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# Cholesteryl Ester Storage Disease – A Rare Presentation

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***Abstract:***

*Cholesteryl Ester Storage Disease (CESD) is a rare genetic disease characterized by accumulation of cholesteryl esters and triglycerides in many tissues due to deficiency of Lysosomal Acid Lipase (LAL/ LIPA) enzyme, which is essential for hydrolysis of triglycerides and cholesterol esters in lysosomes.[1] The diagnosis is indicated by abnormal lipid profile, deposition of cholesterol crystals in internal organs and reduced acid lipase activity in leukocytes. Here we report a 16 year-old girl who presented with repeated episodes of hepatic encephalopathy with onset of first symptom at 9 years of age with history of consanguinity of marriage between parents. On examination, we found hepatosplenomegaly. Laboratory examination showed abnormal lipid profile and reduced activity of acid lipase enzyme in leukocytes. After exclusion of other possible pathological conditions and on the basis of lab criteria, we diagnose the case as Cholesteryl Ester Storage Disease (CESD).*

***Keywords:*** *Cholesteryl Ester Storage Disease (CESD), cholesteryl esters, triglycerides, Lysosomal Acid Lipase.*

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**Introduction:**

CESD is inherited as an autosomal recessive condition [1] So parents who are close relatives (consanguineous) have a higher chance to have children with a recessive genetic disorder. CESD affects males and females in equal numbers.[2] Approximately 50 cases have been reported in the medical literature but the data is in disagreement with the small no of cases probably due to many CESD are misdiagnosed or undiagnosed making it difficult to determine its true frequency in general populations. The majority of patients with CESD present an exon 8 splice junction mutation (E8SJM), G to A transition at position 1 (E8SJM) as one of the defective alleles in the LIPA gene.[3]

The symptoms and severity of CESD are highly variable. Some individuals may develop symptoms during childhood; others may have extremely mild cases that cause few symptoms. Still other individuals may not have any noticeable symptoms and may go undiagnosed until adulthood. CESD is characterized by alterations of blood lipoprotein profile; patients present with hypercholesterolemia, hypertriglyceridaemia, HDL deficiency with abnormal lipid deposition in many organs. Hepatomegaly usually becomes progressively worse eventually causing scarring (fibrosis) of the liver. In approximately one third of patients, the spleen may also be enlarged (splenomegaly). Abnormal enlargement of the adrenal glands (adrenalomegaly) may also occur in few individuals. Infants may present with feeding difficulties with frequent vomiting, diarrhea, swelling of the abdomen and failure to gain weight.[1]

CESD belongs to a group of diseases known as lysosomal storage disorders, another closely associated disease is Wolman Disease. CESD causing mutations for LAL which retains some enzyme activity while Wolman disease produce an enzyme with no residual activity or no enzyme at all and it is often fatal within the first six months of life. In 1956, Moshe wolman, along with two other doctors, published the first case study of a LAL deficiency in a child born to closely related Persian Jews; 12 years later a case study on an older boy was published, which turned out to be the first case study of LAL deficiency.[1,7]. LAL-D was historically referred to as 2 separate disorders:

- Wolman disease, presenting in infant patients
- Cholesteryl Ester Storage Disease, presenting in pediatric and adult patients

Around 2010 both presentations have come to be known as LAL-Deficiency.[1]

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Diagnosis of CESD may be suspected based upon identification of characteristic symptoms such as abnormally enlarged liver. Thus a thorough clinical evaluation, a detail patient history (including family history) and specialized tests those reveal deficient activity of the LIPA enzyme in certain cells of the body. Molecular genetic testing for mutations in the LIPA gene is also available.[3]

In 2015 FDA approved Kanuma (Sebelipase alfa) as first treatment for LAL deficiency.[5] A hypolipidemic diet and lipid lowering drugs are other therapeutic tools used against CESD.The combination of diet and drug administration has led to dramatic reductions in the levels of lipids such as cholesterol and triglycerides in the blood of affected individuals.[6] A few individuals with CESD who developed Chronic Liver Disease have been treated with a liver transplant with positive results.[3] Genetic counseling is recommended for affected individuals and their families. Other treatment is symptomatic and supportive.

