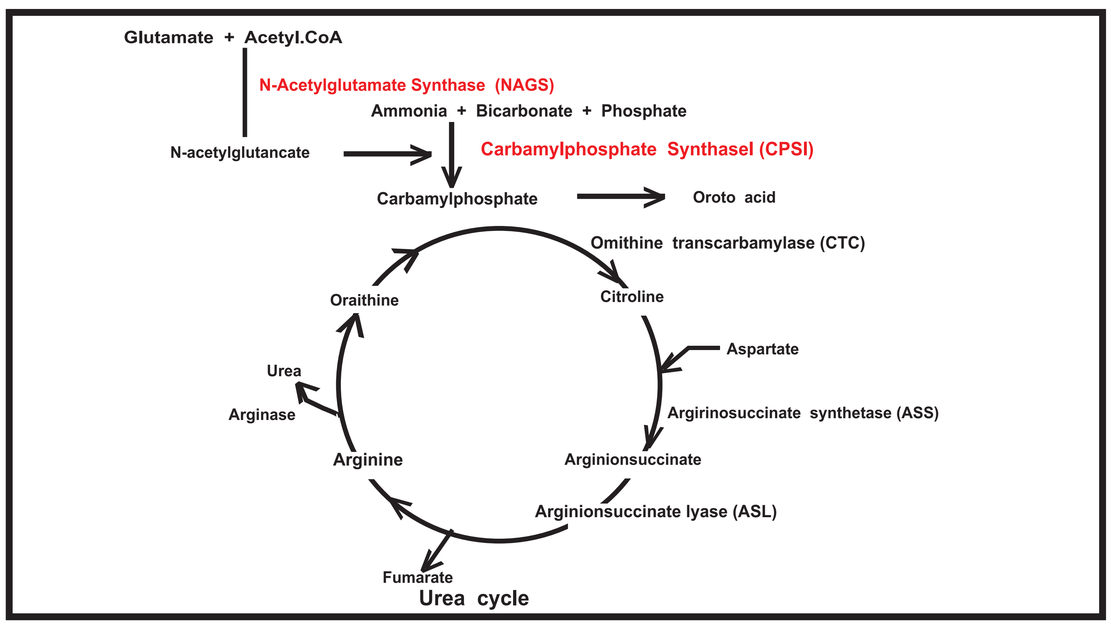
Role of low plasma citrulline and arginine for the diagnosis of proximal urea cycle disorders.

Borugale MA[1], Jalan AB[1], Joshi MM[1], Mahakal JM[1], Sonalkar ND[1], Kudalkar KV[1], Jalan RA[1], Shinde DH[1], Häberele J[2]

1. NIRMAN: Div of Biochemical Genetics, Navi-Mumbai, India-400705. www.metabolicerrors.com
2. Division of Metabolism and Children's Research Center,University Children's Hospital Zurich,Switzerland

Abbreviations : NAGS : N - acetylglutamate synthase, CPS1: Carbamyl phosphate synthase I, OTC : Ornithine transcarbamylase, UCDs: Urea cycle defects.

Introduction : Urea cycle disorders (UCDs) comprise a group of inherited defects of amino acid metabolism with an estimated cumulative incidence of 1:8000 to 1:44, 000[1]. Normal function of urea cycle requires six enzymes : N-acetylglutamate synthase (NAGS), Carbamyl phosphate synthase I (CPS1), Ornithine trans - carbamylase (OTC), Arginino - succinate synthase (ASS), Arginino - succinate lyase (ASL) and Arginase (ARG1). Carbamyl phosphate synthetase 1 (CPS1) deficiency (OMIM # 237300) (CPS1D) is an inborn error of the urea cycle having autosomal (2q34) recessive inheritance that can cause hyperammonemia and neonatal death or mental retardation[2]. The enzyme catalyzing the initial condensation of ammonia & bicarbonate, carbamylphosphate synthase 1 (CPS1), requires activation by N - acetylglutamate which itself is formed by N - acetylglutamate synthase (NAGS) (OMIM # 237310). N - acetylglutamate synthase deficiency is an inherited disorder that causes ammonia to accumulate in the blood. CPS / NAGS deficiencies are proximal urea cycle defects (UCDs) characterized by low plasma citrulline and arginine with low urinary orotic acid.



Objective : To determine the role of low plasma citrulline and arginine in cases with hyperammonemia and normal / low urinary orotic acid for the diagnosis of proximal urea cycle disorders.

