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Can Congenital CMV-related Hearing Loss be Evaluated Without Systematic Neonatal CMV Screening?

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- **SNHL is the most common sequelae of cCMV in both asymptomatic and symptomatic infants.**

- **Without cCMV neonatal screening:**
  - **only a small proportion of infants with clinical findings and SNHL will have the opportunity to be early identified.**
  - **testing in asymptomatic infants only occurs after hearing loss is confirmed**

- **The absence of specimens (saliva and/or urine) within 21 days of life from asymptomatic infants may underestimate the true contribution of CMV for permanent hearing impairment in infancy.**

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- **Due to costs of universal neonatal CMV screening, there are some important unanswered questions:**

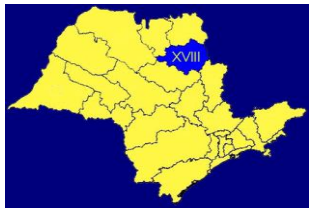
1. Can the true contribution of cCMV to the permanent hearing loss in childhood be evaluated without universal cCMV screening?

2. How many infants with SNHL related to cCMV would be missed if the alternative to universal cCMV screening was target screening in infants who failed universal hearing screening?

Specific aims:

- To determine the contribution of congenital CMV infection to overall neonatal permanent hearing loss.
- To determine the proportion of congenital CMV-related hearing loss that can be detected by targeting infants who fail universal hearing screening for CMV testing.

Study design:



- The study was carried out at two public maternities at Ribeirão Preto city, state of São Paulo, Brazil.
- Part of “Brazilian Cytomegalovirus Hearing and Maternal Secondary Infection Study” (BraCHS)
- A total of 11,899 infants were screened for cCMV infection and hearing from September 2013 to April 2016 .
- Approved by the Research Ethics Committee of the University Hospital (Process number 16.928/2013), and written informed consent was obtained from all participants.

Study design:

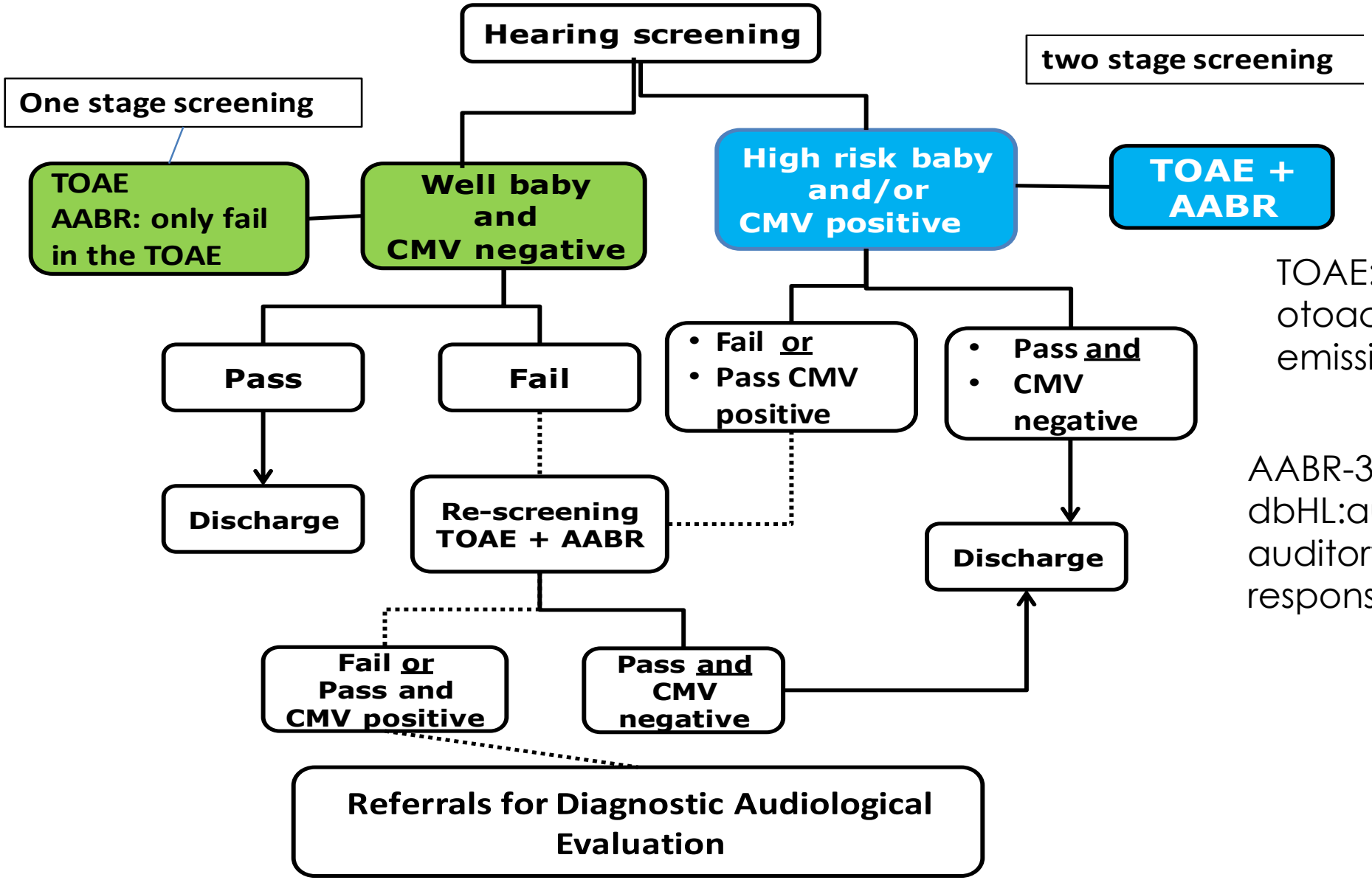
Congenital CMV screening and diagnosis:

