

A case report of neurological complications owing to lately diagnosed hyperargininemia emphasizing the role of national neonatal screening policies in the kingdom of Bahrain

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Abstract

Introduction: Arginine is an essential amino acid that plays an important role in various body functions including cell division, wound healing, removal of ammonia, immune function, and release of hormones. Hyperargininemia, an autosomal recessive genetic disorder, is considered one of the least common urea cycle disorders. It rarely presents in the neonatal period but rather appears in children at the age between 2 and 4 years.

Case Presentation: Herein, we demonstrate a case of a 14-year-old female who presented to the neurology clinic with several neurological complications, which were found to be a consequence of high levels of arginine discovered after performing a metabolic screening test. The hyperargininemia was because of a point mutation of A1 gene on 6q23 resulting in deficiency in arginase enzyme. The complications of this lately diagnosed case of hyperargininemia would have been avoided if a newborn screen were done as a part of a national program.

Conclusion: This study presented certain neurological complications in a 14-year-old female who was lately diagnosed with hyperargininemia. Our case report strongly emphasizes the importance of establishing a national neonatal screening policy to ensure early detection of inherited metabolic disorders, in particular those which can be easily treated, in the Kingdom of Bahrain.

Abbreviations: CNS = central nervous system, EEG = electrocardiography, MRI = magnetic resonance imaging, RFT = renal function test.

Keywords: arginase, arginine, mutation, newborn screening

1. Introduction

The urea cycle is a physiological pathway by which waste nitrogen is eliminated as urea. The cycle consists of 5 serial enzymatic reactions along with other essential mitochondrial amino acids and enzymes. One of the important intermediates in the urea cycle is Arginine. It is a complex essential amino acid that plays an important role in cell division, wound healing, immune

function, and release of hormones. Towards the end of the cycle, L-Arginine is converted via the enzyme Arginase to L-Ornithine and urea. L-Ornithine is then transported back to the mitochondria to resume the cycle, whereas urea is excreted.^[1]

A range of acquired as well as inherited disorders may affect the function of the urea cycle. Among those is hyperargininemia, an autosomal recessive disorder that involves a point mutation of A1 gene on 6q23 resulting in deficiency in arginase enzyme and

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hence ultimately causing hyperammonemia. It rarely presents in the neonatal period, but rather appears in children at the age between 2 and 4 years.^[1]

Nevertheless, arginase deficiency is considered one of the least common urea cycle disorders. The incidence has been estimated to range between 1:350,000 and 1:1,000,000, which may be underestimated. Furthermore, this incidence may have geographical variance, as it might be more common among French Canadian and Japanese populations.^[2] However, cases have also been reported in the Middle East such as in Saudi Arabia and Palestine.^[3]

This report will present a case of hyperargininemia in which diagnosis was delayed. It will highlight the significance of newborn screening and the importance of implementing a newborn screening program in the Middle East particularly in the Kingdom of Bahrain.

2. Case

This is a case of a 14-year-old female, who was diagnosed with Arginase deficiency at the age of 14 years. The patient first presented to the clinic at the age of 14 years following an acute episode of a tonic-clonic convulsion that lasted for <1 minute. Apart from the seizure episode, the mother described a long-term history of lack of concentration as well as an impaired short-term memory.

Physically, the mother described an abnormal gait as well as weakness in both upper and lower limbs with a muscle power grade of 4/5. The patient finds it difficult to use a fork and is unable to brush her hair. Nevertheless, apart from the recent seizure episode, there was no history of any acute incidents such as irritability or previous seizure activity. The patient was not on any anti-epileptic medications. There was also no history of reduced appetite, vomiting, or drowsiness and the patient has full voluntary control over her bowel and bladder function.

A detailed medical history was obtained from the mother. It revealed an insignificant birth history as the patient was born at full term via a spontaneous vaginal delivery with a birth weight of 3.7 kg and no antenatal or postnatal complications were present. However, the mother's first worry was that the patient's speech was delayed. She only started to talk at the age of 2 years. Nonetheless, the mother did not observe any delay in other developmental milestones. For example, the patient started to walk at the age of 11 and was active and social.

Later at the age of 5 years, the patient was taken to kindergarten. It was then that the mother started noticing her child behaving slightly differently from her peers. She was overactive and her concentration was lacking. The mother said that by the end of the year, her classmates were able to read and write letters but her child could not.

The child was taken to several doctors. A neurologist first saw her at the age of 5 and the mother was informed that her child has a learning difficulty (dyslexia). A psychiatrist then saw her at the age of 7 and diagnosed her with attention deficit hyperactivity disorder. She was given a medication but the mother did not notice any improvement and hence, stopped the treatment.

Her family history was unremarkable. She has 3 siblings and all are well and healthy. Moreover, she is not a product of a consanguinity marriage and there are no metabolic or inherited diseases running in the family.

