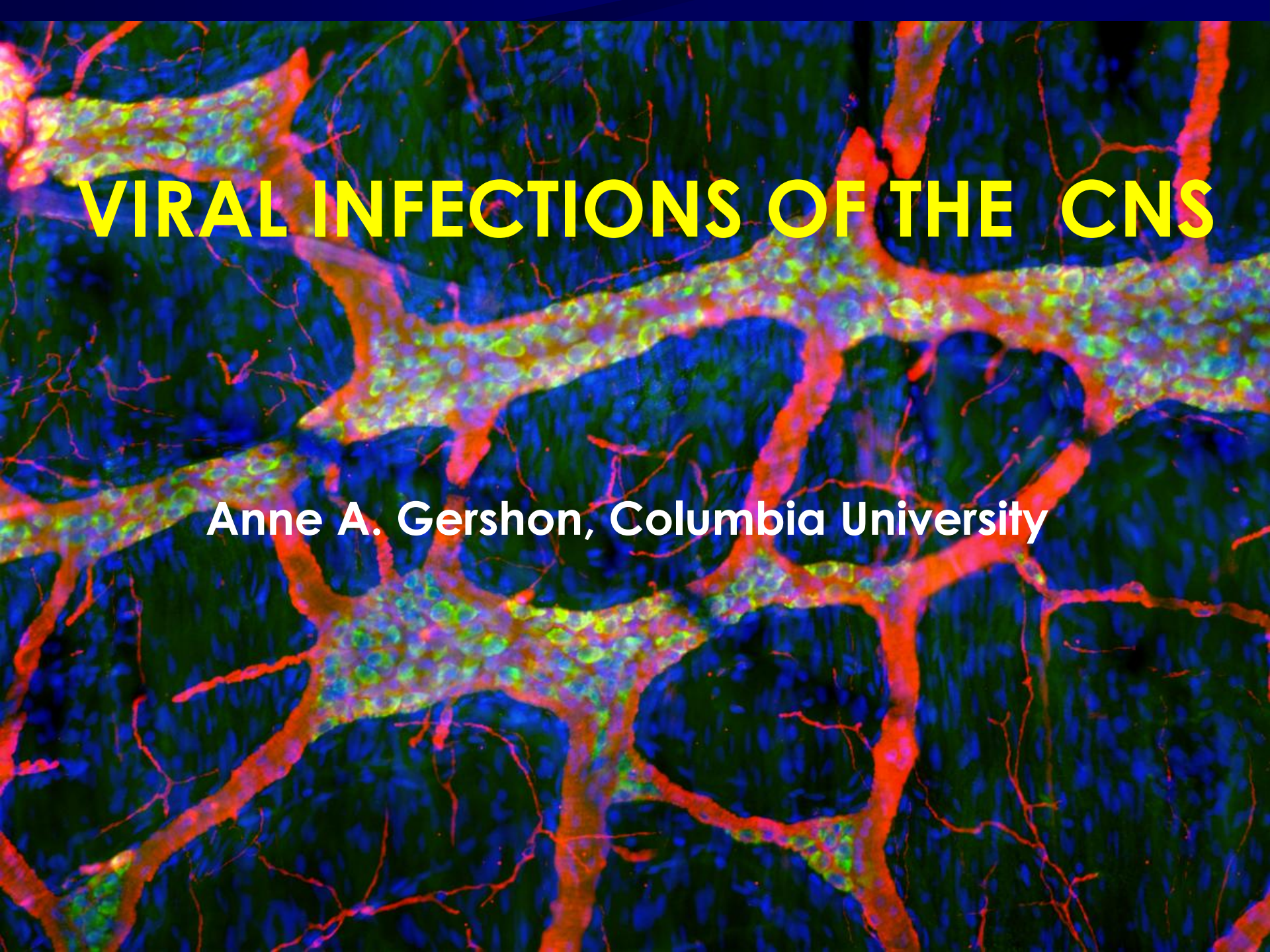


VIRAL INFECTIONS OF THE CNS

Anne A. Gershon, Columbia University

A Patient with Aseptic Meningitis

- 15 yo female, previously in good health
- Seen in ER at Columbia Presbyterian Medical Center , Feb. 2012
- Complained of severe headache, stiff neck, fever
  - No rash
  - LP: 323 WBS's >90% lymphocytes; protein 87, glucose 50
  - Seemed clinically well the next morning
  - Disposition: sent home; no therapy given
- CSF: sent to NY State Program for Identification of NYC CNS pathogens
- PCR identified varicella-zoster virus (VZV) DNA; currently being tested to determine whether VZV is WT or vaccine (Oka strain)
  - Patient doing well

