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Clinical characteristics, audiological and neurodevelopmental outcomes of newborns with congenital cytomegalovirus infection

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Summary

BACKGROUND: Congenital cytomegalovirus (cCMV) infections are the leading nongenetic cause of congenital sensorineural hearing loss (SNHL); however the true impact of cCMV infections remains unknown.

AIMS OF THE STUDY: (1) To identify the number of asymptomatic and symptomatic cCMV infections diagnosed between 1999 and 2014 at the Lausanne University Hospital; (2) to describe the audiological and neurodevelopmental outcomes of infants with cCMV infection; and (3) to compare clinical outcomes between infants born to mothers with primary versus nonprimary infection.

METHODS: This was a single-centre, observational, exploratory, retrospective study of newborns diagnosed with cCMV infection at the Lausanne University Hospital between 1999 and 2014.

RESULTS: Fifty newborns with cCMV infection were identified; 39 (78%) were symptomatic at birth, of whom 29 (74%) were neurologically symptomatic. Twelve children (24%) presented with subsequent abnormal audiological and/or neurodevelopmental outcomes. Newborns born to mothers with a nonprimary infection were more often symptomatic at birth than those born to mothers with a primary infection.

CONCLUSIONS: All infants with subsequent SNHL or abnormal neurodevelopment were symptomatic at birth. Similar long-term neurodevelopmental and audiological outcomes were observed in infants born to mothers with a primary and nonprimary infection.

Key words: *congenital CMV infection, sensorineural hearing loss, neurodevelopment, primary infection, nonprimary infection*

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Introduction

Congenital cytomegalovirus (cCMV) infections, with a global estimated prevalence of 0.6 to 0.7%, are the leading nongenetic cause of congenital sensorineural hearing loss (SNHL) [1–6]. Cytomegalovirus (CMV) can be transmitted from the mother to the fetus despite pre-existing immunity [1–7], from either reactivation or reinfection [6]. Evidence from the literature suggests that infants born to mothers with primary infection have an equivalent audiological and neurodevelopmental outcome to those born to mothers with a nonprimary infection [4, 5]. Almost all newborns with cCMV infections are asymptomatic at birth. From these asymptomatic neonates, 10 to 15% will develop neurological sequelae [5]. Overall, 17 to 20% of all neonates with symptomatic and asymptomatic cCMV infection will have an abnormal neurological outcome, mainly SNHL, cognitive delay, neuromotor impairment such as cerebral palsy and balance disturbances, seizures or visual impairment [8–10].

Diagnosis of cCMV infection relies on the documentation of a positive CMV polymerase chain-reaction (PCR) in urine or saliva during the first 3 weeks of life [11–13]. Whereas some centres have introduced universal neonatal screening for cCMV [9], others, such as ours, perform targeted neonatal testing [14] in newborns with microcephaly, subependymal pseudocysts or thrombocytopenia [15–17]. Documentation of cCMV disease in newborns is crucial as prompt initiation of oral valganciclovir treatment improves audiological and, possibly, neurodevelopmental outcomes [16, 18, 19]. Universal screening programmes of newborns have not been implemented in part because of a lack of epidemiological data [20]. As a consequence, asymptomatic newborns will be diagnosed late through identification of SNHL [21].

From recent data, we estimate that cCMV infection could affect 500 newborns each year in Switzerland, of whom up to 100 could suffer from lifelong disabilities [9, 22, 23]. We aimed to provide information on neurodevelopmental and audiological outcomes of newborns with cCMV infection diagnosed at the Lausanne University Hospital. In addition, clinical outcomes of infants born to mothers with primary infection were compared with those born to mothers with nonprimary infection.

Methods

Study design and definitions

This was a single-centre retrospective study of neonates born between 1999 and 2014 presenting with cCMV infection and treated at the Lausanne University Hospital, Switzerland. Congenital CMV infection was defined from 1999 to 2004 as a positive CMV viral culture [24], and from 2005 to 2014 by quantitative measures of viral load with molecular assays (detection limit 100–1000 copies/ml [25]) in urine, collected within the first 3 weeks of life [11–13]. Infants born during the study period and diagnosed retrospectively with CMV PCR testing on stored dried blood spots (Guthrie cards) were also included [26].

