Clinicopathologic Conference: “9-year-old with mutism and lower extremity weakness, and a history of exudative pharyngitis”

William Pomputius III, MD
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Grand Rounds- 26 Feb 2009

4) Kimura H. Pathogenesis of chronic active Epstein-Barr virus infection: Is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? Reviews in Medical Virology 2006;16:251-261

An additional article which may be of practical interest to pediatricians and family practitioners counseling athletes recovering from IM…
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**Viewing Time**

The program will take up to one hour to complete.

**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**

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**Faculty Disclosure**

William Pomputius III, MD, has disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity Dr. Pomputius will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

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A lecture discussing different presentations of Epstein-Barr Virus (EBV).
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### Program Objectives

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

- Identify unusual presentations of common pediatric problems
- Identify specific difficulties in the diagnosis of specific pediatric problems
- Discuss potential difficulties in the management of pediatric problems

### Disclaimer

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### Accreditation

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### Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

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*A 9 year-old with mutism and lower extremity weakness, and history of exudative pharyngitis*  
**Pediatric Grand Rounds**  
26 February 2009  
*Dr. William F. Pomputius III*  

Illustration by Sir John Tenniel
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### Case history
- 8 yr old Cauc female, previously healthy
- Along with sibs, viral gastroenteritis x 3 days
- 1 week into illness, fever to 101 and exudative pharyngitis. + Monospot
- Within 1-2 days, stumbling, and by day #10, ataxia
- Outside hospitalization for dehydration and neuro w/u. LP normal.
- Day #15-mutism and refusal to walk. Transfer to MCHC

### MCHC course
- Afebrile (had received methylpred on outside), with 3+ non-exudative tonsils, spleen tip, and only cervical LN
- Neuro consult: aphasia, encephalomyelitis
- CSF: 57 WBC, 928 RBC (2% N, 84% L, 14% M), gluc 90, prot 47 (nl 15-40)
- MRI of brain and spine with gadolinium contrast normal
- EEG-interrim diffuse theta slowing, with no evidence of sz
- EMG with NCV normal

### Denouement
- MCHC CSF: + EBV DNA PCR
- Blood EBV DNA PCR negative
- CMV IgG neg but CMV IgM positive (as are all arbovirus IgM on panel)
- Discharged home still mute but walking with assistance
- Convalescent EBV titers (2 months after d/c): VCA IgG and EBNA Ab now +, and VCA IgM neg
- Telephone follow-up at 3 months: gait/strength almost back to normal, talking

### History
- **Description of Infectious Mononucleosis**
  - By early 1900’s, “leukemia with spontaneous cure”
- **Discovery of heterophile antibodies in IM**
  - Paul and Bunnell (1932)
- **Identification of the virus**
  - Burkitt’s “sarcoma”-Epstein & Barr perform EM on cultivated tumor cells (1964)
- **Association of EBV and IM**
  - Lab tech with clinical IM and seroconversion (1968)

### Herpesvirus 4 structure
- **Viral capsid around linear double-strand DNA, surrounded in turn by envelope**
- **Genomic composition**
  - Nearly 100 proteins
  - Of these, 3 latent membrane proteins (LMP) and 6 nuclear proteins (EBNA)
  - A multitude of functions, primary among them immune system evasion
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**Replication**
- Infects nasopharyngeal epithelial cells and B-lymphocytes
- Cell surface receptors for C3d and MHC class II
- Epithelial cells lyse, while B-cells do not

**Latency**
- Reservoir of 1-50 million B-cells
- Limited number of proteins expressed to avoid detection by cytotoxic T-cells
- Different patterns of latent gene expression depending on the type of EBV-related disease
- In the healthy carrier, only LMP-2 is expressed

**Transformation**
- In vitro immortalization of B-cells
- Polyclonal expansion (and activation), leading to oligoclonal and monoclonal populations
- With decreased immune surveillance, potential for malignant lymphoproliferation in vivo

**Model of EBV infection**

**Seroprevalence and means of spread**
- In developing countries, 80-100% by 3-6 years of age
- In developed countries, peak incidence between 10-30 years of age
- Transmission via oral secretions (and possibly sex)
- Incubation period 30-50 days

**Clinical syndromes**
- Non-specific fever (young children)
- Infectious mononucleosis
- Chronic Active EBV infection
- EBV-associated malignancies
  - Nasopharyngeal carcinoma
  - Burkitt’s lymphoma
  - Hodgkin’s disease (Reed-Sternberg cells)
  - B-cell lymphoma
  - EBV lymphoproliferative disease
  - EBV-associated hemophagocytic syndrome

