NEONATAL CASES

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Patient 1

- mother : primigravida, GBS+, 1 dose peni
- vacuümextraction for fetal distress
- ♂, 3.340kg, 51cm, 35cm, term
- Apgarscore: 9/9
- Iraqi, consanguinity
- bloodculture taken because of incomplete antibiotic coverage

Day 2 : parents want to go home

- Breastfeeding, weight -10%
- Clinical exam : alert, icterus, no abnormalities
- bilirubin : 13,9 mg/dl

  Coombs negative

→ breastfeedingjaundice

- fototherapy and feedingsupplements

Day 3 : Subfebrilitas temp 37.9 C

- Feeding well
- Mildly lethargic, icterus, fontanel normotone, normal perfusion
- bilirubin 16 mg/dl
  CRP 3 mg/l
  leucocytosis 6.700/mm³
  neutrophils 52%
  natrium 143 mmol/l
  bloodculture (umbilicalcordblood) : sterile

Evaluation

- dehydrationfever in context of weightloss due to suboptimal milkproduction and hyperbilirubinemia

or

- infection

Evaluation

- **dehydrationfever** in context of weightloss due to suboptimal milkproduction and hyperbilirubinemia

or

- infection

→ continue phototherapy and close observation

Day 4: temp 38.5 C on bilibed

- infant in good general condition, well hydrated and circulated, somewhat irritable, still jaundice
- quid sepsis?
- sepsisscreening
  - bloodculture
  - urineculture (bag)

- leucocytes : 8.400/mm³
- neutrophils 63 % - lymphocytes 20 %
- platelets : 202.000/mm³
- CRP 10 mg/l
- bilirubin 18 mg/dl
- urine : *E. Coli* 10-100.000/ml

Would you do a lumbar puncture ?

- A: yes
- B: no

- Cerebrospinal fluid

  leucocytes : 3.8/µl – no differentiation done

  protein: 332 mg/l

  glucose : 73 mg/dl
- start amoxicilline en amikacin
- extra IV fluid and double fototherapy
- G-6-PD-deficiency : stop vitamin K and follow hemolysis

Day 5-7 : persistent fever

- Feeding well (expressed milk), diarrhea
- icterus, irritable when manipulated, rhinitis, vesicle on tip of tongue, palpable liver, no spleen palpable
- bloodculture, urine (suprapubic puncture), lumbal puncture, faecesculture : negative
- leucocytes 5.100/µl N 32 % - L 43%
  bilirubin 6 mg/dl (unconjugated)
  CRP 50 mg/l
  AST 103 mmol/l, ALT 38 mmol/l
  γGT 104 mmol/l

What is your first diagnosis ?

- A: (para)influenza
- B: enterovirus
- C : adenovirus
- D: herpesvirus

Further anamnesis

- Mother feels tired and was sweating at night (fever ?). She has painful nipples. Never had cold sores.
- Father has recurrent labial herpesinfections, recently 2 weeks before the delivery during 3 days. Did not want to cuddle the baby.

complementary diagnostic tests : virology

- swab oro-naso-pharynx : culture
- swab lesion tongue : culture
- faeces : culture
- new lumbar puncture for PCR

Would you stop the antibiotics ?

- A: yes
- B: no

Would you consider to treat with acyclovir ?

- A: yes, 3 x 15 mg/kg IV
- B : yes, 3 x 15 mg/kg per os
- C : yes, 3 x 20 mg/kg IV
- D : yes, 3 x 20 mg/kg per os
- E : no, wait for viral cultures
- F : no, wait for PCR CSF

When to initiate acyclovir in a newborn ?

- Sepsis syndrome (incl. hypothermia), particularly if accompanied by liver dysfunction (AST) or skin vesicles
- Fever and irritability with abnormal CSF findings (mononuclear predominance) particularly when accompanied by seizures
- “Rule-out” hospitalisation 3-5 days

- HSV-infection is very rare

AND

- Acyclovir has possible side-effects :
  - neutropenia (20%) – harmful if serious bacterial infection
  - nephrotoxicity : adequate hydration
  - resistant virus
  - pharmacokinetics in VLBW-infants ?

