

Neonatal Onset Argininosuccinic Acidemia in a Set of Twins: A Case Report

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Abstract

Aim: To highlight the challenge in the management of Argininosuccinic acidemia as well as demonstrate the importance of newborn screening for inborn errors of metabolism. **Method:** Report of two cases of neonatal onset ASA with encephalopathy and review of relevant literature. **Conclusion:** Early diagnosis and institution of appropriate intervention can significantly improve outcome. Routine newborn metabolic screening should not only be implemented universally, the result should be available promptly.

Keywords: Neonatal; Onset; Argininosuccinic; Aciduria.



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1. Introduction

Argininosuccinic acidemia (ASA) also known as Argininosuccinate lyase deficiency is an inborn error of metabolism affecting the urea cycle. ASA is caused by mutations in the *ASL* gene (7q11.21) that encodes the enzyme argininosuccinate lyase. This enzyme catalyzes the conversion of argininosuccinic acid into arginine and fumarate during the fourth step of the urea cycle. Defects in this step of the urea cycle lead to an accumulation of plasma ammonia, argininosuccinic acid, citrulline, and urinary orotic acid, and to a plasma arginine deficiency [1-3].

It is the second most common urea cycle disorder. It is a potentially fatal, but treatable inborn error of metabolism with a prevalence of 1 in 70,000 live births [2, 4]. Clinical findings are usually non-specific and similar to those seen in infants with other inborn errors of metabolism or infections.

The disease has pleiotropic presentations, a severe neonatal form and a milder late onset form [Summar, *et al.* [2]. The severe neonatal form is characterized by hyperammonemia within the first few days of life with poor feeding, vomiting, lethargy, and seizures, with subsequent progression to coma. The late onset form manifests late in infancy or in childhood; it presents with mental retardation, vomiting, failure to thrive and behavioral problems [2, 5, 6]. The absence of specific features means that a high index of suspicion is required to make the diagnosis.

The clinical diagnosis is confirmed by measuring ammonia and argininosuccinate levels in plasma.

Long-term complications associated with both forms of ASA include chronic hepatomegaly, liver dysfunction (fibrosis or cirrhosis), neurocognitive deficits (i.e. cognitive impairment, seizures, and developmental delay), brittle hair (i.e. trichorrhexis nodosa), hypokalemia and arterial hypertension [4, 5].

ASA is inherited in an autosomal recessive manner and genetic counseling is advisable. Prenatal diagnosis is possible in families with a known disease causing mutation on both alleles. Prior to the newborn screening era, the diagnosis of late-onset ASL deficiency could be delayed by more than a year in some cases [1, 2, 4-6].

With early diagnosis and treatment, hyperammonemic episodes can be avoided but long-term complications (neurocognitive impairment, hepatic disease and arterial hypertension) are frequent and have a negative effect on life-expectancy and quality of life. We present fatal argininosuccinic acidemia in a set of twins, born in a setting where routine newborn screening was not established. We highlight the challenges in management, course and outcome.

