Bibliography

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

William Pomputius III, MD
Pediatric Infectious Disease
Children's Hospitals and Clinics of Minnesota
Grand Rounds- 26 Feb 2009

1) Cohen, Jeffrey I. Epstein-Barr Virus Infection. New England Journal of Medicine 2000;343(7):481-492
2) Sumaya CV and Ench Y. Epstein-Barr Virus Infectious Mononucleosis in Children: I. Clinical and General Laboratory Findings and II.Heterophil Antibody and Viral-Specific Antibody Responses. Pediatrics 1985;75(6):1011-1019
3) Yamashita N, Kimura H and Morishima T. Virological Aspects of Epstein-Barr Virus Infections. Acta Medica Okayama 2005;59(6):239-246
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
5) Okano M, Kawa K, et al. Proposed Guidelines for Diagnosing Chronic Active Epstein-Barr Virus Infection. American Journal of Hematology 2005;80:64-69
6) Ohshima K, Kimura H. et al. Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder in children and young adults. Pathology International 2008;58:209-217
7) Yamamoto M, Kimura H, et al. Detection and Quantification of Virus DNA in Plasma of Patients with Epstein-Barr Virus-Associated Diseases. Journal of Clinical Microbiology 1995;33(7):1765-1768
8) Kimura H, Ito y. et al. Measuring Epstein-Barr virus (EBV) load: the significance and application for each EBV-associated disease. Reviews in Medical Virology 2008;18:305-319
9) Hung K-L, Liao H-T, Tsai M-L. Epstein-Barr Virus Encephalitis in Children. Acta Paediatr Tw 2000;(41):140-146
10) Caruso JM, Tung G, et al. Persistent Preceding Focal Neurologic Deficits in Children with Chronic Epstein-Barr Virus Encephalitis. Journal of Child Neurology 2000;15:791-796.
11) Hausler M, Ramaekers VT, et al. Neurological Complications of Acute and Persistent Epstein-Barr Virus Infection in Paediatric Patients. Journal of Medical Virology 2002;68:252-263
12) Doja A, Bitnum A, et al. Pediatric Epstein-Barr Virus-Associated Encephalitis: 10-Year Review. Journal of Child Neurology 2006;21:384-391
13) Weinberg A, Bloch KC, et al. Dual Infections of the Central Nervous System with Epstein-Barr Virus. Journal of Infectious Diseases 2005;191:234-237
14) Grose C, Henle W et al. Primary Epstein-Barr Virus Infections in Acute Neurologic Diseases. New England Journal of Medicine 292:392-395
15) Schnell RG, Dyck PJ, et al. Infectious Mononucleosis: Neurologic and EEG Findings. Medicine 1966;45(1):51-63

16) Baskin HJ and Hedlund G. Neuroimaging of herpesvirus infections in children. Pediatric Radiology 2007;37:949-963

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

Auwaerter, Paul. Infectious Mononucleosis: return to play. Clinics in Sports Medicine 2004;23(3)

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.

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

William Pomputius III, MD
Pediatric Infectious Disease, Children’s Hospitals and Clinics of Minnesota

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

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

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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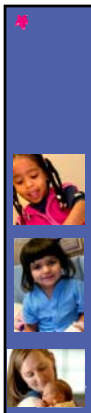
Receiving CME Credit

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



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

Children's Hospitals and Clinics of Minnesota

Illustration by Sir John Tenniel

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-intermittent 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

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

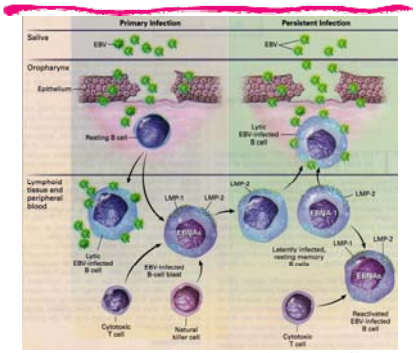
Latency

- 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 lympho-proliferation in vivo

Model of EBV infection



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

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

Complications

- **Skin manifestations (up to 15%)**
  - Maculopapular
  - Urticarial
  - Scarlatiniform
  - 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

Red Book Online Visual Library, 2006. Image 043_08. Available at: http://aapredbook.aappublications.org/visual. Accessed November 29, 2007

RED BOOK ONLINE

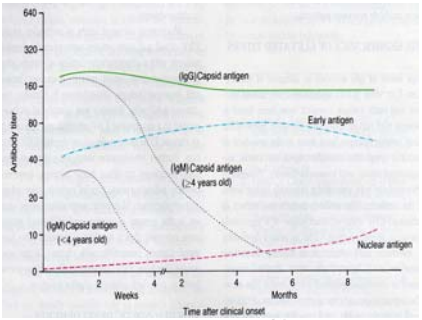
Complications

- **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

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

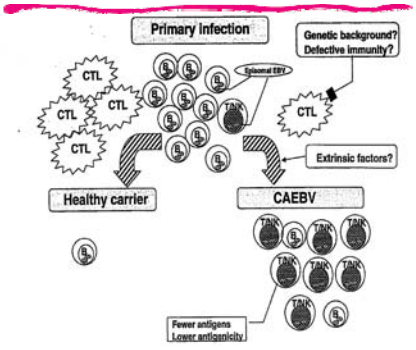
Complications of CAEBV

- 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 lympho-proliferative 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



