The Clinical Burden of Propionic Acidemia in Patients with or without Metabolic Decompensation Events Stratified by Age, in the United States

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BACKGROUND

- Patients with propionic acidemia (PA), a rare inherited metabolic disorder, can experience life-threatening acute metabolic decompensation events (MDEs) that are characterized by lethargy, seizures and vomiting, and lab findings of metabolic acidosis, ketosis, elevated anion gap and hyperammonemia, with the risk of coma or death[1,2]
- Current disease management of PA mostly involves medical nutrition therapy that focuses on MDE prevention and management, while liver transplants may be considered for severe cases[3]
- Clinical burden in the overall PA population in a large claims database in the United States (US) has been previously presented;[4] however, to date, there are limited real-world data on the clinical burden associated with MDEs in PA

OBJECTIVE

- To understand the real-world clinical burden of PA among patients with PA with or without MDEs in the US across age strata

METHODS

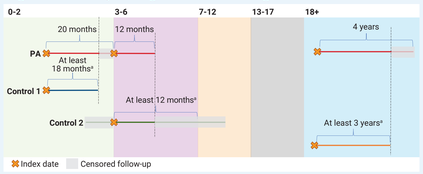
Study design and data source

- This retrospective matched cohort study included patients with PA (with or without MDEs) and matched control subjects (without PA) from the IQVIA PharMetrics® Plus claims database (10/2015-06/2022)
- Patient follow-up time was partitioned into five age strata: 0–2 years, 3–6 years, 7–12 years, 13–17 years, and 18+ years. Within each age stratum (**Figure 1**):
  - Index date: first observed PA diagnosis (International Classification of Diseases, Tenth Edition [ICD-10-CM]: E71.121; for patients with PA only), or first medical or pharmacy claim (for control subjects only) in the earliest age stratum, or first day of continuous health plan enrollment within subsequent age strata
  - End of observation: the earliest of either end of health plan enrollment, or end of age stratum, or end of data availability

Study population

- Eligible patients with PA (ICD-10-CM diagnosis of PA) and control subjects (no presence of ICD-10-CM diagnosis of PA) had a known age and at least 6 months of post-index continuous eligibility in at least one age stratum
  - Patients with PA were further stratified by presence and absence of MDEs (defined as a hospitalization with an ICD-10-CM diagnosis of metabolic acidosis and/or hyperammonemia) during the entire follow-up
- Within each age stratum, control subjects (without PA) were exactly matched 1:1 to patients with PA on age at index, index year (±1 year), month of index date (±1 month), sex, geographic region (three-digit zip code, or state when no match could be made using a three-digit zip code), insurance plan type, and partially on follow-up time (**Figure 1**)

Figure 1. Study design and matching schema



[a] Minimum follow-up requirement for control subjects (without PA) was the follow-up time of matched patients with PA rounded down to the nearest 6-month increment. For example, the control subjects for a patient with PA with 20 months follow-up within an age stratum must have had at least 18 months (3x6 months) of follow-up in that age stratum. The maximum time requirement for control subjects was 3 years.

Abbreviations: PA, propionic acidemia

Statistical analysis

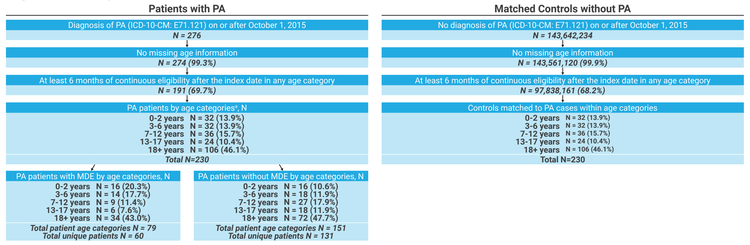
- Patient demographic, clinical characteristics, and PA treatments during the 6 months after the index date were described and compared within each age stratum between patients with PA with MDEs vs. those without MDEs
  - PA symptoms (i.e., metabolic acidosis, anorexia and failure to feed, vomiting, seizures, and hyperammonemia) were compared between 1.) patients with PA with MDEs vs. controls, and 2.) patients with PA without MDEs vs. controls, separately
- MDE rates per patient-year (PPY) with the corresponding 95% confidence interval (CI) were summarized for patients with PA with MDEs, overall and by age strata
- Rates of hospitalizations with PA signs and symptoms PPY and their corresponding 95% CIs were described and compared between patients with PA with MDEs vs. those without MDEs, overall and by age strata

