Lenticulostriated Vasculopathy and Congenital Cytomegalovirus

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Conflict of interest

- None

The story of G.A

- Date of birth –04.2005
- Pregnancy – primary maternal infection with CMV in the 1st trimester.
- Pregnancy ultrasonographic evaluation – normal.

- Birth: 37weeks. Birth Weight: 2,646 grams
- Positive urine culture for CMV at the age of 1 week.

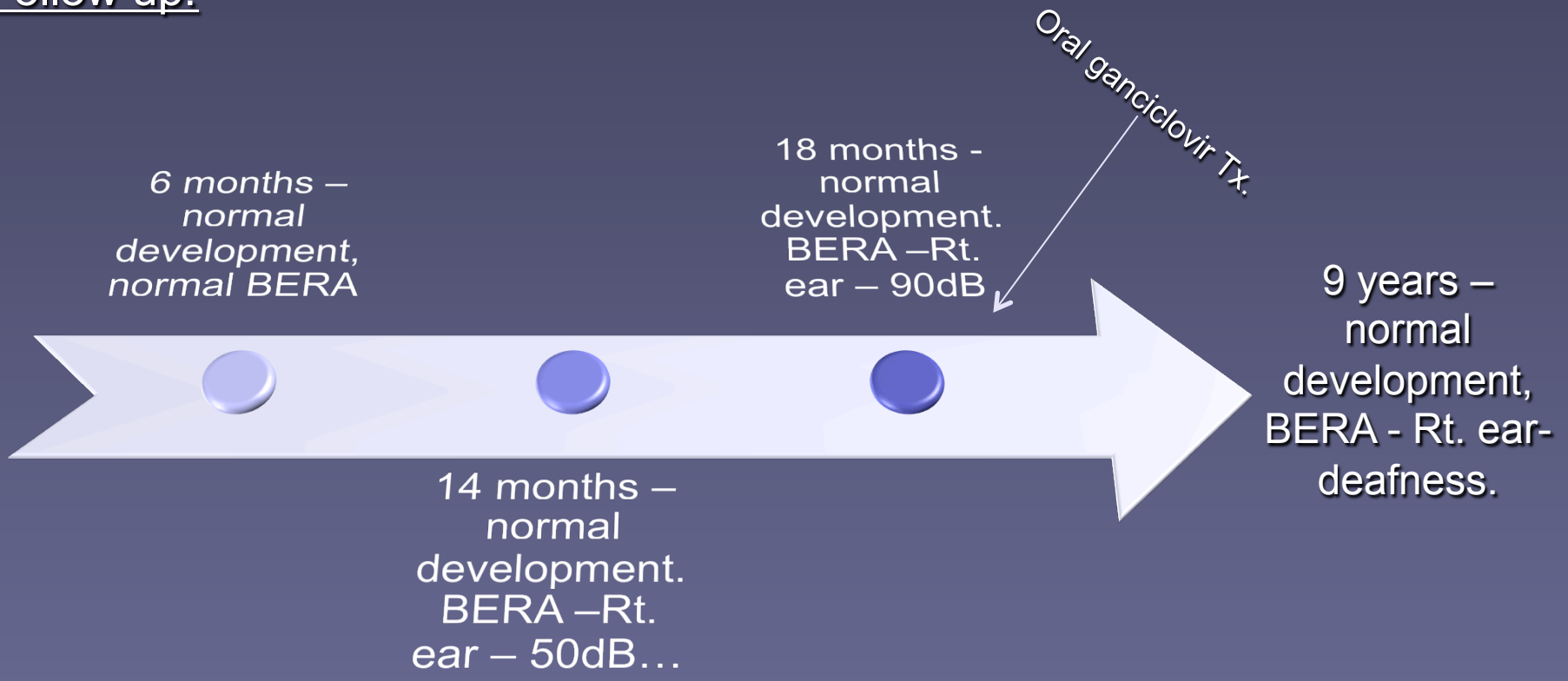
Primary Evaluation for cCMV

- Complete physical examination (including head circumflex) - normal
- Laboratory evaluation (complete blood count, liver and renal function tests) - normal
- Funduscopy - normal
- Brainstem evoked audimetry (BERA) - normal
- Brain ultrasound - Lenticulo-Striate Vasculopathy (LSV) in the right thalamic region. No other abnormalities.