Indications for neonatal CMV testing included documented maternal seroconversion during pregnancy, abnormal prenatal ultrasounds, documentation of CMV by molecular assays from amniotic fluid (detection limit 100–1000 copies/ml) and postnatal indications such as being small for gestational age (SGA), microcephaly, subependymal pseudocysts and/or thrombocytopenia [15–17, 20, 25]. Screening of pregnant women and newborns relied on physician-based practice and not on predefined screening policies. Maternal seroconversion during pregnancy was defined either as documentation of CMV-specific immunoglobulins in a patient previously known to be seronegative, or a newborn with proven cCMV infection born to a mother without any demonstrable CMV-specific antibodies during pregnancy [1, 5, 27]. A nonprimary maternal infection was defined as positive IgM and IgG serology with an IgG avidity of ≥70% determined within the first 12 weeks of pregnancy. The assay used to measure IgG avidity was an in-house assay based on the Enzygnost CMV IgG assay (Siemens) using an 8 M urea wash, as described elsewhere [28]. The avidity threshold defining remote infection was set using in-house seroconversion panels, and by comparison with the work of Grangeot-Keros et al. [29].

Symptomatic cCMV infection was defined as one or more of the following: SGA (birthweight <10th percentile), petechiae, hepatosplenomegaly, elevated conjugated bilirubinaemia, thrombocytopenia, elevated transaminases or central nervous system involvement [15, 16]. Neurologically symptomatic cCMV disease referred to one or more of the following: microcephaly (head circumference <3rd percentile), abnormal neurological examination, chorioretinitis, SNHL measured with brainstem-evoked response (BSER) testing, an abnormal brain ultrasound or magnetic resonance imaging (MRI) scan [16, 18, 30]. An abnormal brain ultrasound scan was defined by the presence of periventricular calcifications, white matter hyperechogenicities, ventriculomegaly or hydrocephaly. Subependymal pseudocysts and/or lenticulostriated vasculopathy were considered as nonspecific lesions and were thus not included in the criteria for an abnormal brain ultrasound [5, 17, 19, 31]. An abnormal brain MRI referred to white matter abnormalities (particularly in temporal, occipital and parietal white matter), neuronal migration disorders such as schizencephaly, pachygyria, lissencephaly, polymicrogyria or cortical dysplasia, and cerebellar hypoplasia, periventricular calcifications and ventriculomegaly [32–35].

Treatment options for neurologically symptomatic newborns consisted of a 6-week intravenous ganciclovir regimen from 2006 to 2012, 6 weeks of intravenous ganciclovir with 6 to 12 additional months of oral valganciclovir in 2013, or 6 to 12 months oral valganciclovir thereafter [16, 18, 19, 36].

Collection of clinical information, audiological and neurodevelopmental assessments

Retrospective chart review and use of the database from the neonatology clinic follow-up unit provided information on relevant baseline characteristics and outcomes. This study was approved by the ethics committee on research involving humans of the canton of Vaud (protocol number 426/14).

Audiological assessment

BSER was assessed at birth and between 3 and 24 months by an ear-nose-throat (ENT) specialist. Hearing thresholds were defined as follows: 0 to 30 dB for normal hearing, 31 to 45 dB for mild hearing loss, 46 to 70 dB for moderate hearing loss and above 71 dB for severe hearing loss [16, 18]. We used total and best ear analyses as described [18]. Audiological outcomes were adjudicated on the latest BSER.

Neurodevelopmental assessments

Neurodevelopmental follow-up was offered to neurologically symptomatic patients from 2001. Infants were examined with the revised Griffiths Mental Development Scales (GMDS) at 6 months of age [37], and the Bayley Scales of Infant and Toddler Development second and third editions (Bayley-II and III) at 12 months and 18 months of age [38]. Older infants were tested with the Kaufman Assessment Battery for Children (K-ABC) first edition [39], or with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) [40]. Neurodevelopmental outcomes were based on the latest scores determined with the GMDS, Bayley-II and III, WPPSI-R, K-ABC, all with an expected mean of 100 and a standard deviation of 15 within the normal population [37–40]. Hence test results were classified as abnormal if one test component was below 85. Sequelae were defined as an abnormal audiological and/or an abnormal neurodevelopmental outcome.

Statistical analysis

Descriptive statistics were used. Z-scores of the growth parameters weight, height and head circumference of newborns were calculated using the Fenton 2013 Growth Calculator for Preterm Infants [41].

