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Prediction of Lyme Meningitis in Children From a Lyme Disease–Endemic Region: A Logistic-Regression Model Using History, Physical, and Laboratory Findings

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ABSTRACT

BACKGROUND. Differentiating Lyme meningitis (LM) from other forms of aseptic meningitis (AM) in children is a common diagnostic dilemma in Lyme disease–endemic regions. Prior studies have compared clinical characteristics of patients with LM versus patients with documented enteroviral infections. No large studies have compared patients with LM to all patients presenting with AM and attempted to define a clinical prediction model.

OBJECTIVE. To create a statistical model to predict LM versus AM in children based on history, physical, and laboratory findings during the initial presentation of meningitis.

METHODS. Children older than 2 years presenting to the Alfred I. duPont Hospital for Children between October 1999 and September 2004 were identified if both Lyme serology and cerebrospinal fluid (CSF) were collected during the same hospital encounter. Patients were considered to have Lyme disease only if they met Centers for Disease Control and Prevention criteria (documented erythema migrans and/or positive Lyme serology). Patients were eligible for study inclusion if they had documented meningitis (CSF white blood cell count: >8 per mm^3). Retrospective chart review abstracted duration of headache and cranial neuritis (papilledema or cranial nerve palsy) on physical examination and percent CSF mononuclear cells. Using logistic-regression analysis, the type of meningitis (LM versus AM) was simultaneously regressed on these 3 variables. The Hosmer-Lemeshow test was performed and the area under the receiver operating characteristic curve was calculated.

RESULTS. A total of 175 children with meningitis were included in the final statistical model. Logistic-regression analysis included 27 patients with LM and 148 patients classified as having AM. Duration of headache, cranial neuritis, and percent CSF

mononuclear cells independently predicted LM. The Hosmer-Lemeshow test revealed a good fit for the model, and the Nagelkerke R^2 effect size demonstrated good predictive efficacy. Odds ratios based on the logistic-regression results were calculated for these variables. The final model was transformed into a clinical prediction model that allows practitioners to calculate the probability of a child having LM.

CONCLUSIONS. Longer duration of headache, presence of cranial neuritis, and predominance of CSF mononuclear cells are predictive of LM in children presenting with meningitis in a Lyme disease–endemic region. The clinical prediction model can help guide the clinician about the need for parenteral antibiotics while awaiting serology results.

L YME DISEASE IS caused by the spirochete *Borrelia burgdorferi* and represents the most common vector-borne illness in the United States.[1] In 2002, 23 763 cases of Lyme disease were reported, and an overwhelming majority of these cases came from 10 northeastern and mid-Atlantic states.[1] The peak incidence of Lyme disease occurs in a bimodal age distribution around children 5 to 14 years old and adults 50 to 65 years old and primarily during the summer months.[1,2] According to Centers for Disease Control and Prevention (CDC) guidelines, the diagnosis of Lyme disease requires the presence of the erythema migrans rash diagnosed by a physician or the presence of other clinical manifestations accompanied by positive Lyme-serology testing with confirmatory immunoblotting.[1] Although Lyme disease often is easily treatable, patients with central nervous system or cardiac involvement require long-term intravenous antibiotics.

In children with Lyme disease, 2% have an initial clinical manifestation of meningitis[3] that requires 2 to 4 weeks of parenteral antibiotics.[1,4] Although a minority of children with Lyme disease present with Lyme meningitis (LM), distinguishing LM from aseptic meningitis (AM) in children who live in a Lyme disease–endemic region can be challenging, especially during the summer months when both LM and AM are at peak incidence.[5–7] Lyme-serology and viral cerebrospinal fluid (CSF) studies (eg, enterovirus polymerase chain reaction [PCR]) often require several days to report results; therefore, the clinician must decide whether to initiate treatment of LM with parental antibiotics while awaiting these results.

