Epilepsy in argininosuccinic aciduria: natural history and perspectives

Authors: Nour Elkhateeb¹, Stephanie Grunewald¹, Andrew Morris², Thomas Hartley², Laura Crowther², Maureen Cleary³; Karolina Stepień³; Helen Mundy⁴; Anupam Chakrapani⁵; Robin Lachmann⁵; Elaine Murphy⁵; Saikat Santra⁶; Mari-Liis Ududelepp⁷; Mildrid Yeo¹; Philippa Mills⁸; Paul Gissen¹,⁷; Julien Baruteau¹,⁷.

1 Great Ormond Street Hospital for Children NHS Trust, London, UK
2 Willink Unit, Manchester Centre for Genomic Medicine, Manchester, UK.
3 Mark Holland Metabolic Unit, Adult Inherited Metabolic Diseases Department, Salford Royal NHS Foundation Trust, Salford, UK.
4 Evelina London Children’s Hospital; St Thomas’s Hospital, London, UK.
5 Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.
6 Clinical IMD, Birmingham Children’s Hospital, Birmingham, UK
7 Great Ormond Street Institute of Child Health, London, UK

Background

Argininosuccinic aciduria (ASA) (OMIM#207900) is an autosomal recessive urea cycle disorder caused by argininosuccinate lyase (ASL) deficiency, a cytosolic enzyme converting argininosuccinic acid into arginine and fumarate (1). This is an essential reaction in ammonia detoxification through urea cycle and also for arginine synthesis (2) (Fig 1).

ASL deficiency leads to accumulation of argininosuccinic acid in tissues, and excretion of argininosuccinic acid in urine (1). In addition, it results in decreased synthesis of arginine which is essential for synthesis of creatine, glutamate, proline, nitric oxide (NO), polyamines and agmatine. (1) (3) (fig 2). NO deficiency, agmatine deficiency and high guanidinoacetate have been hypothesized to have a role in the pathophysiology of ASA (4).

Patients can present either with an early neonatal-onset phenotype with acute hyperammonaemia and neonatal encephalopathy, or with a heterogeneous late-onset phenotypic spectrum with chronic neurological, cognitive, gastrointestinal and hepatic symptoms with or without intercurrent episodes of acute hyperammonaemia (1) (2). Epilepsy has been reported to be common among patients with ASA, with two phenotypes of seizure disorders in patients with ASA. The first is acute symptomatic seizures associated with acute hyperammonaemia, and late onset epilepsy which is not linked hyperammonaemia (5). Herein, we present the natural history and severity of epilepsy, frequently observed in ASA, and correlation with biochemical and electroencephalographic data.

Fig. 1: Role of ASL in urea cycle. ASL converts argininosuccinic acid into arginine and fumarate, an essential step in urea cycle (6).

Fig. 2: Metabolic fates of Arginine. Arginine is essential for synthesis of essential for synthesis of creatine, glutamate, proline, nitric oxide (NO), polyamines and agmatine (6).
Results

Clinical Features:
This study included 18 patients with ASA and epilepsy, with median age 16 yrs (range 47 mo - 28 yrs). Twelve patients were males and 6 were females. Twelve patients had early onset ASA while 6 patients had late onset ASA. Median age at onset of symptoms of ASA was 0.4 months (range: 1 day– 12 months) while median age at diagnosis was 1.75 months (range: 2 days– 216 months).

Clinical characteristics of epilepsy
All patients in the study presented with epilepsy. Median age at onset of epilepsy was 19.5 months (range 3.5-192 months). Four patients had neonatal seizures during initial hyperammonaemia decompensation. Seizure types were highly variable (Fig 3). Multiple seizure types were common (n=14). Six patients had status epilepticus. Fourteen patients required treatment with antiepileptic drugs (AEDs). Twelve patients continue to require AEDs for management of epilepsy. Number of AEDs in the study patients are shown in figure 4. One patient required use of vagal nerve stimulation for epilepsy control, which was initiated at the age of 8.5 years. Epilepsy control is shown in figure 5.

Additional neurological features
All studied patients presented with variable degrees of intellectual disability and learning difficulties. Additional neurological features are shown in figure 6.
Non-neurological characteristics
Transaminitis was the most common feature (n=11), followed by hepatomegaly (n=8). Tubulopathy & hyperkalemia was seen in 3 patients, while hair changes and gall bladder polyps were seen in 2 patients each.

Neuroimaging characteristics
Brain MRI was performed in 9 (50%) patients. The most common abnormalities included cerebral white matter changes (n=4), and cerebral atrophy (n=2). Multiple bilateral hemisphere infarcts (in non-vascular territories) (n=1), cerebellar atrophy (n=1), bilateral subtle signal abnormality within the basal ganglia structures (n=1). No neuroimaging abnormality was seen in 3 patients.

Electroencephalographic features
Electroencephalography was done in 15 (83.33%) patients. Electroencephalographic features are shown in table 1. Focal epileptic discharges were central (n=5), temporal (n=4), frontal (n=2), occipital (n=1), parietal (n=1), bilateral multifocal (n=1) and unilateral Electrical status epilepticus during slow-wave sleep (ESES) in 1 patient.