The story of G.A…

Asymptomatic cCMV

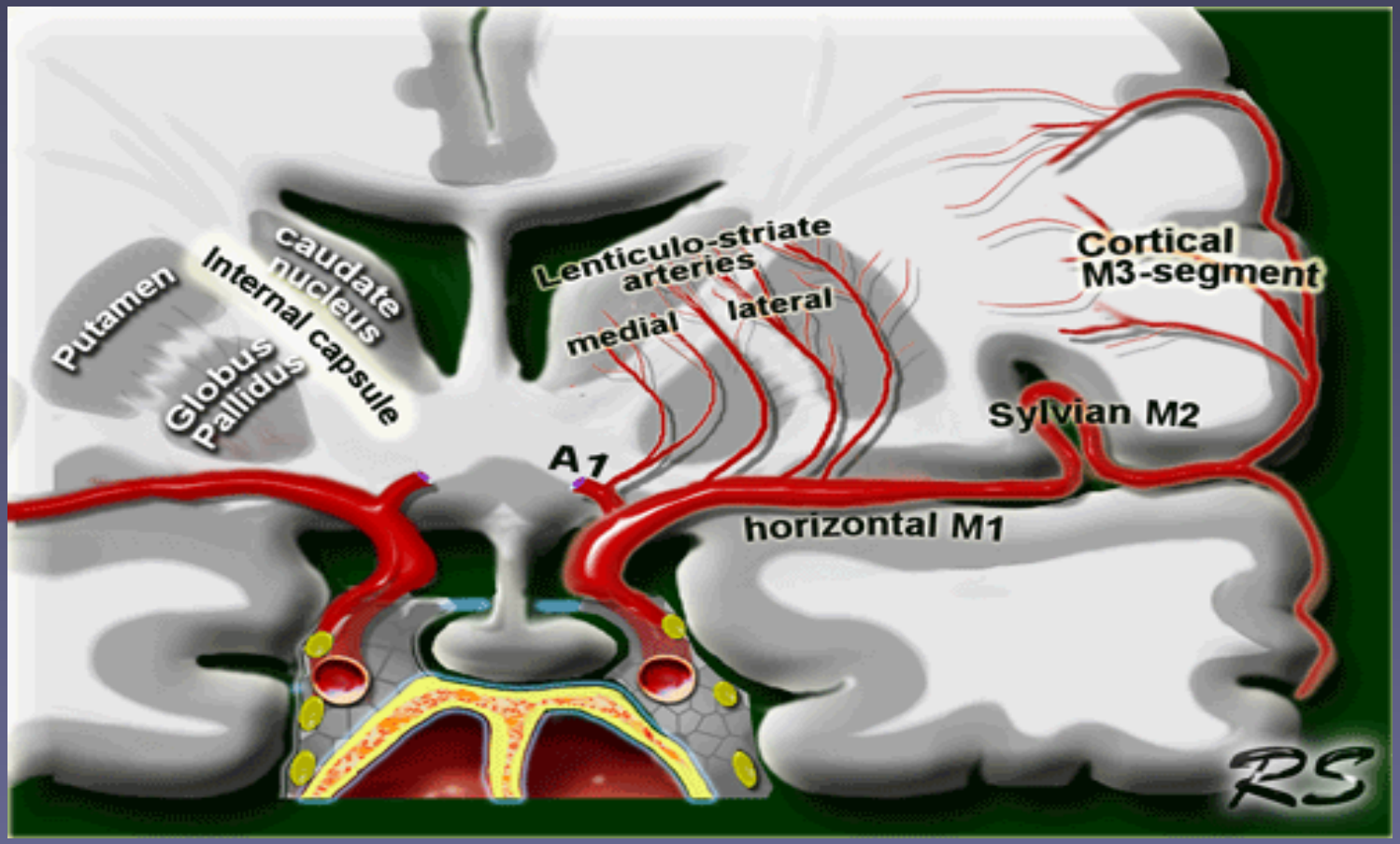
Follow up:



The questions

- Is it a coincidence?
- Is it another case of the natural history of asymptomatic cCMV?
- Should LSV be considered a sign for CNS involvement?

