

# **Approach to Congenital Infections**

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# Outline

- Introduction
- Congenital Infections: Key Features
- When to suspect congenital infection
- What work-up to request
- Summary

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# Congenital Infection: Need For Early Diagnosis

- Can be life-threatening
- Can lead to life-long/ debilitating sequelae
- Early intervention can be done
- Treatment can be given
- Help families cope with burden and anxiety through counselling or work-up

# Congenital Infections:

- Toxoplasmosis
- Syphilis
- Rubella
- Cytomegalovirus
- Herpes simplex
- Parvovirus B19
- Varicella
- Tuberculosis
- Listeria

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- Hepatitis B
- Lymphocytic choriomeningitis virus (LCMV)
- Human immunodeficiency virus (HIV)
- Brucella melitensis
- Chlamydomphila abortus
- Babesia microti
- Trypanosoma cruzi
- Coccidioides immitis
- Histoplasma capsulatum
- Human herpesvirus 6
- others

# Foreign Incidence: US Data

- Congenital CMV – 8 (less than 1%) in 1,000 live births
- Congenital Rubella – 5-6 cases since 1980s
- Neonatal HSV infection - 7 of 20 infants born to women with *primary genital HSV infection*
- Congenital Toxoplasmosis - 0.1 to 1 in 1,000 live births, resulting in 400 to 4,000 cases each year
- Congenital Syphilis - 9.1 to 10.5 cases per 100,000 live births
- Parvovirus infection in pregnancy about 3.3% to 3.8%

# PPS Registry 2006-2012

Congenital Infection	No. of Cases reported to PPS
Congenital Rubella	56 out of 1,705,205
Congenital CMV	20 out of 1,705,205
Congenital HSV	7 out of 1,705,205
Congenital Toxoplasmosis	7 out of 1,705,205
Congenital Syphilis	3 out of 1,705,205

# Profile of Symptomatic CMV Infection at PCMC\*



- 19 patients diagnosed as CMV infection, 1994-2001
- 17 charts reviewed
- congenital infection: n=12
  - 3 (+) urine culture <3 wks old+S/Sx
  - 3 (+) urine culture >3 wks old + S/Sx < 3 wks old
  - 6 (+) CMV IgM + S/Sx< 3 wks old
- perinatal/postnatal infection: n=5
- 9 cases of congenital infection from 2002 to present

DeocadezT,ReyesA,BanezM,Santos J(unpublished) 2001



# Congenital Infections: Under-diagnosed!!

- Majority are asymptomatic at birth
- Low index of suspicion
- Lack of public awareness
- Lack of laboratory diagnostic facilities
- High cost of work-up
- Except for Hepatitis B, no public funded programs exist
- Lower age of infection – lower incidence of primary infection in pregnancy??

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# Transmission of CMV to the Newborn

- **Intrauterine**

- primary maternal infection (32%\*)

- recurrent maternal infection (reactivation or reinfection) (1.4%\*)

- **Intrapartum**

- up to 57% transmission from ingestion of CMV(+) cervicovaginal secretions

- **Post-natal**

- up to 53% transmission from CMV (+) breastmilk

Demmler-Harrison G. Cytomegalovirus in Feigin RD, Cherry JD .et al (editors). Textbook of Ped Inf Dse(6<sup>th</sup>ed). 2009,2022-43

\*Kenneson A and Cannon MJ.Rev .Med.Virol.2007;17:253-76

# Symptomatic Congenital CMV: Key Features

- Periventricular intracranial calcifications
  - Microcephaly
  - Thrombocytopenia
  - Hepatosplenomegaly
  - Petechiae/purpura
  - Chorioretinitis
  - Deafness
- Karen E Johnson et al. Overview of TORCH infections, Uptodate, Oct 11, 2012
  - CuixiaTian, et al; Congenital Infections, Part I: Cytomegalovirus, Toxoplasma, Rubella, and Herpes Simplex; *Neoreviews* 2010;11:e436