Kimura, H. Rev Med Virol 2006;16:251-261

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 plasma/serum or cells (CAEBV)

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

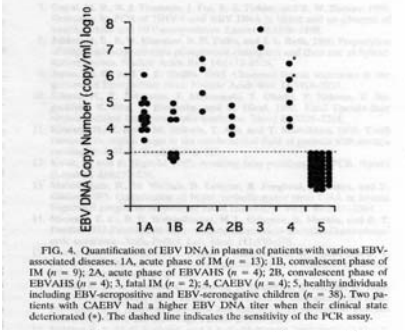


FIG. 4. Quantification of EBV DNA in plasma of patients with various EBV-associated diseases. 1A, acute phase of IM (n = 13); 1B, convalescent phase of IM (n = 9); 2A, acute phase of EBVAHS (n = 4); 2B, convalescent phase of EBVAHS (n = 4); 3, fatal IM (n = 2); 4, CAEBV (n = 4); 5, healthy individuals including EBV-seropositive and EBV-seronegative children (n = 38). Two patients with CAEBV had a higher EBV DNA titer when their clinical state deteriorated (+). The dashed line indicates the sensitivity of the PCR assay.

Yamamoto M et al. J Clin Microb 1995;33:1765-8

Time-course of EBV DNA PCR in IM

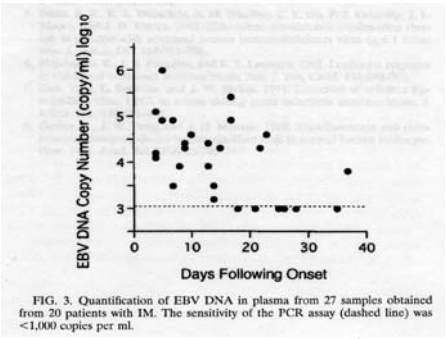


FIG. 3. Quantification of EBV DNA in plasma from 27 samples obtained from 20 patients with IM. The sensitivity of the PCR assay (dashed line) was <1,000 copies per ml.

Yamamoto M et al. J Clin Microb 1995;33:1765-8

Quantification of EBV-specific cell immunity

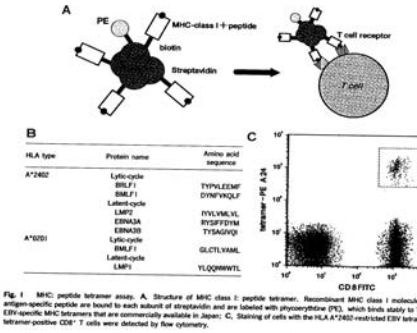


Fig. 1 MHC peptide tetramer assay. A, Structure of MHC class I peptide tetramer. Recombinant MHC class I molecules with an antigen-specific peptide are bound to each subunit of streptavidin and are labeled with phycoerythrine (PE), which binds stably to T cells. B, EBV-specific MHC tetramers that are commercially available in Japan; C, Staining of cells with the HLA A*2402-restricted EBV tetramers. The tetramer-positive CD8+ T cells were detected by flow cytometry.

Yamashita N et al. Acta Medica Okayama 2005;59:239-246

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 cerebellitis
  - 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

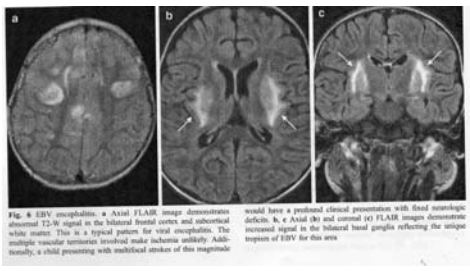
Diagnosis of neurological EBV disease

- **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



Baskin HJ and Hedlund G. Pediatr Radiol 2007;37:949-963

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**

Hung Kun-Long et al. Acta Paediatr Tw 2000; 41:140-6

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)

Doja A et al. J Child Neurol 2006;21:384-391

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 + CSF 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

Caruso JM et al. J Child Neurol 2000;15:791-6

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
  - If + 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

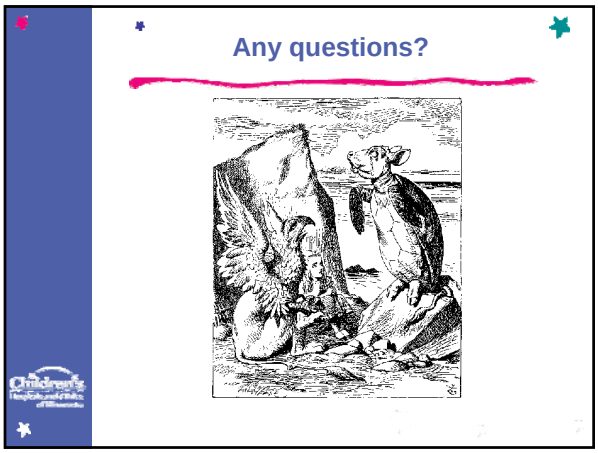
Casting the net further (II)

- 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

Hausler M et al. J Med Virol 2002;68:253-263

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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