

Suppl. Table S2-A

| | Erythema Migrans | Lyme Neuroborreliosis (LNB) | Late LNB with Polyneuropathy |
|--|---|---|---|
| <i>Source</i> | Adapted from Stanek et al., 2011 | Adapted from Mygland et al., 2010 and Stanek et al., 2011 | Adapted from Mygland et al., 2010 and Stanek et al., 2011 |
| Confirmed case | <p>- Clinical criteria:</p> <p>- "typical erythema migrans" diagnosed by a clinician, i.e., Expanding red or bluish-red patch (\geq 5 cm in diameter), with or without central clearing.</p> <p>- or atypical erythema migrans</p> <p>- And \geq1 Laboratory Criterion for Diagnosis:</p> <p>i) Detection of <i>Borrelia burgdorferi</i> sl. by culture from skin biopsy</p> <p>ii) Positive PCR from skin biopsy</p> | <p>- Clinical criteria: In adults mainly meningo-radiculitis, meningitis; rarely encephalitis, myelitis; very rarely cerebral vasculitis. In children mainly meningitis and facial palsy. Without other obvious reasons.</p> <p>- And 2 Laboratory Criteria for Diagnosis:</p> <p>i) Cerebrospinal fluid pleocytosis</p> <p>ii) demonstration of intrathecal specific antibody synthesis or positive PCR from CSF (early LNB)</p> | <p>- Clinical criteria: peripheral neuropathy and acrodermatitis chronica atrophicans</p> <p>- And 1 Laboratory Criterion for Diagnosis:</p> <p>i) High level of specific antibodies in serum</p> |
| Laboratory-confirmed case without or with unknown clinical criteria | NA | NA | NA |
| Probable case | <p>- Clinical criteria: typical erythema migrans diagnosed by a clinician</p> <p>- Without Laboratory Criterion for Diagnosis</p> | | |
| Possible case | <p>- Clinical criteria: non-typical erythema migrans diagnosed by a clinician or compatible lesion reported by a patient after a tick bite</p> <p>- And \geq1 Laboratory Criterion for Diagnosis:</p> <p>i) Sero-conversion or x4 increase of specific antibodies in paired serum samples</p> <p>ii) Elevated IgG or IgM titers</p> | <p>- Clinical criteria</p> <p>- And 1 Laboratory Criterion for Diagnosis:</p> <p>i) Cerebrospinal fluid pleocytosis</p> <p>ii) demonstration of intrathecal specific antibody synthesis or positive PCR from CSF (early LNB)</p> <p>- After a duration of evolution \geq 6 weeks, there have to be found specific IgG antibodies in the serum</p> | |
| Undefinable | | <p>- Clinical criteria</p> <p>- With or without supportive serology result: Specific serum IgG antibodies</p> <p>- Without Laboratory Analysis conducted from CSF</p> | |
| Unlikely case | | <p>- Non-matching clinical criteria</p> <p>- Laboratory Analysis conducted from CSF: Absence or doubtful</p> | |
| Isolated positive serology | NA | NA | NA |

Suppl. Table S2-B

| | Lyme Arthritis | Acrodermatitis Chronica Atrophicans (ACA) | Lyme Carditis |
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| <i>Source</i> | Adapted from Stanek et al., 2011 | Adapted from Stanek et al., 2011 | Adapted from Stanek et al., 2011 |
| Confirmed case | <p>- Clinical criteria: Recurrent attacks or persisting objective joint swelling in one or a few large joints diagnosed by a clinician. Alternative explanations must be excluded.</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) Detection of <i>Borrelia burgdorferi</i> sl. by culture from synovial fluid and/or tissue</p> <p>ii) Positive PCR from synovial fluid and/or tissue</p> <p>iii) Specific serum IgG antibodies, usually in high concentrations</p> | <p>- Clinical criteria: "typical ACA" diagnosed by a clinician, i.e., Long-standing red or bluish-red lesions, usually on the extensor surfaces of extremities. Initial doughy swelling. Lesions eventually become atrophic. Possible skin induration and fibroid nodules over bony prominences.</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) Detection of <i>Borrelia burgdorferi</i> sl. by culture from skin biopsy</p> <p>ii) Positive PCR from skin biopsy</p> <p>iii) High level of specific serum IgG antibodies</p> | <p>- Clinical criteria: Acute onset of atrio-ventricular (I–III) conduction disturbances, rhythm disturbances, sometimes myocarditis or pancarditis. Alternative explanations must be excluded.</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) Detection of <i>B. burgdorferi</i> sl. by culture from endomyocardial biopsy</p> <p>ii) Positive PCR from endomyocardial biopsy</p> |
| Laboratory-confirmed case without or with unknown clinical criteria | NA | NA | NA |
| Probable case | | | <p>- Clinical criteria: Acute onset of atrio-ventricular (I–III) conduction disturbances, rhythm disturbances, sometimes myocarditis or pancarditis. Alternative explanations must be excluded.</p> <p>- Recent or concomitant erythema migrans and/or neurologic disorders.</p> <p>- And 1 supportive serology result: Specific serum IgG antibodies</p> |
| Possible case | <p>- Clinical criteria: compatible clinical case</p> <p>- And 1 supportive serology result: Specific serum IgG antibodies, usually in high concentrations</p> | <p>- Clinical criteria: "typical ACA" diagnosed by a clinician</p> <p>- Without Laboratory Criterion for Diagnosis or</p> <p>- Clinical criteria: compatible clinical case</p> <p>- And 1 supportive serology result: High level of specific serum IgG antibodies</p> | <p>- Clinical criteria: Acute onset of atrio-ventricular (I–III) conduction disturbances, rhythm disturbances, sometimes myocarditis or pancarditis.</p> <p>- Possible other alternative explanations</p> <p>- And 1 supportive serology result: Specific serum IgG antibodies</p> |
| Undefinable | - Clinical criteria: Recurrent attacks or persisting objective joint swelling in one or a few large joints | | |

