Hyperargininemia Due to Arginase 1 Deficiency: Variability in Clinical and Biochemical Presentations in Malaysian children

Clinical Pathology
Volume 15: 1–3

DOI: 10.1177/2632010X221093274

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ABSTRACT

OBJECTIVE: Hyperargininemia due to Arginase 1 deficiency is a rare inborn error of the urea cycle with an incidence estimated at 1:950 000. It has typical severe and progressive abnormal neurological features with biochemical findings of hyperargininemia and hyperexcretion of orotic acid. The aim of our study is to review the clinical and biochemical presentations of 4 children diagnosed with Arginase 1 deficiency in Malaysia and compare with the literature review.

DESIGN AND METHODS: We retrospectively reviewed the medical records of 4 patients with molecularly confirmed Arginase 1 deficiency. Patients were identified from a selective high-risk screening of 51 682 symptomatic patients from January 2006 to December 2020.

RESULTS: Our patients exhibited heterogeneous clinical presentations with acute and progressive neurological abnormalities and varying degrees of plasma arginine and urine orotic acid excretions. Interestingly, an unusual hyperexcretion of homocitrulline was found in 3 patients.

CONCLUSIONS: Hyperargininemia due to Arginase 1 deficiency can present acutely and hyperexcretion of homocitrulline can be an additional biochemical feature of Arginase 1 deficiency.

KEYWORDS: Urea cycle defect, hyperargininemia, arginase 1 deficiency, orotic acid, homocitrulline

RECEIVED: October 6, 2021. **ACCEPTED:** March 22, 2022.

TYPE: Brief Report

FUNDING: The author(s) received no financial support for the research and authorship of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Urea cycle disorders are a group of inborn errors of liver metabolism that affect the transfer of waste nitrogen to urea.[1] The urea cycle functions to detoxify waste nitrogen into water-soluble urea and is responsible for the de novo biosynthesis of arginine. Hyperargininemia due to arginase 1 deficiency; OMIM 207800 is one of the rarest of urea cycle disorders with an incidence estimated at 1:950 000.[2] The gene responsible for Arginase 1 enzyme is *ARG1* located in the long arm of chromosome 6 (6q23).[3] It is one of the defects of the urea cycle that is not typically characterized by the early onset of hyperammonemia.[4] Accumulation of arginine, which is the substrate proximal to the metabolic block, is the biochemical hallmark of hyperargininemia due to arginase deficiency.[4] In this study, we review the clinical and biochemical characteristics of 4 patients with this rare disease and compared them with the literature review. Mohseni et al[5] had found novel complex rearrangement of *ARG1* gene in all 4 patients. The detail of the molecular analysis of these 4 patients had been illustrated and published.[5]

Materials and Methods

The medical records of 4 Malay patients with molecularly confirmed Arginase 1 deficiency were retrospectively reviewed. They were identified from a selective high-risk screening of 51 682 patients from government hospitals in Malaysia from January 2006 to December 2020. Laboratory biochemical investigations for inborn metabolism errors were carried out at the Institute of Medical Research Kuala Lumpur. Patients eligible for selective high-risk screening were patients with symptoms suspicious for inborn metabolism errors including unexplained metabolic acidosis, hypoglycemia, hyperammonemia, jaundice, hepatosplenomegaly, recurrent vomiting, seizures, encephalopathy, developmental delay, and learning disabilities. Hyperargininemia in the 4 samples was detected by tandem mass spectrometry (LCMS/MS); Micromass Quattro (Waters Corp., Wilmslow, UK) and/or cation-exchange high performance liquid chromatography (HPLC); Amino acid analyzer Biochrom 30 (Biochrom Ltd. UK). Urine for homocitrulline quantitation was analyzed using cation-exchange HPLC Biochrom 30. The orotic acid in the urine samples was

quantitated using a reverse phase HPLC system (Agilent 1000 series). Clinical data was recovered from the request forms. This study received exemption from the Malaysia Medical Research and Ethics Committee (MREC), NMRR-21-676-59550, and was performed according to the Declaration of Helsinki. Informed consents were obtained from the parents of the patients.