Results

Study population

From 1999 to 2014, 38,423 newborns were born at Lausanne University Hospital of whom 2274 were tested for CMV in urine samples. Of these 2274, 48 were found positive by viral culture or PCR. Among the 48 newborns diagnosed with cCMV infection, 24 (50%) were tested for CMV as a result of maternal seroconversion, 21 (44%) because they were SGA, 2 (4%) because of thrombocytopenia and 1 (2%) as a result of abnormal antenatal ultrasounds. Two additional patients (twins) with SNHL (and subependymal pseudocysts on neonatal brain ultrasound) tested positive by PCR on stored dried blood-spots at the age of 3.5 years.

Baseline characteristics and clinical outcomes of all patients at birth

Maternal serology status was available for 46 of 50 (92%) women; 35 of the 46 (76%) had a primary infection. Of the 50 newborns with cCMV infection, 18 (36%) were born prematurely with a median gestational age of 38.6 weeks; 12 (67%) of these were late preterm (34 0/7 to 36 6/7 weeks of gestation) (table 1). Among the 50 newborns with cCMV infection, 39 (78%) were symptomatic, of whom 29 (58%) were neurologically symptomatic and 24 (48%) were SGA. Five (10%) were born with microcephaly and none presented with chorioretinitis. Among the 45 newborns in whom a brain ultrasound was performed, 12 (27%) were abnormal, mostly with periventricular hyperechogenicity (50%). An MRI was done in 20 (40%), of whom 55% presented abnormal findings, all white matter abnormalities. Audiological examination was performed in 40 newborns, of whom 35 (88%) had normal hearing with regards to best ear analysis (supplementary table S1 in appendix 1).

Audiological and neurodevelopmental outcomes of all patients at 3 months of age and onwards

From the 50 infants with a cCMV infection, audiological assessment (range 3–26 months) performed by the ENT specialist was available for 29 (58%), 27 (93%) of whom had normal hearing in the best ear; among the 58 ears assessed, 81% had normal thresholds. Among the 50 newborns with cCMV infection, neurodevelopment follow-up (range 6–72 months) from 2001 to 2015 was available for 26 (52%) infants born between 2001 and 2014. Of these 26, 21 (81%) were offered follow-up as a result of neurologically symptomatic cCMV infection. Of those 26, 6 (23%) patients presented with abnormal neurodevelopment of whom 3 had SNHL (table S2, appendix 1).

Baseline characteristics, audiological and neurodevelopmental outcomes of all children with sequelae

Of the 34 infants for whom audiological and/or neurodevelopmental follow-up was available, 12 (35%) had sequelae. Of these 12, 3 (25%) presented with SNHL and abnormal neurodevelopment, 1 (8%) with SNHL and unknown neurodevelopment, 5 (42%) with isolated SNHL and 3 (25%) with an isolated abnormal neurodevelopmental outcome. All 12 were symptomatic at birth, including 10 (83%) with neurological symptoms. Among the 9 infants with SNHL, 7 (78%) had unilateral, and 2 (22%) bilateral hearing loss (fig. 1 and table 2).

Clinical characteristics at birth, audiological and neurodevelopmental outcomes of all infants born to mothers with a primary compared with those born to mothers with a nonprimary infection

Newborns born to mothers with nonprimary infection were more often symptomatic and SGA at birth than those born to mothers with a primary infection. In contrast, petechiae were more frequent in newborns born to mothers with primary infection than in newborns born to mothers with a nonprimary infection. In the two groups, the rates of microcephaly and abnormal audiological outcome at birth were similar (table 3).

Results of hearing assessments and neurodevelopmental outcomes at 3 months of age and onwards were similar in children born to mothers with a primary infection and those with a nonprimary infection (table 4).

Discussion

In this first exploratory study to address the burden of cCMV infections in Switzerland, three important observations were made: (1) cCMV infections were detected equally among newborns born to mothers with primary infection and nonprimary infection; (2) most infants who presented with SNHL or abnormal neurodevelopment were neurologically symptomatic at birth; (3) newborns of

Table 1: Baseline characteristics at birth of all newborns with congenital cytomegalovirus infection.

