

A Case of Hyperargininaemia Presenting at Unusually Low Age

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ABSTRACT

Arginase or *ARG1* gene deficiency is a Type V Urea Cycle Disorder (UCD) (catalysing the fifth reaction of urea cycle), associated with hyperammonaemia. Here, we discuss a rare case of a 13-month-old female, having Severe Acute Malnutrition (SAM) and failure to thrive, with serial high plasma ammonia, normal plasma lactate with high arginine and glutamine levels on Amino Acid Assay (AAA) which was performed on 1220 Agilent HPLC. She was admitted for about a month and eventually succumbed to her ailment after a month of discharge.

Keywords: Arginase, Glutamate, Hyperammonaemia, Normal lactate, Orotate, Urea cycle disorder

CASE REPORT

A 13-month-old female presented with initial complaints of not gaining weight since birth, recurrent vomiting and tonic posture till tenth day of her life. She had a past history of seizures at the age of 6-7 months associated with fever with a frequency of 1-2 episodes per month which lasted till 11 months of age. She was admitted at another tertiary care hospital at the age of 10 months for not gaining weight and was diagnosed with global developmental delay.

She was the third child of a second degree consanguineous marriage. Mother's antenatal period was uneventful with proper intake of iron and folate supplementation. The girl was born full term by Lower Segment Caesarean Section (LSCS) in hospital. The birth weight was 1.8 kg, with immediate cry after birth. Breast feeding was started 3-4 hours after birth. The early neonatal period was uneventful. She received complete immunisation with DPT/OPV/Hep B vaccination.

On general physical examination, she was found undernourished with presence of pallor. Her height/weight ratio was less than -3 SD. A differential diagnosis of global developmental delay, sepsis, SAM, iron deficiency anaemia or inborn error of metabolism was made. Then, the child was admitted and started with nasogastric feed.

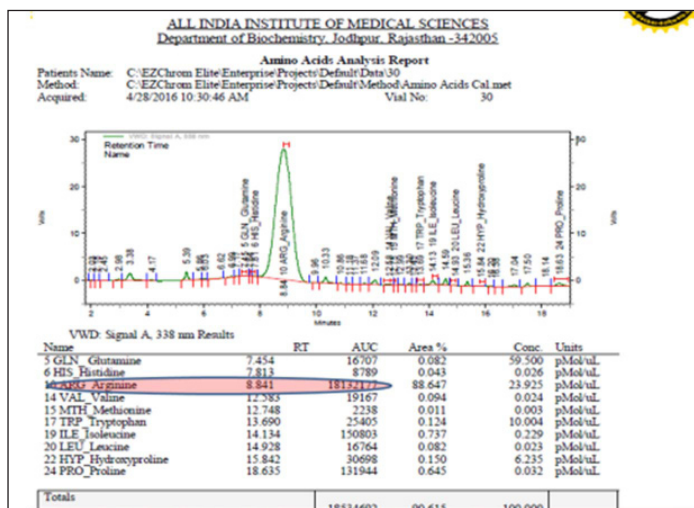
In addition to routine investigations, some special investigations to rule out inborn error of metabolism were also done. High sensitivity C Reactive Protein (Hs-CRP) was 8.89 mg/dl (normal range <1 mg/dl), plasma ammonia levels was 117.64 $\mu\text{mol/l}$ (normal range 10-

45 $\mu\text{mol/l}$) and plasma lactate level was 13 mg/dL (normal range 4.5-20 mg/dL). Plasma amino acid analysis revealed high serum arginine 387 $\mu\text{mol/l}$ (normal range 39.5-42.5 $\mu\text{mol/l}$) and high serum glutamine 466 $\mu\text{mol/l}$ (normal range 322-400 $\mu\text{mol/l}$). Urinary Orotic Acid (OA)/creatinine ratio was 3.2 (normal-0.5-3.3 mmol/mole of creatinine) [Table/Fig-1,2].