2. Case Summary

2.1. Case 1

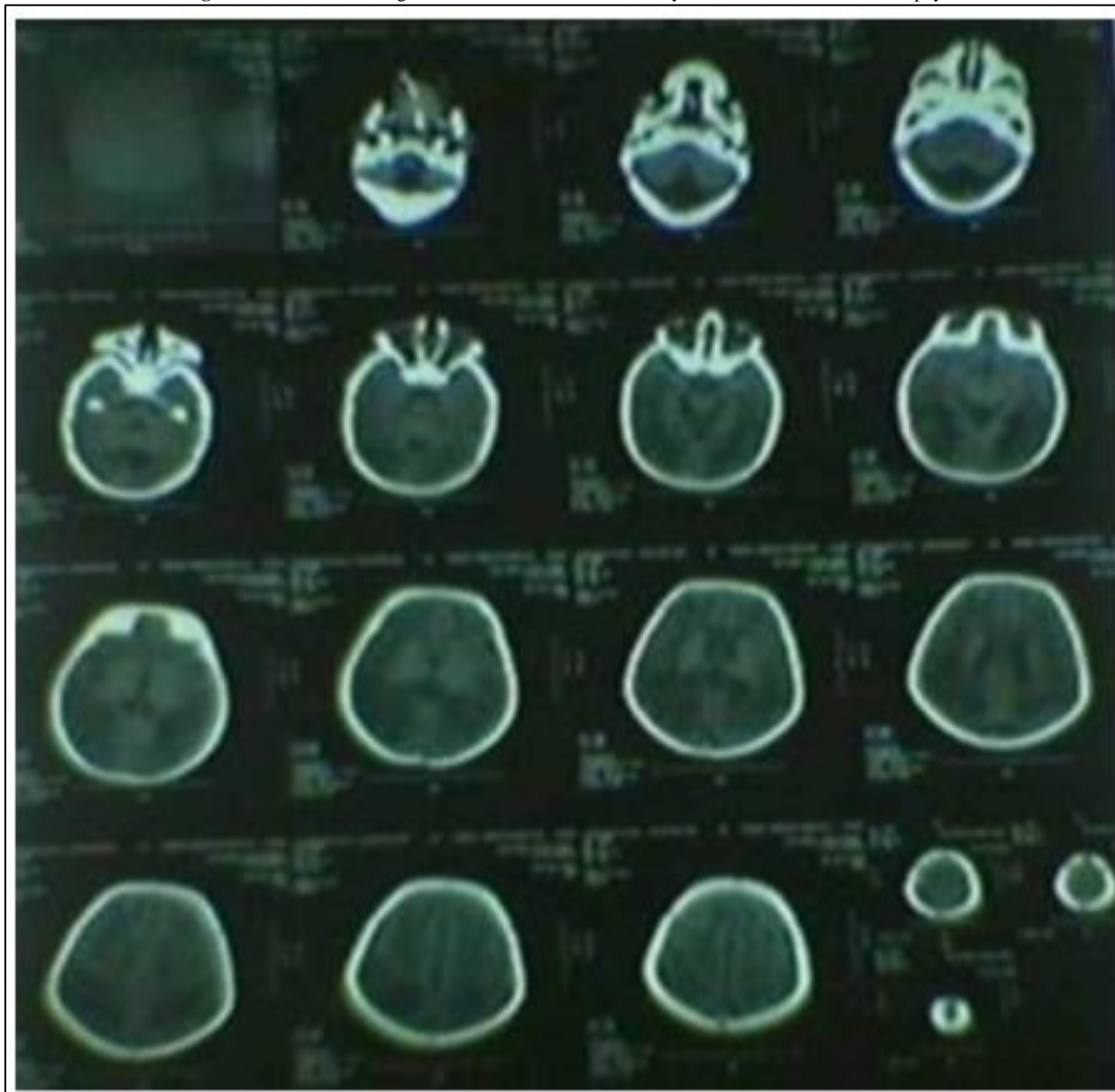
We present a nine day old male late preterm neonate admitted to the neonatal intensive care unit (NICU) with a two day history of reduced activity and poor suck. He was the second of a set of twins, born at 35 weeks gestation in good condition with a birth weight of 2390g, to a 29-year old multigravida with a positive history of consanguinity. He had an initially uneventful course and was discharged against medical advice after 24 hours.

At readmission, he was pink with cold extremities, hypotensive, lethargic and hypotonic. The serum ammonia was elevated (149 $\mu\text{mol/L}$), with hypoglycemia (1.3 mmol/L), while the blood gas, infection markers and electrolytes were unremarkable. Further metabolic tests were conducted on the sample at a regional tertiary centre. His initial treatment included intravenous fluids, inotropes and empirical antibiotics. He however continued to deteriorate with

onset of seizures, rising ammonia levels (peaking at 1256 μ mol/L), until he became deeply comatose with. He had sessions of peritoneal dialysis, while been ventilated.

His metabolic screen received on the seventh day of admission revealed elevated serum argininosuccinic acids and citrulline, as well as argininosuccinic aciduria, in keeping with argininosuccinase deficiency (ASL). He thereafter received arginine hydrochloride and sodium benzoate with protein free milk formula, following which he improved progressively and was discharged after four weeks. The brain CT scan can done on admission revealed diffuse white matter demyelination, with features of atrophy (Figure 1).