		Infected n = 50
Maternal infection	Primary	35/46 (76%)
	Nonprimary	11/46 (24%)
	Unknown	4
Sex	Female	30/50 (60%)
Prematurity <37 weeks		18/50 (36%)
Median gestational age in weeks		38.6 (IQR 36–40)
Mean weight z-score		−1.02 (SD 1.06)
Mean height z-score		−1.00 (SD 1.07)
Mean head circumference z-score		−0.57 (SD 1.10)
Anti-viral treatment*	Yes	13/50 (26%)
	No	37/50 (74%)

IQR = interquartile range; SD = standard deviation * Intravenous ganciclovir or oral valganciclovir

mothers with a primary infection had similar audiological and neurodevelopmental outcomes as those born to mothers with a nonprimary infection.

We documented a higher proportion of infants born to mothers with a primary infection (76%) versus nonprimary infection, compared with a previous report of countries with a low seroprevalence, like Switzerland (44%) [5]. This finding most likely resulted from the systematic testing for CMV among newborns born to mothers with seroconversion at our centre. We report a lower proportion of symptoms among symptomatic newborns with cCMV infection compared with others studies [15, 16], whereas our proportion of neurological symptoms among symptomatic newborns was similar. These discrepancies could result from a less rigorous assessment of clinical and laboratory outcomes than of neurological outcomes in our setting compared with other studies [15, 16]. Careful clinical and laboratory assessment is warranted in all newborns with

Figure 1: Clinical characteristics at birth and audiological and neurodevelopmental outcomes.

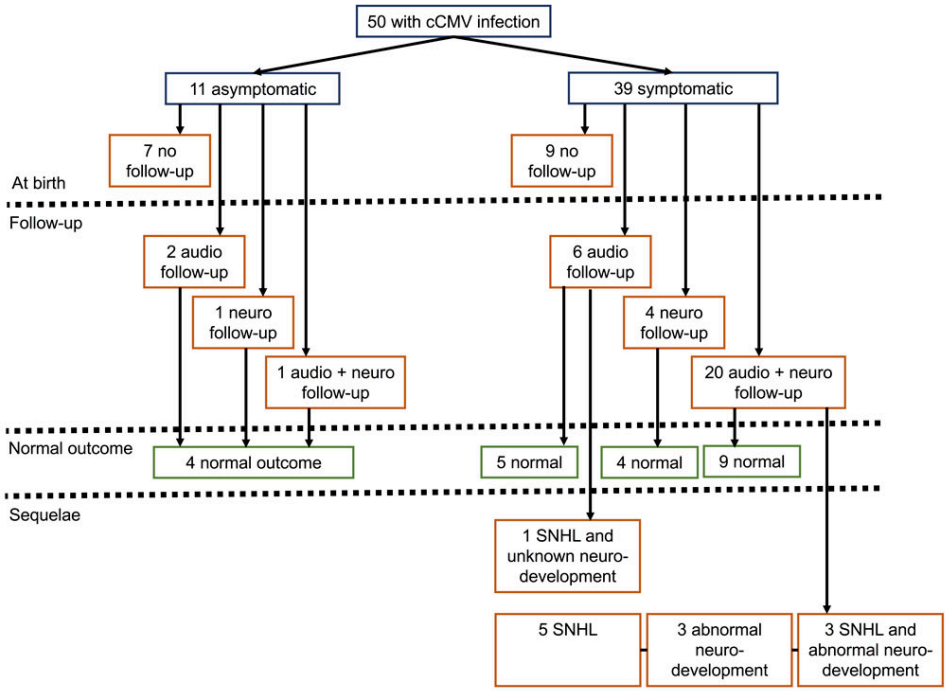

Table 2: Baseline characteristics, audiological and neurodevelopmental outcomes of children with sequelae.

