Postnatal outcome of fetuses with congenital cytomegalovirus-associated cerebral lesions

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ABSTRACT

Background and purpose: Congenital cytomegalovirus (CMV) infection is an important cause of hearing impairment and neurodevelopmental delay. Outcome is related to fetal cerebral injury. When cerebral lesions are discovered, termination of pregnancy is often proposed. Therefore, we wanted to evaluate the prognosis of congenital cerebral lesions associated with prenatal cytomegalovirus infection to enhance prenatal counselling.

Methods: This was a retrospective observational study of CMV-infected children with fetal and/or early neonatal cerebral lesions from a tertiary referral university hospital.

Results: Of the 25 cases, 36% had normal outcome, 16% sensorineural hearing loss (SNHL), 28% psychomotor development disorders (PDD), and 20% combined PDD and SNHL. In fetuses infected before the second trimester, outcome was poorer and the number of cerebral injuries higher. The cerebral lesions were discovered at a median of 27w3d but could appear until the end of pregnancy. Subependymal and paraventricular pseudocysts, lenticulostriate vasculopathy, ventricular asymmetry and mild ventriculomegaly were common unspecific cerebral findings associated with good outcomes. Isolated white matter abnormalities on magnetic resonance imaging had also good outcomes. The other CMV-associated cerebral lesions were less common but more specific to CMV infection and carried poorer prognosis.

Conclusion: Neurodevelopmental prognosis is better when CMV infection occurs after the first trimester and depends mainly on the type and extension of cerebral lesions. Indeed, one third of the children with cerebral imaging findings developed normally. Since some brain lesions do not necessarily have a poor prognosis, antiviral treatments may be an alternative to termination of pregnancy in these cases.

KEYWORDS

Cytomegalovirus, congenital infection, outcome, cerebral lesions, prenatal diagnosis, fetal imaging.

Introduction

Cytomegalovirus (CMV) infection is the main cause of congenital neurodevelopmental delay and hearing loss. Between 1.5 and 20 out of 1,000 newborns are infected [1-6]. About 10-15% newborns are symptomatic [2,7-10] and develop long-term sequelae in 40-90% of cases [8-10].

There is little literature regarding the outcome of live births with prenatal CMV-associated cerebral lesions [11-15], and the prognosis of each kind of cerebral lesion is still unknown. Nevertheless, termination of pregnancy is usually proposed [16,17].

The aim of this study was to investigate the outcome of children with congenital CMV-associated cerebral lesions to enhance prenatal counselling after fetal CMV infection.

Methods

This was a retrospective observational study from a tertiary referral university hospital (Cliniques Universitaires Saint-Luc, Brussels, Belgium).

CMV registers from 1999 to 2015 were screened with the following eligibility criteria: prenatal or early neonatal CMV-associated cerebral findings and proven CMV infection at birth. 25 mother-and-child cases met the eligible criteria after review (Figure 1).

We classified the children's global outcomes into four groups based on their medical records: normal, sensorineural hearing loss (SNHL), psychomotor development disorders (PDD), and PDD+SNHL. Psychomotor development referred to the cognitive, motor, socio-emotional and language development.