clinical evolution week 2

- worsening clinical condition
- gray and pale infant, irritable, poor perfusion
- tachycardie 180/min

  tachypnoe 60-80/min
- hepatosplenomegaly

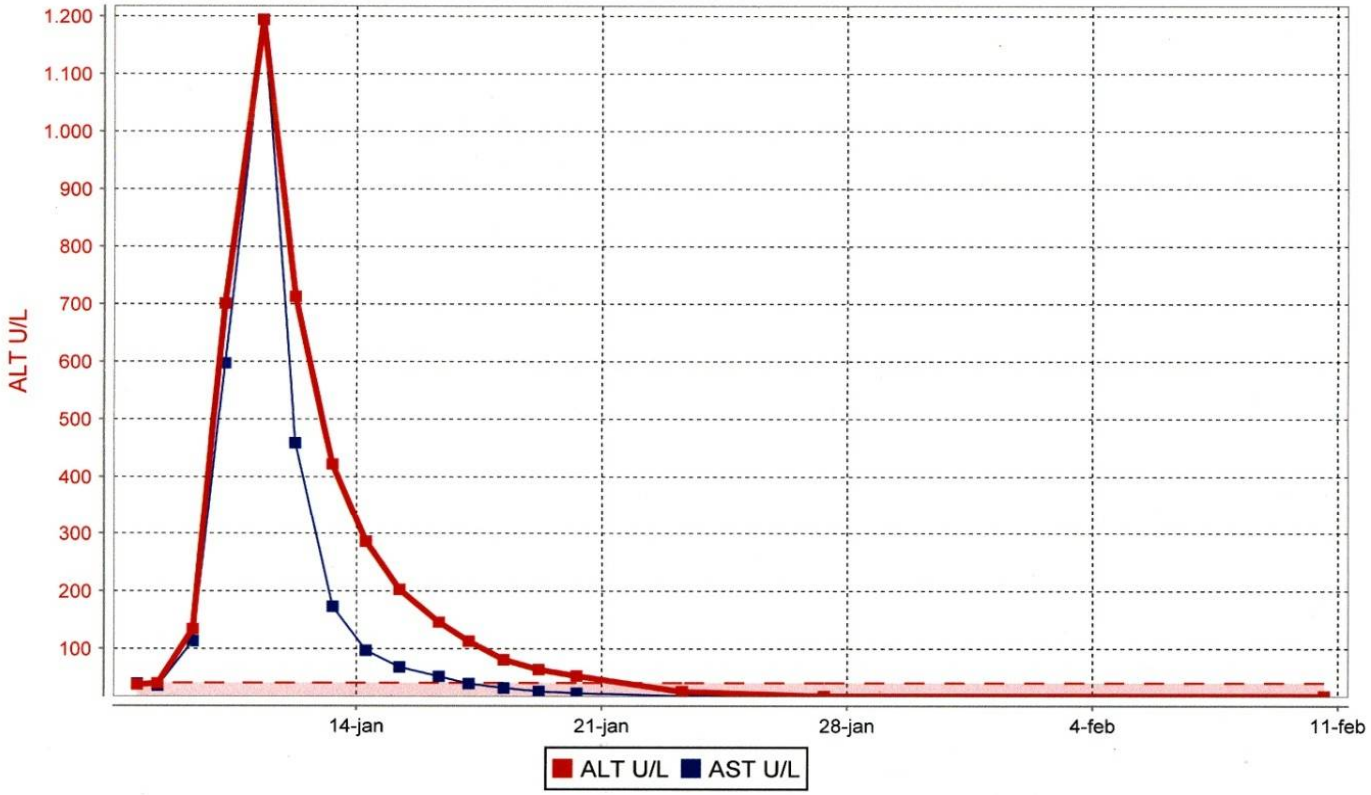
Results virology (day 7)

Ag-detection	
faeces	
Adenovirus type 40-41	negative
Rotavirus	negative
Culture followed by Ag-detection	
swab oro-naso-pharynx	
Adenovirus	negative
Parainfluenzavirus	negative
Virusisolation on celculture	
faeces : virusisolation (entero,adeno)	negative
swab oro-naso-pharynx	
virusisolation (entero,adeno)	negative
Virusisolation (infl,RSV,hMPV)	negative
Virusisolation (HSV)	positive Herpes simplex, type 1
Virology Serology blood	
Herpes simplex virus IgG	negative
Herpes simplex virus IgM	negative
Molecular test :	
swab oro-naso-pharynx	
Influenzavirus A PCR	negative
Influenzavirus B PCR	weakly positive
RSV-A PCR	negative
RSV-B PCR	negative
hMPV PCR	negative
cerebrospinal fluid	
Herpes simplex virus 1 PCR	*very weakly positive for HSV1 (retest)*
Herpes simplex virus 2 PCR	negative
Enterovirus PCR	negative

- Increase in liverdysfunction
  maximum AST 4000 U/l
- Serum day 9 : IgM positive 1.4 OD/cutoff
- CSF day 10 : HSV-1 PCR strongly positive
- Swab nipple mother : HSV-1 positive

