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Epilepsia®

RESEARCH ARTICLE

Natural history of epilepsy in argininosuccinic aciduria provides new insights into pathophysiology: A retrospective international study

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Abstract

Objective: Argininosuccinate lyase (ASL) is integral to the urea cycle, which enables nitrogen wasting and biosynthesis of arginine, a precursor of nitric oxide. Inherited ASL deficiency causes argininosuccinic aciduria, the second most common urea cycle defect and an inherited model of systemic nitric oxide deficiency. Patients present with developmental delay, epilepsy, and movement disorder. Here we aim to characterize epilepsy, a common and neurodebilitating comorbidity in argininosuccinic aciduria.

Methods: We conducted a retrospective study in seven tertiary metabolic centers in the UK, Italy, and Canada from 2020 to 2022, to assess the phenotype of

epilepsy in argininosuccinic aciduria and correlate it with clinical, biochemical, radiological, and electroencephalographic data.

Results: Thirty-seven patients, 1–31 years of age, were included. Twenty-two patients (60%) presented with epilepsy. The median age at epilepsy onset was 24 months. Generalized tonic-clonic and focal seizures were most common in early-onset patients, whereas atypical absences were predominant in late-onset patients. Seventeen patients (77%) required antiseizure medications and six (27%) had pharmacoresistant epilepsy. Patients with epilepsy presented with a severe neurodebilitating disease with higher rates of speech delay ($p = .04$) and autism spectrum disorders ($p = .01$) and more frequent arginine supplementation ($p = .01$) compared to patients without epilepsy. Neonatal seizures were not associated with a higher risk of developing epilepsy. Biomarkers of ureagenesis did not differ between epileptic and non-epileptic patients. Epilepsy onset in early infancy ($p = .05$) and electroencephalographic background asymmetry ($p = .0007$) were significant predictors of partially controlled or refractory epilepsy.

Significance: Epilepsy in argininosuccinic aciduria is frequent, polymorphic, and associated with more frequent neurodevelopmental comorbidities. We identified prognostic factors for pharmacoresistance in epilepsy. This study does not support defective ureagenesis as prominent in the pathophysiology of epilepsy but suggests a role of central dopamine deficiency. A role of arginine in epileptogenesis was not supported and warrants further studies to assess the potential arginine neurotoxicity in argininosuccinic aciduria.

KEYWORDS

ammonia, arginine, argininosuccinate lyase, argininosuccinic aciduria, epilepsy, nitric oxide, urea cycle

1 | INTRODUCTION

Argininosuccinate lyase (ASL) is the only enzyme in mammals enabling endogenous arginine synthesis.[1] This cytosolic enzyme, which breaks down argininosuccinic acid into arginine and fumarate, is integral to the citrulline-nitric oxide (NO) cycle, which enables NO synthesis from arginine, and the urea cycle, a liver-based pathway enabling nitrogen wasting through clearance of neurotoxic ammonia.[1] ASL deficiency causes argininosuccinic aciduria (ASA) (OMIM#207900), an autosomal recessive metabolic disease and the second most common urea cycle disorder with a prevalence of one in 110 000 live births.[2] Patients present acute hyperammonemia either in the neonatal period defined as early-onset phenotype, or later in life in late-onset presentation.[3] Most patients will present a multisystemic phenotype with chronic neurological, hepatic, and gastrointestinal conditions, and anemia and high blood pressure.[4] The neurological phenotype entails intellectual and motor disability, behavioral changes, and epilepsy, which can occur in the absence

Key points

- Epilepsy in argininosuccinic aciduria (ASA) is frequent, polymorphic, occurring in early childhood, and associated with a more severe neurodevelopmental phenotype.
- Early-onset epilepsy and electroencephalographic background asymmetry are prognostic for pharmacoresistance of epilepsy in ASA.
- There is no correlation between hyperammonaemia and other biomarkers of the ureagenesis defect and epilepsy, suggesting that hyperammonaemia is not the primary pathophysiological mechanism for epileptogenesis in ASA.
- Visual-related electroencephalography (EEG) findings and poor response to vagus nerve stimulation suggest that central dopamine deficiency plays a role in pathophysiology of epilepsy in ASA.

of hyperammonemia. The pathophysiological role of hyperammonemia, argininosuccinate toxicity,[5] and deficiency of arginine and downstream metabolites (i.e., creatine and polyamines)[2] has been proposed to account for the neurological phenotype in ASA. However novel pathophysiological insights have highlighted the role of reversible neuronal nitro-oxidative stress[6] and central catecholamine deficiency caused by NO deficiency.[7,8] The standard of care in ASA relies on ammonia control using a protein-restricted diet, ammonia scavengers, and arginine supplementation (which promotes nitrogen waste through the urea cycle),[9,10] with an increasing number of patients treated by liver transplantation.[11]

Epilepsy is a common comorbidity in ASA, which is thought to affect 40% of patients.[4] The notion that seizures are a consequence of acute hyperammonemia episodes is not supported by the evidence that patients with epilepsy usually have well-controlled ammonia levels.[4,12] Recently, a mouse model of ASL deficiency showed increased firing rate in ASL-deficient dopaminergic neurons and a lower epileptic threshold, the latter corrected by NO supplementation, highlighting the role of central catecholamine biosynthesis and its regulation by NO in the epileptogenesis of ASA.[7]

Herein we present an international multicenter retrospective study assessing the phenotype of epilepsy in ASA, its severity and correlation with age at onset of the disease, and biochemical and electroencephalographic data. We show that the seizures in ASA are frequent and polymorphic, and they can be severe. We describe an increased rate of neurodevelopmental comorbidities in patients with epilepsy, and we identify prognostic markers of epileptic severity in this population. Age at onset of hyperammonemia, related biomarkers, and therapies are not predictors for epilepsy onset and severity. Our study does not support defective ureagenesis having a prominent role in the pathophysiology of epilepsy but supports the pathophysiological role of central dopamine deficiency and raises questions around a potential neurotoxic role of arginine.

2 | PATIENTS AND METHODS

We conducted a retrospective study in seven pediatric and adult tertiary metabolic centers in the UK, Italy, and Canada. Epidemiological, clinical, biochemical, radiological, and electroencephalographic data of ASA patients with neurological disease and/or epilepsy were collected between July 2020 and June 2022.