Two small studies have made basic quantitative comparisons between demographic, clinical, and laboratory characteristics of LM versus AM in children.[5,7] Eppes et al reported that 12 children with LM had a longer duration of headache, predominance of CSF mononuclear cells, and presence of cranial neuritis (eg, cranial nerve palsy or papilledema) when compared with children with confirmed enterovirus meningitis.[7] A recent European study of 14 children with LM and 16 children with AM described similar clinical and laboratory results.[5] Despite the similar results of these 2 studies, the authors only compared the proportions or means of their findings between groups (eg, χ^2, Kruskal-Wallis, and Fischer's exact tests). None of these statistical tests can determine what factors predict LM versus AM, nor can they simultaneously control for the influence of other variables on the outcome measure. Also, these 2 studies failed to include every patient who was evaluated for suspected LM in their analysis. We therefore attempted to create a clinical prediction model to define the probability of LM among all children presenting with meningitis who were being evaluated for suspected LM in a Lyme disease–endemic region.

METHODS

Study Sample

The computerized physician order-entry system at the Alfred I. duPont Hospital for Children was electronically searched for children older than 2 years who were evaluated between October 1999 and September 2004. The search was limited to this age range to avoid inclusion of an incomparable population (ie, neonates and infants with enterovirus meningitis) and because children younger than 2 years rarely contract Lyme disease. Our electronic search criteria identified patients from whom routine CSF studies (eg, cell count, differential, protein, and glucose) and either Lyme-serology or Lyme-CSF studies (eg, Lyme CSF PCR or Lyme CSF antibody) were collected during the same hospital visit. Inclusion criteria were (1) available Lyme-serology results that included Western blot analysis from either our hospital laboratory or a commercial laboratory, (2) confirmed meningitis (CSF white blood cell [WBC] count of >8 mm³) obtained from an atraumatic lumbar puncture, (3) the identified encounter was the initial evaluation for the presenting illness, and (4) history and physical examination documented by an attending physician. Exclusion criteria were (1) positive CSF Gram-stain for bacteria, (2) concurrent work-up for a chronic neurologic condition, (3) indwelling ventricular shunt, (4) past diagnosis and treatment for Lyme disease, and (5) unavailable medical charts.

Patients were classified as having LM if they met the criteria established by the CDC for Lyme disease (positive serology with Western blot confirmation or erythema migrans observed by a physician) and had meningitis.[1] Criteria for serologic diagnosis were based on published criteria for results from commercial laboratories[8] and our hospital's laboratory.[9] If initial Lyme-serology results were equivocal but follow-up testing was positive, these children were considered to have Lyme

disease. Patients with meningitis who did not meet CDC criteria for Lyme disease were classified as having AM. The final discharge diagnosis of all patients was extracted from the medical chart.

Laboratory values (Lyme serology, CSF red blood cell count, CSF WBC, CSF WBC differential, CSF bacterial culture, CSF viral culture, and CSF enterovirus PCR) and demographic information (age, gender, race, and month of presentation) were abstracted electronically from our hospital's laboratory database. Lyme serology was completed by our hospital laboratory using a previously described protocol.[9] Standard techniques were used for CSF bacterial and viral cultures. The virology laboratory of the Children's Hospital of Philadelphia (Philadelphia, PA) performed all enterovirus CSF PCR testing.

The charts of patients meeting inclusion criteria for the study were reviewed for patient history and physician physical examination. Duration of headache (in days) documented by the attending physician was recorded. When this duration was reported as a range, the mean of the range was recorded (eg, headache lasting between 1 and 2 days was recorded as 1.5 days). Data from the physical examination included observation of erythema migrans and cranial neuritis (cranial nerve palsy or papilledema). Patient history and physical findings that were not documented in the medical chart were considered missing data points. The percent CSF mononuclear cells was calculated by adding the percent of CSF lymphocytes and monocytes. The study was approved by the institutional review board of the Alfred I. duPont Hospital for Children and the Nemours Foundation.

Statistical Analysis

Direct logistic-regression analyses were used to examine data in SPSS 11.0 (SPSS Inc, Chicago, IL). The outcome diagnosis was the presence or absence of LM and was simultaneously regressed on the independent predictors: duration of headache, presence or absence of cranial neuritis, and percent CSF mononuclear cells.