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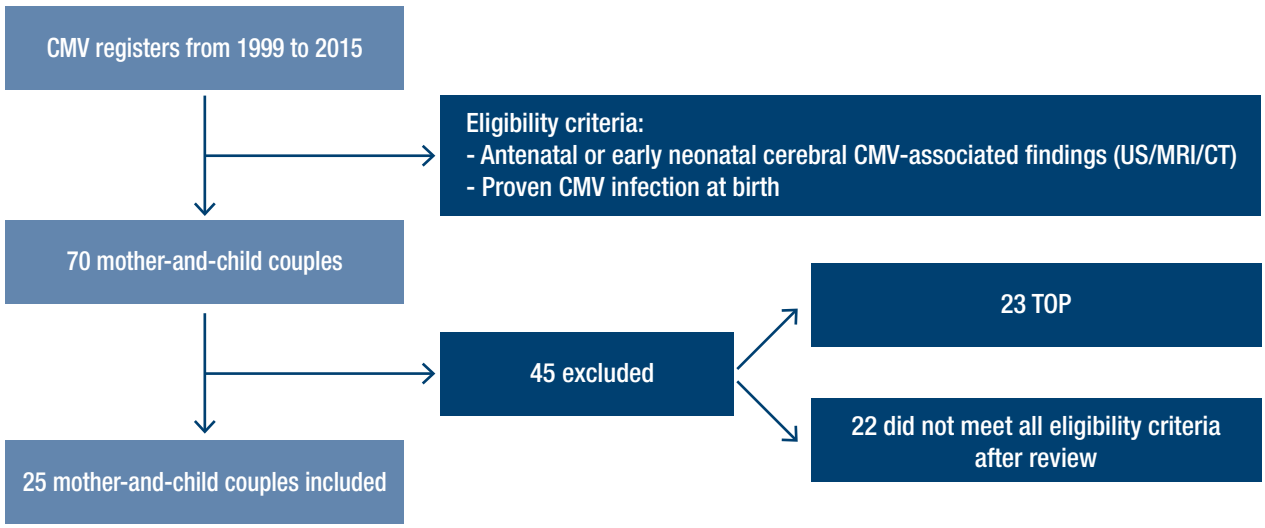
Figure 1 Patient inclusion flow chart



US/MRI/CT: ultrasound/magnetic resonance imaging/computed tomography; **TOP:** termination of pregnancy

Results (Table 1)

CMV infection diagnosis

Mother – Most mothers had primary [8,9,17-20] CMV infection before the second trimester of pregnancy (4/23 periconceptional period (before 4 gestational weeks), 15/23 first trimester (from 4 to 14 gestational weeks), 4/23 second trimester (from 15 to 28 gestational weeks). There were two non-primary [6] CMV infections: one diagnosed at birth and one following fetal ultrasound (US) abnormalities.

Fetus – Amniocentesis (17/25) was performed at a median of 21w2d of gestation. CMV infection was detected by polymerase chain reaction (PCR) and viral culture in amniotic fluid.

Newborn – Newborn urines were tested for CMV by culture (21/25) and/or PCR (4/25). Additionally, CMV was searched by PCR in cerebrospinal fluid (4/13 positive) and in blood (11/11 positive). CMV IgM were found in 5/13 cases.

Imaging findings

Twelve fetuses presented at least one extracerebral damage at a median of 27w1d: hyperechogenic bowels, hepatomegaly, splenomegaly, growth retardation, polyhydramnios or placentomegaly.

Prenatal cerebral findings were seen on US at a median of 27w3d [22w3d-36w2d]. Fetal cerebral magnetic resonance imaging (MRI) was performed in 15 cases at a median of 32w2d.

Other information

Delivery occurred at a median of 38w2d. Three newborns (#3, #17, #23) had an Apgar score below 4 at one minute of life and suffered from multiple brain lesions and psychomotor disorders (± SNHL).

Table 1 Description of the cases

#	Serocon-Version	Imaging	Birth	Treatment	Auditory Outcome	Psychomotor Outcome	Follow-Up (Y)
1	T1	SEPC, LSV, calc, hyperUS ependyma, temp cyst, occipit cyst, intravent septa	39+5, hypotrophy	Ganc 6w	Deafness	Axial hypotonia with good evolution	5
2	T1	LSV	38+2	Valg 6w	Normal	Normal	2.3
3	R°	SEPC, LSV, WM abn, temp cyst, occipit cyst, perivent halo	32+4, C/S (female genital mutilation + PROM), transient neonatal cholestasis	Valg 6w	Normal	Cognitive and language delay	4
4	T1	SEPC, PVPC, LSV, WM abn, bilat vent, calc, temp cyst, perivent halo, hyperUS bowel, placentitis	38+3, purpura, HSM, thrombocytopenia	Ganc 6w	Deafness	Cerebral palsy, diplegia, global developmental delay, autistic features, cognitive deficits, behavioural disorders	15
5	T2	WM abn, hyperUS ependyma, microcephaly	35+0, C/S (PROM + bleeding placenta praevia), microcephaly	No	Normal	Microcephaly, mild lower limb hypertonia	1
6	T1	SEPC, LSV, vent asym, hepatoM	38+0	No	Normal	Normal	13