Evolution

- fever for 14 days in total
- liverenzymes decrease progressively, hepatosplenomegaly↓
- clinical recovery from day 17 on
- on full enteral feeds on day 19
- total IV treatment 21 days acyclovir, 5 days IV immuneglobulins
- normal oftalmological examination
- normal neuromotor development and imaging at 3 months of age


1.200
1.100
1.000
900
800
700
600
500
400
300
200
100
ALT U/L
14-jan
21-jan
28-jan
4-feb
11-feb
ALT U/L
AST U/L

Response to treatment

- PCR blood
  - Day 1 : Ct 23.4
  - Day 9 : Ct 24.1
  - Day 13 : Ct 27.9
  - Day 20 : Ct 36.1

Would you consider to continue treatment beyond 3 weeks ?

- No
- No, only if LP is repeated and CSF PCR is negative at 21 days of treatment
- Yes, oral acyclovir for 6 months

patient 2

- first pregnancy
- CMV-primo-infection 1st trimester

IgG at 10 weeks	152 AU/mL
IgM	3 .6 OD/cutoff
IgG avidity	low 44 %
urine	negative

Amniocentesis ?

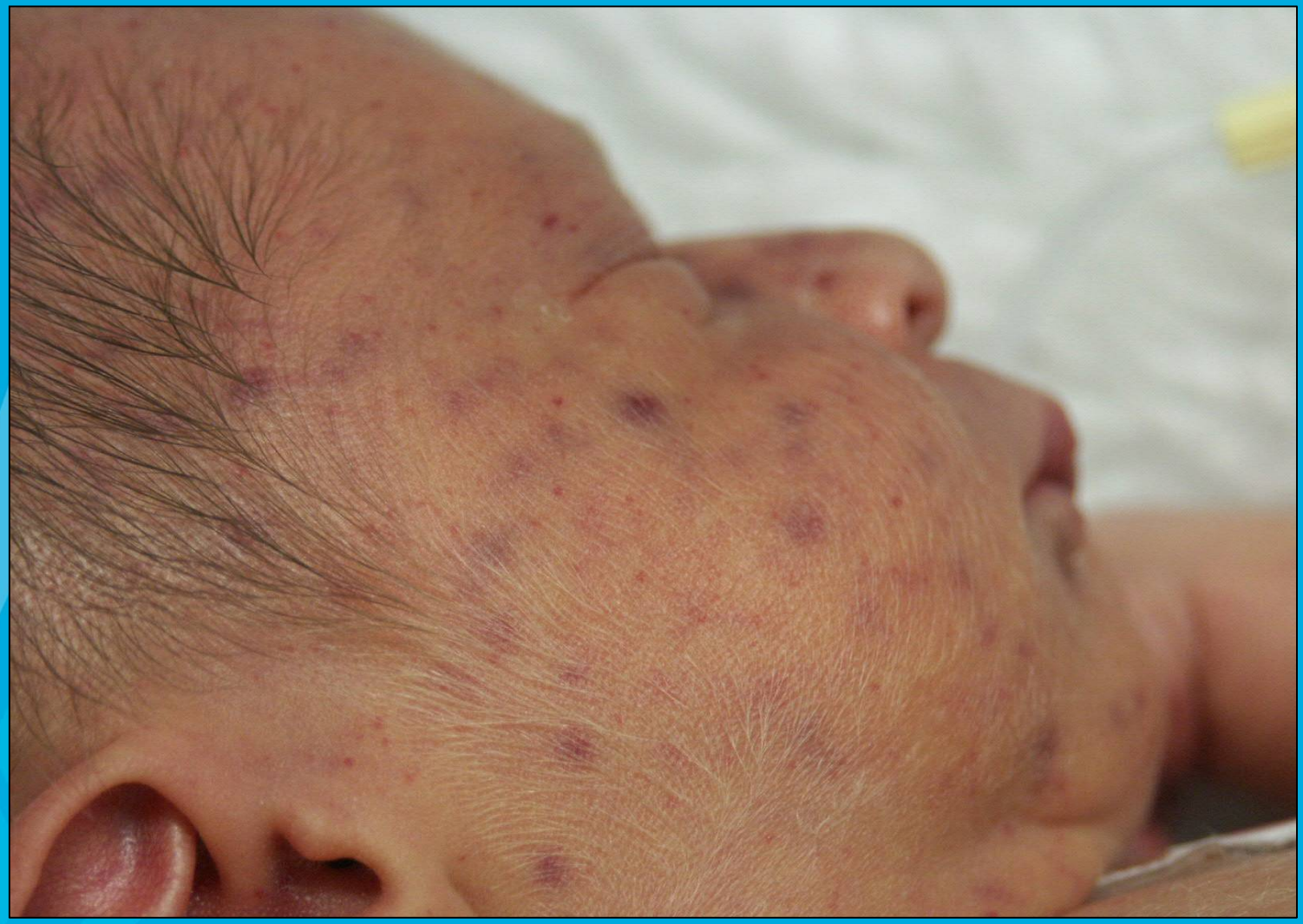
- A : Not indicated because no therapy available
- B : Useful for planning of follow-up
- C : Clinical predictive value of PCR quantification of CMV DNA in amniotic fluid

