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Original Research Paper

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A RARE ASSOCIATION OF NEIMANN-PICK DISEASE WITH ADRENAL CALCIFICATIONS AND COOMB'S POSITIVE HAEMOLYTIC ANAEMIA.

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ABSTRACT

Background: Lysosomal lipid storage diseases are inherited metabolic disorders characterised by lipid accumulation in cells and tissues. They comprise mainly the sphingolipidoses, Niemann-Pick disease, and Wolman disease (Schulze & Sandhoff, 2011). The definitive method of diagnosing these disorders is by detection of genetic mutations. But, these tests are expensive, not universally available and may take a long time for results, making them impractical as first line/screening investigations (Rodrigues et al., 2006). Bone marrow examination is a safe, quick and effective test to undertake in critically ill children with liver disease, and is very useful in the diagnostic algorithm of suspected lysosomal storage disorders, particularly in Niemann-Pick disease (Rodrigues et al., 2006) (Akhtar, Fitzpatrick, Hadic, & Chakravorty, 2018).

Clinical description and Management: We present a rare case of a 3 months old child with bilateral adrenal calcifications, massive hepatosplenomegaly, Coomb's positive haemolytic anaemia and failure to thrive. The differential diagnosis of such findings includes Niemann-Pick disease, Wolman disease, Gaucher's disease, glycogen storage disease type IV, haemophagocytic lymphohistiocytosis, etc. (Bay et al., 2017). Suspecting a storage disorder, a bone marrow examination was done that diagnosed Neimann-Pick disease. Despite supportive therapy, the patient succumbed to the fatal disease.

Conclusion: Bilateral adrenal calcification in infants is an infrequent occurrence with limited literature suggesting it's presence in Wolman disease (Sen, Satija, Saxena, Rastogi, & Singh, 2015). There are limited reports of a lipid storage disorder like Neimann-Pick disease presenting with a haemolytic anaemia (Amla, Gopalakrishna, & Kannan, 1970; Keshavamurthy, Basavaraja, Rajeshekarmurthy, Sanjay, & Premalatha, 2015). Thus, we present a unique case of Neimann-Pick disease with bilateral adrenal calcifications and Coomb's positive haemolytic anaemia, a rare constellation of findings.

KEYWORDS : Adrenal calcification, Neimann-Pick disease, Bone marrow, Wolman disease.

INTRODUCTION:

Neimann-Pick disease (NPD) is a fatal, autosomal recessive lysosomal storage disorder. It is caused by inherited deficiency of an enzyme, acid sphingomyelinase which leads to deposition of sphingomyelin and cholesterol within the lysosomes of reticuloendothelial cells of various organs. It is characterized by failure to thrive, hepato-splenomeagaly and neurodegenerative changes (Narayana, Rafi, Ramisetti, Tumati, & Belavadi, 2019).

The definitive method for diagnosing NPD is the demonstration of undetectable or low rates of cholesterol esterification accompanied by excess storage of free cholesterol by filipin staining in cultured fibroblasts or by the detection of two pathogenic mutations by genetic testing. These tests are expensive, available only at a few specialised centres and may take a long time for results to become available. This makes them impractical as first line/screening investigations (Rodrigues et al., 2006).

Bone marrow aspiration has been shown retrospectively to be a sensitive and relatively non-invasive method for demonstrating storage material in children. As a result, bone marrow aspiration has been recommended in the investigation of unexplained hepatosplenomegaly as a diagnostic tool (Rodrigues et al., 2006).

Thus, we present a rare case of infantile liver failure with adrenal calcification and Coomb's positive haemolytic anaemia in a child diagnosed as Neimann-Pick disease.

CASE DETAILS:

A 3 months old male child, born of third degree consanguineous marriage, presented with gross abdominal distension, intermittent fever since 20 days and failure to thrive. Child was referred from a private hospital with a previous diagnosis of late onset sepsis, having received a course of antibiotics and a suspected metabolic disease. No significant family history was present. Child was delivered by an uneventful, full term normal delivery and had a birth weight of 2.7kg. Weight on admission was only 4 kg that signified failure to thrive.

