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

Anasufiza Habib1 and Norashareena Mohamed Shakrin2
1Biochemistry Unit, Specialised Diagnostic Centre, Institute for Medical Research, Ministry of Health Malaysia, National Institute of Health, Kuala Lumpur, Malaysia. 2Inborn Error of Metabolism and Genetic Unit, Institute for Medical Research, Ministry of Health Malaysia, National Institute of Health, Setia Alam, Malaysia.

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.

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 rarer of urea cycle disorders with an incidence estimated at 1:950,000.3 The gene responsible for Arginase 1 enzyme is ARGL located in the long arm of chromosome 6 (6q23).1 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.5 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 al6 had found novel complex rearrangement of ARGL 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., Wilsom, 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
Clinical Pathology

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 hypertonia, loss of motor and mental skills, spastic paraplegia of the lower extremities, seizures, ataxia, dysarthria, and dysphagia in the absence of hyperammonemia, decompenation.9 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. Arginine in these patients was generally elevated to 700 to 800 μmol/L, but in our patient series, arginine concentrations were more variable and ranged from 516 to 2451 μmol/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. However, the sensitivity of NBS for the identification of children at high risk of developing arginase deficiency has been debated and is generally seen from the late infancy to the second year of life. Arginine in these patients was generally elevated to 700 to 800 μmol/L, but in our patient series, arginine concentrations were more variable and ranged from 516 to 2451 μmol/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. However, the sensitivity of NBS for the identification of children at high risk of developing arginase deficiency has been debated and is generally seen from the late infancy to the second year of life.

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

| CONSENSUITY | 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          | 52.7 490 17 516 43 57 1018 | 194 407 30 736 23 Not available 1188 | 81 592 28 729 30 24 706 | 530 934 29 2451 62 174 675 |
| Yes         | 6-y-old boy presented with generalized hypotonia, gross motor delay, and microcephaly. History of neonatal jaundice requires phototherapy. | 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. | 6-y-old male sibling to patient 2 with normal development milestones. Had prolonged fever, seizures, abnormal behavior, drowsiness, and hyperreflexia. | Full-term 3-month-old girl with insignificant history of birth and medical history. She presented with acute seizures and drowsiness. |
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 provided the biochemical data and reviewed the manuscript. Both authors agreed with the content and approved the last version of the manuscript.

ORCID iD
Anasufiza Habib https://orcid.org/0000-0001-5529-5115

Supplemental Material
Supplemental material for this article is available online.

REFERENCES
1. Scaglia F, Lee B. Clinical, biochemical, and molecular spectrum of hyperargininemia due to arginase 1 deficiency. *Am J Med Genet Part C Seminar Med Genet*. 2006;142C:113-120.
2. Summar ML, Koehler S, Freeddenberg D, et al. The incidence of urea cycle disorders. *Mol Genet Metab*. 2013;110:179-180.
3. Iyer R, Jenkinson CP, Vockley JG, Kern RM, Grody WW, Cederbaum SD. The human arginases and arginase deficiency. *J Inherit Metab Dis*. 1998;21(suppl. 1):86-100.
4. Jain-Ghai S, Nagamani SC, Blaser S, Siritwadana K, Feigenbaum A. Arginase I deficiency: severe infantile presentation with hyperammonemia: more common than reported? *Mol Genet Metab*. 2011;104:107-111.
5. Mohseni J, Boon Hock C, Abdul Razak C, et al. Novel complex re-arrangement of ARG1 commonly shared by unrelated patients with hyperargininemia. *Gene*. 2014;533:240-245.
6. Saudubray JM, Rabier D. Biomarkers identified in inborn errors for lysine, arginine, and ornithine. *J Nutr*. 2007;137:1669S-1672S.
7. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease*. 6th ed. McGraw-Hill; 1995:656.
8. Therrell BL, Currier R, Lapidus D, Grimm M, Cederbaum SD. Newborn screening for hyperargininemia due to arginase 1 deficiency. *Mol Genet Metab*. 2017;121:308-313.
9. Cederbaum SD, Shaw KN, Valente M. Hyperargininemia. *J Pediatr*. 1977;90:569-573.
10. Simell O. Lysinuric protein intolerance and other cationic aminoacidurias. In: Scriver CR, Beaudet AL, Sly SW, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease* (Chapter 192). 2002. http://genetics.accessmedicine.com