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Outcome of Children with Congenital Cytomegalovirus Infection: A Retrospective Observational Study

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Abstract

Objective Congenital cytomegalovirus (CMV) infection is a common intrauterine infection and the leading cause of nonhereditary sensorineural hearing loss. This study aims to assess the long-term outcome of the infection and to identify infants at risk of developing long-term sequelae.

Methods This retrospective single-center observational study includes infants born between 2003 and 2019 with confirmed congenital CMV (based on current criteria). Brain imaging (ultrasound and magnetic resonance imaging [MRI]), clinical monitoring of neurosensory development, and auditory brainstem evoked responses were performed, as well as long-term neurodevelopmental follow-up to assess sequelae.

Results A total of 66 infants with congenital CMV were included in the study. Median gestational age at birth was 38.6 weeks (interquartile range: 36.9–40.1). Clinical findings included intrauterine growth restriction (39%), microcephaly (29%), thrombocytopenia (17%), and jaundice (11%). Brain abnormalities were observed on ultrasound (30%) and MRI (42%). Neurodevelopmental scores were abnormal in 21 subjects (43%) and associate with the vacuolization of anterior temporal lobe and ventricular septations on MRI (both $p = 0.05$). Fourteen patients (21%) had sensorineural hearing loss, which was more common in patients with abnormal cerebral images at birth, determined by ultrasound ($p = 0.06$). Microcephaly ($p = 0.05$) and abnormal MRI ($p = 0.03$) at birth were associated with poor long-term outcomes.

Conclusion Early detection of congenital CMV infection is important to prevent long-term complications in affected infants. Understanding the predictors of poor outcomes may help improving management and treatment strategies for this condition.

Keywords
- congenital infection
- cytomegalovirus
- long-term sequelae

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Introduction

Congenital cytomegalovirus infection (cCMV) is a common intrauterine infection and the leading cause of nonhereditary sensorineural hearing loss (SNHL). It affects 0.2 to 2.5% of all newborns[1–3] and the rate varies based on the seroprevalence of CMV antibodies in the maternal population and screening policies.[4,5] Intrauterine transmission may occur through primary maternal infection, where the mother acquires the infection for the first time or through nonprimary infection, resulting from reactivation (latency and periodic reactivation of CMV replication) or reinfection (infection with a different viral strain).[6] Primary maternal infection is more likely to cause fetal damage and leads to higher risk of vertical transmission than nonprimary infection (32 vs. 1.4%).[7–10] Also, infection acquired earlier in pregnancy is associated with more severe disease and worse outcome.[6,7,11]

Most infants with cCMV are asymptomatic at birth (85–90%) and approximately 10 to 15% show apparent signs of infection, including microcephaly, petechiae, anemia, thrombocytopenia, and hepatosplenomegaly. Cases of myocarditis related to congenital CMV infection have also been described in some reports, and fetal hydrops with pericardial effusion is commonly found in CMV-seroconverted women (around 7%).[12] Even if asymptomatic at birth, approximately 10 to 15% of infants with cCMV can develop anomalies later in life. Long-term consequences include SNHL, vestibular disorders, developmental delay, and ocular abnormalities.[1,10,13–15] SNHL is the most frequent sequelae, observed in 40 to 50% of symptomatic children and 10% of those asymptomatic at birth. Approximately 30% of children with cCMV-related SNHL experience delayed onset of disability and progressive deterioration throughout childhood.[15–18]

cCMV is often underdiagnosed due to its diverse and nonspecific manifestations. Lack of awareness among health care workers and the public contributes to the unrecognized impact of cCMV on public health.[19] Early diagnosis is crucial to prevent or minimize long-term complications. Additionally, identifying predictors for good prognosis can alleviate parental anxiety and reduce health care costs.

This retrospective study aims to evaluate the rate of poor long-term outcome in infants with cCMV, and to identify infants at risk of developing long-term sequelae, even if asymptomatic at birth, to improve routine follow-up strategies and provide more accurate assessments.

