כללית

מרכז שניידר לרפואת ילדים בישראל
مركز شنايدر لطب الأطفال في اسرائيل
Schneider Children's Medical Center of Israel

Short-term-intermediate follow-up of infants born with congenital CMV after primary maternal infection detected by positive amniotic fluid and normal fetal imaging

Jacob Amir

2014

Congenital CMV

- Is the most common cause of non-hereditary hearing loss.
- Is the most frequent viral cause of mental retardation in developed countries.
- In approximately 1:750 live birth infants, permanent disabilities occur (Dollard SC: Rev Med Virol, 2007)

Congenital CMV Epidemiology

- **Congenital infection** occurs in approximately 1% of live births.
- Most cases are **subclinical.**
- In the USA, out of approximately **44,000** infants annually - **4,400** have S & S of cong. CMV.
- In Israel, the calculated numbers of infants will be **1,500** per year.

CONGENITAL CMV INFECTION - nomenclature

- **Congenital infection** - viral isolation from urine/blood/ saliva just after birth (2-3 weeks)
- **Symptomatic infection –** neonatal S&S
- **Asymptomatic infection**
- **Primary infection**
- **Non primary infection -**reactivation or re-infection

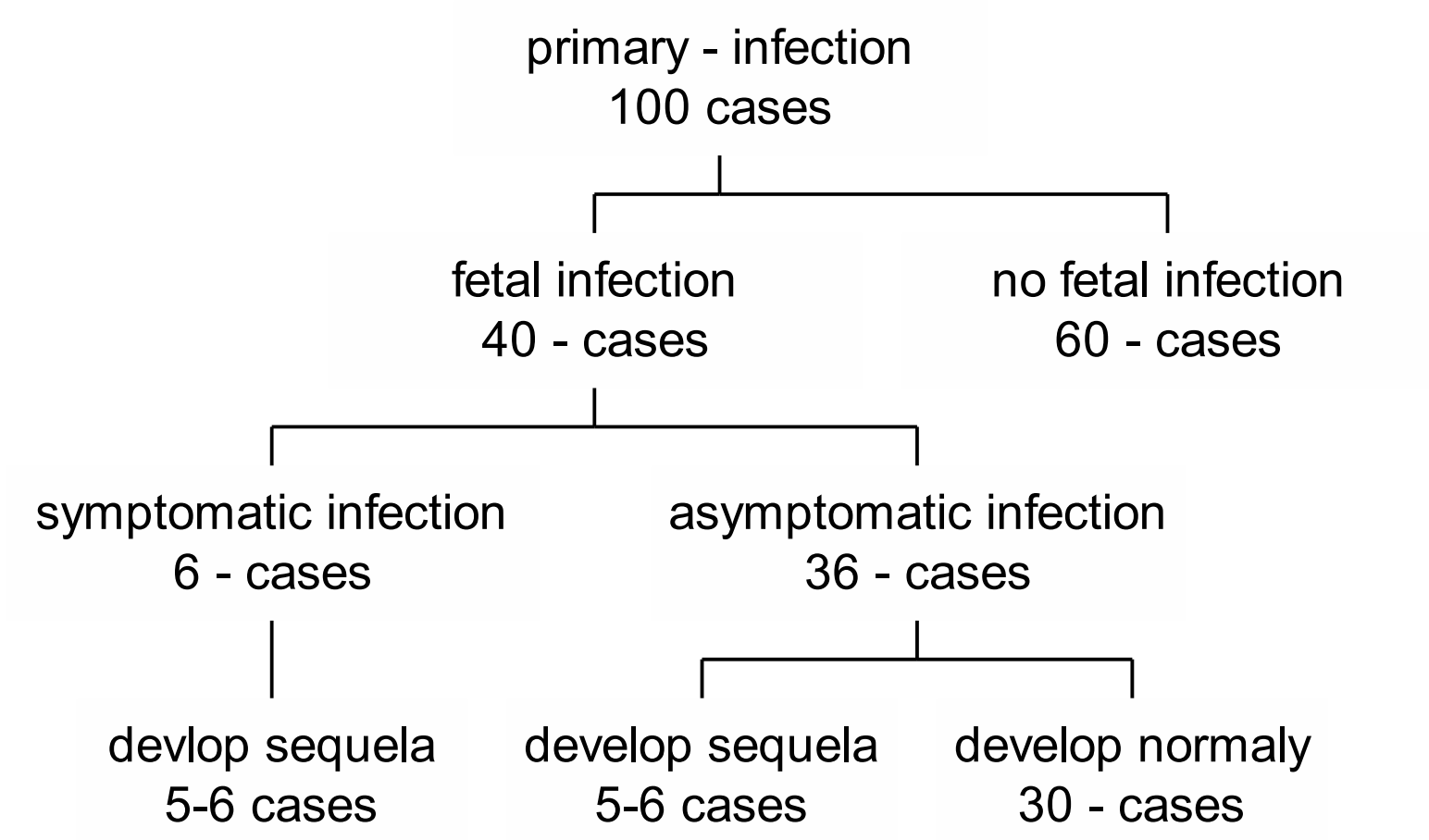
Congenial CMV infection

- **Most symptomatic cases - primary infection**

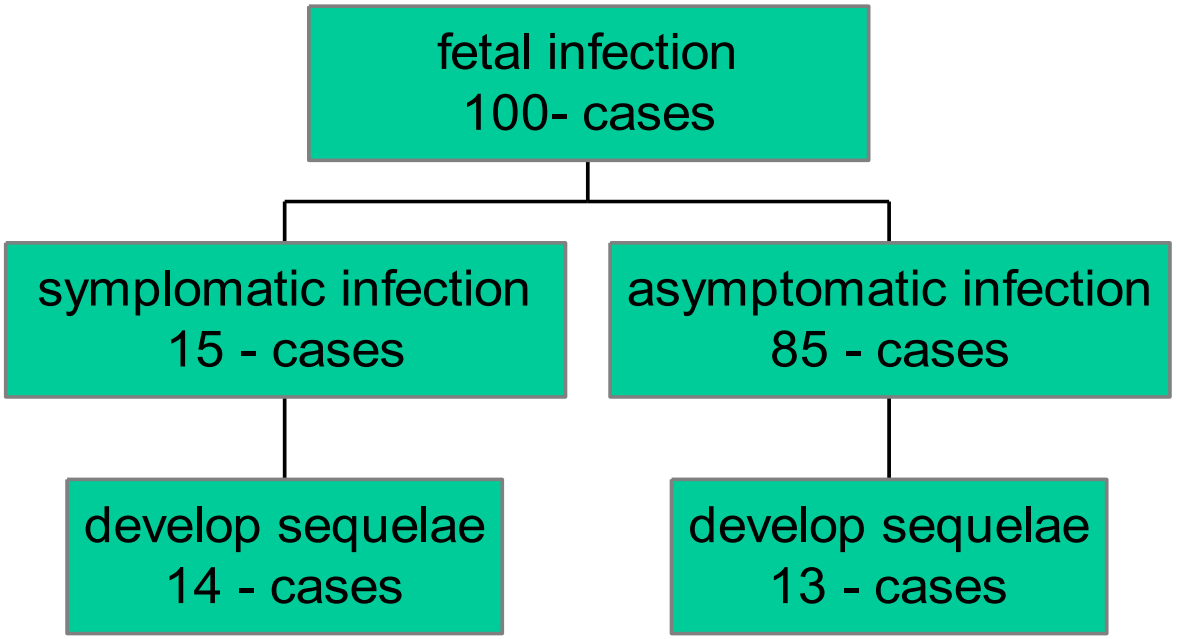
- Most asymptomatic cases- reactivation of latent virus
- Reinfection - symptomatic cases?
- Maternal immunity may prevents congenital CMV

(Fowler: JAMA, 2003)