Clinical data included epilepsy characteristics and treatment, and neurological and non-neurological characteristics, which were collected from patients' notes retrospectively. Early-onset ASA was defined as hyperammonemia occurring on or before 28 days of age, and late-onset ASA after 28 days of age.

Seizure types were classified according to the International League Against Epilepsy (ILAE) 2017 operational classification of seizure types.[13] Epilepsy was defined according to the ILAE 2014 guidelines[14] by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) Diagnosis of an epilepsy syndrome. Epilepsy syndromes were defined according to the ILAE 2017 classification of the epilepsies[15] as a cluster of features incorporating seizure types, electroencephalography (EEG), and imaging features that tend to occur together. Pharmacoresponsive epilepsy was defined as sustained seizure freedom on one or two tolerated and appropriately chosen and used ASM schedules, with seizure freedom for a minimum of three times the longest pre-treatment inter-seizure interval, or 12 months, whichever is longer. Pharmacoresistant epilepsy was defined as a failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[16] Within the pharmacoresistant epilepsy group, partial seizure control was described as a decrease of 50% or more in seizure frequency but without a complete seizure freedom after treatment. Refractory seizures were described as a less than 50% decrease in seizure frequency after treatment.

Biochemical data included the mean values of plasma ammonia, glutamine, arginine, and argininosuccinic acid measured serially on regular follow-up visits for each patient during compensated metabolic state and were collected from patients' notes retrospectively. Biochemical results during the initial hyperammonemia decompensation, subsequent hyperammonemia episodes, and after liver transplantation were not included. Radiological data included computed tomography/magnetic resonance imaging (CT/MRI) of the brain. Electroencephalographic data included data from standard EEG or EEG telemetry that were collected from patients' EEG reports retrospectively without secondary analysis. Treatment data included natural protein intake, ammonia scavengers, and epilepsy treatment.

Visual-related EEG abnormalities included photoparoxysmal responses (PRRs) on photic stimulation (an activation procedure), eye closure sensitivity (which describes transient epileptic abnormalities following eye closure and represents the physiological loco-regional differentiation and maturation of brain electrical activity),

and scotosensitive discharge elicited by darkness. Epilepsy severity was assessed by U.S. Department of Veterans Affairs (VA) Seizure Type and Frequency Rating Scale (as revised for VA-2),[17] Chalfont Seizure Severity Scale,[18] modified Grand Total EEG,[19] and 2HELPS2B scores.[20]

2.1 | Statistical analysis

Statistical analysis was performed using Prism 9.0 software (San Diego, CA, USA). Differences between groups were assessed using a two-tailed Mann–Whitney *U* test between two groups of quantitative variables, Kruskal–Wallis H test between more than two groups of quantitative variables, and a two-tailed Fisher's exact test for categorical data. *p* Values ≤.05 were considered statistically significant. Correlation between continuous variables was assessed by Spearman's rank correlation test.

3 | RESULTS

Demographics and clinical features are summarized in Tables 1 and 2. Biochemical features are summarized in Table 2 with an exhaustive data set in Table S1.

3.1 | Demographic and clinical characteristics

Thirty-seven patients were included with a median age of 12 years (range: 15 months to 31 years) and a sex ratio male/female of 21/16. Twenty-five patients (67%) had early-onset ASA. The median age at onset of ASA symptoms was 10 days (range: 1 day to 24 months). The median age at diagnosis was 15 days (range 1 day to 18 years) (Table 1). Diagnosis of ASA was obtained biochemically in all patients and was confirmed molecularly in seven patients.

3.2 | Clinical characteristics of epilepsy

This study included 22 ASA patients with epilepsy (60%), with a median age of 16 years (range: 3.5–31 years) and a sex ratio male/female of 15/7. Fourteen patients (64%) had early-onset ASA. The median age at onset of ASA symptoms was 10 days (range: 1 day to 12 months), whereas the median age at diagnosis of ASA was 15 days (range: 1 day to 18 years). The median age at onset of epilepsy was 24 months (range: 3.5 months to 16 years). Epilepsy onset preceded ASA diagnosis in four of eight patients with late-onset epilepsy. Seven patients (32%) with epilepsy had symptomatic seizures during neonatal hyperammonemia (Table 1).

Seizure types were highly variable. The most common types were generalized tonic-clonic ($n=15$, 68%), focal ($n=13$, 59%) seizures, and atypical absences ($n=13$, 59%). Multiple seizure types were commonly present ($n=18$, 82%). These were either concurrent or evolving from one type to another. One patient presented with epileptic spasms at 7 months that evolved subsequently to atypical absence seizures. This patient was identified to have West syndrome with hypsarrhythmia on EEG and developmental stagnation. Six patients (27%) presented status epilepticus. Median age at onset of the first episode of status epilepticus was 36 months (range 9–12 years). The main trigger of status epilepticus was febrile intercurrent illnesses with associated hyperammonaemic decompensation (Table 1).

Seventeen patients (77%) required anti-seizure medications (ASMs). ASMs were tapered and stopped completely in two patients. Five patients (23%) had very infrequent seizure episodes and were not started on ASMs. The number of ASMs currently administered was 1 ($n=10$; 59%), 2 ($n=4$; 24%), or 3 ($n=1$; 6%). One patient required vagus nerve stimulation for epilepsy control, which was initiated at the age of 8.5 years, with initial favorable response for 2 years followed by recurrence of refractory seizures. ASMs enabled sustained seizure freedom in nine patients (41%), whereas seizures were pharmacoresistant in six patients (27%) patients partial seizure control in five patients (23%) and refractory seizures in one patient (Table 1). The patient with epileptic spasms was treated with vigabatrin with initial good seizure control, and topiramate was added for breakthrough seizures. Seizures then recurred frequently and were pharmacoresistant to phenobarbital and valproic acid. Vigabatrin and topiramate were weaned off after seizures evolved to atypical absence seizures. Ethosuximide was subsequently added with good seizure control.

3.3 | Additional neurological features in ASA epileptic patients

Twenty-one patients (95%) presented with variable degrees of intellectual disability and learning difficulties. Speech delay was seen in 20 patients (91%), motor delay in 13 patients (59%), and behavioral disorders in 12 patients (55%). Autistic features were seen in 11 patients (50%) and a formal diagnosis of autistic spectrum disorder was made in 9 patients (41%). Ataxia was seen in eight patients (36%), whereas movement disorders were seen in six patients (27%) (Table 2).

TABLE 1 Epidemiological and clinical characteristics of recruited ASA patients. Comparison of patients with and without epilepsy and with early- and late-onset ASA.