Materials and Methods

This retrospective single-center observational study includes infants with cCMV born between July 2003 and August 2019 and either born or referred for follow-up to the University Hospitals of Geneva, Switzerland. Potential cases of cCMV were identified through laboratory virus detection in any biological fluid within the first month of life, using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes in the electronic medical records. Infants with postnatally acquired CMV were excluded from the study. To be eligible, patients had to meet the current criteria for confirmed cCMV.[20,21] Confirmed diagnosis required positive polymerase chain reaction (CMV-PCR) or CMV-antigen isolation, before 3 weeks of life. Confirmation of cCMV by CMV-PCR on dried blood spots collected on the fourth day of life (newborn screening test) were also considered as confirmed cases. The trimester of infection was determined based on maternal serologies, when available, or anamnestic information, such as reporting flu-like episodes. Infants were classified as symptomatic at birth if they exhibited at least one of the following: microcephaly ($<3^{rd}$ percentile), intrauterine growth restriction (IUGR) (birth weight and size $<10^{th}$ percentile), thrombocytopenia, hepatosplenomegaly, elevated liver enzymes, jaundice requiring treatment, petechiae, pathological neurological examination, brain abnormalities on ultrasound or magnetic resonance imaging (MRI), or absence of otoacoustic emissions (OAE) at birth.

Data were collected from the electronic medical charts, including demographics (age, sex, gestational age, and anthropometric measures at birth), imaging studies (brain ultrasound and/or MRI), viral diagnostic tests, and the antiviral therapy. Clinical parameters at birth and during follow-up were collected, such as microcephaly, hepatosplenomegaly, anemia, thrombocytopenia, jaundice, epilepsy, petechia, cardiovascular parameters, neurological status, hearing tests, ophthalmologic exams, and neurodevelopmental data.

Prenatal CMV screening is not routine in Switzerland or in our institution, and the recommended intervention to prevent cCMV is hygiene measures. The institutional protocol for cCMV management was changed in 2011 and since then various investigations, including imaging studies and viral diagnostic tests, are performed routinely on neonates with confirmed cCMV infections at birth when suspected. Treatment with oral valganciclovir is considered when central nervous system is involved.[22] Hearing assessments using OAE and auditory evoked potentials (AEP) or Visual-Reinforcement Audiometry were conducted during follow-up visits. Hearing thresholds were defined as pure tone average (on 500–1000–2000–4000 Hz) between 0 and 20 dB as normal hearing, 21 to 40 dB mild hearing loss, 41 to 70 dB moderate hearing loss, and 71 dB or higher as severe hearing loss. Vestibular tests were performed from 6 years of age onward and included caloric test, video head impulse testing, and vestibular-evoked myogenic potentials.

Infants with cCMV were followed at the Division of Development and Growth by a multidisciplinary team, including a neuropsychologist, physiotherapist, and specialized pediatrician. Developmental evaluations were conducted using the Bayley Scales of Infant and Toddler Development (BSID-II or BSID-III) to assess motor, language, and cognitive development. Cognitive outcome in older children is assessed using the French version of the Kaufman Assessment Battery for Children (K-ABC, 1^{st} or 2^{nd} edition) yielding a cognitive score comparable to the one found in general intelligence tests.[23] The scores obtained during the last development evaluation were used and categories were defined as: normal development (score $\geq$ 85), mild

developmental delay (score 70–85), and moderate to severe development delay (score < 70).

Statistical analysis was performed using Stata v16.1 (StataCorp LP, College Station, Texas, United States). Participant's characteristics and neurodevelopmental outcome were described using descriptive statistics. Association between adverse health outcome (hearing loss, vestibular defect, developmental delay) and clinical, laboratory, or radiological abnormalities were assessed using the chi-square or Fisher's exact tests, as appropriate. A *p*-value less than 0.05 was considered as statistically significant.

The study was approved by the Regional Human Research Ethics Committee (CCER 2017-01446).

Results

A total of 74 patients were screened and 66 subjects with confirmed cCMV infections were included in the study. We excluded eight cases of suspected cCMV who had symptoms presumably CMV-related but in which the virus detection was made after 3 weeks of life, and dried blood spots were not available or requested. In five of the included cases, the congenital infections were confirmed by positive CMV-PCR on amniotic fluid. Presumed timing of infection is reported in ►**Table 1**; only 14/66 women (21%) had a documented seroconversion during pregnancy. For another 26/66 women (39%), the timing of infection was estimated based on clinical history of flu-like symptoms. The median gestational age at birth was 38.6 weeks. None received antiviral treatment during pregnancy.

