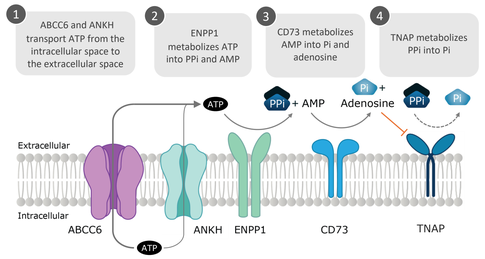
The Medical Burden of ENPP1 Deficiency and Early-Onset ABCC6 Deficiency from a Retrospective Observational Study

David R. Weber[1], M. Zulf Mughal[2], Alix Besancon[3], Klaus Dieterich[4], Thomas Perouse de Montclos[5], Suma Uday[6], Deborah Wenkert[7],Kurt Gunter[8], Alex Lai[8], Frank Rutsch[9]

[1]Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA; [2]Al Jalila Children's Specialty Hospital, Dubai, UAE; [3] Hôpital Universitaire Necker Enfants Malades, Paris, France; [4]Univ. Grenoble Alpes, Grenoble, France; [5]Centre Hospitalier Universitaire (CHU) de Lyon, Lyon, France; [6]Birmingham Children's Hospital, Birmingham, England; [7]Wenkert & Young, LLC; [8]Inozyme Pharma, Boston, MA, USA; [9]Muenster University Children's Hospital, Muenster, Germany

Introduction

- ENPP1 and ABCC6 are key proteins involved in the metabolic pathway that produces pyrophosphate (PPi), an inhibitor of skeletal mineralization, and adenosine, a regulator of vascular intimal proliferation[1-4]



- Patients with biallelic variants in the ENPP1 or ABCC6 genes suffer from multi-system medical complications as a consequence of dysregulated mineralization and intimal proliferation.[4-6]
- There is significant overlap in the clinical phenotypes of ENPP1 and ABCC6 Deficiency.[4-5]
- Generalized arterial calcification of infancy (GACI), the infant-onset phenotype of ENPP1 or ABCC6 Deficiency, is characterized by widespread vascular calcification, cardiovascular morbidity, and high infant mortality.[4-5]
- In patients with GACI due to ENPP1 Deficiency, the majority of survivors develop hypophosphatemic rickets in childhood (ARHR2). Some patients present with ARHR2 without a medical history of GACI.[5]
- The progression and burden of disease in patients with GACI due to ABCC6 Deficiency is poorly characterized.

Phenotype	Generalized Arterial Calcification of Infancy (GACI)[4-5]	Autosomal Recessive Hypophosphatemic Rickets Type 2 (ARHR2)[5]	Pseudoxanthoma Elasticum (PXE)[6]
Genotype	ENPP1 > ABCC6	ENPP1	ABCC6 >> ENPP1
Age of Onset	Prenatal – Infancy	Childhood (often progression from GACI)	Adolescence – adulthood
Mineralization Defect	Ectopic calcification of medium-large sized arteries	Impaired skeletal mineralization; calcification of joints and ligaments	Ectopic calcification of elastic fibers in skin, eyes, peripheral arteries

Objective & Methods

Objective: To describe the medical history, particularly clinical events and interventions, in patients with ENPP1 Deficiency or early-onset (GACI phenotype) ABCC6 Deficiency

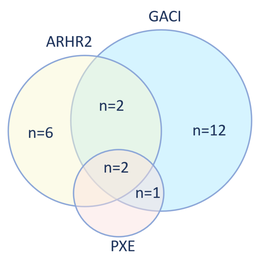
Methodology: Multicenter longitudinal retrospective chart review in participants with a clinical and molecular diagnosis of ENPP1 Deficiency or early-onset ABCC6 Deficiency. Data was abstracted from medical charts.