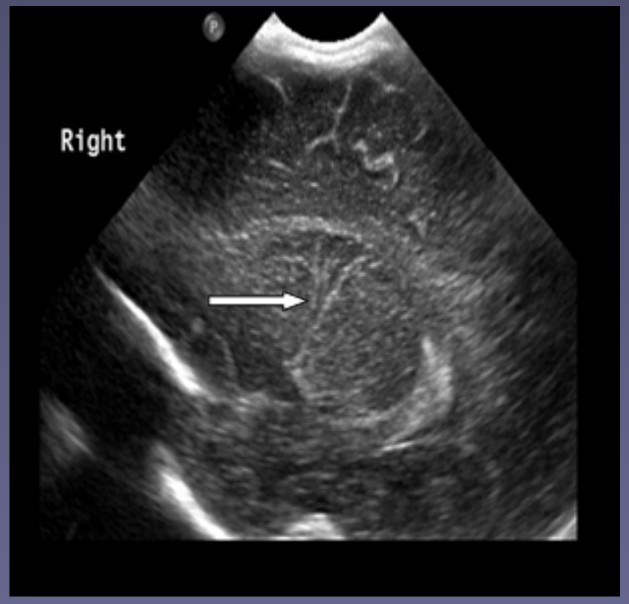
What is Lenticulostriated vasculopathy ?

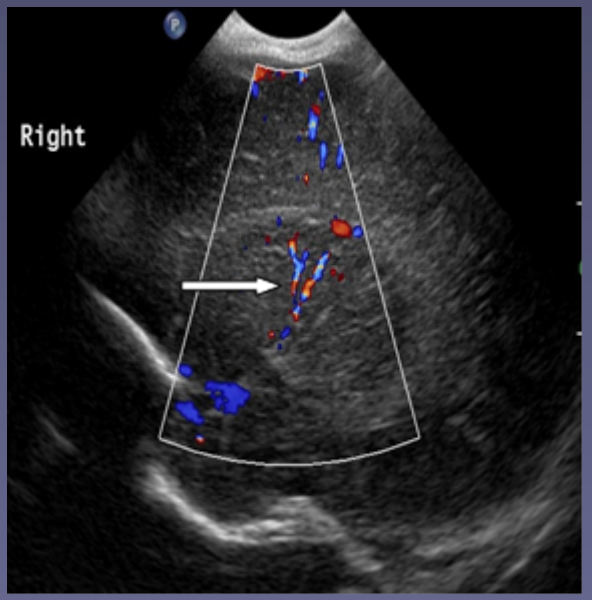


These end arteries are indistinct from the brain parenchyma!

Lenticulostriated vasculopathy

Bright linear *'candlestick-like'* strips in these regions are suggestive of lenticulostriate vasculopathy (LSV)





Lenticulostriated vasculopathy (LSV)

- The rate of LSV detection in neonates has been reported as 0.4% to 5.8%. (variance is attributed to differences between healthy vs. sick neonates, Term vs. preterm, Exc.)
- LSV is associated with many congenital or acquired neonatal disorders including prematurity, fetal alcohol or drug exposure, congenital heart defects, congenital malformations, hypoxic-ischemic conditions and congenital or perinatal infections.

Wang et al. Sonographic lenticulostriate vasculopathy in infants: some associations and a hypothesis. *AJNR Am J Neuroradiol* 1995.

Amir et al. Is lenticulostriated vasculopathy a sign of central nervous system insult in infants with congenital CMV infection? *Arch Dis Child* 2011.

Makhoul et al. Neonatal lenticulostriate vasculopathy: further characterisation. *Arch Dis Child Fetal Neonatal Ed*. 2003.

LSV & CMV

- Not much data.
- Results are inconsistent
- De Jong et al. – 2088 infants, 80 (4%) with LSV on Ultrasound.
  - All 80 were evaluated for congenital infections (TORCH) – none were found positive.
  - Conclusion: 'Routinely applied efforts to diagnose congenital infections in cases presenting with LSV have a poor yield. Routine TORCH screening in neonates with LSV cases should only be regarded as mandatory once well-designed studies demonstrate a clear diagnostic benefit'.