The practical utility of each logistic solution was evaluated according to 4 criteria: (1) comparison of each obtained model to a constant-only model using the log-likelihood technique distributed as χ^2[10]; (2) comparison of each model to a perfect, hypothetical model using the Hosmer-Lemeshow test[11]; (3) comparison of Nagelkerke R^2 effect sizes available in SPSS; and (4) comparison of receiver operator characteristic (ROC) curve analyses, considering the correlation between the 2 models because they were based on the same cases.[12] The final analysis was transformed into a clinical prediction model that allows practitioners to calculate the probability (from .01 to .99) of children having LM.

RESULTS

Study Sample

Our computerized physician order-entry system identified 349 patients who had both Lyme-serology and routine CSF studies ordered. A total of 162 patients were excluded from the study for incomplete Lyme serology ($n = 1$), concurrent evaluation for chronic neurologic condition ($n = 1$), no CSF studies being completed ($n = 18$), absence of meningitis ($n = 141$), or unavailable medical charts ($n = 1$). We identified 187 patients with meningitis. Twenty-seven patients with meningitis met criteria for LM by having either erythema migrans observed by the attending physician or positive Lyme serology with confirmatory Western blot analysis. A single erythema migrans lesion was found in 8 patients with LM, and multiple erythema migrans lesions were observed in 10 patients with LM. Twenty-one LM patients had positive Lyme serology, including the 9 patients who did not have erythema migrans (immunoglobulin M [IgM] positive only: $n = 5$; both IgM and IgG positive: $n = 4$). One hundred sixty patients did not meet criteria for LM and were classified as having AM. Final diagnoses noted in the medical chart for the patients classified as having AM included enterovirus meningitis (confirmed by CSF culture or CSF PCR: $n = 71$), viral meningitis without a known etiology (culture/PCR negative: $n = 65$), acute disseminated encephalomyelitis ($n = 8$), viral cerebellitis ($n = 2$), viral encephalitis ($n = 1$), multiple sclerosis ($n = 1$), transverse myelitis ($n = 1$), epidural abscess ($n = 1$), and LM despite not meeting CDC criteria ($n = 10$). The 10 patients who were given a final diagnosis of LM despite not meeting CDC criteria were classified as having AM for the purpose of this study. However, all were treated with a course of long-term parenteral antibiotics, likely on the basis of their physician's clinical impression using history or physical findings suggestive of Lyme disease. Three of the patients with a final diagnosis of LM despite not meeting CDC criteria had repeat Lyme-serology testing that was negative.

Logistic Regression

Data were available for 187 cases; 2 cases were excluded because of missing values. Among the 185 patients with complete data, 27 had LM and 158 were classified as having AM. This regression analysis was statistically significant when compared with a constant-only model ($P = .001$). The Hosmer-Lemeshow test revealed a good fit ($\chi^2 = 7.866$), and the Nagelkerke R^2 effect size ($R^2 = 0.353$) demonstrated good predictive efficacy. Area under the curve (AUC) from the ROC was 0.814. Because this model reached significance, the 10 patients who were classified as having AM but were given a final diagnosis of LM despite not meeting CDC criteria were removed from the model, and the analysis was repeated.

The second analysis included 27 patients with LM and 148 classified as having AM. Similar to the first regression analysis, statistical significance was reached when compared with a constant-only model ($P = .001$). The Hosmer-Lemeshow test revealed a better fit than the first analysis ($\chi^2 = 7.400$) and a better predictive efficacy (Nagelkerke R^2 effect size: 0.489). The AUC from the ROC was superior for this analysis (AUC = 0.883; $P < .01$). See Table 1 for demographic, history, physical examination, and laboratory findings for this analysis.

