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Case Report

A Novel Variant of ASL Gene Mutation in a Lebanese Neonate with Severe Argininosuccinic Aciduria Phenotype

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Abstract

Argininosuccinic aciduria is a urea cycle defect associated with deficiency in argininosuccinate lyase enzyme, leading to a severe hyperammonemic encephalopathy, epilepsy and hepatopathy. Only very few known mutations have been linked with a severe phenotype. Here we report the case of a Lebanese newborn child with a very early manifestation of argininosuccinic aciduria, his genetic studies confirmed the presence of a mutation in the ASL gene (c.697A>C p.(Thr233Pro) at the homozygous state. To our knowledge, this is the first time this variant has been reported in literature.

***Keywords:** Argininosuccinic aciduria, Urea Cycle defect, ASL gene, Hyperammonemia, Neonatal Screening*.

Introduction

Argininosuccinic aciduria (ASA) is a rare genetic disorder associated with deficiency in argininosuccinate lyase (ASL), the enzyme needed for the catalysis of the fourth reaction of the urea cycle, essential for urea detoxification and arginine synthesis [1,2]. It is a rare condition occurring in 1 over 70,000 live births, however it's still the second most common urea cycle defect (UCD) [1]. ASA can present with an early severe phenotype in neonates or a milder form in older children. Only few ASL mutations have been associated with the severe phenotype with the variant (c.857A>G, p.Gln 286Arg) being the most frequent[3]. Here we report the case of a newborn Lebanese male presenting with a previously unreported variant of the ASL gene leading to a severe neonatal phenotype.

Case Presentation

Hereby we report the case of a full-term newborn boy from the southern Lebanon, transferred to our medical center at day 9 of life from a peripheral hospital. The patient was born by normal vaginal delivery, with no perinatal complications, to consanguineous parents with a previous history of a child dying at the neonatal period with the same manifestations, but not investigated.

The family history is pertinent for multiple deaths in infancy in male and female individuals at both sides of the family (Figure 1), to notes that no one of these patients had a neonatal screening for metabolic disorders.

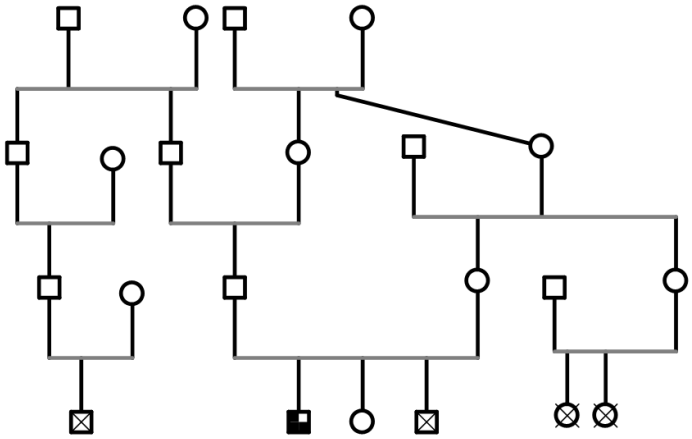

Figure 1: *Family's Pedigree.*

The symptom free period extended until the 7th day of life; the child was first discharged home normally after birth with a birth weight of 2.8kg. 3 days after discharge, the child started to have poor feeding with constant irritability. At day of life 7, he became hypoactive and started vomiting, not tolerating oral intake, with severe generalized jaundice.

Preliminary laboratory workup showed indirect hyperbilirubinemia of 17.6mg/dL and the patient was placed under phototherapy. Liver enzymes levels were normal. With persisting hypotonia a brain MRI was done and showed no abnormalities. On the second day of hospitalization, patient was still deteriorating with increasing somnolence. He had one episode of right sided tonic seizure of 15 minutes duration and levetiracetam was started. Ammonia level was taken and found to be 423 mcg/dL, so sodium benzoate was immediately started at 100mg/kg/day, then increased to 200mg/kg/dL.

At day of life 9, the patient was transferred to our center in Beirut in a comatose state requiring immediate intubation for airway protection. The patient had bulging fontanelles and grade 2 papilledema. Laboratory workup was repeated, and ammonia level was found to be 877.6mcg/dL, with direct bilirubin of 2.46mg/dL, total bilirubin of 9.77mg/dL, normal liver enzymes, INR: 3.84 with PTT showing no clot. The patient also had hypoalbuminemia 2.7g/dL and hyponatremia 117mEq/L.

With the absence of other therapeutic options oral sodium phenylbutyrate was started at a dose of 600mg/kg/day, along with an increasing dose of sodium benzoate, reaching 500mg/kg/day. ammonia level started to decrease gradually, till reaching 75mcg/dL after 5 days. The patient became more awake and responsive, and was safely extubated. Doses of Pheburane and sodium benzoate were kept the same with the introduction of oral diet. Protein concentration was started at 0.2mg/kg/day and was being gradually increased and well tolerated until reaching a level of 0.6 mg/kg/dL. Abdominal ultrasound was done and showed mild hepatomegaly. He received vitamin K after which PT and PTT values normalized.