De Jong et al. Is routine TORCH screening warranted in neonates with lenticulostriate vasculopathy? Neonatology. 2010.

LSV and CMV

- Ben-Ami et al. – 12 infants with LSV.
  - 8 (67%) congenital (or perinatal) infections identified, 2 cases of cCMV.
  - Conclusion: 'Echogenicity of these vessels is highly suggestive of intracranial infection because it is not encountered normally or in babies with non infectious intracranial disorders except trisomy 13. The prognostic significance of this finding is yet to be determined".

Ben-Ami et al. Lenticulostriate vasculopathy in infants with infections of the central nervous system sonographic and Doppler findings. Pediatr Radiol. 1990.

Meantime in our clinic…

- Until mid 2009, infants with isolated LSV on brain US were considered asymptomatic and were followed with periodic BERA.
- 9/9 showed hearing deterioration.

The paradigm has changed…

We started to offer Tx. to these infants.

Amir J et al. Is lenticulostriated vasculopathy a sign of central nervous system insult in infants with congenital CMV infection? Arch Dis Child. 2011.

study goals

- To report our experience in treating a large group of infants with cCMV.
- To determine the relationship between LSV and hearing loss.

Methods:

- ✓ A retrospective study.
- ✓ The study was conducted at the Schneider Children's Medical Center of Israel (the largest pediatric hospital in Israel).
- ✓ Data of all infants with cCMV infection followed in our pediatric clinic between January 2005 and December 2012 were reviewed (all with more than one year of follow up).
- ✓ No exclusion criteria.

Methods (cont.):

- ✓ cCMV - a positive urine culture (shell vial) collected during the first 2 weeks of life.
- ✓ Workup:
  1. Complete physical examination, including head circumference.
  2. Complete blood count, liver and kidney function tests
  3. Funduscopy performed by a pediatric ophthalmologist
  4. Brain ultrasound (US) performed by a pediatric radiologist
  5. Brainstem evoked response audiometry (BERA) – on the first 4 weeks of life and than every 4-6 months.

Methods (cont.):

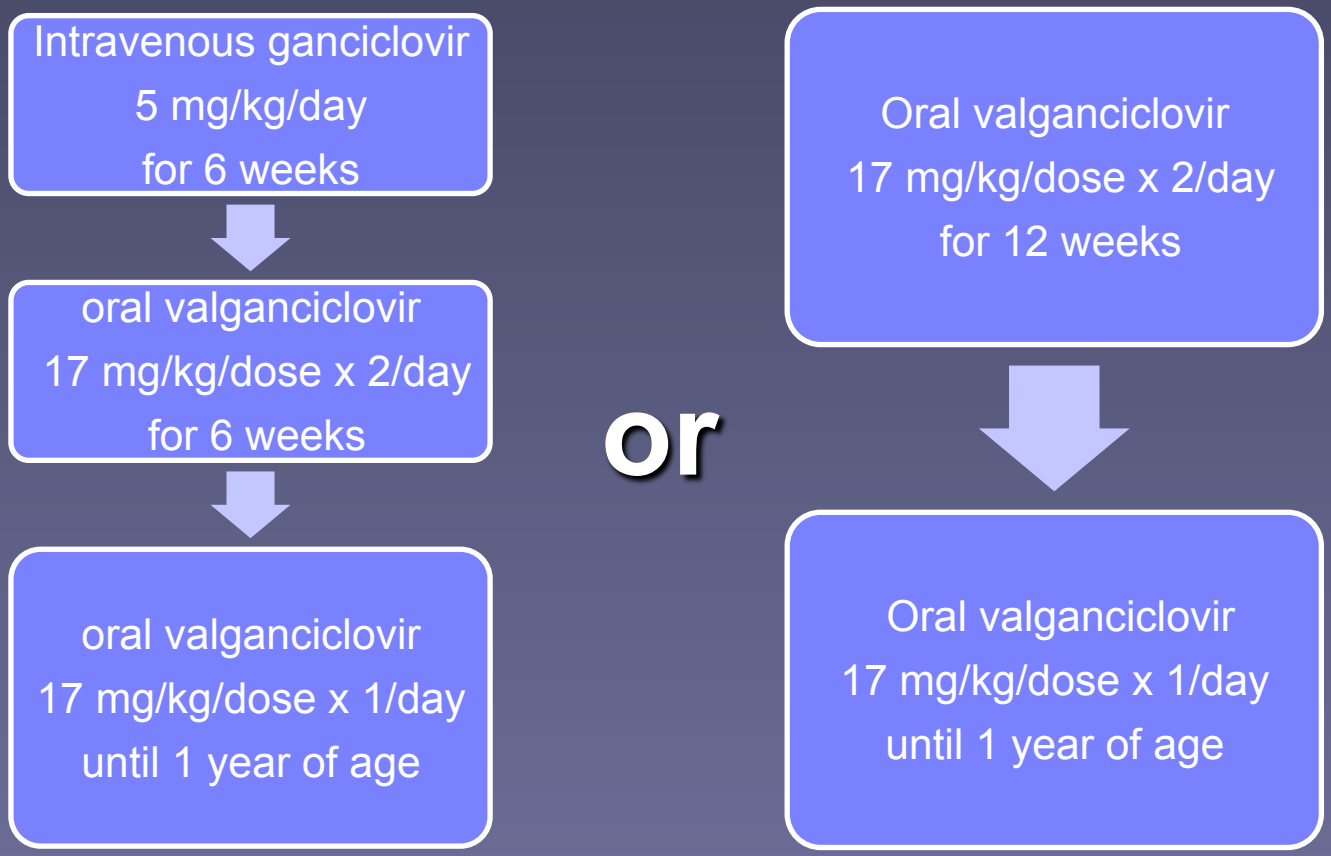
Symptomatic infection:

1. Microcephaly (head circumference <3%)
2. Hearing impairment detected by BERA test
3. Chorio-retinitis
4. Abnormal findings on brain US including the following:
   - Calcifications
   - Periventricular hyperechosity
   - Ventricular dilatation
   - Pseudocysts
   - LSV*

* LSV was not considered a sign of CNS involvement until mid-2009. However, since mid-2009, LSV has also been considered a sign of symptomatic cCMV infection and an indication for antiviral treatment.

Treatment and follow up:

Symptomatic infants were treated by 1 of 2 protocols:



Hearing deterioration :

Definitions:

- normal thresholds - less than 25 dBHL
- mild hearing loss - between 25 to 44 dBHL
- moderate hearing loss - 45 to 69 dBHL
- severe hearing loss - greater or equal than 70 dBHL

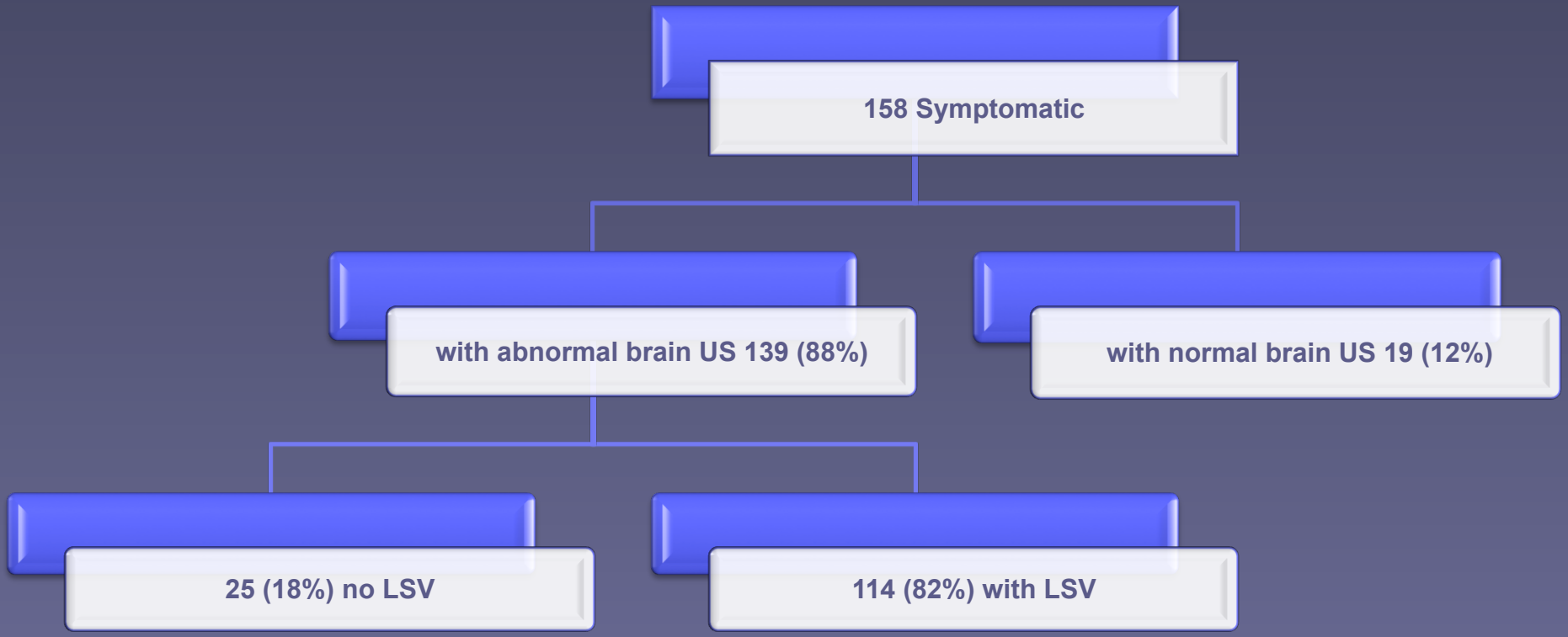
Hearing deterioration - definitions:

Increase of ≥10 dB in the auditory threshold of one or both ears on consecutive two BERA assessments resulting in a change in hearing category (normal to mild, mild to moderate or moderate to severe hearing loss).