Clinical findings are summarized in ►**Table 2**. IUGR was the most frequent manifestation, present in 39% of subjects

Table 1 Demographics of the 66 infants with congenital cytomegalovirus

Characteristics	*n* (%) or median (IQR)
Sex, male	27 (41%)
Gestational age at birth (median, IQR)	38.6 (36.9–41.1)
Trimester of infection (serology)	
First	5 (36%)
Second	2 (14%)
Third	7 (50%)
Trimester of infection (history)	
First	17 (26%)
Second	14 (21%)
Third	9 (14%)
Unknown	26 (39%)
Siblings	
Yes	36 (55%)
No	24 (36%)
Unknown	6 (9%)

Abbreviation: IQR, interquartile range.

Table 2 Clinical findings at birth in 66 children with congenital cytomegalovirus

		n (%) or median (IQR)
Preterm	*n* (%)	16 (24%)
Weight at birth	Median (IQR)	2.96 (2.52, 3.32)
Low birth weight	*n* (%)	25 (39%)
IUGR	*n* (%)	25 (39%)
Microcephaly	No	39 (59%)
	Yes	19 (29%)
	Missing	8 (12%)
Clinical exam at birth	Abnormal	5 (8%)
	Normal	56 (85%)
	Missing	5 (8%)
Neurological status at birth	Abnormal	2 (3%)
	Normal	58 (88%)
	Missing	6 (9%)
Hepatomegaly	No	52 (79%)
	Yes	5 (8%)
	Missing	9 (14%)
Anemia	No	44 (67%)
	Yes	4 (6%)
	Missing	18 (27%)
Thrombocytopenia	No	38 (58%)
	Yes	11 (17%)
	Missing	17 (26%)
Elevated ALT	No	14 (21%)
	Yes	12 (18%)
	Missing	40 (61%)
Elevated gGT	No	3 (5%)
	Yes	23 (35%)
	Missing	40 (61%)
Epilepsy	No	58 (88%)
	Yes	1 (2%)
	Missing	7 (11%)
Petechiae	No	54 (82%)
	Yes	4 (6%)
	Missing	8 (12%)
Jaundice	No	47 (71%)
	Yes	7 (11%)
	Missing	12 (18%)
Chorioretinitis	No	63 (95%)
	Missing	3 (5%)
Cataract	No	63 (95%)
	Missing	3 (5%)

(*Continued*)

Table 2 (*Continued*)

		n (%) or median (IQR)
Clinical exam at birth	Abnormal	5 (8%)
	Normal	56 (85%)
	Missing	5 (8%)
Neurological status at birth	Abnormal	2 (3%)
	Normal	58 (88%)
	Missing	6 (9%)
Hearing test at birth (OAE)	Abnormal	7 (11%)
	Normal	54 (82%)
	Missing	5 (8%)

Abbreviations: ALT, alanine transaminase; GA, gestational age; gGT, gamma-glutamyl transferase; IQR, interquartile range; IUGR, intrauterine growth restriction; OAE, otoacoustic emissions.

overall. Microcephaly was the most frequent neurological finding, present in 29% of subjects. Only two patients (3% of all children) presented with a neurological abnormality at birth, consisting of axial hypotonia. All patients had normal ophthalmologic examination in the neonatal period. The clinical examination was described as abnormal in five patients (8%), but not directly related to cCMV. Petechiae and purpura were rare (6%).

Laboratory findings showed that 17% of infants presented with thrombocytopenia, with only one preterm newborn having critically low platelet levels (20 G/L). Anemia was reported in 6% of subjects. Jaundice was present in seven newborns, all successfully treated with phototherapy. No infant experienced myocarditis or pericardial effusion.

OAE at birth was available for 61 infants; 7 of them failed the test (11%) and 3 of them were confirmed to have hearing loss following additional investigations (5%).

Neurological imaging is summarized in ►**Table 3**. Brain ultrasound was abnormal in 30% of cases, with the most common findings being subependymal cysts (16/20 infants, 80%), lenticulostriate vasculopathy (9 infants, 45%), and anterior temporal vacuolization (8 infants, 40%). Brain MRI was performed in 34 subjects (52%) at birth, with 82% showing abnormal results (28/34). In addition, five subjects had an MRI performed after 1 year of life: it was abnormal in all children. White matter abnormalities (WMAs) were the most common findings (67% of all MRI) (26/39). Vacuolization of anterior temporal lobe was also a common finding (62% of all MRI), as well as cerebellar hypoplasia and periventricular cysts, that were seen in 7 and in 5 infants, respectively (18 and 13%).