Symptoms and signs of viral meningitis, encephalitis

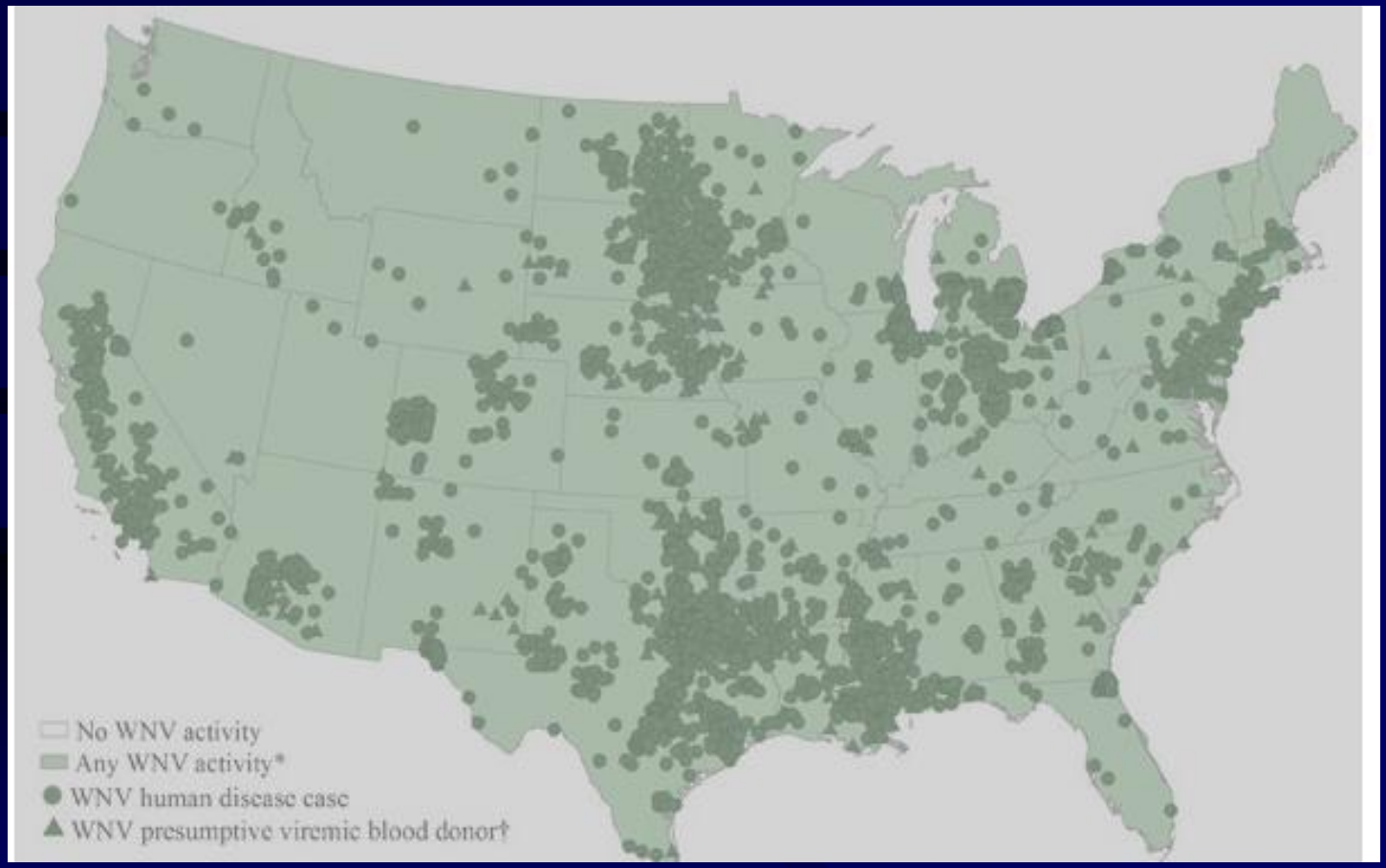
- Meningitis: fever, headache, photophobia, stiff neck, irritability, nausea, vomiting, rash
  - Frequently there is recovery in a few days
- Encephalitis: above symptoms, plus altered mental status, weakness, loss of consciousness, coma, personality change, seizures, paralysis
  - May recover completely, have significant morbidity, or death
- Importance of history: recent illnesses, occupation, exposure to animals, ticks, mosquitoes, immune status
- Available therapy: acyclovir, ganciclovir, foscarnet