RESULTS

Study sample

- The study sample included 191 patients with PA (60 [31.4%] with MDEs and 131 [68.6%] without MDEs) contributing a total of 230 observations across age strata (one patient may contribute to multiple age strata), and 230 matched control subjects (without PA) (**Figure 2**)
  - Specifically, there were 32 pairs in 0-2 years, 32 pairs in 3-6 years, 36 pairs in 7-12 years, 24 pairs in 13-17 years, and 106 pairs in 18+ years

Figure 2. Sample selection flowchart



[a] Patients with PA can contribute to multiple age categories. Therefore, the sum of age categories exceeds the total number of patients with PA in the study sample.

Abbreviations: ICD-10-CM, International Classification of Diseases, Tenth Edition; MDE, metabolic decomposition event; PA, propionic acidemia

Characteristics of patients with PA with MDEs vs. those without MDEs

- Patients with MDEs had similar demographics as those without MDEs (mean age: 25.2 vs. 24.7 years; female: 43.3% vs. 52.7%; commercial insurance/self-insured: 85.0% vs. 93.9%) (**Table 1**)
- Patients with MDEs experienced typical PA symptoms more frequently overall (86.7% vs. 42.8%; p<0.05) and across age strata (**Table 2**)
  - The biggest difference was observed in patients 3-6 years old (92.9% vs. 44.4%) and adults (18+ years: 88.2% vs. 44.4%; both p<0.05)
- Compared to patients without MDEs, patients with MDEs had a higher frequency of PA-related comorbidities, including cytopenias, growth complications, heart conditions, and neurologic and nervous system conditions across age strata (**Table 2**)
- Patients with MDEs more commonly received medications and procedures typically associated with PA treatment, including L-carnitine, nutritional supplementation, and gastrostomy/nasogastric-tube use (**Table 2**)

Table 1: Demographic characteristics of patients with PA with any MDEs vs. no MDEs at index

	All patients with PA		Age strata									
			0-2 years		3-6 years		7-12 years		13-17 years		18+ years	
	MDE	No MDE	MDE	No MDE	MDE	No MDE	MDE	No MDE	MDE	No MDE	MDE	No MDE
	N = 60	N = 131	N=16	N=16	N=14	N=18	N=9	N=27	N=6	N=18	N=34	N=72
Age, mean ± SD (years)	25.2 ± 25.3	24.7 ± 20.7	0.6 ± 0.7	0.4 ± 0.5	3.7 ± 1.2	4.2 ± 1.1	7.2 ± 0.5	9.0 ± 1.9	16.2 ± 1.4	14.3 ± 1.6	42.7 ± 20.4	39.7 ± 16.2
Female, n (%)	26 (43.3)	69 (52.7)	9 (56.3)	10 (62.5)	5 (35.7)	10 (55.6)	2 (22.2)	8 (29.6)	2 (33.3)	6 (33.3)	13 (38.2)	42 (58.3)
Census region, n (%)												
Midwest	23 (38.3)	45 (34.4)	8 (50.0)	6 (37.5)	7 (50.0)	8 (44.4)	4 (44.4)	9 (33.3)	4 (66.7)	6 (33.3)	11 (32.4)	25 (34.7)
South	19 (31.7)	44 (33.6)	5 (31.3)	9 (56.3)	4 (28.6)	4 (22.2)	3 (33.3)	9 (33.3)	0 (0.0)	4 (22.2)	11 (32.4)	24 (33.3)
Northeast	13 (21.7)	24 (18.3)	3 (18.8)	0 (0.0)	3 (21.4)	2 (11.1)	2 (22.2)	6 (22.2)	2 (33.3)	2 (11.1)	7 (20.6)	16 (22.2)
West	5 (8.3)	17 (13.0)	0 (0.0)	1 (6.3)	0 (0.0)	4 (22.2)	0 (0.0)	3 (11.1)	0 (0.0)	6 (33.3)	5 (14.7)	6 (8.3)
Unknown	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Insurance type, n (%)												
Commercial/ Self-insured	51 (85.0)	123 (93.9)	15 (93.8)	14 (87.5)	14 (100.0)	18 (100.0)	9 (100.0)	26 (96.3)	6 (100.0)	18 (100.0)	26 (76.5)	67 (93.1)
Medicare	7 (11.7)	4 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (20.6)	4 (5.6)
Medicaid	2 (3.3)	4 (3.1)	1 (6.3)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)

