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Plasma arginine levels in arginase deficiency in the "real world"

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ABSTRACT

Background: Deficiency of arginase-1, the final enzyme in the urea cycle, causes a distinct clinical syndrome and is characterized biochemically by a high level of plasma arginine. While conventional therapy for urea cycle disorders can lower these levels to some extent, it does not normalize them. Until now, research on plasma arginine levels in this disorder has primarily relied on data from specialized tertiary centers, which limits the ability to assess the natural history and treatment efficacy of arginase-1 deficiency due to the small number of patients in each center and technical variations in plasma arginine measurements among different laboratories.
Method: In this study, we reported plasma arginine levels from 51 patients with arginase-1 deficiency in the database of Quest Diagnostics. The samples were collected from different US regions.
Results: The mean plasma arginine level in these treated patients was 373 μmol/L and the median level was 368.4 μmol/L. Our data set from 30 arginase deficiency patients with plasma amino acid data from five or more collections revealed significant correlations between the levels of arginine and five other amino acids (citrulline, alanine, ornithine, glutamine, and asparagine).
Conclusion: Despite treatment, the arginine levels remained persistently elevated and did not change significantly with age, suggesting the current treatment regimen is inadequate to control arginine levels and underscoring the need to seek more effective treatments for this disorder.

1. Introduction

The urea cycle in mammals is a six-enzyme, two-transporter pathway for ammonia detoxification and conversion to urea for excretion [1]. Arginase is the final enzymatic step in the process and converts arginine to urea and ornithine, the latter recycled into the metabolic pathway [1,2]. Deficiency of arginase results in an increase of arginine and other guanidino compounds in the plasma and other tissues. The clinical consequence of this accumulation is a syndrome comprising the gradual onset of spasticity, intellectual disability, growth deficits, and several other abnormalities. In contrast to other urea cycle disorders, ammonia toxicity and encephalopathy appear to play a lesser role [3].

The treatment of arginase deficiency mirrors that of other urea cycle disorders save for the obvious exclusion of arginine and/or citrulline from the treatment regimen. For other urea cycle disorders, the standard treatment of dietary protein restriction, supplemental essential amino acids, nitrogen scavengers and arginine are generally successful in keeping ammonia in the normal or near-normal range; however, this regimen has proven to be less successful in normalizing arginine levels, even in the hands of programs specializing in urea cycle disorders [3].

The United States is unusual among developed countries in that specialized metabolic testing is commercially available; therefore, patients with known metabolic disorders may be treated outside of tertiary, or highly specialized metabolic centers. In this paper, we present the experience of one of these national companies, Quest Diagnostics, with patients with arginase deficiency. The two authors who are based

Abbreviations: (Ala), alanine; (Arg), arginine; (Asn), asparagine; (BCAAs), branched-chain amino acids; (Cit), citrulline; (Gln), glutamine; (Iso), isoleucine; (Leu), leucine; (Orn), ornithine; (ULN), upper limit of normal; (UCD), urea cycle defect; (Val), valine.

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in a tertiary care center were astonished that Quest had data on 82 patients with this ultra rare disorder., most of whom we infer may be treated in a hospital setting without independent amino acid analytic capability. We are able to confirm many of these labs were ordered by physicians outside of specialized metabolic centers. However, we cannot exclude the possibility that some of the patients were managed by a specialized metabolic center given limited information available in the Quest database. We do not make any invidious comparisons with those treated in specialized centers, but our data support the notion that current approaches to treatment are insufficient to reduce plasma arginine levels to normal or near-normal and may be sub-optimal in preventing neurological damage and symptoms [3].

2. Methods

2.1. Study design

This study aims to evaluate the mean arginine (Arg) levels as well as other amino acid levels and their correlation with the levels of arginine in arginase deficiency patients. We collected the levels of arginine and other eight amino acids including major nitrogen carriers (glutamine (Gln), asparagine (Asn), and alanine (Ala)) and amino acids involved in urea cycle (citrulline (Cit), and ornithine (Orn)). Since decreased branched chain amino acids (leucine (Leu), isoleucine (Iso) and valine (Val)) have been reported in urea cycle defect (UCD) patients receiving sodium phenylbutyrate-containing medications to include glycerol phenylbutyrate [4], the levels of branched chain amino acids were also included in this study.

