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RESEARCH ARTICLE

LESCH NYHAN SYNDROME- UNUSUAL PRESENTATION- A CASE REPORT

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Abstract

Lesch Nyhan Syndrome (LNS) is a rare hereditary disorder with an incidence of 1 in 380,000. It is a condition characterized by neurological and behavioral abnormalities and uric acid over production in the body. The authors here report a case where developmental delay, a common presentation was complicated by presence of pathological jaundice in neonatal period. It was further complicated by parents shifting to another country and lost to follow up. By the time case was diagnosed and parental counseling was done, mother was already pregnant and 20 weeks into her 2nd pregnancy and abortions were prohibited by law in that country. It is unfortunate that 2nd child is also a male child who is affected.

Introduction:-

Lesch Nyhan Syndrome is a rare X-linked recessive inborn error of purine metabolism characterized by the absence of the activity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) caused by mutation in the HPRT1 gene present in long arm of X chromosome(q26-q27) occuring almost exclusively in males.. Purines are nitrogen-containing compounds found in many foods. In the absence of HPRT, the purines hypoxanthine and guanine are not built into nucleotides. This results in overproduction of uric acid and abnormal accumulation of urate crystals in the joints and kidneys. The symptoms of LNS include impaired kidney function, acute gouty arthritis, and self mutilating behaviors such as lip and finger biting, involuntary muscle movements and neurological impairment. Self-hitting and head and limb banging are the most common initial presentations in other syndromes with developmental delay while in LND self mutilation that is biting of lips, digits is pathognomonic .Treatment is symptomatic and supportive. Affected people often do not survive past the first or second decade of life due to renal failure.

Case Report:

A 9 months old male child, product of 2nd degree consanguineous marriage presented to our hospital with complaints of delayed motor and language milestones namely no neck holding, not able to sit with support. Baby was delivered through normal vaginal delivery at 37 weeks and cried after stimulation and routine care. He was admitted to NICU within 24 hours of birth for hyperbilirubinemia for 2 days. Baby was apparently normal after that. There was no significant family history similar to this.

In view of delayed milestones, MRI-Brain was done which showed normal study. Thyroid Profile, karyotyping, metabolic profile and routine investigations (CBC/LFT/RFT) were sent. All the reports were reported normal and patient was suspected to have Bilirubin- encephalopathy. Patient was lost to follow-up for next one and half year.
At the age of 2 years, child was again brought to the hospital with complaints of global developmental delay and self mutilating behavior (Lip biting), crying and screaming and anxiety. On examination, dystonia and hyper-reflexia

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were noted. Baseline investigations revealed high S.Uric acid level of 8.2 mg/dl with normal Urea and Creatinine. USG abdomen showed medullary calcification in kidneys. Patient was suspected to have Lesch Nyhan Syndrome and gene sequencing for molecular diagnosis was advised. The test result showed a hemizygous -likely pathogenic variant in HPRT1 gene. Later, Maternal testing also confirmed carrier status of mother. Genetic Counseling was done and prognosis was explained to the parents.

But mother again conceived and the genetic status and gender of the child could not be determined at the country of residence. Later, she gave birth to a male child who also tested positive for the HPRT1 gene mutation. Presently at 6 months of age, the second child is symptomatic. Both the children are now in follow up.

Discussion:-

LNS is caused by complete HPRT deficiency due to mutations in the HPRT1 gene. Uric Acid Overproduction (UAO) is due to deficient recycling and enhanced synthesis of purine bases. The cause of neurological and behavioral symptoms is unknown.The HPRT enzyme is normally present in all the cells.

The symptoms of Lesch-Nyhan syndrome may become apparent as early as six months of age. Earlier urate crystal formation, resulting from abnormally increased levels of uric acid in the urine, leads to the presence of orange colored deposits ("orange sand") in the diapers of infants. This may be the first manifestation of Lesch-Nyhan syndrome, but it is seldom recognized in early infancy.

