with osteopetrosis, neurodegeneration, retinal atrophy, and tubulopathy born to consanguineous parents who had CLCN7 gene with a novel homozygous R561Q variant. Both healthy parents were heterozygous for this amino acid substitution indicating autosomal recessive inheritance. The same homozygous nucleotide transition was found prenatally in a second child and the pregnancy was terminated at 17th week of gestation. A full autopsy was performed to the fetus, which confirmed the presence of osteopetrosis, thereby indicating that the variant observed indeed represents the disease-causing mutation.[5]

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for severe infantile osteopetrosis. However, outcomes in CLCN7-related disease may be variable, particularly in cases associated with neurodegeneration, necessitating careful patient selection [4].

Follow up and Outcome

The child is currently on supportive management and remains clinically stable on follow-up. Hematopoietic stem cell transplantation (HSCT) was discussed with the family and is being considered as a potential therapeutic option. Regular monitoring for disease progression and complications is ongoing.

Clinical Implications

This case highlights the importance of maintaining a high index of suspicion for osteopetrosis in infants presenting with cytopenias, developmental delay, and characteristic skeletal changes.Early integration of clinical, laboratory, radiological, and genetic findings is essential for timely diagnosis and management. Identification of genetic variants should be interpreted cautiously, particularly when classified as VUS, and should be correlated with clinical findings.

Limitations

The identified CLCN7 variant is classified as a VUS, limiting definitive pathogenic interpretation. Lack of parental testing precluded segregation analysis, and no functional studies were performed to validate its biological impact. Additionally, limited database evidence and reliance on in silico predictions restrict robust genotype–phenotype correlation.

Take-home messages

Biochemical parameters (calcium, parathyroid hormone, and alkaline phosphatase) are essential for supporting the diagnosis of osteopetrosis and excluding mimicking conditions.

Variants of uncertain significance should be reported with supporting evidence from population databases and in silico prediction tools.

Timing and appropriateness of hematopoietic stem cell transplantation require careful consideration in CLCN7-related osteopetrosis

Author Contributions (CRediT Statement)

Meena Shree A V (MSAV): Conceptualization; Data Curation; Investigation; Writing – Original Draft; Visualization.

Ranjith Kumar Manokaran (RKM): Conceptualization; Methodology; Supervision; Writing – Review & Editing; Project Administration.

Dhaarani Jayaraman (DJ): Resources; Investigation; Writing – Review & Editing; Validation.

Jai Prakash Srinivasan (JPS): Resources; Visualization; Data Curation.

Elayaraja Sivaprakasam (ES): Clinical Management; Validation; Writing – Review & Editing.

All authors contributed to patient care, reviewed the manuscript critically for intellectual content, and approved the final version for submission.

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No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Disclosures

None. The authors have no competing interests to declare that are relevant to the content of this article.

Conflicts of Interest

None.

Ethical statements

The study is in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki.

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Author contributions
MSAV, RKM, DJ and JPS worked on the data analysis and wrote the initial draft; DJ, RKM and ES revised it for the clinical content and final revision for intellectual content by DJ and RKM. All the other authors were involved in the management of the child. All authors read and approved the final manuscript.

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