- Amniocentesis discussed but refused
- First signs of fetal infection at 32 weeks
  - US : mild ventriculomegaly, periventricular hyperechogenecity
  - NMR : occipital 'pseudocyst‘ ventriculitis-sequel, discrete hyperintens periventricular white matter, splenomegaly
- FU at 36 wks :

  growth P42, brainsparing, no other changes

A boy is born

- PML 37.6 wks
- BW 2440 g (P3) – L 47 cm (P25) – HC 32 cm (P3)
- Apgar 9-10
- Petechiae, splenomegaly



- Thrombocytes : 28.000/mm³
- Culture and Ag-detection : urine CMV positive
- Virology Serology serum

  IgG positive > 250 AU/mL

  IgM negative
- Molecular test blood PCR CMV DNA : 161.560 copies/mL (5 .21 log copies/mL)

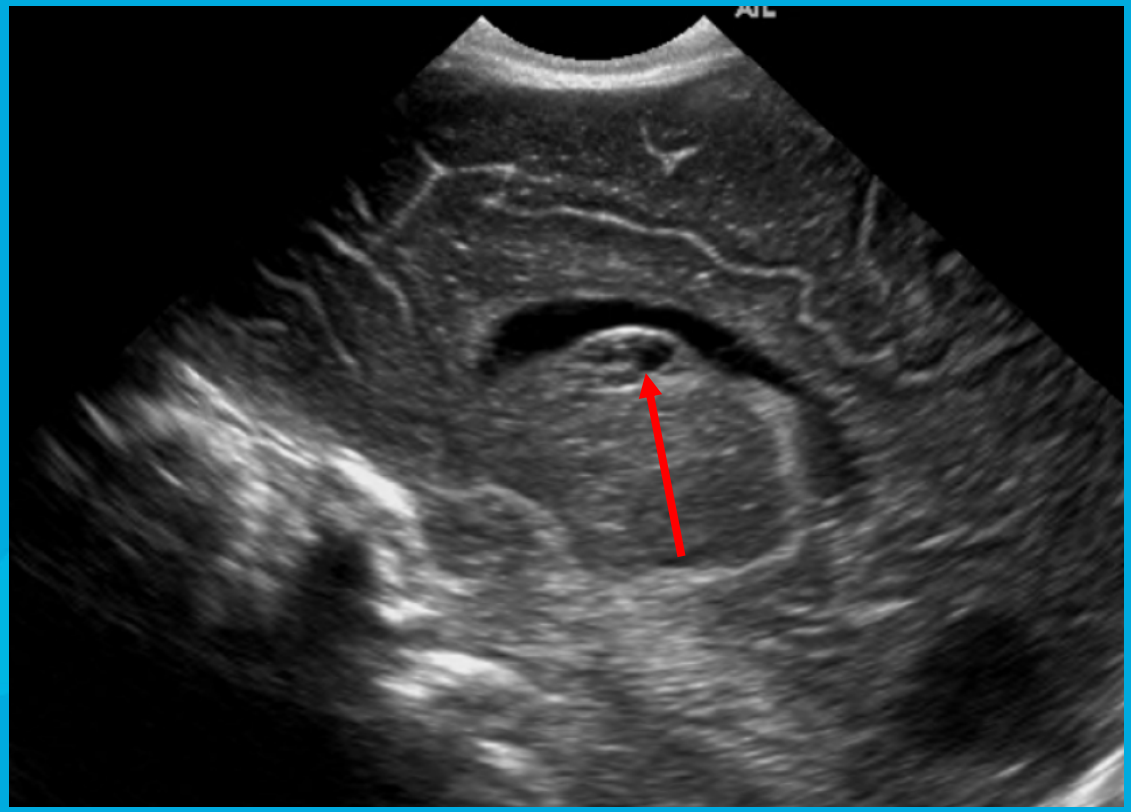
Neonatal work-up

- US – MRI scan
- Hearingtest – BERA audiometry
- Ophtalmologic examination

Is a lumbar puncture necessary ?

