From the Voice of Patients and Caregivers: Burden of Illness in Infantile Onset ABCC6* and ENPP1* Deficiency (GACI and ARHR2)

Christine O'Brien[1], Beth Leiro PT[2], Gus Khursigara PhD[3], Catherine Nester BScN[3],

1. GACI Global 2. Clinical Outcomes Consultant, 3. Inozyme Pharma, Boston MA, USA

Objective

Inorganic pyrophosphate (PPi) acts as a potent inhibitor of mineralization (fig 1). Patients deficient in ENPP1 or ABCC6, proteins involved in PPi metabolism, are characterized with low serum PPi resulting in pathological calcification and skeletal complications at all ages (fig 2).

Objective: This study was intended to characterize the burden of disease from a patient or caregiver/parent perspective.

Methods

Primary qualitative patient-reported outcomes research under institutional review board approval was performed by Engage Health to determine disease burden in patients with ENPP1 deficiency across all ages.

- Patients were recruited through GACI Global, social media, and health care professionals.
- A list of burdens and symptoms was prepared after review of the medical literature and input from families impacted by GACI/ARHR2.

Patient Demographics

Thirty-eight respondents from 9 countries were assessed. Of those, 11 patients were deceased (n=11/38), 10 of which died before 12 months of life. Parents or caregivers responded on behalf of patients aged <18 years.

	Participants	Deceased	Age at Diagnosis (Mean)	Age at Interview (mean)
ABCC6	6	0.0	0.3	2.5
Adult ENPP1	7	0.0	15.6	31.6
InfEndPP1	12	10.0	0.0	1.0
PedENPP1	13	1.0	1.5	7.7
Total	38	11.0	3.4	12.2

Role of ENPP1 and ABCC6: Generation of PPi and Adenosine

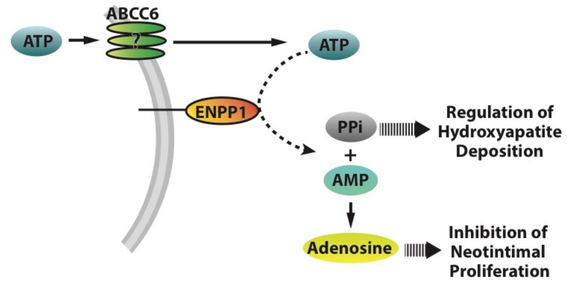

Figure 1. The ENPP1 gene codes for an extracellular endonuclease which cleaves ATP to AMP and inorganic pyrophosphate (PPi). The ABCC6 gene codes for a transmembrane transporter involved in the cellular export of ATP.

Loss of function in ENPP1 or ABCC6 activity leads to a decrease in extracellular PPi and adenosine, which lead to pathogenic mineralization and neointimal proliferation, respectively.

ENPP1 Deficiency Manifests At All Ages

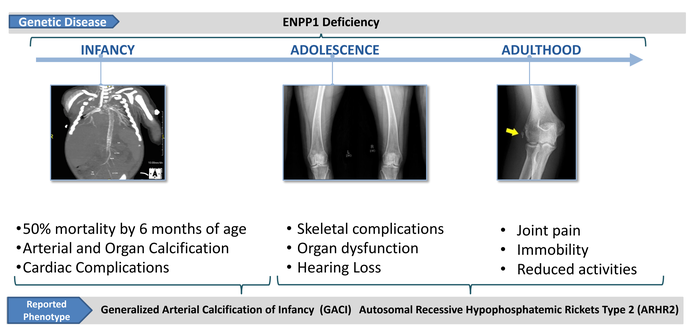

Figure 2. Representative evolution of ENPP1 deficiency

Reported Symptoms All Time Points

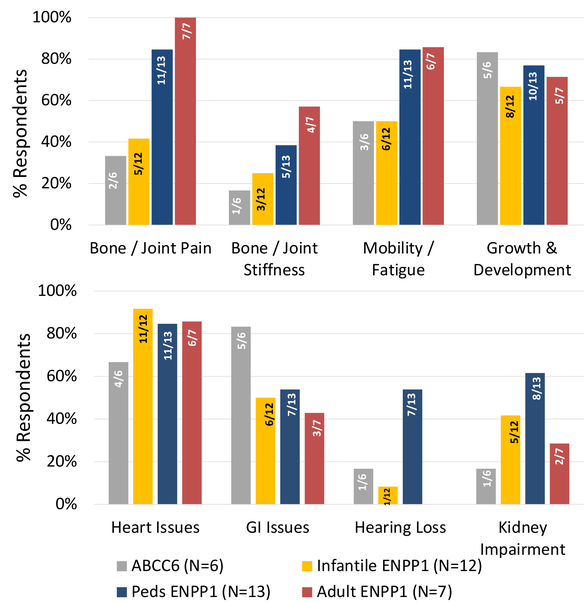

Figure 3. Respondents were asked to identify which symptoms were burdensome

Top Reported Burdens

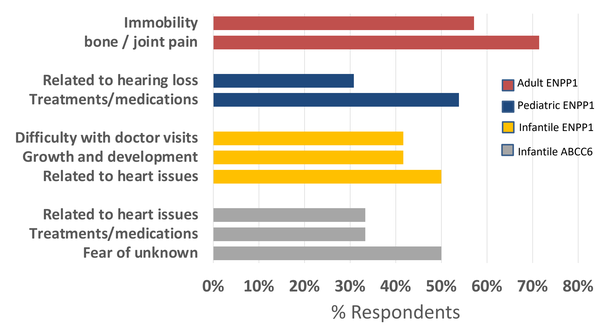

Figure 4. Respondents were asked to identify top 3 burdens

Burden Rank Importance

Each burden was assigned points (pts) based on the order of mention (3 pts - most important, 2 pts - second most important, 1 pt - third most important). A weighted score was determined based on the points multiplied by number of mentions The results are summarized in the table.

ABCC6 Deficiency Cohort (n=6)	Sum Score (0-18)
Fear of unknown	10
Related to heart issues	6
Difficulty with hospital experience	5

Pediatric ENPP1 Cohort (n=13)	SUM (0-39)
Related to treatments/medications	15
Related to hearing loss	9
Related to stress / anxiety	9

Infantile ENPP1 Cohort (n=12)	SUM (0-36)
Related to heart issues	18
Difficulty with hospital experience	9
Related to growth and development	8

Adult ENPP1 Cohort (N=7)	SUM (0-12)
Related to bone / joint pain	16
Related to mobility	8
Related to fatigue	5
Related to fear of unknown	5

Conclusions

The study shows patients with ENPP1 deficiency can experience burdens at all ages. The top burdens reported in each age group reflects the evolution of the disease.

- The cardiac complications and hospital experience in infants.
- The complex medical management to address cardiovascular and skeletal issues in pediatric patients.
- The cumulative impact of the cardiovascular and skeletal complications could be reflected in the reports of pain, mobility impairment, and fatigue in adults.

This study recruited a small number of respondents per age group but given the rarity of the disease and the pathophysiology, these results suggest patient burdens should be investigated in a clinical workup and treatment expectations.

* ENPP1 - ectonucleotide pyrophosphatase/phosphodiesterase 1. ABCC6 - ATP Binding Cassette Subfamily C Member 6

American College of Medical Genetics and Genomics, Annual Meeting 2021: eP024