Newborn Screening for Arginase Deficiency in the U.S. – Where Do We Need to Go?

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Presented at the 2017 ACMG Annual Clinical Genetics Meeting – March 21-25, 2017 | Phoenix, Arizona

Background

- Arginase I deficiency is one of the least frequent urea cycle disorders
- Late-onset presentation usually results in irreversible neurological symptoms – loss of intellectual milestones, spasticity and mild liver dysfunction
- A strict dietary and pharmacologic regimen has been shown to reduce the plasma arginine level to normal or near normal levels
- Improvements can occur even in the presence of irreversible neurological damage
- Newborn screening is an available mechanism for detecting Arginase I deficiency
- Overlap between normal arginine levels in affected and unaffected newborns makes determining an optimal arginine cutoff level problematic
- Arginase deficiency is not a primary newborn screening target
- Until now, little data exist as to the case determination protocol and cutoff values for determining hyperargininemia risk among U.S. newborn screening programs
- The development of an effective screening algorithm is needed to make arginase I eligible for designation as a primary target for newborn screening

Methods

- A short questionnaire was emailed to state newborn screening laboratories and/or follow-up personnel identified as primary program contact persons
- The questions sought to assess the extent to which U.S. newborn screening programs include arginase I deficiency in their newborn screening and related screening information
- Included were questions regarding whether arginase deficiency screening was formally a part of the screening mandate, what and how laboratory data were assessed, follow-up processes, and case detection information
- All data were reviewed and summarized. A table of screening mandates and laboratory information was prepared and sent to all screening programs for validation
- Newborn screening data from California from 2010 to 2015 were analyzed to determine parameters that would have picked up all 9 cases diagnosed in this time period and have minimized the number of false positive results

Results of current practices

Is screening for hyperargininemia (ARG I deficiency) a part of the current screening panel?

- 51 U.S. jurisdictions were surveyed
- 34 jurisdictions reported that hyperargininemia is required as part of the screening panel
- 5 reported that hyperargininemia screening is not required but likely would be detected by the screening algorithm currently in use for other metabolic conditions
- One program reported that, while arginine levels were observable by the methodology in use, its observation was not reported since it is not included in the screening mandate

What analytical cutoffs are currently in use?

- All jurisdictions screening for hyperargininemia use arginine as the initial action indicator
- Cutoff levels varied and included values based on weight or age in some jurisdictions
- The range of arginine values considered actionable (requiring additional follow-up of any type) for babies <7 days of age varied from 20 µmol/L to 125 µmol/L
- The range of arginine values considered actionable for babies >7 days of age in programs requiring 2 specimens varied from 35 µmol/L to 130 µmol/L
- Several programs reported using the Arg/Orn ratio as a secondary discriminator; cutoff values varied from 0.45 to 1.5
- Other ratios in use included arginine/[leucine x phenylalanine] (Arg/[Leu x Phe]), arginine/alanine (Arg/Ala), arginine/phenylalanine (Arg/Phe), and citrulline/arginine (Cit/Arg)

What type of follow-up occurs?

- Most programs utilize two levels of follow-up: repeat specimen and clinical referral
- In some instances, any elevated arginine values are referred for clinical evaluation
- Most programs utilize academic medical centers for clinical follow-up

Table 1. Estimated screen positive rate for arginase deficiency based on alternative screening strategies (Data from California, 2015, N=486,591)

<table>
<thead>
<tr>
<th>Method</th>
<th>Arg</th>
<th>Arg/Orn</th>
<th>Arg/</th>
<th>Phe x Leu</th>
<th>Newborns requiring follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using specified cutoff concentration for Arg</td>
<td>33</td>
<td>2.18%</td>
<td>40</td>
<td>1.39%</td>
<td>50</td>
</tr>
<tr>
<td>Using specified cutoff for Arg and indicated ratio cutoff(s)</td>
<td>30</td>
<td>0.45%</td>
<td>35</td>
<td>0.6%</td>
<td>50</td>
</tr>
<tr>
<td>Using R4S Tool Runner</td>
<td>Proprietary</td>
<td>not available</td>
<td>0.0006%</td>
<td>&lt; 0.005%</td>
<td></td>
</tr>
</tbody>
</table>

Arg = arginine; Orn = ornithine; Phe = phenylalanine; Leu = leucine; R4S = Region 4 Stork international MS/MS database.

Arginase I-deficient patients in CA 2010-2015

- 9 individuals with arginase 1-deficiency were diagnosed in CA during this time
- No cases were known to be missed (reportable disorder)
- Using an arginine cutoff level of 50 and a ratio of arginine to ornithine of 1.4, all 9 cases would have been ascertained
- Using the Massachusetts arginine cutoff level of 60 and the ratio of arginine to leucine x isoleucine of >0.0006 all 9 cases would have been ascertained
- The 9 individuals were also ascertained using the online R4S Toolrunner and the recall rate would have been <0.005%
- The recall rate in California was <0.01%

Conclusions

- Ideally, newborn screening should be uniform across jurisdictions with a very low (or zero) false negative rate and a low screen positive (recall) rate
- Currently in the U.S., screening practices vary widely across states, with little documented scientific evidence for the variations
- We show that using a low cutoff for arginine and ratios of arginine to other amino acids, in this case arginine to leucine x phenylalanine, patients with arginase 1 deficiency can be distinguished from those unaffected, with a very high degree of sensitivity and specificity
- With this high degree of specificity arginase 1 deficiency is an excellent candidate to become part of the recommended newborn screening panel despite its low prevalence

Prevalence from the literature

- Evidence is limited
- 1/250,000 live births in Northern Portugal
- >1/1,300,000 births worldwide
- True prevalence is unknown but arginase I deficiency is one of the least common of the urea cycle disorders

Support

Creative support was provided by Peloton Advantage, LLC, and was funded by Aeglea BioTherapeutics, Inc.

Disclosures

SC, BT and DL are consultants to Aeglea BioTherapeutics, Inc. MG is an employee of Aeglea BioTherapeutics, Inc.