Argininaemia presenting as acute encephalitis in a child

***K. Jagadish Kumar[1], Nandish H R[2], Devesh Bhaskar Yerrapragada[3], Manjunath V G[1]**

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Introduction

Ammonia is a by-product in the metabolism of nitrogenous compounds and is highly toxic to tissues[1]. It is converted to urea during the urea cycle in the liver[1]. The urea cycle consists of six consecutive enzymatic reactions that convert waste nitrogen into urea[2]. Argininaemia is a rare autosomal recessive metabolic disorder due to arginase deficiency characterized by hyperammonaemia secondary to arginine accumulation[2]. The estimated incidence of argininaemia is 1 in 2,000,000 live births[1,2]. Patients with argininaemia are usually asymptomatic in the neonatal period and early infancy[2,3]. Argininaemia presents in late infancy and childhood with spastic paraparesis/paraplegia, seizures and cognitive impairment[4]. Hyperammonaemic encephalopathy, a common feature in other urea cycle disorders is rarely seen in argininaemia[4]. We report a 2 year and 8-month-old boy presenting as acute meningoencephalitis which was later diagnosed as hyperammonaemic encephalopathy due to argininaemia.

Case report

A 2-year and 8-month-old developmentally normal boy, 3rd by birth order, born to second-degree consanguineous parents, presented with a 4-day history of fever, loose stools and excessive crying for 2 days. There was no history of convulsions or altered sensorium. On examination, he was crying continuously with vacant spells along with tonic posturing of limbs. His Glasgow coma scale (GCS) score was 9/15. A provisional diagnosis of acute meningoencephalitis was made and he was started on an intravenous (IV) bolus of fosphenytoin 30mg/kg, IV mannitol 20% 5ml/kg in addition to IV ceftriaxone, IV acyclovir, IV azithromycin and oral doxycycline through Ryle's tube. As the tonic posturing continued, a second dose of IV fosphenytoin 15 mg/kg was given along with 3% saline 0.5 ml /kg/hour to decrease suspected raised intracranial tension. The child's condition worsened with deterioration of sensorium (GCS score 5/15) and development of intermittent decerebrate posturing for which he was commenced on mechanical ventilation.

Investigations are depicted in Tables 1 and 2.

In view of the elevated serum ammonia level (highest recorded on day 1 =248µmol/L), metabolic encephalopathy/hyperammonaemic encephalopathy was suspected. He was started on sodium benzoate through a Ryle's tube and an inborn errors of metabolism (IEM) cocktail (containing vitamin B1, vitamin B2, biotin, folinic acid, vitamin B12, carnitine, coenzyme Q and pyridoxine) was added. His consciousness improved and seizures and posturing disappeared over the next 12-24 hours. Serum ammonia levels decreased to 31µmol/L by day 6 and he was extubated on day 6. Tandem Mass Spectrometry (TMS) identified elevated levels of arginine, suggestive of arginase deficiency suggestive of a urea cycle defect causing metabolic encephalopathy. A urea cycle defect diet powder was started with 3 level scoops (25g) of UCD-1 in 100 ml of water and his feeds were gradually increased. He became seizure free on treatment with oral phenytoin and phenobarbitone by day 7. His GCS score was 15/15 and he was responding to commands. His upper limb tone was normal but tone was increased in his lower limbs and he was fit for discharge on day 15. Whole exome sequencing (DNA test performed by MedGenome Labs Ltd, Bangalore, India) revealed a homozygous 5' splice site variation in intron 3 of the ARG1 gene (chr6:g.131579287T>G;G;Depth:128x) that affects the invariant GT donor splice site of exon 3 (c. 329+2T>G;ENST0000035692.2) suggestive of autosomal recessive inheritance of pathogenic argininaemia. He was seizure free, walking with support despite having hypertonia of both lower limbs 3 months after initial admission. At present he is on UCD-1 diet powder 25g three times a day with rice, gangi and vegetables without protein.

