Cerebrospinal fluid lactate dehydrogenase isoenzymes in children with bacterial and aseptic meningitis

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Differentiation of bacterial from aseptic meningitis may be difficult. Our aim was to determine the pattern of distribution of lactate dehydrogenase (LDH) isoenzymes in the cerebrospinal fluid (CSF) of patients with bacterial and aseptic meningitis. One hundred and fifty-seven patients with suspected meningitis were enrolled in the study. They were divided into 3 groups according to the culture- or bacterial antigen assay-proven diagnosis and CSF findings: bacterial meningitis (n = 31), aseptic meningitis (n = 65), and non-meningitis (n = 61). Total LDH level and percentages of LDH isoenzymes in the CSF were measured in each patient. Each group showed a distinct LDH isoenzyme distribution pattern, with a statistically significant difference among the groups in the percentages of the various isoenzymes. Compared with the non-meningitis group, total LDH activity in the CSF was high in the aseptic meningitis group (49.82±35.59 U/L, $P < 0.001$) and exaggerated in the bacterial meningitis group (944.53±112.3 U/L, $P < 0.001$). Low LDH-2 levels were unique to bacterial meningitis ($P < 0.01$), whereas high LDH-3 levels were characteristic of aseptic meningitis ($P < 0.05$). Both groups had low levels of LDH-1 and high levels of LDH-4 and LDH-5. In conclusion, the LDH isoenzyme pattern may be of clinical diagnostic value in meningitis, particularly when culture results are pending. (Translational Research 2009;154:214–218)

Abbreviations: CSF = cerebrospinal fluid; HSD = honestly significant difference; LDH = lactate dehydrogenase; WBC = white blood cells

Bacterial meningitis is a severe, life-threatening, infection with a worldwide distribution.[1] Because bacterial and aseptic meningitis require different therapeutic approaches and carry different prognoses, their early differentiation is crucial. However, lumbar puncture opening pressure is of limited diagnostic value.[1] Moreover, diagnosis may be difficult owing to the often-inconclusive findings in the cerebrospinal fluid (CSF) specimen on analysis of white blood cell (WBC) count, glucose and protein level, or fastidious pathogens. Some studies found that in up to 20% of cases in which a bacterial pathogen was isolated in culture, the initial CSF WBC count and glucose levels were nondiagnostic.[2] In addition, children and immunocompromised patients may

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AT A GLANCE COMMENTARY

Background

Differentiating bacterial from aseptic meningitis may be difficult. The diagnostic value of total cerebrospinal fluid (CSF) lactate dehydrogenase (LDH) in meningitis remains controversial. There is limited data regarding LDH isoenzyme pattern in bacterial and aseptic meningitis. Moreover, there is no data on LDH isoenzyme activity throughout the course of the disease.

Translational Significance

Bacterial and aseptic meningitis are each associated with a unique LDH isoenzyme pattern. Determination of LDH isoenzymes fractions in the CSF may increase the sensitivity of the evaluation conducted in suspected meningitis. LDH isoenzymes may be used for follow-up purposes.

have a low WBC count, making this a less reliable measure in these cases.[1] Gram staining has a variable sensitivity of 50% to 90%.[1] Therefore, additional markers for early and reliable diagnosis need to be identified.

Lactate dehydrogenase (LDH) is a fermentative enzyme present in many tissues and body fluids, including the CSF. There are 5 different LDH isoenzymes.[3] Increased total CSF LDH has been reported in patients with cerebral infarction, subarachnoid hemorrhage, and central nervous system leukemia,[2] and in patients with tuberculous meningitis and bacterial meningitis.[3] Studies have also reported a higher total CSF LDH activity in bacterial meningitis than in aseptic meningitis.[4] Pathological distribution patterns of the LDH isoenzymes have been observed in neurological disorders such as Guillain-Barre syndrome, infantile spasms, febrile convulsions, and hydrocephalus.[5-8]

The diagnostic value of total CSF LDH in meningitis remains controversial.[9] Some authors concluded that despite the high sensitivity of total CSF LDH for the detection of bacterial meningitis (~86%), it has no advantage over other CSF markers.[10] However, that study did not evaluate LDH isoenzyme patterns. Kamat and Chakravorty[3] noted a dominant increase in LDH-3 in bacterial meningitis, but they did not report statistical comparisons with other groups. In a related study of 9 patients, Neches and Platt[2] reported that the LDH CSF analysis in the 2 healthy patients yielded equal percentages of LDH-1, LDH-2, and LDH-3, and small amounts of LDH-4 and LDH-5. The 3 patients with aseptic meningitis had an increased percentage of LDH-4 and, to a lesser extent, of LDH-5, whereas the 4 patients with bacterial meningitis had marked elevations of LDH-5 and a slight increase in LDH-4.[2] Nelson et al[11] noted a prominent increase in total CSF LDH and in LDH-5 in 12 patients with acute bacterial meningitis, and a slight increase in total LDH with a predominance of LDH-1 and -2 in 10 patients with aseptic meningitis. However, these finding were not presented in a quantitative manner.

The aim of the present study was to determine the pattern of distribution of LDH isoenzymes in the CSF of patients with bacterial and aseptic meningitis.

METHODS

The study was conducted in accordance with the ethical guidelines for human research. The study included 157 children aged 1 day to 18 years who were evaluated for suspected meningitis at our tertiary referral medical center during an 8-year period. All were previously healthy, and none was taking medication on a regular basis. Therefore, drug-induced aseptic meningitis was excluded from the differential diagnosis.

The first CSF sample was collected on the day of admission, before antibacterial treatment was initiated. Analysis included total and differential WBC counts, glucose and protein concentrations, and bacterial and viral cultures. Bacterial antigen assay (Bactigen; Wampole Laboratories, Cranbury, NJ) was performed in the presence of abnormal findings on the initial CSF WBC count or chemistry profile or a negative bacterial CSF culture.

According to accepted practice,[12] the diagnosis of bacterial meningitis was based on the isolation of a bacterial pathogen on CSF culture or, when deemed necessary, positive findings on bacterial antigen assay to one of the tested bacteria (ie, *Escherichia coli*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or Streptococcus group B). The diagnosis of aseptic meningitis was based on accepted criteria for CSF findings as well as on negative bacterial Gram stain and negative bacterial cultures.[13] Patients in whom none of these criteria were met (ie, normal CSF WBC parameters and negative CSF culture) were classified as meningitis-free and served as the reference group.

One milliliter of each CSF specimen was either sent immediately for analysis of total LDH and LDH isoenzyme activity or stored at –20°C until assayed. Bloody specimens were excluded to avoid errors caused by hemolysis. Total LDH activity was measured on a Hitachi-747 analyzer (Boehringer Mannheim Corp., Indianapolis, Ind) with an LDH kit using the optimized standard method. LDH catalyzed the reduction of pyruvate to lactate in the presence of NADH, and the consumption of NADH was followed at 340 nm. The reaction was performed at 37°C. Isoenzymes of LDH