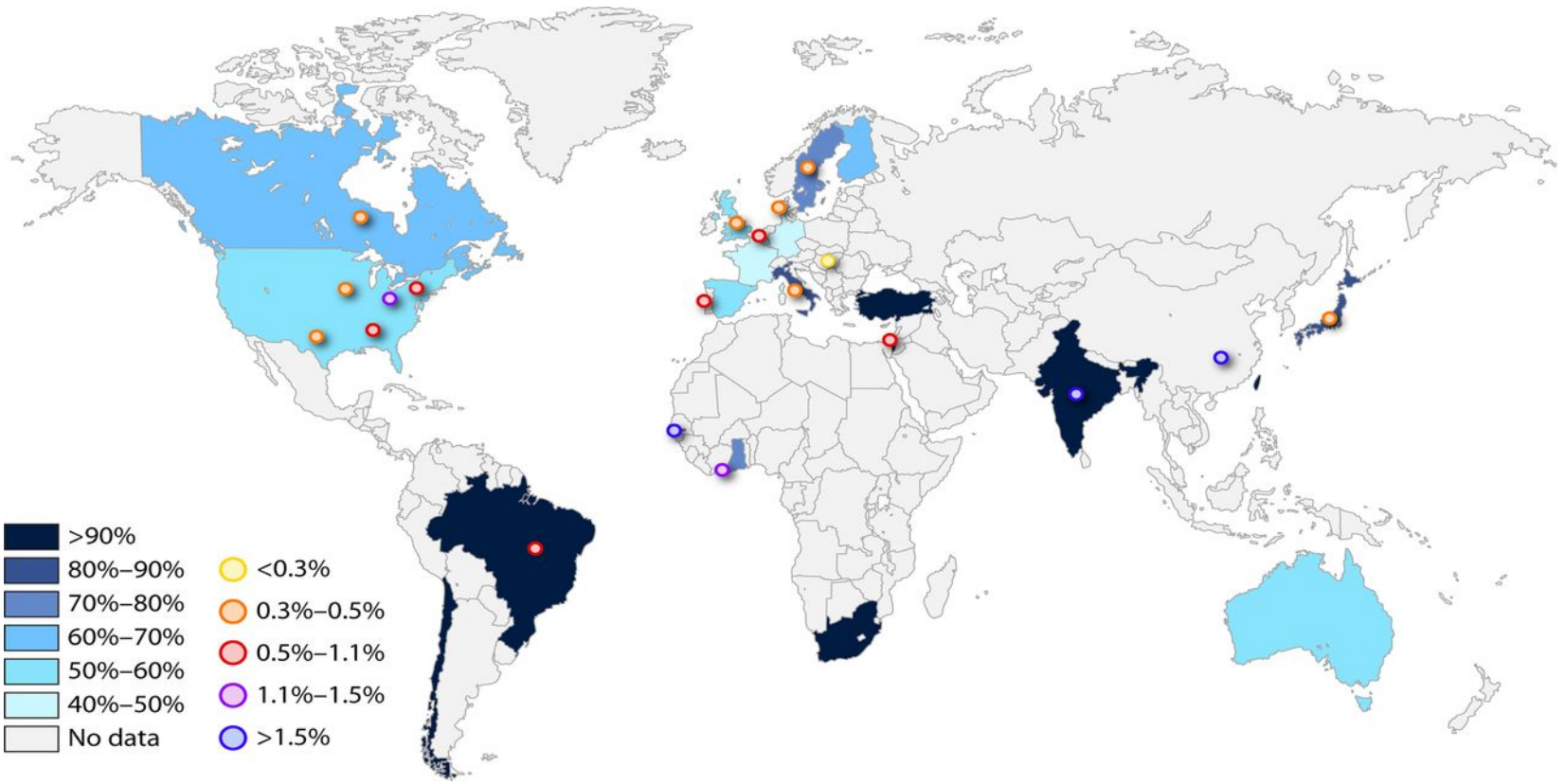
Consequences of CMV in pregnancy



Fetal infection in primary maternal CMV



Worldwide CMV seroprevalence rates among women of reproductive age and birth prevalence of congenital CMV infection.



Manicklal S et al. Clin. Microbiol. Rev. 2013;26:86-102

Seronegative women

- **The risk of primary maternal infection** during pregnancy is about 2%, with intrauterine transmission rates ranging from **30% - 42%** in the first trimester and **38% - 44%** in the second trimester.
- **Primary infections** are more likely than non-primary infections to be associated with fetal damage.

Symptomatic CMV infection

- **18%** of infants exposed to primary maternal infection were symptomatic at birth compared to almost none exposed to a recurrent infection. **(Fowler KB, *N Engl J Med* 1992)**
- Sensorineural hearing loss (SNHL) is found in **15%** of infants born to mothers with a primary infection, and it is severe and bilateral in about half of them. **(Foulon I, *J Pediatr* 2008)**

What can be done?

1 CMV immunization

2 Maternal screening and consultation

3 Infants screening

4 Treatment of symptomatic infants

Screening for congenital CMV in Israel

2014

- In Israel, **screening** for CMV infection **is not recommended** by the ministry of health
- However, **screening is frequently performed** before or during the first trimester of pregnancy
- **Amniocentesis** is performed in mothers with a primary infection in order to detect fetal infection.

Congenital CMV- **maternal screening and consultation**

- Serology for CMV at first trimester of pregnancy:
- IgG
- IgM → Confirmatory IgM assay
- IgG avidity

Screening results

- **Past Infection** – Education (prevention of re-infection)
- **No Past infection** – follow up serology and education (prevention of primary infection)
- **Primary infection** – amniotic fluid for CMV

Amniocentesis for CMV detection

- At least 7-8 weeks post assumed maternal infection
- At 21 weeks of pregnancy or later
- Try to avoid tapping between 24-32 weeks
- CMV detection: PCR + Shell vial culture
- Results in 2-3 days

Past common practice

- **In the past**, owing to the high rate of neurological sequelae in children infected with CMV in utero, most women preferred to terminate their pregnancy if the virus was isolated from the amniotic fluid after a primary infection.

During the last decade:

- improvements in serology assays
- fetal brain imaging- US and MRI
- All have led to **earlier** and **more accurate** intrauterine detection of **fetal brain damage**.

Ultrasound Obstet Gynecol. 2010 Apr 15. [Epub ahead of print]

The value of prenatal ultrasound and MR imaging in the assessment of congenital primary CMV infection.

Lipitz S, Hoffmann C, Feldman B, Tepperberg-Dikawa M, Schiff E, Weisz B.

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Abstract

OBJECTIVE: Our aim was to evaluate the outcome of pregnancies with proven and well dated primary CMV infection with and without US and MRI findings.