[1]*Professor of Paediatrics,* [2]*Senior Resident in Paediatrics,* [3]*Resident in Paediatrics, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India*
**Correspondence:* jagdishmandya@gmail.com
https://orcid.org/0000-0001-9059-986X
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Table 1: Blood investigations

Investigation (normal range)	Result
Haemoglobin level (11-14 g/dl)	8.9
Packed cell volume (34-40%)	30.4
White blood cell count (4000-11000 cells/cu mm)	9610 (N=58%, L=37%, E=1%, M=4%)
Platelet count (150000-450000/cu mm)	450,000
C-reactive protein (0-5mg/L)	0.07
Erythrocyte sedimentation rate 1st hour (<10mm in 1 hour)	90
Blood urea (12-42 mg/dL)	12
Serum creatinine (0.2-0.7 mg/dL)	0.27
Serum sodium (136-145mEq/L)	140
Serum potassium (3.5-5mEq/L)	5.1
Blood sugar (70-140 mg/dL)	151
Aspartate transaminase (0-40 U/L)	46
Alanine transaminase (0-40 U/L)	39
Prothrombin time / Control INR (15 seconds/1.01)	20.9/13.1, 1.74
Activated partial thromboplastin time / Control (30 seconds/1.0)	52.9/32
Serum magnesium (1.5-2.6 mg/dL)	2.6
Serum phosphorus (2.5-7.7 mg/dL)	4.8
Serum total calcium (8.4-10.2 mg/dL), Ionised (1.16-1.32)	9.4 (1.24)
CK-NAC (20-200 U/L)	227
Blood lactate (4.5 -19.8mg/dl)	15.8
Serum amylase (13-53 U/L)	21
Serum lipase (13-60 U/L)	21.7

INR: International normalised ratio, CK: creatine kinase

Table 2: ***Additional investigations***

Blood ammonia [Normal =11 to 32 µmol/L]	Day 1	Day 2	Day 3	Day 6	Day 10
	248	166	53	31	33
Cerebrospinal fluid (CSF) analysis	Cell count=0, protein=18 mg/dL, sugar=84mg/dl, culture=no growth ELISA for JE virus = Negative				
CSF PCR Panel	Negative for Enterovirus, HSV1, HSV2, VZV, CMV, Haemophilus influenza, Pan bacteria, Streptococcus pneumonia, Neisseria meningitidis, Mycobacterium tuberculosis, Cryptococcus, Plasmodium species, Toxoplasma gondii.				
Arterial Blood Gas	pH 7.46, p02=216, pC02=24, HCO3=17.4, Base excess= -5.4				
Covid RT-PCR	Negative				
Urine for porphobilinogen	Negative				
MRI Brain (Plain and Contrast)	Normal				
Electroencephalogram	Bi-hemisphere dysfunction (EEG showed slowing of the background waves with theta and delta waves)				
Tandem Mass Spectrometry	Serum Arginine concentration 371.75 µmol/L [Normal < 50]				
DNA Exome sequencing	Gene (Transcript) Location Variant ARG (+) (ENST00000356962.2) Intron 3 c.329+2T>G(5' Splice site) pathogenic				
Other tests	Blood, CSF and stool culture sterile, Widal and Weil Felix negative Peripheral blood smear=Microcytic hypochromic anaemia				

PCR: polymerase chain reaction, MRI: magnetic resonance imaging, DNA: deoxyribonucleic acid

Discussion

Argininaemia is an inborn error of the urea cycle due to arginase 1 deficiency. Hyperammonaemic encephalopathy, which is usually observed in other urea cycle defects is rarely seen in argininaemia[2]. However, our child was diagnosed as acute meningoencephalitis with status epilepticus, GCS score of 5/15 and needing mechanical ventilation. His ammonia level of 248 µmol/L was the probable cause of his encephalopathy, which we initially managed as acute meningoencephalitis. His consciousness improved with reduction of ammonia levels after starting sodium benzoate. Hyperammonaemic crises can be precipitated by catabolic events like fever, protein overload or certain drugs like valproate[5] and in our child, it is likely to have been triggered by his pyrexial illness. The irritability reported in this child, as manifested by excessive crying, is rarely reported in argininaemia[4] but was a major feature in his presentation.