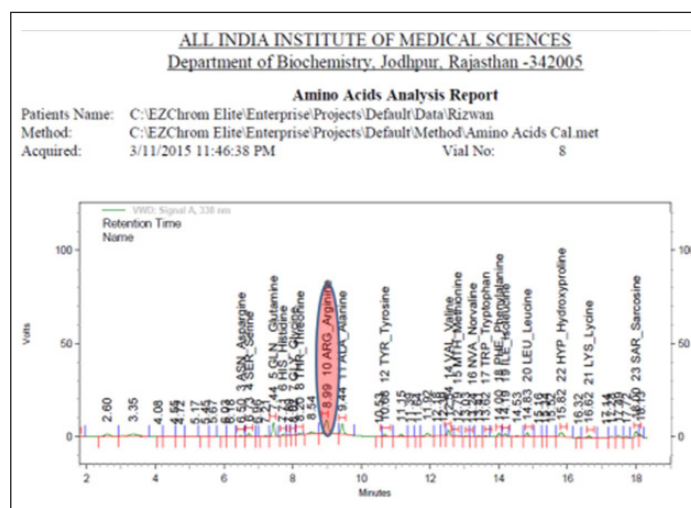
MRI head showed symmetric patchy regions of white matter abnormalities of periventricular areas and bilateral symmetric abnormalities of posterior limbs of internal capsules suggestive of inborn error of metabolism.

Child was kept on Intravenous (IV) antibiotic initially in view of fever and positive CRP. SAM management was started accordingly, feed given initially F-75 then F-100 and rest multivitamin given accordingly. Initially she was kept on IV antibiotics (ceftriaxone), in view of persistent fever, vomiting and feed intolerance. After initial improvement, patient deteriorated after seven days and clinically aspiration pneumonia was suspected. She was kept on IV fluid and injection vancomycin (20 mg/kg IV) was started. Patient improved after 3-4 days, feeding was restarted. After five days, she again developed fever, irritability and refusal to feed. Blood culture was done and IV antibiotic upgraded to injection meropenem, (40 mg/kg IV every eight hours for five days), in view of aspiration pneumonia.

She was discharged after 20 days of stay and was gaining weight and accepting feed well at the time of discharge. Dietary recommendation included low protein diet and special dietary supplements like calolipid.



[Table/Fig-1]: Amino Acid Assay (AAA) on 1220 Agilent HPLC showing increased arginine peak in plasma (Sample cup 30).



[Table/Fig-2]: Urine analysis for amino acid assay on 1220 Agilent HPLC system.

Authors	Presentation	Age reported
Present case	Seizures, poor feeding, global developmental delay, later pneumonia	7 months
Schiff M et al., [11]	Respiratory distress, seizures	3 weeks
Ghai SJ et al., [1]	Poor feeding, lethargy, seizures	6 weeks
Picker JD et al., [12]	Poor feeding, lethargy, seizures	3 days
Braga AC et al., [2]	Jaundice, cirrhosis, vomiting, palpable liver and spleen	2 months
Jorda A et al., [13]	Tremor, seizures, jaundice, cirrhosis, vomiting	5 days
Scholl-Bürgi S et al., [14]	Infection, seizures, poor feeding, lethargy	36 days
Segawa Y et al., [15]	Vomiting, seizures, hypertonia	18 days

[Table/Fig-3]: Eight reported cases of hyperargininaemia presenting in infancy.

On follow up, she continued to have recurrent episodes of fever and hyperammonaemia and unfortunately succumbed to death after three months of initial presentation.