METHODS: Singleton pregnancies with proven vertical transmission of CMV who decided to continue the pregnancy and had prenatal ultrasound and MRI scan (38 women) were enrolled to the study. The study design was prospective, with neonatal follow-up being a strict requirement, as was precise dating of the pregnancy and the time of maternal infection. All neonates had fundus examination, brain ultrasound scan and hearing evaluation. All children were followed up by specialists in child development.

RESULTS: Primary CMV infection occurred during the first, second and third trimester of pregnancy in 10,19 and 9 patients, respectively. Twenty-four out of 29 patients with 1(st) or 2 (nd) trimester infections delivered (other 5 patients underwent TOP). Three patients had abnormal sonographic findings with normal MRI. Of those, two had damage to the auditory system. In both cases infection occurred during the 1(st) trimester. In 16 patients with 1(st) or 2(nd) trimester infection, both ultrasound scans and MRI were normal. Outcome of this group was favorable with normal hearing and developmental evaluation. Outcome of 5 pregnancies with subtle MRI findings and normal US was also favorable. None of the children infected during the third trimester were affected.

CONCLUSIONS: The outcome of congenital primary CMV infection with normal prenatal US and MRI is favorable. The prognostic value of subtle MRI findings is probably limited and as an isolated finding it probably does not justify termination of pregnancies. Copyright (c) 2010 ISUOG. Published by John Wiley & Sons, Ltd.

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PRENATAL DIAGNOSIS
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Does normal fetal brain ultrasound predict normal neurodevelopmental outcome in congenital cytomegalovirus infection?

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Objective We evaluated the neuropsychological outcome of children with proven congenital cytomegalovirus (CMV) infection and normal consecutive fetal neurosonographic examinations.

Methods We retrospectively reviewed laboratory and imaging findings of children with congenital CMV infection. The study group consisted of children with a positive polymerase chain reaction (PCR) in amniotic fluid and virus isolation in urine in the first week of life, and normal fetal ultrasonographic (US) examination findings, including a normal multiplanar neurosonographic evaluation. Patients with abnormal magnetic resonance (MR) findings were not excluded. The study and control groups were evaluated for cognitive, language, and motor development at one follow-up examination conducted at 11–81 months of age.

Results Children with congenital CMV infection and normal fetal brain findings in the US examination did not differ from the control group in terms of cognitive, language, motor, emotional–behavioral, and executive functioning. There were no differences between congenitally infected children who had a normal fetal brain MR examination and children whose fetal brain MR examination raised suspicion of a possible brain insult.

Conclusions Normal neurosonographic examinations during pregnancy appear to predict a normal early neuropsychological outcome in fetuses with congenital CMV infection. Outcome did not correlate with suspected abnormal white matter on fetal MR imaging.

KEY WORDS: cytomegalovirus; prenatal diagnosis; ultrasound; MRI; neurodevelopmental outcome

INTRODUCTION

Cytomegalovirus (CMV) is the largest member of the virus family Herpesviridae that infects almost all humans at some point in their lives (Ross and Boppana, 2004). Congenital CMV infection is most likely to occur following primary infection during pregnancy, and it is less common in cases of reactivation of the disease or infection by a different CMV strain (Boppana *et al.*, 1999; Enders *et al.*, 2001). The prevalence of congenital CMV infection varies between 0.15 and 2.2% (Ross and Boppana, 2004; Ross *et al.*, 2006; Malm *et al.*, 2007). While most infants born with congenital CMV infection are asymptomatic, 10–15% show clinical findings at birth (Ross and Boppana, 2004).

It is generally agreed that congenital CMV infection, whether it is symptomatic or not, is a major risk factor for perceptual deficits. However, its influence on children's future neuropsychological functioning is less well established. Symptomatic congenital CMV infection is a major risk factor for poor developmental outcome (Williamson *et al.*, 1982; Conboy *et al.*, 1986) but the available data regarding neuropsychological outcome for asymptomatic children is inconsistent (Conboy *et al.*, 1986; Ivarsson *et al.*, 1997; Kashden *et al.*, 1998; Temple *et al.*, 2000; Zhang *et al.*, 2007).

Several studies based on imaging techniques have shown that the presence of microcephaly at birth and/or intracranial pathologies is associated with a very high risk of neurological abnormalities and mental retardation (Boppana and Fowler, 1997; Noyola *et al.*, 2001; Ancora *et al.*, 2007).

Imaging studies from prenatally diagnosed children are scant and contradictory. Some studies have shown that the presence of abnormal brain findings in the US examination is highly suggestive of a poor neurodevelopmental outcome (Lipitz *et al.*, 1997; Malinger *et al.*, 2003b; Benoist *et al.*, 2008a). Other studies found that

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A new trend in CMV infection….