## Sequelae of Congenital CMV infection according to Symptoms at Birth

Sequela	Symptomatic		Asymptomatic	
	%	(No.)	%	(No.)
Sensorineural hearing loss	58.0	(58/100)	7.4	(22/299)
Bilateral hearing loss	37.0	(37/100)	2.7	(8/299)
Speech threshold $\geq 60$ dB †	27.0	(27/100)	1.7	(5/299)
Chorioretinitis	20.4	(19/93)	2.5	(7/281)
IQ < 70	55.0	(33/60)	3.7	(6/159)

## Sequelae of Congenital CMV infection according to Symptoms at Birth

Sequela	Symptomatic		Asymptomatic	
	%	(No.)	%	(No.)
Microcephaly, seizures, paralysis	51.9	(54/104)	2.7	(9/330)
Microcephaly	37.5	(39/104)	1.8	(6/330)
Seizures	23.1	(24/104)	0.9	(3/330)
Paresis/ paralysis	12.5	(13/104)	0	(0/330)
Death §	5.8	(6/104)	0.3	(1/330)

# Clinical Presentation of Congenital CMV Infection at PCMC



Manifestations	No.of Cases (12)	Percentage (%)
Jaundice	11	92
Hepatomegaly	9	75
Abdominal distention	6	50
Splenomegaly	6	50
Fever	6	50
Seizure	5	42

# Clinical Manifestations of Congenital CMV Infection at PCMC



Manifestations	No. of Cases (12)	Percentage (%)
Cough	5	42
Hydrocephalus	3	25
Rashes	3	25
Microcephaly	2	17
Chorioretinitis	1 / 5	(20)
Hearing loss	1/2	(50)





# Symptomatic Congenital Rubella: Clinical Manifestations

Early Onset	Late Onset
<ul style="list-style-type: none"><li>• Intrauterine/postnatal growth restriction</li><li>• hepatosplenomegaly, jaundice</li><li>• cataracts, “salt and pepper” retinopathy,</li><li>• “blueberry muffin spots,”</li><li>• anemia/thrombocytopenia,</li><li>• CHD (PDA, pulmonary artery stenosis</li><li>• meningoencephalitis</li></ul>	<ul style="list-style-type: none"><li>• Hearing loss, psychomotor retardation, behavioral disorders, school dysfunction;</li><li>• Ocular defects – glaucoma, keratoconus, corneal hydrops, and spontaneous lens absorption</li><li>• Endocrine - Diabetes, thyroid dysfunction, precocious puberty, late degenerative brain disease</li></ul>

# Congenital Rubella: Key Features

- Cataract, congenital glaucoma, pigmentary retinopathy
- Congenital heart disease (PDA, peripheral pulmonary artery stenosis)
- Radiolucent bone disease
- Sensorineural hearing loss



“Blueberry muffin” spots representing extramedullary hematopoiesis

# Congenital HSV

## Transmission

- **Intrauterine 5%**
- **Perinatal 85-90%**
- **Postnatal 5-10%**

## Clinical Manifestations

- (1) HSV disease localized to the skin, eye, and/or mouth (SEM);
- (2) HSV encephalitis with or without skin, eye, and/or mouth
- (3) disseminated HSV which manifests as severe multiorgan dysfunction (liver, lung, brain, adrenals, skin, eye, and/or mouth)

# Congenital HSV: Key Features

- Mucocutaneous vesicles or scarring
- CSF pleocytosis
- Thrombocytopenia
- Elevated liver transaminases
- Conjunctivitis or keratoconjunctivitis



<http://neoreviews.aappublications.org/>



# Congenital Toxoplasmosis

- Transmission - ingestion of cysts from cats

Trimester of maternal acquisition	Incidence of transmission (%)	Relative severity of disease
I	17	Severe
II	25	Intermediate severity
III	65	Milder or asymptomatic

Rima McLeod et al. Why prevent, diagnose and treat congenital toxoplasmosis? *Mem Inst Oswaldo Cruz*. 2009 March ; 104(2): 320–344