- Congenital CMV infection was screened by CMV-DNA detection in two saliva swabs specimens (right and left side of mouth) from each infant obtained in the first 2 weeks of life
- Positive saliva results were confirmed by testing second saliva and urine collected within 3 weeks
- Congenital CMV infection was defined in infants with CMV-DNA detection in at least two saliva and one urine samples obtained before day 21.

Definition of symptomatic cCMV infection:

- Consensus recomendations, 2017, Lancet Infect Dis 2017; 17: e177–88

Methods/ Study design:



TOAE: a transient otoacoustic emission

AABR-35 dbHL:automated auditory brainstem response

Study design:

Diagnostic audiologic evaluation (3-6 weeks of life)

- **Auditory Brain Response (ABR)**
  - **click**
  - **frequency-specific tone-burst stimuli (0.5, 1, 2 and 4 kHz)**
- **TOAE : signal to noise tone (6dB or more) in at least three consecutive frequency bands**
- **Timpanometry**
  - **Hearing loss: ≥ 25dB hearing level ABR tone burst (Stapells et al., 1995).**
    - **Hearing threshold in dBHL over the frequencies 0.5, 1, 2 e 4kHz (WHO, 2013).**
      - **Mild (26-40dB)**
      - **Moderate (41-60dB)**
      - **Severe (61-80dB)**
      - **Profound (over 81dB)**

Study design:

Hearing follow up every 6 months

- Visual reinforcement audiometry (6-24 months of age)
- Play audiometry (2-4 years of age)

} free field or using insert phones

- Older children: conventional audiometric test
- New TOAE: to exclude unilateral hearing loss
- Acoustic immitance measures and tympanometry
- ABR if indicated

Hearing thresholds during follow up

Pure tone average: results of thresholds (dbHL) from 0.5, 1, 2 and 4 Hz

- Normal: < 30 (free fied) and TOAE bilateral response
  < 20 (insert phones)
- Mild: 31 - 45
- Moderate:
- Severe: 71-90
- Profound: > 90

Methods/ Study design:

❑ Normal hearing during follow up

- Stable normal hearing thresholds
- Bilateral TOAEs present

❑ Progressive hearing threshold :

- Worsening of the auditory threshold with at least 10 decibels in successive hearing tests (without transient midle ear problem).