- A : no
- B : yes
- C : yes, if no other signs of CNS-involvement

- US : supependymal cysts + germinolysis
- MRI : generalised dys/demyelinisation of white matter
- BERA : R 50 dB – L nl
- Ophtalmo : no chorioretinitis



Would you give gancyclovir ?

- A : No, only if life-threatening infection
- B : No, because of severe side-effects in neonates
- C : Yes

Selecting neonates with congenital CMV infection for gancyclovir therapy

- Disseminated disease (+/- CNS-involvement)
- symptomatic CNS involvement at birth, excl. treshold > 100 dB at BERA audiometry

– 2 or more signs of disseminated disease

- Small for gestational age (< P3).
- Petechiae
- Hepatosplenomegaly
- Thrombocytes < 75.000/mm^3.
- Alanine aminotransferase (ALT = SGPT) > 100 U/L.

– CNS involvement :

- Clinical: microcephaly, convulsions
- Biochemical: changes in CSF
- Neuro-imaging: calcifications, multiple periventricular ypodensities (subependymal pseudocysts), cortical atrophy, ventriculomegaly, hyperechogeniciteit in de caudothalame groeve, cystische leukomalacia, vermishypoplasia, abnormal gyration, hyperdensity of white matter (MRI). *Excluding isolated striatal vasculopathy and isolated single periventricular pseudocyst*.
- Neurosensorial: hearingloss (treshold > 35 dB); chorioretinitis

Effect of gancyclovir on hearing in symptomatic congenital CMV disease

- only RCT (n=100; 42 FU at 6 mnd+1jr)
- gancyclovir 6 mg/kg q12 h IV 6 wk versus no treatment; < 1 month
- inclusion : evidence of CNS involvement
  - microcephaly
  - intracranial calcifications
  - abnl. CSF for age
  - chorioretinitis
  - and/or hearingdeficits

Kimberlin, J Pediatr 2003; 143:16

Effect : prevention of worsening hearing

	FU 6 mnths		FU 1 year	
	gancyclovir	no R/	gancyclovir	no R/
improved hearing	22 %	17 %	25 %	0 %
normal – no change	47 %	22 %	23 %	22 %
same loss – no change	31 %	19 %	31 %	17 %
worsening hearing	0 % $p < .01$	41 %	21% $p < .01$	61 %

Hematotoxicity during therapy

Laboratory test	Laboratory values constituting "Significant toxicity"*			Number of patients with stated laboratory abnormality: Ganciclovir (N = 47)‡	No treatment (N = 50)‡	*P* value
Creatinine	<7 days old:		≥2.5 mg/dL	1/44 (2%)	0/42 (0%)	1.00
	7–60 days old:		≥1.5 mg/dL			
	61–90 days old:		≥1.2 mg/dL			
ALT	≥540 IU/L (≥10X Upper limit normal)			0/40 (0%)	0/40 (0%)	–
		Preterm infants	Term infants			
Total bilirubin	3–6 days old:	> 25 mg/dL	>25 mg/dL	11/43 (26%)	7/39 (18%)	0.44
	7–30 days old:	≥36 mg/dL	≥21 mg/dL			
	31–90 days old:	≥6 mg/dL	≥3 mg/dL			
Platelets	<50,000/mm^3			3/45 (7%)	2/41 (5%)	1.00
	Grade 3–4 ANC			**29/46 (63%)**	**9/43 (21%)**	**<0.01**
	Grade 3 ANC					
	2–7 days old:		**750–1,249/mm^3**			
	8–56 days old:		**500–899/mm^3**	**18/46 (39%)**	**8/43 (19%)**	
	57–90 days old:		**250–399/mm^3**			
ANC	**Grade 4 ANC**					
	2–7 days old:		**<750/mm^3**			
	8–56 days old:		**<500/mm^3**	**11/46 (24%)**	**1/43 (2%)**	
	57–90 days old:		**<250/mm^3**			

