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Case Report

Maple Syrup Urine Disease with Concomitant Congenital Adrenal Hyperplasia in a Setting of Consanguineous Marriage.

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Consanguineous marriage is deeply embedded in the fabric of South-East Asian society. Maple Syrup Urine Disease (MSUD) and congential adrenal hyperplasia (CAH) are autosomal recessive diseases, with an increased risk of transmission amongst progeny of consanguineous relationships. Maple syrup urine disease (MSUD) is an autosomal-recessive disorder of branched-chain amino acid (BCAA) metabolism, namely leucine, isoleucine and valine. It is rare in most populations occurring in about 1 in 185,000 live births.[1] Deficiency of branched chain keto acid dehydrogenase(BCKD) results in accumulations of the aforementioned AAs, allo-isoleucine and alpha-ketoisocaproic acid (aKIC), resulting in cerebral edema and encephalopathy.Classic sign is "Burnt Sugar" or "Maple Syrup" smell in urine due to Alpha-Hydroxy Acid . [2-4] MSUD is further divided into four types i.e. Classic , intermediate, intermittent and thiamine responsive , based on age of onset, severity and residual BCKAD enzyme activity. Clinical manifestations of Classic MSUD are manifested in early neonatal life and range from Maple syrup odor in cerumen within 12 hours after birth; elevations of allo-leucine and branched chain AAs in plasma by 12-24 hours; irritability, vomiting, poor feeding, and ketonuria and 2-3 days after birth; followed by neonatal encephalopathy: lethargy, apnea, opisthotonus, "Bicycling" and "Fencing" posturing by age four to five days. Respiratory failure ultimately sets in around days 7 to 10. If left untreated can result in developmental delay,cerebral palsy, seizures, and mortality. [5-10]

MSUD like other Autosomal recessive disorders follows a pattern where there is a 25% chance of being affected, 25% chance of being spared and not a carrier, while 50% chance of being a carrier and unaffected.[3] Progeny born out of a consanguineous relationships or inbreeding have a higher risk of mortality, morbidity, congenital anomalies .Incidence of inborn error of metabolism carries a higher weightage in Pakistan, Turkey and Arab countries compared to a Western country such as Denmark where consanguinity is rarely a norm. [7] Treatment consists of leucine restriction in diet, management of precipitating stressful states with judicious supplementation of valine and isoleucine.[4]

CAH is an autosomal recessive disorder, characterized by deficiency of 21 α hydroxylase enzyme (90% of cases) and elevated levels of 17-OH Progesterone. This results in elevated levels of androgens causing virilization in females and diminished mineralocorticoids and cortisol. Based on correction for age and birth weight threshold values of 17 OH-Progesterone spectrum ranges from normal, possible CAH and probable CAH. [11-16]

Case Report:

A 16 day old girl, born from a first-degree consanguineous marriage, as a second child, at term initially had no symptoms of any respiratory distress or irritability. She was easily taking breast feeds except delayed crying for 3 minutes immediately after birth and ambiguous genitalia. On the 4th day she developed marked difficulty in breathing, cyanosis and grunting, with repeated bouts of vomiting with inability to feed. Antenatal History was significant for Vacuum Assisted Delivery at term with polyhydramnion . There was a prior history of neonatal demise in the first sibling with unknown cause though it was suspected that she might be a case of undiagnosed MSUD as well after the second child was diagnosed. Parents also denied any genetic testing done after the death of their first born. Patient was referred to our hospital NICU for ventilator support by the private hospital, where her condition further deteriorated ,with a 6 days history of shortness of breath, odour of "burnt sugar" in urine, poor feeding and vomiting with episodes of tachypnea and grunting, cyanosis, seizures. Upon examination patient appeared pale, lethargic, and afebrile with bulging fontanel, thin extremities and normal anthropometry. Patient had a weight of 2500 grams, hypotonia, hyporeflexia appreciated in extremities, with bilateral basilar crackles and lower edge of liver and spleen palpable subcostally 4cm and 3cm respectively. Cardiovascular examination appeared normal.Initial

Lab testing revealed marked urinary levels of branched chain amino acids (ILE 2360 umol/L, LEU 447 umol/L) with serum levels suggesting hyperammonemia (123 umol/l). She had elevated 17 OH-Progesterone on day 7th (47 nmol/l-possible CAH), with Lactate levels of 1.79 mmol/L and Serum TSH 1.5. Her condition further deteriorated with a raised anion gap acidosis of 17-Na+143, K+3.6, Cl+107.HCO3 19.Her BSR on admission to the NICU was 107 mg/dl a marked decrease in level from 253 mg/dl from 5 days prior in the private hospital.Patient was placed on ventilator after resuscitation with inotropic support, given IV antibiotics, IV fluids, SpO2 monitoring and vitals monitoring hourly. She showed no signs of improvement and died after a couple of days of Ventilator support.

Discussion

This report highlights a case of MSUD associated with elevated levels of 17 OH-Progesterone; product of a consanguineous marriage. This case demonstrates Classic MSUD presentations; with maple syrup urine odor, episodes of difficulty breathing, grunting, neonatal encephalopathy; seizures, vomiting, irritability, lethargy, inability to take regular feeds, vomiting, apnea later complicated with central respiratory failure. Due to elevated levels of 17 OH-Progesterone (47.2 nmol/l) corrected for age and birth weight patient was a suspected case of another autosomal recessive "Possible" CAH.[16] Lack of proper genetic counseling and Antenatal screening resulted in an inadequate management warranting better planning and implementation of genetic counseling and screening in high risk families.

It is an established fact that consanguinity results in a higher prevalence of genetic anomalies.[7] Discouraging against consanguineous marriage is in direct conflict with medical ethics and completely disregards cultural footing that this practice has in a country like Pakistan where consanguineous marriage is seen as a means to maintain Kinship and strong sociocultural bonds. [17] However, emphasis should be laid on proper genetic counseling, evaluating relatives at risk rooting out misconceptions on inheritance, identifying families at risk and screening should be instituted, none of which was implemented in this case as laid down by the National Society of Genetic Counselors. [4,18] Thus it was advised further to the parents of the child to undergo genetic testing and antenatal screening to be better prepared for future unwanted occurrences if any.

MSUD and CAH like other autosomal recessive disease are seen in direct proportion consanguinity. More than one such disease is not usually seen in a single individual. Genetic counselling is highly desired in such high risk families to prevent such future outcomes.

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