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A CASE REPORT ON WOLCOTT RALLISON SYNDROME

KEY WORDS:

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ABSTRACT

A Case Report of Wolcott–Rallison syndrome, it is a rare, autosomal recessive disorder with infancy-onset diabetes mellitus, multiple epiphyseal dysplasia, osteopenia, mental retardation or developmental delay, and hepatic and renal dysfunction as main clinical findings. Patients have most common history of consanguineous marriage. Patients with WRS have mutations in the EIF2AK3 gene, which encodes the eukaryotic translation initiation factor 2-alpha kinase 3. Most common cause of death is fulminant hepatitis in early childhood. The EIKF2AK3 gene codes for PERK (pancreatic endoplasmic reticulum kinase), an explanation for the spectrum of symptoms. PERK is associated with the activity of beta cells in the pancreas. A broad range of bodily systems is affected, including pancreas, kidney, liver, bone, and nervous system, because of deficient stress response to improperly folded proteins inside the endoplasmic reticulum. A two months old male child born out of non-consanguineous marriage, Hindu by religion, presented with complain of fever since 4 days, respiratory distress since 12 hours. Patient was admitted and on regular blood sugar screening on arrival was high. Repeat random blood sugar was also elevated. Arterial blood gas was done which was suggested metabolic acidosis. Due to persistent high blood sugar, insulin drip was started and HbA1c was done which was 11 gm% and other investigations done. Diagnosis of neonatal diabetes mellitus was kept and managed accordingly. Studies for other endocrinopathies and autoimmune disease done which was negative. Child was having normal growth and development according to age. Genetic studies for neonatal diabetes was planned and EIKF2AK3 gene mutation was found homozygous. Both the parents were heterozygous for the mutation. So diagnosis was kept and regular follow up was advised. Key-words: Infant, Neonatal Diabetes, Endocrinopathy

INTRODUCTION

Wolcott–Rallison syndrome (WRS), it is a rare, autosomal recessive disorder with infancy-onset diabetes mellitus, multiple epiphyseal dysplasia, osteopenia, mental retardation or developmental delay, and hepatic and renal dysfunction as main clinical findings. Patients with WRS have mutations in the EIF2AK3 gene, which encodes the eukaryotic translation initiation factor 2-alpha kinase 3[1]. Most common cause of death is fulminant hepatitis in early childhood. The EIKF2AK3 gene codes for PERK (pancreatic endoplasmic reticulum kinase), an explanation for the spectrum of symptoms. PERK is associated with the activity of beta cells in the pancreas. A broad range of bodily systems is affected, including pancreas, kidney, liver, bone, and nervous system, because of deficient stress response to improperly folded proteins inside the endoplasmic reticulum [1,7].

CASE REPORT

A two months old male child born out of non-consanguineous marriage, Hindu by religion, presented with complain of fever since 4 days, respiratory distress since 12 hours. He has no complain of cough, cold, convulsion, refusal to feed, altered sensorium. There was no significant past history, no history of similar complaints in past. Patient was admitted and on regular blood sugar screening on arrival was high. Chest radiograph and other blood investigations (complete blood count, c-reactive protein, electrolytes, blood culture) were normal. Repeat random blood sugar was also elevated. Arterial blood gas was done which was suggested of metabolic acidosis. Due to persistent high blood sugar, insulin drip was started and HbA1c was done which was 11 gm%. There were no significant findings on general examination. Head to toe examination was normal. On systemic examination, there were no significant respiratory findings, cardiovascular system was normal and no organomegaly was present. Diagnosis of neonatal diabetes mellitus was kept and gradually patient was shifted to basal bolus regimen. Studies for other endocrinopathies and autoimmune disease done which was negative. Child was having normal growth and development according to age. Genetic studies for neonatal diabetes was planned and we sent serum samples of patient and parents to Madras Diabetes Research Foundation, Chennai, where they ran a genetic test panel for neonatal diabetes. and EIKF2AK3 gene mutation was found homozygous. Both the parents were heterozygous for the mutation. So diagnosis was kept as Wolcott Rallison Syndrome. During the course of illness patient had highly fluctuating blood sugar and episodes of hypoglycaemic convulsion were also noticed on regular insulin. Regular insulin was shifted over to long acting Glargine insulin to reduce the fluctuations in the blood sugar, and dose was adjusted to 0.6 IU/Kg/Day. Patient was screened for other associated renal and hepatic dysfunction which were normal. Skeleton growth was normal for age. Child was discharged on subcutaneous insulin lispro and glargine.