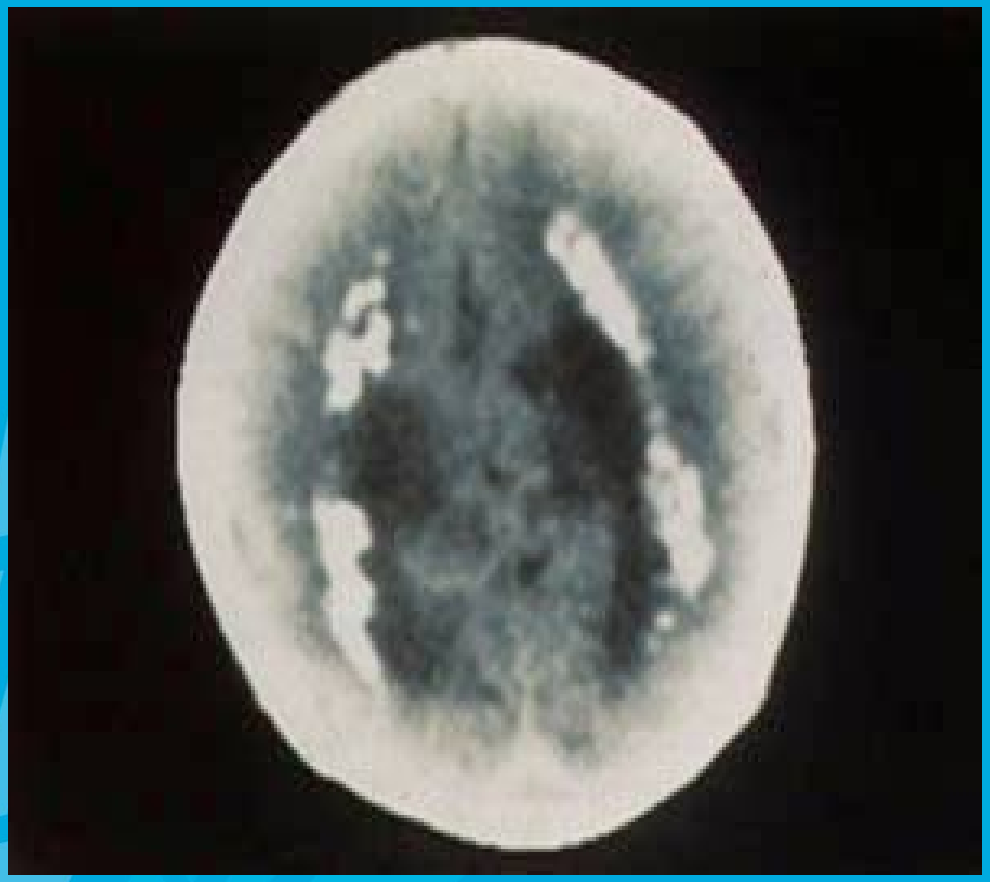
Evolution

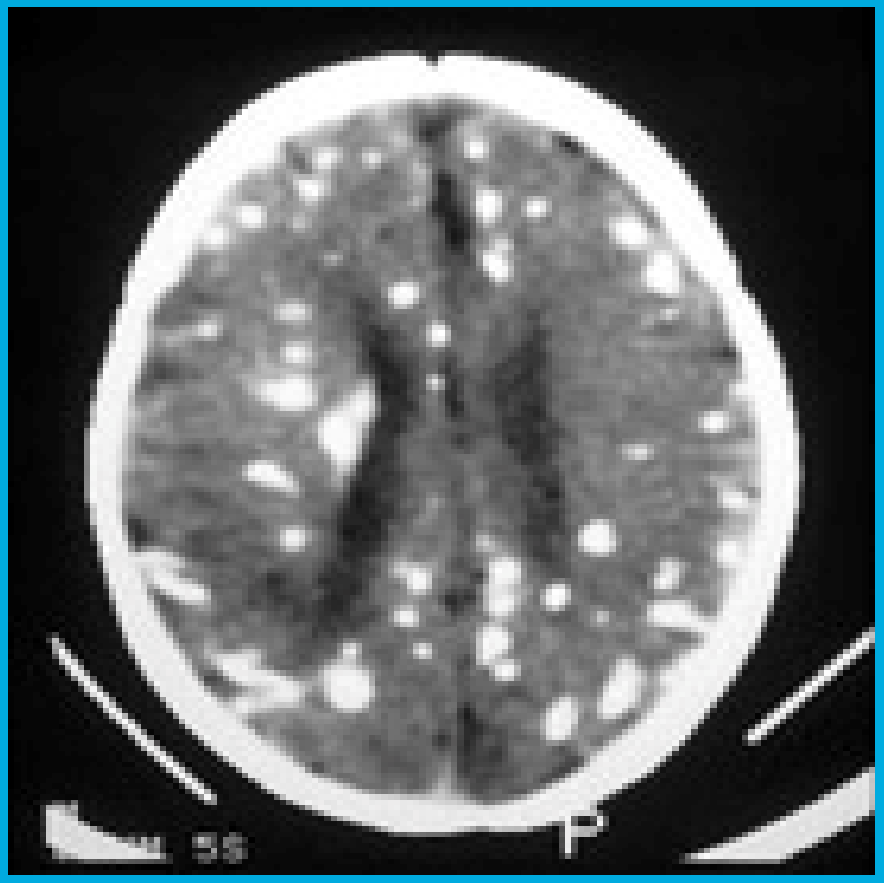
- gancyclovir for 12 + 6 d, interrupted because of severe neutropenia
- progressive hearingdeficit – diabolo for serotympanon – persistent deficit 60 dB unilateral
- mental development BSID-II-NL scale developmental age 24 months at calendar age of 29 months (OI 81). mild retardation of motoric development