Patient number	Comorbidities and social difficulties	Gestational age (weeks and days)	Weight z-score	Height z-score	Head circumference z-score	Maternal primary infection	Neurodevelopmental outcome	Hearing loss
1	No	40 1/7	0.04	−1.13	−1.29	Yes	Language delay	Moderate right
2	No	37 3/7	0.86	0.4	0.54	Yes	Language delay	No
3	No	39 1/7	−1.31	−1.04	−1.1	No	Normal	Moderate right
4	Maternal HIV infection; difficult psychosocial situation	38 2/7	−1.57	−1.1	−0.07	No	Global delay	No
5	Very preterm	28 3/7	−2.05	−3.01	−3.56	Unknown	Global delay	Moderate right
6	Chronic maternal hepatitis B infection	38 1/7	−1.87	−0.3	−0.47	No	Unknown	Severe left
7	Late preterm	36 0/7	−0.06	0.27	0.16	Yes	Normal	Severe right, mild left
8	Late preterm	36 0/7	−0.29	−0.55	−0.17	Yes	Normal	Severe bilateral
9	No	38 0/7	−2.72	−2.3	−2.16	Yes	Normal	Severe, left
10	No	41 5/7	−2.75	−2.25	−2.64	Yes	Normal	Severe, right
11	Moderate preterm	33 0/7	−2.4	−2.5	−1.18	Unknown	Global delay	Normal
12	Late preterm	34 6/7	−1,54	−0.33	−1.21	No	Motor delay and visual problems	Moderate left

HIV = human immunodeficiency virus Very preterm = 28 0/7 to 31 6/7, moderate preterm = 32 0/7 to 33 6/7, late preterm = 34 0/7 to 36 6/7 weeks of gestation

cCMV infection, as petechiae and SGA, as well as thrombocytopenia, were identified as significant predictors of subsequent SNHL [42].

Our study reported a similar rate of SNHL or abnormal neurodevelopmental outcomes at 3 months of age and onwards compared with other studies (24% vs 17–20%) [9]. All our children with subsequent SNHL or abnormal neurodevelopmental scores were symptomatic at birth, in contrast to a systematic review [9] that reported that only one third of children with subsequent SNHL or abnormal neurodevelopmental outcomes were symptomatic at birth. As supported by the systematic review [9], neurodevelopmental and audiological follow-up should be offered to all children with cCMV infection identified through universal newborn screening [9, 43].

Confirming findings of prior reports [4, 7], our study indicated that infants born to mothers with a nonprimary infection are at least as often symptomatic at birth as those born to mothers with a primary infection. As documented in other studies [4, 7], we report equivalent rates of abnormal audiological and neurodevelopmental outcomes of children born to mothers with a primary infection compared with those born to mothers with a nonprimary infection.

Table 3: Clinical characteristics at birth categorised by newborns born to mothers with primary versus nonprimary infection.

		Maternal primary infection n = 35	Maternal nonprimary infection n = 11
Symptomatic		25/35 (71%)	10/11 (91%)
Neurologically symptomatic		18/35 (51%)	8/11 (73%)
SGA		12/35 (34%)	9/11 (82%)
Petechiae		12/35 (34%)	1/11 (9%)
Thrombocytes Abnormal: <150 G/l	Abnormal	9/26 (35%)	6/11 (55%)
	Normal	17/26 (65%)	5/11 (45%)
	Unknown	9	0
Microcephaly		3/35 (9%)	1/11 (9%)
Fundus	Abnormal	0/31 (0%)	0/9 (0%)
	Normal	26/31 (100%)	9/9 (100%)
	Unknown	9	2
Brain ultrasound	Abnormal	7/31 (23%)	4/10 (40%)
	Normal	24/31 (77%)	6/10 (60%)
	Unknown	4	1
MRI	Abnormal	5/11 (45%)	5/8 (63%)
	Normal	6/11 (55%)	3/8 (38%)
	Unknown	24	3
BSER best ear	Normal	25/28 (89%)	8/10 (80%)
	Mild	0/28 (0%)	2/10 (20%)
	Moderate	2/28 (7%)	0/10 (0%)
	Severe	1/28 (4%)	0/10 (0%)
	Unknown	7	1
BSER total ears	Normal	45/56 (80%)	15/20 (75%)
	Mild	3/56 (5%)	2/20 (10%)
	Moderate	5/56 (9%)	3/20 (15%)
	Severe	3/56 (5%)	0/20 (0%)
	Unknown	14	2

BSER = brain stem evoked response; MRI = magnetic resonance imaging; SGA = small for gestational age

Table 4: Audiological and neurodevelopmental outcome at 3 months of age and onwards, categorised by newborns born to mothers with a primary versus a nonprimary infection.