An early neonatal tandem mass screening showed an increased level of arginosuccinate in the dried blood spot sample, and was confirmed by a qualitative chromatography of organic acids in urine showing also elevated levels of argininosuccinic acid and orotic acid.

Whole-Exome Sequencing (WES) test was done showing a novel missense mutation in the ASL gene (c.697A>C p.(Thr233Pro)), confirming the diagnosis of a previously unreported ASL homozygous variant.

Discussion

The advances in molecular genetics and the accessibility of genetic studies have helped identify many patients with rare disorders during the past decade, and in a country like Lebanon with a very high rate of consanguinity, many new variants in genes responsible for orphan diseases have been identified during the recent years [4]. And even though the mitochondrial diseases remain the most common inborn error of metabolism in the Lebanese population [5], yet the urea cycle defects remain very common [6] but with a challenging diagnosis due to the fact that neonatal screening for inborn errors of metabolism is still not mandatory [7], and the referral of suspected metabolic patients to specialized pediatric centers not always very prompt. Here we report a patient from a family with multiple children deceased during the neonatal period following the same symptoms, thus most likely affected with the same disorder, none of these patients was screened at birth and no conclusive diagnosis was reached.

In our patient the diagnosis of a severe form argininosuccinic aciduria was confirmed by identifying a previously unreported variant in a mutation in the ASL gene (c.697A>C p. (Thr233Pro)).

The patient presented with a crisis of severe hyperammonemia secondary to the deficiency in argininosuccinate lyase (ASL), leading to a comatose state necessitation extensive reanimation.

In addition to the hyperammonia resulting for the urea cycle dysfunction in ASA, the clinical manifestations of are essentially attributed to the accumulation of argininosuccinic acid and the decreased production of arginine, a semi-essential amino acid, required as a precursor for urea, proline, and protein synthesis as well as production of nitric oxide [1]. By this, patients with ASA will have nitric oxide (NO) deficiency resulting in accumulation of free radicals and further brain damage as well as impaired vascular functions [1,8]. Arginine also functions as a precursor for four different enzymes. In that sense, arginine is a substance on which many tissues rely. Arginine, hyperammonemia and defective ureagenesis are considered to be directely responsible for the abnormal epileptic activity in patients with ASA, yet a recent study by ElKhateeb et al. suggest the role of central dopamine deficiency as major contributor to the epilepsy in these patients [9].

Severe neonatal forms and late onset forms of ASA are described in literature [3]. Like in the case of our patient, the neonatal form is more severe and characterized by hyperammonemia, respiratory alkalosis, vomiting, lethargy which are mainly common with all the UCDs. However, ASA may also present unique features such as hepatitis, cirrhosis and trichorrhexis nodosa in the older less severe forms.

The pattern of inheritance of ASA is autosomal recessive with the ASL gene responsible for the disorder being located on chromosome 7. A range of diverse mutations have been described encompassing variations such as nonsense mutations, missense mutations, insertions, deletions, and those affecting mRNA splicing[1]. These mutations are distributed throughout the gene, with exons 4, 5, and 7 being particularly prone to mutational events.

There is little literature available on ASL gene mutations and the number of documented mutations thus far has been relatively limited when compared to other UCDs. Reporting all pathogenic new variant of the mutation would help enrich the international gene databases in order to have more accurate diagnoses.

The therapeutic options vary from the classical sodium benzoate therapy, to sodium phenylbutyrate, and Glycerol phenylbutyrate, even reaching dialysis in extreme cases. The intravenous forms are not always available and the access to the new molecules is limited due to the pricing. Therapeutic guideline should thus be tailored to the medication availabilities in every country. I our case with the absence of intravenous forms, we had no success with oral sodium benzoate at 500 mg/kg/day, the only remaining option was PHEBURANE® (sodium phenylbutyrate) in the form of oral pellets, which was already reported in neonates earlier in rare cases [10]. The combination of sodium benzoate at 500 mg/kg/day and oral sodium phenylbutyrate at 600mg/kg/day, proved to be safe and successful in reducing our patient's hyperammonemia to normal levels, and allowed the introduction of proteins at a dose of 0.5 g/kg/day.

Conclusion

We hereby report the case of a Lebanese male neonate patient, presenting with a severe form of neonatal Argininosuccinic aciduria, the patient was found to be affected with a homozygous variant of an ASL mutation that has not been described previously to our knowledge, this adds to the list of rare variants of ASL mutations leading to early severe forms of ASA. This patient had multiple siblings who died with the same clinical presentation without a definitive diagnosis. This highlights the importance of newborn screening of inborn errors of metabolism in societies with high rates of consanguinity.

Conflict of Interest

None of the authors has a conflict of interest with the material presented in this paper.

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