Long term outcome symptomatic congenital CMV infection

- mild to severe handicap 90-95%
- psychomotor retardation 70%
- hearing loss 58 % - bilateral 37 %
- chorioretinitis 13 % - epilepsy11 %

Neuro-imaging and long-term outcome



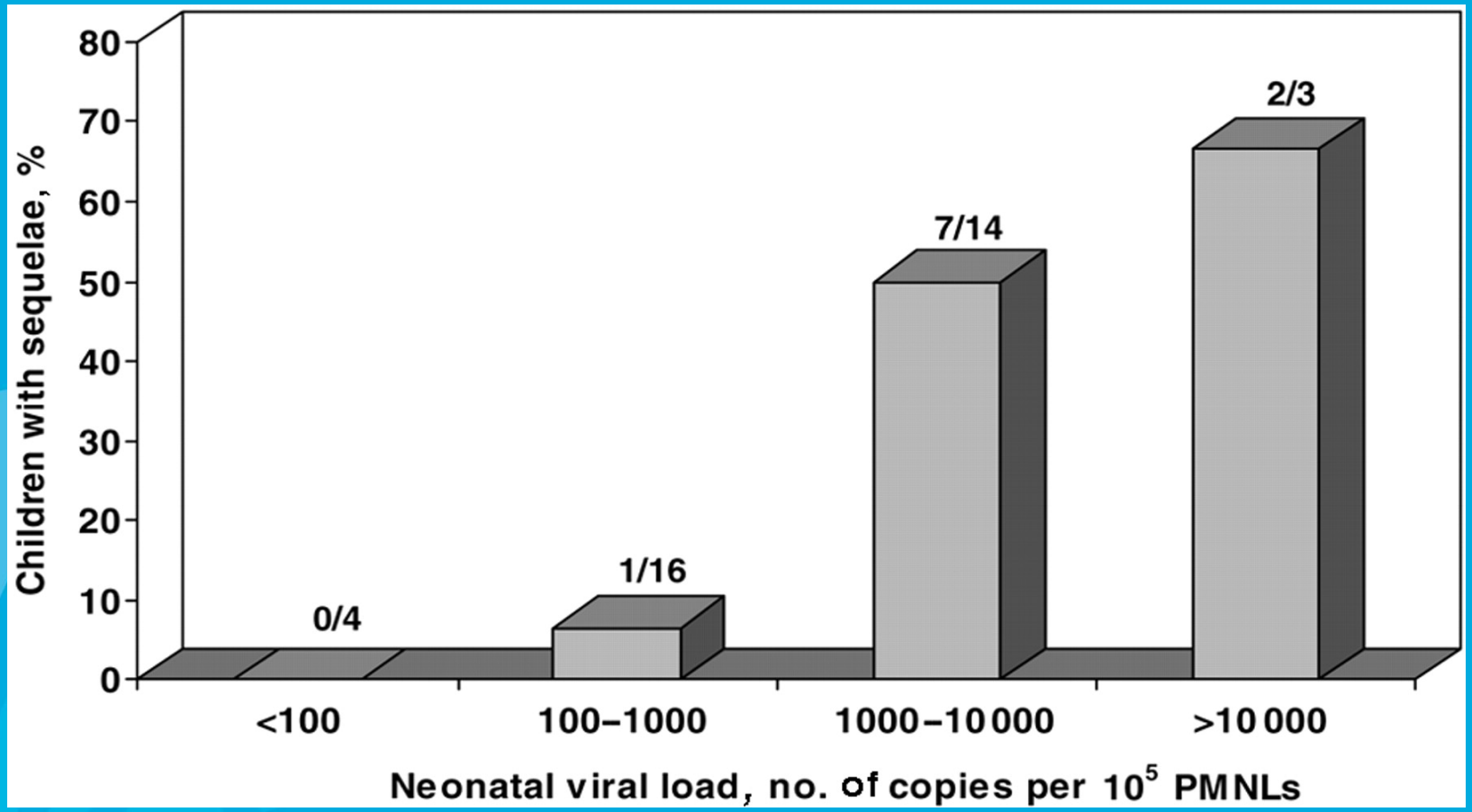


Long term outcome asymptomatic congenital CMV infection (90%)