# Signs, symptoms and sequelae in congenital toxoplasmosis patients

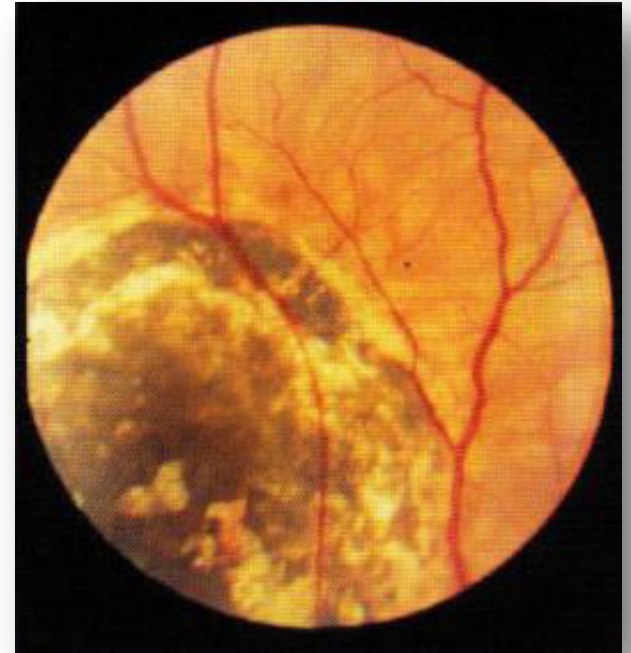
	Frequency of occurrence in infants with (%)	
Signs and symptoms	Neurologic disease <sup>a</sup> n = 108	Generalized disease <sup>b</sup> n = 44
Chorioretinitis	94	66
Abnormal spinal fluid	55	84
Anemia	51	77
Convulsions	50	18
Intracranial calcification	50	4
Jaundice	29	80

	Frequency of occurrence in infants with (%)	
Signs and symptoms	Neurologic disease <sup>a</sup> n = 108	Generalized disease <sup>b</sup> n = 44
Hydrocephalus	28	0
Fever	25	77
Splenomegaly	21	90
Lymphadenopathy	17	68
Hepatomegaly	17	77
Vomiting	16	48
Microcephaly	13	0

Eichenwald HF. A study of congenital toxoplasmosis, with particular emphasis on clinical manifestations, sequelae and therapy. 1960.

# Congenital Toxoplasmosis: Key Features

- Intracranial calcifications (diffuse) - 37%
- Hydrocephalus - 20%
- Chorioretinitis - 86%
- Otherwise unexplained mononuclear CSF pleocytosis  
or elevated CSF protein



chorioretinitis with  
pigmentation and scarring  
*Red book Atlas*

• Cuixia Tian, et al; Congenital Infections, Part I: Cytomegalovirus, Toxoplasma, Rubella, and Herpes Simplex; *Neoreviews* 2010;11:e436

• Karen E Johnson et al. Overview of TORCH infections, Uptodate, Oct 2012



# Congenital Syphilis

- Approximately 30% to 40% of fetuses are stillborn
- Approximately 75% of live born infants are asymptomatic at birth
- Symptoms develop between 3<sup>rd</sup> and 14<sup>th</sup> weeks after birth
- Clinical symptoms split into early or late (2 years is cutoff)

# Early Congenital Syphilis

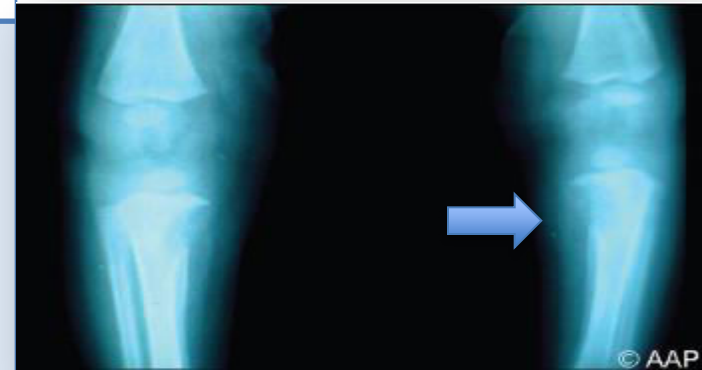
Systemic	Hepatomegaly, generalized lymphadenopathy, failure to thrive, edema, fever
Muco-cutaneous	Snuffles, maculopapular rash, vesicular rash (pemphigus syphiliticus), condyloma lata, jaundice
Hematologic	Anemia, thrombocytopenia, leukopenia or leukocytosis