❑ Late onset of SNHL:

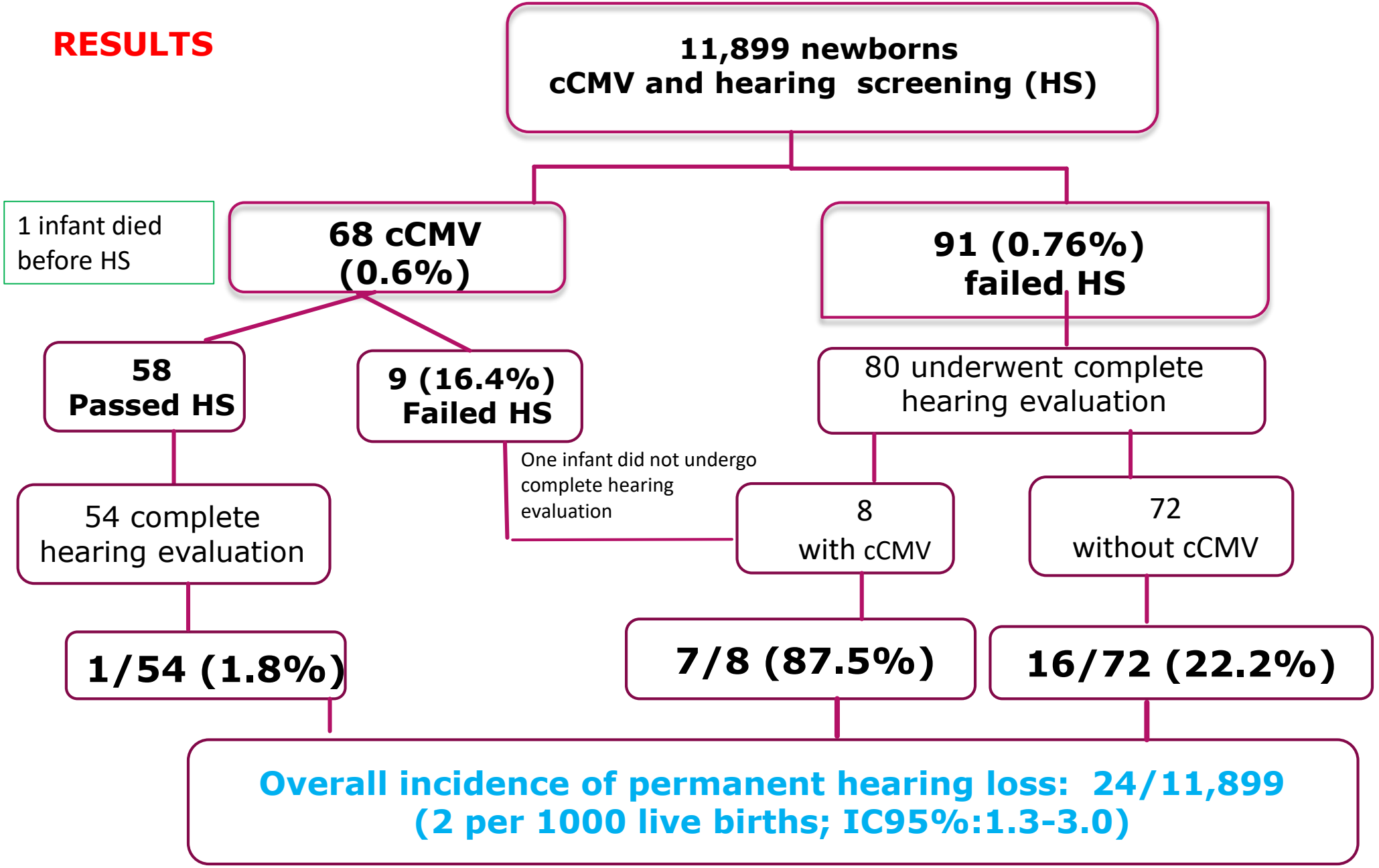
- Occurrence after the first month of life in infants who passed in their hearing screening and had a confirmed normal complete audiologic evaluation
- Confirmed hearing loss in two successive tests without transient middle ear problem.