Current Events: in the news recently

- Enterovirus 71
  - Mainly seen in Asia Pacific (Cambodia 2012); occurs in epidemics
  - Causes hand-foot-mouth disease
  - If neurological complications, cardiorespiratory compromise (pulmonary edema, cytokine storm)
- Chikungunya virus (arbovirus; arthropod borne)
  - Transmitted by Aedes mosquito
  - Symptoms: fever, rash, headache, severe arthralgia, myalgia, encephalitis
    - ~15% of patients: PCR + in CSF
  - Usually self-limited
  - No longer confined to Africa/Asia: infected humans can infect mosquitoes
    - Potential risk from blood
    - transplantation (viremia)
- Influenza
  - Recently recognized to have an encephalitic component
- **West Nile Virus (arbovirus)**

Reported West Nile virus (WNV) activity US, 2012

(as of September 25, 2012; over 3000 cases, ~50% m/e 147 deaths)



CDC data 2012

West Nile Virus

- First identified in Uganda in 1977
  - RNA flavivirus related to St. Louis Encephalitis (SLE) and Japanese encephalitis viruses
  - Since 2002 have identified at least 8 different strains
  - Strain currently spreading in US (1999) is similar to strain in Israel
- Spread by Culex mosquito that feeds on infected birds
  - Mosquito bites humans
  - ~80% of disease is subclinical
  - No therapy or vaccine for humans; CDC's advice: avoid mosquito bites
- As late September over 3000 human cases reported to CDC
  - ~50% classified as meningitis/encephalitis; 147 deaths
    - ~75% of cases from Texas, Mississippi, Louisiana, S. Dakota, Oklahoma
- **Affect spread: weather, # infected birds, # mosquitoes**
- **Diagnosis: nucleic acid amplification tests on serum, CSF, tissues;**
  - **Antibody titers (including IgM)**

West Nile Virus, cont.

- Can resemble polio with damage to anterior horn cells
  - May progress to respiratory paralysis requiring mechanical ventilation
  - Has also been associated with Guillian-Barre syndrome
- Rarely associated myocarditis, arrhythmias, rhabdomyolosis, optic neuritis, chorioretinitis, pancreatitis,orchitis, hepatitis
  - Case fatality rate 5%; higher in encephalitis than meningitis
  - More severe (neuroinvasive) in older, immunocompromised patients
  - Diabetes, hypertension also risk factors
  - Single case of possible congenital infection reported (mom infected in 27th week)
- Viral loads in humans do not cause infection of mosquitoes
  - Infection can spread by blood transfusion and organ transplantation
  - CDC has concern about protecting the blood supply in US
- **Incubation period 2-14 days; usually ~4 days**

Additional Important Causes of viral CNS infections

- HSV 1, 2; VZV
- EBV, CMV (immunocompromised)
- HHV6 (B): integrated into human germ cell and produces free virus
  - In infants, primary infection causes roseola (rash, febrile seizures), encephalitis, congenital (1%); high reactivaton rate (~50%) post-transplant
  - With encephalitis PCR on CSF +
    - Must differentiate between latent virus and reactivated virus causing disease
    - Inimunocompromised patients (plus graft rejection, marrow suppression, pneumonia)
    - MRI abnormal, seizures frequent, temporal lobe epilepsy (maybe)
  - no approved antiviral therapy
    - May try foscarnet, ganciclovir, cidofovir; treat ~21 days
- Measles (post-infectious, 10 times rate for varicella; SSPE)
- Rubella (post-infectious, rare)
- Rabies, polio, HIV

Molecular identification of Causes of Meningitis, Encephalitis, NY State 2004-2007

- Enabled by development of multiplex technology for PCR
  - Identified 340 agents found (14%) of 2,357 specimens submitted
- Specifically looking for: enteroviruses (6%), EBV (4%) , HSV (3%), VZV (2%), HHV6, (1%) Adenoviruses, West Nile virus, EEE; other encephalitis viruses
- Experience with RTPCR or PCR on CSF
  - Most samples submitted between June-October
  - 9 patients positive for 2 agents (e.g. CMV + EBV, EBV + HHV6, HSV 1, 2)
  - Not looking for rare viruses (eg deer tick encephalitis, which can be fatal)
  - Technology does not identify other agents such as bacteria, fungi, parasites

California has screened for viral encephalitis since 1998 (1% positive for VZV)

- 26 VZV Cases from 1998-2009 reported by Pahud et al (JID, 2011)
- Based on diagnosis using PCR to demonstrate VZV DNA in CSF
- Meningitis 50%, encephalitis 42%, acute disseminated encephalomyelitis 8%
  - Rash seen in only 42% of patients
- Age range of patients 12-85 years (median 47); 7 (27%) <18 years old
  - 11 patients(43%) healthy and less than 60 years old
  - Meningitis more likely in young, healthy; encephalitis more likely in old, immunocompromised (including HIV +); prognosis not good
  - 4 children were vaccinated; vaccine VZV (Oka) in ¼
  - A few encephalitis patients had abnormalities in brain imaging
    - Possibly had vasculopathy