Red book atlas

# Early Congenital Syphilis

Musculo-skeletal	Pseudoparalysis of Parrot; Radiographic abnormalities – periostitis, Wegner sign, Wimberger sign
Neurologic	Reactive CSF VDRL, elevated CSF WBC & protein; acute syphilitic leptomeningitis



bony destruction of the medial portion of the proximal tibial metaphysis  
Red book atlas

# Stigmata of Late Congenital Syphilis

Facial features	Frontal bossing, saddle nose, short maxilla, protuberant mandible
Eyes	Interstitial keratitis, chorioretinitis, secondary glaucoma, corneal scarring, optic atrophy
Ears	Sensorineural hearing loss
Mouth	Hutchinson teeth, mulberry molars, perforation of hard palate



# Stigmata of Late Congenital Syphilis

Skin	Rhagades, gummas
CNS	Intellectual disability, arrested hydrocephalus, seizures, optic atrophy, juvenile general pareses
Skeletal	Saber shins (anterior bowing of the tibia), Higoumenakis sign (enlargement of the sternoclavicular portion of the clavicle), Clutton's joints (painless arthritis), scaphoid scapula



*From Fitzpatrick's Dermatology*



# Congenital Syphilis: Key Features

- Skeletal abnormalities (osteochondritis & periostitis)
- Pseudoparalysis
- Persistent rhinitis
- Maculopapular/vesicular rash (particularly on palms and soles or in diaper area)

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# Diagnosing Congenital Infections

- Thorough exam of infant
- Good maternal/prenatal history
- Directed labs/studies based on most likely diagnosis...



# Index of Suspicion

In the absence of suggestive maternal laboratory results, suspect congenital infections in neonates with:

Hydrops fetalis

Microcephaly

Seizures

Cataract

Hearing loss

CHD

Hepatosplenomegaly

Jaundice

Rash

Thrombocytopenia

IUGR

**Majority clinically inapparent  
("asymptomatic") at birth**

## Findings in infants with congenital infection

Finding(s)	Possible congenital infections
Intrauterine growth retardation	<ul style="list-style-type: none"><li>• Rubella, cytomegalovirus (CMV), toxoplasmosis</li></ul>
Anemia with hydrops	<ul style="list-style-type: none"><li>• Parvovirus B19, syphilis, CMV, toxoplasmosis</li></ul>
Bone lesions	<ul style="list-style-type: none"><li>• Syphilis, rubella</li></ul>
Cerebral calcification	<ul style="list-style-type: none"><li>• Toxoplasmosis (widely distributed)</li><li>• CMV and herpes simplex virus (HSV) (usually periventricular)</li><li>• Parvovirus B19, rubella, human immunodeficiency virus (HIV)</li><li>• Lymphocytic choriomeningitis virus</li></ul>
Congenital heart disease	<ul style="list-style-type: none"><li>• Rubella</li></ul>

## Findings in infants with congenital infection

Finding(s)	Possible congenital infections
Hearing loss (commonly progressive)	• Rubella, CMV, toxoplasmosis, syphilis
Hepatosplenomegaly	• CMV, rubella, toxoplasmosis, HSV, syphilis, enterovirus, parvovirus B19
Hydrocephalus	• Toxoplasmosis, CMV, syphilis, possibly enterovirus

## Findings in infants with congenital infection

Finding(s)	Possible congenital infections
Jaundice with or without thrombocytopenia	• CMV, toxoplasmosis, rubella, HSV, syphilis, enterovirus
Limb paralysis with atrophy and cicatrices	• Varicella
Maculopapular exanthem	• Syphilis, measles, rubella, enterovirus
Microcephaly	• CMV, toxoplasmosis, rubella, varicella, HSV
Myocarditis/encephalomyocarditis	• Echovirus, coxsackie B, other enterovirus