Notes: Demographic characteristics were summarized at the index date. Highlighted cells indicate a statistically significant difference (p<0.05) between patients with PA with any MDEs vs. no MDEs.
Abbreviations: MDE, metabolic decomposition event; PA, propionic acidemia; SD, standard deviation

Table 2: Clinical characteristics of patients with PA with any MDEs vs. no MDEs

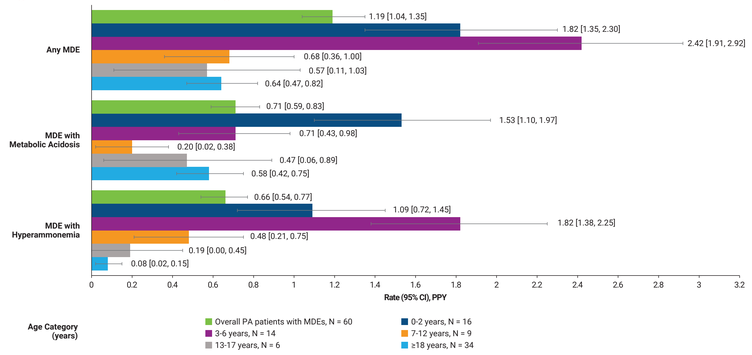
	All patients with PA		Age strata									
			0-2 years		3-6 years		7-12 years		13-17 years		18+ years	
	MDE	No MDE	MDE	No MDE	MDE	No MDE	MDE	No MDE	MDE	No MDE	MDE	No MDE
	N = 60	N = 131	N=16	N=16	N=14	N=18	N=9	N=27	N=6	N=18	N=34	N=72
PA symptoms, n (%)	52 (86.7)	56 (42.8)	14 (87.5)	8 (50.0)	13 (92.9)	8 (44.4)	4 (44.4)	8 (29.6)	4 (66.7)	6 (33.3)	30 (88.2)	32 (44.4)
Metabolic acidosis	40 (66.7)	10 (7.6)	12 (75.0)	1 (6.3)	4 (28.6)	1 (5.6)	1 (11.1)	1 (3.7)	3 (50.0)	0 (0.0)	24 (70.6)	7 (9.7)
Anorexia/Failure to feed	27 (45.0)	26 (19.9)	13 (81.3)	6 (37.5)	10 (71.4)	5 (27.8)	3 (33.3)	1 (3.7)	4 (66.7)	5 (27.8)	5 (14.7)	12 (16.7)
Vomiting	26 (43.3)	24 (18.3)	8 (50.0)	3 (18.8)	10 (71.4)	6 (33.3)	3 (33.3)	2 (7.4)	2 (33.3)	0 (0.0)	12 (35.3)	15 (20.8)
Seizures	14 (23.3)	14 (10.7)	4 (25.0)	1 (6.3)	3 (21.4)	3 (16.7)	4 (44.4)	4 (14.8)	2 (33.3)	1 (5.6)	9 (26.5)	6 (8.3)
Hyperammonemia	13 (21.7)	1 (0.8)	9 (56.3)	0 (0.0)	4 (28.6)	0 (0.0)	2 (22.2)	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.9)	1 (1.4)
PA-related comorbidities, n (%)												
Metabolic-related conditions	12 (20.0)	18 (13.7)	6 (37.5)	4 (25.0)	8 (57.1)	6 (33.3)	1 (11.1)	5 (18.5)	1 (16.7)	1 (5.6)	2 (5.9)	4 (5.6)
Cytopenias	23 (38.3)	10 (7.6)	11 (68.8)	2 (12.5)	2 (14.3)	1 (5.6)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	10 (29.4)	7 (9.7)
Growth complications	15 (25.0)	16 (12.2)	8 (50.0)	6 (37.5)	5 (35.7)	3 (16.7)	3 (33.3)	5 (18.5)	3 (50.0)	1 (5.6)	4 (11.8)	4 (5.6)
Heart conditions	12 (20.0)	5 (3.8)	1 (6.3)	0 (0.0)	0 (0.0)	1 (5.6)	1 (11.1)	2 (7.4)	5 (83.3)	1 (5.6)	9 (26.5)	3 (4.2)
Neurologic and CNS/PNS conditions	31 (51.7)	33 (25.2)	6 (37.5)	5 (31.3)	10 (71.4)	7 (38.9)	6 (66.7)	10 (37.0)	4 (66.7)	4 (22.2)	19 (55.9)	16 (22.2)
Medication/procedure, n (%)												
L-Carnitine	25 (41.7)	26 (19.9)	11 (68.8)	3 (18.8)	9 (64.3)	5 (27.8)	7 (77.8)	7 (25.9)	6 (100.0)	3 (16.7)	6 (17.7)	13 (18.1)
Any antibiotic use	25 (41.7)	26 (19.9)	8 (50.0)	4 (25.0)	5 (35.7)	4 (22.2)	2 (22.2)	3 (11.1)	5 (83.3)	2 (11.1)	10 (29.4)	16 (22.2)
Carglumic acid	4 (6.7)	0 (0.0)	3 (18.8)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.9)	0 (0.0)
Nutritional supplementation	21 (35.0)	21 (16.0)	9 (56.3)	3 (18.8)	6 (42.9)	2 (11.1)	3 (33.3)	4 (14.8)	4 (66.7)	2 (11.1)	8 (23.5)	12 (16.7)
G-tube/NG-tube	20 (33.3)	12 (9.2)	10 (62.5)	3 (18.8)	5 (35.7)	2 (11.1)	5 (55.6)	2 (7.4)	2 (33.3)	2 (11.1)	5 (14.7)	5 (6.9)
Hemodialysis	7 (11.7)	3 (2.3)	1 (6.3)	1 (6.3)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (14.7)	2 (2.8)
Other renal therapies[a]	3 (5.0)	1 (0.8)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)	0 (0.0)