As a result of UAO, urate stones may develop in the kidneys of infants causing hematuria and increased risk of urinary tract infections. Urate crystals may also be found in the joints in late teens or adulthood with recurring and progressive episodes of pain and swelling. In older children deposits of urate may collect in cartilaginous tissues and ears which form "bulges"called tophi.

Neurological symptoms associated with Lesch-Nyhan syndrome usually begin before the age of 12 months. Brain has the highest concentrations of HPRT enzyme, more so in Basal Ganglia. Abnormal movements include dystonia, chorea and athetosis .Initially; there may be hypotonia and difficulty in head holding. There maybe developmental delay and also regression. Eventually, most children experience hypertonia and rigidity or spasticity with hyperreflexia and intellectual disability.

The most striking feature of Lesch-Nyhan syndrome is self-mutilation. This behavior most often begins as soon as there is onset of dentition. Self-injurious behavior may include repeated biting of the lips, fingers, and/or hands leading to loss of tissue. They may scratch their face repeatedly and have vomiting, and spitting. They may require restraints after which they become slightly calm but when restrains are removed patient seems terrified and stereotypically place fingers in mouth. LND individual may have aggressive and abusive behavior and may inflict injury to others through pinching, grabbing, hitting and using verbal forms of aggression. Afterwards they may apologize.

Children may be difficult to feed as they have dysphagia and vomiting, and most affected children are underweight for their age. Additional symptoms may include irritability or screaming. Some may also develop megaloblastic anemia which is supposed to be due to increased folic acid consumption but it does not respond to folic acid supplementation.

Another symptom of Lesch-Nyhan syndrome may be a severe muscle spasm that causes opisthotonus. Affected children may also experience hip dislocation, fractures, scoliosis and contractures.

Female carriers usually do not have symptoms of the disorder, but may develop gout later in life as a result of hyperuricemia.

Diagnosis:

Diagnosis is suspected when psychomotor delay occurs in a patient with elevated Uric Acid in blood and urine. Undetectable HPRT enzyme activity in peripheral blood or in intact cells (erythrocyte, fibroblast) and molecular genetic testing confirm the diagnosis. Antenatal diagnosis can be done by amniocentesis or chorionic villus sampling if the mutation has been identified in the family.Since this is X-linked recessive inheritance, genetic counseling is essential.

Management and treatment:
Proper hydration, Urine alkalinization, and allopurinol help manage UAO. Drug therapy should be closely monitored as to avoid xanthine urolithiasis. There is no treatment for the neurological dysfunction. Spasticity and dystonia can be managed with benzodiazepines (diazepam, alprazolam) and gamma-aminobutyric acid inhibitors (baclofen, tizanidine). Physical rehabilitation (i.e. management of dysarthria and dysphagia), devices to enable hand control, walking aids, and posture management to prevent deformities are recommended. Self-injury requires physical restraints, behavioral and pharmaceutical treatment (gabapentin, carbamazepine). S-adenosylmethionine (SAMe) which is thought to act by countering nucleotide depletion in the brain has been reported to specifically reduce the rate of self injury in some cases. Bone marrow transplantations (BMT) have been unsuccessfully tried in some cases based on hypothesis that central nervous system damage is produced by circulating toxin but patients died of complications of BMT

Support organizations and learning more about the disease and ongoing research empowers parents to better manage the patient. So they should be encouraged to join or subscribe to these websites and organizations and keep themselves updated about latest treatment options and avail financial and counselling aids as per availability

The purpose of reporting this case of Lesch-Nyhan syndrome is that sometimes diagnosing these rare cases becomes a challenge as some routine neonatal morbidity like neonatal asphyxia, hyperbilirubinemia and sepsis can mislead the diagnosis. A high index of suspicion is needed for diagnoses of these high morbidity, high mortality & untreatable, rare cases. As diagnosis is delayed genetic counselling may not be given for next pregnancy. Parents undergo lot of mental trauma and financial setback. We aim to emphasize about importance of timely diagnosis and counseling.

Fig:- Child showing pathognomonic features of LNS.

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