Out of the 66 infants, 56 were considered as symptomatic at birth (85%) (►**Table 4**). Clinical characteristics at birth and audiological and neurodevelopmental outcomes are summarized in ►**Fig. 1**. The characteristics of the 24 patients with long-term sequelae are detailed in ►**Table 5**. Twenty infants (30%) received antiviral treatment, primarily oral valganciclovir until 6 months of age. Among the treated

Table 3 Radiological findings in 66 children with congenital cytomegalovirus

		n (%) or median (IQR)
Cerebral ultrasound at birth	Abnormal	20 (30%)
	Normal	38 (58%)
	Missing	8 (12%)
Subependymal cysts	*n* (%)	16 (28%)
Lenticulostriate vasculopathy	*n* (%)	9 (16%)
Vacuolization of anterior temporal lobe	*n* (%)	8 (14%)
Periventricular pseudocysts	*n* (%)	3 (5%)
Intracranial calcifications	*n* (%)	3 (5%)
Ventricular septation	*n* (%)	2 (4%)
Ventriculomegaly	*n* (%)	1 (4%)
Cerebral MRI at birth	Abnormal	28 (42%)
	Normal	6 (9%)
	Missing	32 (48%)
Cerebral MRI after 1 y of life	Abnormal	5 (100%)
	Normal	0 (0%)
White matter disease	*n* (%)	26 (67%)
Vacuolization of anterior temporal lobe	*n* (%)	24 (62%)
Cerebellar hypoplasia	*n* (%)	7 (19%)
Intracranial calcifications	*n* (%)	4 (11%)
Subependymal cysts	*n* (%)	5 (14%)
Ventricular septation	*n* (%)	3 (8%)
Ventriculomegaly	*n* (%)	2 (5%)
Delayed myelination	*n* (%)	3 (8%)
Periventricular pseudocysts	*n* (%)	3 (8%)
Migrational abnormalities	*n* (%)	1 (3%)

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging.

patients, 19 were symptomatic at birth. One asymptomatic patient was treated at the age of 7 following the diagnosis of cCMV-induced SNHL. All treated infants had CMV-related brain injuries on cerebral MRI, except one infant with IUGR and no cerebral abnormalities on MRI. This child was treated with antivirals after discussion with parents. Among those treated with valganciclovir, four infants (20%) experienced neutropenia, one had transient anemia, and one had pancytopenia. The treatment was temporarily suspended until resolution of the neutropenia, which was monitored weekly.

Fourteen patients (25%) showed abnormal results in AEP response or audiometry, 13 of which still showed abnormalities at last follow-up and 1 patient who showed normal audiometry at 4 years of age (►**Table 4**). Progressive SNHL was observed in one patient, appearing at 5 years of age. Among the cases of SNHL, it was unilateral in seven cases

Table 4 Clinical outcome of 66 children with congenital cytomegalovirus

		N (%)
N		66
Symptomatic at birth	*n* (%)	56 (85%)
Treated with valganciclovir	*n* (%)	20 (30%)
Hearing deficiency	*n* (%)	14 (25%)
Vestibular defect	*n* (%)	4 (21%)
Number of ears affected	1	7 (50%)
	2	7 (50%)
Developmental score at last follow-up	Normal	33 (50%)
	Mild delay	11 (17%)
	Moderate to severe delay	2 (3%)
	Missing	20 (30%)
Early interventions and therapies	*n* (%)	21 (45%)

(50%) and bilateral in the other seven (50%). Clinical abnormalities at birth ($p = 0.02$), such as axial hypotonia ($p = 0.04$) or petechia ($p = 0.004$), were associated with SNHL. SNHL was not correlated with an abnormal ultrasound or MRI. SNHL was possibly more common in patients with abnormal cerebral images at birth, determined by ultrasound ($p = 0.06$) or MRI ($p = 0.1$). Ultrasound findings possibly associated with SNHL were mainly periventricular hyper echogenicity ($p = 0.07$), ventriculomegaly ($p = 0.1$), and ventricular septation ($p = 0.2$). Vestibular abnormalities were seen in 4 out of 21 tested patients (6% of the entire cohort or 21% of those tested) and 3 cases were with associated severe hearing loss.