- **Since 2006**, a percentage of women with **positive amniotic fluid** for CMV, chose to continue their pregnancy
- US and fetal MRIs were carried out on all the mothers
- Most mothers had **normal US and MRIs**
- **Abnormal imaging-TOP**
- **Since 2007**, infants born to these mothers have been attended our clinic.

Presentation aims

- To evaluate the **outcome** of infants born to mothers with positive amniotic fluid for CMV after primary infection in the first and second trimester.

- Short- and intermediate term follow-up of these infants .

Patients and Methods

The diagnosis of primary CMV infection:

1. **Seroconversion of IgG** from negative to positive during pregnancy;
2. **Low IgG with low avidity** in the presence of specific **IgM** and a significant rise in **IgG** at a later date
3. **Clinical symptoms** (fever >10 days, rash, weakness, elevated liver enzymes, thrombocytopenia) in the presence of positive specific **IgM** and increased titers of IgG with low avidity.

Amniocentesis

- Amniocentesis to detect fetal CMV is performed after **21 completed weeks** of gestation and at least **7 weeks** after the assumed date of infection.
- **Fetal CMV infection** is diagnosed when the virus is detected in the amniotic fluid by both **PCR** and rapid **shell vial culture**.

Follow up during pregnancy

- Fetal brain US
- Fetal brain MRI
- **Normal fetal brain imaging**

Post natal evaluation

- **Funduscopy**
- **Ultrasonography** (brain US)
- **Blood tests**, CBC, liver and kidney function.
- **Brainstem evoked response audiometry** (BERA) during the first 2 weeks of life and again every 3-6 months through age 2 years.
- **behavioral hearing tests** are performed from age 2 to 5 years.
- **Tympanometry** is performed in patients with an abnormal BERA test and suspected conduction problems. If middle ear dysfunction is found, BERA is repeated after a few weeks, and only the bone-conduction results are used.

Early- and intermediate-term postnatal follow-up

- **Full physical examination** and neurological and developmental assessments are performed in the neonatal period, and every 3-6 months thereafter.
- **Bayley Scales** of Infant and Toddler Development, 3rd Edition (Bayley-III) was administered to a subgroup of the patients at age 1-3 years by a clinical psychologist

Treatment protocol

- IV ***ganciclovir*** 5mg/kg twice a day for **6 weeks** followed by oral ***valganciclovir,*** 17mg/kg/dose in 2 daily doses for another **6 weeks** and then 1 daily dose for **9 months. (2007- 2011)**
- **Valganciclovir** 17mg/kg/dose in **2 daily** doses for **12 weeks** followed by 1 daily dose for **9 months. (2011-2014)**