Figure-1. Brain CT showing bilateral diffuse white matter demyelination, with features of atrophy



He was followed up in a specialized tertiary hospital, therefore details of his neurodevelopment are not provided. He however presented after 13 months in status epilepticus and subsequently died from metabolic encephalopathy.

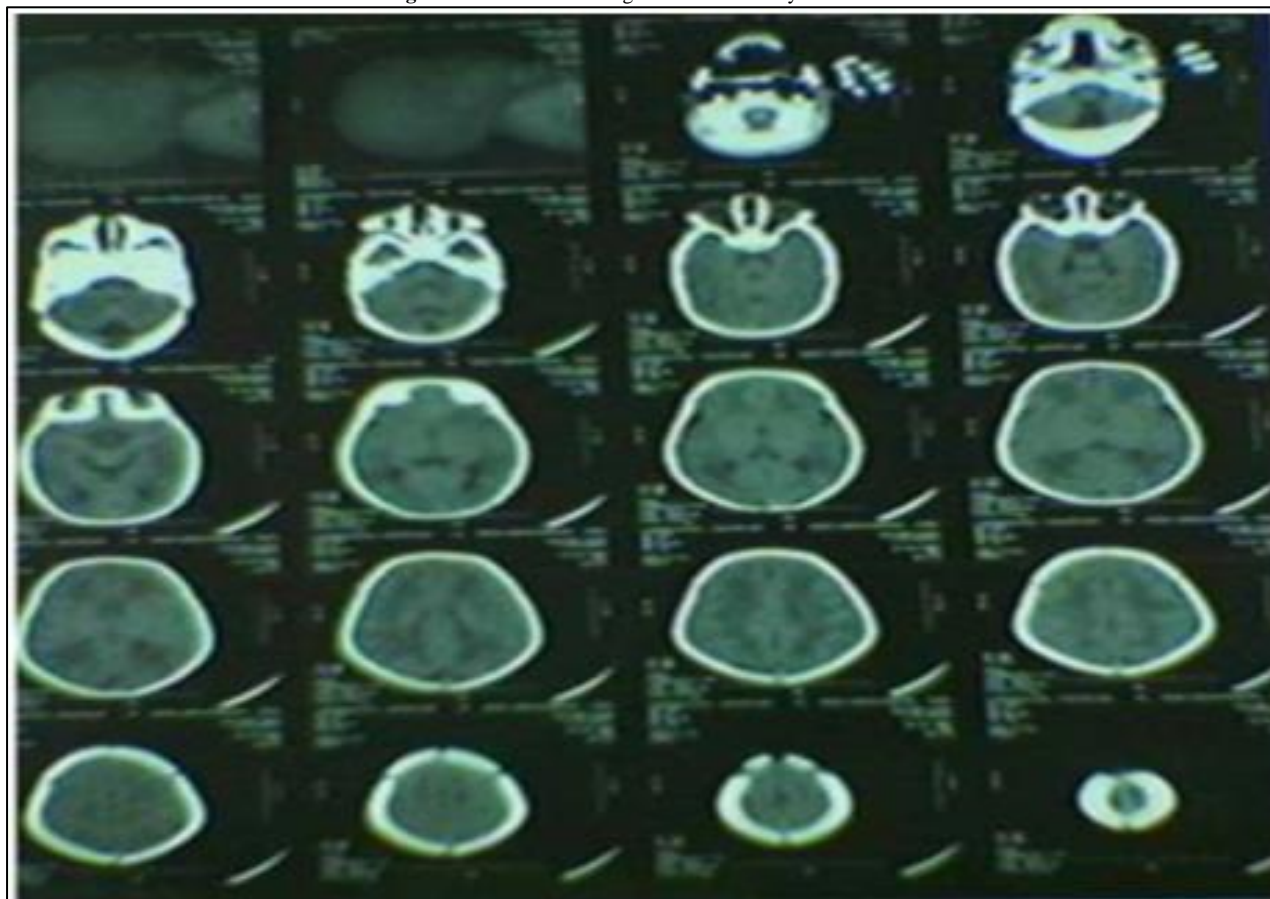
2.1. Case 2

We present a male neonate, first twin of case 1, delivered with a birth weight of 2150g. He was discharged home against medical advice after 24 hours. His parents were advised to bring him for screening around day 16 of life, following the diagnosis of ASA in twin II; however this was delayed until he became lethargic with poor feeding on day 28 of life.