Biochemical profile:
Mean plasma ammonia for patients after the neonatal period/initial metabolic decompensation was 53.76 umol/L (range 22-190 umol/L). Mean plasma glutamine was 678.05 umol/L (range 481-964 umol/L) and mean plasma arginine was 76.65 umol/L (range 29-139 umol/L). Mean plasma argininosuccinate was 248.51 umol/L (range 30-489.96).

Table 1: EEG features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Count (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized background slowing</td>
<td>8 (44.44%)</td>
</tr>
<tr>
<td>Focal background slowing</td>
<td>5 (27.78%)</td>
</tr>
<tr>
<td>Temporal slowing</td>
<td>5 (27.78%)</td>
</tr>
<tr>
<td>Temporo-occipital slowing</td>
<td>2 (13.33%)</td>
</tr>
<tr>
<td>Background asymmetry</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Inter-ictal epileptogenic activity</td>
<td>11 (61.11%)</td>
</tr>
<tr>
<td>Focal discharges</td>
<td>10 (66.67%)</td>
</tr>
<tr>
<td>Generalized discharges</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>photo-paroxysmal discharges</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Eye closure sensitivity</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Paroxysmal response during hyperventilation</td>
<td>1 (6.67%)</td>
</tr>
<tr>
<td>Scotosensitive discharge</td>
<td>1 (6.67%)</td>
</tr>
</tbody>
</table>
ASA treatment data
Seventeen (94.4%) patients were on protein restricted diet. Nine (50%) patients were on sodium benzoate with a median dose 188 mg/kg/day (range 41-275). Five patients were on sodium phenylbutyrate with a median dose 230 mg/kg/day (range 126-250). Two patients were on glycine phenylbutyrate (dose 198 and 438 mg/kg/day each). All patients were on arginine treatment with a median dose 124 mg/kg/day (range 52.8-300) (Figure 8).

Comparison data between early and late onset ASA groups:
Subgroup comparisons between patients with early onset ASA and late onset ASA groups were performed (by Fisher's exact test and Mann-Whitney U Test). There was no significant difference between both groups as regards age at onset of epilepsy, seizure type, requirement of treatment with AEDs, number of AEDs used, seizure control, EEG characteristics, presence or absence of neuroimaging abnormality, mean plasma ammonia, glutamine and arginine, requirement and dose of ammonia scavengers.

Patients in the early onset ASA group were diagnosed at a younger age and had higher mean plasma arginosuccinic acid compared to the other group (table 2).

Correlation between clinical features with biological markers
There was a positive correlation (by Spearman test) between age at onset of epilepsy and mean plasma arginine and plasma ASA in the study patients. Epilepsy severity scores did not show a significant correlation with biochemical markers (table 3).

Table 2: Comparison data between early and late onset ASA groups

<table>
<thead>
<tr>
<th></th>
<th>Early onset ASA (no=12)</th>
<th>Late onset ASA (no=6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis of ASA (months)</td>
<td>0.275 (0.067 – 9)</td>
<td>25.5 (3-216)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean plasma ASA (umol/L)</td>
<td>303.63 (129.59)</td>
<td>127.25 (55.77)</td>
<td>0.0232</td>
</tr>
</tbody>
</table>

Table 3: Correlation between clinical features with biological markers

<table>
<thead>
<tr>
<th></th>
<th>Plasma ammonia</th>
<th>Plasma glutamine</th>
<th>Plasma arginine</th>
<th>Plasma ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of postnatal seizures</td>
<td>0.30299</td>
<td>0.28321</td>
<td>0.02309</td>
<td>0.0063</td>
</tr>
<tr>
<td>Number of AEDs</td>
<td>0.18326</td>
<td>0.92576</td>
<td>0.19299</td>
<td>0.35772</td>
</tr>
<tr>
<td>Shalfont seizure severity scale</td>
<td>0.38489</td>
<td>0.76928</td>
<td>0.05133</td>
<td>0.72118</td>
</tr>
<tr>
<td>Modified grand total EEG score</td>
<td>0.62861</td>
<td>0.91486</td>
<td>0.81663</td>
<td>0.98577</td>
</tr>
</tbody>
</table>
Discussion
This study describes a group of patients with ASA and epilepsy, including paediatric and adult patients both with early and late onset ASA.

Polymorphic semiology was seen and patients presenting with multiple seizure types were common yet with a favourable therapeutic response, similar to previous reports (5).

Our data show that abnormal background EEG and epileptogenic activity were common (44% and 61% respectively), which is similar to previous reports (5,7).

Plasma ASA levels were higher in early-onset compared to late-onset, consistent with previous reports (4). There was no difference between mean plasma ammonia between both groups, unlike previous reports (4).

Lower plasma arginine and lower plasma ASA were associated with a later age at onset of epilepsy. This suggests that NO deficiency has a role in epileptogenesis in ASA patients. It was suggested that NO supplementation in mice has improved abnormal electrophysiology (8). Epilepsy severity scores did not correlate with the biochemical markers.

Our results also suggest that hyperammonemia and ASA levels are not the dominant factors causing epileptogenesis in ASA patients, supporting data from previous reports (4,5).

Conclusions
Epilepsy in ASA is common with polymorphic semiology, frequent abnormal background EEG and favourable therapeutic response to antiepileptic drugs in most patients.

No predictive factor of severity was identified suggesting that the cause of epilepsy in ASA is independent of impaired ureagenesis. Lower plasma arginine and lower plasma ASA were associated with a later age at onset of epilepsy.

References