ENPP1-DEFICIENT PATIENTS PRESENT WITH BOTH SKELETAL COMPLICATIONS AND ECTOPIC CALCIFICATION

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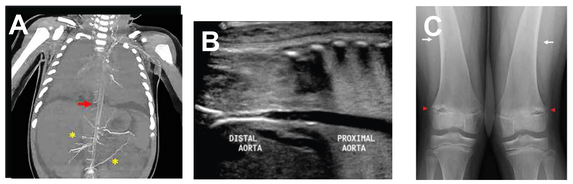
NIH National Human Genome Research Institute
NIH National Institute of Dental and Craniofacial Research

INTRODUCTION

ENPP1 Deficiency is a genetic condition caused by loss-of-function mutations in the *ENPP1* gene. Infants can manifest with ectopic arterial calcifications **(Fig 1A),** stenoses (Fig 1B) and cardiac complications, usually diagnosed as generalized arterial calcification of infancy (GACI).[1] Approximately 50% of infants with GACI do not survive the first 6 months of life. Paradoxically, children and adults with ENPP1 Deficiency often develop autosomal recessive hypophosphatemic rickets type 2 (ARHR2), due to inappropriately high FGF23 levels.[1,2] The presentation of ENPP1 Deficiency rickets can mimic the femoral bowing and metaphyseal irregularities of other hypophosphatemic rickets **(Fig 1C)**



Boyce AM et al. *Curr Osteoporos Rep.* 2020;18(3):232-241

***Figure 1. A**. CT showing arterial calcification. **B**. Ultrasound showing calcification of the aorta. **C**. Radiographs demonstrating genu valgum secondary to hypophosphatemic rickets*

AIM

We report on a cross-sectional retrospective review of 74 patients with ENPP1 Deficiency, characterizing the prevalence and onset of skeletal complications to accelerate diagnosis and management.

METHOD

A retrospective, cross sectional chart review of 127 medical data sets from 19 countries was conducted as a collaboration between National Institutes of Health (NCT03478839) and Münster University Children's Hospital (NCT03758534).[2]

Includes 116 patients diagnosed with GACI and 11 patients diagnosed with ARHR2. The methodology of the study has previously been described. [2]

This subgroup analysis included patients with a confirmed ENPP1 variant, assessed for rickets and cardiovascular complications (Fig 2).

RESULTS

Prevalence of Rickets / Osteomalacia

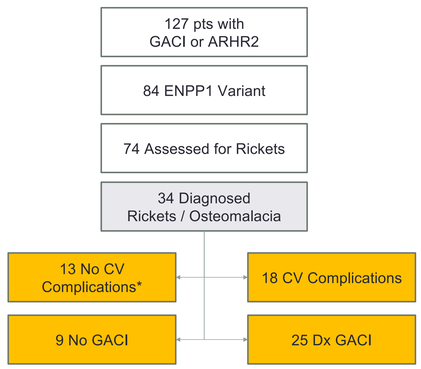


***Figure 2**. Prevalence of Rickets and CV complications in ENPP1 Deficient patients*

- Ricket / osteomalacia defined by altered gait, bowed extremities, metaphyseal cupping or short stature.
- Rickets reported in 46% (34/74) of patients.
- Median age of reported rickets/osteomalacia was 4.3 yr (range: 0.09-13.8 yr);
- CV complications reported in 58% (18/31) of patients with rickets*
- 25% of patients with rickets did not have a diagnosis of GACI
- Calcification of the aorta (68%) and arteries (71%) was was present in (1) most (2) but not all patients with rickets from ENPP1 Deficiency, (3) including in some without a history of GACI

* 3 patients did not report assessment for CV complications

Risk of Developing Rickets / Osteomalacia

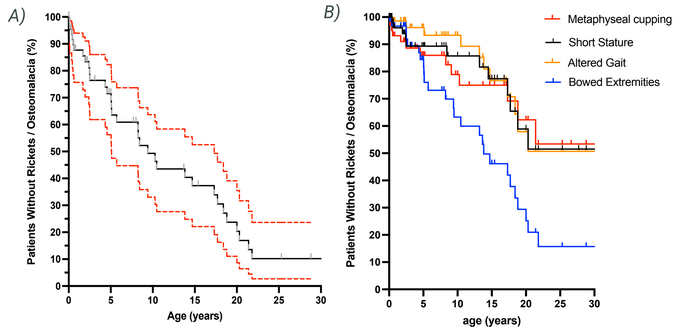


***Figure 3.** KM Estimate for risk of developing Rickets. A) 90% risk of rickets /osteomalacia by age of 25. B) KM Estimate for each reported individual skeletal complications*

CV Complications

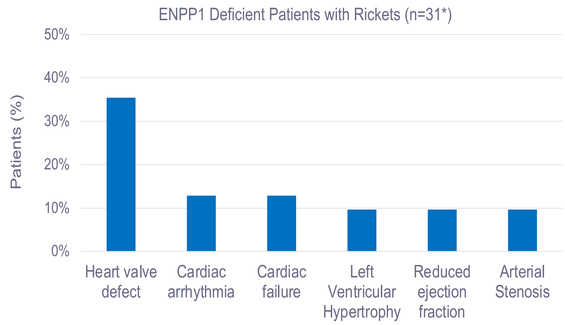


***Figure 4.** Patients with Rickets have documented cardiovascular complications*

CV Complications Before and After Rickets

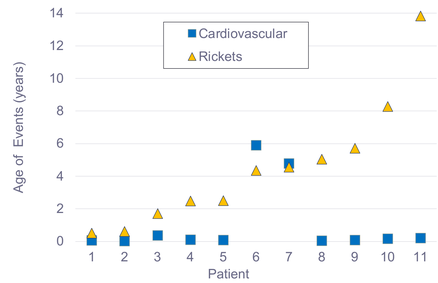


***Figure 5.** Three of 11 (27%) patients recorded CV complications within 6 months or after evidence of rickets. Includes patients with recorded dates for both CV and ricket symptoms*

Patients With Rickets / Osteomalacia Not Diagnosed with GACI

Patient	*Cardiac Complication*	*Arterial Calcification*
Pt 14	*Heart Valve defect*	
Pt 13	*Heart Valve defect, Aortic regurgitation*	
Pt 12	*Heart Valve defect*	*Renal*
Pt 5	*Heart Valve defect*	*Aorta, Carotid, Femoral, Illiac,*
Pt 11	*Arrhythmia, Card failure, Myocardial Fibrosis*	
Pt 15	-	-
Pt 16	-	-
Pt 17	-	-
Pt 18	-	-

***Table 1.** 5 of the 9 pts with no diagnosis of GACI have evidence of CV complications or arterial calcification in the medical history*

CONCLUSIONS

In this study the majority of patients with ENPP1-deficiency will develop skeletal complications suggesting continued monitoring for rickets.

- Genetic testing for ENPP1 Deficiency should be considered for any patient with hypophosphatemic rickets.
- History of arterial calcification or cardiovascular complications should trigger consideration of ENPP1 Deficiency as the etiology.
- No prior history of ectopic calcification or diagnosis GACI should not rule out ENPP1 Deficient rickets since rickets may be the first presentation.
- Identification of rickets due to ENPP1 Deficiency warrants further and continued evaluation of disease related cardiovascular complications and ectopic calcification.

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