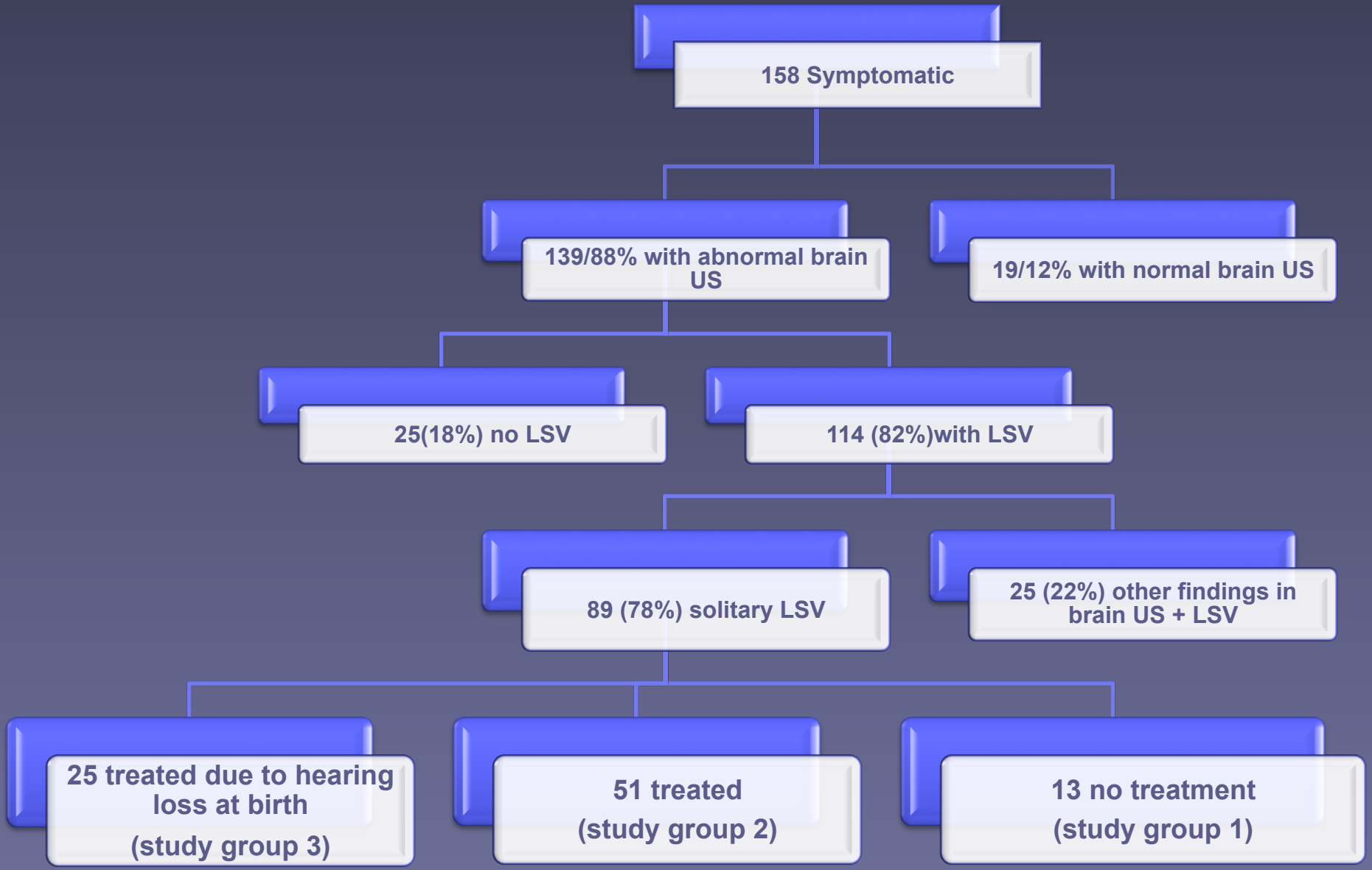
Results

- 210 enrolled infants during the study period (>1 year of follow up).
- 158 (75%) – symptomatic cCMV
- 52 (25%) – asymptomatic cCMV (study group 4)

Results (cont.)



Results (cont.)



Study groups:

- Study group 1: infants with solitary LSV, normal hearing, without treatment (n=13).
- Study group 2: infants with solitary LSV, normal hearing, who were treated (n=51).
- Study group 3: infants with solitary LSV, abnormal hearing, who were treated (n=25).
- Study group 4: asymptomatic infants, without treatment (n=52).

Additional data:

- Primary maternal infection in 92% of cases (no significance differences between groups).
- Time of maternal infection:
  - 1st trimester – 53% (more in groups 1&2 compered to 4)
  - 2nd trimester – 28%

Hearing loss:

- Study group 1: infants with isolated LSV, normal hearing.

  without treatment - 84.6%

- Study group 2: infants with isolated LSV, normal hearing.

  with treatment- none

- Study group 3: infants with isolated LSV, abnormal hearing.

  with treatment – not relevant

- Study group 4: asymptomatic infants.

  without treatment – 9.6%

Difference between groups is Statistically significant!

Adverse events :

- Neutropenia (ANC<1000) –22/76 infants in groups 2&3. (30 episodes in 22 (28.9%) infants), mostly during IV treatment, none during the single daily dose oral regimen.
- *No cases* of severe neutropenia (<500).
- None changed/stopped treatment.

How can I convince you that LSV should be considered a sign of CNS involvement in cCMV?

1. Show that hearing deterioration in infants with LSV is frequent? ✓
2. Show that the treatment does not have severe adverse event? ✓
3. Show that LSV is not just a coincidental findings on brain US in healthy infants.