On examination, severe pallor with tachycardia was found. Anthropometry wise, the child had a weight and length for age less than -3SD. Child had fullness of cheeks signifying subcutaneous fat accumulation. Systemic examination revealed gross hepatosplenomegaly (Liver span of 13 cm and spleen palpable upto umbilicus). Signs of liver cell failure in the form of palmar erythema, paper money skin and deranged PT- INR were present. Child had an apathetic look but was alert. Ophthalmological examination of the child was normal.

Figure No. 1: Gross Hepatosplenomegaly In The Patient.

MANAGEMENT AND OUTCOME:

Upon investigating further, child had severe microcytic hypochromic anaemia with a normal WBC count and platelets (Hb- 7.2gm%, WBC 6200/mm3, platelets- 3,54,000/mm3, MCV-63.9 fl, MCH-22.4 pg, MCHC-22.4 gm%). Peripheral blood smear showed microcytosis, hypochromia with anisopoikilocytosis and polychromasia+. Few atypical lymphocytes with deep blue cytoplasm were seen. Coagulation profile was grossly deranged with a PT of 120 and INR of 11.6. Multiple FFP transfusions and vitamin K were given to normalise the coagulation profile. Child received PCV transfusion in view of severe anaemia with tachycardia. Direct Coombs test was strongly positive suggesting a haemolytic anaemia (4+) with a reticulocyte count of 1.0/cu mm.

Serum triglycerides and LDL cholesterol was elevated with a low HDL cholesterol and blood samples of the child were lipemic. Liver function tests showed a normal serum bilirubin with moderately elevated transaminases and reversal of A/G ratio (SGOT 415 U/L, SGPT- 75 IU/L, ALP- 894 U/L, Serum Albumin- 2.9gm%, Serum Globulin – 6.6gm%). Renal function was normal. CRP was positive and ESR was elevated to 58mm/ 24 hr. Blood cultures came to be sterile. A Koch's disease work up was done, which was negative (Mantoux – negative, CXR – normal, no history of Koch's contact). HIV of the mother was non-reactive.

Radiological investigations revealed adrenal calcifications with hepatosplenomegaly on a radiograph of chest and abdomen. This was further confirmed by an ultrasound examination of the abdomen. This characteristic finding can be found in a lipid storage disorder like Wolman disease. Suspecting a storage disorder, a bone marrow examination was performed which confirmed the suspicions of a lipid storage disorder i.e. Neimann Pick disease.

The deranged coagulation profile preluded us from doing a liver biopsy whereas genetic testing could not be done unfortunately due to monetary concerns. Despite supportive therapy, the child died after a week of admission secondary to a pulmonary haemorrhage with disseminated intravascular coagulation.

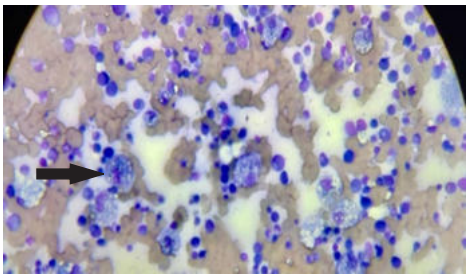

Figure No. 2: Bone Marrow Slide Showing Cytoplasmic Vacuoles In Reticulum Cell, Suggestive Of A Lipid Storage Cell (Black Arrow).

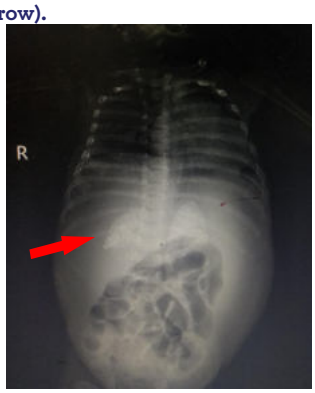

Figure No. 3: X-ray Chest And Abdomen Showing Bilateral Adrenal Calcifications (Red Arrow)

DISCUSSION:

Neimann-Pick disease was first described by Albert Niemann in 1914. Ludwig Pick conclusively showed the tissues affected due to deposition of sphingomyelin in 1927, hence the name "Niemann-Pick disease". It is an autosomal recessive lysosomal storage disorder caused by inherited deficiency of an enzyme, acid sphingomyelinase which leads to deposition of sphingomyelin and cholesterol within the lysosomes of reticuloendothelial cells of various organs. It is characterized by failure to thrive, hepatosplenomegaly and neurodegenerative changes (Narayana et al., 2019).

