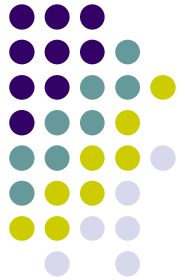
Subacute Sclerosing Panencephalitis (SSPE)

中華民國防疫學會

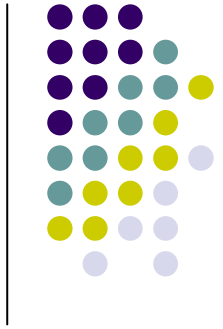
王任賢 秘書長

Overview



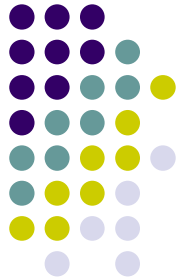
- Introduction
- Virus information and Life Cycle
- Clinical Features
- Pathogenesis
- Subacute Sclerosing Panencephalitis
- Immune response and persistence
- Vaccine

Introduction



- Genus: Morbillivirus
- Family: *Paramyxoviridae*
- *(-)ssRNA virus*
- Highly contagious
- Lifelong immunity
- Persistent infections can occur

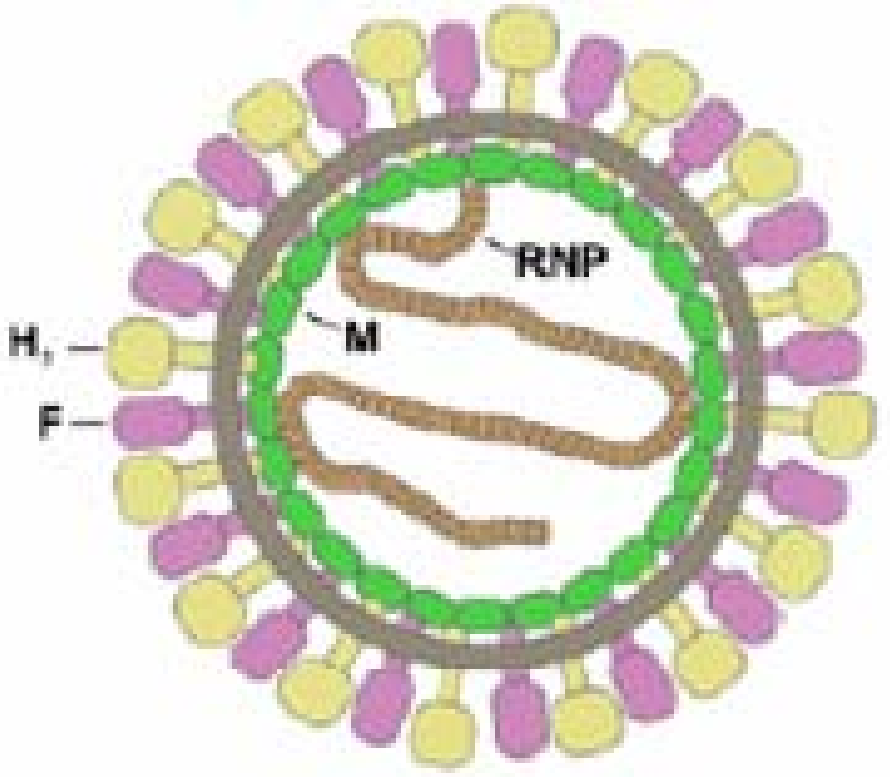
Introduction



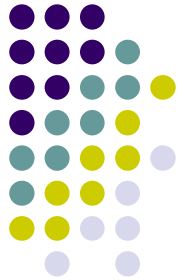
- 30 million cases, with 345 infant deaths each year
- 95% of fatal cases in third world countries
  - Malnutrition
  - Secondary infections
  - Low vaccination rates
  - Overcrowding

Virus Information

- Enveloped, pleomorphic
- 100-250nm diameter
- RNPs=
  - Nucleoprotein
  - Phosphoprotein
    - C + V proteins
  - Large Polymerase protein