Physical examination revealed hypotonia, dehydration and pitting oedema of the lower limbs. Blood results showed elevated levels of ammonia (787 μ mol/L), argininosuccinic acid and citrulline, confirming a diagnosis of argininosuccinic acidemia (ASA). Sodium benzoate, arginine hydrochloride and protein free milk were administered and he was discharged after three weeks.

His outpatient follow up was done in a specialist centre in another part of the country, therefore details of his neurodevelopment are not provided.

The CT scan of the brain (Fig 2), showed white matter demyelination.

Figure-2. Brain CT showing white matter demyelination

Similarly, at the age of 12 months, he was brought in dead to the hospital emergency department following intractable seizures at home.

3. Discussion

Argininosuccinic aciduria (ASA) is a rare genetic disorder characterized by deficiency or lack of the enzyme argininosuccinate lyase (ASL). It has an estimated prevalence of 1 in 70,000 live births [1-3].

Argininosuccinate lyase (ASL) cleaves argininosuccinic acid to yield fumarate and arginine. The lack of this enzyme leads to the accumulation of argininosuccinic acid and ammonia in blood with concomitant argininosuccinic aciduria [2, 4]. The early signs are usually non-specific, mimicking other common childhood problems, later, patients present with acute life-threatening symptoms of encephalopathy and signs of central nervous system (CNS) dysfunction due to the toxic effects of accumulating metabolites in the CNS [1, 3].

The disease displays variations in its clinical pathology with three distinct phenotypes: neonatal, subacute, and late onset [2, 5, 6]. The index cases had the neonatal phenotype, with poor feeding and hypotonia manifesting in the first and third weeks respectively. Case 1, had an earlier onset and more severe course than the second case, this is likely related to the severity of hyperammonemia. Whereas case 1 had ammonia level over 1200 $\mu\text{mol/L}$ in the second week of life, the second case presented with ammonia level of about 800 $\mu\text{mol/L}$ in the fourth week. This difference may be related to the degree of deficiency of the enzyme ASL in both cases.

The mode of inheritance of ASA is autosomal recessive; it is therefore not unusual to find it in a set of twins, particularly in the setting of consanguinity in the parents. Antenatal testing can be beneficial where there is a positive family history. Pijpers, *et al.* [7] established the diagnosis of argininosuccinic acidemia in both fetuses of a dizygotic pregnancy, using transabdominal chorionic villus sampling at 10 weeks gestation, while Kleijer, *et al.* [8] have also documented molecular prenatal diagnosis in affected families. In our case, prenatal testing was not available to the family to make informed reproductive health choices, even after the demise of the twins.

Due to the nonspecific nature of the symptoms and the possibility for therapeutic management, ASL deficiency is part of the recommended uniform screening panel for newborn screening in the USA [1]. The newborn screening programme in Saudi Arabia has also been recently reviewed to include ASL deficiency, although the process is rather time consuming.

Early administration of arginine hydrochloride and sodium benzoate for argininosuccinic acidemia cases is very effective in reducing blood ammonia and minimizing neurological complications.

While haemodialysis is the most effective measure for treating hyperammonemia, this is not usually feasible, therefore peritoneal dialysis is commonly done in neonates and young infants [9, 10]. Institution of prompt and appropriate treatment before the confirmation of a diagnosis may be life-saving and will reduce the neurological sequelae [11].

Abnormal EEG and intellectual disability have been reported even in patients diagnosed and treated appropriately from early neonatal period. The most decisive prognostic factor is the degree of cerebral damage sustained prior to the diagnosis and treatment [11, 12].

4. Conclusion

Inborn errors of metabolism contribute to childhood morbidity and childhood mortality. Argininosuccinate lyase deficiency is a recognized cause of encephalopathy and cerebral palsy. The presenting features are non-specific and a high threshold of suspicion is required to make accurate diagnosis. Early diagnosis and institution of appropriate intervention can significantly improve outcome. Routine newborn metabolic screening should not only be implemented universally, the result should be available promptly.

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