Target Audience

- This program is designed for primary care physicians.
- Other health care professionals working with patients and their families may also find this program of interest.

Faculty Disclosure

- It is the policy of Children’s Hospitals and Clinics of Minnesota to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. Our faculty have been asked to disclose to our program audience any real or apparent conflicts of interest related to the content of their presentations.
- They have also been requested to let you know when any products mentioned in their presentations are not labeled for the use under discussion or are still under investigation.

Speaker Faculty Disclosure

- Richard D. Andersen, MD has disclosed no actual or apparent conflict of interest in relation to this educational activity.
- During this educational activity Dr. Andersen will not be discussing the off-label use of commercial or investigational products not approved by the FDA.
Encephalitis in Children

Pediatric Grand Rounds: July 11, 2013

A lecture about Encephalitis in newborns, Encephalitis occurring year-round, and summer Encephalitis in Minnesota

Program Objectives

Upon completion of this program, participants should be able to:

- Discuss the etiologic agents of encephalitis in newborns and in children of all ages.
- Describe the clinical features of encephalitis in children.
- Review appropriate diagnostic strategies for evaluation of children with apparent encephalitis.

Disclaimer

- Children’s Hospitals and Clinics of Minnesota accepts no responsibility for the materials presented through these Grand Rounds seminars. Each professional presenter assumes all responsibility for maintaining confidentiality or obtaining authorization, in accordance with all applicable laws.

Accreditation

- Children’s Hospitals and Clinics of Minnesota is accredited by the Minnesota Medical Association to provide continuing medical education for physicians.
- Children’s Hospitals and Clinics of Minnesota designates this educational activity for a maximum of 1 AMA Category 1 Credit™ toward the AMA Physician’s Recognition Award.

- Each Physician should only claim credit for the actual time he/she spent in the activity.

Retention of CME Records

- It is the policy of Children’s Medical Education program that we cannot offer to retain CME records for physicians attending or viewing the online CME activity.
- The Minnesota Medical Association designates that physicians are responsible for maintaining their own CME records.

Receiving CME Credit

- To receive CME credit, you must view the entire program. When the program is completed, click the Post Test button on the interface to access the Post Test.
- You must successfully pass the Post Test to receive CME credit.
Some Neurologic Manifestations of Infectious Disease

- Meningitis/encephalitis/meningoencephalitis
- abscess
- ventriculitis
- empyema
- transverse myelitis
- poliomyelitis
- cranial and peripheral neuropathies
- cerebellar ataxia
- Guillain-Barre Syndrome
- acute demyelinating encephalomyelitis
- post-infectious meningoencephalitis

Encephalitis in Children

Grand Rounds, July 11, 2013

Richard D. Andersen, MD
Departments of Infectious Disease and Medical Education
Children’s Hospitals and Clinics of Minnesota

Some Neurologic Manifestations of Infectious Disease

- Meningitis/encephalitis/meningoencephalitis
- abscess
- ventriculitis
- empyema
- transverse myelitis
- poliomyelitis
- cranial and peripheral neuropathies
- cerebellar ataxia
- Guillain-Barre Syndrome
- acute demyelinating encephalomyelitis
- post-infectious meningoencephalitis

Terminology

Meningitis---------------------Encephalitis
Meningoencephalitis

Encephalitis in Children

I. Encephalitis in Newborns

II. Encephalitis Occurring Year-Round

III. Summer Encephalitis in Minnesota

Terminology

Meningitis---------------------Encephalitis
Meningoencephalitis

Clinical Features of Encephalitis

- Fever
- Headache / myalgia / arthralgia
- Encephalopathy
- Seizures
- Fatigue / weakness / ataxia / paralysis
- Confusion/personality change / hallucination
- Sensory/visual/olfactory/speech alterations
Key Elements of History in Child w/ Apparent Encephalitis

- Season and Community Epidemiology
- Travel – regional, international
- Vector exposure – esp. mosquito, tick
- Animal exposures:
  a) Domestic – e.g. dog, cat, hamster
  b) Wild – e.g. raccoon, horse,
- Immunization history, esp. MMR
- Associated symptoms – esp. rash, respiratory

Neonatal Encephalitis: A Simplified Milieu

- Season and Community Epidemiology?
- MATERNAL HISTORY?
- Travel: in utero → ex utero
- Vector exposures: none
- Animal exposures: none
- Immunizations: none
- Associated symptoms – rash? Respiratory?

