Outcome and clinical-biochemical spectrum of Arginosuccinicaciduria in patients from India

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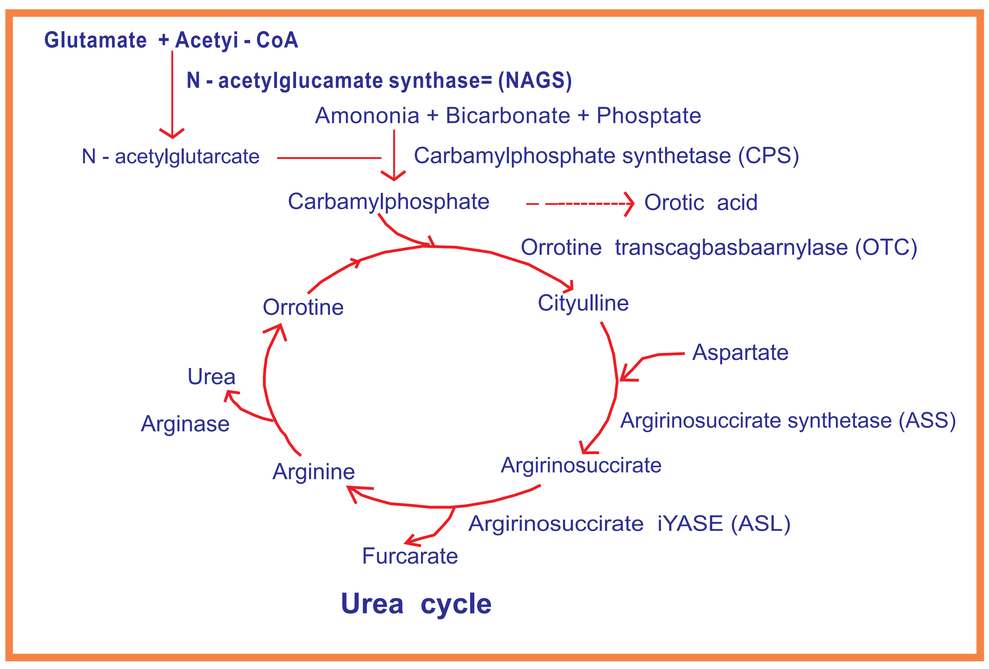
Introduction : Arginosuccinic aciduria (ASA) (OMIM # 207900), a type of urea cycle defect, is an autosomal recessive disorder caused by deficiency of Argininosuccinate lyase (ASL) enzyme, that cleaves Argininosuccinic acid to produce arginine and fumarate. Children with Argininosuccinic aciduria may have lethargy, loss of appetite ; respiratory distress, seizures or unusual body movements. Features may also include mental and physical retardation, liver enlargement, and skin lesions, dry and brittle hair. Argininosuccinic aciduria occurs in approximately 1 in 70,000 live births[1]. Many patients can now be detected by newborn screen if their blood citrulline is elevated.



Urea cycle

Objective : To evaluate the clinical and biochemical spectrum of patients with Argininosuccinic aciduria and their outcome in India.

Materials and method : This is a retrospective study of patients with Argininosuccinic aciduria over a period of 10 yrs (2004-2014). Various biochemical parameters such as ammonia, urinary orotic acid, plasma and urine amino acids and Argininosuccinic acid were studied in these patients

Result : We diagnosed 5 patients (F=1, M=4) with ASA. These patients presented with lethargy, convulsions and feeding problems. 3 patients presented in the neonatal period and had markedly elevated blood ammonia levels (993±485 µM/l). 2 patients presenting late (2 months and 2 yrs) had mildly elevated blood ammonia levels (92±2 µM/l). ASA levels have been available only recently at our center. One patient had plasma ASA 2188.0 µm/l (n=1) and others urine ASA 7427±4933 µM/mMCr. (n=3)