Table 2 lists the regression coefficients, Wald statistics, statistical significance levels, odds ratios (ORs), and 95% confidence intervals for the second analysis. According to the Wald criterion, all 3 predictors (duration of headache, presence or absence of cranial neuritis, and percent of CSF mononuclear cells) made a statistically significant contribution to the prediction. Using the scores assigned to each predictor, we derived the following prediction model:

$$\text{predicted probability} = 1/\{1 + e^{-2.063 + 0.026}$$

$$\times \text{ \% CSF mononuclear cells} + 0.128 \times \text{duration}$$

$$\text{of headache } + [-2.833 \times (1 - \text{cranial neuritis})]\}$$

The sensitivity, specificity, and positive and negative predictive values of different cutoff points for the model-derived predicted probability of LM versus AM are listed in Table 3. Patients with LM had a greater predicted probability of LM (mean: 0.510; median: 0.619) than those classified as having AM (mean: 0.086; median: 0.044). Only 9 (6%) of the 148 patients with AM (enterovirus: $n = 1$; viral meningitis without a known etiology: $n = 4$; multiple sclerosis: $n = 1$; and acute disseminated encephalomyelitis: $n = 3$) had a predicted probability of LM of >0.20. Examples of patients with low, moderate, and high predicted probability of LM are presented in Table 4.

The OR listed in Table 2 for duration of headache and

percent CSF mononuclear cells (both continuous variables) increase by 0.136 and 0.027, respectively, for every increase of 1 for that variable. For example, the OR of having LM in a patient with a headache lasting 14 days is 2.9 [1.136 + (0.136 × 13)], whereas an OR of 90% CSF mononuclear cells would be 3.4 [1.027 + (0.027 × 89)]. The OR for cranial neuritis is 16.9 (calculated as 1/0.059 = 16.9). The ORs calculated here are based on the regression model and represent the contribution of that specific variable after the contributions of the other variables are considered.

Calculation of the equations shown above (predictive probability and OR) is tedious. However, the process was made more convenient by using a Microsoft Excel program that is available from the corresponding author (R.A.A.). All that is required is entry of the 3 values: duration of headache ($\geq$0), presence or absence of cranial neuritis (1 for presence and 0 for absence), and percent of CSF mononuclear cells (whole number ranging from 0 to 100). The program calculates the predicted probability based on the contributions from all 3 variables and lists the specific OR of each variable.

TABLE 2 Logistic-Regression Results for the Best-Fitting Model

Variables	B	Wald Test, z Ratio	P	OR	95% Confidence Interval for OR
Duration of headache	0.128	8.285	.004	1.136	1.042–1.239
Cranial neuritis	−2.833	19.243	.001	0.059	0.017–0.209
% CSF mononuclear cells	0.026	4.138	.0420	1.027	1.001–1.053
(Constant)	−2.063	2.415			

TABLE 3 Sensitivity, Specificity, and Positive and Negative Predictive Values for Different Cutoff Points for the Model-Derived Predicted Probability of LM

Probability of LM	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
≥.10	85.1	73.6	37.0	96.4
≥.20	70.3	93.9	67.8	94.5
≥.30	66.6	95.2	72.0	94.0
≥.40	59.2	96.6	76.1	92.8
≥.50	59.2	96.6	76.1	92.8
≥.60	51.8	96.6	73.6	91.6
≥.70	40.7	98.6	84.6	90.1
≥.80	14.8	99.3	80.0	86.4
≥.90	11.1	99.3	75.0	85.9

TABLE 4 Examples of Low, Moderate, and High Probability of LM Based on the Model-Derived Predicted Probability

Clinical Variables	Case 1	Case 2	Case 3
Headache duration, d	2	14	7
Cranial neuritis	Absent	Absent	Present
% CSF mononuclear cells	45	87	90
Predicted probability of LM	.03 (low)	.30 (moderate)	76 (high)

TABLE 1 Demographic, History, Physical, and Laboratory Values for Children With LM and AM Included in the Predictive Model

	LM ($n = 27$)	AM ($n = 148$)
Demographics		
Age, mean (range), y	9.4 (2.7–13.1)	9.1 (2.9–17.9)
Gender, % male	67	68
Race, % white	93	61
Patient history		
Duration of headache, mean (median), d	7.5 (6)	2.8 (2)
Physical exam		
Cranial neuritis, no. of patients (% of group)	15 (56)	5 (3)
Papilledema[a]	9 (33)	4 (2)
Cranial nerve palsy[b]	9 (33)	1 (1)
Laboratory		
% CSF mononuclear cell, mean (median)	86.7 (94)	57.6 (62)

[a] Three patients with LM were found to have papilledema and CN-VII palsy simultaneously.
[b] One patient with LM had bilateral facial nerve palsy as well as ipsilateral abducens nerve palsy.

