Comparison of Methods of Initial Ascertainment in 58 Cases of Propionic Acidemia Enrolled in the Inborn Errors of Metabolism Information System Reveals Significant Differences in Time to Evaluation and Symptoms at Presentation

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Objectives To compare time to evaluation and symptoms at diagnosis of propionic acidemia (PA) by method of ascertainment, and to explore correlations between genotype and biochemical variables.

Study design Clinical symptoms, genotype, and biochemical findings were analyzed retrospectively in 58 individuals with PA enrolled in the Inborn Errors of Metabolism Information System (IBEM-IS) based on the type of initial ascertainment: abnormal newborn screening (NBS), clinical presentation (symptomatic), or family history.

Results The average age at initial evaluation and treatment was significantly younger in patients ascertained via abnormal NBS compared with those referred for clinical symptoms. Furthermore, the majority of individuals ascertained because of abnormal NBS were asymptomatic at diagnosis, compared with a minority of clinical presentations. A notable difference in the frequency of metabolic acidosis at initial presentation was observed between those with abnormal NBS (12.5%; 2 of 16) and those with an abnormal clinical presentation (79%; 19 of 24). The frequency of hyperammonemia was similar in the 2 groups.

Conclusion Our data support the continued value of NBS to identify individuals with PA, who are diagnosed and treated earlier than for other modes of ascertainment. There were no statistically significant correlations between genotype and NBS for C3 acylcarnitines. Although expanded use of NBS has allowed for early diagnosis and treatment, long-term outcomes of individuals with PA, especially with respect to mode of ascertainment, remain unclear and would benefit from a longitudinal study. *(J Pediatr 2017;180:200-5).*

Propionic acidemia (PA) is a rare inborn error of metabolism with autosomal recessive inheritance. The disorder is characterized by deficient propionyl-CoA carboxylase (PCC) enzyme, affecting catabolism of propiogenic amino acids and odd-chain fatty acids and impairing production of intermediates of the tricarboxylic acid cycle.[1] PPC is a dodecamer comprised of α and β subunits, encoded by the *PCCA* and *PCCB* genes, respectively.[2]

Incidence figures for PA range from 1 in 165 000 to 1 in 300 000, and the condition is more common in the Middle East and in Old Order Amish.[3-7] Early presentations occur in the neonatal period, and late-onset presentations occur at variable ages.[8-10] Data from European groups indicates that newborn screening (NBS) leads to earlier diagnosis than symptomatic testing,[11] but objective information regarding the impact of NBS on age at evaluation and treatment, and on long-term outcomes, is limited. The Inborn Errors of Metabolism Information System (IBEM-IS) is a multicenter collaborative database initiated in 2007 that collects longitudinal information on metabolic conditions included in NBS. We analyzed available data on the initial presentation of individuals with PA participating in the IBEM-IS to answer the following questions: (1) Can the method of ascertainment impact age at initial evaluation? We hypothesized that individuals with a abnormal NBS will have earlier evaluation; (2) Is there a difference in the type and frequency of symptoms at initial evaluation based on the method of ascertainment? We hypothesized that ascertainment early in life results in fewer and less severe symptoms; and (3) Are

GI	Gastrointestinal
IBEM-IS	Inborn Errors of Metabolism Information System
NBS	Newborn screening
PA	Propionic academia
PCC	Propionyl-CoA carboxylase

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there genotype–phenotype correlations? We hypothesized that null mutations lead to lower residual enzyme activity, which would result in higher NBS C3 acylcarnitine levels.

Methods

We reviewed available data for 61 patients with PA enrolled in the IBEM-IS. Three patients with no information on initial presentation were excluded. The data review was retrospective and included data entered between June 13, 2007, and November 6, 2015. The abstracted data did not include direct or indirect identifiers. This study was reviewed and granted exempt status by the Institutional Review Board for Clinical Investigations at Duke University and at the University of Wisconsin at Madison.