In argininaemia, typically a brief period of normal development is followed by neurological symptoms starting by 2–4 years of age[2,3,6,7]. Our child also had normal development until this presentation to hospital. Common presentations include spastic paraparesis/paraplegia, seizures and cognitive impairment[4]. A study reported cognitive decline, spasticity and seizures seen in 100%, 87.4% and

73.7% in 15 affected children respectively[1]. Carvalho DR, *et al*[8] observed that among 16 patients with argininaemia, 37% had microcephaly and lower limb spasticity was the first neurologic manifestation in 12 patients and spasticity, predominately affecting the lower limbs, was the commonest reported manifestations at the time of diagnosis in other reports[6].

Garg D, *et al*[7] reported three genetically proven argininaemia siblings who presented with diverse phenotypes, spasticity being a common feature. After recovery from the acute crisis, we also noticed spasticity of both lower limbs in our child. This spastic diplegic presentation may mimic cerebral palsy (CP) but the presence of progressive spasticity, cognitive and language deterioration, protein avoidance and absence of hypoxia at birth will distinguish argininaemia from CP[4]. Microcephaly has been described in some affected patients[8] although this was not present in our patient (head circumference of 48.5cm, between 3rd and 97th centiles). MRI in some affected cases is reported to show variable degrees of cerebral and cerebellar atrophy[2] but in our child, it was normal. Arginine levels in the blood can be increased by more than 15-fold[2] and it was 370 (normal <50) in the present case during the acute presentation. The neuropathogenic effect of argininaemia is not clearly understood[2,4] but increased levels of arginine metabolites like guanidino compounds and nitric oxide may exert neurotoxic effects on the brain[2,4].

The gene coding for arginase 1 enzyme is *ARG1* which is located on the long arm of chromosome 6 (6q23). Argininaemia is caused by pathogenic variants in the *ARG1* gene[2,3]. Our child had a homozygous mutation in the splice site variation in intron 3 of the *ARG1* gene (chr6:g.131579287T>G;Depth: 128x) that affects the invariant GT donor splice site of exon 3 (c. 329+2T>G;ENST0000035692.2). Üstünkoyuncu PS, *et al*[4] found a novel homozygous mutation c. 231C>A (p. S77R) in one case and a common homozygous mutation c. 703G>C (p. G235R) in the other case. Valproate should not be used to treat seizures in this condition since it induces hyperammonaemia[5] and treatment options include phenobarbital or carbamazepine.

Argininaemia is a treatable metabolic disorder[2] and early diagnosis, restricted protein and arginine diet are life-saving and improve the quality of life[1,7]. Ammonia-lowering drugs like sodium benzoate should be considered if plasma ammonia remains elevated[5] and this can be discontinued once the plasma levels normalize. Therefore, we had started on sodium benzoate and continued till ammonia levels returned to normal. Liver transplantation can be considered as the best available treatment at present to reduce recurrent hyperammonaemia[5]. Cui B, *et al*[9] reported improvement in neurophysiological characteristics of argininaemia child after living donor liver transplantation. Newborn screening by TMS may be used to assess affected cases [6] but this is currently unavailable routinely in Sri Lanka, although future siblings of this child will need this or genetic testing to assess their status.

Conclusion

Argininaemia and other urea cycle disorders should be one of the differential diagnoses of any child who presents with acute encephalitis / encephalopathy. Early diagnosis and prompt treatment reduces morbidity and mortality but lifelong dietary modification and / or liver transplantation may be needed.

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