	Early-onset ASA with epilepsy (n = 14)	Late-onset ASA with epilepsy (n = 8)	*p* value[a]	ASA with epilepsy (n = 22)	ASA without epilepsy (n = 15)	*p* value[b]	Study population (no = 37)
Demographic data							
Male *n* (%)	10 (71.4%)	5 (62.6%)	.19	15 (68.2%)	6 (40%)	.11	21 (56.8%)
Current age (months) median (range)	196.5 (86–371)	130 (42–336)	.5	192 (42–371)	134 (15–289)	.4	144 (15–371)
Clinical data							
Early onset ASA *n* (%)	14 (100%)	0	N/A	14 (63.64%)	13 (86.7%)	.2	25 (67.6%)
Age at onset of symptoms of ASA (months) median (range)	0.2 (0.03–0.5)	5.6 (2–12)	**.0007**	0.3 (0.03–12)	0.2 (0.07–24)	.4	0.3 (0.03–24)
Age at diagnosis of ASA (months) median (range)	0.3 (0.05–9)	15 (3–216)	**.0005**	0.5 (0.05–216)	0.25 (0.03–59)	.1	0.5 (0.03–216)
Clinical characteristics of epilepsy							
Age at onset of epilepsy (months) Median (range)	36 (9–191.7)	13.5 (3.5–9)	.06	24 (3.5–191.7)	N/A	N/A	N/A
Neonatal seizures *n* (%)	7 (50%)	0	**.02**	7 (31.8%)	2 (13.3%)	.3	9 (24.3%)
Seizure type *n* (%)							
Generalized tonic-clonic	11 (78.6%)	4 (50%)	.3	15 (68.2%)	N/A	N/A	N/A
Focal	9 (64.3%)	4 (50%)	.7	13 (59.1%)	N/A	N/A	N/A
Atypical absence	6 (42.9%)	7 (87.5%)	.07	13 (59.1%)	N/A	N/A	N/A
Myoclonic and myoclonic astatic	0	4 (50%)	**.0096**	4 (18.2%)	N/A	N/A	N/A
Epileptic spasms[c]	0	1 (12.5%)	.4	1 (4.6%)	N/A	N/A	N/A
Tonic	0	1 (12.5%)	.4	1 (4.6%)	N/A	N/A	N/A
Multiple seizure types *n* (%)	11 (78.6%)	7 (87.5%)	1	18 (81.8%)	N/A	N/A	N/A
Status epilepticus *n* (%)	4 (28.6%)	2 (25%)	1	6 (27.3%)	N/A	N/A	N/A

(Continues)

TABLE 1 (Continued)

	Early-onset ASA with epilepsy (n = 14)	Late-onset ASA with epilepsy (n = 8)	*p* value[a]	ASA with epilepsy (n = 22)	ASA without epilepsy (n = 15)	*p* value[b]	Study population (no = 37)
Age at first episode of status epilepticus (months) median (range)	36 (9–140)	58.5 (14–103)	.4	36 (9–140)	N/A	N/A	N/A
Epilepsy treatment data *n* (%)							
Treatment with ASMs	10 (71.4%)	7 (87.5%)	.6	17 (77.3%)	N/A	N/A	N/A
Treatment with ASMs (current)	9 (64.3%)	6 (75%)	1	15 (68.2%)	N/A	N/A	N/A
Seizure control							
Pharmacoresponsive	6 (42.9%)	3 (37.5%)	.7	9 (40.9%)	N/A	N/A	N/A
Pharmacoresistant	3 (21.4%)	3 (37.5%)		6 (27.3%)	N/A		N/A
Not on ASMs	5 (35.7%)	2 (25%)		7 (31.8%)	N/A		N/A
VNS	0	1 (12.5%)		1 (4.6%)	N/A		N/A
EEG characteristics *n* (%)							
Visual-related EEG abnormalities	4/12 (33.3%)	3/7 (42.9%)	1	7/19 (36.8%)	N/A	N/A	N/A
Epilepsy and EEG severity scores mean (SD)							
VA-2 seizure severity score	33 (32.5)	1904.2 (4936.4)	.4	713.5 (3110)	N/A	N/A	N/A
Chalfont Seizure Severity scale	56.4 (28.3)	68 (82.3)	.4	60.6 (54.8)	N/A	N/A	N/A
Modified Grand Total EEG score (0–54)	11.34 (5)	15.1 (6.26)	.5	12.7 (5.8)	N/A	N/A	N/A
2HELPS2B score (0–7)	2.1 (1–4)	2 (2–3.2)	.9	2 (1–4)	N/A	N/A	N/A

Note: Bold values highlight statistically significant results.

Abbreviations: ASA, argininosucinic aciduria; ASM, anti-seizure medication; SD, standard deviation.

[a]*p* value represents the comparison between early and late ASA patients with epilepsy.

[b]*p* value represents the comparison between patients with epilepsy and without.

[c]This patient has a paternally inherited *CACNA1A* variant of uncertain significance (VUS), which could be contributing to the epilepsy phenotype. Seizures preceded the onset of initial ASA decompensation.

TABLE 2 Clinical and biochemical characteristics of recruited ASA patients. Comparison of patients with and without epilepsy and with early- and late-onset ASA.