## Findings in infants with congenital infection

Finding(s)	Possible congenital infections
Ocular findings	<ul style="list-style-type: none"><li>• CMV, toxoplasmosis, rubella, HSV, syphilis, enterovirus, parvovirus B19</li></ul>
Progressive hepatic failure and clotting abnormalities	<ul style="list-style-type: none"><li>• Echovirus, coxsackie B, other enterovirus, HSV, toxoplasmosis</li></ul>
Pseudoparalysis, pain	<ul style="list-style-type: none"><li>• Syphilis</li></ul>
Purpura (usually appears on first day)	<ul style="list-style-type: none"><li>• CMV, toxoplasmosis, syphilis, rubella, HSV, enterovirus, parvovirus B19</li></ul>
Vesicles	<ul style="list-style-type: none"><li>• HSV, syphilis, varicella, enterovirus</li></ul>

# Diagnosing Congenital Infections

- Thorough exam of infant
- Good maternal/prenatal history
- Directed labs/studies based on most likely diagnosis...

# Maternal History suggestive of Congenital infection

History	Infection
Exposure	
Season	Parvovirus B19 (winter, spring) Rubella (winter, spring) Enterovirus (summer, autumn)
Handling or ingestion of raw meat that has never been frozen	Toxoplasmosis
Contact w/ diapered children in daycare, household or school	CMV, parvovirus

# Maternal History suggestive of Congenital infection

History	Infection
Exposure	
Exposure in travel to certain geographic regions	Toxoplasmosis, TB, malaria, trypanosomiasis, hepatitis B virus (HBV)
Kitten or cat feces in 21 days after the animal's primary infection (handling animal or kitty litter, gardening)	Toxoplasmosis
Number of sexual partners, sex industry worker/partner, illicit drug use	Syphilis, HSV, HBV, hepatitis C virus, HIV



# Maternal History suggestive of Congenital infection

History	Infection
Exposure	
Sexually active adolescents	CMV, HSV, HBV, HIV
Unimmunized	Rubella
Screening in pregnancy	HBV, rubella, syphilis, HIV
Fetal ultrasonography	Variable

# Maternal History suggestive of Congenital infection

History	Infection
Illness	
Rash	Syphilis, rubella, parvovirus B19, enterovirus
Arthritis	Parvovirus B19, rubella
Mononucleosis-like fatigue, lymphadenopathy	CMV, toxoplasmosis, HIV

