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Case Report

Wolman's Disease, Haemopagocytic Lymphohistiocytosis and Cytomegalovirus Infection: Association or Coincidence?

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Abstract

Wolman's disease, an infantile form of lysosomal acid lipase deficiency, is very rare and usually fatal in infancy. In this article we present two infants with Wolman's disease associated with cytomegalovirus infection, one with surrenal calcifications and the other with histopathological liver calcifications and haemophagocytic lymphohistiocytosis.

Both cases had complaints of vomiting and fever for two months. A family history of consanguinity and infant deaths of unknown cause was reported. Physical examination revealed jaundice and hepatosplenomegaly. Cytomegalovirus infection, unresponsive to ganciclovir treatment, was diagnosed in both cases. While haemophagocytic lymphohistiocytosis and histopathological calcifications in the liver were observed in the first case, classical surrenal calcifications were seen in the second case.

It is not clear whether the presence of cytomegalovirus infection in both cases and haemophagocytic lymphohistiocytosis in one case are coincidental. Furthermore, histopathological calcification in the liver appears to be a diagnostic criterion, as is adrenal calcification, although it has never been reported before.

Keywords: Hemophagocytic Lymphohistiocytosis, Cytomegalovirus Infection, Wolman's Disease

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Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal storage disorder caused by LIPA gene variants (chromosome 10q23.2-q23.3), resulting in defective hydrolysis of cholesteryl esters and triglycerides and subsequent accumulation in multiple organs. Two clinical forms are recognized: Wolman disease (WD), the severe infantile form, and cholesteryl ester storage disease (CESD), the milder phenotype due to partial enzyme activity. Affected individuals are homozygous or compound heterozygous for LIPA variants, and more than 100 variants have been described.[1,2] Severe variants, such as nonsense or frameshift changes, typically present in infancy. The most common (>50%) variant is E8SJM (c.894G>A).[1]

In WD, fetal ascites and polyhydramnios may be observed in utero. The incidence is estimated at 1:100,000–1:300,000 live births. The disease manifests in early infancy with absent LAL activity. The hallmark feature is adrenal enlargement with calcifications, frequently detected on imaging, although not mandatory for diagnosis. Adrenal insufficiency has also been reported.[1]

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Secondary hemophagocytic lymphohistiocytosis (HLH) may complicate WD, and cytomegalovirus (CMV) infection is among the recognized infectious triggers of HLH. Here, we present two cases of WD: the first with HLH secondary to CMV infection and hepatic calcifications identified on histopathology, and the second with adrenal calcifications and a strong family history of infantile deaths.

Case Report

Case 1 – A two-month-old girl presented with persistent vomiting since birth, worsening over the last 20 days, fever, and weight loss for one week. The parents were second-degree relatives. In the extended family, the mother's aunt and uncle had died in infancy with a suspected storage disorder.

Examination: Body temperature: 38.5 °C; weight: 4 kg (3rd–10th percentile); height: 60 cm (75th percentile). Hepatomegaly (liver palpable 4 cm below the right costal margin) and splenomegaly (2 cm below the left costal margin) were noted.

Laboratory tests: WBC 30,000/µL; Hb 7.9 g/dL; PLT 109,000/µL; INR 2.2; AST 1456 U/L; ALT 287 U/L; total protein 5.2 g/dL; albumin 2 g/dL; total bilirubin 1.09 mg/dL; direct bilirubin 0.58 mg/dL; ALP 148 U/L; GGT 150 U/L; LDH 2726 U/L; TG 923 mg/dL; cholesterol 136 mg/dL; HDL 9 mg/dL; LDL 55 mg/dL.

Microbiology: CMV IgM and CMV PCR were positive. Empirical cefotaxime and amikacin were started, and ganciclovir was initiated for CMV.

Follow-up: One week later, fever persisted, WBC decreased to 2100/µL, Hb 7.4 g/dL, and PLT 27,000/µL. Peripheral smear showed vacuolization of lymphocytes; bone marrow aspiration demonstrated foam cells with hemophagocytosis. HLH criteria were fulfilled (ferritin 2500 µg/mL, fibrinogen 64 mg/dL). HLH-2004 protocol was initiated.