Description of Group Differences for History, Physical, and Laboratory Findings

The demographic characteristics of the LM and AM groups included in the predictive model were well matched (see Table 1). The patients with AM had a mean duration of headache of 2.8 days. Sixteen (59%) of the 27 patients with LM and 37 (25%) of the 148 patients with AM (enterovirus: $n = 14$; viral meningitis without a known etiology: $n = 19$; multiple sclerosis: $n = 1$; and acute disseminated encephalomyelitis: $n = 3$) had a headache duration of >3 days.

One patient who was classified as having AM had an abducens nerve palsy and was ultimately diagnosed with multiple sclerosis. Eight patients with LM had facial nerve palsy, and 1 patient had bilateral facial nerve palsy as well as abducens nerve palsy. Four patients classified as having AM had papilledema (enterovirus: $n = 1$; viral meningitis without a known etiology: $n = 2$; and acute disseminated encephalomyelitis: $n = 1$). Nine patients with LM were found to have papilledema, 3 of whom also had a coexisting facial nerve palsy.

The patients with LM had a mean of 86% CSF mononuclear cells. Nineteen (70%) of the 27 patients with LM and 42 (28%) of the 148 patients with AM (enterovirus: $n = 14$; viral meningitis without a known etiology: $n = 18$; multiple sclerosis: $n = 1$; viral cerebellitis: $n = 1$; viral encephalitis: $n = 1$; transverse myelitis: $n = 1$; and acute disseminated encephalomyelitis: $n = 6$) had CSF mononuclear cells >86%. Although not included in the prediction model, patients with LM had fewer CSF WBCs per mm^3 (mean: 100 per mm^3; range: 13–762 per mm^3) than patients with AM (mean = 207; range 9–2165).

DISCUSSION

This is the largest cohort of North American children studied during the initial evaluation of suspected LM. We included all patients who were evaluated for LM (as indicated by ordered Lyme-serology testing) in hopes of representing the population with which the clinician is faced during the initial presentation of meningitis. We defined a clinical prediction model using history, physical, and laboratory findings that are immediately available to all clinicians and can help guide management decisions until diagnostic results are received. Because neither AM nor LM are true medical emergencies, our prediction model could reduce unnecessary parenteral antibiotic use while awaiting serology results. Additionally, Lyme-serology results may not be definitive when patients initially present with central nervous system Lyme disease, again supporting the need for clinical predictors of LM.

Our clinical prediction model will be most helpful in children who do not have erythema migrans at presentation. The largest prospective study of Lyme disease in children reported that 84% of all children presenting with early disseminated Lyme disease were found to have erythema migrans on physical examination.[3] However, children in our study (18 of 27 [66.7%]) and others did not seem to have erythema migrans as frequently during LM.[5,7,13,14] The absence of erythema migrans in children with AM should not deter the clinician from obtaining Lyme serology, especially in Lyme-endemic regions.

Longer duration of headache was found to be a significant predictor of LM in our study. Although headache is frequently reported as the predominant or most frequent symptom in both AM[15,16] and LM,[7,13,17,18] a previous study found that patients with LM reported a longer duration of headache at presentation when compared with those with enterovirus meningitis.[7] Unlike patients with LM, patients with enterovirus meningitis typically have a rapid onset of headache and fever and are likely to present, on average, within 2 days of onset of symptoms.[16] In a large study of children with acute disseminated encephalomyelitis, less than half of the patients presented with a complaint of headache.[19] Admittedly, the assessment of headache and headache duration in young children can be difficult and potentially unreliable.

