

0150 - CLINICAL AND BIOCHEMICAL CLUES TO DIFFERENTIATE HEREDITARY HYPOPHOSPHATEMIC RICKETS WITH HYPERCALCIURIA (HHRH) FROM X-LINKED HYPOPHOSPHATEMIA (XLH) IN A PEDIATRIC COHORT WITH SLC34A3 VARIANTS

Mode: Research paper

Thematic Unit: Phosphocalcic Metabolism

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Background/Objectives: Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare form of hypophosphatemic rickets caused by pathogenic variants in SLC34A3, which encodes the renal sodium-phosphate cotransporter NaPi-IIc. Distinguishing HHRH from FGF23-mediated hypophosphatemic disorders, particularly X-linked hypophosphatemia (XLH), is essential due to major differences in treatment. In many settings in our region, molecular diagnosis is not always available; therefore, clinical recognition is crucial to allow early treatment adjustment and to avoid unnecessary exposure to calcitriol or anti-FGF23 antibodies. We aimed to describe the clinical, biochemical, and radiological characteristics of a pediatric cohort with molecularly confirmed HHRH and to identify features that may help differentiate it from XLH.

Methods: Pediatric patients evaluated for suspected hypophosphatemic rickets between 2017 and 2025 were included. Molecular analysis was performed in 73 unrelated families. Clinical, biochemical, and radiological parameters were assessed in patients with pathogenic SLC34A3 variants and their pediatric relatives.

Results: Among the 73 unrelated families, pathogenic variants were identified in PHEX (n=62), ENPP1 (n=1), and SLC34A3 (n=4; two homozygous, one compound heterozygous, and one heterozygous case). Three HHRH cases were sporadic and one was familial; all affected individuals were male and presented with lower limb misalignment. At diagnosis, median age was 7.4 years (2.4 to 10), median height was -1.8 SD (-1.3 to -2.3), and median sitting height/height ratio was 2.3 SD (1 to 5.4). None of the patients with HHRH had craniosynostosis, whereas it was observed in approximately half of the patients with XLH in our cohort. All index HHRH cases presented with hypophosphatemia [2.7 mg/dL (2.2–3.6)], normocalcemia, low PTH levels [9.8 pg/mL (7.1–15.7)], elevated alkaline phosphatase [655 U/L (594–1274)], reduced tubular phosphate reabsorption [77.8% (77–83)], and hypercalciuria [urine calcium/creatinine ratio 0.37 (0.30–0.56)]. Median PTH levels were significantly lower than in XLH patients (9.8 vs 57 pg/mL; p=0.02). All index cases showed radiographic rickets, but none developed nephrocalcinosis or nephrolithiasis after a median follow-up of 7.1 years (0.9–11.5). One younger sibling with biallelic SLC34A3 variants had no clinical, biochemical, or radiological abnormalities during the first year of life and developed hypophosphatemia thereafter. In contrast, three heterozygous siblings older than 10 years remained asymptomatic throughout follow-up.



Conclusion: HHRH was the second most common molecularly confirmed subtype of hypophosphatemic rickets in our cohort, although markedly less frequent than XLH. The absence of craniosynostosis together with hypercalciuria and low PTH levels were key features distinguishing HHRH from XLH. Importantly, normal clinical, biochemical, and radiological findings during early childhood do not exclude HHRH in children with biallelic SLC34A3 variants, highlighting the need for longitudinal follow-up to ensure timely diagnosis and treatment.