Materials and Methods : Urine and blood sample of the 8 patients (5 males, 3 females) were analyzed for various biochemical parameters such as ammonia by dry chemistry (VITROS-DT 60), urinary orotic acid by HPLC, plasma and urine amino acid estimated by UHPLC. Genetic analyses were performed by Professor Häberle J at Zurich. We present a retrospective analysis of these patients.

Sr. No.	Name	Sex	Ammonia (uMol/L)	Orotic Acid (uM/mMol of cr)	Cit (uMol/L)	Arg (uMol/L)	Gene Study
1	A	M	849.00	2.20	2.00	13.00	CPS1 deficeny (c.2339G>Ap. (Arg780His)
2	B/o N	M	437.00	1.29	2.70	2.00	CPS/NAGS*
3	B/o SB	M	238.00	9.47	7.90	1.90	CPS/NAGS*
4	OC	M	5.00	2.43	1200	37.00	NP
5	B/o VP	F	318.00	2.81	10.00	20.00	NP
6	B/O N	F	1,008.00	3.95	5.00	16.00	NAGS
7	B/o R	M	309.00	5.98	2.00	15.00	CPS/NAGS*
8	ZI	F	381.00M	1.08	2.00	4.00	NAGS

NP : Not performed * No mutation identified

Result : We studied 8 children (5males and 3 females) with hyperammon - emia, low citrulline, arginine and orotic acid. These patients presented with lethargy, altered sensorium, poor feeding, vomiting and seizures. Out of these patients only 6 patients had undergone genetic studies (2 patients did not consent for molecular studies). Biochemical profile of these patient's revealed hyperammonemia (381±328µmol/L), low orotic acid (1.08±2.82µmol/L), low Citrulline (2±4.02µmol/L) and arginine (4±11.71µmol/L). Molecular studies were performed in 4 patients for CPS/NAGS deficiency, of which only one patient was CPS1 deficient (c.2339G>A/p. Arg780 His homozygous). Two patients were analyzed for only NAGS, who were normal. Two patients denied molecular analysis and hence no gene studies are available for these patients. However, all the 7 patients are perfectly healthy on normal diets and are not on any medication at present.

Discussion : UCDs classically manifest themselves in the neonatal period, with hyperammonemia, which causes encephalopathy and is rapidly progressive[1]. If not treated promptly, may be even fatal. Therefore a suspicion of UCD must be entertained when a neonate or older infant presents with signs of encephalopathy and hyperammonemia. Proximal urea cycle defects usually present with low citrulline, low orotic acid and low arginine.

In our cohort of eight patients who documented low citrulline, low orotic acid, low arginine and hyper ammonia, only 1 patient was molecularly proven to have CPS1 Deficiency. Two patients who denied any molecular study are perfectly healthy and are not on any medication and receiving normal diet. The true incidence of UCDs is not known in India, as there is no newborn screening data available. In our experience Citrulline Type I (ASS Deficiency) is the commonest form of UCD in India[5]. However Rüegger CM1 et al have reported OTC (58%) to be the commonest, followed by ASSD (20%). CPS / NAGS formed only 2 % of all UCDs in their cohort[1].

Low levels of citrulline and arginine have also been reported in adults and children with sepsis, ARDS and other critical illness[3]. Van Waardenburg et al have also shown that plasma citrulline and arginine levels were lower in patients with sepsis or trauma and were inversely associated with severity of inflammation[4]. Thus other causes of hyperammonemia, low citrulline and arginine need to be evaluated in patients along with close monitoring of symptoms and initiation of appropriate treatment.

In India proximal Urea Cycle defect can only be treated with oral sodium Benzoate, Arginine and Citrulline supplementation. Sodium Phenylbutyrate, Injectable Sodium benzoate, Sodium Phenylbutyrate and Arginine are still not available[5]. In any infant with suspected UCD, the therapy must be initiated awaiting further biochemical and molecular diagnostic results. Detailed discussion on therapy is beyond the scope of this paper. Stopping protein intake, IV Fluids with Glucose or Glucose – Insulin drip and Sodium benzoate – 250 mgm/kg/day must be initiated[5].

Conclusion : Low citrulline and arginine are not always indicative of CPS/NAGS deficiency. In our cohort of 8 patients, only 1 was confirmed to have CPS1 deficiency. In the remaining patients no mutation in CPS/NAGS genes could be ascertained. Therefore other causes of low Citrulline and arginine need to be assessed in newborns with this biochemical profile.

Conflict of interest : None

References :

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