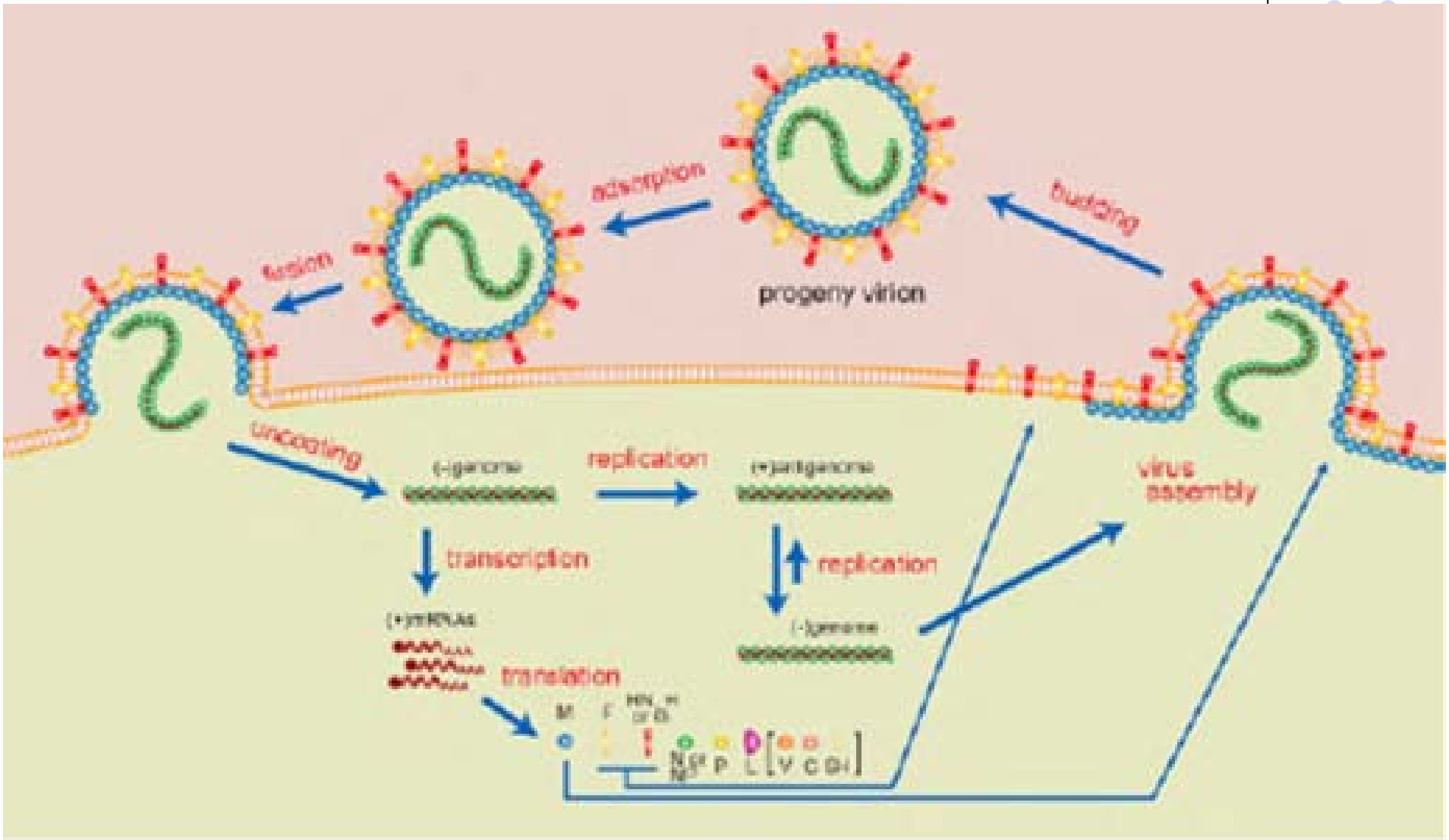


Virus Life Cycle

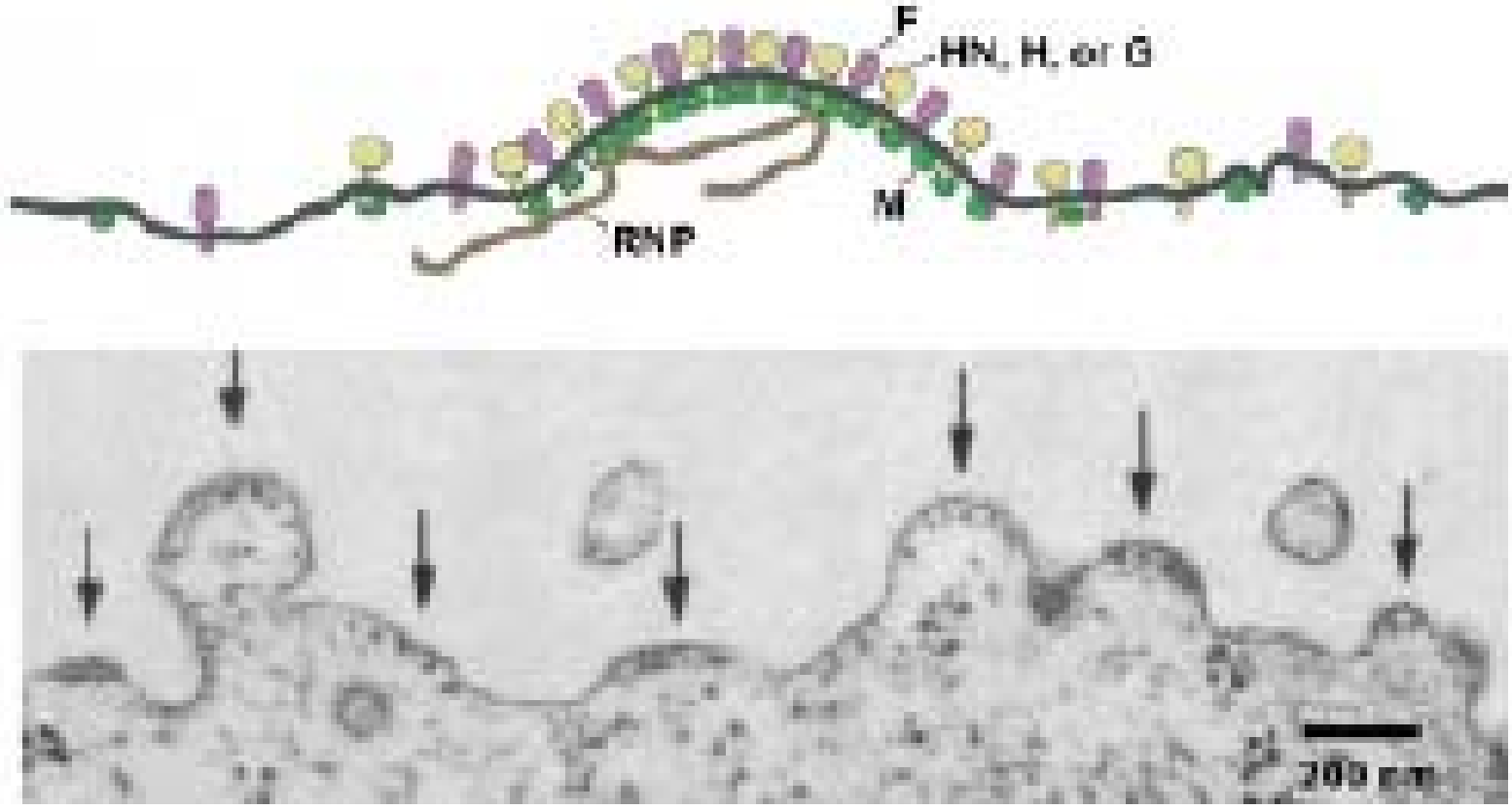


- Receptors:
  - CD46 = all nucleated cells
  - CD150 = Activated T and B cells, dendritic cells, monocytic cells
  - ? = epithelial, endothelial, brain cells