History of VZV Meningitis

- Patients with zoster (even when not trigeminal) often experience headache and may have CNS involvement with pleocytosis
  - Treatment may not be necessary; more important to treat immunocompromised than immunocompetent patients
  - It is not surprising that virus reaches CNS frequently because neurons are pseudounipolar with a process that bifurcates to terminate in skin and brain
- With development of PCR on CSF for diagnosis of VZV, meningitis increasingly recognized; MRI normal
  - Publications describing meningitis rare before 2000; now about 20 annually
  - Treatment with acyclovir or valacyclovir is becoming increasingly common
- Annual US cases seem to be about as frequent as HSV encephalitis (may have similar symptoms) but prognosis better, and sequelae rare

Reports of Oka meningitis (9)

Case	Year	Medical History	Age	ORFs tested	Location of zoster rash	Author
1	2003	Neuroblastoma	1 yr	62	R. thigh	Levin
2	2008	Neuroblastoma	21 mo	62	Hands, R. leg,abdomen	Bryan
3	2008	Leukemia	4 yr	38, 54	arm	Galea, Chavez
4	2008	Healthy	4 yr	38, 54	R. arm	Chavez
5	2008	Healthy	8 yr	38, 54, 62	L. shoulder	Levin
6	2009	Healthy	9 yr	38, 54, 62	L. arm	Iyer
7	2010	Healthy (encephalitis)	3 yr	62	Trigeminal	Chouliaras Goulleret
8	2011	Healthy	7 yr	38, 54, 62	R. Arm, shoulder	Han
9	2011	Healthy	12 yr	38, 54, 62	Neck	Pahud

VZV causes nervous system vasculopathies

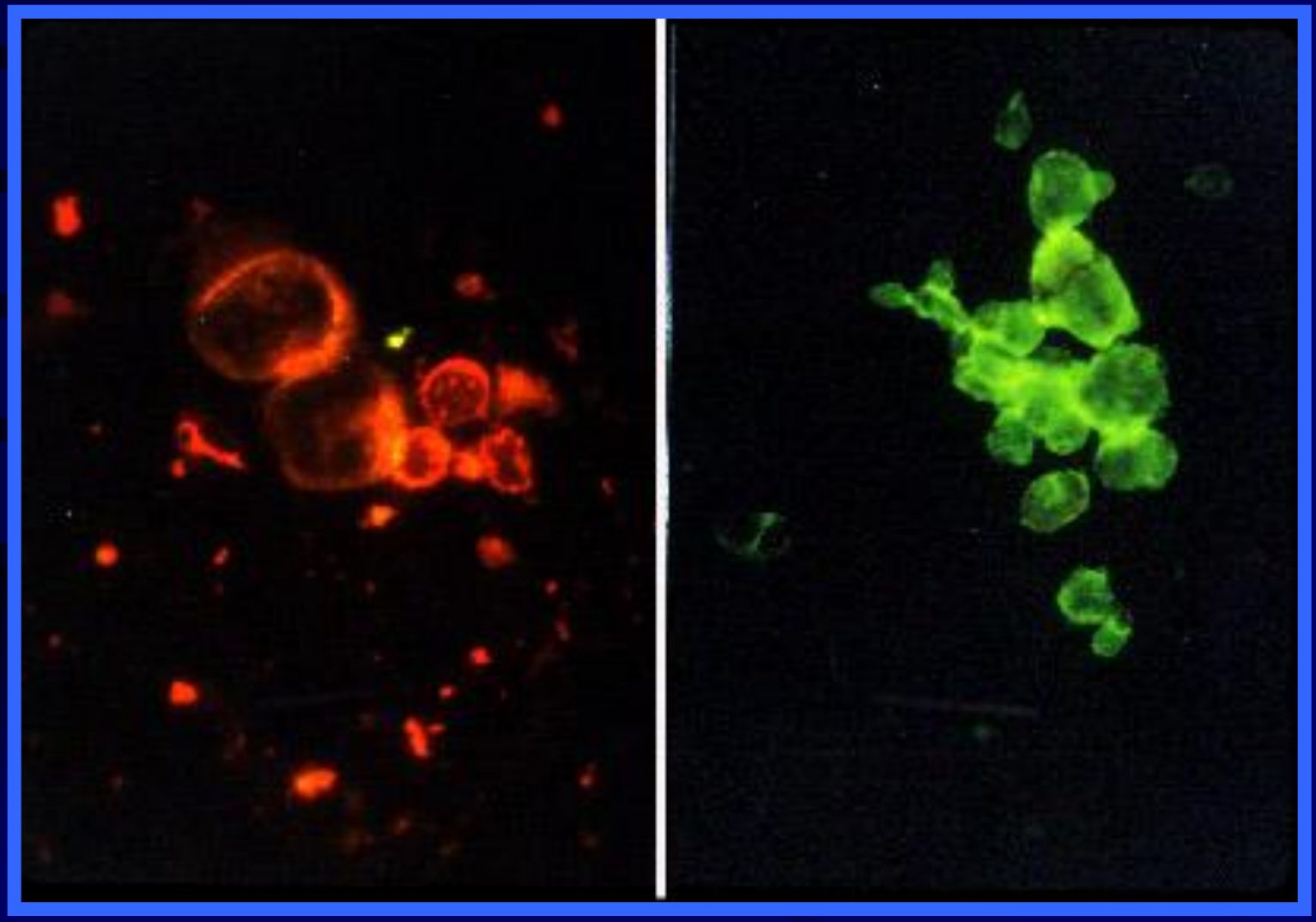
- VZV vasculopathies are more chronic and more serious than VZV meningitis; often wax and wane for long periods; cause of TIAs
  - Formerly called granulomatous angiitis (delayed contralateral hemiparesis); after varicella or zoster, adults > children; ischemia/hemorrhage
    - In older and immunocompromised patients, “stroke” weeks after zoster
  - Productive infection of arteries; MRI + at grey-white matter junctions
    - Diagnosed by presence of VZV antibodies in CSF, but PCR may be +
- Treat with ACV for at least 14 days (Category 3)