RESULTS

Characteristics of 11,899 infants screened for both cCMV and hearing:

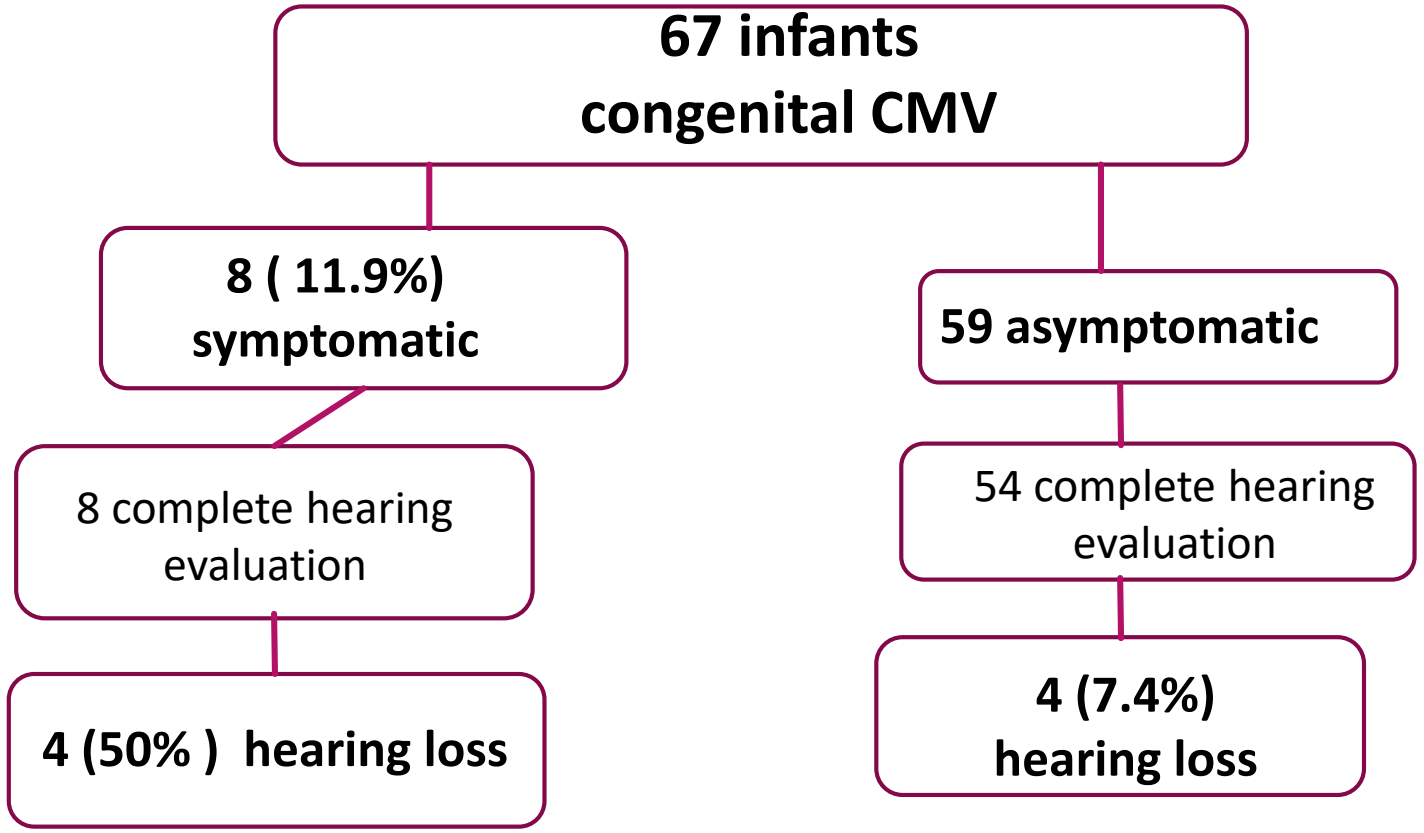
Infant characteristics	Total: N=11,899
Maternal age (year) [median(range)]	26 (12- 50)
Parity (primiparous)	4586 (38.0%)
Gestational age: ≥ 37 weeks	10,312 (86.6%)
< 37 weeks	1587 (13.4%)
Gender : Girls	5,717 (48.0%)
Boys	6,175 (51.9%)
Indeterminated	7 (0.1%)
Hospital nursery: Well baby	10,301 (86.6%)
NICU	1,598 (13.4%)
Birth weight (grams, median, range)	3180 (490-5540)