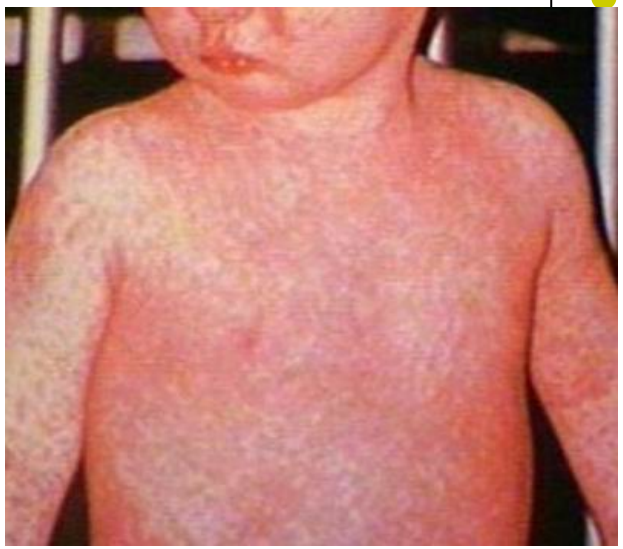
Virus Life Cycle



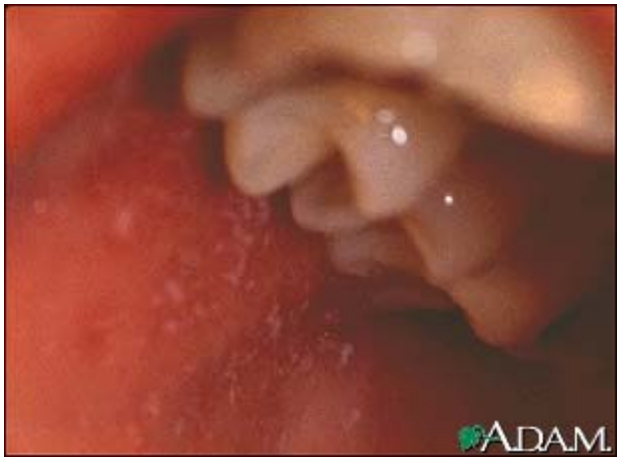
Budding of the Virus



Symptoms



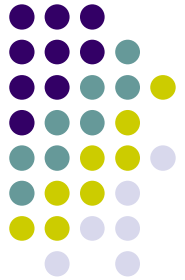
- 40^{o}C fever
- Conjunctivitis
- Cough
- Coryza
- Erythematous maculopapular rash
- Koplik spots



Transmission

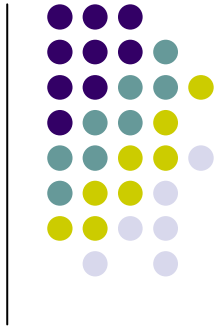
- Very contagious from the onset of symptoms until 4 days after the rash
- Aerosols or droplets in the air
- Coughing
- Sneezing

Complications



- Secondary infections due to immunosuppression
  - Pneumonia
  - Respiratory tract infections
  - Gastroenteritis
- Encephalitis – APME, MIBE, SSPE
- Congenital abnormalities or stillbirth during pregnancy

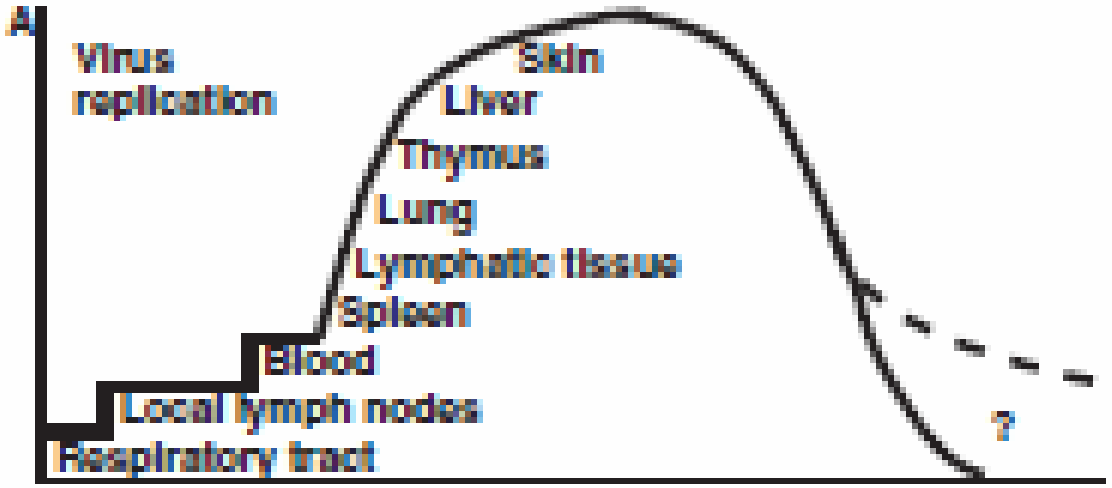
Treatment



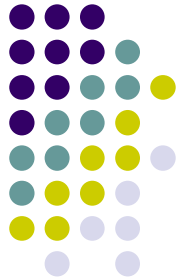
- Treat symptoms
  - Plenty of fluids
  - Bed rest
  - Antipyretics
- Ribavirin and interferon for particularly severe infections in immunocompromised people

Pathogenesis

- Enters through upper respiratory tract
- Spread to lymph nodes
  - Infects T cells, B cells, monocytes
  - Causes leukopenia
- Can spread to CNS

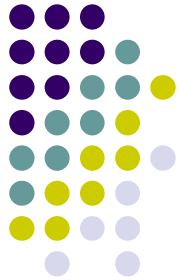


Pathogenesis



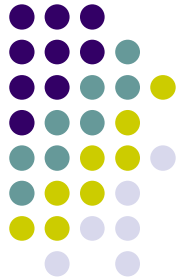
- Free virus can infect cells
- Virus spread by cell fusion
  - Syncytia formation
  - F protein fuses cells together
  - Important but not necessary for infection
    - MV that cannot fuse can still cause disease

MV Encephalitis



- Acute postinfectious measles encephalitis
  - Most frequent = 0.1% of patients
  - 1/5 cases are lethal
  - Can cause permanent neurological damage
  - Autoimmune response in the brain
- Measle inclusion body encephalitis
  - Opportunistic infection of the CNS in immunocompromised patients