Incidence of LSV

Name	Year published	Number of infants	Infants with LSV N (%)	Infants without underline major diagnosis N (%)	Infants with cCMV N (%)
Hughes et al.	1991	1324	25 (1.9%)	0 (0%)	4 (0.3%)
Weber et al.	1992	3600	15 (0.4%)	3 (0.08%)	2 (0.06%)
Cabañas et al.	1993	1893	37 (2%)	3 (0.2%)	1 (0.05%)
Wang et al.	1995	586	34 (5.8%)	0 (0%)	3 (0.5%)
Coley et al.	2000	1500	63 (4.2%)	0 (0%)	4 (0.3%)
Makhoul et al.	2003	857	21 (2.5%)	0 (0%)	1 (0.1%)
De Jong et al.	2010	2088	80 (4%)	not reported	0 (0%)
Total		**11848**	**275 (2.3%)**	**6/9760=0.06%**	**0.13%**

Incidence of LSV – term healthy infants

Name	Year published	Number of infants	Infants with LSV N (%)
Heibel et al.	1993	1000	0
Mercuri et al.	1998	177	0
Haataja et al.	2000	103	0
Wang et al.	2004	2309	0
Gover et al.	2011	493	0
Total	**-**	**4082**	**0**

How can I convince you that LSV should be considered a sign of CNS involvement in cCMV?

1. Show that hearing deterioration in infants with LSV is frequent? ✓
2. Show that the treatment does not have severe adverse event? ✓
3. Show that LSV is not just a coincidental findings on brain US in healthy infants. ✓

And yet, where did the LSV hide all these years?

If it is so frequent, where was it before?

- Selection bias – the study was conducted in a tertiary center.
- Selection bias –Israel has high maternal follow-ups, not many TOP due to CMV infection during pregnancy.

- Brain US is the routine imaging test performed in Israel.
  - CT/MRI – does not show LSV!

•Boppana et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J. 1992

•Boppana et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. Pediatrics. 1997 Mar;99(3):409-14.

•Kimberlin et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr. 2003 Jul;143(1):16-25.

Further Research

- Prospective, larger studies
- International studies
- Grading of LSV

My Take home message

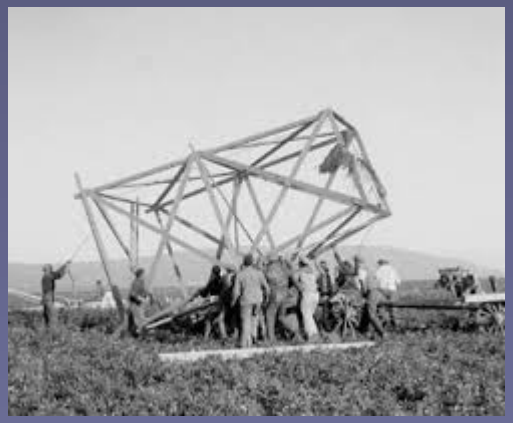
- LSV is not a coincidental finding in infants with cCMV.
- Hearing deterioration in infants with solitary LSV and cCMV is frequent.
- Treatment of infants with solitary LSV may be prudent.

Thanks – Schneider Medical Center

- *Prof. Itzhak Levy* - Infectious Diseases Unit
- *Dr. Yishai Haimi-Cohen* - Day Hospitalization Unit
- *Dr. Joseph Attias* - Institute of Audiology and Clinical Neurophysiology Center
- *Prof. Joseph Pardo* - Department of Gynecology and Obstetrics, Rabin Medical Center
- *Dr. Michael Schwarz* - Department of Pediatric Radiology

And special thank to…

The ‘pioneer’ of cCMV in Israel



About the BERA

- The auditory tests were performed during natural sleep, without sedation. Auditory evoked potentials were recorded in response to rarefaction **clicks** of 100 μS duration presented at a rate of 13/s through insert earphone transducers attached to a plastic tube, providing an acoustic delay of 80ms ((Eartone 5A; Aearo Company, Indianapolis, Ill., USA). ABRs were acquired via an active electrode attached to the vertex or forehead and referred to an electrode at the ipsilateral mastoid. A third (ground) electrode was placed on the contralateral mastoid. Amplification band-pass filters were set at 30–3000 Hz; the analysis period was set at 15.36 ms for two replications of 1024 sweeps each. Monaural ABRs were recorded in response to Air conduction decreasing stimulus levels from 90 dB HL up to thresholds. If air conduction thresholds were elevated, bone conduction click-stimuli were applied. The auditory responses were digitized at a sampling rate of 10 kHz with 12-bit accuracy using the Bio-Logic Explorer System (Bio-Logic Systems Corp., Mundelein, Ill., USA).