RESULTS



Contribution of cCMV to overall hearing loss: 8/24 (30%)

RESULTS



- All bilateral

2 profound

2 moderate to severe

- 1 bilateral severe/profound
- 3 unilateral profound

Sensorineural hearing loss (SNHL) related to CMV: 8/62 (12.9%) (IC95%: 6.12-24.4%)

RESULTS

Characteristics of SNHL in four asymptomatic infants with cCMV

	Hearing screening		Hearing loss level	Follow up	
	TOAE	Automatic ABR	ABR Tone burst	ABR Tone burst	
Infant 1 (bilateral)	Left ear: **pass** Right ear: fail	**Fail bilateral**	Left: mild SNHL Right: severe/ profound	Left: severe/profound Right: severe /profound (8 months of age)	**Progressive** AASSI IC
Infant 2 (unilateral)	Left ear: fail Right ear: pass	Discharge before the cCMV diagnosis	Left : moderate/severe Right : normal hearing	Stable hearing threshold	Hearing monitorization
Infant 3 unilateral	Left ear: fail Right ear: pass	Left ear: fail Right ear: pass	Left : profound Right : normal hearing	Stable hearing threshold	Hearing monitorization
Infant 4 (unilateral)	Left ear: **pass** Right ear: **pass**	Discharge before the cCMV diagnosis	Left : normal hearing Right : **profound SNHL** (21 days of life)	Stable hearing threshold	Hearing monitorization

No infants received antiviral therapy

RESULTS:

SNHL in four symptomatic infants with cCMV: moderate to severe findings with neurologic involvement

	Hearing screening		Hearing loss level	Follow up	
	TOAE	Automatic ABR	ABR Tone burst	ABR Tone burst	
Infant 1 (bilateral)	Left ear: fail Right ear: fail	**Fail bilateral**	Left: moderate/severe Right: moderate/severe	Left:moderate/severe Right: profound	Progressive AASSI IC
Infant 2 (bilateral)	Left ear: fail Right ear: fail	**Fail bilateral**	Left : profound Right : profound	Left : profound Right : profound	AASSI IC
Infant 3 (bilateral)	Left ear:fail Right ear: fail	**Fail bilateral**	Left : moderate/severe Right : moderate/severe	Left : stable thresholds Right : stable thresholds	AASSI IC
Infant 4 (bilateral)	Left ear: fail Right ear: fail	**Fail bilateral**	Left : profound Right : profound	Left : profound Right : profound	AASSI IC

2 first infants : ganciclovir therapy for 6 weeks
2 last infants: valganciclovir therapy for 6 months

RESULTS

Hearing follow up of 54 infants with congenital CMV and normal hearing at birth

- 49/54 (92.4%) infants with cCMV with normal hearing at birth (4 symptomatic and 44 asymptomatic)
- The median follow-up was 36 months (range 12-48)
- The median number of audiological monitoring was 5 visits (3-8)
- 19/49 (38%) infants were diagnosed with a conductive hearing loss in one or more time points due to middle ear problem as documented by curve B tympanometry and no response to TOAE
- all of these 19 infants recovered and had a normal hearing in their last follow up visit, confirming a transitory conductive loss
- Stable hearing thresholds in the remaining 30 infants with cCMV and normal hearing at birth

No late-onset SNHL was observed

Summary:

- Incidence of all permanent hearing loss: 2 per 1000 live births
- Contribution of cCMV to overall hearing loss: 30%
- Hearing screening: identified 87.5% of cCMV-related hearing loss
- Prevalence of permanent hearing loss at birth in infants with cCMV: 12.9%
- 7.4% of asymptomatic infants with cCMV had confirmed hearing loss
- Progressive hearing thresholds occurred in 25% of infants with cCMV
- No late onset of SNHL was observed during a median of 36 months follow up

Conclusions:

- One-third of all permanent HL identified by cCMV and hearing screening was related to cCMV.
- Integrating targeted cCMV screening among infants who fail hearing screening will likely identify the majority of CMV-related neonatal HL.
- No infants with delayed onset CMV-related HL have been identified at least during 36 months of follow up.

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