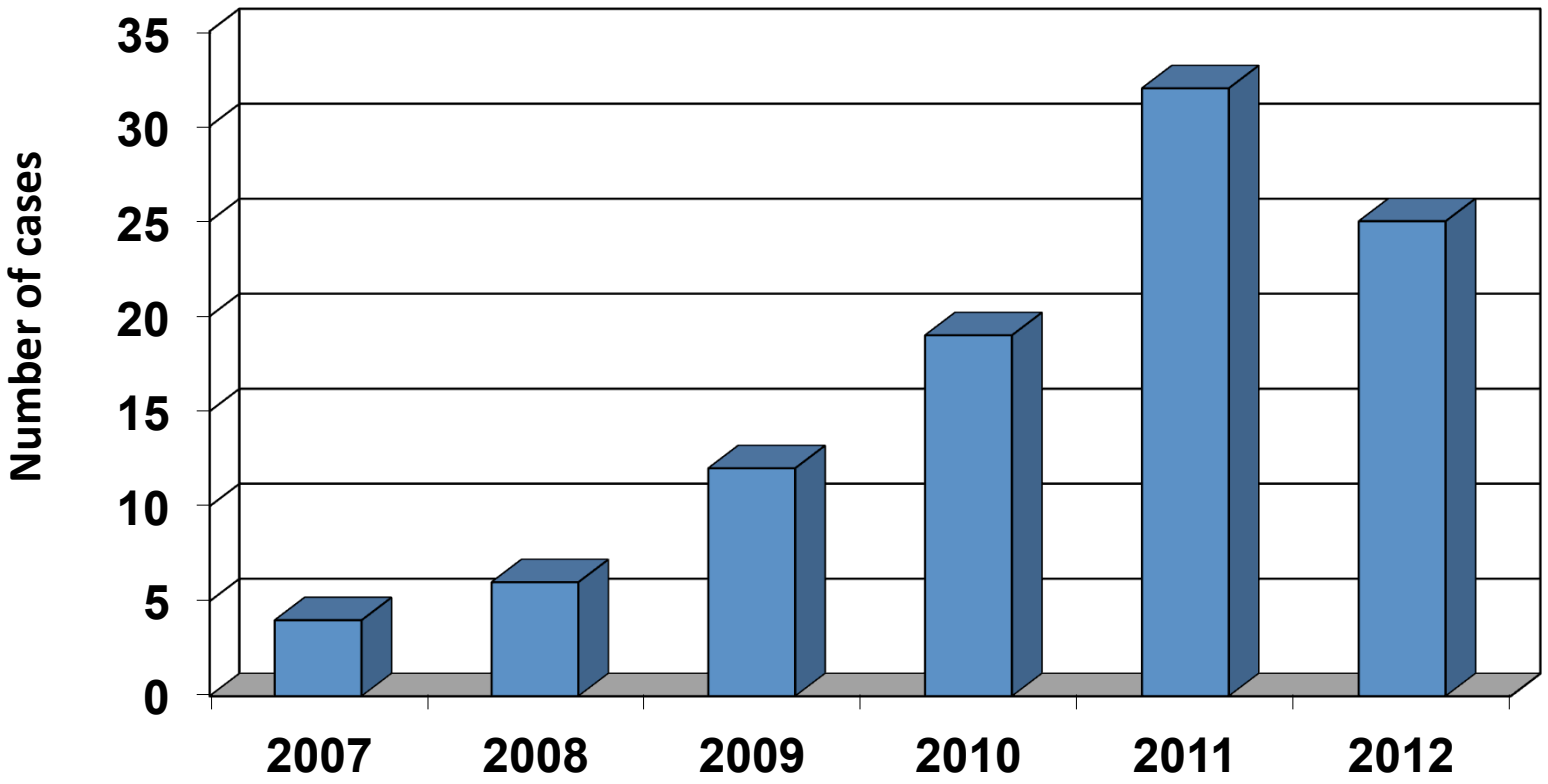
Results

Between January 2007 and January 2013, 101 infants (>1Y) with known primary maternal CMV infection in our clinic.

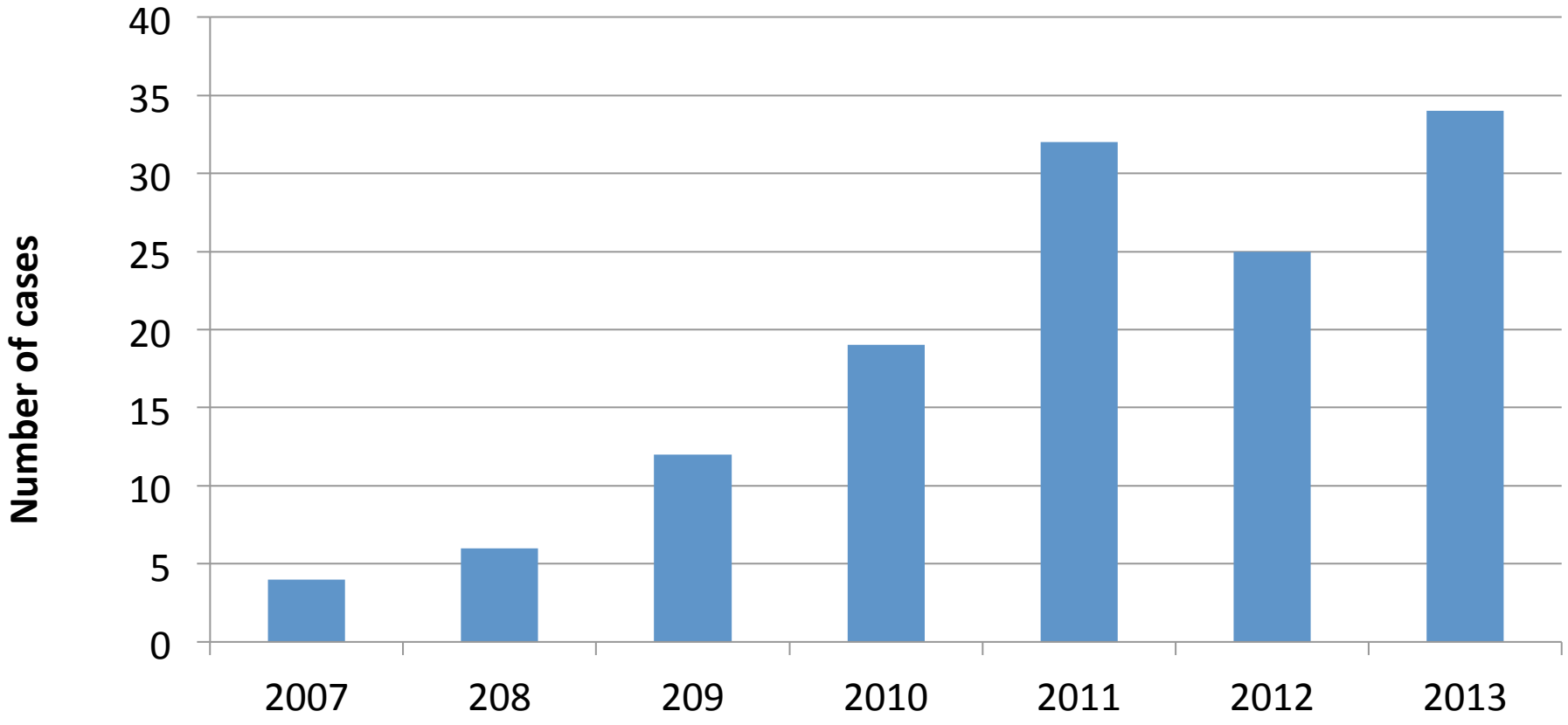
3 cases were lost to follow-up

- All infants were diagnosed by positive amniotic fluid confirmed by positive urine culture after birth.
- 98 are seen routinely in our clinic