Neurodevelopment was assessed at initial and last follow-up consultations, with a median age of 34 months (interquartile range: 18.6 months) at last assessment. In the study population, 21 abnormal neurodevelopmental assessments (32%) were recorded across all follow-ups. Considering that 17 patients had no neurodevelopmental follow-up, the proportion of abnormal neurodevelopmental assessments was of 43% (21 out of 49). At the last follow-up, 13 patients still had an abnormal clinical evaluation, including 2 with moderate to severe developmental delay and 11 with mild developmental delay. Mild developmental delays were initially detected in 8 patients, who finally showed normal scores at last follow-up (median: 44.7 months). Among these patients, 4 received early interventions and therapies between the initial and the last assessment.

Developmental delay was not correlated with an abnormal ultrasound or MRI. The only radiological element related to mental delay were vacuolization of anterior temporal lobe and ventricular septations on MRI (both $p = 0.05$).

Adverse health outcome, defined as the presence of deafness (unilateral or bilateral), developmental delay and/or abnormal vestibular function, was associated with microcephaly ($p = 0.05$) and abnormal MRI ($p = 0.03$) at birth. Developmental delay alone was not directly associated with microcephaly ($p = 0.4$).

Discussion

We report a higher proportion of symptomatic cCMV cases (85%), than in the literature (10–15%).[9,14,24] Dollar et al estimate that 12.7% (range: 0.3–25.0%) of infected children exhibited symptoms at birth, based on a sample of 810 infants.[25] Townsend et al reported similar findings, observing a percentage of symptomatic patients of 11% (95% confidence interval: 6.6–16.3) in British and Swedish populations.[26] The high proportion of symptomatic cases may be partly attributed to three different explanations. First, the absence of universal neonatal screening, which targets patients who will be considered as symptomatic (IUGR, microcephaly, hepatitis, etc.). Second, the lack of screening in pregnant women prevents the identification of those who become infected unknowingly, resulting in the omission of asymptomatic cases. The final reason could be the absence of a standardized definition for symptomatic infection. As in some recent studies, we also categorized infants with IUGR or low birth weight as symptomatic, even without other clinical abnormalities, as IUGR has been shown to independently predict hearing loss in cCMV-infected infants.[3,25,27] Other authors used similar criteria to define symptomatic children, including thrombocytopenia, petechiae, hepatosplenomegaly, jaundice, IUGR, hepatitis, or central nervous system involvement.[22,27] This study found similar frequency of symptoms at birth as previously reported, with IUGR and microcephaly being common manifestations (39 and 29%, respectively, of our cohort).[22,27–29] Symptomatic infants with microcephaly are known to have a poor cognitive prognosis, reflecting a generalized loss of cerebral volume.[30] However, our study did not confirm microcephaly as a specific predictor of developmental delay and motor disability, as reported by Noyola et al.[30]

Abnormalities in neonatal brain imaging have been shown to predict long-term neurological outcome in cCMV-infected infants.[31–33] Isolated WMAs seen on MRI have been significantly correlated with neurodevelopmental impairment, and its prevalence has been reported around 22–70%, as in our study (67%).[29,31,34–36] This association was not confirmed in our study since we found that only ventricular septations and vacuolization of anterior temporal lobe were directly associated with developmental delay. Recently, Alarcón et al demonstrated the association between temporal lobe WMAs and adverse outcome, including severe hearing loss and hearing impairment combined with other moderate/severe disabilities, emphasizing the importance of early brain MRI for guiding treatment and follow-up decisions in cCMV patients.[36] Although other temporal lobe lesions (WMAs, cyst) were frequently observed in our population, we did not confirm this particular association. Ventriculomegaly, another common finding in cCMV known to predict an increased risk of poor neurological outcome, was observed in 5% of cases. This prevalence is lower than previously reported rates (30–50%) in other studies.[29,33,37] Similarly, intracranial