2.2. Data collection

We used the Quest Diagnostics database to search for known cases of arginase deficiency (diagnosis was confirmed by ICD, clinicians, molecular diagnosis, or characteristic plasma amino acids patterns). We performed a retrospective review of plasma amino acid analysis results performed by the Quest Diagnostics (San Juan Capistrano, CA USA) Biochemical Genetics Laboratory on arginase deficiency patients. All tests were analyzed by the same methodology: liquid chromatography/mass spectrometry (LC-MS) [5].

A total of 82 arginase deficiency patients were identified in the Quest Diagnostics database. We were able to retrieve the results of comprehensive plasma amino acids analysis and identified 51 patients with at least three plasma amino acids measurements, 30 of whom had plasma amino acids data from five or more samples.

2.3. Data analysis

Patient characteristics were reported in medians and ranges. The differences in baseline variables between genders were assessed using Wilcoxon rank sum tests. Age at baseline was defined as the patient's age when the first amino acid analysis measurement was performed by Quest Diagnostics and follow-up time was calculated as duration between the follow-up and baseline dates of sample collections. The correlations between Arg and age at the time of sample collection and the correlations between Arg and other 8 amino acids were assessed with the method of repeated measures correlation [6]. The linear mixed model was used to estimate the means (95% confidence intervals [CIs]) of Arg levels in the age groups and assess the differences with accounting for within-subject and between-subject variations as well as variations within and between families. Linear mixed models were also used to assess the change of Arg level per unit increase of other amino acid levels with adjustment for age, gender, and follow-time in all patients, or for age and follow-time time in gender groups. All the analyses were performed in R software.

3. Results

3.1. Study characteristics and patient demographics

Among the 51 patients, the study included 30 patients with five or more amino acids analyses. After excluding missing values in Arg, a total of 411 tests were included in our analysis. Age at baseline (patient's age when the first amino acid analysis measurement by Quest Diagnostics) ranged from 5 days to 45 years, with the majority of patients younger than 18 years of age (76.67%) (Fig. 1). The median values of nine amino acids are shown in Table 1. Approximately 60% (19/30) were male. There were 5 sets of siblings (2–3 patients per family). The median follow-up time was about 49 months (1 month −13.8 years) and the median number of amino acid tests was 10 per patient. The samples were submitted from all 5 US regions. The tests were ordered by either metabolic specialists, clinical geneticists or primary care providers.

3.2. Arginine levels

The mean Arg level of the 51 patients was 373 μmol/L and the median level was 368.4 μmol/L with standard deviation (SD) 94.35 and coefficient of variation (CV) 25.3%. The correlation between Arg levels and age at the time of sample collection from 411 tests in 30 patients was shown in Fig. 2, demonstrating the biochemical spectrum of this condition. The overall correlation between Arg and age at the time of sample collection was weak and not statistically significant with a correlation coefficient of 0.02. They were also not statistically significant within each age group with correlation coefficients of 0.11, 0.04, and −0.02 in the group of 1 to 23 months, 2 to 17 years, and ≥18 years, respectively. The distributions of Arg levels in the age groups were also shown in Table 2. The mean Arg levels of <1 month-old was 229 μmol/L (95% CI ranges 117–341 and the age-specific reference intervals were 14–135 μmol/L), 1–23 months-old was 357 μmol/L (95% CI ranges 325–389 and the age-specific reference intervals were 30–147 μmol/L), 2–17 years old was 379 μmol/L (95% CI ranges 369–388 and the age-specific reference intervals were 38–122 μmol/L) and ≥18 years-old was 387 μmol/L (ranges 377–396 and the age-specific reference intervals were 43–107 μmol/L). The means (95% CIs) of Arg levels in the age groups were estimated and the differences were assessed in a linear mixed model. The differences were not statistically significant.