		Maternal primary infection n = 35	Maternal nonprimary infection n = 11
Latest BSER ≥3 months best ear	Normal	16/18 (89%)	9/9 (100%)
	Mild	1/18 (6%)	0/9 (0%)
	Moderate	0/18 (0%)	0/9 (0%)
	Severe	1/18 (6%)	0/9 (0%)
	Unknown	17	2
Latest BSER ≥3 months total ears	Normal	29/36 (81%)	15/18 (83%)
	Mild	1/36 (3%)	0/18 (0%)
	Moderate	1/36 (3%)	2/18 (11%)
	Severe	5/36 (14%)	1/18 (6%)
	Unknown	34	4
Neurodevelopment score ≥6 months	Abnormal	2/14 (14%)	2/8 (25%)
	Normal	12/14 (86%)	6/8 (75%)
	Unknown	21	3

BSER = brain stem evoked response

Our exploratory study represents an important first step in reporting audiological and neurodevelopmental outcomes of newborns with cCMV infection in Switzerland. An important strength relates to the precise documentation of BSER measures, including best ears analysis and total ears analysis, as well as the use of standardised developmental tests [16]. Limitations of our study include the retrospective design, inhomogeneous timeframe of the audiological follow-up and the absence of follow-up of asymptomatic newborns, which may have biased our findings towards more severe outcomes among symptomatic children with longer follow-up. This limitation is inherent to all retrospective studies on cCMV infections conducted before the establishment of recent guidelines on auditory outcomes measures [3], as reflected in a recent European surveillance study [44]. However, at each visit at the neurodevelopmental clinic, hearing was examined by the paediatrician and those with any abnormal findings were systematically referred to the ENT specialist. Therefore, we believe that the wide timeframe of auditory assessment conducted by the ENT specialist minimally affected our findings. Other shortcomings of our study relate to the small sample size inherent to monocentric retrospective studies conducted in a country with a low prevalence of cCMV infection [5]. In addition, the absence of universal screening of newborns may have biased our study towards selecting mothers with a primary infection and mostly symptomatic newborns, who presented mostly with normal BSER and neurodevelopmental scores.

In conclusion, our study supports current findings on the burden and severity of cCMV infections [4, 7, 9] and provides national data on outcomes of newborns with cCMV infection. Combined information on clinical outcomes from the current study and epidemiological data provided by the Swiss Paediatric Surveillance Study (SPSU) will hopefully encourage the establishment of a national registry, which will in turn serve as foundation for future prospective studies.

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Appendix 1

Supplementary tables

Table S1: Clinical outcomes at birth of all newborns with congenital cytomegalovirus infection.

		Infected n = 50
Symptomatic		39/50 (78%)
Neurologically symptomatic		29/50 (58%)
SGA		24/50 (48%)
Petechiae		13/50 (26%)
Thrombocytes Abnormal: <150 G/l	Abnormal	17/41 (41%)
	Normal	24/41 (59%)
	Unknown	9
Microcephaly		5/50 (10%)
Fundus	Abnormal	0/39 (0%)
	Normal	39/39 (100%)
	Unknown	11
Brain ultrasound	Abnormal	12/45 (27%)
	Normal	33/45 (73%)
	Unknown	5
MRI	Abnormal	11/20 (55%)
	Normal	9/20 (45%)
	Unknown	30
BSER best ear	Normal	35/40 (88%)
	Mild	2/40 (5%)
	Moderate	2/40 (5%)
	Severe	1/40 (3%)
	Unknown	10
BSER total ears	Normal	64/80 (80%)
	Mild	5/80 (6%)
	Moderate	8/80 (10%)
	Severe	3/80 (4%)
	Unknown	20
BSER = brain stem evoked response; MRI = magnetic resonance imaging; SGA = small for gestational age		

Table S2: Audiological and neurodevelopmental outcome at 3 months of age and onwards of all newborns with congenital cytomegalovirus infection.

		Infected n = 50
Latest BSER ≥3 months best ear	Normal	27/29 (93%)
	Mild	1/29 (3%)
	Moderate	0/29 (0%)
	Severe	1/29 (3%)
	Unknown	21
Latest BSER ≥3 months total ears	Normal	47/58 (81%)
	Mild	1/58 (2%)
	Moderate	4/58 (7%)
	Severe	6/58 (10%)
	Unknown	42
Neurodevelopment score ≥6 months	Abnormal	6/26 (23%)
	Normal	20/26 (77%)
	Unknown	24
BSER = brain stem evoked response		