The presence of a cranial nerve palsy (typically the facial nerve) is not pathognomonic for LM, yet it occurred frequently in our patients with LM as well as in other studies of Lyme disease in children.[5,7,13,14,20–23] The etiology of a peripheral facial nerve palsy in children without Lyme disease includes a variety of infectious, neoplastic, structural, and idiopathic causes, most of which do not typically present with meningitis.[24–27] The only patient with AM in our study who had a cranial nerve palsy was found to have an abducens nerve palsy, which is also known to occur in Lyme disease, and was eventually diagnosed with multiple sclerosis.[13,17,21,28] Both peripheral facial nerve and abducens nerve palsy have been reported in children with Lyme disease who do not have a CSF pleocytosis or symptoms suggestive of meningitis.[14,20,28] Lyme serology should be obtained in these patients, especially if other systemic symptoms suggestive of Lyme disease are present.[29]

Raucher et al first described the association between Lyme disease and papilledema.[30] Since then, numerous investigators have reported this finding in children diagnosed with Lyme disease with and without a CSF pleocytosis.[7,13,21,28,31] In our study, papilledema was found in 9 patients with LM and 4 patients classified as having AM (acute disseminated encephalomyelitis: $n = 1$; confirmed enterovirus: $n = 1$; and AM with no known etiology: $n = 2$). To our knowledge, papilledema has been reported previously in only 1 patient with enterovirus meningitis.[32] We are unaware of any studies describing an association between papilledema and acute disseminated encephalomyelitis.

The first studies of LM in children described a CSF mononuclear cell predominance.[6,23] Two reports have

recommended that a CSF lymphocytic or mononuclear predominance (or a paucity of percent CSF neutrophils) can help clinicians distinguish between LM and AM.[5,7] Our study extends this observation by demonstrating an increasing predicted probability and OR of having LM as the percent of CSF mononuclear cells increase even after controlling for the influence of cranial neuritis and duration of headache. Our regression model calculates that patients with 90% CSF mononuclear cells have an OR of 3.4 for LM, whereas the OR is only 2.0 for patients with 40% CSF mononuclear cells. When calculating our model-derived predicted probability and ORs, the clinician should consider that it is exceedingly rare for patients with LM to have <50% CSF mononuclear cells. AM is known to have a predominant percentage of CSF polymorphonuclear neutrophils early in the disease course, with later shift to a lymphocyte predominance. We found that 6 of the 7 patients diagnosed with acute disseminated encephalomyelitis in our study had >86% CSF mononuclear cells. Despite a large percentage of CSF mononuclear cells found in LM, this finding is not specific to LM and further supports the need to rely on other factors (eg, cranial neuritis and duration of headache) when attempting to predict LM. The presence of weakness, ataxia, and MRI findings readily differentiates LM from acute disseminated encephalomyelitis.[19]

One limitation of our study is that we collected our data retrospectively, and thus our clinical prediction model would be considered "level 4" evidence.[33] Before our prediction model can be used to make clinical decisions, our findings need to be validated in a large, prospective study. Another limitation is that our model does not address the small, albeit significant, possibility of classifying a child as having AM when he or she ultimately has bacterial meningitis. However, many excellent clinical prediction models exist to predict bacterial meningitis and could be used in conjunction with our model.[34–40] Although Lyme serology is obtained for most children presenting with nonbacterial meningitis at our hospital, it is possible that Lyme serology was not collected for all of these children, potentially creating a selection bias in our population of patients with AM. However, we excluded those patients without Lyme serology because we felt that their inclusion might result in misclassification of some patients with LM as having AM, with greater consequences for the validity of the results. It is also possible that some patients who were included in the LM group might have had Lyme disease in the past with persistent antibodies irrelevant to the current CSF pleocytosis, resulting in misclassification of AM as LM. However, with the background seroprevalence in our region, that would be unlikely. Finally, it is unclear whether the presence of prolonged headache, cranial neuritis, or CSF mononuclear predominance in a child with meningitis would have the same predictive value in regions with a low incidence of Lyme disease.

CONCLUSIONS

We present the first predictive model of LM. The identification of LM or AM, based on our model, can help the clinician determine the need for parenteral antibiotics while awaiting Lyme-serology results or other CSF study results (eg, bacterial culture and enterovirus PCR), which typically require several days for final results. To validate our model, a large multicenter, prospective study must be done on all patients being evaluated for meningitis. Until then, clinicians can use this model only as an adjunct and not as a replacement for evidence-based clinical decision-making.

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