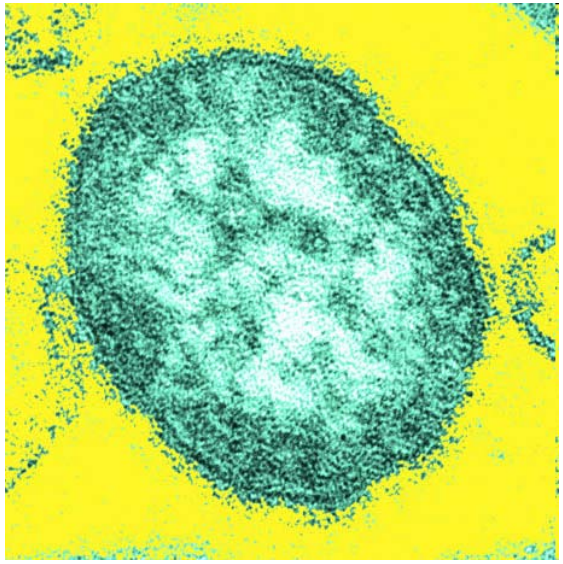
Subacute Sclerosing Panencephalitis



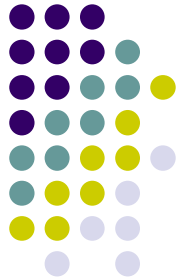
- Occurs in patients who developed measles under the age of 2
- Symptoms appear 7-10 years after infection
- Risk factors include
  - Crowding
  - Rural upbringing
  - Mental disabilities

Pathophysiology

- Thought to immune resistant variant of measles virus
- Persistent virus reactivated via unknown mechanism

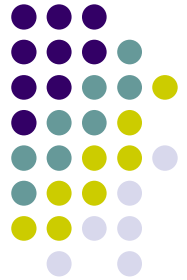


Epidemiology



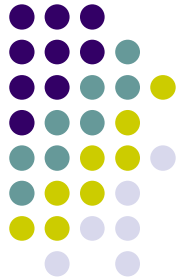
- Prevalence 0.6 cases/million 1970 → 0.06 cases/million 1980 (increasing MMR vaccination, MMR licensed in mid 60s)
- Incidence 8.5 cases/million cases measles

SSPE: Symptoms



- Personality changes, cognitive impairment
- Head, trunk, limb spasms
- Abnormal gait, ocular symptoms
- Coma
- Death by hyperpyrexia, cardiovascular collapse, hypothalamic disturbances