#	Serocon-Version	Imaging	Birth	Treatment	Auditory Outcome	Psychomotor Outcome	Follow-Up (Y)
7	concept	SEPC, splenoM	39+4	No	Left deafness + mild right hypoacusis	Normal	1.6
8	R°	WM abn, bilat vent, calc, hyperUS ependyma, gyral abn, microcephaly, intravent septa, c callosal hypoplasia, cerebellar hypoplasia	38+2	Ganc 2w + Valg 2w	Normal	Encephalopathy, cerebral palsy, spastic quadriplegia, gastrostomy, epilepsy	3
9	T1	WM abn, calc, splenoM, plexus choroid cyst	38+5	No	Normal	Global psychomotor delay (mostly language)	3.5
10	T1	SEPC, PVPC, LSV, calc	38+0	No	Normal	Normal	10
11	T1	SEPC, PVPC, LSV	39+1, iterative C/S	No	Normal	Normal	1.8
12	T1	SEPC, WM abn, calc, hyperUS bowel	41+0, C/S (AFD), purpura, thrombocytopenia, HSM	No	Left deafness	Spastic diplegia, language and behavioral disorders	7.5
13	T2	SEPC, LSV, vent asym	39+1	Valg 6w	Normal	Normal	3.5
14	T1	SEPC, LSV, WM abn, unilat vent, gyral abn, temp cyst, occipit cyst, hepatoM, abn caudate nucleus echogenicity	38+3 Transient allo-immune thrombocytopenia	Ganc 1w + Valg 6m	Unilateral hypoacusis	Axial hypotonia	0.5
15	concept	SEPC, plexus choroid cyst	36+4, C/S (breech) Transient neonatal cholestasis, growth retardation	Valg 6w	Left deafness	Axial hypotonia with good evolution	2
16	concept	SEPC, WM abn, bilat vent, calc, hyperUS ependyma, gyral abn, microcephaly, perivent halo, cerebellar hypoplasia, growth retardation	34+0, purpura	No	Normal	Global developmental delay, cerebral palsy, right hemiparesis, microcephaly, mental retardation, epilepsy	9.5
17	concept	SEPC, LSV, WM abn, hyperUS ependymal, hepatoM, splenoM, placentitis	35+5, C/S (AFD), anaemia, thrombocytopenia, coagulation disorders, cholestasis, splenoM	Ganc 6w + Valg 6w	Deafness	Normal	7.5
18	T1	SEPC	38+6	Ganc 6d	Normal	Normal	3
19	T2	LSV	37+4	No	Normal	Normal	1
20	T1	SEPC, PVPC, LSV, WM abn, growth retardation, PHA, septum pellucidum cyst	40+2	No	Normal	Language delay	4
21	T1	SEPC, LSV, WM abn, vent asym, temp cyst, c callosal hypoplasia	40+5	No	Normal	Cerebral palsy, mild psychomotor delay, right hemiparesis, microcephaly, febrile + absence seizure	2.8
22	T1	SEPC, vent asym, temp cyst, occipital cyst, cavum vergae	39+3, Klinefelter chimerism	Valg 6m	Deafness	Normal	1.8
23	T1	SEPC, LSV, WM abn, bilat vent, calc, hyperUS ependymal, gyral abn, occipit cyst, microcephaly, perivent halo, growth retardation	41+0, C/S (AFD)	Ganc 1m + Valg 5m	Right deafness	Cerebral palsy (left hemiplegia), epilepsy, microcephaly, microphthalmia	1.7
24	T2	PVPC, plexus choroid cyst	40+1	No	Normal	Normal	2.4
25	T1	SEPC, PVPC, hyperUS bowel	39+0	Ig anti-CMV Valg 6w	Normal	Normal	2