Notes: Clinical characteristics were summarized during the 6-month period after the index date. Highlighted cells indicate a statistically significant difference (p<0.05) between patients with PA with any MDE vs. no MDE.
[a] Included peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies.
Abbreviations: CNS, central nervous system; G-tube, gastrostomy tube; NG-tube, nasogastric tube; PA, propionic acidemia; SD, standard deviation; PNS, peripheral nervous system

Rate of MDEs among patients with PA with MDEs

- Over a median (range) of 2.7 (0.5–6.7) years of follow-up, patients with MDEs experienced 1.19 [1.04, 1.35] MDEs PPY
  - Across age stratum, MDE rates were highest in pediatric patients aged 3-6 years (2.42 [1.91, 2.92] PPY) and lowest in those aged 13-17 years (0.57 [0.11, 1.03] PPY), before increasing again among adults (0.64 [0.47, 0.82] PPY) (Figure 3)

Figure 3. Rate of MDEs[a] among patients with PA with any MDE



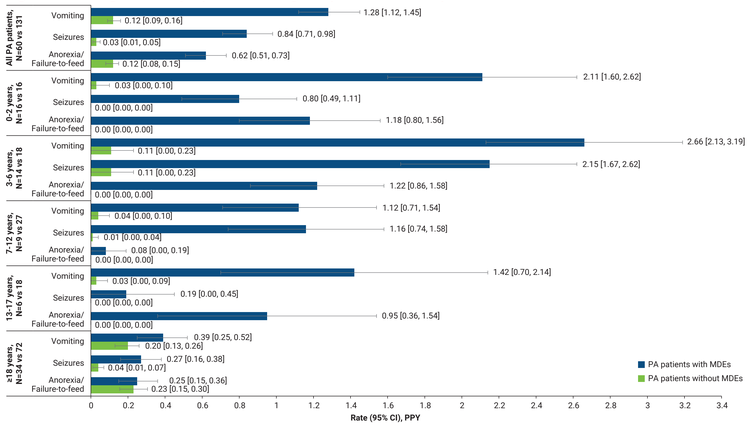
[a] MDE was defined as a diagnosis of metabolic acidosis or hyperammonemia occurring in the inpatient setting.