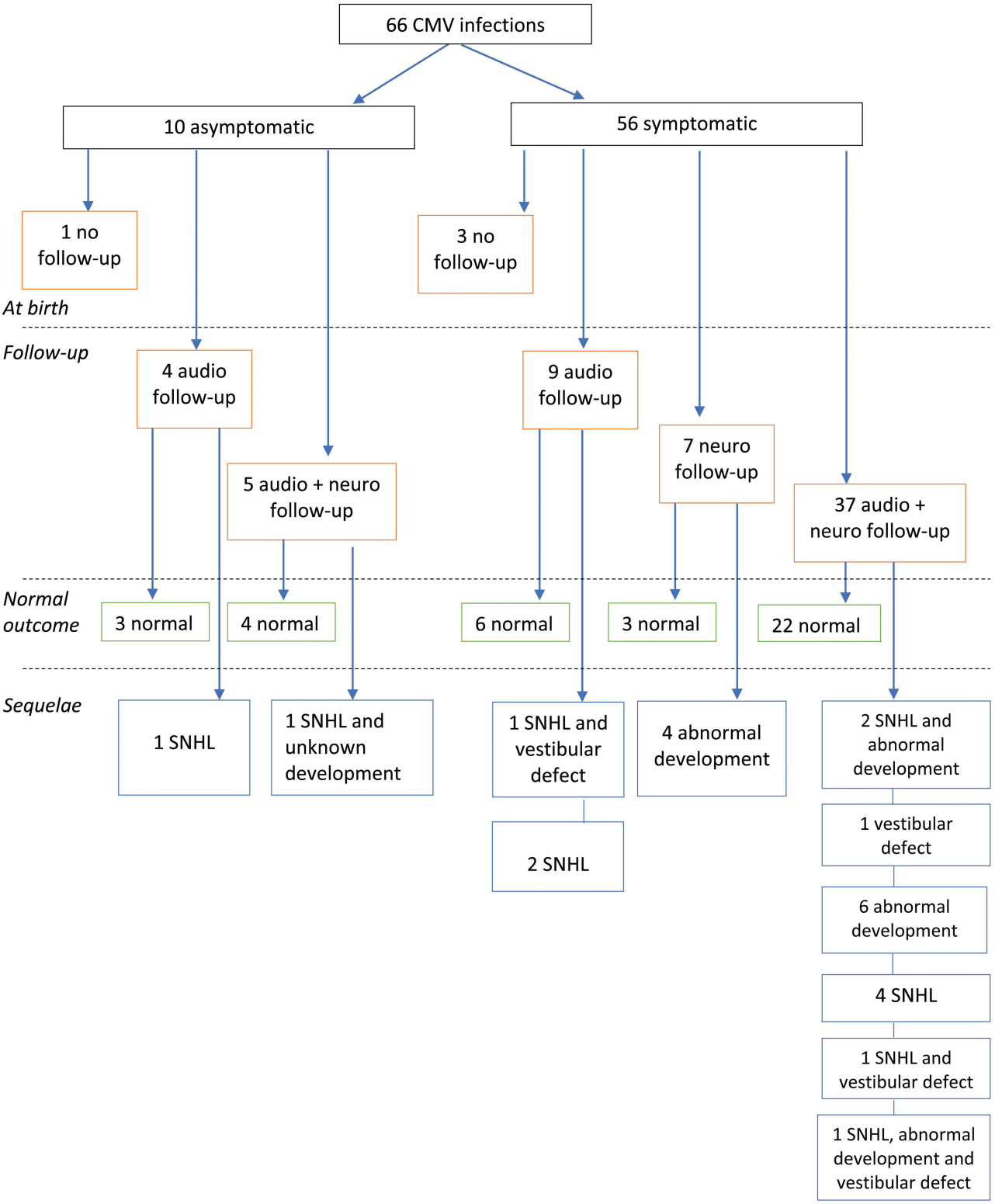

Fig. 1 Clinical characteristics at birth and audiological and neurodevelopmental outcomes of 66 children with cCMV. cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss; unknown = no follow-up.

calcifications were also less common compared with findings in other studies (35–70%).[26,29,30,35] Cerebral ultrasound and MRI showed periventricular pseudocysts in three patients, but ultrasound was superior to MRI in the detection of subependymal cysts (16 vs. 5 patients), unlike what was reported by Doneda et al.[38] While cerebellar anomalies, hypoplasia and dysplasia, are also commonly observed in cCMV and occur in up to 60% of affected patients, the prevalence of such anomalies was lower in our population.[29,35] The timing of maternal infection with CMV was

Table 5 Characteristic of 24 patients with congenital cytomegalovirus with long-term sequelae