Results – Demographics

	ENPP1 Deficiency (N=14)	ABCC6 Deficiency (N=9)	Overall Population (N=23)
Sex			
Male (n (%))	8 (57.1)	5 (55.6)	13 (56.5)
Female (n (%))	6 (42.9)	4 (44.4)	10 (43.5)
Age at enrollment (years)			
Median (range)	19.5 (4-33)	12.0 (4-16)	14.0 (4-33)
GACI diagnosis/ history*			
Participants (%)	8 (57.1)	9 (100)	17 (73.9)
Age at GACI diagnosis (months)			
Median (range)	0.0 (0-71)	0.0 (0-77)	0.0 (0-77)
ARHR2 diagnosis/ history*			
Participants (%)	10 (71.4)	0 (0)	10 (43.5)
Age at ARHR2 diagnosis (months)			
Median (range)	38.0 (4-160)	-	38.0 (4-160)
PXE Diagnosis/ history*			
Participants (%)	2 (14.3)	1 (11.1)	3 (13.0)
Age at PXE diagnosis (months)			
Median (range)	94.5 (87-102)	42 (42-42)	87.0 (42-102)

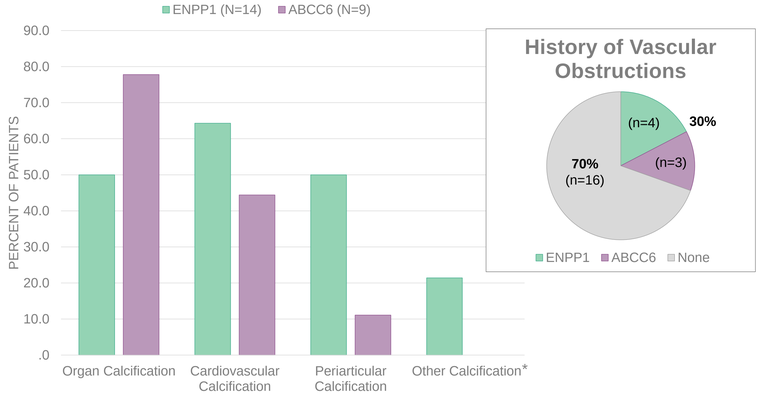
*Based on age at diagnosis or earliest disease event reported in the medical record

Enrolled Participants' Diagnoses (N=23)



