Lifetime Accumulation of Calcification and Clinical Complications in Patients with ENPP1 Deficiency (GACI and ARHR2)

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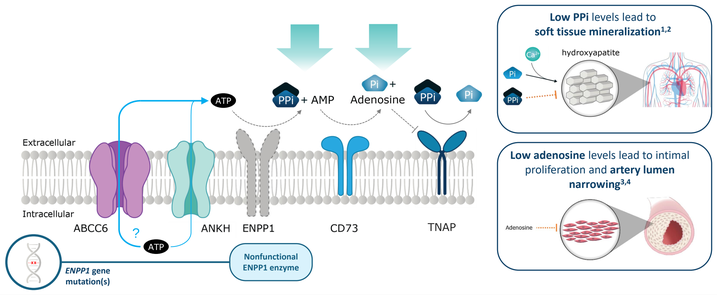
Introduction

- Ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (ENPP1) is a critical enzyme involved in the generation of pyrophosphate (PPi), a mineralization inhibitor, and adenosine, a regulator of vascular smooth muscle cell proliferation.[1-4]
- Biallelic variants in the *ENPP1* gene lead to two primary age-related phenotypes: Generalized arterial calcification of infancy (GACI) and autosomal recessive hypophosphatemic rickets type 2 (ARHR2), which evolve on a phenotypic continuum.[5-6]
- ENPP1 Deficiency typically presents in infancy (GACI) with widespread arterial calcification, severe cardiovascular complications, and high infant mortality.
- Patients with ENPP1 Deficiency who survive beyond infancy develop phosphate-wasting rickets (ARHR2).[5-6]
- Across the age spectrum, ENPP1 Deficiency is associated with other multi-system organ complications, and there is considerable variability in clinical presentation across individual patients.[5-6]



Objective & Methods

- **Objective:** to characterize the onset and prevalence of clinical manifestations of ENPP1 Deficiency across the lifetime
- Retrospective sub-group analysis compiled from two primary chart review studies (NCT03478839 and NCT03758534). Data was extracted via e-CRF.
- Included individuals with biallelic variants in *ENPP1* and diagnosis of GACI or ARHR2
- Cumulative incidence curves were generated for ectopic calcifications and cardiovascular (CV), musculoskeletal, and other organ manifestations
  - Where no date was attributed to an event, age at last follow-up was used
  - Patients were censored from the "at risk" population when they did not experience event during the follow-up, or died without experiencing the event

References

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Results

Table 1. Subject Demographics, Survival Status, and Diagnostic History

Characteristic	Overall (N=84)	GACI-only (n=51)	GACI and ARHR2 (n=22)	ARHR2-only (n=11)
Sex, n (%)				
Female	41 (48.8%)	21 (41.2%)	15 (68.2%)	5 (45.5%)
Age at symptom onset, months				
N	65	40	19	6
Median (Q1, Q3)	0.4 (0.0, 0.8)	0.3 (0.0, 0.6)	0.2 (0.0, 0.8)	43.1 (18.4, 58.3)
Age at diagnosis, months				
N	78	45	22	11
Median (Q1, Q3)	1.3 (0.1, 32.9)	0.8 (0.1, 3.3)	1.0 (0.0, 25.8)	137.7 (54.3, 296.8)
Survival status, n (%)				
Alive	50 (59.5%)	19 (37.3%)	21 (95.5%)	10 (90.9%)
Deceased	34 (40.5%)	32 (62.7%)	1 (4.5%)	1 (9.1%)
Age at death, months				
N	23	22	0	1
Median (Q1, Q3)	1.4 (0.6, 3.4)	1.4 (0.5, 3.3)	NA (NA, NA)	58.1 (58.1, 58.1)
Age at last follow-up, months*				
N	50	19	21	10
Median (Q1, Q3)	111.1 (47.4, 214.2)	60.7 (28.1, 174.9)	117.6 (62.0, 228.4)	219.4 (147.3, 323.7)

Table 2. Medical History

Medical History, n (%)	Overall (N=84)	GACI-only (n=51)	GACI and ARHR2 (n=22)	ARHR2-only (n=11)
Ectopic Calcification	74 (88.1%)	45 (88.2%)	22 (100.0%)	7 (63.6%)
Arterial calcification	68 (81.0%)	43 (84.3%)	22 (100.0%)	3 (27.3%)
Aortic calcification	56 (66.7%)	36 (70.6%)	19 (86.4%)	1 (9.1%)
Cardiac calcification	30 (35.7%)	16 (31.4%)	11 (50.0%)	3 (27.3%)
Organ calcification	34 (40.5%)	22 (43.1%)	11 (50.0%)	1 (9.1%)
Periarticular calcification	31 (36.9%)	15 (29.4%)	13 (59.1%)	3 (27.3%)
Cardiovascular manifestations	64 (76.2%)	41 (80.4%)	16 (72.7%)	7 (63.6%)
Musculoskeletal manifestations	46 (54.8%)	13 (25.5%)	22 (100.0%)	11 (100.0%)
Other organ manifestations	72 (85.7%)	42 (82.4%)	21 (95.5%)	9 (81.8%)