	Early-onset ASA with epilepsy (n = 14)	Late-onset ASA with epilepsy (n = 8)	*p* value[a]	ASA with epilepsy (n = 22)	ASA without epilepsy (n = 15)	*p* value[b]	Study population (n = 37)
Neurological abnormalities *n* (%)							
Motor delay	7 (50%)	6 (75%)	.4	13 (59.1%)	5 (33.3%)	.2	18 (48.7%)
Intellectual disability/ learning difficulties	13 (92.86%)	8 (100%)	1	21 (95.5%)	11 (73.3%)	.1	32 (86.5%)
Speech delay	13 (92.86%)	7 (87.5%)	1	20 (90.9%)	9 (60%)	**.04**	29 (78.4%)
Autistic spectrum disorder/ autistic traits	6 (42.86%)	5 (62.5%)	.7	11 (50%)	1 (6.7%)	**.01**	12 (32.4%)
Behavioral disorder	7 (50%)	5 (62.5%)	.7	12 (54.6%)	4 (26.7%)	.2	16 (43.2%)
Movement disorder	4 (28.57%)	2 (25%)	1	6 (27.3%)	3 (20%)	.7	9 (24.3%)
Ataxia	4 (28.57%)	4 (50%)	.4	8 (36.4%)	1 (6.7%)	.06	9 (24.3%)
Biomarkers mean (SD)							
Mean plasma ammonia (μmol/L)	54 (44)	38 (14)	.7	48 (38)	43 (41)	.4	46 (39)
Mean plasma glutamine (μmol/L)	712 (120)	675 (141)	.4	699 (130)	762 (137)	.3	724 (136)
Mean plasma arginine (μmol/L)	88 (31)	51 (20)	**.009**	74 (33)	83 (26)	.4	78 (30)
Mean plasma argininosuccinic acid (μmol/L)	325 (105)	120 (49)	**.0009**	253 (133)	306 (167)	.4	275 (150)
ASA management *n* (%)							
Protein restriction	12 (85.7%)	7 (87.5%)	1	19 (86.4%)	9 (60%)	.1	28 (75.7%)
Nitrogen scavengers							
Sodium benzoate	8 (57.1%)	3 (37.5%)	.7	11 (50%)	6 (40%)	.7	17 (45.9%)
Sodium phenylbutyrate	4 (28.6%)	1 (12.5%)	.6	5 (22.7%)	1 (6.7%)	.4	6 (16.2%)
Glycine phenylbutyrate	4 (28.6%)	0	.3	4 (18.2%)	3 (20%)	1	7 (18.9%)
Arginine	13 (92.9%)	8 (100%)	1	21 (95.5%)	9 (60%)	**.01**	30 (81.1%)

Note: Reference ranges: plasma ammonia: 0–40 μmol/L, plasma glutamine: 480–800 μmol/L, plasma arginine: 40–120 μmol/L, plasma ASA: 0–5 μmol/L. Bold values highlight statistically significant results.

Abbreviations: ASA, argininosucinic aciduria; ASM, anti-seizure medication; SD, standard deviation.

[a]*p* value represents the comparison between early and late ASA patients with epilepsy.

[b]*p* value represents the comparison between patients with epilepsy and without.

3.4 | Neuroimaging characteristics in ASA epileptic patients

Brain MRI was performed in 13 patients (59%). Neuroimaging abnormalities were seen in 8 of 13 (62%). The most common abnormalities included cerebral white matter changes ($n = 4$), cerebral atrophy ($n = 2$) and basal ganglia abnormalities ($n = 2$), multiple bilateral hemisphere infarcts crossing arterial territories ($n = 1$), and cerebellar atrophy ($n = 1$) (Figure 1). Neuroimaging was normal in five patients (38%) (Table S1).

3.5 | Electroencephalographic characteristics in ASA epileptic patients

Electroencephalography was performed in 19 patients (86%). Generalized background slowing was seen in 12 patients (63%). Focal background slowing was seen in seven patients (32%), predominantly in the temporal ($n = 4$) and occipital ($n = 3$) regions. Background asymmetry was noted in eight patients (42%). Inter-ictal epileptogenic activity was detected in 15 patients (79%), with focal discharges ($n = 13$, 68%), generalized discharges ($n = 4$, 21%),

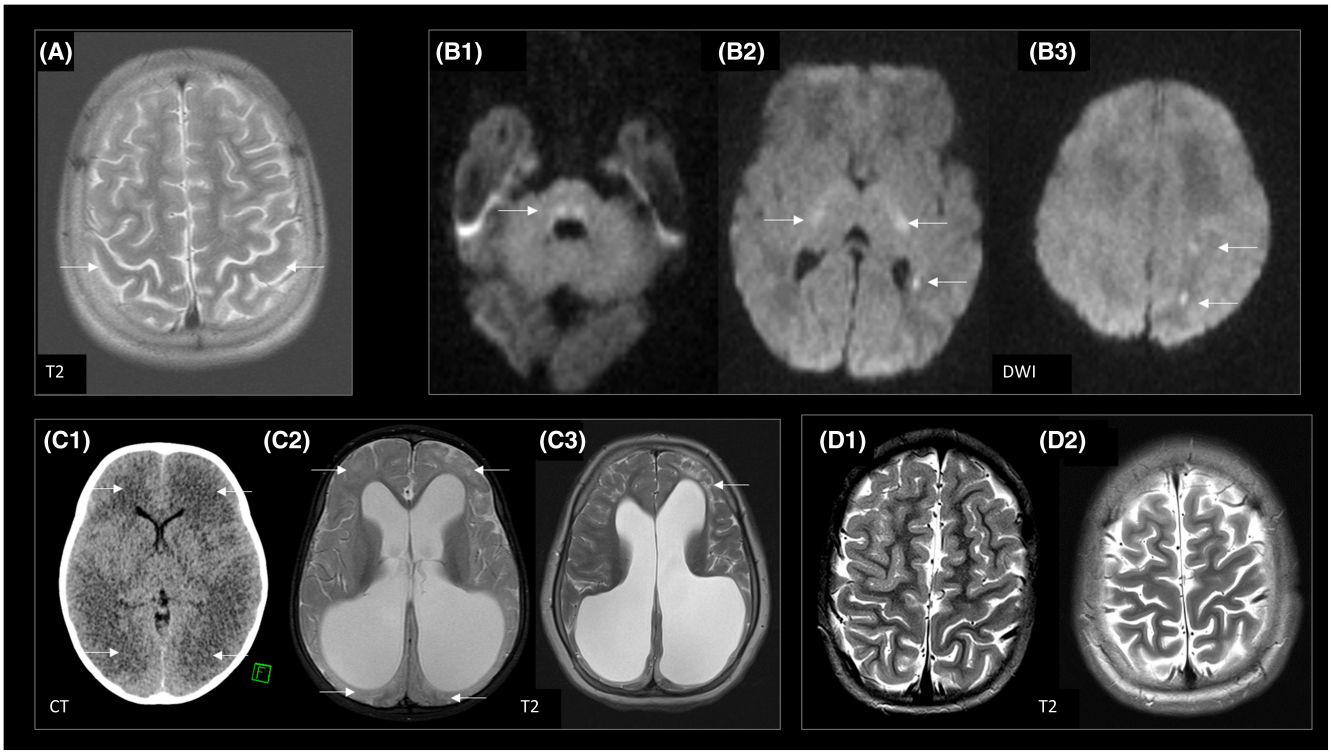

FIGURE 1 Neuroimaging abnormalities in ASA patients in the study. (A) MRI brain in a patient with early onset ASA at age 15 years showing mild, high frontoparietal volume reduction. (B) MRI brain in a patient with early onset ASA at age 4 days showing diffusion restriction along bilateral central tegmental tracts and corticospinal tracts with punctate white matter foci. (C) CT of the brain in a patient with late-onset ASA at age 12 months showing bilateral anterior and posterior watershed acute ischemic infarcts with swelling and hypodensity. MRI at ages 21 months and 10 years showing chronic sequelae in the form of encephalomalacic changes with ulegyria and gliosis. White matter volume loss and ex vacuo ventricular dilatation is also seen. (D) MRI brain in a patient with early-onset ASA at ages 7 years and 16 years showing minimal high frontoparietal volume loss with minimal interval progression. ASA, argininosuccinic aciduria; CT, computed tomography; MRI, magnetic resonance imaging.