Cohen JI NEJM 2000;343(7):481-492
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Complications

- Skin manifestations (up to 15%)
  - Maculopapular
  - Urticarial
  - Scarlatiform
  - Erythema multiforme
  - Papular acrodermatitis (Gianotti-Crosti syndrome)
    - Edematous, erythematous papules to plaques
    - Cheeks, buttocks, extensor surfaces of extremities
    - Usually 1-6 years of age

Papular acrodermatitis

“Ampicillin rash” in conjunction with EBV

Complications

- Marrow
  - Hemolytic anemia
  - Thrombocytopenia
  - Neutropenia

- GI
  - Splenomegaly
    - Spontaneous rupture
    - Athletic restrictions
  - Fulminant or chronic hepatitis
  - Pancreatitis
  - Cholecystitis

Complications

- Airway obstruction
- Neck abscess
  - Secondary bacterial infection
- Interstitial infiltrates
- Pleural effusions

Time-course of EBV serologies in Infectious Mononucleosis

Sumaya CV. Pediatr Infect Dis 1986;5:337
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**Chronic Active EBV infection**
- Immunocompetent host
- Chronic or recurrent IM sx > 6 months
- Unusual pattern of EBV antibodies
  - Very high IgG or
  - Negative EBNA (20%) or
  - Positive VCA IgM
- High viral load in peripheral blood or
- Presence in tissues (by in situ RNA probe hybridization)
- Hallmark: T and/or NK cells EBV-infected, with unique EBV latent gene expression

**CAEBV-clinical signs**
- IM-like: fever, hepatosplenomegaly, abnormal LFT’s or coagulopathy, thrombocytopenia, anemia, lymphadenopathy
- Hypersensitivity to mosquito bites, rash, hydroa vacciniforme
- Diarrhea
- Uveitis
- Less common: CNS dz (or calcifications), pancytopenia, parotitis, sinusitis, oral ulcers, and other GI disease

**Hydroa vacciniforme**

**Complications of CAEBV**
- Lymphoma
- Leukemia
- Hemophagocytic syndrome
- Liver failure
- GI tract ulceration or perforation
- Coronary artery aneurysms
- Myocarditis
- Interstitial pneumonia

**What is CAEBV?**
- Best summarized as a T/NK cell lymphoproliferative disorder
- Difficulty regulating lymphocyte activation or proliferation
  - NK cells serve to immunomodulate as well as cause lysis of virally-infected cells
- Decrease in not only EBV, but CMV-specific CD8+ cells

**Immune evasion in CAEBV**

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- **Measurement of EBV load in blood**
  - Potential for management as well diagnosis (Hodgkin’s lymphoma, NP carcinoma)
  - Techniques are not standardized
  - Ideal specimen source varies with EBV-associated dz
    - Plasma or serum (IM)
    - Mononuclear cells (Post-transplant lymphoproliferative dz and EBV-associated hemophagocytic syndrome (EBV-AHS))
    - Either plasmacellular or cells (CAEBV)

- **Comparison of EBV DNA PCR levels in various EBV-associated diseases**

- **Time-course of EBV DNA PCR in IM**

- **Quantification of EBV-specific cell immunity**
  - Neurology of EBV
    - Neurotropic, like all herpesviruses
    - CSF pleocytosis in 25% of patients with IM
    - Acute neurological symptoms in up to 5% of patients with IM
    - Manifestations
      - Encephalitis (and rhombencephalitis)
      - Aseptic meningitis
      - Post-infectious cerebritis
      - Transverse myelitis
      - Facial nerve palsy

- **More neurology**
  - Guillain-Barre syndrome
  - Acute demyelinating encephalomyelitis (ADEM)
  - Acute hemorrhagic leukencephalitis
  - Acute onset movement disorder
EBV Neurohistopathology
- Acute encephalitis
  - Peri-vascular mononuclear infiltrate and occ'l viral inclusion bodies
  - Direct invasion of neurotropic virus
- Acute demyelinating encephalomyelitis or other autoimmune dz
  - Peri-vascular lymphocytes without viral inclusion bodies
  - Infiltration of EBV-specific CD8+ T-cells into neural tissue