**Case Summary:**

A 16 year old, unmarried, Muslim girl, hailing from Bandar, Narayangonj was admitted in DMCH with the complaints of abnormal behavior followed by one episode of convulsion with several episodes of vomiting for 1 day**.** Patient's mother stated 7 years back her daughter's first symptom started with abnormal behavior followed by confused conversation, excessive sleepiness and several episodes of vomiting. With these complaints she got admitted in a hospital of Dhaka city and was diagnosed as a case of Chronic Liver Disease (on the basis of liver biopsy) with short stature with dyslipidaemia. Since then she had experienced 4/5 episodes of similar illness with decreased severity. Every episode lasted for several hours and was associated with abnormal behaviour in the form of excessive eating, biting others and aggressiveness followed by sometimes convulsion with post ictal confusion. After 4-5 hours she became fully conscious and oriented. She had history of one episode of epistaxis 15 days prior to admission and history of gum bleeding one year back but no history of bleeding from any other site. On query she stated frequent passages of stool about 10-12 times per day upto age 5 years, then decreased gradually. But the stool colour and consistency was normal and it was not mixed with blood. Her mother also reported vomiting just after feeding since her daughter's childhood for which she gave her frequent small feeding. She didn't give history of abdominal pain, swelling, itching, haematemesis or melaena. No history of fever, shortness of breath, cough, joint Pain, skin rash, pigmentation, oral ulceration and Raynaud's phenomenon. Also no history of chronic headache, head trauma, fall, loss of consciousness. Her appetite was poor but no recent history of weight loss. She suffered from Jaundice 10 years back and measles at the age of 1 year. There was consanguinity of marriage between her parents. She had 3 brothers. One brother died of liver disease at the age of 6 years. Other two brothers were in good health. She was fully immunized according to EPI schedule. Her menstruation yet not started. She read up to class one in 2012 with good performance then quit studying due to chronic illness. She was born at term by uncomplicated vaginal delivery. Her developmental milestone was age appropriate except delayed head control at age 10 months and she started walking at age 2 years.

On examination, patient was short statured but trunk and limbs were proportionate. Her facial expression and eye contact was normal. No of fingers and palmar creases were also normal. Her height was below 3$^{rd}$ percentile and BMI was 15.36 kg/m$^2$. She was anaemic, axillary and pubic hair was absent. There was no stigma of chronic liver disease. Liver was palpable, 2 cm from right costal margin in midclavicular line, nontender, firm, smooth surfaced with well defined margin. Upper border of liver dullness was in right 5$^{th}$ ICS and there was no hepatic bruit. No other organomegaly was found. Reproductive system examination revealed breasts were underdeveloped, Tannar stage III. External genitalia exam revealed absent pubic hair. Vulva appeared normal, hymen intact with normal distal part of vagina.

Investigation showed her hemoglobin was always low 7.9 gm/dl, after 2 units of blood transfusion it raised to 9.7 gm/ dl. PBF showed normocytic normochromic anaemia with thrombocytopenia. Liver function test showed normal bilirubin, SGPT, alkaline phosphatase but prothrombin time was 17.40 sec and serum albumin was 2.71 gm/ dl. Her Fasting Lipid Profile was always abnormal. Her Triglyceride level was 575 mg/dl on 13.06.2012, 377 mg/dl on 04.02.2013, 169 mg/dl on 27.06.15, 147 on 27.11.2016 and 228 mg/dl on 12.02.2017. To find out the cause of liver disease we did viral markers which were all negative, ANA was negative, serum ferritin, blood copper level, cecruloplasmin level and urinary copper level all were within normal range. Endoscopy of upper GIT showed Grade II esophageal varices, Liver biopsy done on 11.06.2012 which showed Moderate Chronic Hepatitis, Fibro scan of Liver showed Fibrosis score 63.9 and Fibrosis stage : F4. We also did penicillamine Challenge test which was negative. Due to her Short Stature we assessed her hormone profile (TSH, T3, T4, LH, FSH, Prolactin, PTH, ACTH) which were all found to be normal. USG of whole Abdomen showed enlarged liver with coarse and non homogenous parenchymal echotechture with multiple