Fig 3A. Prevalence of ectopic calcification within the first year of life

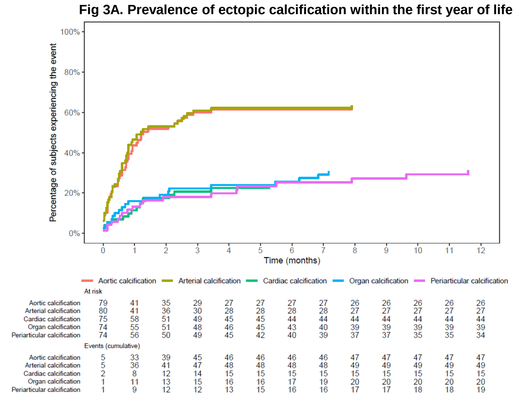


Fig 3B. Prevalence of CV, musculoskeletal, and other organ manifestations within the first year of life

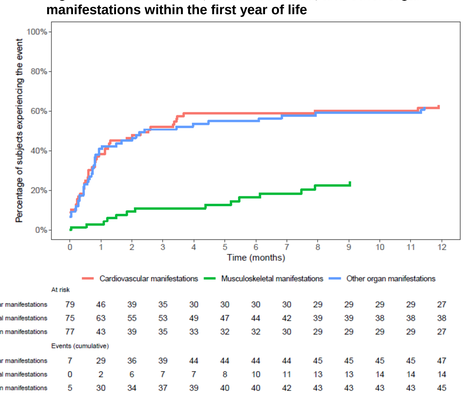


Fig 4A. Prevalence of ectopic calcification over the follow up period

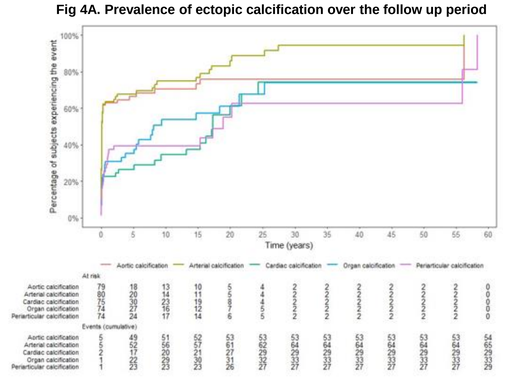
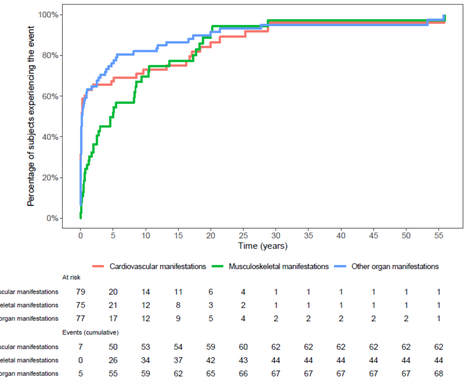


Fig 4B. Prevalence of CV, musculoskeletal, and other organ manifestations over the follow-up period



- Of the 84 patients with ENPP1 Deficiency, 51 were diagnosed with GACI-only (of whom 32 died at a median age of 1.4 months); 22 were diagnosed with GACI, survived beyond infancy and developed ARHR2, and 11 first presented with ARHR2 (Table 1).
- The overall prevalence of ectopic calcification was 88% (Table 2). Arterial and aortic calcification developed early, with approximately 60% prevalence within the first 3 months of life in subjects at risk (Fig 3A), whereas cardiac, organ, and periarticular calcification was first documented over a wider age range (Fig 4A).
- Sixty-four patients (76%) had a history of cardiovascular complications (Table 2) including hypertension, heart valve defect, left ventricular hypertrophy, and heart failure. CV manifestations onset predominately within the first few months of life, corresponding to the onset of vascular calcifications (Fig 3A).
- Musculoskeletal complications including rickets, bowed extremities, and pain were documented in all patients diagnosed with ARHR2 (Table 2); 45% of the at-risk population had manifestations by age 3, and 75% by age 11 (Fig 4B).

Conclusions

- This analysis from a large retrospective study characterizes the onset and accumulation of calcification and clinical events over time in 84 patients with biallelic ENPP1 Deficiency, confirming that GACI and ARHR2 are on a phenotypic continuum.
- Vascular calcification and cardiovascular complications develop early in infancy, while surviving patients may first develop extra-vascular calcifications and musculoskeletal complications in childhood, adolescence, or adulthood.
- **By age 55, over 95% of surviving patients with ENPP1 Deficiency are expected to have a medical history of cardiovascular, musculoskeletal, and/or other organ complications.**

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