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| | diagnosed by a clinician. Alternative explanations must be excluded. - Without Laboratory Analysis conducted | | |
| Unlikely case | Absence of specific IgG in serum | Incompatible clinical case or Absence of specific IgG in serum | |
| Isolated positive serology | NA | NA | NA |

Suppl. Table S2-C

| | Human Granulocytic Anaplasmosis | Rickettsiosis | Human Babesiosis | Neoehrlichiosis |
|--|--|---|---|---|
| <i>Source</i> | Adapted from Dahlgren et al., 2015 | Adapted from Portillo et al., 2017 | Adapted from Krause et al., 2021 | <i>This study</i> |
| Confirmed case | <p>- Clinical criteria: fever and at least one of the following symptoms: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases.</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) $\times 4$ or greater increase in IgG titer by IFA between paired serum samples (acute serum taken during first week of illness and convalescent sample taken 2–4 weeks later)</p> <p>ii) Detection of DNA by PCR in blood</p> <p>iii) Demonstration of antigen in a biopsy or autopsy by immunohistochemical (IHC) methods</p> <p>iv) Isolation by culture from a clinical specimen.</p> | <p>- Clinical criteria: fever, rash, and eschar with different combinations</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) positive PCR and/or culture in blood or skin biopsy</p> <p>ii) positive immunohistochemical assays in tissues</p> <p>iii) Sero-conversion or $\times 4$ increase of specific antibodies in paired serum samples</p> | <p>- Epidemiological risk factors</p> <p>- Clinical criteria: typical symptoms (fever, fatigue, chills, sweats, headache, and anorexia) and characteristic routine laboratory test abnormalities (anemia, thrombocytopenia, elevated liver enzymes, and/or evidence of intravascular hemolysis (LDH \uparrow, Bilirubin \uparrow, haptoglobin \downarrow))</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) positive PCR in blood</p> <p>ii) intraerythrocytic <i>Babesia</i> parasites on blood smear</p> <p>iii) Sero-conversion or $\times 4$ increase of specific antibodies in paired serum samples</p> | <p>- Clinical criteria: Flu-like syndrome and/or thrombosis</p> <p>- And Laboratory Criterion for Diagnosis</p> <p>i) positive PCR in blood</p> |
| Laboratory-confirmed case without or with unknown clinical criteria | ≥ 1 Laboratory Criterion for Diagnosis without or with unknown clinical criteria | ≥ 1 Laboratory Criterion for Diagnosis without or with unknown clinical criteria | ≥ 1 Laboratory Criterion for Diagnosis without or with unknown clinical criteria | Laboratory Criterion for Diagnosis without or with unknown clinical criteria |
| Probable case | <p>- Clinical criteria</p> <p>- And 1 supportive result:</p> <p>i) Elevated IgG or IgM titers</p> <p>ii) Presence of morulae in the cytoplasm of neutrophils or eosinophils.</p> | <p>- Clinical criteria</p> <p>- And 1 supportive result:</p> <p>i) Elevated IgG and IgM titers</p> | <p>- Epidemiological risk factors</p> <p>- Clinical criteria</p> <p>- And 1 supportive serology result:</p> <p>i) Elevated titer of specific serum IgG $>1/1024$</p> <p>ii) Elevated titer of specific serum IgM</p> | |
| Possible case | | <p>- Clinical criteria</p> <p>- And 1 supportive result:</p> <p>i) Elevated IgG or IgM titers</p> | <p>- Epidemiological risk factors</p> <p>- Clinical criteria</p> <p>- And 1 supportive serology result:</p> <p>i) Elevated titer of specific serum IgG $<1/1024$</p> | |
| Undefinable | Positive PCR from other biological samples | Positive PCR from other biological samples | Positive PCR from other biological samples | Positive PCR from other biological samples |