Results

Our patients exhibited varying degrees of plasma ammonia, glutamine, arginine, and urine orotic acid excretions. Unusual hyperexcretion of homocitrulline was found in 3 patients. The biochemical and clinical features were summarized in Table 1. Supplementary Figure 1 illustrate the abnormal amino acid peaks on the chromatogram.

Discussion

Arginase 1 deficiency patients typically present with severe progressive neurological involvement such as hypertonicity, loss of motor and mental skills, spastic paraplegia of the lower extremities, seizures, ataxia, athetosis, and dysarthria in the absence of hyperammonemia decompensation.[6] Hyperammonemia in patients with Arginase 1 deficiency tends to be moderate and is generally seen from the late infancy to the second year of life.[7] Arginine in these patients was generally elevated to 700 to 800 mmol/L,[3] but in our patient series, arginine concentrations were more variable and ranged from 516 to 2451 umol/L. The advent of expanded newborn screening (NBS) for amino acid disorders using tandem mass spectrometry allows for earlier detection of an increased risk of hyperargininemia at or near birth.[8] However, the sensitivity of NBS for the identification of children at high risk of developing arginase deficiency has been debatable as arginine concentrations can be normal in the first days of newborn life. Two of our patients (patients 3 and 4) presented with non-typical acute intoxication symptoms. A biomarker that had been detected in patients with hyperammonemia hyperornithinemia homocitrullinuria syndrome (HHH) and lysinuric protein intolerance (LPI); homocitrulline was detected in the urine of 3 patients (patients 1, 3, and 4). To our knowledge, no homocitrulline has been reported in patients with Arginase deficiency, except for transient homocitrullinuria in 1 patient.[9] The pathophysiology of the formation of homocitrulline in our patients had not been ascertained. However as in patients with Lysinuric protein intolerance, the accumulation of the carbamoyl phosphate in the urea cycle in the untreated patients had resulted in the formation of orotic acid by activation of the pyrimidine pathway and also caused a formation of homocitrulline by carbamylation of lysine.[10] The same mechanism could also be responsible in the untreated Hyperargininemia patients due to the mutation in the *ARG1* gene as in our patients.

Table 1. Clinical and biochemical findings of 4 patients with Arginase 1 deficiency.

CONSANGUINITY	CLINICAL FEATURES	REFERENCE RANGE						
		AMMONIA 10-40 µMOL/L	GLUTAMINE 86-567 µMOL/L	CITRULLINE 3-42 µMOL/L	ARGININE 14-104 µMOL/L	ORNITHINE 8-156 µMOL/L	URINE HOMOCITRULLINE 0 µMOL/MOLCREATININE	URINE OROTIC ACID 1-3.2 µMOL/MOLCREATININE
No	Full-term 11-month-old boy presented with generalized hypotonia, gross motor delay, and microcephaly. History of neonatal jaundice requires phototherapy.	52.7	490	17	516	43	57	1018
Yes	6-y-old girl, was born term with an uneventful birth history. She presented clinically with mental retardation, seizures, frequent spasms with hypertonicity of lower extremities, hyperreflexia, and progressive diplegia.	194	407	30	736	23	Not available	1188
Yes	6-y-old male sibling to patient 2 with normal development milestones. Had prolonged fever, seizures, abnormal behavior, drowsiness, and hyperreflexia.	81	592	28	729	30	24	706
Yes	Full-term 3-month-old girl with insignificant history of birth and medical history. She presented with acute seizures and drowsiness.	530	934	29	2451	62	174	675

Conclusions

Hyperargininemia due to Arginase 1 deficiency can also present acutely, and hyperexcretion of homocitrulline can be an additional biochemical feature of Arginase 1 deficiency.

Acknowledgement

We would like to thank the Director General of Health Malaysia for permission to publish this paper. We also thank the staff of Biochemistry Unit, Institute for Medical Research, for their assistance in the laboratory work.

Author Contributions

Anasufiza Habib prepared the first draft of the manuscript. Norashareena Mohamed Shakrin provide the biochemical data and reviewed the manuscript. Both authors agreed with the content and approved the last version of the manuscript.

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Supplemental Material

Supplemental material for this article is available online.

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