(Gilden, Lancet Neurology, 2009)

There Are Several Useful Laboratory Methods for Diagnosis

- Culture (difficult), DFA, PCR, cytology on skin rash (Tzanck)
  - Can distinguish the Oka virus from wild type virus (PCR)
- Antibody titers, IgG (ELISA)
  - Acute serum, early in illness
  - Convalescent serum, 10-14 days after onset
- Antibody titers, IgM
  - False positives and false negatives can be a problem

Indirect immunofluorescence is useful to diagnose VZV, HSV



VZV DNA was first identified in saliva of astronauts after space travel

(Mehta, J. Med.Virol, 2004)

VZV DNA Shedding In saliva (PCR)	Before	During	After	None
Astronauts (8)	1% +	30% +	30% +	
Controls (10) Sampled multiple times	0	0	0	0

Stress (space flight) can reactivate asymptomatic VZV, diagnosed by PCR on saliva

There is a rationale for study of VZV in saliva

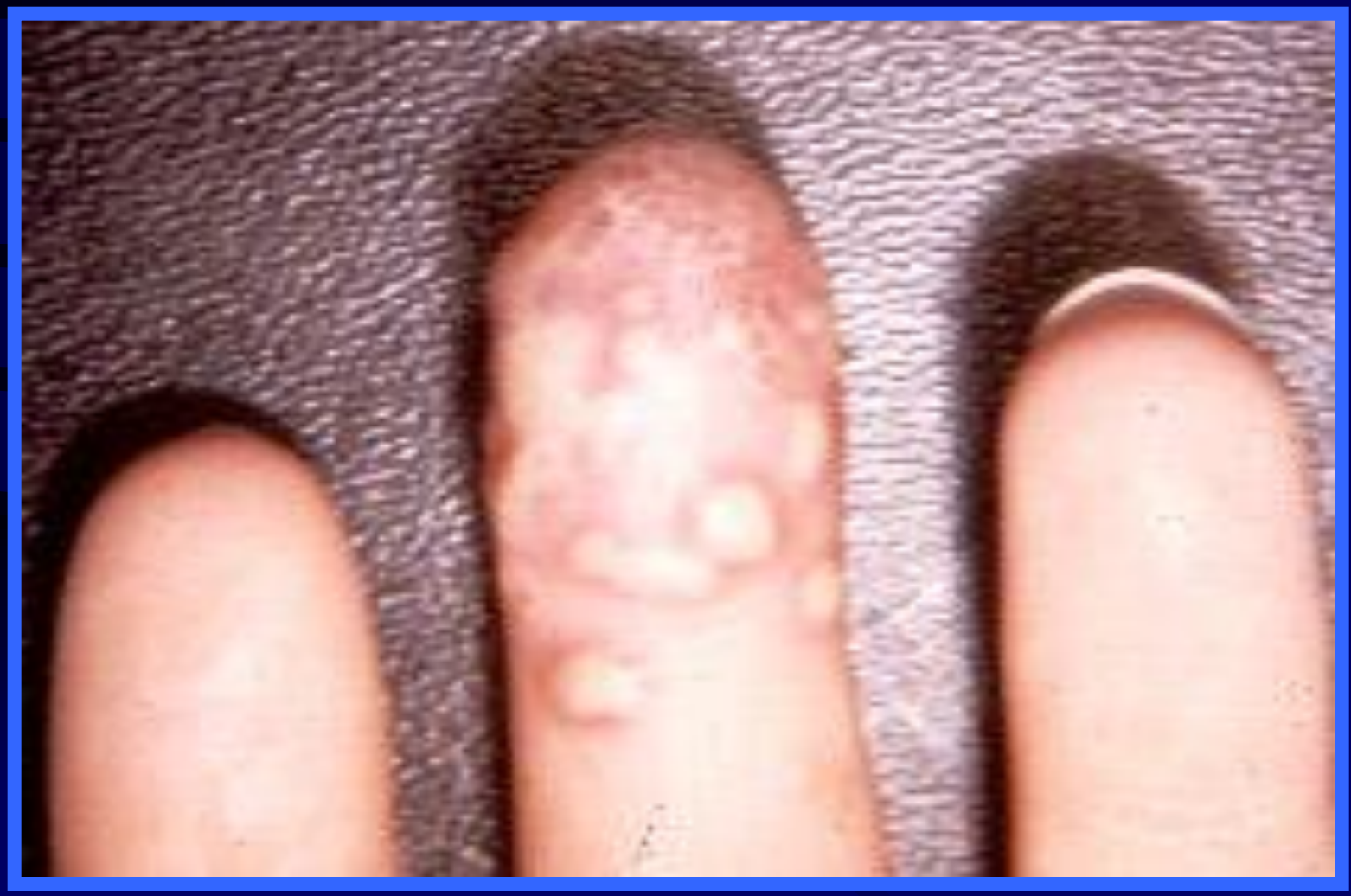
- A rapid, non-invasive, specific test would be clinically useful to diagnose infections with VZV
  - It would facilitate treatment and also infection control for VZV
- Published data on elderly patients with zoster suggest the diagnostic utility of identifying VZV DNA in saliva
  - Elderly zoster patients have been reported to secrete VZV DNA in saliva for months (Mehta, J Infect Dis 2011)
- This test could also be potentially useful for identifying patients with occult VZV infections
  - Patients with visceral (enteric) and/or CNS zoster could be promptly treated with specific antiviral therapy, potentially improving prognosis