Most of the Arg levels were above the age-specific reference intervals. The most elevated arginine levels, compared against the respective age-specific upper limit of normal (ULN), were detected in patients >1 month of age; values exceeding 6-fold the ULN were observed in patients >1 month old, whereas in patients below one month of age, the highest arginine value measured represented only 2.5-fold the ULN (Table 2).

The overall p value for the effect of the age group on Arg levels was

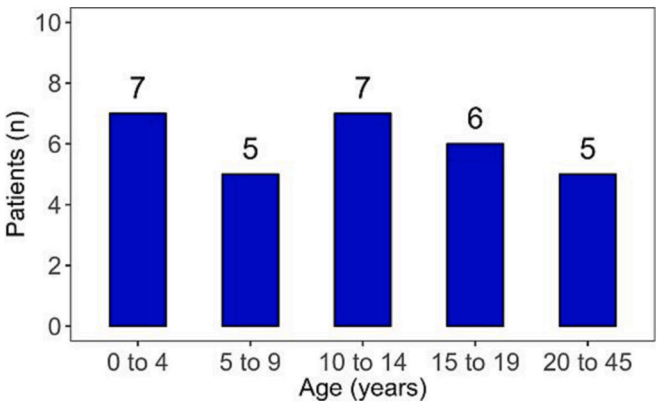

Fig. 1. Age Distribution at the Time of Sample Collection.

Table 1
Patient Characteristics at the time of the first amino acid analysis by Quest Diagnostics.

Characteristics	All Patients	Gender		*P* value
		Female	Male	
Patients (N)	30	11	19	
Alanine	248 (158–479)	213 (163–366)	277 (158–479)	0.21
Arginine	352 (137–755)	378 (253–638)	339 (137–755)	0.30
Asparagine	32 (14–87)	31 (22–47)	33 (14–87)	0.91
Citrulline	21 (10–43)	24 (10–43)	21 (12–36)	0.44
Glutamine	600 (425–892)	607 (484–892)	545 (425–753)	0.13
Isoleucine	29 (13–71)	29 (17–65)	29 (13–71)	0.91
Leucine	60 (25–166)	56 (25–139)	61 (34–166)	0.29
Ornithine	24 (12–88)	21 (12–35)	30 (12–88)	0.045
Valine	115 (78–261)	101 (82–202)	119 (78–261)	0.32

Data were reported in median (range).
P values assessed the differences in baseline characteristics between gender groups.
Unit of amino acid is μmol/L.
Reference intervals of age group: ≤30 days, 31 days-23.9 months, 2–17.9 yrs. and ≥18 yrs
Asn: 12–70;20–77;23–70;31–64. Gln: 240–1194;303–1459;405–923;428–747. Cit: 3–35;4–50;9–52;16–51. Arg: 14–135;30–147;38–122;43–407. Ala: 83–447;119–523;157–481;200–483. Val: 57–250;84–354;130–307;132–313. Iso: 12–92;10–109;33–97;34–98. Leu: 23–172;43–181;65–179;73–182. Orn: 29–168;19–139;33–103;27–83.