Encephalitis in Newborn

- Congenital infection (CMV, toxoplasmosis, rubella, parvovirus) tends to present with more static CNS involvement.
- Encephalitis in neonate generally arises acutely following natal/postnatal acquisition and an interval of well-being.
- The clinical distinction of meningitis vs. encephalitis is often more ambiguous

Encephalitis in Newborn: Diagnostic Sequence

- Suspected neonatal infection = urine, blood and CSF cultures, empiric antibiotics.
- Suspected encephalitis begins with abnormal CSF, negative Gram stain, no obvious bacterial focus and clinical features of infection (of CNS)
- CSF : send for usual bacterial studies and PCR for HSV, enterovirus; viral culture if adequate CSF
- Empiric acyclovir is indicated while viral studies are pending, even if in enterovirus season.

Neonatal Encephalitis? An Instructive Case

- Case 1a is an 7-day old girl admitted to Children’s with progressive respiratory distress and lethargy. 34 wk. gestation.
- Maternal primary genital HSV 3d before delivery, oral acyclovir, C-sxn <3 hrs ROM
- Lethargy, clinical decline, cultures pending, CSF = bloody tap, negative Gram stain
- Amp/gentamicin/azithromycin/acyclovir

Treatment of Neonatal HSV Encephalitis

- Day 9 of life, PCR from HSV CSF (outside hospital) reported to be +. ID consulted.
- Recommended LFT’s, coagulation studies: AST >17,000, INR >9, PTT >120
- High dose acyclovir continued (now at 48 hours), fresh frozen plasma, protracted multi-system support. Survived and completed 21-day course.
HSV Encephalitis?

- Maximal ventilator settings, critically ill with slow, progressive improvement, slow normalization of LFT’s, coagulation studies
- Discharged to home after 21 days IV acyclovir, then oral acyclovir suppression begun until 6 months of age.
- MRI assessment before discharge

Fever and Seizures in a Neonate

- Case 1b is a 5 day old male, term pregnancy, vague maternal illness at delivery
- Fever, rash prompted admission, seizure early in hospitalization
- CSF pleocytosis, nl glucose, protein

Neonatal Enterovirus Infection

- Usually natafly acquired, interval of well being. +/- Hx of maternal illness @ delivery
- Variable neurotropism, both ECHO and Coxsackie reported.
- Meningitis features > encephalitis
- Multi-organ involvement (liver, heart, CNS)
- Prognosis overall more favorable than HSV

Encephalitis in Newborn:

SUMMARY

- Herpes simplex virus and enteroviruses are principal considerations
- Usually natal/post-natal acquisition, often presentation is 2nd – 3rd week of life
- CSF studies: include HSV PCR, enterovirus PCR. Viral cultures of throat, rectal swab, if possible
- Empiric IV acyclovir until HSV PCR negative and/or enterovirus PCR +.

Encephalitis in Children:

Pathogens for All Seasons

- Measles/Mumps/Rubella
- Rabies, Lymphocytic choriomeningitis, Bartonella
- Herpesviruses: HSV, VZV, EBV, CMV, HHV 6-7-8
- Adenovirus, Mycoplasma, M. tuberculosis
Child with Encephalitis: Is the Patient Fully Immunized?

- Ask about general immunization status and M-M-R specifically
- Is there disease activity in the community?
- If immunized and no community disease, defer testing for M-M-R

Child with Encephalitis: Domestic or Wild Animal Exposure?