98 Infants borne to mother with positive amniotic fluid for CMV



132 Infants borne to mother with positive amniotic fluid for CMV



Data on maternal CMV infection

- Primary CMV infection in all
- First trimester - 52 cases
- Second trimester - 46 cases
- Amniocentesis performed-mean 27.5±4.8 wks. range- 21-36 wks.

Clinical data of 98 infants born after pregnancy with amniotic fluid positive for CMV

- Full term infants – **92**
- Preterm infants – 6 (34-36 weeks)
- Birth weight – mean **3094 ± 494** grams
- **A.G.A – 94** infants (96%)
- **S.F.D** – 4 infants (1900, 2300, 2460,2490 Gr')

Table 1 Postnatal signs and symptoms in infants with congenital CMV infection (n=98), by trimester of infection

Signs & symptoms	1st trimester N=52 (%)	2nd trimester N=46 (%)	P
Abnormal brain US	25 (48.1)	21 (45.7)	0.671
Small head circumference.	4 (7.7)	2 (4.4)	0.542
Thrombocytopenia	3 (5.6)	1 (2.2)	0.442
Elevated liver enzymes	2 (3.9)	2 (4.4)	0.885
Chorioretinitis	1 (1.9)	0 (0)	0.557
Splenomegaly	9 (17.3)	9 (19.6)	0.769
SNHL* (ears)	16 (15.4)	9 (9.8)	0.240

