Abstract:
Inborn errors of metabolism are rare, difficult to diagnose and treat. We had such a rare case scenario of a 22 year old women whose first child was a diagnosed case of Wolman disease, came to our og opd with 8 weeks of pregnancy for further evaluation. Wolman disease is a rare genetic disorder caused by a deficiency of an enzyme known as lysosomal acid lipase. It is an autosomal recessive condition involving the breakdown and use of fats and cholesterol in the body. She was counseled regarding the prognosis of the disease and need for detailed evaluation by chorionic villous sampling or amniocentesis.

Keyword: Wolman disease, Lysosomal acid lipase

CASE REPORT OF WOLMAN DISEASE IN SIBLINGS:
Introduction:
Wolman disease is a rare autosomal recessive condition involving the breakdown and use of fats and cholesterol in the body. It is a rare genetic disorder caused by a deficiency of an enzyme known as lysosomal acid lipase. In affected individuals, harmful amounts of lipids accumulate in the spleen, liver, bone marrow, small intestine, adrenal glands and lymph nodes, arteries and veins. In addition to fat deposits, calcium deposits in the adrenal glands are also seen. Wolman disease was named after Dr. Moshe Wolman who discovered the disease. Wolman disease is estimated to occur in 1 in 350,000 newborns. About 50 cases have been reported worldwide.

Case report
A 22 year old female with obstetric score - G2P1L0 came to our OPD with 8 weeks of pregnancy for regular antenatal check up. She got married 3 years back (non consanguinous marriage), with no relevant family history. During her 1st pregnancy she was booked and immunized with ultrasound check up done in all three trimesters in a private hospital elsewhere.
Her Antenatal period was uneventful. Her first child was a female baby delivered by emergency LSCS (indication- Non progression of labor). Birth weight was 3.4 Kg. Early neonatal period was uneventful. Later baby developed recurrent fever and failure to thrive from 3rd month of life. No stigmata of intrauterine infections. No history of jaundice, vomiting, diarrhoea or bleeding diathesis. There was progressive abdominal distension. On examination there was pallor, hepatosplenomegaly and generalized lymphadenopathy. Basic investigations were done, which showed hemoglobin of 7 gm/L with leucocyte count of 18,000. Peripheral smear was normal. Liver functions were grossly deranged with SGOT - 236 IU/L, SGPT 398 IU/L, and LDH was 1245 U/ml. Prothrombin time was prolonged with INR of 2.5. X ray abdomen showed bilateral adrenal calcification which was confirmed by ultrasonography. In view of adrenal calcification, elevated liver enzymes and signs and symptoms, there was a suspicion of Wolman’s disease hence lipid profile was sent which was grossly deranged (total cholesterol 320, triglycerides 450) and the diagnosis was narrowed down to Wolman’s disease. The confirmatory test for this condition is decreased Lipid acid esterase enzyme assay, which was done and was found to be 3.75 nmol/hr/mg (normal range - 12-43.8 nmol/hr/mg). Baby died after 15 days of diagnosis due to cachexia.

Plain X ray abdomen - Bilateral Adrenal Calcification:
In her second pregnancy, nuchal translucency scan along with double marker (with beta HCG (human chorionic gonadotropin), and PAPP-A (pregnancy associated plasma protein – A) was done and was normal. Patient was advised to do Chorionic Villous Sampling / amniocentesis, but patient refused because of financial reasons. She was sent for level 2 scanning in the second trimester—the report was normal. Fetal adrenals were normal with normal Doppler study and major anomalies were ruled out. Subsequently a growth scan with AFI and Doppler was done in 3rd trimester at 34th week and was normal with no detected anomalies and AFI (amniotic fluid index) was 11 with growth corresponding to period of gestation and a normal doppler study. At 38 weeks she delivered a full term female baby with 3.5 kg by elective cesarean section. Baby cried immediately after birth and there were no detectable anomalies. On evaluation her second baby was also detected to have elevated lipid levels (total cholesterol 310 mg/dl, triglycerides 420mg/dl) and adrenal calcification on post natal x ray abdomen and ultrasound, thus confirmatory of Wolman disease. The enzyme assay was done which was also found to be reduced (7 nmol/hr/mg). Baby is now 35 days old. Weighs 3.5 kgs. No organomegaly / lymphadenopathy. Baby has occasional vomiting and diarrhoea and is under regular Paediatric followup.
Discussion:

Wolman's disease occurs due to lysosomal acid lipase deficiency, leading to massive accumulation of cholesterol esters and triglycerides in most body tissues. The structural gene for the acid lipase enzyme is located on chromosome 10. Wolman disease is a result of mutations in the DNA on the LIPA gene in particular on chromosome 10. This particular mutation, called a "splice-site mutation," which is the substitution of nucleotide guanine in place of nucleotide adenine, in a sequence that codes for enzyme lipase production, near the site called exon (8). This swap in the nucleotides leads to a shift in the amino acid sequence causing an omission of 24 amino acids during the translational process. As a result, the amino acid sequence codes for none or less production of the proteins that make up the enzyme lipase (lysosomal acid lipase).

The onset of symptoms is typically very early, within the first few weeks of life as in this case. Infants usually present with failure to thrive, developmental delay, diarrhoea, hepatosplenomegaly and mild anaemia. Adrenal failure is relatively rare. The neurological manifestations include mental retardation, spasticity and clonus, is also seen. The extent of the neurological disease is not very clear as these infants usually succumb to gastrointestinal and haematological complications and die early. Prenatal diagnosis is possible by chorionic villous sampling and amniocentesis. Wolman's disease can be diagnosed in the first trimester of pregnancy by the direct demonstration of acid lipase deficiency in chorionic villi. The diagnosis was confirmed by studies on cultured chorionic villus cells or cultured amniotic fluid cells and fetal skin fibroblasts.

Currently there are no approved treatments for Wolman disease. Usually individuals die within first year after birth as they develop cachexia from malabsorption related to the accumulation of engorged macrophages in the villi of the small intestine. The mean life span for patients with WD is 6 months. No treatments have been shown in clinical trials to stop or reverse the abnormalities in patients with Wolman disease.

Management is only symptomatic with restricted diet with low cholesterols and triglycerides.

2 with cholesterol lowering drugs

Bone marrow transplant - hematopoietic stem cell transplantation (HSCT)

In future pregnancy couple can be offered Pre implantation Genetic Diagnosis (PGD) after IVF (in vitro fertilization). PGD by FISH (fluorescence in situ hybridization) and PCR (polymerase chain reaction) techniques we can identify those embryos which are normal and abnormal, and normal embryos can be transferred to get a healthy fetus.

References:
1 Lohse et al. Molecular defects underlying wolman disease appear to be more heterogenous than those resulting in cholesteryl ester storage disease. Journal of lipid research. 1999 Feb;40(2):221-8