- 10-15 % sequelae
  - sensori-neuronal hearing loss (15% at 6 yrs)
  - microcephaly
  - psychomotor retardation
  - dental problems
  - chorioretinitis

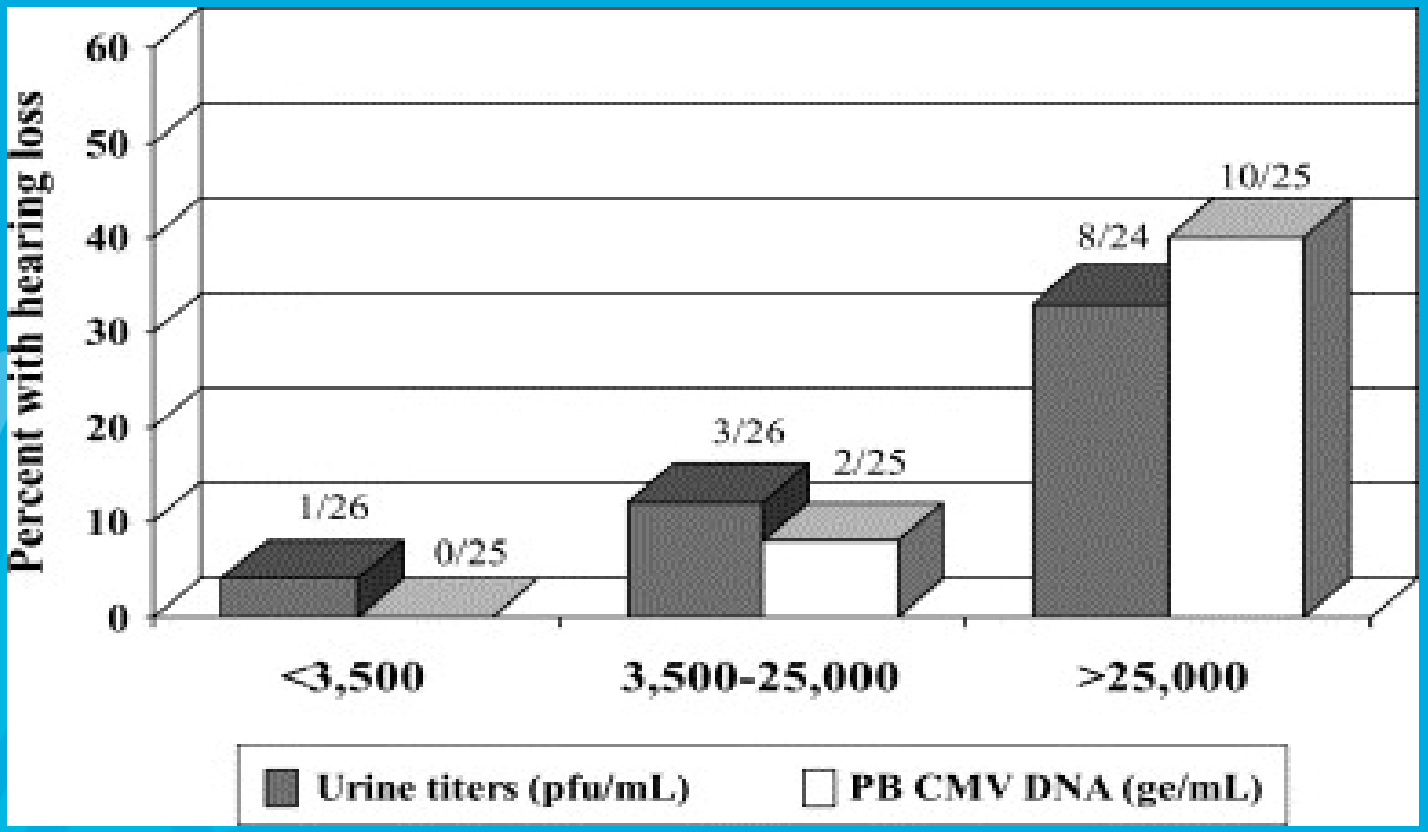
→ **Do we have any predictors for risk for sequelae ?**

The proportion of children who developed sequelae at 12 months according to the neonatal CMV blood load



Lanari, M. et al. Pediatrics 2006;117:e76-e83

The relationship between urine (shaded bars) and PB (open bars) CMV burden and hearing loss in children with congenital CMV infection



Boppana et al, J Ped 2005;146:817-23