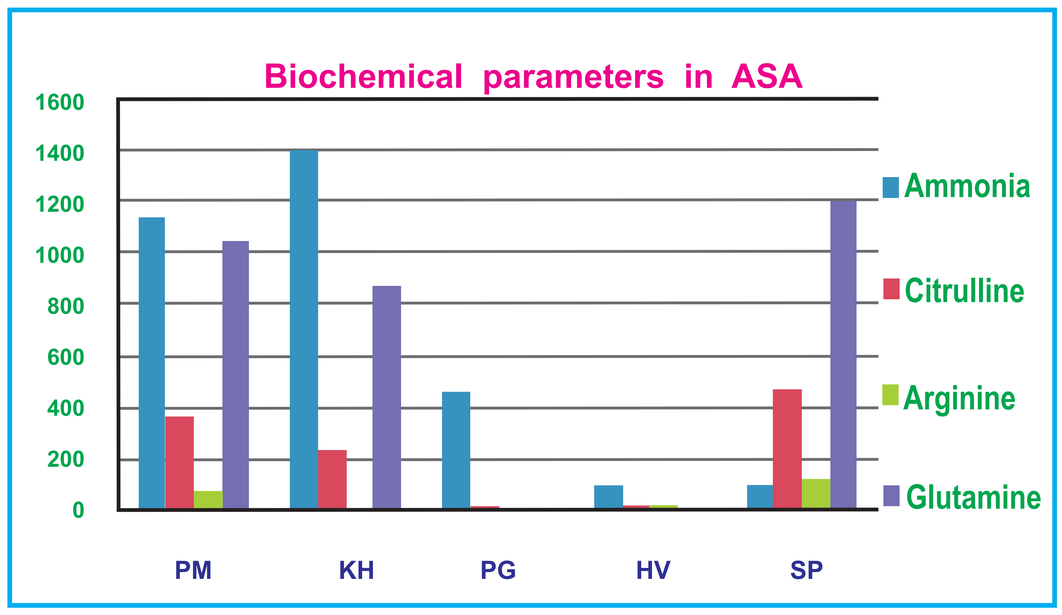
	NH_3µM/L	Cit µM/L	Arg µM/L	Cln µM/L	ASA-PL µM/L	ASA-Ur µM/mM Cr	Outcome
NR	9 - 30	19-52	19-52	457-857	<2	<5	<5
PM	1131	362	362	1041	2188.92	3342	Expired
KH	1395	233	233	869	NP	4573	Expired
PG	454	12	12	NP	NP	np	Expired
HV	9086	10	10	162	NP	np	Alive
SP	93.22	468	468	1200	NP	14368	Alive

(NP- not performed, NR-Normal Range)

Discussion : Argininosuccinate lyase (ASL) is a cytosolic enzyme which catalyzes the fourth reaction in the cycle and the first degradative step, that is, the breakdown of argininosuccinic acid to arginine and fumarate. Deficiency of ASL results in an accumulation of argininosuccinic acid in tissues, and excretion of argininosuccinic acid in urine leading to the condition argininosuccinic aciduria (ASA). ASA is an autosomal recessive disorder and is the second most common urea cycle disorders urine ASA 7427±4933 µM/mMCr. (n=3)

In addition to the accumulation of argininosuccinic acid, ASL deficiency results in decreased synthesis of arginine, a feature common to all UCDs except argininemia[2]

We analysed 1226 patients with suspected urea cycle defects out of which 5 were confirmed to have Arginosuccinic aciduria. These patients presented with lethargy, hyperammonemia, convulsions, mental retardation, hepatomegaly and respiratory distress. Out of these 5 patients, 3 patients presented in the neonatal period with severe form. They mainly showed symptoms like lethargy, convulsions and respiratory distress. These patients had markedly elevated blood ammonia levels (993±485 µM/l). These three patients expired before any specific treatment could be initiated.



HV (11Yrs / Male) : One patient (patient HV) presented at the age of 2 years with delayed motor and mental milestone, convulsions and has been on treatment since 2 years of life. From the age of 1 yr 4 month he started with convulsions, 4 - 5 episodes of GTC occurred with fever. After the first attack of convulsion he lost his speech and had neuroregression which he regained. He has been followed up on regular basis and various clinical and biochemical parameters are being monitored including ammonia, urinary orotic acid, plasma and urine amino acids and Argininosuccinic acid levels. His ammonia level at the time of first presentation was 90.8 µM/l. He was supplemented with carnitine, sodium benzoate and arginine. He was suggested with special urea cycle diet amino acid mix (UrC-A) and low protein diet. As he is not following proper diet his blood ammonia levels are fluctuating. Now at 11 yrs of age this child has developed mild mental retardation and hyperactivity. He has poor scholastic performance and now goes to special educator and started learning.

SP (2 Yrs/ Female) : This patient presented at the age of 2 months with increased level of ammonia and LC - MS - MS analysis of blood revealed elevated Citrulline. Her ammonia levels at the onset of disease were 93.22 umol/L. Urinary Argininosuccinic acid at the time of presentation was 14,368.18umol/mmolCr. Since then she has had multiple episodes of hyperammonemia with repeated vomiting, altered sensorium and coma. Her ammonia has risen to 309 umol/L requiring peritoneal and hemodialysis on 2 - 3 occasions. She also has hepatomegaly, abnormal LFT and delayed milestones. She has been posted for liver transplant. She has been managed on Sodium Benzoate, L Arginine and protein restriction. Her intake of Special Urea Cycle Formula is very erratic.

Conclusion : In our cohort of patients with ASA, overall mortality is 3/5 (60%). The survival rate is 2/5 (40%). Surviving patients have liver function abnormalities, one of them has neurological symptoms with mild hepatomegaly and slightly deranged LFT, while other have hepatomegaly with grossly abnormal LFT.

References :

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2. Erez A, Nagamani SC, Lee B. Argininosuccinate lyase deficiency - argininosuccinic aciduria and beyond. Am J Med Genet C Semin Med Genet. 2011 Feb 15; 157C (1):45-53.

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