On examination, the patient was conscious, alert, and oriented. However, a diminished recent memory as well as lack of attention and concentration was noted. Detailed neurological

examination revealed a scissoring gait, decreased power in both upper and lower limbs, and exaggerated knee and ankle reflexes. The rest of the examination, however, was normal.

Investigations were done including: complete blood count, renal function test, liver function test, electrolytes, electrocardiography (EEG) and magnetic resonance imaging (MRI) of the brain all of which were normal and no abnormalities were detected.

A metabolic abnormality was suspected and hence a screening test was done and showed significantly elevated levels of arginine. The family was informed and consent was obtained for diagnostic investigations. A diagnostic molecular test was carried out and revealed a point mutation on A1 gene on 6q23 chromosome. Thus, a diagnosis of arginase deficiency was made (a urea cycle defect).

The family was thoroughly counseled regarding the diagnosis. The plan of management given compromised of the following: natural protein restriction, arginine-free amino acid supplement, sodium benzoate, as well as physiotherapy.

Currently, patient is following up with a private neurology clinic. She is doing relatively well. She is still complaining of residual neurological deficits including upper and lower limbs weakness and gait abnormality. The mother also mentioned that mild cognitive impairment is still present. She is attending a regular governmental school but requiring constant assistance with her academic performance.

3. Discussion

The case presented in this report demonstrated a 14-year-old female who presented to the clinic with several neurological symptoms due to hyperargininemia that was not detected early. Such complications could have been avoided if the underlying cause was early diagnosed via metabolic neonatal screening.

According to the National Institute of Health (Genetic and Rare Disease Information Center), the management guidelines for Arginase deficiency is divided into acute and long-term management. The acute management of hyperammonaemia includes strict dietary protein restriction for no longer than 36 to 48 hours, administration of intravenous fluids with dextrose and intra-lipids, providing ammonia scavenger medications (intravenous Ammonul), and preparing for the possibility of hemodialysis to prevent irreversible central nervous system (CNS) damage.^[4]

On the contrary, long-term management includes: monitoring of dietary protein intake under the supervision of a metabolic dietician. The dosage of protein is initiated at 0.6 g/kg/day and then increased gradually by 0.25 to 0.5 g/kg/day according to the tolerance of the patient, reaching to a maximum dose of 2 g/kg/day; promoting nitrogen excretion by using ammonia scavenger medications (sodium benzoate and sodium phenylacetate); providing thorough education and genetic counseling for the patient and family.^[4]

Furthermore, it has been well documented that late detection of hyperargininemia causes long-term irreversible CNS damage owing to uncontrolled levels of ammonia.^[4]

As in the case discussed above, hyperargininemia was lately discovered after the manifestation of several neurological complications that would have been evaded by the early diagnosis. Those complications include impaired cognitive function (impaired short-term memory and poor concentration) and persistent muscle stiffness (as seen in physical examination; the patient had a scissoring gait). Moreover, if the diagnosis was

further delayed the patient would have been subjected to further complications including inability to walk, loss of bladder control, and some degree of intellectual disability.^[2]

The most efficient way to avoid devastating complications of inborn errors of metabolism as reported in our herein case is conduction of newborn screening programs that include common diseases in the region, especially treatable ones. A number of cases have been reported with late diagnosis in the Middle East. One of them was published in Saudi Arabia in which diagnosis was made at the age of 7 years.^[3] However, only few countries in the Middle East currently have established newborn screening programs.

Moreover, the prevalence of consanguinity marriages in the Middle East ranges between 25% and 70% with high percentage of first-cousin marriages.^[5] Owing to this fact, the frequency of inborn errors of metabolism is higher than in other regions of the world. In particular, in one study conducted in Bahrain during a period of 3 years, 25 infants were diagnosed with metabolic conditions out of nearly 2000 screened infants. Out of those 25 infants, 21 were products of consanguinity marriages.^[6]

On the contrary, considering the fact that the annual birth rate in Bahrain has increased during the last 5 years reaching to 20,354 live births in 2016^[7] and that tandem mass spectrometry used for metabolic screening is reasonably expensive and technically challenging, establishing a national neonatal screening program may have a considerable effect on the government finances. Nevertheless, the cost of such screening program will still be relatively less than the cost of treatment of lately diagnosed cases in which multiple severe complications have already manifested. Besides, as in the case presented, multiple comprehensive investigations were done including laboratory investigations, MRI scans, and EEGs to finally consider the diagnosis of a metabolic abnormality. All of those investigations required are costly and may be unnecessary in case a screening test was done early in the neonatal period.

Finally, Bahrain is one of the Middle East countries, which already have an established newborn screening program. However, this program only includes certain conditions such as common hemoglobinopathies and congenital hypothyroidism. Neonatal metabolic screening, however, is only selectively done upon request. Therefore, health professionals aspire to add metabolic screening to the newborn screening program in Bahrain, particularly, adding common metabolic conditions and treatable ones.

4. Conclusion

In this case study, we have attempted to emphasize the high incidence of metabolic conditions in the region and thus promote to consider taking big steps toward creating new strategies toward newborn screening program.

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