Enzyme studies: Lysosomal acid lipase activity <0.02 nmol/h/mg (normal 0.37–2.30). Diagnosis: WD with secondary HLH triggered by CMV. The patient died one day later before enzyme replacement therapy could be started.

Histopathology: Post-mortem liver biopsy showed diffuse macrovesicular steatosis, pericentral hepatocyte loss, calcification and fibrosis, ductular proliferation with bile plugs, and severe pericellular/central fibrosis. Findings were consistent with a metabolic storage disorder with lipid accumulation.

Case 2 – A two-month-old boy presented with vomiting, one month of abdominal distension (worsening in the last few days), and fever for three days. The parents were first-degree relatives. Eight of the father's siblings had died in infancy of unknown causes.

Examination: Body temperature: 38.6 °C; weight: 5 kg (50th percentile); height: 60 cm (75th percentile); icterus, abdominal distension, and hepatosplenomegaly (liver and spleen palpable 4 cm below the costal margins).

Laboratory tests: WBC 17,000/µL; Hb 6.3 g/dL; PLT 65,000/µL; INR 3.5; AST 1522 U/L; ALT 541 U/L; total protein 4.7 g/dL; albumin 2 g/dL; total bilirubin 4 mg/dL; direct bilirubin 3.1 mg/dL; GGT 118 U/L; LDH 4046 U/L; TG 613 mg/dL; cholesterol 130 mg/dL; HDL 29 mg/dL; LDL 21 mg/dL.

Microbiology: CMV IgM and CMV PCR positive; ganciclovir was initiated.

Imaging: Abdominal tomography demonstrated bilateral adrenal calcifications.

Enzyme studies: Lysosomal acid lipase activity <0.02 nmol/h/mg. Diagnosis: WD. The patient died three days later before therapy could be initiated.

Histopathology: Post-mortem liver biopsy showed diffuse macro- and microvesicular steatosis, scattered necrosis, and extramedullary hematopoiesis.

Discussion

WD typically presents within the first weeks of life with vomiting, diarrhea, hepatosplenomegaly, and cachexia, progressing rapidly to death within 2–6 months. CESD is milder, often presenting later in childhood with deficient, but not absent, LAL activity.[3,4]

Our first case presented with fever, hepatosplenomegaly, hypertriglyceridemia, and liver failure at two months, and developed HLH secondary to CMV infection. The second case exhibited adrenal calcifications, a classic feature, but bone marrow examination could not be performed due to coagulopathy. Both cases showed marked hypertriglyceridemia with low HDL and LDL cholesterol, consistent with the characteristic dyslipidemia of LAL-D.[5] Elevated LDH and prolonged INR indicated severe hepatocellular injury and impaired synthetic function.

Histopathology in WD usually demonstrates micro- and macrovesicular steatosis, periportal fibrosis, and lipid-laden histiocytes.[6-8] In our first case, hepatic calcification was also noted—an unusual finding. While adrenal calcification is well described in WD, hepatic calcification is rarely reported. Given the concomitant CMV infection, it remains uncertain whether hepatic calcification represents an atypical manifestation of WD or a secondary effect of CMV infection.

Reports have described WD complicated by HLH, but infection-associated HLH in this context is rarely documented. The proposed mechanism involves cholesteryl ester crystal accumulation in macrophages, triggering cytokine release

and HLH activation.[9,10] Despite initiation of HLH therapy and antiviral treatment, the outcome remained fatal, underscoring the severity of this association.

Conclusion

LAL-D should be considered in infants with consanguinity, family history of infant deaths, persistent vomiting, hepatosplenomegaly, hypertriglyceridemia, low HDL, cholestasis, and adrenal calcifications. Infants presenting with HLH should also be screened for WD. Although hepatic calcifications are not a specific finding, their presence, as in our case, highlights the need for further studies on their diagnostic significance.

Disclosures

Informed Consent: Written informed consent was obtained from the patients' legal guardians for publication of this case report and accompanying images.

Conflict of Interest: None declared.

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