A Systematic Approach to the Differential Diagnosis of Encephalitis in Children

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Scenario

In the past week your team has been consulted to evaluate a 6-year-old boy with a febrile illness that progressed to altered mental status with seizures and a 15-year-old girl with recent behavioral changes, hallucinations and unusual facial movements. A resident on the general service that is managing both patients asks you if there is a standard diagnostic approach that can be taken with such patients that does not require ordering “too many tests.”

- How do you respond?
- What are the most common etiologies of encephalitis in children?
- What are the best ways to confirm or exclude important entities?

Children presenting for evaluation of acute alteration of mental status present a significant diagnostic challenge. Identification of a specific etiology is a priority, since it allows for prompt, specific, and potentially life-saving therapeutic intervention, promotes discontinuation of unnecessary medications or laboratory tests, and may provide prognostic information to the medical team, patients and caregivers.

Encephalitis should be considered when patients present with encephalopathy (altered mental status) for ≥24 hours and at least one of the following: fever >38°C, seizures, focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis, focal electroencephalogram or epileptiform activity, or abnormal neuroimaging [1, 2]. The many etiologic agents of infectious encephalitis include viruses, bacteria, fungi, and parasites, and causes of noninfectious origin include immune-mediated, metabolic, and toxic conditions.

Guidelines regarding the diagnosis and treatment of encephalitis have recently been published by the Infectious Diseases Society of America [2]. These emphasize approaching each case individually, because historical clues, physical examination findings, and laboratory test results may be unique for each patient [2]. The practical implementation of this approach remains a challenge, and often invites broad, “shotgun” testing. A more prioritized and tiered diagnostic approach, based on relative likelihood of causes (Table 1), patient characteristics, epidemiologic features, and physical findings may lead to avoidance of unnecessary and costly diagnostic testing, as well as optimized evaluation of limited amounts of body fluid specimens, such as CSF. Figures 1 and 2 illustrate such an approach.

In large epidemiologic studies of encephalitis, the most commonly identified infectious etiologies include...
<table>
<thead>
<tr>
<th>Organism</th>
<th>Exposures and Exam Findings</th>
<th>Diagnostic Testing</th>
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<tbody>
<tr>
<td><strong>More common</strong></td>
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<tr>
<td>Herpes group (HSV, VZV, EBV, CMV)</td>
<td>Rash, adenopathy (EBV), retinitis (CMV, VZV), olfactory hallucinations (HSV), cranial nerve palsy (HSV, VZV), ataxia (VZV)</td>
<td>Blood: EBV, CMV, and VZV serology CSF: HSV, VZV, EBV, CMV PCR Other: HSV and/or VZV PCR of skin lesions (or DFA and culture if PCR unavailable), ophthalmology exam if suspected CMV</td>
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<tr>
<td>Enterovirus</td>
<td>Rash (hand, foot and mouth disease), soft palate erosions (herpangina), diarrhea</td>
<td>Blood: PCR CSF: PCR Other: Nasopharyngeal and rectal swab PCR or culture</td>
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<tr>
<td>Arbovirus (West Nile, La Crosse, EEE, WEE, SLE)*</td>
<td>Mosquito/outdoor exposure (all), horse deaths (EEE, WEE) Flaccid Paralysis (WNV)</td>
<td>Blood: WNV serology, arboviral serology CSF: WNV serology, arboviral serology, WNV PCR if immunocompromised (not sensitive in immunocompetent host)</td>
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<tr>
<td>Respiratory viruses</td>
<td>Respiratory tract symptoms</td>
<td>Other: Nasopharyngeal respiratory virus PCR, CXR</td>
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<tr>
<td><em>Mycoplasma</em></td>
<td>Preceding respiratory tract infection, rash (polymorphous)</td>
<td>Blood: Serology CSF: PCR (low yield) Other: Nasopharyngeal aspirate or swab PCR, CXR</td>
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<td><strong>Less common</strong></td>
<td></td>
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<tr>
<td>Bartonella*</td>
<td>Cat exposure Regional adenopathy</td>
<td>Blood: Serology Other: Ophthalmology exam if suspected</td>
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<td>HIV</td>
<td>Sexual activity, intravenous drug use Rash, adenopathy, mono-like illness</td>
<td>Blood: Serology and DNA PCR CSF: DNA PCR</td>
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<tr>
<td>Lyme</td>
<td>Tick/outdoor exposure Rash (erythema migrans), cranial nerve palsy, arthritis, carditis, papilledema</td>
<td>Blood: EIA screen serology with reflex Western blot CSF: EIA screen serology with reflex Western blot Other: Ophthalmology exam if suspected</td>
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<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Respiratory tract symptoms, cranial nerve palsy</td>
<td>CSF: PCR, AFB smear and culture Other: PPD, CXR, PCR and culture of respiratory secretions</td>
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<tr>
<td><em>Rickettsia</em>: RMSF, Ehrlichia, Anaplasma</td>
<td>Tick/outdoor exposure Rash (petechial, centripetal spread), hyponatremia, thrombocytopenia</td>
<td>Blood: RMSF serology, Ehrlichia serology, Anaplasma serology, PCR for Ehrlichia or Anaplasma Other: Review blood smear for morula if suspected Anaplasma, PCR of skin biopsy specimen if rash present and RMSF suspected</td>
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<tr>
<td>Parechovirus</td>
<td>Similar to enterovirus</td>
<td>CSF: PCR</td>
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<tr>
<td>Rare</td>
<td></td>
<td></td>
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<tr>
<td>Malaria</td>
<td>Mosquito/exposure in endemic areas</td>
<td>Blood: Thin and thick smears</td>
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<td>Rotavirus</td>
<td>Gastroenteritis (vomiting, diarrhea)</td>
<td>Other: Stool/rectal rotavirus antigen</td>
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<tr>
<td>Parvovirus</td>
<td>Rash (“slapped cheek” or lacy waxing/waning rash)</td>
<td>Blood: Serology and PCR CSF: PCR</td>
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<tr>
<td>Rabies</td>
<td>Bat, raccoon, fox, skunk exposure</td>
<td>CSF: PCR Other: Nape of neck skin biopsy, conjunctiva, and saliva PCR and DFA</td>
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<td>Syphilis</td>
<td>Sexual activity</td>
<td>Blood: VDRL or RPR, followed by FTA-ABS if + CSF: VDRL</td>
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Endemic fungi: *Histoplasma*, *Coccidioides*, *Blastomyces*