Background on HSV Infections

- Classification: primary, non-primary, first episode, recurrent, reinfection
- HSV-1: above waist, HSV-2: below waist
  - Reactivation: trauma, sunlight, stress
    - Despite antibodies
    - May be related to deficient gamma IF response
    - May recur in same area of skin (unlike VZV)
- Many/most infections are asymptomatic
  - asymptomatic shedding can transmit HSV to others
- Host factors: immunocompromised, newborn baby

Primary HSV-1 gingivostomatitis

Herpetic whitlow, HSV 1



Herpes simplex virus (HSV) Infections

- Mucocutaneous, neonatal, CNS
- Type 1: gingivostomatitis, whitlow, keratitis, encephalitis, eczema herpeticum
- Type 2: genital, meningitis, neonatal
  Main serious clinical problems are in newborn, and immunocompromised hosts
- Healthy hosts may develop gingivostomatitis, encephalitis,acute and recurrent genital HSV
- Disease from viral- and immuno-pathology

HSV causes about 1000 cases of encephalitis annually in USA

- Most common form of focal encephalitis in USA
- Primary or recurrent HSV-1 ; skin lesions may be present (not helpful for diagnosis)
- Symptoms, signs: headache, fever, personality change, focal seizures, abnormal EEG, CT, MRI
- Differential diagnosis: TB meningitis, arbovirus, VZV, enterovirus, flavivirus, mycoplasma, tumor, toxoplasmosis, aneurysm
- Diagnosis: CSF culture is usually negative, but PCR is usually positive for HSV
- Treat (ACV) if suspect disease; prognosis better in children than adults; early therapy is best

Genetic susceptibility increases chances of developing HSV encephalitis

- First investigated in mouse models of HSV
  - Used strain-dependent variability (forward genetics) and targeted knockouts (reverse genetics)
  - Identified role of interferon (IF) alpha/beta in innate immunity to HSV 1
- Two children with rare, specific STAT1 or NEMO* mutations (due to TLR 3 and UNC93B1 mutations) had impaired IF responses and developed HSV 1 encephalitis
  - **TLR 2, 4 also important in immunity to HSV (related to NF-κB)**
- *NF-κB essential modulator

