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Nasopharyngeal Lactate Dehydrogenase Concentrations Predict Bronchiolitis Severity in a Prospective Multicenter Emergency Department Study

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Abstract

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We re-examined the finding of an inverse relationship between values of nasopharyngeal lactate dehydrogenase (LDH), a marker of the innate immune response, and bronchiolitis severity. In a prospective, multicenter study of 258 children we found in a mutlivariable model that higher nasopharyngeal LDH values in young children with bronchiolitis were independently associated with a decreased risk of hospitalization.

Keywords

Severity of illness; biomarker; respiratory syncytial virus; human rhinovirus

Introduction

An inverse linear relationship between increased values of nasopharyngeal aspirate (NPA) lactate dehydrogenase (LDH), which is released from injured cells, and the severity of bronchiolitis was reported in early 2010 by Laham et al.[1] The investigators speculated that higher nasopharyngeal LDH values in a normal host may represent a more robust innate immune response, which has been shown to be protective for respiratory syncytial virus (RSV) bronchiolitis.[2, 3] Indeed, Laham and colleagues showed strong positive correlations between the value of LDH and Th1 cytokines, Th2 cytokines, and other pro-inflammatory cytokines as well as caspase 3/7, a marker of apoptosis activity.

Despite identified risk factors for severe bronchiolitis, and objective physical examination findings for respiratory distress (e.g. respiratory rate and degree of retractions), there is variability in the disposition decisions for children with bronchiolitis.[4, 5] Therefore, introducing a rapidly available, simple test that would help predict severity of illness could help clinicians more appropriately triage children with bronchiolitis.

Materials and Methods

We conducted a prospective cohort study from December 14, 2005 through March 19, 2006, as part of the Multicenter Airway Research Collaboration (MARC) of the Emergency Medicine Network (http://www.emnet-usa.org). Investigators at 14 emergency departments (ED) in 10 U.S. states recruited consecutive ED patients 18–24 hours per day for 2 or 3 weeks. Inclusion criteria were final ED attending physician diagnosis of bronchiolitis, patient age <2 years, and parent/guardian informed consent. The Institutional Review Board at each site approved this study.

The details of the data collection[6] as well as the nasopharyngeal aspirate collection and virology testing[7] have been reported previously.

Of the original 277 samples collected in the virology study,[7] 19 did not have enough remaining volume to test for LDH. Therefore, LDH activity was able to be tested in 258 samples. The NPA samples were diluted 1:1 in phosphate-buffered saline and assayed in duplicates following protocol instructions (Cytotoxic Detection Kit, Roche Applied Science [Indianapolis, IN]). To calculate absolute values, LDH (Roche Applied Science) was used to construct a standard curve that demonstrated an ample linear dynamic range ($r = .998$) at the dilutions tested from 0.8 to 110 U/mL. All samples were tested in Dr Pedro Piedra's laboratory at Baylor College of Medicine.

There is variability in the disposition decisions for children with bronchiolitis.[4, 5] As a result, children discharged home from the ED and discharged home from the hospital within

24 hours of admission may have a similar severity of illness. Therefore, for the purposes of this analysis, severe bronchiolitis was defined as hospitalization for ≥24 hours.

All analyses were conducted using Stata version 11.0 (StataCorp, College Station, TX). Kruskal-Wallis rank tests were used to compare LDH across viruses, demographic characteristics, and clinical characteristics. Multivariable logistic regression was used to evaluate the association between LDH and severe outcome, defined as hospitalization ≥24 hours. Because of the non-linear relationship between LDH and severe outcome, LDH was divided into quartiles. The multivariable model accounted for clustering and adjusted for factors considered to be clinically meaningful and found to be predictors of bronchiolitis outcomes in earlier studies by our group (age <2 months, sex, history of intubation, retractions, and oxygen saturation).[6, 8]

Results

The median LDH value in NPA among the 258 samples was 6.7 U/mL (IQR, 1.3 – 43.3) with a range from 0 to 8,408 U/mL. The top five values were 693.5, 953.9, 965.3, 3,166, and 8,408 U/mL. Among the 258 children with enough sample available for LDH values, 160 (62%) were positive for RSV, 41 (16%) for HRV, 25 (10%) for hMPV, 17 (7%) for Flu A, and none was positive for Flu B. LDH was found to be higher in children with RSV compared with those without RSV and higher in children with HRV bronchiolitis compared with those without HRV (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B186). When examining both RSV and HRV together, children with HRV only (n=29) or HRV and RSV co-infection (n=12) had higher LDH than children with RSV only (n=148) or neither virus (n=69). Other viruses did not appear to influence LDH (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B186).