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| Unlikely case | | | | |
| Isolated positive serology | Elevated titer of specific serum antibodies without clinical criteria | Elevated titer of specific serum antibodies without clinical criteria | Elevated titer of specific serum antibodies without clinical criteria | Elevated titer of specific serum antibodies without clinical criteria |

Suppl. Table S2-D

| | <i>B. miyamotoi</i> Disease | Bartonellosis | Tick-Borne Encephalitis | Powassan Encephalitis |
|--|---|--|---|---|
| <i>Source</i> | <i>This study</i> | <i>This study</i> | Adapted from EU 2012 | Adapted from CDC 2001 |
| Confirmed case | <p>- Clinical criteria: Flu-like syndrome and/or meningoencephalitis</p> <p>- And 1 Laboratory Criterion for Diagnosis</p> <p>i) positive PCR in blood (flu-like syndrome)</p> <p>ii) positive PCR in CSF (meningoencephalitis)</p> | <p>- Clinical criteria: Flu-like syndrome with fever, splenomegaly, lymphadenopathy, or infective endocarditis or encephalitis or neuroretinitis</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) positive PCR in blood or tissues</p> <p>ii) positive culture from blood or tissues</p> | <p>- Clinical criteria: inflammation of the CNS (e.g. meningitis, meningo-encephalitis, encephalo- myelitis, encephaloradiculitis)</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) TBE specific IgM AND IgG antibodies in blood</p> <p>ii) TBE specific IgM antibodies in CSF</p> <p>iii) Sero-conversion or x4 increase of TBE-specific antibodies in paired serum samples</p> <p>iv) Detection of TBE viral nucleic acid in a clinical specimen,</p> <p>v) Isolation of TBE virus from clinical specimen</p> | <p>- Clinical criteria: fever $>38^{\circ}\text{C}$ with any peripheral of CNS dysfunction</p> <p>- And ≥ 1 Laboratory Criterion for Diagnosis:</p> <p>i) x4 or greater change in virus-specific serum antibody titer</p> <p>ii) Isolation of virus from or demonstration of specific viral antigen or genomic sequences in tissue, blood, cerebrospinal fluid (CSF), or other body fluid</p> <p>iii) Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF by antibody-capture enzyme immunoassay (EIA)</p> <p>iv) Virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum immunoglobulin G (IgG) antibodies in the same or a later specimen by another serologic assay (e.g., neutralization or hemagglutination inhibition).</p> |
| Laboratory-confirmed case without or with unknown clinical criteria | Laboratory Criterion for Diagnosis without or with unknown clinical criteria | ≥ 1 Laboratory Criterion for Diagnosis without or with unknown clinical criteria | ≥ 1 Laboratory Criterion for Diagnosis without or with unknown clinical criteria | ≥ 1 Laboratory Criterion for Diagnosis without or with unknown clinical criteria |
| Probable case | <p>- Clinical criteria: Flu-like syndrome</p> <p>- And 1 supportive serology result:</p> <p>i) Sero-conversion or x4 increase of specific antibodies in paired serum samples</p> | <p>- Clinical criteria</p> <p>- And 1 supportive serology result:</p> <p>i) Sero-conversion or x4 increase of specific antibodies in paired serum samples</p> | <p>- Clinical criteria</p> <p>- And 1 supportive serology result:</p> <p>i) Detection of TBE-specific IgM-antibodies in a unique serum sample</p> | <p>- Clinical criteria</p> <p>- And 1 supportive serology result:</p> <p>i) a single or stable (less than or equal to twofold change) but elevated titer of virus-specific serum antibodies</p> <p>ii) serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen.</p> |

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| Possible case | - Clinical criteria: Flu-like syndrome - And 1 consistent serology result: i) Elevated titer of specific serum antibodies | - Clinical criteria - And 1 consistent serology result: i) Elevated titer of specific serum antibodies | | |
| Undefinable | | | | |
| Unlikely case | | | | |
| Isolated positive serology | Elevated titer of specific serum antibodies without clinical criteria | Elevated titer of specific serum antibodies without clinical criteria | Elevated titer of specific serum antibodies without clinical criteria | Elevated titer of specific serum antibodies without clinical criteria |