DISCUSSION

UCDs are a group of inborn errors of hepatic metabolism that affect the transfer of waste nitrogen into urea. The urea cycle has two main functions: the detoxification of waste nitrogen into excretable urea and the de novo biosynthesis of arginine [1]. The cycle consists of six sequential enzymatic steps for conversion of nitrogen derived from proteins to urea. All the enzyme deficiency disorders of urea cycle have been identified. Most of these disorders like N-acetyl glutamate synthase deficiency, carbamoyl phosphate synthetase I deficiency, argininosuccinate synthetase deficiency, argininosuccinate lyase deficiency and arginase I deficiency are inherited as an autosomal recessive, but Ornithine Transcarbamylase (OTC) deficiency is inherited as X-linked [2]. Any of these deficiencies can result in hyperammonaemia and accumulation of different metabolites. Each specific disorder usually presents in the newborn period or in early infancy with hyperammonaemic encephalopathy and hyperglutaminaemia except hyperargininaemia [3]. Hyperargininaemia occurs due to the deficiency of the enzyme arginase I (*ARG1*) which is predominantly found in liver, RBCs and salivary gland. Arginase II, another type of arginase, is found in renal tissues. Arginase hydrolyses L-arginine to ornithine and urea. Unlike other UCDs, symptoms of hyperargininaemia typically do not occur until the age of four years [4].

The present case is of *ARG1* deficiency, presenting in early infancy with hyperammonaemia. The literature describes only seven such cases and these cases demonstrate a wide variation in neonatal presentation of *ARG1* deficiency. Argininaemia is a disorder in which the clinical picture is quite different from the other disorders of urea cycle. It was first reported in 1965 by Prasad AN [5]. The disease is caused by complete absence of the activity of the enzyme arginase [6]. Most common genetic mutation associated with argininaemia is that of *ARG1* gene located on chromosome 6 at band q23 [2,3]. A small number of mutations have been heterogeneous. They are often picked as abnormal, because of delayed developmental milestones. In the neonatal period, patients may have convulsions and repeated cyclic vomiting, anorexia, irritability and failure to thrive. They can present as spastic diplegia or quadriplegia. Usually, the patients have spastic toe walking gait, if they are able to walk with scissoring of lower limb [7]. Convulsions are regularly observed with associated EEG abnormalities. Patients may develop microcephaly and cerebral atrophy. Psychomotor impairment may be severe. Liver dysfunction has been reported in some cases of *ARG1* deficiency but severe liver disease in form of cirrhosis or hepatic failure is rare [8].

An interesting biochemical abnormality noted in *ARG1* deficiency is orotic aciduria which was also present in the proband [8]. There are

two mechanisms proposed for orotic aciduria in *ARG1* deficiency. According to the first one, there is a functional decrease in OTC activity as a result of low ornithine because of *ARG1* deficiency and as per the second mechanism, it is as a back up phenomenon due to accumulation of distal substrates affecting OTC activity [8]. As a result, accumulated carbamoyl phosphate is shunted towards the pyrimidine biosynthetic pathway and leads to orotic aciduria [4]. Urinary OA is also increased in other enzyme defects viz., OTC deficiency, citrullinaemia, argininosuccinic aciduria, mitochondrial DNA defects, occasionally in Rett's syndrome, Lesch Nyhan syndrome and other disorders of pyrimidine metabolism. Direct derivatives of arginine like alpha keto guanidinovaleric acid, N-acetyl arginine and arginonic acid are also found in urine in hyperargininaemia as well as guanidinoacetic and guanidinobutyric acids which are compounds formed by transamination [9].

The metabolic blocks, at times may not be complete in this disorder; therefore, arginine levels could be normal. The current modality for the management of hyperammonaemia includes arginine bolus and/or infusion [10] which is needed in most of the other UCDs as arginine provides citrulline which is further condensed with carbamoyl phosphate to quench ammonia and reduce its toxicity. We suggest that in light of *ARG1* deficient cases with hyperammonaemia, though rare, the specific diagnosis be made even more urgently and if possible, before intravenous arginine therapy is initiated, to avoid any added insult to the case diagnosed. There are only few cases published in literature which are presented in [Table/Fig-3] [1,2,11-15].

CONCLUSION

Here, we highlight the fact that, though rare, *ARG1* deficiency with hyperammonaemia can present at an unusually early age either in infancy or neonatal period, much more than previously considered. Therefore, the above presentation in early infancy with hyperammonaemia and normal plasma lactate on repeated investigation, Type V UCD should be considered in listing the differential diagnosis, as recurrent hyperammonaemia of any grade is a risk factor for significant brain injury and associated mortality.

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