Filippin staining of cultured skin fibroblasts is the historical gold standard method to establish diagnosis but it is no longer considered as a first line test (Parker, 2012; Vanier & Latour, 2015). Gene sequencing is currently the most universally acceptable diagnostic technique to confirm Neimann-Pick disease (Narayana et al., 2019). Other tests like bone marrow examination, NPD suspicion Index tool, plasma levels of certain cholesterol oxidation products, elevated chitotriosidase activity can also be used as adjuncts (Alobaidy, 2015).

Symptomatic treatment may be effective in the management of seizures, dystonia and cataplexy but there is no curative therapy yet found. Miglustat is the first disease specific approved therapy for the treatment of neurological manifestations and should be initiated at the earliest signs of neurological manifestations (Alobaidy, 2015).

Jinka L. Narayana, et al showed a case of a 5 month old child diagnosed as Neimann-Pick disease (Narayana et al., 2019) whereas Irit Krause et al. and Nofar Amtai et al. showed similar cases who were diagnosed Wolman disease (Krause & Gavrieli, 2018) (Amitai, Grozovski, & Landau, 2015). Genetic testing was available in the above cases for definitive diagnosis. Similarly, we present a case of a 3 months old child with hepatosplenomegaly, adrenal calcifications and failure to thrive which was diagnosed as Neimann-Pick disease on bone marrow examination.

A F Rodrigues, et al. have showed that positive results on a bone marrow examination can be used to diagnose Neimann-Pick disease (Rodrigues et al., 2006) and R. Akhtar et al. has showed that bone marrow examination is a safe, quick and effective test to undertake in critically ill children with liver disease, where urgent decisions regarding liver transplantation need to be taken. It is very useful in the diagnostic algorithm of suspected lysosomal storage disorders, particularly in Niemann-Pick disease, where nearly all cases have specific morphological findings and where it requires a significantly longer time to obtain definitive molecular diagnoses (Akhtar et al., 2018). Similarly, we had diagnosed Neimann-Pick disease in our patient on a bone marrow examination. However, the additional finding of bilateral adrenal calcifications needed further investigation.

Enlarged lysosomes are a common cellular phenotype for both Neimann-Pick and Wolman diseases with a similar clinical profile and hence often present as a diagnostic dilemma.

There are limited reports of a lipid storage disorder like Neimann-Pick disease presenting with a haemolytic anaemia. Amla G. S. et al. showed the presence of haemolytic anaemia in a case of Neimann-Pick disease the exact nature of which could not be found (Amla et al., 1970). Keshavamurthy ML, et al. reported an unusual presentation of NPD presenting as haemolytic anaemia (Keshavamurthy et al., 2015). Similarly, the finding of Coomb's positive haemolytic anaemia in our case is extremely rare.

Despite extensive literature search and to the best of our

knowledge, we could not find a similar case and thus the finding of bilateral adrenal calcifications along with Coomb's positive haemolytic anaemia in a case of Neimann-Pick disease is an unusual occurrence.

CONCLUSION:

The need for prompt diagnosis of NPD is evident, but the current diagnostic techniques are relatively invasive, costly and time-consuming. Thus, bone marrow examination can be used as a diagnostic tool in resource limited settings. Hence, we present a very rare case of Neimann Pick disease with Coomb's positive haemolytic anaemia with adrenal calcifications. However, this rare constellation of findings still presents a diagnostic dilemma and genetic testing is required for confirming the diagnosis.

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