- Any bite or scratch from dogs, cats, mice, hamsters, other?
- Any contact with wild animals?
- If no, defer testing for rabies, LCM, and Bartonella species

Herpesviruses and Encephalitis

- Herpes simplex (1,2), (Varicella-zoster virus)
- Epstein-Barr virus, (cytomegalovirus)
- Human herpesvirus 6, (HHV-7, HHV-8)

Encephalitis in a 15-year-old Male

- Case 2 is a 15-year-old boy in good health, who was transferred from northern Minnesota with disorientation, confusion, and lethargy.
- Headache and fever preceded neurologic symptoms by several days
- MRI scan performed showed temporal lobe enhancement with significant mass effect

HSV Encephalitis Beyond the Newborn Period

- Nearly always HSV-1. Approx 1/3 appear to be primary, 2/3 secondary
- Presumed access via olfactory nerve to temporal lobe, or from trigeminal nerve
- Early CT/MRI changes in temporal lobe, focal hemorrhagic necrosis
- Prognosis related to age, CNS compromise
Child with Encephalitis: Why is it Not Herpes Simplex Virus?

- Absence of past/present HSV-1 not helpful
- Occurrence in arbovirus season?
- Absence of temporal lobe clinical features?
- Absence of CT/MRI abnormalities?
- Absence of RBC’s in CSF?
- Negative HSV PCR in CSF

Acute Psychosis in an Adolescent Boy

- Case 3 is a 15-year-old boy who developed fever, sore throat 6 days prior to admission.
- Developed headache, myalgia & coughing over days preceding admission
- Day of admission, he became confused, speaking “nonsense,” sounding paranoid to family. No drug or alcohol use known

Differential Considerations

- Measles/Mumps/Rubella
- Rabies, LCM, Bartonella
- Herpesviruses: HSV, VZV, EBV, CMV, HHV 6-7-8
- Adenovirus, Mycoplasma, M. tuberculosis

Early Diagnostic Assessment

- Peripheral WBC 5500, plts 146K, hgb 14.9 CRP 8.77, AST 15, drug screen negative
- Negative Lyme, histo, blasto, EBV serology, negative arbovirus serology
- CSF: 33 RBC’s, 1 WBC, glu 60, protein 30, negative HSV, enterovirus PCR.
- Mycoplasma IgM 1.09, IgG 0.61, IgM FA--
Ongoing Evaluation

- Histoplasma, blastomyces serology negative
- PPD negative
- Mycoplasma PCR of throat +
- Mycoplasma serology (week 3-4) + with >4-fold rise in IgM, IgG, positive IgM FA
- Adenovirus serology not done

Neurologic Complications of Mycoplasma Infection

- Usually encephalopathy 1-2 weeks after onset of resp symptoms
- Cerebellar ataxia, meningitis, transverse myelitis, psychosis, Guillain-Barre described
- Mortality ~10%? w/ est. ~30 neuro sequelae
- Treatment – antibiotics unlikely to benefit, steroids unproven; other anti-inflammatory?

Early Diagnostic Assessment

- Peripheral WBC 5500, plts 146K, hgb 14.9
- CRP 8.77, AST 15, drug screen negative
- Negative Lyme, histo, blasto, EBV serology, negative arbovirus serology
- CSF: 33 RBC’s, 1 WBC, glu 60, protein 30, negative HSV, enterovirus PCR.
- Mycoplasma IgM 1.09, IgG 0.61, IgM FA--

Neurologic Complications of Mycoplasma Infection

- Usually encephalopathy 1-2 weeks after onset of resp symptoms
- Cerebellar ataxia, meningitis, transverse myelitis, psychosis, Guillain-Barre described
- Mortality ~10%? w/ est. ~30 neuro sequelae
- Treatment – antibiotics unlikely to benefit, steroids unproven; other anti-inflammatory?

Encephalitis of Summer

- Arboviruses predominate worldwide. In upper Midwest, nearly all arboviruses of USA present:
  - A) LaCrosse (California) encephalitis
  - B) Western (& Eastern) equine encephalitis
  - C) St. Louis encephalitis
  - D) West Nile encephalitis
  - E) Powassan encephalitis

Approach to Non-viral Causes of Encephalitis in Summer

- Is there a rash -- present or past?
- Has there been a known tick exposure?
- Has the child been swimming in a warm lake, especially in the southern U.S.?
- Are the clinical features more subacute and meningitic, rather than encephalitic?
**Encephalitis of Summer: A Child with Non-Viral Etiology**

- Case 4 is a 7 year old female who presented with a 3-day history of vomiting and fever.
- Found unresponsive on day of admission and mother noted lip-smacking and abnormal eye movements.
- Adm temp = 39.3°C. CSF showed 8150 WBC’s, 800 RBC’s glu <6, protein 481