or paroxysmal response to hyperventilation ($n = 1$, 5%). Focal epileptic discharges were central ($n = 7$, 37%), temporal ($n = 5$, 26%), frontal ($n = 4$, 21%), occipital ($n = 1$, 5%), or parietal ($n = 2$, 11%). Discharges were unilateral ($n = 3$, 16%) or bilateral/multifocal ($n = 9$, 47%). Unilateral electrical status epilepticus during slow-wave sleep (ESES) was observed in one patient. Hypsarrhythmia pattern with epileptic spasms was seen in one patient (5%). This patient had a paternally inherited *CACNA1A* variant of uncertain significance (VUS) (Table S1). Visual-related EEG abnormalities ($n = 6$, 32%) were observed with PPRs on photic stimulation with flickering light ($n = 2$, 11%) between 6 and 60 Hz ($n = 1$, 5%) and 16 and 30 Hz ($n = 1$, 5%), eye closure sensitivity ($n = 3$, 16%), and scotosensitive discharges in darkness ($n = 1$, 5%). Age at PPRs ranged between 1 and 18 years, whereas age at eye closure sensitivity ranged between 5.5 and 10 years. There was no fixation-off sensitivity (Table 1, Table S1; Figure 2, Figure S1).

3.6 | Epilepsy and EEG severity scores

Epilepsy clinical severity scores were calculated for all ASA epileptic patients ($n = 22$). The mean values of clinical severity scores were 713.5 for the VA-2 seizure severity score (range: 7.5–14 964) and 61 for the Chalfont Seizure Severity Scale (range: 10–268). EEG severity scores were calculated for 18 patients. The mean values of EEG severity scores were 12.66/54 (range: 4–27) for the mean modified Grand Total EEG score and 2.33/7 (range: 1–4) for the 2HELPS2B score (Table 1).

3.7 | Non-neurological characteristics in ASA epileptic patients

Transaminitis was the most common feature ($n = 11$, 50%), followed by hepatomegaly ($n = 11$, 50%). Tubulopathy with hypokalaemia was seen in six patients (27%) and hair changes as trichorrhexis nodosa were seen in five patients (23%) (Table S1).

3.8 | Biochemical characteristics in ASA epileptic patients

Mean plasma ammonia after the neonatal period/initial metabolic decompensation was 46 μmol/L (range:

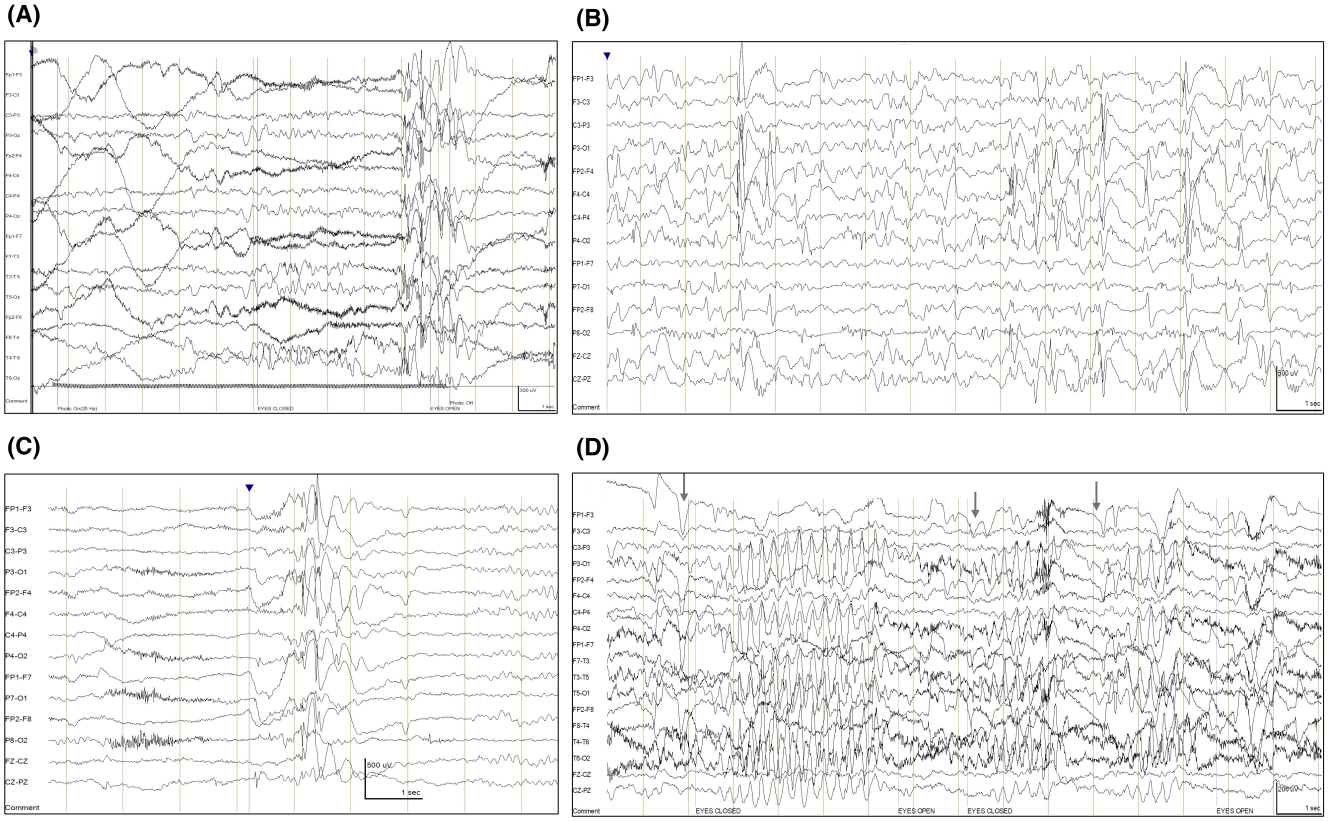

FIGURE 2 Electroencephalographic abnormalities in ASA patients in the study. (A) Interictal EEG in a patient with late-onset ASA at age 9 years showing photoparoxysmal responses that were reproducible at 8 Hz and (shown here) 25 Hz. (B) Interictal EEG in a patient with late-onset ASA at age 2 years showing background asymmetry with higher amplitudes and slower frequencies of ongoing activities over the right hemisphere, in addition to the epileptiform spikes seen independently over the right anterior and posterior quadrants. (C) Interictal EEG in a patient with late-onset ASA at age 9 years showing eye closure sensitivity with widespread burst of spike–wave complexes 1 s after eye closure (marked). (D) Interictal EEG in a patient with early-onset ASA at age 4 years showing rhythmic 3.5 to –4/s spike–wave complexes over the occipital region following eye closure (arrows). ASA, argininosuccinic aciduria; EEG, electroencephalography.

14.5–190 μmol/L, reference range 0–40 μmol/L). Mean plasma glutamine was 724 μmol/L (range: 481–1060 μmol/L, reference range 480–800 μmol/L) and mean plasma arginine was 78 μmol/L (range: 25–139 μmol/L, reference range 40–120 μmol/L). Mean plasma argininosuccinate was 275 μmol/L (range: 17–641, reference range 0–5 μmol/L) (Table 2).

3.9 | Metabolic management of ASA epileptic patients

Nineteen patients (86%) were on a protein restricted diet. Eleven patients (50%) were on sodium benzoate with a median dose of 188 mg/kg/day. Five patients (23%) were on sodium phenylbutyrate with a median dose of 230 mg/kg/day. Four patients (18%) were on glycerol phenylbutyrate with a median dose of 189 mg/kg/day. Five patients (23%) were on two nitrogen scavengers, 10 patients (45%) were on one scavenger, and seven patients (32%) did not require any nitrogen scavenger. Twenty-one patients (95%) were on arginine supplementation with a median dose of 124 mg/kg/day (Table S1). Arginine was started before the onset of epilepsy in 17 patients (81%) 4 (with late-onset ASA) and was started after onset of epilepsy in 4 patients (19%) patients with late-onset ASA. Liver transplantation was performed in six patients and infusion of hepatic stem cells (as a part of a clinical trial) was performed in one patient. The six transplanted patients had stopped arginine and ammonia scavenger therapy and liberalized their dietary protein intake. We compared data between liver transplanted and non-transplanted patients (Table S2).

3.10 | Comparison between ASA patients with and without epilepsy

We compared data from 22 epileptic and 15 non-epileptic ASA patients (Tables 1 and 2 and Table S1). Neurological and behavioral abnormalities were significantly more frequent in epileptic patients, especially for speech delay

($p = .04$) and autistic spectrum disorder ($p = .01$) and with a trend for ataxia symptoms ($p = .06$). Seven of nine patients (78%) with symptomatic seizures in the neonatal period developed epilepsy. Neonatal seizures were not associated with a higher risk of developing epilepsy ($p = .3$), (relative risk at age 5 years of age = 0.96). No statistical difference was observed for plasma ammonia, glutamine, arginine, and argininosuccinic acid. Epileptic patients were more frequently treated with arginine supplementation ($p = .01$). They received a higher mean dose of sodium benzoate (182 vs. 152 mg/kg/day; $p = .5$) and glycerol phenylbutyrate (180 vs 124 mg/kg/day; $p = .2$). No significant difference was observed for the following variables: gender, age at disease-onset, neonatal seizures, neuroimaging features, non-neurological abnormalities, and ammonia scavenger requirement.

3.11 | Comparison between early- and late-onset ASA epileptic patients

We compared the early- and late-onset cohorts of ASA epileptic patients with 14 and 8 patients, respectively (Tables 1 and 2 and Table S1). Both groups showed variable seizure types with generalized tonic-clonic seizures and focal seizures being more frequent, although statistically non-significant, in early-onset ASA patients, whereas atypical absence seizures were more frequent, although statistically non-significant, in late-onset ASA patients. Myoclonic seizures were reported only in patients with late-onset ASA. Early-onset ASA patients had a significantly higher mean plasma arginine ($p = .009$) and argininosuccinic acid ($p = .0009$). Mean plasma ammonia and glutamine were non-significantly different. There was a trend for the patients in early-onset group to be on more ammonia scavengers and a higher dose of sodium benzoate than the late-onset group. The numbers of patients with protein restriction and oral arginine supplementation were not different between groups. No significant difference was observed for the following variables: gender, age at epilepsy-onset, number of ASMs, seizure control, epilepsy severity scores, additional neurological features, non-neurological features, EEG characteristics, EEG severity scores, and neuroimaging abnormality.

3.12 | Comparison of ASA epileptic patients with pharmacoresponsive vs pharmacoresistant epilepsy

We compared ASA patients with pharmacoresponsive epilepsy ($n = 16$, 73%) vs ASA patients with pharmacoresistant epilepsy ($n = 6$, 27%). Well-controlled epileptic patients were either without or with ASMs (Table 3 and Table S3). Pharmacoresistant epilepsy was significantly associated with epilepsy onset at a younger age (median 36 months vs 13.5 months; $p = .05$), EEG background asymmetry ($p = .0007$) and did not present with visual-sensitive EEG abnormalities, although this last finding was not statistically significant ($p = .15$). No significant difference was observed for the following variables: gender, age at disease-onset, neonatal seizures, seizure types, epilepsy and EEG severity scores, neuroimaging abnormalities, neurological and non-neurological abnormalities, biochemical biomarkers, ammonia scavengers, and arginine dose and requirement.

3.13 | Correlation between severity scores and biological markers in ASA epileptic patients

Chalfont seizure severity scale showed a significant positive correlation with plasma arginine levels in ASA epileptic patients (Spearman's correlation coefficient $r_s = .43$, $p = .047$). Number of ASMs and other epilepsy and EEG severity scores did not show any other significant correlation with selected biomarkers (plasma ammonia, glutamine, argininosuccinate, or arginine) (Table S4).