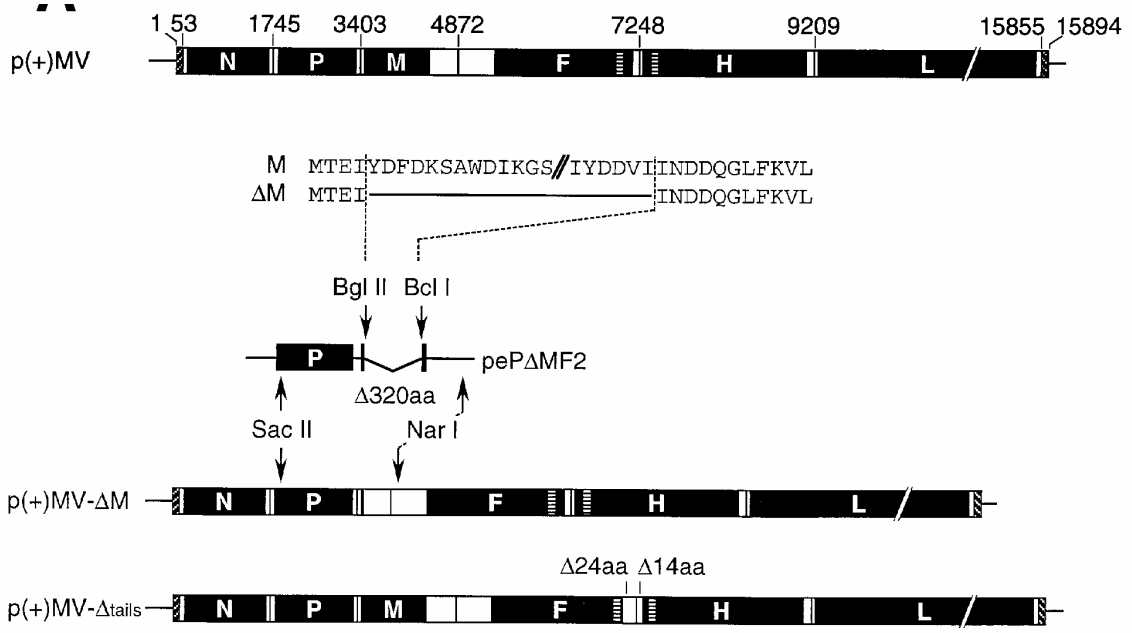
SSPE: Viral Defects



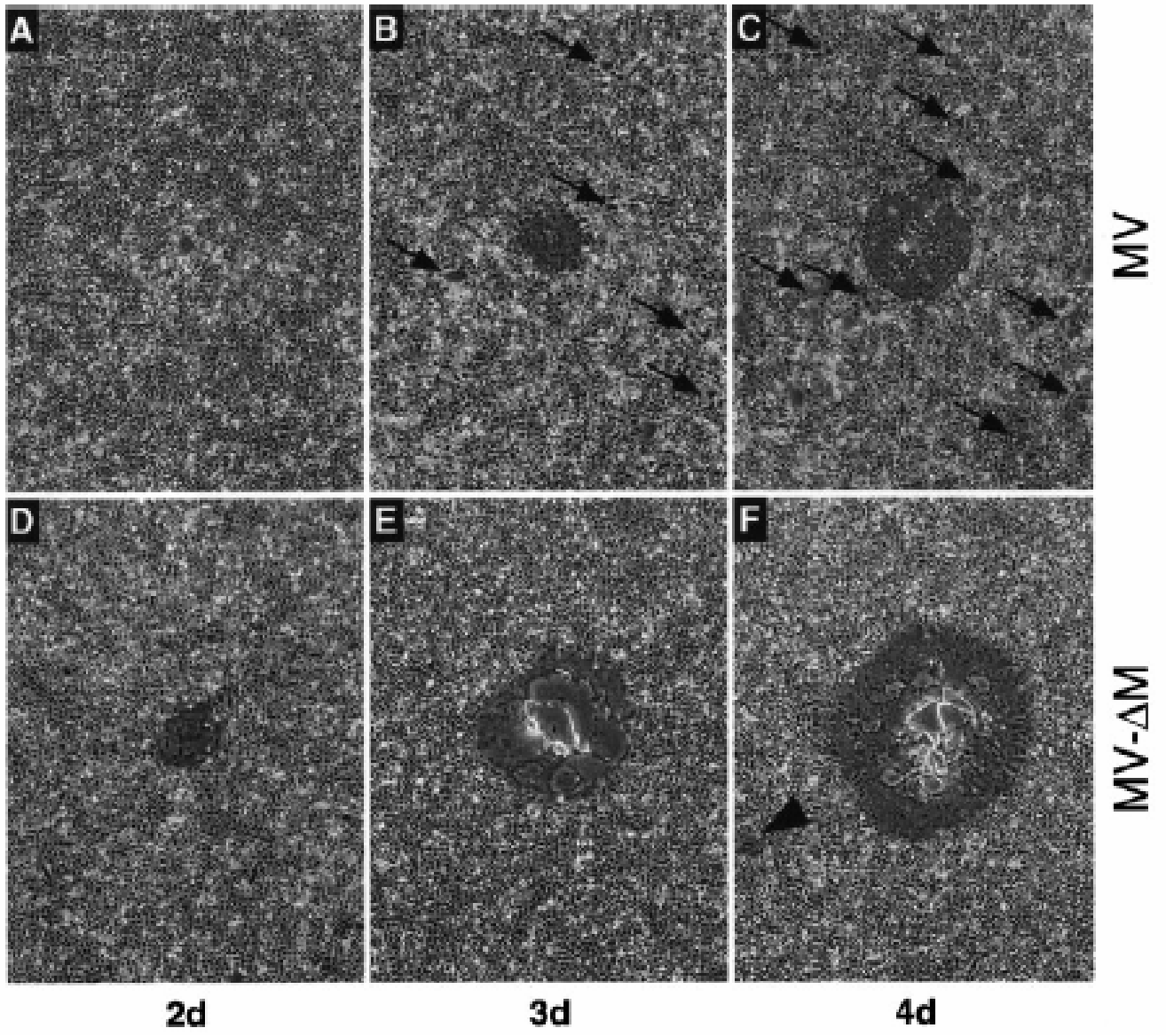
- Defective M protein
  - Hypermutated and unstable
  - Virions do not assemble
  - Viral spread is by cell fusion
  - Avoids humoral immune response
- Can also be caused by H or F defects that affect virion budding