echogenic solid masses. Spleen was mildly enlarged, Uterus Infantile, left ovary could not be visualized.MRI showed hyperintensity in the caudate nucleus. EEG showed generalized Encephalopathy. Karyotyping showed 46 XX. For her treatment purpose we did x-ray to determine her age which showed her radiological age was about 11 to 12 years. We also did her MRI of whole Abdomen showing multifocal dysplastic nodules in both lobe of Liver, infantile uterus, bilateral smaller ovaries. To exclude Gaucher's disease we sent blood to see Beta Glucocerebrosidase enzyme activity which was found to be normal.Then we assessed her Lysosomal Acid Lipase enzyme suspecting CESD and it was found 12.1 nmol/hr/mg which indicated lower activity and went in favour of Cholesteryl Ester Storage Disease.

**Discussion:**

Considering all the problem lists…repeated abnormal behavior and convulsion, repeated vomiting, frequent passage of stool, poor appetite, short stature/ failure to thrive, underdeveloped breast, primary amenorrhea, absent axillary and pubic hair, anaemia, hepatosplenomegaly, infantile uterus, and early onset of symptoms at age 9 years, consanguinity of marriage among parents, younger brother died at age 6 years due to liver disease, features of chronic liver disease with evidence in liver biopsy and features of hepatic encephalopathy, we had the differentials of chronic liver disease due to Wilson's disease or Storage Disease. Short stature and hypothalamic amenorrhea due to Chronic Disease like CLD.

Though young patient with Chronic liver Disease with neuropsychiatric symptom, our first consideration was Wilson's Disease, but absence of KF ring, normal serum copper level, ceruloplasmin level and normal 24 hour urinary copper virtually excludes Wilson's disease.

Then our next consideration was Storage Disease. Among all the Storage Diseases,Gaucher's disease was a possibility as she had anaemia, thrombocytopenia, hepatosplenomegaly but Beta Glucocerebrosidase enzyme level was normal which virtually excluded the diagnosis. Then our next consideration was Cholesteryl Ester Storage Disease (CESD) as her lipid profile was always abnormal since her childhood. Her recurrent passage of stool and vomiting can also be explained by CESD where deposition of lipid particle in gut mucosa can give rise to these symptoms. Then we decided to measure enzyme activity of lysosomal acid lipase and it was found to be in lower limit. We also did her parents fasting lipid profile to exclude familial causes and that was found within normal limit.Thus we diagnose our case as CESD.

We treated our patient symptomatically with atorvastatin and fibrates and was discharged with improving symptoms and near normal lipid profile. Though she was 16 years of age, her radiological age was about 11-12 years evidenced by X-ray, then with consultation of endocrine department we treated our patient with growth hormone (Inj Norditropin Simplex 1 mg/day s/c ) and she was responsive very well, she gained 2.5 cm height within 3 months period of growth hormone treatment. For her short stature Estrogen priming could be an option but contraindicated due to CLD. So during discharge the patient was advised to continue growth hormone therapy if can afford and to come in follow up after 6 months with X ray Dorsal spine (B/V).

**Conclusion:**

Older children or adults with CSED (decreased enzyme activity ) may remain undiagnosed or be misdiagnosed until they die early from a heart attack or stroke or die suddenly of liver failure. The first enzyme replacement therapy was approved in 2015. Because LAL deficiency/ decreased activity is inherited, each sibling of an affected individual has a 25% chance of having pathological mutations in LAL genes from both their mother and their father, a 50% chance of having a pathological mutation in only one gene, and a 25% chance of having no pathological mutations. Genetic testing of the family members and genetic prenatal diagnosis of pregnancies for women who are at increased risk are possible if family members carrying pathological mutations have been identified and is the best way to prevent the disease.

**Conflict of interest:** None.

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