	Maternal infection (anamnestic)	Maternal serology	Diagnostic test	Clinical manifestation	Laboratory result	Imaging at MRI	Hearing loss	Vestibular defect	Developmental score	Treatment valganciclovir
1	Unknown	IgG positive 1st trimester	Urine Ag + blood PRC (1 wk)	Microcephaly and IUGR	Thrombopenia, ⇑gGT	WMAs, intraventricular septations	No	Yes unilateral	Normal	Yes (52 wk)
5	Unknown	Missing	Urine Ag + blood PCR (1 week)	Microcephaly and IUGR	⇑gGT	Not done cUS normal	No	Not tested	Mild delay	No
6	Unknown	Missing	Urin Ag (1 week)	IUGR	Normal	Not done cUS normal	No	Not tested	Mild delay	No
7	Unknown	Missing	Urine Ag (3rd DoL)	Microcephaly and IUGR	Normal	Not done cUS normal	No	Not tested	Mild delay	No
9	3rd trimester	IgG positives 1st trimester	Viral culture in urine (3rd DoL)	Microcephaly and IUGR	Missing	Anterior temporal vacuolization	Mild and bilateral	Not tested	Normal	No
10	Unknown	Missing	Viral culture in urine (5th DoL)	IUGR	Missing	WMAs and anterior temporal vacuolization	Not tested	Not tested	Mild delay	No
15	1st trimester	Missing	Urine Ag (2nd DoL)	Normal	Normal	WMAs and anterior temporal vacuolization	Not tested	Not tested	Mild delay	No
17	Unknown	IgG positives 1st trimester	Urine PCR (6th DoL)	Microcephaly, HSM, 21 trisomy	⇑gGT, icterus	WMAs, anterior temporal vacuolization, and cerebellum hypoplasia	No	Not tested	Mild delay	No
21	Unknown	IgG positives 1st trimester	Urine PCR (10th DoL)	IUGR and hypotonia	Missing	Not done, cUS periventricular cysts	Severe and bilateral	Yes bilateral	Missing	No
22	Unknown	Missing	CMV DNA in dried blood spot at 1 y	Missing	Missing	WMAs, anterior temporal vacuolization	Severe bilateral	Yes bilateral	Normal	No
23	1st trimester	PCR in amniotic fluid	Urine Ag (3rd DoL)	Microcephaly and IUGR	Anemia and icterus	WMAs, anterior temporal vacuolization, and periventricular calcifications	No	No	Mild delay	No
28	Unknown	Missing	CMV DNA in dried blood spot at 2 y	Microcephaly	Normal	WMAs, anterior temporal vacuolization, and intraventricular synechiae	Severe and bilateral	No	Severe delay	No
34	1st trimester	Positive IgG and IgM in 1st trimester	Urine et blood PCR (2nd DoL)	Microcephaly, IUGR and petechiae	Anemia	WMAs, anterior temporal vacuolization, intraventricular synechiae, cerebellum hypoplasia, delayed myelination, periventricular calcifications and cysts, migrational abnormalities, ventriculomegaly	Severe unilateral	No	Severe delay	Yes (52 wk)
36	Unknown	IgG positives 1st trimester	Urine PCR (1st DoF)	Normal	Missing	WMAs and delayed myelination	Mild unilateral	No	Missing	Yes (26 wk)

(*Continued*)

Table 5 (*Continued*)

	Maternal infection (anamnestic)	Maternal serology	Diagnostic test	Clinical manifestation	Laboratory result	Imaging at MRI	Hearing loss	Vestibular defect	Developmental score	Treatment valganciclovir
40	Unknown	Missing	Dried blood spot at 5 y	Normal	Missing	WMAs and anterior temporal vacuolization	Severe unilateral	Yes bilateral	Mild delay	No
45	1st trimester	Positive IgG and IgM et blood PCR	Urine PCR (1st week of life)	Normal	Missing	WMAs and anterior temporal vacuolization	Severe unilateral	No	Normal	Yes (26 wk)
46	1st trimester	Positive IgG and IgM	Urine PCR (2nd DoL)	Microcephaly and IUGR	Normal	WMAs	Severe unilateral	Not tested	Normal	Yes (26 wk)
48	Unknown	Missing	Done abroad	Missing	Missing	Not done	Severe unilateral	Not tested	Missing	No
49	Unknown	Missing	Urine PCR (5th DoL)	Microcephaly and IUGR	Icterus	Anterior temporal vacuolization	No	Not tested	Mild delay	Yes (ganciclovir 2 wk)
58	1st trimester	Missing	Urine Ag and blood PCR (1st DoL)	Cardiac murmur (aortic stenosis)	⇑gGT, ⇑ALT and thrombopenia	WMAs, anterior temporal vacuolization, and periventricular cysts	Severe unilateral	Not tested	Normal	Yes (52 wk)
61	Unknown	Missing	Blood PCR (3 wk)	Normal	Missing	WMAs and cerebellum hypoplasia	Severe bilateral	No	Normal	Yes (duration unknown)
72	Unknown	Missing	Viral culture in urine (3rd DoL)	IUGR	⇑gGT and ⇑ALT	Not done cUS normal	Missing	Not tested	Mild delay	No
73	2nd trimester	Missing	Viral culture in urine (2nd DoL)	Normal	⇑gGT and ⇑ALT	Not done cUS normal	Missing	Not tested	Mil delay	No
80	1st trimester	Missing	Dried blood spot at 1 y	Microcephaly and IUGR	Missing	Anterior temporal vacuolization	Severe bilateral	No	Missing	Yes (16 wk)