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# Imaging Studies

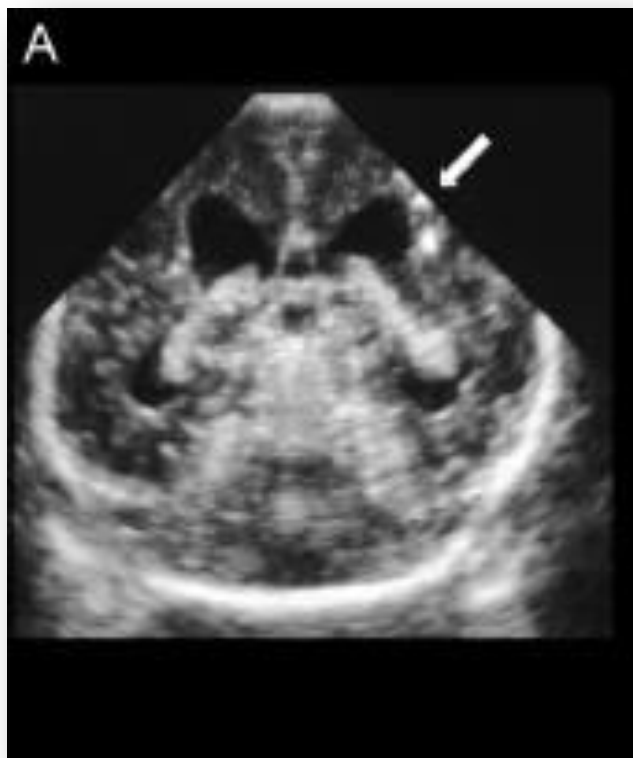
## 1. Cranial ultrasound, CT scan, MRI

- CMV
- Toxoplasmosis

## 2. Skeletal Survey

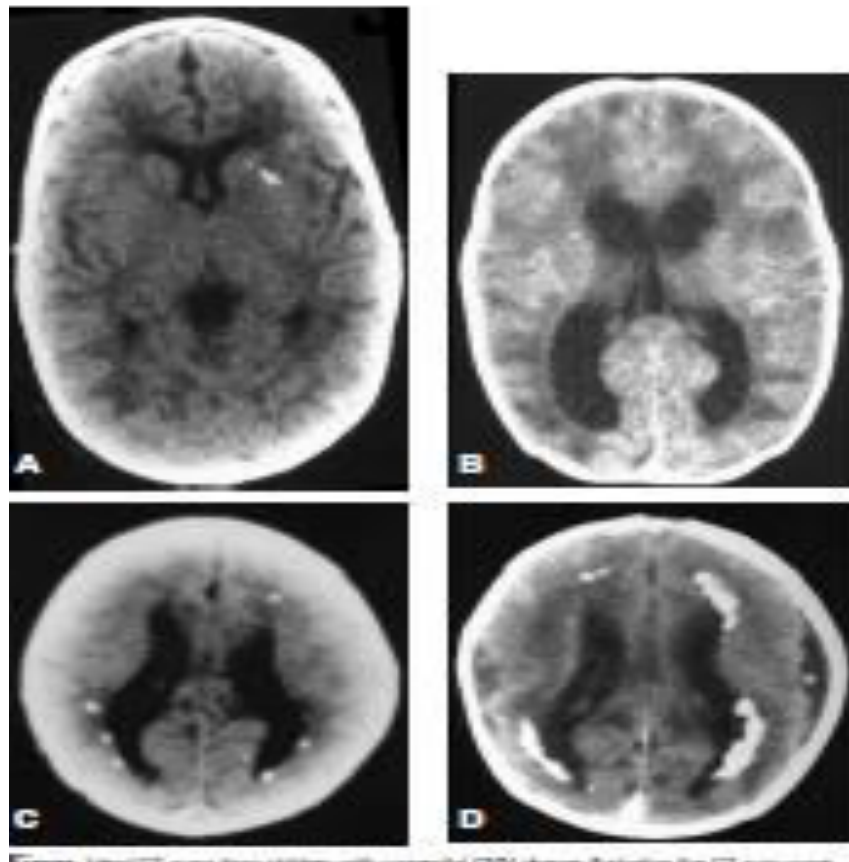
- Syphilis
- Rubella

## Cranial Ultrasound



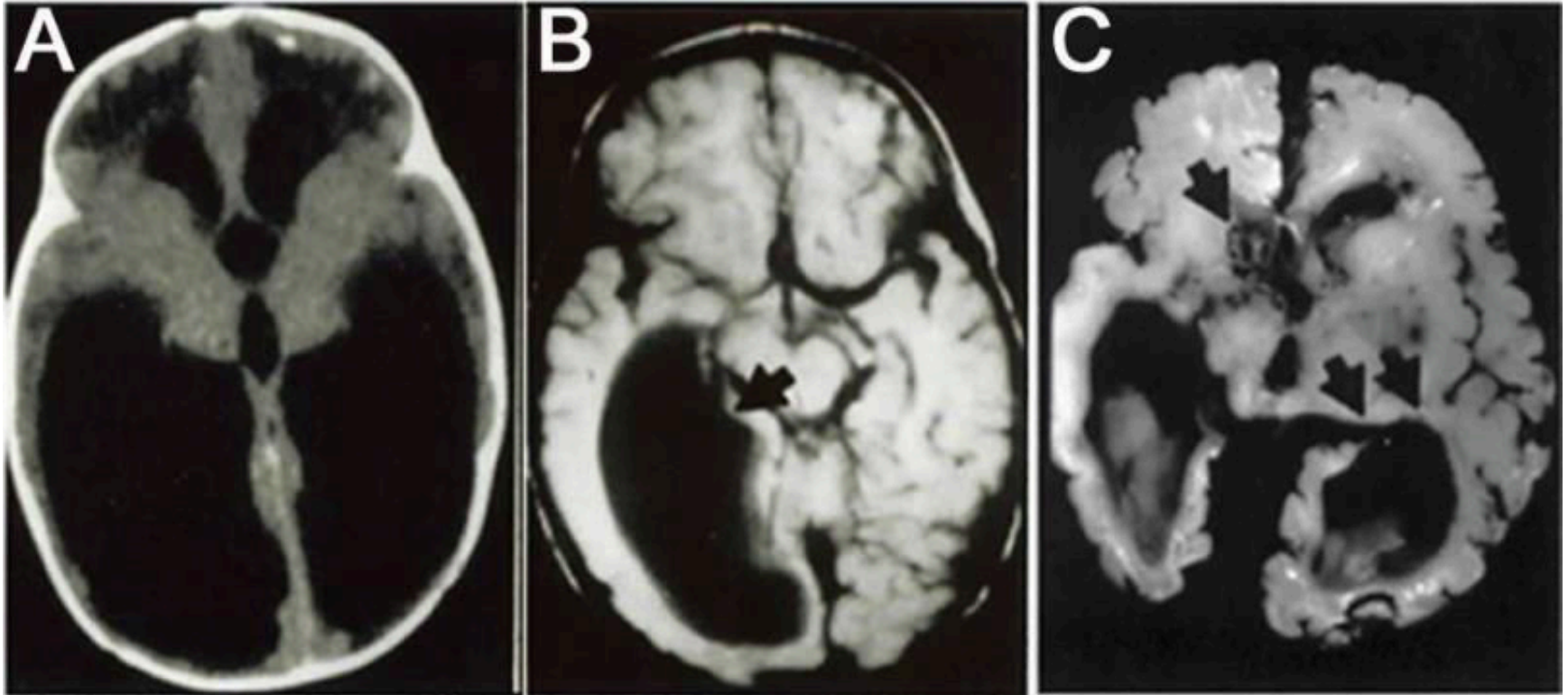
<http://neoreviews.aappublications.org>

## Cranial CT



Noyola D, Demmler G, Nelson C et al. J of Ped. March 2001;138(3):325-31

# NEURO IMAGING STUDIES of TOXOPLASMOSIS



presence of hydrocephalous “shown in **brain CT scan and MRI image** of brains of congenitally infected children” (A, B) and brain at pathologic examination showing characteristic periaqueductal inflammation and necrosis (C)

Mack D, Johnson J, Roberts F, Roberts C, Estes R, David C, Grumet C, Estes R, McLeod R. HLA-Class II genes modify outcome of *Toxoplasma gondii* infection. Int J Parasitol. 1999;29:1351–1358.

# Skeletal Survey



4-year-old child with diaphyseal cortical thickening secondary to **congenital syphilis** (a late finding) *Red book Atlas*



radiolucent areas (celery stalk) at the metaphyses in Congenital rubella

# Serology

## *CMV IgM*

- if (+) in cord/infant's blood in 1<sup>st</sup> 3 wks of life
- if (-), congenital infection not ruled out.
- **insensitive (22%)** compared with urine culture for diagnosis of congenital CMV

Nelson C, et al. J Clin Microbiol. 1995;33:3317

## *Rubella*

- rubella specific IgM remain detectable for 6–12 months of age
- Persistence of anti-rubella IgG antibodies in the infant's serum beyond 3–6 months of age