Abbreviations: CI, confidence interval; MDE, metabolic decompensation event; PA, propionic acidemia; PPY, per person-year

PA signs and symptoms during hospitalization among patients with PA with MDEs vs. those without MDEs

- Patients with MDEs had higher rates of PA signs and symptoms during hospitalization compared with patients without MDEs (vomiting: 1.28 [1.12, 1.45] vs. 0.12 [0.09, 0.16] PPY; seizures: 0.84 [0.71, 0.98] vs. 0.03 [0.01, 0.05] PPY; anorexia/failure to feed: 0.62 [0.51, 0.73] vs. 0.12 [0.08, 0.15] PPY) (**Figure 4**)

Figure 4. PA signs and symptoms during hospitalization for patients with PA with and without MDEs

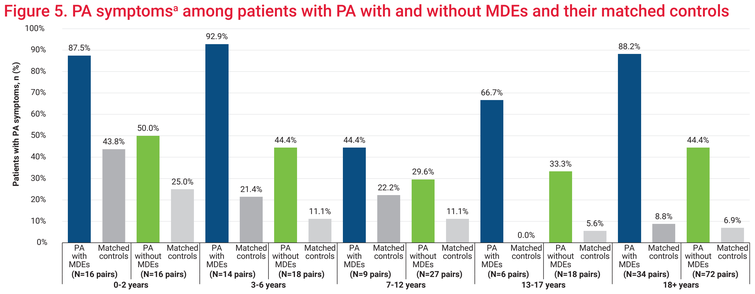


Abbreviations: CI, confidence interval; MDE, metabolic decompensation event; PA, propionic acidemia; PPY, per person-year

Prevalence of PA symptoms in patients with PA with or without MDEs vs. respective controls

- Patients with PA, with or without MDEs, had more PA symptoms than their respective matched controls across all age strata (**Figure 5**)
- The difference was more pronounced in patients who experienced MDEs vs. their controls (**Figure 5**)

Figure 5. PA symptoms[a] among patients with PA with and without MDEs and their matched controls



[a] PA symptoms include metabolic acidosis, anorexia and failure to feed, vomiting, seizures, and hyperammonemia.

Abbreviations: MDE, metabolic decomposition event; PA, propionic acidemia

Limitations

- Due to data period censoring, data around initial diagnosis of PA may not be visible in the database. However, diagnosis was confirmed by encounters for PA and patients were followed from first observed PA diagnosis
- Certain age strata within subgroups of patients with or without MDEs had limited sample size due to the rarity of PA; median follow-up was less than 3 years overall. Future studies with greater sample size and longer follow-up would be beneficial to validate the findings from our study
- Since most patients in this study were covered by commercial insurance, results may not be generalizable to other pediatric patients without commercial insurance (for example, Medicaid)

CONCLUSIONS

- Our study is the first claims data analysis to assess the burden of PA with a focus on MDEs, presenting data on patients with MDEs and those without MDEs. Consistent with prior literature, about one-third of patients with PA in our study experienced MDEs[5] and on average more than 1 MDE PPY. Our findings suggest that patients with PA with MDEs experienced a higher clinical burden compared to those without MDEs. The burden is mostly attributable to frequent PA-related symptoms and conditions, treatments, and higher rates of PA signs and symptoms during hospitalizations
  - Consistent with existing evidence, younger patients with PA in our study had a greater disease burden than older patients,[3] while adult patients also exhibited a high burden
  - With or without experiencing MDEs, patients with PA had an increased clinical burden compared to controls without PA, but the difference was more pronounced in patients with MDEs
- Findings from this study highlight the urgent need for therapies that can effectively reduce MDEs and PA symptoms for patients with PA, thereby alleviating the high burden associated with this population

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