– See Casanova, Ann Rev Immunol 29: 447, 2012

Perinatal HSV is usually due to HSV 2

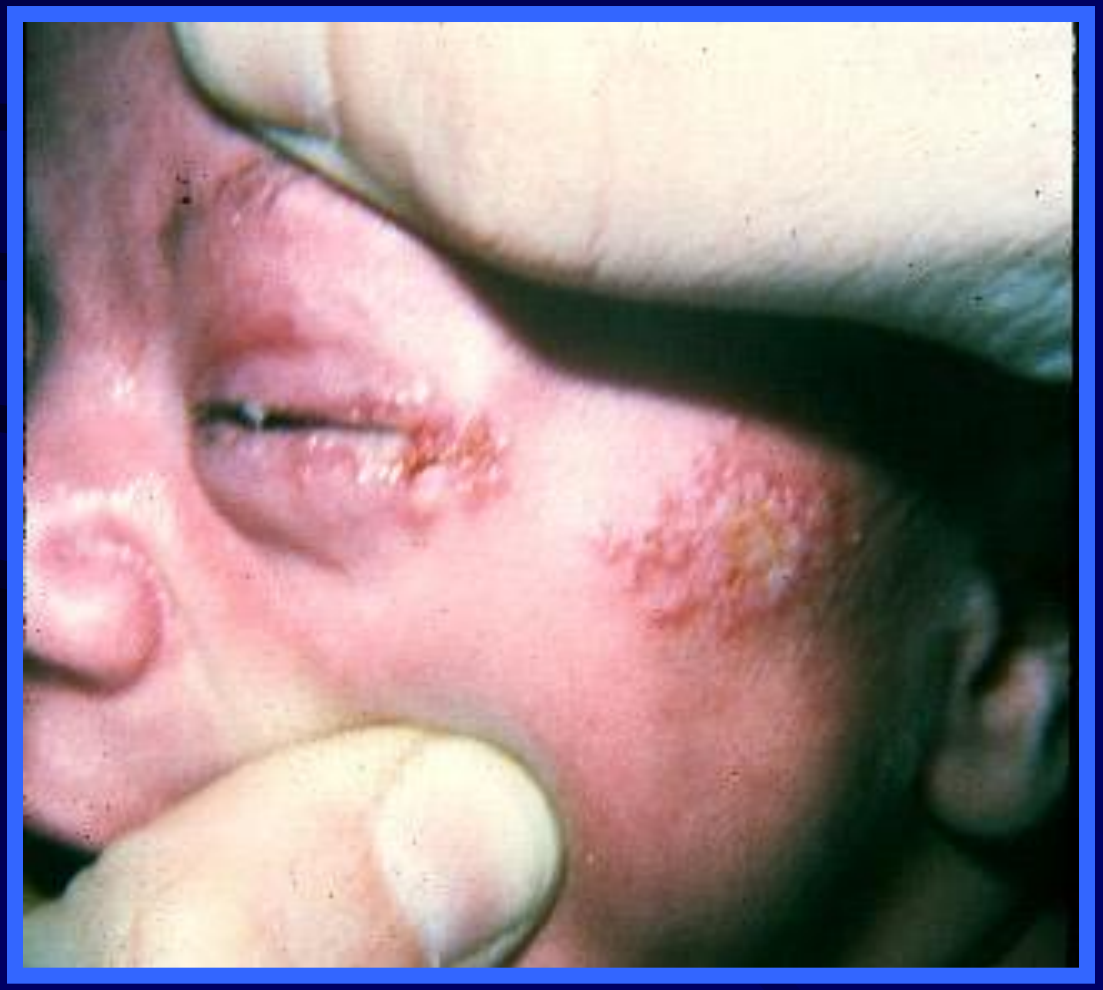
- 95% neonatal, 5% congenital
- Usually the mother is asymptomatic
- Attack rate >10 times higher in maternal primary infection than recurrence; attack rate about 50%
- Clues: skin vesicles in 70%, fever, seizures, pneumonia, DIC, conjunctivitis
- Diagnosis: immunofluorescence, culture, PCR
- Treat all infants with this diagnosis, even if all they have are a few skin vesicles but seem otherwise well