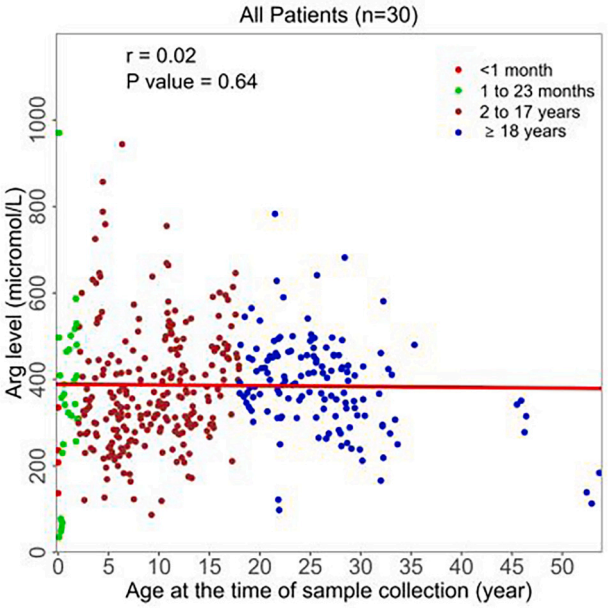

Fig. 2. Correlation of Arg and age at the time of sample collection. The overall correlation between Arg and age at the time of sample collection was weak and not significant. They were also not significant in each age group with correlation coefficient of 0.11, 0.04, and -0.02 in the group of 1 to 23 months, 2 to 17 years, and ≥ 18 years, respectively.

0.43; *p* values were 0.20, 0.87, and 0.34 for those in <1 month, 1 to 23 months, and 2 to 17 years, respectively, as compared to those in ≥18 years. The mean Arg level was lowest in the age group of <1 month (Table 2), but the difference compared to other age groups was not significant. The explanation could be a lack of power to observe a significant difference, with a low count of 4 test results (Fig. 3). One explanation could be that infants and toddlers are growing rapidly and may be utilizing more Arg for protein synthesis; for example, protein tolerance per kilogram for patients with phenylketonuria (PKU) is also the highest among this age group [7]. The age-related differences in the flux of ornithine-δ-aminotransferase (OAT) reaction in mammalian neonates versus adults could also be another explanation [8].

3.3. Correlations among amino acids

The median values and ranges of Arg and eight other amino acids at the first time of sample collection are shown in Table 1. The medians (ranges) of Arg were 352 (137–755) μmol/L, 378 (253–638) μmol/L, and 339 (137–755) μmol/L in all patients, females, and males, respectively. The distributions of Arg levels between females and males were not significant (*p* value = 0.30). All amino acids except Arg fell within the normal range. Of special note are the levels of the branched-chain amino acids (BCAAs), Leu, Iso and Val with median (range) of 60 (25–166) μmol/L, 29 (13–71) μmol/L, and 115 (78–261) μmol/L in all patients, respectively. BCAAs were not abnormally low in these patients, many of whom are likely to have been treated with sodium phenylbutyrate-containing medications to include glycerol phenylbutyrate.

We evaluated the correlations (r) between Arg levels and other eight amino acids levels that were measured over time (supplemental table S1). The most noteworthy positive correlation was between the plasma levels of Arg and Gln (supplemental table S2 and Fig. 4). The correlation coefficient was 0.45 (*p* value <0.001) in all patients. The correlation coefficients were similar in both males and females. Weaker correlations were seen between Arg and Cit ($r = 0.32$, *p* value <0.001) and Arg and Orn ($r = 0.22$, p value <0.001). A weak negative correlation ($r = -0.18$, *p* value <0.001) was seen between Arg and Orn and was driven entirely

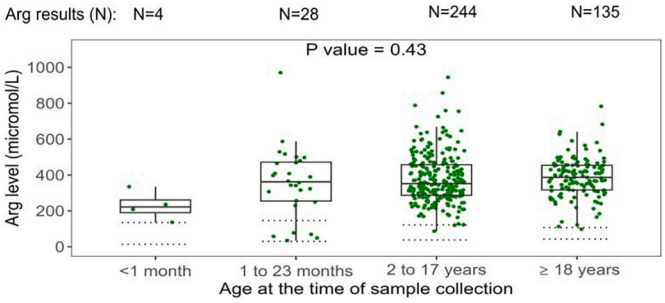

Fig. 3. Arg and age groups at the time of sample collection. Distribution of arginine of each age group, box and whisker plots to visualize the medians (the center lines in the boxes) and 4 quartiles (the boxes represent the interquartiles, and the whiskers are the lower and upper quartiles) of the data. Dotted line represents age specific reference intervals.

Table 2
Arginine levels according to age at the time of sample collection.