4 | DISCUSSION

Epilepsy is a common feature in urea cycle disorders affecting 3%–14% of patients.[21,22] ASA is a multisystemic disease with complex pathophysiology and a model of inherited NO deficiency.[23] This international multicentric retrospective study is the largest to focus on the epilepsy phenotype in ASA patients. Our work suggests an even higher frequency (60%) of epilepsy in ASA patients, compared with previous publications reporting an incidence of 42%[4] to 55%.[12] Seizure types are polymorphic, although our study shows that tonic-clonic and multifocal seizures are more frequently observed in early-onset ASA (without statistical significance), whereas atypical absences are the more common seizure type in late-onset ASA (without statistical significance). The epilepsy phenotype occurs early in the natural history of ASA with a median at 24 months of age, which is earlier than the median ages of 3 years and 5.5 years reported by Grioni et al[12] and Baruteau et al,[4] respectively. The epilepsy phenotype is severe, with 27% of patients presenting with pharmacoresistant seizures, and 27% presenting with status epilepticus, usually triggered by a febrile illness. The main prognostic factors predicting epilepsy pharmaco-resistance were epilepsy onset

TABLE 3 Comparison between ASA patients with pharmacoresponsive vs pharmacoresistant epilepsy.

	Well-controlled epilepsy ($n=16$)	Partially controlled and refractory epilepsy ($n=6$)	p value
Demographic data			
Sex n (%)			
Male	12 (75%)	3 (50%)	.3
Current age (months) median (range)	196.5 (42–371)	168 (116–336)	.7
Clinical data			
Onset of ASA			
Early onset ASA n (%)	11 (68.8%)	3 (50%)	.6
Age at onset of symptoms (months) median (range)	0.3 (0.03–12)	0.5 (0.07–3.5)	.7
Age at diagnosis (months) median (range)	0.3 (0.05–216)	3.3 (0.3–12)	.3
Clinical characteristics of epilepsy			
Age at onset of epilepsy (months) median (range)	36 (7–191.7)	13.5 (3.5–60)	**.05**
Neonatal seizures n (%)	5 (31.3%)	2 (33.3%)	1
EEG characteristics n (%)			
Background asymmetry	2/14 (14.3%)	6/6 (100%)	**.0007**
Epilepsy and EEG severity scores mean (SD)			
VA-2 seizure severity score	35.2 (37.8)	2522.2 (5564.3)	.1
Chalfont Seizure Severity scale	50.9 (34)	86.5 (83.7)	.5
Modified Grand Total EEG score (0–54)	11.97 (5)	14.9 (7.4)	.4
2HELPS2B score (0–7)	2.4 (0.8)	2 (0.7)	.3
Biomarkers mean (SD)			
Mean plasma ammonia (μmol/L)	49 (43.3)	45.6 (10.8)	.3
Mean plasma glutamine (μmol/L)	719.5 (131.3)	644.9 (107.9)	.3
Mean plasma arginine (μmol/L)	78.3 (30.6)	63.9 (35.2)	.3
Mean plasma argininosuccinic acid (μmol/L)	275.7 (138.1)	164.5 (43.5)	.2

Note: Reference ranges: plasma ammonia: 0–40 μmol/L, plasma glutamine: 480–800 μmol/L, plasma arginine: 40–120 μmol/L, plasma ASA: 0–5 μmol/L. Bold values highlight statistically significant results.

Abbreviations: ASA, argininosucinic aciduria, EEG, electroencephalography, SD, standard deviation.

in early infancy before the age of 2 years and electroencephalographic background asymmetry. The absence of visual-related EEG abnormalities (i.e. photosensitivity or eye closure sensitivity on EEG) could be a pejorative indicator, although this association was not significant in this work.

ASA phenotype is associated with a severe neurodebilitating disease, characterized by developmental delay, learning difficulties, ataxia, and motor symptoms.[4] Our study shows that epileptic ASA patients have a significantly higher rate of speech delay and autistic spectrum disorder, and a trend for ataxia symptoms. Acute symptomatic

seizures and subclinical electrographic seizures are observed in 33%–50% of neonatal hyperammonemia,[24–26] with acute symptomatic seizures developing during the rise of glutamine levels, which occurs before ammonia increase.[27] Our study showed that neonatal hyperammonemic seizures in ASA were not associated with a higher risk of developing epilepsy subsequently.

The prevalence of epilepsy is also common in another urea cycle disorder, arginase deficiency (OMIM 207800), affecting 60%–75% of patients. The pathophysiology of epilepsy is multifactorial and thought to be caused by a combination of high arginine and subsequent downstream metabolite guanidinoacetate and its neurotoxicity.[28–30] Guanidinoacetate metabolites have a neurotoxic role by impairing redox homeostasis and mitochondrial bioenergetics.[31,32] In ASA, increased guanidinoacetate has been documented by MRI spectroscopy,[4,33,34] and could play a role in the pathophysiology of epilepsy.[35] In this work, arginine supplementation was significantly more frequent in the epilepsy group, although exogenous arginine dose and plasma arginine levels were not different. Plasma arginine levels had a positive correlation with epilepsy severity as indicated by the Chalfont Seizure Severity scale. However, half of patients with late-onset ASA developed epilepsybefore being diagnosed with ASA and started on exogenous arginine. These results do not provide compelling evidence for arginine-related neurotoxicity and warrant further studies to assess whether a high dose of arginine supplementation can be neurotoxic and favor epileptogenesis. Previous publications have suggested that exogenous arginine supplementation may have a role in the epileptogenesis in ASA by raising neurotoxic guanidinosuccinic acid levels.[2] Additional clinical data on arginine metabolites including guanidinoacetate levels in cerebrospinal fluid would be of interest in ASA patients to better characterize this association. Of interest, a high dose of arginine supplementation has shown liver toxicity in this disorder.[9] However, we noted in our study that epilepsy onset preceded ASA diagnosis and arginine administration in a subset of late-onset ASA patients, mitigating the role of arginine toxicity in epileptogenesis in this group of patients and suggesting that high arginine is not the only contributing factor in epileptogenesis in ASA.