Demographic characteristics are also presented in Supplemental Table 1. LDH was similar in boys and girls, but found to be higher in Black children compared with children of other races/ethnicities. Children with an ED length of stay >3 hours had similar LDH to those with shorter lengths of stay (5.7 [0.9–72.7] vs. 10.4 [3.2–32.4]; P=0.44), however children who received corticosteroids in the ED had lower LDH compared with children who did not.

Among the 258 children, 140 (54%) children were discharged to home, 30 (12%) were admitted for <24 hours (observation status), and 88 (34%) were admitted for ≥24 hours. Children with severe bronchiolitis, defined as admission to the hospital ≥24 hours, had lower LDH. In multivariable analysis examining quartiles of LDH, higher values of LDH were associated with a decreased risk of hospitalization for ≥24 hours when adjusting for age <2 months, sex, history of intubation, retractions, and oxygen saturation ≤94%. Specifically, the upper 3 quartiles were associated with a reduced risk of hospitalization: OR 0.58 [95% CI, 0.24–1.40; P=0.23]; OR 0.23 [95% CI, 0.09–0.58; P=0.002]; and 0.65 [95% CI, 0.28–1.53; P=0.33]. To avoid overfitting we used the simplest model, but it is interesting to note that the association between LDH and corticosteroid treatment remained after adjustment for other factors such as race/ethnicity and exposure to second hand smoke (data not shown). Furthermore, the results of the multivariable model did not materially change after excluding the two outlying values (data not shown). Additional analysis examined LDH ≥1.34 (highest three quartiles) vs. LDH <1.34 (lowest quartile) and found a reduced risk of hospitalization for ≥24 hours when adjusting for the same 5 factors (OR 0.45; 95% CI, 0.23–0.90; P=0.02).

Discussion

In this prospective, multicenter study of children age <2 years presenting to the ED with bronchiolitis, we found that higher nasopharyngeal LDH values were associated with a

lower odds of hospitalization for ≥24 hours even after adjusting for common factors associated with severe bronchiolitis. In the highest quartile, the association between nasopharyngeal LDH and hospitalization appeared blunted for unclear reasons. While LDH values are usually determined during the assessment of pulmonary fluid and bronchoalveolar lavage fluid, its measurement in nasopharyngeal fluid in children with bronchiolitis is novel. As a result, little is known about normal LDH values or variation in values in these children. However, based on the results of the recent single-center study by Laham and colleagues[1] and our multicenter data, nasopharyngeal LDH has potential utility as a marker of bronchiolitis severity. Ideally, this marker would assist clinicians, especially those working in the ED, when the disposition decision is unclear.

LDH is an intracellular protein and therefore, its presence in the extracellular space is indicative of cell injury. Beyond cell injury, Laham and colleagues were able to demonstrate that higher LDH values correlated with higher values of innate immune cytokines and chemokines.[1] While other data have demonstrated an association between a robust inflammatory response and more severe bronchiolitis,[9] the data from both the present study and the one conducted by Laham and colleagues[1] suggest that a higher nasopharyngeal LDH value (i.e. more robust inflammatory response) is associated with *less* severe bronchiolitis. Indeed, the association between a more robust inflammatory response and improved clinical outcomes in bronchiolitis has been noted previously[2, 3] and nasopharyngeal LDH may function as a summary measure of a child's inflammatory response.

The administration of corticosteroids was associated with a lower LDH value and it is conceivable that the corticosteroid administration could have influenced the inflammatory response. And although smoke exposure increases the incidence and severity of bronchiolitis,[10] the LDH value in children exposed to smoke was higher than in non-exposed children. However, neither corticosteroids nor smoke exposure changed the association between LDH and hospitalization ≥24 hours in multivariable analysis.

The limitations of this study include having a NPA sample from only one time point during the illness, the lack of consensus about clinically relevant LDH values, and having no standardization of NPA collection and analysis methods.

In this multicenter study of children presenting to the ED with bronchiolitis, we have confirmed that nasopharyngeal LDH values have the potential to assist clinicians who are deciding if a child with bronchiolitis requires hospitalization. Further research is required to understand better the potential blunting of the association between LDH and hospitalization at the highest values of LDH and the specific cytokines or chemokines responsible for the LDH finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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