Age at the time of sample collection	Numbers of tests	Patient's Arginine median (range), μmol/L	Patient's Arginine mean (95% CI), μmol/L	Arginine reference intervals, μmol/L	Tests above normal range (%)	Fold elevation of Arginine*
<1 month old	4	222 (137–335)	229 (117–341)	14–135	4 (100)	1× - 2.5×
1–23 months old	28	362 (35–970)	357 (325–389)	30–147	23 (82)	0.2× - 6.6×
2–17 years old	244	352 (87–944)	379 (369–388)	38–122	241 (99)	0.7× - 7.7×
≥ 18 years old	135	387 (98–783)	387 (377–396)	43–107	134 (99)	0.9× - 7.3×

* Fold elevation was calculated by patient's Arginine level divided by the upper normal value of age-specific reference range.

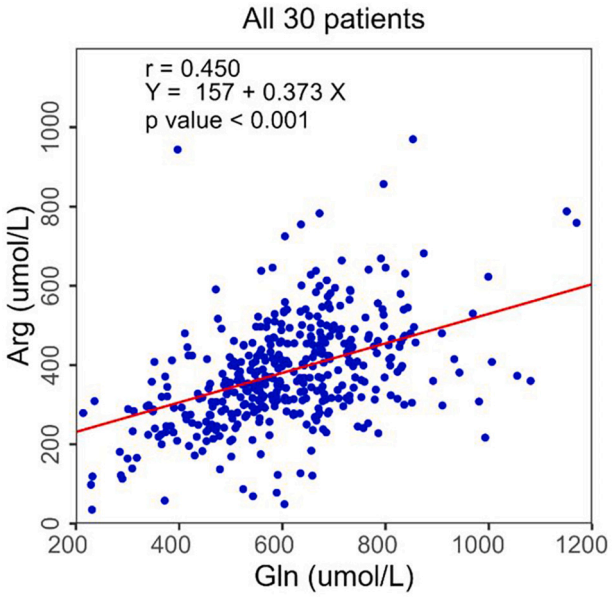

Fig. 4. Correlation over time between Arg and Gln repeated measurement. A positive correlation between Arg and Gln. The correlation coefficient was 0.45 (p value <0.001) in all patients.

by observations in males. We also estimated the change of Arg levels according to the change of the other eight amino acids by assessing the associations between Arg and each amino acid. The Arg levels were expected to increase 0.37 μmol/L (95% CI, 0.30–0.44; p value <0.001) per 1 μmol/L of Gln increase, 5.18 μmol/L (95% CI, 3.81–6.55; p value <0.001) per 1 μmol/L of Cit increase, and 3.28 μmol/L (95% CI, 2.07–4.48; p value <0.001) per 1 μmol/L of Orn increase, and were expected to decrease −0.35 μmol/L (95%, −0.51 - -0.18; p value <0.001) per 1 μmol/L of Ala increase after adjusting for baseline age, gender, and follow-up time (supplemental table S2).

4. Discussion

This is a retrospective descriptive study from single biochemical laboratory. The plasma amino acids results and diagnosis data were extracted from the Database of Quest Diagnostics, in which 82 arginase deficiency patients were identified. We analyzed data of comprehensive plasma amino acids results in 51 patients, including 30 individuals with >5 comprehensive amino acids measurements. The majority of samples (379/411 tests or 92%) were collected when patients were older than 2 years of age. This age distribution may be explained by the nature of reference laboratories where most samples were collected in an outpatient setting and patients' clinical and metabolic status were quite stable.

This study was undertaken to ascertain the plasma arginine levels in patients with arginase deficiency in patients seen and treated outside of specialized metabolic centers for the treatment of urea cycle disorders. Our hypothesis was that plasma arginine levels would have been as high or higher than the unacceptably high levels seen in those patients from specialized centers whose results have been reported in the literature [2,9,10]. The mean values were similar. The absence of specific patient data makes any further inferences difficult. However, patients who decline treatment are not usually monitored unless their symptoms change, and the patients in this study had frequent blood draws for plasma amino acid analysis (5 or more) for some periods of time. Thus, we can assume that the patients in this study were likely to receive treatment. We can conclude, however, that the standard treatment of diet and nitrogen scavenging agents is not adequate to bring arginine near the normal range, the minimum target for adequate patient care. Since the early 1980s, the role of arginine or a derivative in the clinical syndrome has been established and recent literature has confirmed this assertion [11].