Role of antibodies in EBV neurological dz
- Antibody/antigen complex deposition
- Autoimmune reaction
  - Proposed mechanism for post-infectious cerebellitis
  - Polyclonal B-cell activation with autoantibody expression
  - Anti-basal ganglia antibodies

Diagnosis of neurological EBV disease
- EBV DNA PCR
  - Lacks sensitivity and specificity
  - Appearance with reactivation (by other viral infections or non-viral CNS infection)
- EBV serology
  - Development over time of full array of antibodies (as in our patient)
- In-situ hybridization (EBER RNA probe)
  - Detection of two non-coding nuclear RNA fragments

Psychiatric sx in EBV
- Schizophrenic-like state during acute IM
  - Delusions
  - Hallucinations
  - Agitation
- Metamorphopsia or “Alice in Wonderland Syndrome” (AWS)
  - Distortions in size, form, color
  - Also seen in migraine HA, epilepsy, hallucinogenic drug exposure

EBV Encephalitis on MRI

EBV Encephalitis
- 14 pts (1988-98)-ages 10 mo to 14 yrs with acute EBV infection diagnosed by serology only
  - Acute encephalitis (5)
  - Cerebellitis (1)
  - AWS (5)
  - ADEM (3)
- None with IM sx
- Fever 43%, LOC 50%, sz 36%
- CSF pleocytosis (9-94) only in ADEM and cerebellitis
- Recovery in <2 wks except ADEM
- MRI study of choice, but one AWS + by SPECT with negative MRI
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**EBV Encephalitis**
- Prospective registry (1994-2003)—21/216 (6%) with evidence of EBV infection (serology +/or CSF PCR)
- 1 with acute IM
- Fever (81%), HA (66%), seizures (48%)
- CSF pleocytosis (81%)
- Abnormal MRI (71%)
- CSF EBV DNA PCR + 11/20 (!)
- 12 showed evidence of co-infection
  - CSF HSV and/or Mycoplasma PCR (5)
  - HHV-7 (1)
- Fatal outcomes: status epilepticus (2)
- Sequelae: focal weakness (1), mood/psych (1)


**The problem of dual infections**
- Co-infection?
- Superinfection?
  - Inflammatory response to another CNS infectious agent reactivates EBV, latent in either circulating lymphocytes which then infiltrate and infect CNS
- Reactivation?
  - Latency site already in CNS
- Immunocompetent patients: think HSV, VZV, mycoplasma, and in MN West Nile Virus and anaplasmosis or Borrelia

**Broadening the spectrum...**
- 5 pts (5-17 yrs) with cognitive changes 2 wks to 5 months prior to hospitalization and EBV dx
- 4/5 + EBV DNA PCR
- Persistent residual deficits:
  - word-finding
  - impulsiveness and gait abnormality
  - name writing, R/L orientation, motor sequencing tasks
  - Obsessions with clothing
- Some treated with methylprednisolone / steroid taper
- Brain biopsy: immunohistochemistry + for EBV viral inclusion bodies


**Casting the net further...**
- Prospective search for acute primary/ reactivation/CAEBV in all children with possible infection-related neurological dz (1999-2000)
- Diagnostic panel:
  - EBV antibody panel, including early antigen
  - EBV IgG in CSF (antibody index or AI)
  - CSF EBV DNA PCR
  - AI or serology c/w reactivation, EBV DNA PCR of blood
- 24/48 with neg EBV titers: HSV, adenovirus, VZV, rubella, Borrelia, mycoplasma, connective tissue disease (2)
- 12 with past EBV infection, unrelated to current illness

**Casting the net further (II)**
- Acute EBV infection (2)
  - Cerebellitis, hypoglossal nerve palsy
- Reactivated (EBV PCR, IgG anti-Early +/or VCA IgM (7)
  - AWS (3), facial nerve palsy (1)
  - Macrocephaly (1), Complex sz and movement disorder (1), sz and cognitive dysfxn (1), all with evidence of intrathecal Ab synthesis
- CAEBV (1)
  - mediastinal T/NK lymphoma with CNS involvement
  - Persistent + blood EBV DNA PCR
  - Only patient with + CSF EBV DNA PCR


**Lessons to draw**
- EBV should remain a suspect in all pediatric neurological dz of unknown origin
- Expect a diversity of findings, both on exam and imaging
- Consider metabolic imaging (SPECT)
- Usually but not always, onset is acute and residual sx unlikely
- Impact of EBV reactivation may be higher than commonly assumed
- Consider dual infections
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