Lyme Neuroborreliosis

Presenter:

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Disclosures

- None

Utilization Message

- As you view this presentation, consider the following important points regarding testing:
  - How is the testing going to be used in your practice?
  - When should the tests be used?
  - How will results impact patient management?
Lyme Neuroborreliosis (LNB) – Background\textsuperscript{1,2,3}

- *Borrelia burgdorferi* sensu lato members (>15 species)
  - *B. burgdorferi* sensu stricto, *B. garinii*, *B. afzelii* and ~4 others
  - Transmitted through *Ixodes* sp. ticks
- Lyme disease can progress through multiple stages
  - LNB is seen in ~3%-15% of untreated patients
    - Symptoms develop 4-6 (range 1-12) weeks post infection
  - Most common manifestations:
    - Meningoradiculitis
    - Lymphocytic meningitis
    - Cranial nerve palsy
- “…neurologic manifestations are too nonspecific to warrant a purely clinical diagnosis [of LNB]; laboratory support [for diagnosis] is required.” – 2006 IDSA Guidelines

Diagnostic Testing Considerations for LNB

- Consider risk of infection first!
  - Exposure history (eg, travel to a Lyme disease endemic area)
  - Time of year (eg, lack of tick activity in winter)
- CSF findings
  - Lymphocytic pleocytosis
  - Mildly elevated protein
  - *Glucose levels are typically normal*
  - Testing for CXCL13
    - B-cell attractive chemokine
    - Elevated in patients with LNB and in patients with other neuroinflammatory diseases
    - Not recommended as an aid for diagnosis of LNB
Diagnostic Testing for LNB

- Direct detection of Lyme Borrelia
  - <10% of CSF cultures for *B. burgdorferi* are positive
  - Culture no longer performed in hospital or reference laboratories
- RT-PCR for Lyme Borrelia
  - Most PCR assays are laboratory developed tests and methods vary

<table>
<thead>
<tr>
<th>Clinical Specimen</th>
<th>No. of studies</th>
<th>Median Sensitivity (range)</th>
<th>Specificity (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial Fluid</td>
<td>12</td>
<td>77.5 (23-100)</td>
<td>100</td>
</tr>
<tr>
<td>EM Biopsy</td>
<td>28</td>
<td>68 (30-89)</td>
<td>98-100</td>
</tr>
<tr>
<td>CSF</td>
<td>22</td>
<td>22.5 (5-100)</td>
<td>99-100</td>
</tr>
<tr>
<td>Blood</td>
<td>11</td>
<td>18 (0-100)</td>
<td>95-100</td>
</tr>
</tbody>
</table>

Serologic Testing for Lyme Disease

First Test

- Enzyme Immunoassay (EIA)
  - OR
- Immunofluorescence Assay (IFA)

Negative Result

Consider alternative diagnosis
- OR
  - If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum

IgM Positive: Ab to ≥ 2/3 *Bb* proteins
IgG positive: Ab to ≥ 5/10 *Bb* proteins

https://www.cdc.gov/lyme/resources/twotieredtesting.pdf
Challenges with Standard Serologic Testing for LNB

- Limitations of testing for anti-*B. burgdorferi* serum antibodies only:
  - Up to 15% of patients with LNB will be seronegative
  - Background seropositivity rate is ~5%
- Standard two-tiered testing algorithm developed for evaluation of serum, *not CSF*
- Important to differentiate intrathecal antibody synthesis in the CNS versus passive diffusion of serum antibodies into the CSF across a compromised blood-CSF barrier

Use of a Lyme Antibody Index (AI) as an Aid for Diagnosis of LNB

- Normalizes the level of *Borrelia*-specific antibodies in CSF versus serum to total IgG in both specimen sources
  - Corrects for blood-CSF permeability and abnormally elevated intrathecal Ab synthesis
  - CSF & serum collected *concurrently*
- Lyme AI is recommended by both the IDSA and EFNS for diagnosis of LNB
  - Methods and AI criteria vary between labs
- EFNS criteria for definite LNB:
  - Neurologic symptoms consistent with LNB
  - CSF pleocytosis (> 5 cells/µL)
  - Elevated anti-*Borrelia* AI

**Lyme Disease Antibody Index: Summary of Formulas**

<table>
<thead>
<tr>
<th>Quotient</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSQ&lt;sub&gt;Borrelia&lt;/sub&gt;(IgG)</td>
<td>U/mL (CSF) × dilution factor&lt;sub&gt;CSF&lt;/sub&gt; + U/mL (serum) × dilution factor&lt;sub&gt;serum&lt;/sub&gt;</td>
</tr>
<tr>
<td>CSQ&lt;sub&gt;total&lt;/sub&gt;(IgG)</td>
<td>Total IgG in CSF + Total IgG in serum</td>
</tr>
<tr>
<td>CSQ&lt;sub&gt;albumin&lt;/sub&gt;</td>
<td>Albumin in CSF + albumin in serum</td>
</tr>
<tr>
<td>CSQ&lt;sub&gt;lim.&lt;/sub&gt;(IgG)</td>
<td>0.93 × ([CSQ&lt;sub&gt;albumin&lt;/sub&gt;]&lt;sup&gt;2&lt;/sup&gt; + 6 × 10&lt;sup&gt;-10&lt;/sup&gt;)&lt;sup&gt;1/2&lt;/sup&gt; – 1.7 × 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>AI using CSQ&lt;sub&gt;lim.&lt;/sub&gt;(IgG)</td>
<td>CSQ&lt;sub&gt;lim.&lt;/sub&gt;(IgG) / CSQ&lt;sub&gt;lim.&lt;/sub&gt;(IgG)</td>
</tr>
<tr>
<td>AI using CSQ&lt;sub&gt;total&lt;/sub&gt;(IgG)</td>
<td>CSQ&lt;sub&gt;total&lt;/sub&gt;(IgG) / CSQ&lt;sub&gt;total&lt;/sub&gt;(IgG)</td>
</tr>
</tbody>
</table>

**Lyme Borrelia AI Interpretation:**
- < 0.6 – Invalid
- 0.6 – 1.3: Negative
- 1.3 – 1.5: Equivocal
- ≥ 1.6: Positive
General Performance Characteristics of the Lyme Ai6,7,8

- General performance characteristics
  - Sensitivity:
    - Disease Duration | Sensitivity | Specificity
    - <6 weeks         | 70%-90%     | >95%
    - ≥6 weeks         | >95%        | >95%
  - Remains positive post-treatment!
  - Specificity:
    - >95%
    - False positives (e.g., neurosyphilis, other *Borrelia* spp., etc.)

Resources

Resources Continued


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