Abbreviations: Ag, antigen; ALT, alanine transaminase; cUS, cerebral ultrasound; DoL, day of life; gGT gamma, gamma-glutamyl transferase; IgG, immunoglobulin G; IgM, immunoglobulin M; IUGR, intrauterine growth restriction; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; WMAs, white matter abnormalities.

challenging to estimate due to the lack of prenatal maternal screening and awareness about CMV infection, including in our region.[19] Maternal serology was performed in a minority of cases and timing of infection was unavailable for a significant portion of the population, precluding any analysis by trimester of infection. Therefore, the association between the trimester of infection and the spectrum of cerebral abnormalities could not be determined.

SNHL can be present at birth or appear later, and its incidence varies between symptomatic and asymptomatic cases, with up to 50% occurring in symptomatic infants.[24,39–42] In our study, the proportion of SNHL was similar in both groups, (21% for symptomatic patients and 20% for the asymptomatic ones). Long-term audiometric monitoring is necessary as hearing loss can be progressive and oral language acquisition is slower in children with SNHL due to cCMV, compared with other etiologies.[43] Uni- or bilateral cochlear implantation can be performed for severe bilateral hearing loss.

The influence of cCMV on vestibular function has recently been recognized and previous studies reported a higher prevalence of vestibular disorders (10–50%), especially in symptomatic and hearing-impaired patients, than observed in our study (6%).[41,44,45] An increasing number of studies show the impact of vestibular function loss on motor development as well as other cognitive abilities and recognizes the importance of early interventions.[45]

The negative effects of cCMV on neurodevelopment have been well documented in symptomatic infants, although approximately half of them have a normal cognitive outcome.[30] In this study, approximately two-thirds of symptomatic patients had normal neurological status and developmental scores within the average range. This difference could be due to the definition of symptomatic patients that differs between centers and over time. However, no specific clinical or radiological sign, except for ventricular septation, was associated with developmental delay in this cohort. Less is known about the neurodevelopmental outcomes of asymptomatic infected infants. Novelli et al studied a cohort of 56 asymptomatic cCMV infants and found that over 55% had a slightly abnormal neurological status at 6 months of life,[46] whereas this study found normal neurodevelopmental assessments in all asymptomatic cases, when performed.

This study has limitations inherent to its retrospective design, including the possibility of missing some patients; however, it is unlikely that a severe case was missed. Due to the reliance on private gynecologists for prenatal care in Geneva, there is a possibility of missing maternal serologic results, including the differentiation between primary and nonprimary infection and the timing of infection, resulting in missing data and potentially inaccurate clinically inferred infection timings in the cases without serological results. Nevertheless, substantial efforts were made to obtain maternal serological data from private laboratories for each child included in the study.

In conclusion, this study highlights factors that are directly linked to a poor long-term outcome, including microcephaly and MRI abnormalities. The findings underscore the need for increased awareness and preventive measures among pregnant women, considering the lack of knowledge about cCMV and its potential risks.[19] Maternal immunity acquired before conception does not provide complete protection against infection, transmission, or disease, emphasizing the importance of routine CMV serological screening during pregnancy to identify and monitor infected infants. Interventions during pregnancy are being explored, such as treatment of mothers with antivirals, and may provide new options for preventing poor outcomes in children.[47] While awaiting further clinical trial on maternal treatment and the development of new CMV vaccines, it is crucial to inform pregnant women about measures to prevent transmission. Increasing awareness of cCMV should be a priority to mitigate its impact on newborns and improve long-term outcomes.

Conflict of Interest
None declared.

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