Data on initial ascertainment, diagnostic testing, and clinical symptoms were evaluated. Clinical results were tabulated and analyzed based on 3 categories for initial ascertainment, as indicated by the originating center: abnormal NBS, clinical presentation (many cases in this cohort were ascertained before the initiation of NBS by tandem mass spectrometry), and family history. In some cases, multiple modes of ascertainment were indicated by the originating center. These cases were reviewed and adjudicated to only 1 category based on timing and other clinical data. Early versus late evaluations were categorized based on whether the age at initial subspecialist visit or treatment was <30 days or >30 days of life, respectively. Descriptive statistics were used for quantitative results. Comparisons of age at initial metabolic evaluation, age at initial treatment, and C3 acylcarnitine values were done using the independent-samples Mann-Whitney *U* test. Frequency comparisons were made using the Pearson χ^2 test or Fisher exact test when expected cell counts were <5. SPSS for Windows, version 23.0 (IBM, Armonk, New York) was used for all statistical comparisons and graphical representations. Any discrepant data were clarified by direct query of the institution entering the data via the coordinating center (Michigan Public Health Institute), and responses were deidentified before being shared with the author group.

The clinical classifications used for health status at initial presentation were critically ill, gastrointestinal (GI) complications, respiratory complications, neurologic complications, neurologic and GI complications, and asymptomatic. A patient was deemed critically ill if the laboratory results and symptoms indicated a medical emergency. Such qualifications included combinations of lethargy, hypotension, hypotonia, poor feeding, encephalopathy, sepsis, and/or laboratory findings such as hyperammonemia. These qualifications were presumed to infer significant illness.

Published genotypes were cross-referenced using the PPC mutation database maintained through the University of Colorado (http://cbs.lf1.cuni.cz/pcc/pccmain.htm). Any alleles that had not been published previously were assessed for impact on structure and function using open-source software (Mutation Taster [www.mutationtaster.org], PolyPhen-2 [http://genetics.bwh.harvard.edu/pph2/index.shtml], or SIFT [http://sift.jcvi.org/]). The following reference sequences were used for these analyses: *PCCA*, ENSG00000175198 (gene) and ENST00000376285 (transcript); *PCCB*, ENSG00000114054 (gene) and ENST00000251654 (transcript).

Results

Data for 58 patients with PA entered into the IBEM-IS were evaluated. The dataset represents a fairly balanced distribution with respect to sex (females, n = 26; males, n = 32). The majority of patients were Caucasian (44 of 58), 3 were Black/African American, 1 was American Indian, and 3 were reported as mixed race. Seven patients lacked information regarding race. Seven individuals were also identified as Amish.

Ages at Initial Evaluation and Treatment

Cases were ascertained by abnormal NBS (n = 25), clinical presentation (n = 26), or family history (n = 7). Complete clinical and molecular information is presented in **Table I** (available at www.jpeds.com).

We analyzed the age at initial metabolic evaluation and initiation of treatment for PA among the patients in each group using descriptive statistics. Cases ascertained via abnormal NBS had a mean age at initial metabolic evaluation of 15 days (n = 19) and initiation of treatment of 12 days (n = 16). The majority of patients (11 of 16) ascertained by NBS had metabolic evaluation and initiation of treatment on the same day (**Figure 1**); of the remaining patients, 4 had a metabolic evaluation after initiation of treatment and 1 received treatment after initial metabolic evaluation (**Figure 1**). One patient was excluded from these calculations because the reported value of 1065 days actually represented the age at which the patient was enrolled in the IBEM-IS, and no additional information was available.

The mean age at initial metabolic consultation for clinical presentation was 332 days (n = 24), and the mean age at initiation of treatment (n = 26) was 323 days. The majority of patients (21 of 24) ascertained by clinical presentation had metabolic evaluation and initiation of treatment on the same day (**Figure 1**). Of the remaining patients, 2 had metabolic consultation after the start of treatment and 1 had metabolic consultation before the start of treatment (**Figure 1**).

Patients ascertained by family history had an average age at initial metabolic evaluation (n = 7) and initiation of treatment (n = 7) of 449 days and 427 days, respectively. Three of the 7 patients ascertained by family history had metabolic evaluation before the initiation of treatment, 2 had metabolic evaluation after the initiation of treatment, and 2 had metabolic evaluation on the day of initiation of treatment (**Figure 1**). No outliers were removed from the clinical presentation or family history groups despite large ranges in values, because the time frames were consistent with the method of ascertainment.

The ages at initial evaluation and initiation of treatment were younger for those patients ascertained by NBS versus other presentations (**Figure 2**). The age at initial metabolic evaluation and age at initial treatment were significantly younger for