Results

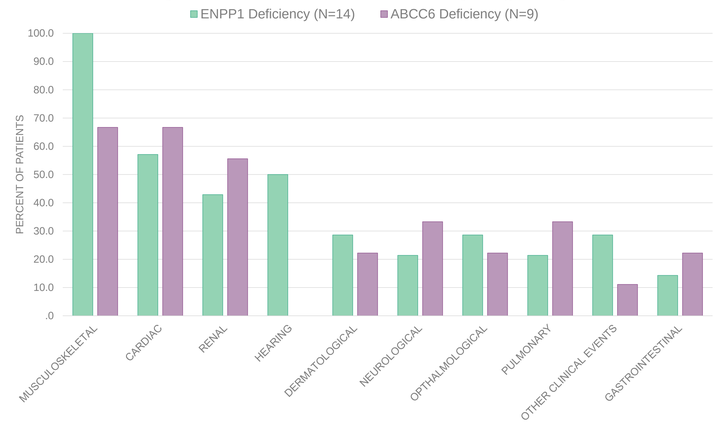
History of Calcifications



*Includes calcification of the ossicles and the ear cartilage

History of Vascular Obstructions

History of Medical Manifestations by Organ System



Manifestations occurring in ≥ 2 participants

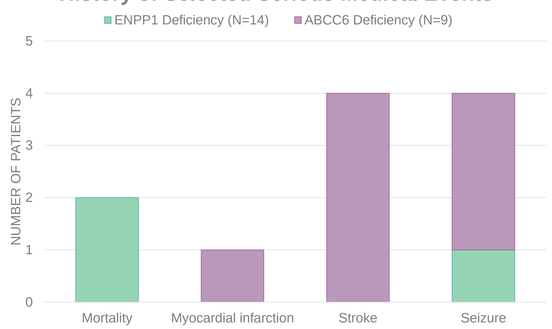
- **Musculoskeletal:** gait abnormality (n=10), rickets (n=8), joint pain (n=7), bone pain (n=6), mobility issues (n=5), scoliosis (n=5), traumatic fracture (n=3), osteopenia (n=2), delayed shedding of teeth (n=2), weakness (n=2)
- **Cardiac:** hypertension (n=9), valvular calcification (n=4), heart valve defect (n=2), reduced ejection fraction (n=2)
- **Renal**: nephrocalcinosis (n=2)
- **Hearing**: hearing loss (n=7), calcification of ear cartilage (n=2)
- **Neurological:** developmental delay (n=4), stroke (n=4), seizure (n=4), paralysis (n=3)
- **Pulmonary:** pulmonary hypertension (n=2)

Treatment and Intervention History

Treatment / Intervention	ENPP1 Deficiency (N=14)	ABCC6 Deficiency (N=9)
Medicinal treatment for GACI during infancy		
N (%)	5 (35.7)	3 (33.3)
Median age at initial treatment, months (range)	3.0 (0-10)	0.0 (0-0)
Medicinal treatment for ARHR2		
N (%)	9 (64.3)	0 (0)
Median age at initial treatment, months (range)	53.0 (7-156)	
Respiratory support / O2 requirement		
N (%)	4 (28.6)	3 (33.3)
Median age at initial treatment, months (range)	0.0 (0-0)	0.0 (0-0)
Cardiovascular surgery/ procedures*		
N (%)	4 (28.6)	2 (22.2)
Median age at initial intervention, months (range)	103.5 (54-153)	85.5 (33-138)
Orthopedic surgery**		
N (%)	9 (64.3)	4 (44.4)
Median age at initial intervention, months (range)	172.0 (69-210)	46.0 (27-79)
Hearing aids		
N (%)	6 (42.9)	0
Median age at initial intervention, months (range)	136.0 (51-178)	
Physiotherapy		
N (%)	4 (28.6)	0
Median age at initial intervention, months (range)	211.0 (211-211)	

*__Cardiovascular surgeries and procedures__ included but not limited to: angioplasty, balloon dilation of pulmonary valve, balloon dilation of renal artery, renal artery stent, PDA repair, Potts shunt, cardiac pacemaker (all n=1)
**__Orthopedic surgeries__ included but not limited to: epiphysiodesis (n=7), osteotomy (n=5)

History of Selected Serious Medical Events



	Median Age (Range) in Months	Median Age (Range) in Months	Median Age (Range) in Months	Median Age (Range) in Months
ENPP1	3.0 (3-3)	-	-	76.0 (76-76)
ABCC6	-	26.0 (26-26)	1.0 (0-44)	48.0 (44-52)

Note: Stroke and seizure co-occurred in 3 patients with ABCC6 Deficiency

Conclusions

- This retrospective chart review underscores the high multi-system medical burden in patients with ENPP1 Deficiency (N=14) and early-onset ABCC6 Deficiency (N=9) who were diagnosed with GACI, ARHR2, and/or PXE, and enrolled at a median age of 14 years.
  - Limitation: due to the retrospective nature of the study, it does not provide accurate quantification of survival rates (inherent bias to enroll surviving patients)
- ENPP1 Deficiency and ABCC6 Deficiency exhibit phenotypic overlap, with a high prevalence of cardiovascular calcification and complications requiring respiratory support or surgical intervention.
- Patients with ENPP1 Deficiency who survived beyond infancy faced medical burdens related to musculoskeletal and hearing complications, while patients with ABCC6 Deficiency had a high prevalence of early-onset stroke and seizure complications.

References

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Disclosures

This study was sponsored by Inozyme Pharma.
KG and AI are employees and stockholder of Inozyme. DW is a former employee and stockholder of Inozyme. MZM has received research grants, speaker honoraria, and consulting fees from Inozyme. DRW and FR have received research grants from Inozyme.

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