Although argininosuccinate is neurotoxic at high doses, generating oxidative stress,[5] no significant difference in plasma argininosuccinate levels was observed between epileptic and non-epileptic patients, or well- and partially controlled patients. Plasma argininosuccinate levels do not adequately reflect the central effect of toxic metabolites produced in situ, as argininosuccinic acid is likely trapped in the brain like other dicarboxylic or tricarboxylic acids[36,37]; therefore, plasma levels are not reliable markers to assess cerebrospinal fluid levels. No significant difference in age at onset of hyperammonemia, ureagenesis biomarkers, and number and dose of ammonia scavengers was observed between epileptic and non-epileptic, well-controlled vs partially controlled or refractory patients, whereas higher plasma argininosuccinate and scavenger doses were found in early-onset patients, supporting previous reports.[4]

These findings suggest that hyperammonemia is not the primary pathophysiological mechanism for epileptogenesis.[2,4] Recently Lerner et al have shown a link between epileptogenesis in ASA and central catecholamine deficiency.[7] A novel mouse model with ASL deficiency exclusively in dopaminergic neurons $Asl^{flox/flox}$;$TH\ Cre^{+/-}$ showed that ASL-deficient dopaminergic neurons from the locus coeruleus have abnormal electrophysiology, that is, more frequent potential firing activity and a sharper after-hyperpolarization recovery slope.[7] This was associated with higher sensitivity to medication-induced epilepsy, which was restored by supplementation with NO donor.[7] The antiepileptic role of the locus coeruleus in limiting the spread and the duration of epilepsy[38,39] is well recognized and is essential for efficacious vagus nerve stimulation.[40,41] One of the patients in this work showed only a short and transient response to vagus nerve stimulation, which could be explained by defective catecholamine synthesis in the locus coeruleus. In addition, the locus coeruleus plays a central role in regulating arousal, wakefulness, and the sleep–wake pattern.[42] This work highlighted a high frequency of visual-related EEG abnormalities (32%), triggered by photic stimulation, eye closure, and elimination of retinal light stimulation. It was suggested recently that increased connectivity of the locus coeruleus is associated with photosensitivity in juvenile myoclonic epilepsy.[43] It is notable that a deficit in dopaminergic inhibitory neurotransmission has been described in generalized photosensitive epilepsy[44] and epileptic photosensitivity in progressive myoclonus epilepsies.[45] This further supports the association between photosensitive-related EEG abnormalities and dopamine deficiency in ASA.

This work has limitations due to the small number of patients affected by this rare disease and the methodology with retrospective analysis. We used the Grand Total EEG and 2HELPS2B scores that have been deemed effective in predicting seizures in acute clinical settings,[20,46] but have yet to be validated in different clinical contexts including estimation of EEG severity in the context of chronic conditions at baseline. However, they can still be informative as the Grand Total EEG Score has been used in seizure prediction in adults with neurodegenerative disorders.[19,47] Neurodegenerative features and neuronal loss have been recently highlighted as characteristics of ASA pathophysiology by Lerner et al[8] and Baruteau et al,[6] respectively. Of interest, the $Asl^{flox/flox}$;$TH\ Cre^{+/-}$ mouse model with Asl

knockout in dopaminergic neurons presents with both reduced seizure threshold[7] and neurodegenerative features,[8] thus providing a pathophysiological link between epilepsy neurodegeneration in ASA, which supports the use of the Grand Total EEG Score in this context.

Our findings warrant further prospective studies from larger cohorts of patients, which could be achieved via registries of patients affected by urea cycle disorders.[48] Understanding the neurological phenotype from levels of metabolites measured in plasma is inadequate. Analyzing metabolites from cerebrospinal fluid and MRI spectroscopy with prospective monitoring will provide better tools to understand the pathophysiology of the epilepsy and neurological disease in ASA. Developing alternatives models with induced pluripotent stem cells derived neurons or neuronal or organotypic cultures will provide surrogates to better study the complex pathophysiology of this disorder.[49,50]

5 | CONCLUSION

Epilepsy is a cardinal symptom of the encephalopathy observed in ASA. Epilepsy is frequent, polymorphic, occurs in early childhood, and is associated with a more severe neurodevelopmental phenotype. Early onset of epilepsy before the age of 2 years and electroencephalographic background asymmetry are prognostic markers for pharmacoresistance in epilepsy. Age at onset of first hyperammonemia and ureagenesis biomarkers and therapies do not differ between epileptic and non-epileptic patients or well and poorly controlled epileptic patients, suggesting that hyperammonemia is not the primary pathophysiological mechanism for epileptogenesis in ASA. The pathophysiology of epilepsy in ASA is multifactorial. Arginine toxicity has been previously suggested to contribute to epileptogenesis, but our data do not support this hypothesis, which warrants further studies to clarify the neurotoxicity of arginine in ASA. Poor response to vagus nerve stimulation in one patient and high frequency of visual-related EEG abnormalities provide clinical context and support the pathophysiological role of central dopamine deficiency.

AUTHOR CONTRIBUTIONS

NE and JB designed the study and wrote and edited the manuscript, which was then approved by all co-authors. NEK, GO, BS, KS, RS, TH, LC, HM, SS, and AC collected the data. NE and JB analyzed the data. DR provided statistical assistance. SB collected and provided the interpretation of EEG recordings. SS and IB collected and provided interpretation of neuroimaging. All authors provided critical comments on the manuscript. All authors approved the submission.

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CONFLICT OF INTEREST STATEMENT

None.

CONSENT TO PARTICIPATE

This research study was conducted retrospectively from medical notes. Participants' data were recorded anonymously. Informed consent approved by the National Research Ethics Service Committee London-Bloomsbury (13/LO/0168) was obtained from all participants and/or legal guardians for the following centres: Great Ormond Street Hospital for Children NHS Trust, National Hospital for Neurology and Neurosurgery, Evelina London Children's Hospital, Salford Royal NHS Foundation Trust and Manchester Centre for Genomic Medicine. The centres, Birmingham Children's Hospital, Bambino Gesù Children's Hospital in Rome and University of Alberta, did not require consents from their institutional review board due to the collection of anonymous data.

CONSENT FOR PUBLICATION

This research study was conducted retrospectively from medical notes. Participants' data were recorded anonymously. Informed consent was obtained from all participants and/or legal guardians for the following centers: Great Ormond Street Hospital for Children NHS Trust, National Hospital for Neurology and Neurosurgery, Evelina London Children's Hospital, Salford Royal NHS Foundation Trust, and Manchester Centre for Genomic Medicine. The centers, Birmingham Children's Hospital, Bambino Gesù Children's Hospital in Rome and University of Alberta, did not require consents from their institutional review board due to the collection of anonymous data.

DECLARATIONS

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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