**Travel to endemic areas**
- Respiratory tract symptoms, cranial nerve palsy, hepatosplenomegaly (*Histoplasma* and *Blastomyces*)

**Blood:** *Coccidioides*, *Histoplasma*, *Blastomyces* serology (complement fixation and immunodiffusion for histoculture)
- *Histoplasma* antigen
- *Histoplasma*, *Coccidioides*, and *Blastomyces* Serology
- Fungal culture
- Other: *Urine Histoplasma* antigen

**Amoeba (Naegleria, Balamuthia > Acanthamoeba, Sappinia)**

**Freshwater exposure (Naegleria, Acanthamoeba), soil exposure (Balamuthia)**

**Blood and CSF:** Serology (IFA and PCR via CDC consultation)
- CSF: Wet prep, Giemsa or Wright-stained cytospin prep

**Immunocompromised**

**Human herpes virus 6**

**Mimics HSV infection**

**CSF PCR**

**Cryptococcus**

**Blood and CSF:** Cryptococcal antigen
- Other: CXR

**JC: Virus**

**Progressive multifocal leukoencephalopathy**

**CSF:** *JC* Virus PCR

**Toxoplasma**

**Cat exposure, retinitis**

**Blood:** Serology
- **CSF:** *Toxoplasma* PCR
- Other: Ophthalmology exam

**Amoeba: Acanthamoeba**

**Freshwater exposure**

**CSF:** Wet prep, Giemsa- or Wright-stained cytospin prep

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**Abbreviations:** AFB, acid-fast bacilli; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CXR, chest x-ray; DFA, direct fluorescent antibody; EBV, Epstein-Barr virus; EEE, Eastern equine encephalomyelitis; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption test; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFA, indirect immunofluorescence assay; JC, John Cunningham; PCR, polymerase chain reaction; PPD, purified protein derivative; RMSF, Rocky Mountain spotted fever; RPR, rapid plasma reagin; SLE, Saint Louis Encephalitis; VDRL, Venereal Disease Research Laboratory; VZV, varicella zoster virus; WEE, Western equine encephalitis; WNV, West Nile virus.

*Repeat serologic testing is recommended 10 to 21 days after initial presentation.*

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Figure 1. A systemic, tiered approach to working through the differential diagnosis of acute encephalopathy in children >3 months of age. Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; HSV, herpes simplex virus; PCR, polymerase chain reaction; NMDA, *N*-methyl-D-aspartate.
Figure 2. An algorithmic view of likely etiologies of acute encephalitis/encephalopathy in children, based on initial presentation and clinical and laboratory findings. Abbreviations: ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; WBC, white blood cells.
management (e.g., signs of shock, dyssynergy, respiratory failure), and a neurologic assessment is made for convulsive and nonconvulsive seizures. Obtaining CSF is critical for the complete evaluation of patients with encephalitis, meningoencephalitis, or meningitis. In general, lumbar puncture may be performed safely (without initial cranial imaging) unless focal neurologic signs (e.g., focal seizures, focal dysfunction, or papilledema) are present. Nevertheless, all patients with encephalitis or meningoencephalitis should undergo central nervous system (CNS) imaging, preferably with magnetic resonance imaging (MRI), ideally within 48 hours of admission [6–8]. If this cannot be done safely, computer-assisted tomography scans (CT) may provide basic information about the presence of masses, cerebral edema, or suggestions of highly elevated intracranial pressure.

Acute disseminated encephalomyelitis is a relatively common cause of pediatric encephalitis [9]. It is thought to be an immune-mediated postinfectious process, and is suggested by MRI findings of asymmetric, multifocal lesions predominantly in the white matter, but can have extension into the gray matter. These lesions are best seen on T2-weighted and fluid-attenuated inversion recovery MRI sequences [9]. The CSF generally shows an elevated protein level with pleocytosis.

Recently, N-methyl-D-aspartate receptor (NMDAR) antibody-mediated encephalitis has been described as the most common noninfectious immune-mediated cause of encephalitis in both adults and children, with an incidence as great as HSV or other viral etiologies of encephalitis [10, 11]. Patients with NMDAR encephalitis exhibit a greater incidence of early behavioral changes, hallucinations, or CNS vasculitis (Table 1) [12–20].

### References