# Serology

## *Toxoplasmosis*

- *T gondii*-specific IgG antibodies are detectable indefinitely 1 to 2 months post-infection
- *T gondii*-specific IgM testing often yields false-positive or false-negative results, and IgM antibodies can persist for 6 to 24 months

confirmatory test: CDC & Palo Alto Medical Foundation  
Research Institute's Toxoplasma Serology Laboratory (650-853-4828)

## *Syphilis*

- quantitative nontreponemal serologic (rapid plasma reagin [RPR]) titer  $\geq$ fourfold the corresponding maternal titer (which is equivalent to two dilutions [eg, neonate's titer 1:32 and maternal titer 1:8])

- CuixiaTian, et al; Congenital Infections, Part I: Cytomegalovirus, Toxoplasma, Rubella, and Herpes Simplex; *Neoreviews* 2010;11:e436

- Simon R Dobson, MD et al. Congenital syphilis: Clinical features and diagnosis. Uptodate January 2013

# Culture

- ❖ Rubella virus isolation from nasal secretions
- ❖ CMV urine culture +/-  
Shell Vial Assay or Early Antigen Determination(EAD):  
inoculated culture cells in small vials are stained w/ fluorescein-conjugated monoclonal antibody to CMV antigen at 24-48 hours
- ❖ HSV viral culture(HSV 1 & 2) from vesicular swab, CSF, whole blood

# Molecular Assays

## PCR CMV-DNA

- rapidly replacing viral culture as the most sensitive and efficient method for detection of CMV (urine, saliva, serum, liver tissue)
- saliva PCR now considered the investigation of choice to detect CMV

Kadambari S, Williams EJ, Luck S. et al. Evidence based management guidelines for the detection and treatment of congenital CMV. *Early Human Dev.* 2011;87:723-728

## HSV viral PCR-DNA and rapid immunofluorescence assays (IFA)

# Tests Cost Money!

CMV	1. Conventional tube culture technique	P 7,000
	2. Early Antigen Determination(EAD)	P 10,700
	3. PCR CMV-DNA	P 4000
RUBELLA	1. Virus Isolation (Rubella)	P 4,200
	2. PCR	P 4,200
HSV	1. HSV viral culture(HSV 1 & 2)	
	•Vesicular swab	P 4,200
	•CSF	P 3,900
	•Whole Blood	P 4,900
	2. HSV viral PCR-DNA	P 4,000
3. Rapid immunofluorescence assays (IFA)	P 2,100	
SYPHILIS	Rapid Plasma Reagin (RPR)	
	<ul style="list-style-type: none"> <li>▪Qualitative P 350.00</li> <li>▪Quantitative P 1,400.00</li> </ul>	

# Treatment for Congenital CMV

**GANCICLOVIR** - Vial 500mg/10 ml (P 3,464)

- Newborns who are likely to benefit immediately from antiviral therapy include those with:
  1. Viral sepsis-like syndrome caused by CMV
  2. Pneumonitis or severe and refractile thrombocytopenia
  3. Sight-threatening retinitis
- Newborns who may benefit long-term from antiviral therapy include those with:
  1. Sensorineural hearing loss
  2. microcephaly

Gail J Demmler-Harrison, MD. Cytomegalovirus infection and disease in newborns, infants, children and adolescents. Uptodate, Sep 2010

# Treatment

Neonatal HSV

Acyclovir IV every 8 hrs

- a. skin-eye-mouth disease - for 14 days
- b. disseminated disease and encephalitis - for at least 21 days
- c. HSV encephalitis - should be continued until CSF PCR test results become negative

Congenital  
Toxoplasmosis

Pyrimethamine-sulfadiazine and folinic acid for 1 year

Congenital Syphilis

IV penicillin G for 10-days

# SUMMARY

- Congenital infections are underdiagnosed in the Philippines for various reasons
- We need to enhance laboratory capability and create programs to enhance awareness
- Congenital infections can be life-threatening and can lead to life-long/ debilitating sequelae
- Presence of key features should lead to immediate proper work-up
- Congenital infections may manifest with late signs and sequelae
- Early intervention can be done to prevent debilitating sequelae
- Treatment can be given in some cases

**THANK YOU !**