* SNHL-sensorineural hearing loss

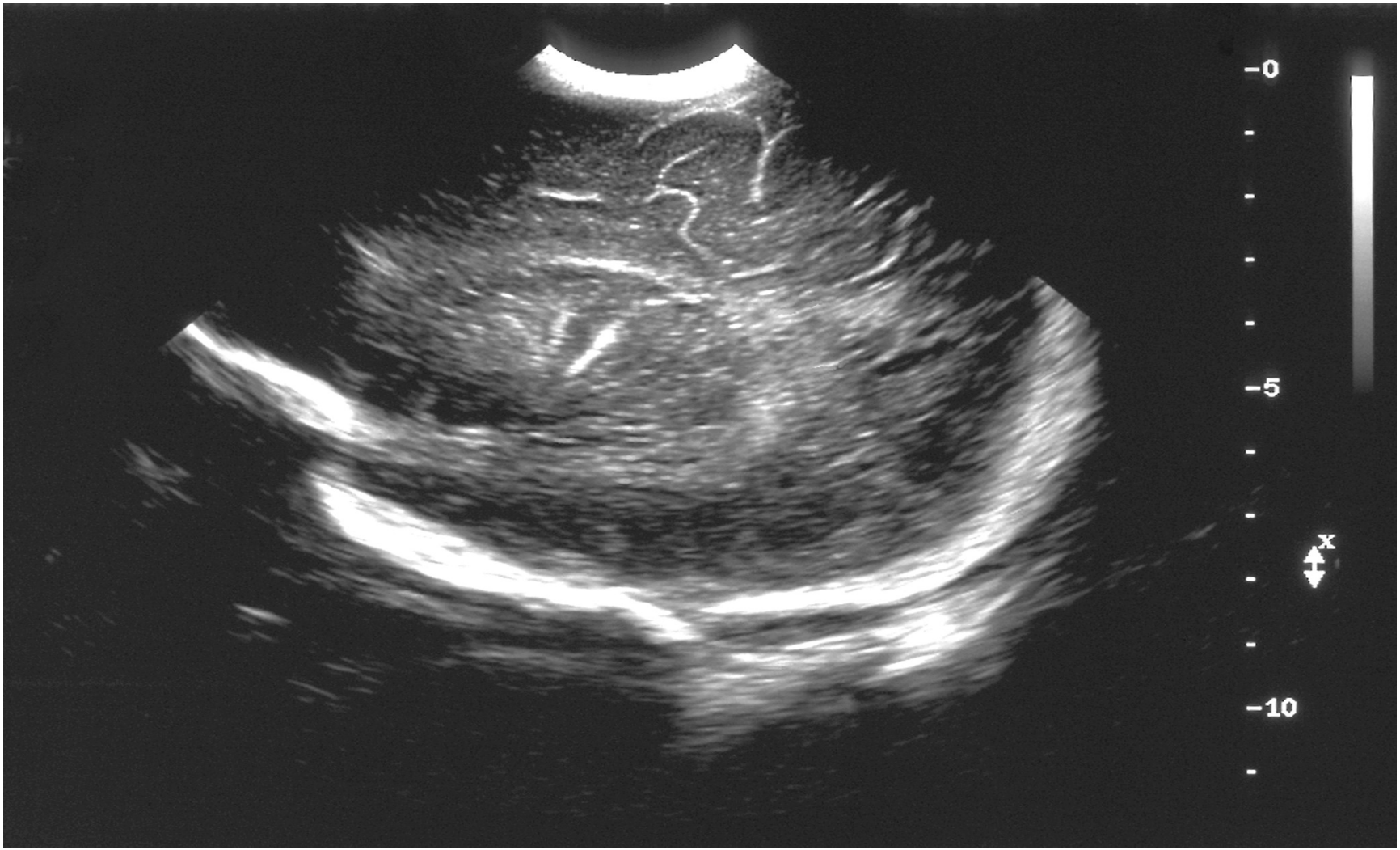
Indication for anti-viral treatment

- Brain imaging – ultrasound
- Hearing loss
- Chorioretinitis
- Microcephaly

Spectrum of brain US abnormalities in congenital CMV

- Calcifications
- Ventricular dilatation
- Periventricular hyperechoisity
- Periventricular pseudocyst
- Lenticulostriated vasculopathy (LSV (

LSV in congenital CMV



Brain US in 98 infants with congenital CMV infection and normal fetal US and MRI

- Normal brain US -52 infants (53%)
- Abnormal brain US – **46** infants **(47%)**

  LSV – 44/46 (95.7%)

  Periventricular hyperechoisity – **1**

  Calcifications (small) **-1**

First hearing BERA in 98 (196 ears) infants with congenital CMV infection

Hearing	Number of ears	%
Normal	171	87.2
Mild hearing loss	13	6.6
Moderate hearing loss	9	4.6
Sever hearing loss	3	1.5

Hearing loss in 12.8%

Treatment with ganciclovir/ valganciclovir

- **52 infants were treated in the first mo -53%**
- **An additional 5** infants started treatment for late onset SNHL (total 58.2%)
- 20 patient started IV ganciclovir
- 37 patient only oral valganciclovir


Follow-up

Follow-up of 98 children

- The mean duration of follow-up was **35.1±16.1** months
- Infants infected during the first trimester were followed for significantly less time than those infected during the second trimester (**29.7±14.2** versus **41.0±15.6** months, **P<0.001**).

Table 2. Initial and last assessments of hearing levels in 98 infants (196 ears) with congenital CMV infection

Hearing level (SNHL)	Initial study	Last study
Normal (<25dB)	171 (87.2)	186 (94.9)
Mild (25-44 dB)	13 (6.6)	4 (2.0)
Moderate (45-69 dB)	9 (4.6)	2 (1.0)
Sever (≥70 dB)	3 (1.5)	4 (2.0)

Last hearing BERA in 98 children with congenital CMV infection **(best ear)**

Hearing	Number of cases	%
Normal	**96**	**98**
Mild hearing loss	**0**	**0**
Moderate hearing loss	**0**	**0**
Sever hearing loss	**2****	**2**

** **Cochlear implantation**

Developmental outcome

- **All 98** children were **attending regular educational institutions. 5** were in first or second grade, **40** in kindergarten, and **53** in day-care centers.
- **Two** children experienced mild motor delays (started independent walking at 18 and 19 months).

Bayley Scales of Infant Development

- The BSID was administered by a trained psychologist
- **27** infants age 12- 33 months were studied
- The mean mental developmental index (MDI) was **102.6 ±10.3** (range 85-127).

Small head circumference

- **Six** patients had a small head circumference on initial examination
- **Two** patients with a small head circumference had normal findings on the next clinic visit.
- **Two** measured in the third percentile at the last follow-up.
- **Two** remained below the third percentile.

Chorioretinitis

- The patient with chorioretinitis had **normal vision with a small retinal scar.**

Conclusions I

- Infants with congenital CMV infection, born after primary maternal infection in the 1 and 2 trimester and **normal fetal imaging** (US & MRI) may have post-natal abnormal findings:
- Abnormal brain US – 47%
- Hearing damage (ears) – 13%

Conclusions II

- **High rate** of anti-viral treatment – **58%**
- **52** infants were treated in **the first mo -53%**

  5 infants treatment for late onset SNHL **-5%**
- The prognosis after short-term-intermediate follow-up is good:

  2% (2 cases) with significant hearing sequela -cochlear implantation

Conclusions III

- Overall, the outcome of these infants is good, with a low rate of sequelae on short- and intermediate-term follow-up.


THANK
YOU