DISCUSSION

Wolcott Rallison Syndrome is rare, autosomal recessive with infancy-onset diabetes mellitus, multiple epiphyseal dysplasia, osteopenia, mental retardation or developmental delay, and hepatic and renal dysfunction as main clinical findings. There are 54 reported cases for this disease so far. 18 of them are from the Kingdom of Saudi Arabia and other cases have been found is Kosovo. It is most common in albanian population due to consanguineous marriages. There were reported cases involving patients from non-consanguineous parents that were carriers for the same mutant allele [2].

The main focus for this autosomal recessive disease is

mutations to the EIF2AK3 gene. This gene is located on the short arm of chromosome 2 (2p11.2)[3,5]. In unrelated families, different mutations have been observed in the EIF2AK3 gene, including missense and nonsense mutations. For some cases for unrelated families, identical mutations were also observed. The EIKF2AK3 gene codes for PERK (pancreatic endoplasmic reticulum kinase). PERK is associated with the activity of beta cells in the pancreas. PERK is a transmembrane protein located in the endoplasmic reticulum (ER), which plays a key role in the translation control during the unfolded protein response (UPR). PERK, together with IRE1 and ATF6, is a stress sensor in the ER, which detects the accumulation of misfolded proteins and initiates the appropriate cellular response of UPR that maintains the cell integrity. Upon activation, it phosphorylates the translation initiation factor eIF2a, which in turn reduces protein synthesis, and it also activates the expression of stress-related proteins, such as ATF4, which increases the expression of other transcription factors such as ATF3 and CHOP, that regulate a variety of cellular processes, including amino acid metabolism, oxidative stress, and apoptosis. Both mechanisms contribute to preventing overload of the secretory process. The endoplasmic reticulum is a major protein sorting and processing centre in every body cell [3,6]. A broad range of bodily systems is affected, including pancreas, kidney, liver, bone, and nervous system, because of deficient stress response to improperly folded proteins inside the endoplasmic reticulum. This is part of the reason why patients suffer from multiple epiphyseal dysplasia and osteopenia. Hyperglycaemia is the only initial manifestation of the disease, rest of the biological assessment being normal. With time short stature and skeletal dysplasia with radiographic abnormalities progressively develop and are generally diagnosed after diabetes onset, early signs being difficulty or delayed walking, deficient mineralisation, and osteoporosis. Liver dysfunction in form of acute liver failure is common presentation associated with biopsy suggestive of ballooning of hepatitis with necrosis. Exocrine pancreatic insufficiency is also commonly seen with similar histological findings as found in liver [2]. Growth retardation and short stature in WRS patients can generally be documented clinically only after the age of one year or so. From that age, gradual slowing of growth rate is generally observed with growth retardation that sometimes becomes extremely severe [3].

Genetic diagnosis is necessary for neonatal diabetes to differentiate from transient neonatal diabetes and permanent neonatal diabetes for management point of view. There are 25% chances of recurrence in the affected sibling [4]. Treatment involves supportive care for hyperglycaemia and dysplasia. No definitive treatment has been identified. The prognosis is poor, patients usually die at a young age within first decade of life. Death occurs usually due to multi-organ failure with predominant liver-renal dysfunction, sometimes associated with encephalopathy[4]

CONCLUSION

Wolcott Rallison Syndrome (WRS) is an autosomal recessive syndrome with most common missense mutation of the gene EIF2AK3 located on short arm of chromosome 2 (2p11.2). The presentation is mostly like neonatal diabetes. Other features of the disease manifestations are bony dysplasias, growth and developmental delay, liver and renal dysfunction. The diagnostic confirmation is by genetic screening only, with no favourable prognosis. Treatment is supportive care for hyperglycaemia and bony dysplasia. Most common cause of death in children is hepatic failure and encephalopathy. [3]

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