Variation in Diagnostic Care and Disease Classification for PAH Deficiency: Initial Findings From the Canadian Inherited Metabolic Diseases Research Network (CIMDRN)


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Background & Objectives
- Care during the diagnostic period for phenylalanine hydroxylase (PAH) deficiency may include:
  - Monitoring of initial/unreated blood phenylalanine during the diagnostic period through repeated testing
  - Evaluating response to biotin amin loading test
  - Molecular genetic testing for identifying pathogenic mutations in the PAH gene
  - Prescription of daily dietary phenylalanine intake and low or phenylalanine-free medical foods
- There is uncertainty about classification of severity of PAH deficiency:
  - How can diagnostic test results be used to classify disease according to severity: classical phenylketonuria (PKU), mild PKU, mild hyperphenylalaninemia (HPA)?
  - How well do different methods for classifying the severity of PAH deficiency agree with each other?
- Study Objectives:
  - To describe patterns of diagnostic care for children with PAH deficiency across Canada.
  - To investigate methods for assigning disease classification and to explore their level of agreement

Methods: CIMDRN Cohort

Sample Source:
- Children born between 2006 and 2015 and receiving care for an inherited metabolic disease at one of 13 CIMDRN centres

Methods: Clinical Data Collection & Analysis

Data Collection:
- Database hosted on REDCap
- Medical chart abstracted data

Analysis:
- Descriptive analysis of diagnostic practices at centre
- Associations between methods of assigning disease severity

Results & Interpretation: Diagnostic Care

Diagnostic Tests Performed Across Centres:
- There was variation in routinely reported diagnostic tests by centre, which likely reflects incomplete reporting of essential diagnostic tests and true variation in diagnostic practices between centres and over time.

Results & Interpretation: Max Blood Phenylalanine Levels

Dietary Interventions Within the First 30 Days of Life:
- Median age at follow-up visit during first month of life, where initial dietary intervention was prescribed (N = 31), was 9 days (range: 4-25 days)
- Recommended diet composition commonly consisted of medical foods (87%) and/or natural food protein (58%)

Results & Interpretation: Molecular Genetic Testing

Alleles Identified Through Molecular Genetic Testing:
- Unique alleles collected from participants (N = 34) were classified according to their pathogenicity noted in ClinVar (as of April 18, 2017)

Pathogenic & Likely Pathogenic: Unclear/Unknown Pathogenicity
- Despite all participants having confirmed cases of PAH deficiency, not all of the identified PAH alleles were classified as “Pathogenic” by the ClinVar database
- 6 alleles classified as “Likely Pathogenic” by ClinVar and 3 alleles classified as “Unclear/Unknown Pathogenicity” by ClinVar have been confirmed as pathogenic by molecular genetic testing in our cohort
- Certain alleles were associated with a single PAH deficiency phenotype noted in patient charts while others were associated with multiple

Methods: Clinical Data Collection & Analysis

Eligibility:
- Diagnosed with phenylalanine hydroxylase deficiency
- Complete baseline data (demographic and diagnostic information)

Data Collection:
- Database hosted on REDCap
- Medical chart abstracted data

Analysis:
- Descriptive analysis of diagnostic practices at centre
- Associations between methods of assigning disease severity

Results & Interpretation: Bioterin Responsiveness

Conclusions & Next Steps

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