There are 1600 cases of neonatal HSV annually

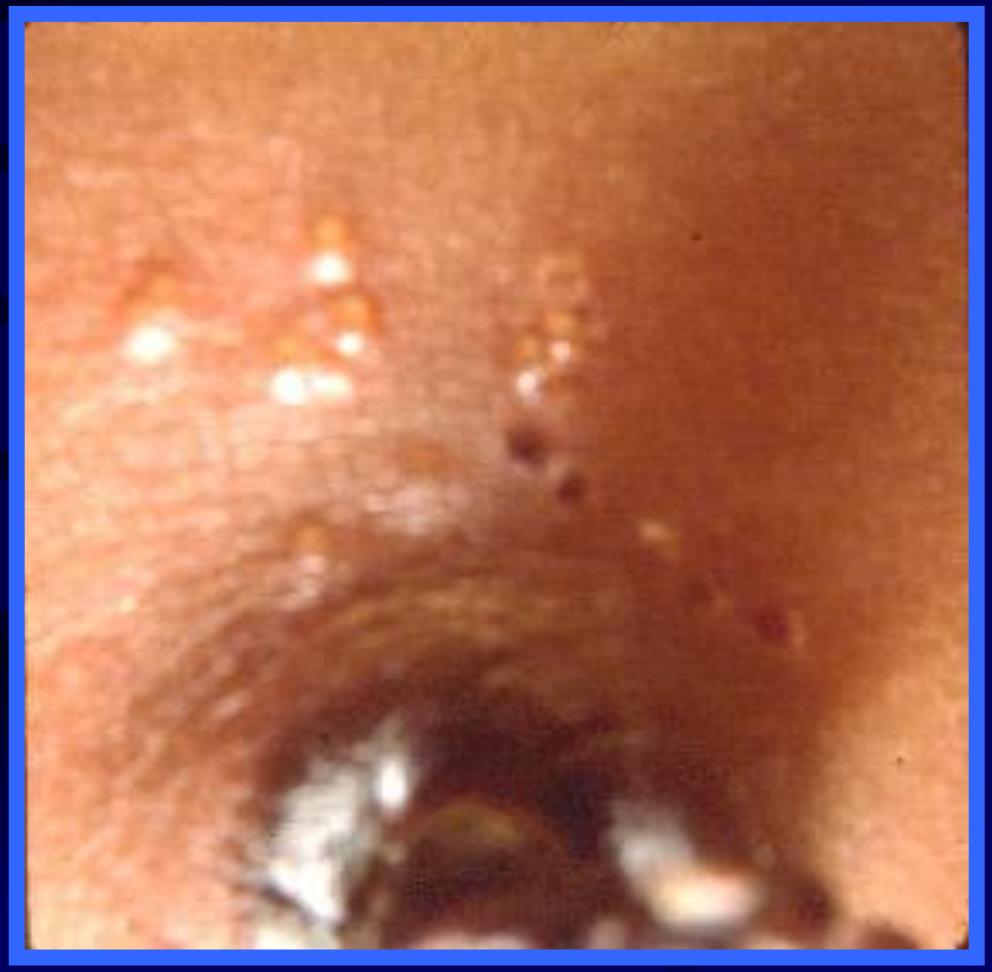
- Skin, eye, mucous membrane (45%)
  - Skin vesicles
  - Good prognosis with early treatment
  - Untreated 75% develop disseminated infection
- CNS Infection (30%)
  - Fever, lethargy, seizures, abnormal CSF
  - 5% mortality; major sequelae if survive
- Disseminated disease (25%)
  - Hepatosplenomegaly, jaundice, hepatitis, pneumonia
  - 2/3 develop skin vesicles
  - 50% mortality

Whitley, et al

Neonatal HSV-1



Neonatal HSV-2



Approaches to Neonatal HSV

- Diagnosis: immunofluorescence, culture, PCR
  - Antibody titers not useful;
  - PCR surfaces; check ALT; PCR blood (once)
  - PCR CSF; if + repeat at end of rx
- Treat all newborn infants with possible HSV
  - Begin therapy while awaiting diagnostic results
  - Specific treatment (ACV) is is very well tolerated
- Recurrent skin vesicles are associated with a poorer prognosis

There are some newer perspectives on therapy

- Treatment of neonatal and disseminated HSV increased to 60 mg/kg/day IV ACV for 14-21 days
  - Safe except need to watch for neutropenia
    - Can decrease dose or give GMCSF
    - Instituted in 2001 (Kimberlin, Pediatrics)
- Study of neonates with proven CNS HSV indicated better outcome if long term oral ACV given (6 mo)
  - These infants have significant morbidity even with high dose ACV for 21 days
  - Evidence of continuing viral multiplication in CNS (CSF PCR remains +)
  - Study
    - Double blind
    - Followed for adverse events
    - Followed for development

Kimberlin et al NEJM 2011

Oral acyclovir given for 6 months improved the prognosis of neonatal HSV encephalitis

300 mg/m sq/dose TID

Bayley Mental Score at 1 year

	<59	60-69	70-79	>80
Morbidity	severe	moderate	mild	normal
Valacyclovir	19%	6%	6%	69%
Placebo	33%	25%	8%	33%

Kimberlin et al, NEJM 2011

Summary and Conclusions

- Many viruses invade the CNS
  - Most common are enteroviruses and herpesviruses
  - Other agents are emerging and need to be followed epidemiologically to assess risk
- Therapy for herpesviruses is available although still developing (treating in late pregnancy did not work)
  - Prevention is an important approach. We need vaccines!
- Immunocompromised patients are at special risk
- Huge diagnostic progress has been made with PCR
- Although we have just scratched the surface, genetic predispositions to CNS infections are emerging