in vitro Mutated M Protein

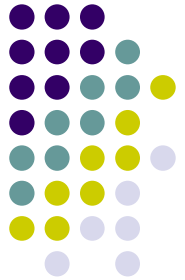
- Cathomen et al generated a ΔM virus



in vitro Mutated M Protein

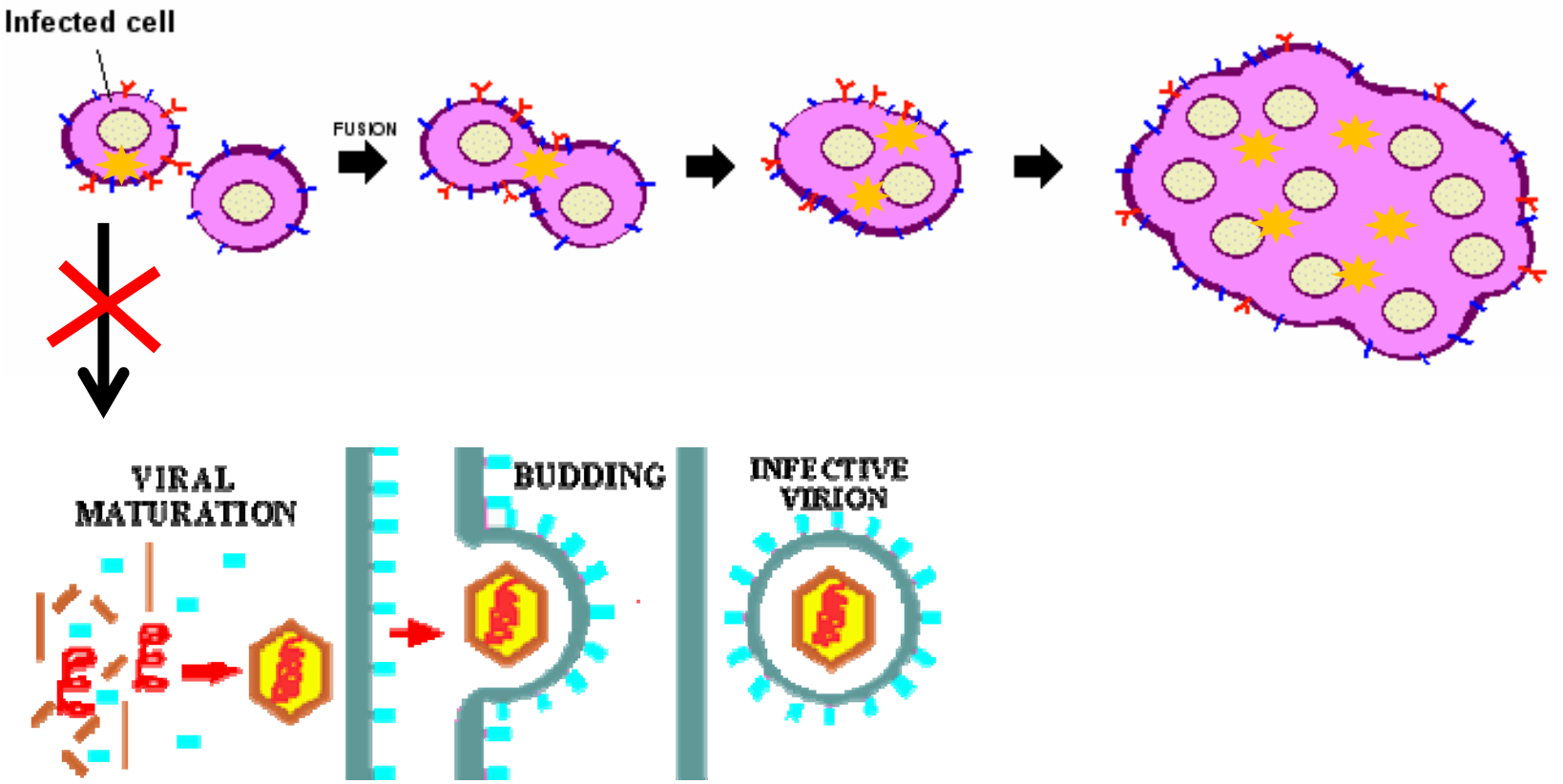


SSPE: Viral Persistence

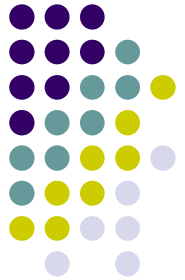


- Mechanism unknown
- Anti-MV antibodies can change virus expression
  - More syncytia formation and less budding
- Very young children have circulating maternal antibodies
- Cell-mediated immune response is underdeveloped in small children
  - Virus stays “under the radar”

SSPE Viral Persistence

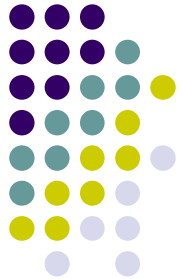


Immune Response



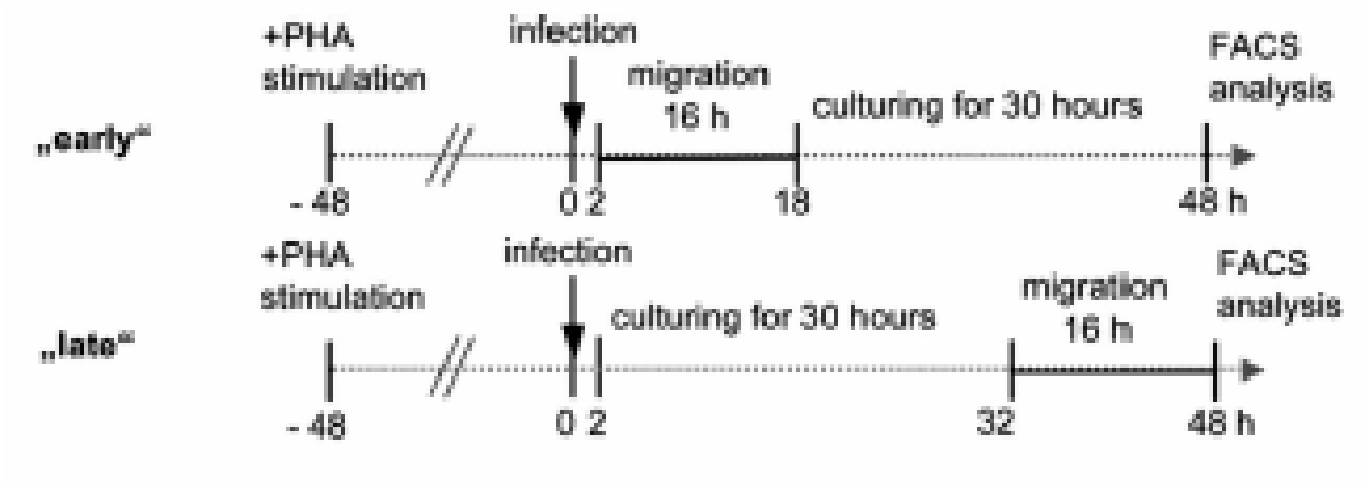
- MV suppresses the immune response
- Immunocompetent can still clear the virus
- CD8+ cells are needed
- Three parts of immunosuppression
  - Lymphopenia
  - Prolonged Th2 response
  - Reduced T cell proliferation