**Case 4 (continued)**

- Gram stain revealed no bacterial organisms
- Vancomycin and cefotaxime begun
- Special stains obtained by pathology lab
- Seizures and pupillary changes overnight
- Neurologic deterioration proceeded rapidly and brain death occurred
- Life support was discontinued

**Amebic Meningoencephalitis**

- Caused by Naegleria fowleri, an amoeba found in warm fresh-water lakes, ponds
- Occurs worldwide, in USA is almost exclusively in southern states
- Results in progressive meningoencephalitis and is almost universally fatal
- Treatment with amphotericin B is of limited value

**Encephalitis in Children: When Rash is Present**

- Case 5 is an 8 year old girl who developed a rash, fever and disorientation over 48 hrs preceding admission
- She had been in previously good health had spent considerable time in the woods over the summer.
- No travel outside of Colorado near home
Rocky Mountain Spotted Fever

Rash usually appears within a few days but may be delayed or absent.

Rash is generally maculopapular but may have petechial element, especially if the patient has severe thrombocytopenia.

Rash generally involves the palms and soles, which narrows differential diagnosis.

Rocky Mountain Spotted Fever

- RMSF occurs much more in southern and eastern USA
- Low incidence in Rocky Mountain states and very low in Minnesota
- Tick species capable of carrying are present in nearly every state

Arboviruses of Minnesota: Before the 21st Century

- LaCrosse encephalitis – historically the most important arbovirus in Minnesota
- Western equine encephalitis – occasional outbreaks, none recent
- Eastern equine encephalitis – no human cases as of July, 2013
- St. Louis encephalitis – fewer cases in Minnesota than elsewhere in Midwest

LaCrosse Encephalitis

- Transmitted by mosquito, 2 species
- Generally occurs in Midwestern state, now spreading to southeastern USA
- “Treehole mosquito” thrives in small pockets of water, e.g. old tires. **Daytime feeding**
- Transovarian transmission of virus in mosquito
- Generally a **childhood** illness, with mortality < 1%. Some have neuro sequelae
Arboviruses New to Minnesota in the 21st Century

- West Nile Virus – mosquito-borne with birds as most commonly infected animal
- Powassan Virus – tick-borne and many rodent and other mammalian secondary hosts

West Nile Virus

- Origins in Africa, first case in western hemisphere in New York City, 1999
- Rapid westward spread, arriving in Midwest in 2002-03.
- Low mortality, growing recognition of sub-clinical cases and West Nile Fever (without encephalitis)
- Dramatic variations in case numbers annually

West Nile Virus in Minnesota 2011 & 2012

Encephalitis in Arriving Travelers: A Few Considerations

- Patients arriving from Rocky Mountain states – consider Colorado Tick Fever
- Patients arriving from Asia – consider Japanese Encephalitis Virus
- Patients arriving from Central/South America – consider Venezuelan Equine Encephalitis
Colorado Tick Fever

- A relatively common disease in Rocky Mtn states in late spring/early summer
- Generally transmitted by D. andersoni, limited to high altitudes
- Caused by RNA virus, self limiting
  - Leukopenia is nearly universal
  - Biphasic fever course is usual

Encephalitis in Arriving Travelers: A Few Considerations

- Patients arriving from Rocky Mountain states — consider Colorado Tick Fever
- Patients arriving from Asia — consider Japanese Encephalitis Virus
- Patients arriving from Central/South America — consider Venezuelan Equine Encephalitis

Powassan Virus

- First case diagnosed in Powassan, Ontario in 1958. It has remained uncommon in US
- Incubation period variable, usually 7-14 days
- Time of tick attachment to infection may be much less than anaplasmosis or Lyme Disease
  - Only symptomatic treatment
  - Diagnosis by serology, PCR in selected labs

- Clinically suspected when patients present with encephalitis or meningitis
- Carried by Ixodes scapularis (deer tick), which carries multiple other human pathogens
- In Minnesota has occurred in north central counties, <50 cases per year since 2010
- Remains rare in the USA but mortality is said to be 10%.