The standard treatment for arginase deficiency is the same as for other urea cycle disorders, save for limiting, as opposed to supplementing arginine and/or citrulline intake. Whereas this standard treatment can maintain plasma ammonia levels in the normal range for this and other urea cycle disorders, we know that this is not true for the elevated metabolites in arginase deficiency nor for defects of the other cytosolic enzymes of the urea cycle, citrullinemia and argininosuccinic acidemia [12]. Like arginine, both citrulline and argininosuccinic acid (ASA) have defined metabolic roles outside of the urea cycle [12].

As shown here and previously reported, arginine levels in patients with arginase deficiency may be several times the upper limit of normal (Fig. 2 and Table 2). In ASA lyase deficiency, ASA in the brain appears to be pathogenic independent of ammonia elevations; similarly, arginine (or guanidino compounds derived from it [2]) appears to largely determine the neurotoxicity in arginase deficiency.

In each of these instances, physicians accustomed to the normalization of ammonia as the benchmark of successful treatment of urea cycle disorders may under-treat the accumulated metabolite levels, which are refractory. The positive correlation between plasma Arg and plasma Gln is significant in our patient cohort. Glutamine elevation is thought of as an important, albeit imperfect, surrogate marker for ammonia elevation. This arginine-glutamine correlation likely indicates that lesser control of arginine levels is associated with a clinically asymptomatic, or unappreciated ammonia elevation and a second neuropathic risk.

One can only wonder if the failure to observe diminished levels of branched-chain amino acids and positive correlation between plasma Arg and plasma Gln in our study are due to lesser doses of sodium phenylbutyrate-containing medications to include glycerol phenylbutyrate than are ordinarily used to lower ammonia.

Our study has several limitations including lacking clinical, dietary, and other treatment information, molecular genetic findings, and other laboratory results, such as ammonia, performed simultaneously with plasma amino acid analysis. Given these limitations, we cannot perform further analysis to identify individual contributing factors to the elevated arginine levels in our patient cohort.

In summary, our studies confirm that patients with arginase deficiency who are treated in any venue have levels of plasma arginine well above the upper limit of normal and which are associated with a suboptimal clinical outcome. Because we cannot normalize these levels with standard care, we must look forward to alternative approaches such as enzyme replacement therapy [13], gene therapy [14] and mRNA therapy [15].

Author contributions

PT,. YH., SDC., and DS. were involved in conception, study design, data collection, interpretation, and manuscript preparation and review. RS. was involved in data collection. JL. provided statistical analysis. PT. takes responsibility for the collection of data, the analyses, interpretation, and publication. All authors have given approval for publication of this manuscript.

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Ethics statement

This study involved retrospective analysis for secondary data use that were collected and analyzed without the 18 direct patient identifiers. This study was considered exempt by the Western Institutional Review Board, in accordance with 45 CFR §160 and §164, because no study participant provided specimens or information not already

existing as part of health care operations.

CRediT authorship contribution statement

Pranoot Tanpaiboon: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Yue Huang:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Judy Z. Louie:** Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Rajesh Sharma:** Data curation. **Stephen Cederbaum:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Denise Salazar:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

PT., JL. and DS., are employees of Quest Diagnostics. RS. was an employee of Quest Diagnostics. SDC. has been a consultant to Aeglea Biotherapeutics, a company that was developing an enzyme therapy for arginase deficiency. They were not aware of, nor did they support this effort. YH. is an advisory board member for Horizon Therapeutics. None of the authors have financial gain or loss from the results of this study.

Data availability

The authors do not have permission to share data.

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We thank Quest Diagnostics Bioinformatics team for data archiving.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2023.101042.

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