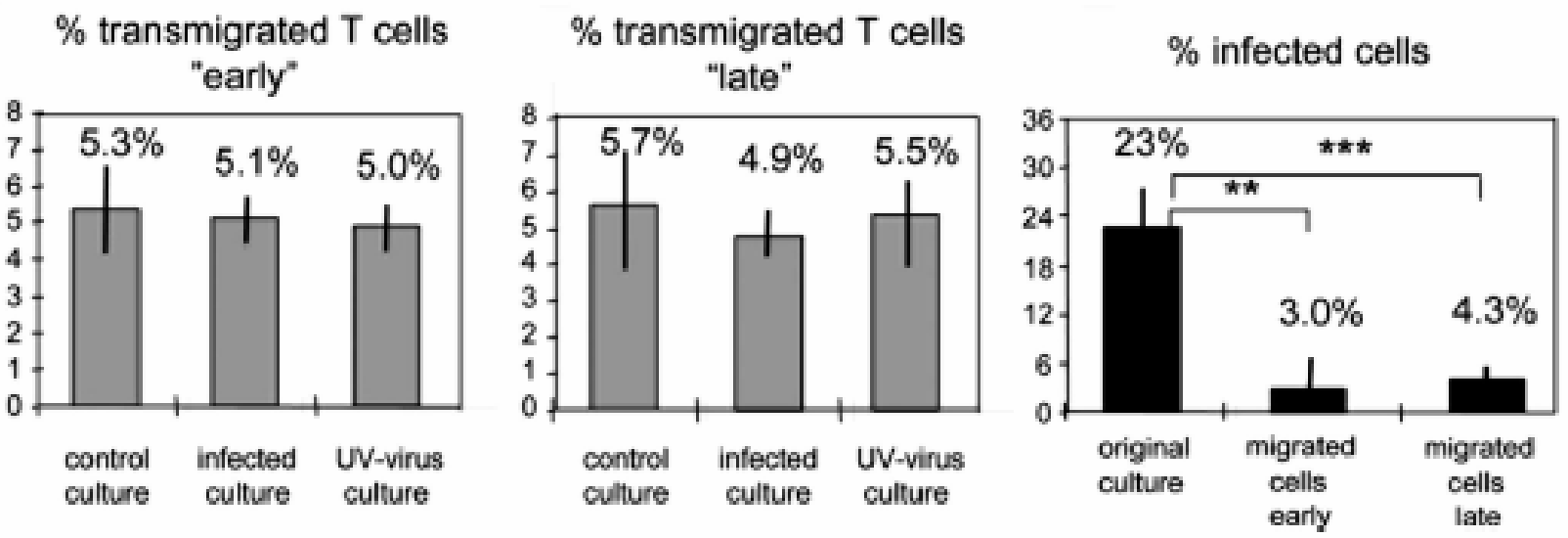
Lymphopenia



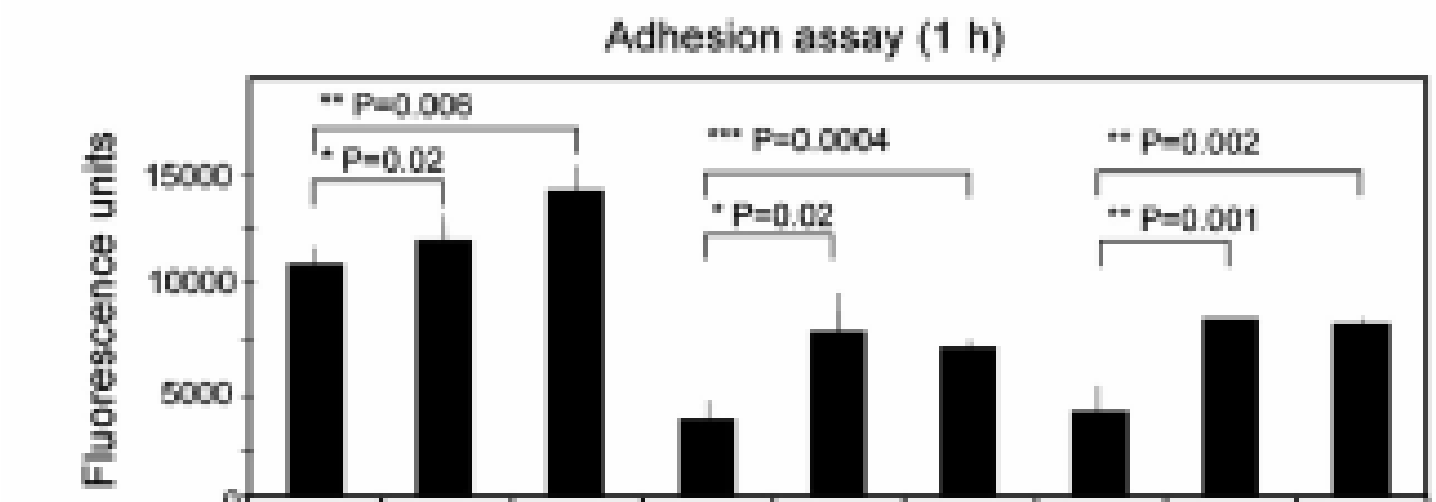
- Increased adhesion of lymphocytes to endothelial cells
- Apoptosis
- Duration:
  - B cells = 6 weeks
  - T cells = 10 days

Lymphocyte Adhesion Assay



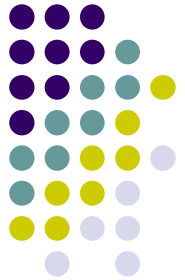


Lymphocyte Adhesion Assay



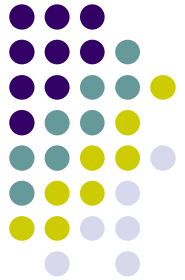
	1	2	3	4	5	6	7	8	9
+ MV (h)	0	24	48	0	24	48	0	24	48
+ antibodies				+18+29	+18+29	+18+29	+I+V	+I+V	+I+V
% adhesion	100%	111%	132%	33%	71%	64%	36%	76%	74%
% inhibition				67%	36%	52%	64%	32%	44%

Th2 Response



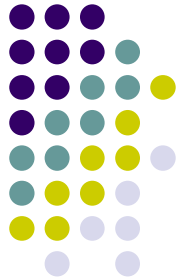
- Switches after the rash clears
- Allows maturation of B cells
  - Lifelong immunity
- Antibody immune response is less effective than cell mediated
  - Agammaglobulinic children have the same disease course as normal children

Lack of T cell Proliferation



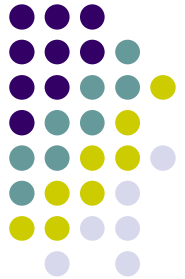
- Suppresses IL-12
- Increases T_{reg} production
- Downregulates CD150 receptor
  - Reduces T cell proliferation
- Suppresses IFN α / β

Natural History



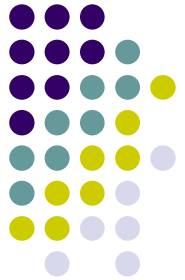
- Typical pt under 20 yrs old
- SSPE usually develops 7-10 yrs after primary infection
- Early infection (< 2 yrs age) is RF
- Possible to develop SSPE after vaccine (live attenuated)
- Potentially worsened by pregnancy due to immune alterations

Clinical



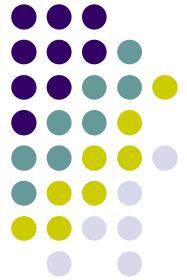
- Stages
  - I: personality changes, lethargy, scholastic probs, unusual behavior. Weeks to yrs
  - II: myoclonus, progressive dementia, sz
  - III: complete neurologic deterioration, flaccidity, autonomic dysfxn

Differential Dx



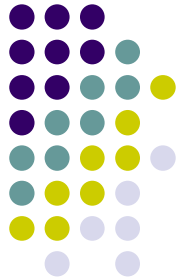
- Viral encephalitis: HSV, arbovirus, West Nile, enterovirus, echovirus, coxsackie
- Paraneoplastic encephalitis (may precede tumor appearance by months or yrs)
- Postinfectious encephalitis: MMR, influenza, EBV, VZV
- Prion dz

SSPE: Diagnosis & Treatment



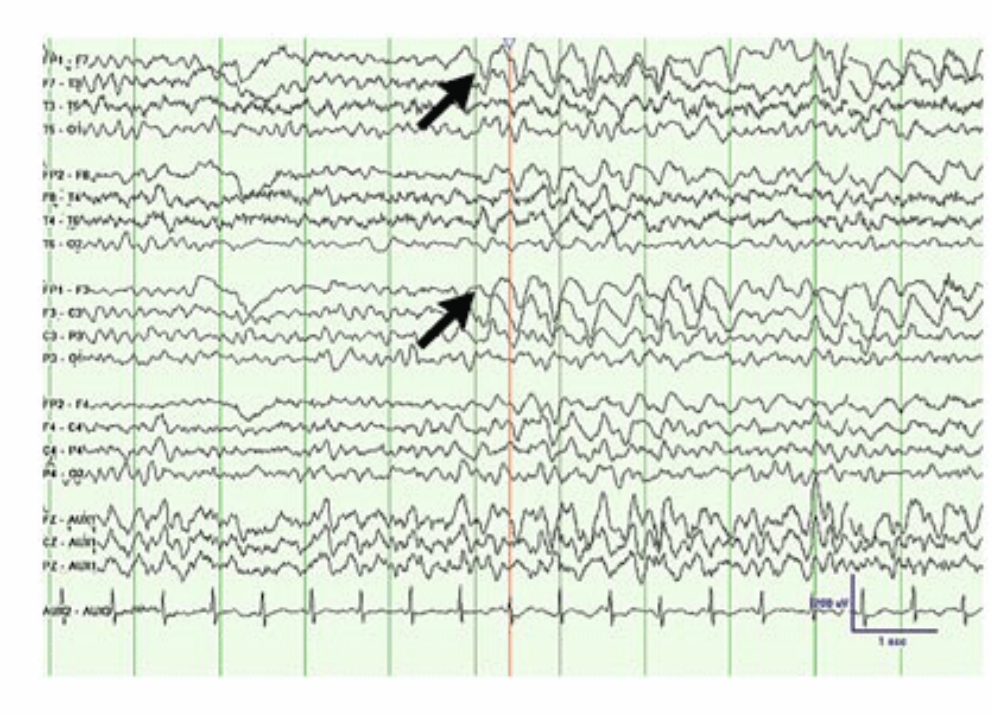
- Diagnosis is based on an EEG and high gammaglobulin levels in the CSF
- Survival is 1-3 years, 18 months average
- Treatments:
  - Isoprinosine (panbiotic) = increases CD4+, NK function, production of IL-1 and IL-2
  - IFN-α = may suppress viral replication
  - Ribavirin = antiviral drug

Diagnosis



- Imaging: not terribly helpful, can see focal abnormalities in subcortical WM
- EEG: for once, quite useful
- CSF: also, extremely helpful. Sp Ab, of course, but also IgG pattern

EEG

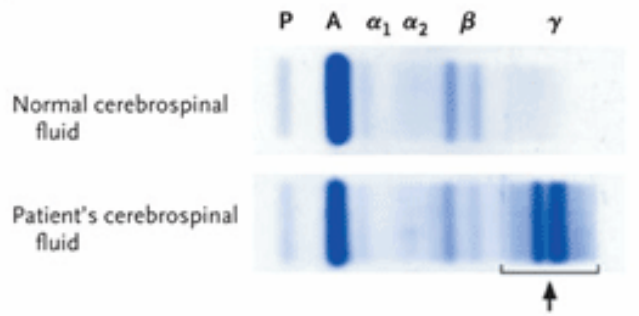


“Burst-suppression” pattern (2-3s of high voltage delta waves followed by flat pattern) seen only in SSPE or CJD.

[from NEJM 2007: 357;6, pg. 595]

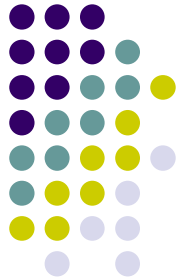
CSF

- Normal CSF albumin: serum albumin ratio (i.e., normal blood-brain barrier function)
- Markedly increased CSF IgG (in this patient, CSF IgG index was 2.7, 4x upper limit nl)
- Only a few things that can cause highly elevated CSF IgG response with intact BBB: syphilis, rubella panencephalitis, SSPE



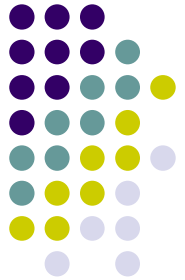
[from NEJM 2007: 357;6, pg. 595]

Treatment



- Antivirals: lamivudine, ribavirin
- Interferon alpha (intrathecally)
- Inosine pranobex (immunomodulatory antiviral agent, not approved in U.S. Obtained from Canada under IRB for this pt)

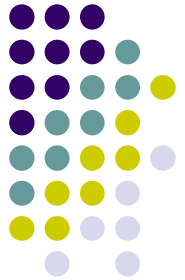
Prognosis



- Not good. Universally fatal if dx in Stg 2. Death typically within 3 yrs.

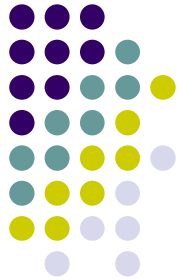
- Remission possible in stg I with treatment, but still only about 5% rate.

Vaccine



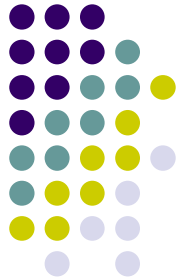
- Available in 1963
- Combined with mumps and rubella
- Adapted M protein
  - Increased virion production
  - Reduced syncytia formation
- Given at 15 months, with a booster later
- Side effects: mild rash, slight fever

Vaccine



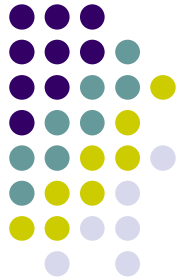
- Infection in USA has decreased by over 99%
- Most cases are linked to travel, lack of immunization
- 90% decline in Eastern Mediterranean and Sub-Saharan Africa
- 74% decline worldwide
  - Still a burden in malnutrition prone areas

Summary



- (-)ssRNA virus causing fever, rash, cough
- Very easily spread through saliva contact
- Infects many different types of cells
- Syncytia formation
- Virus reduces budding due to maternal antibodies
- Infant does not have a strong enough cell mediated immune response

Summary



- Persistence leads to SSPE over many years
- Causes immunosuppression by lymphopenia, induction of Th2 and reduction of T cell proliferation
- Can be prevented by vaccination – but not if child is under 15 months

懇請賜教