#: case number, **abn:** abnormal, **AFD**: acute fetal distress, **bilat vent**: bilateral ventriculomegaly, **c callosal hypoplasia**: corpus callosal hypoplasia, **C/S**: caesarean delivery, **calc**: calcifications, **concept:** periconceptional period, **d/w/m/y**: day/week/month/years, **Ganc**: ganciclovir, **gyral abn**: gyral abnormalities, **HSM**: hepatosplenomegaly, **hyperUS bowel**: hyperechogenic bowel, **hyperUS ependyma**: hyperechogenic ependyma, **hepatoM**: hepatomegaly, **intravent septa**: intraventricular septa, **LSV**: lenticulostriate vasculopathy, **perivent halo**: periventricular halo, **occipit cyst**: occipital horn cyst, **PHA**: polyhydramnios, **PROM**: premature rupture of membranes, **PVPC**: paraventricular pseudocyst, **R°**: CMV reactivation, **SEPC**: subependymal pseudocyst, **splenoM**: splenomegaly, **T1**: first trimester of pregnancy, **T2**: second trimester of pregnancy, **temp cyst**: temporal horn cyst, **unilat vent**: unilateral ventriculomegaly, **Valg**: valganciclovir, **vent asym**: ventricular asymmetry without ventriculomegaly, **w**: weeks, **WM abn**: white matter abnormalities.

Newborn – Six newborns exhibited clinical or biological signs of CMV infection [17,21]: small for gestational age, microcephaly, petechiae, hepatosplenomegaly, thrombocytopenia, anemia, coagulation disorders, cholestasis.

Further examinations – Electroencephalography (12/25) showed signs of epilepsy in three cases. Auditory brainstem evoked responses (24/25) revealed SNHL in 9 children. Fundoscopy (22/25) was pathological in two cases (#12, #18) with nevertheless good visual outcomes.

Treatments – One mother (#25) with a dichorionic diamniotic twin pregnancy and discordant infection [22] was treated with two injections of specific immunoglobulins. Despite this, one fetus had many lesions and was selectively terminated at 34w0d. The other fetus developed normally.

Thirteen newborns were treated with ganciclovir and/or valganciclovir for 6 days to 6 months.

General outcome

Children were followed-up for 6 months to 15 years (median 4.3 years): 36% had normal development, 16% SNHL, 28% PDD and 20% PDD+SNHL. Children with PDD had various severe global clinical disorders, including epilepsy, cerebral palsy and mental, language or motor delay. Outcome worsened when the number of cerebral findings increased. Outcome was better when infection occurred during the second trimester of pregnancy (3/4 normal, 1/4 PDD).

Outcome based on cerebral findings (Figures 2, 3)

Periventricular pseudocysts (20/25), divided into subependymal (SEPC – 19/25) and paraventricular pseudocysts (PVPC – 6/25) [23], had good outcomes. SEPC were isolated in one case with normal development (#18) and one with SNHL (#7). Outcome was normal in co-occurring of SEPC with lenticulostriate vasculopathy (LSV) (#6, #11, #13), PVPC (#11, #25) and ventricular asymmetry without ventriculomegaly (#6, #13). Outcome was normal for PVPC with transient choroid plexus cyst (#24). One case (#15) with SEPC and plexus choroid cyst had transient neonatal cholestasis and growth retardation. This case presented axial hypotonia in the first months of life with normalization after physiotherapy.

Lenticulostriate vasculopathy (LSV) (14/25) was isolated in two cases with normal outcomes (#2, #19). Development was also good when associated to SEPC (#6, #11, #13), PVPC (#11) and ventricular asymmetry (#6, #13).

The next cerebral lesions were never isolated.

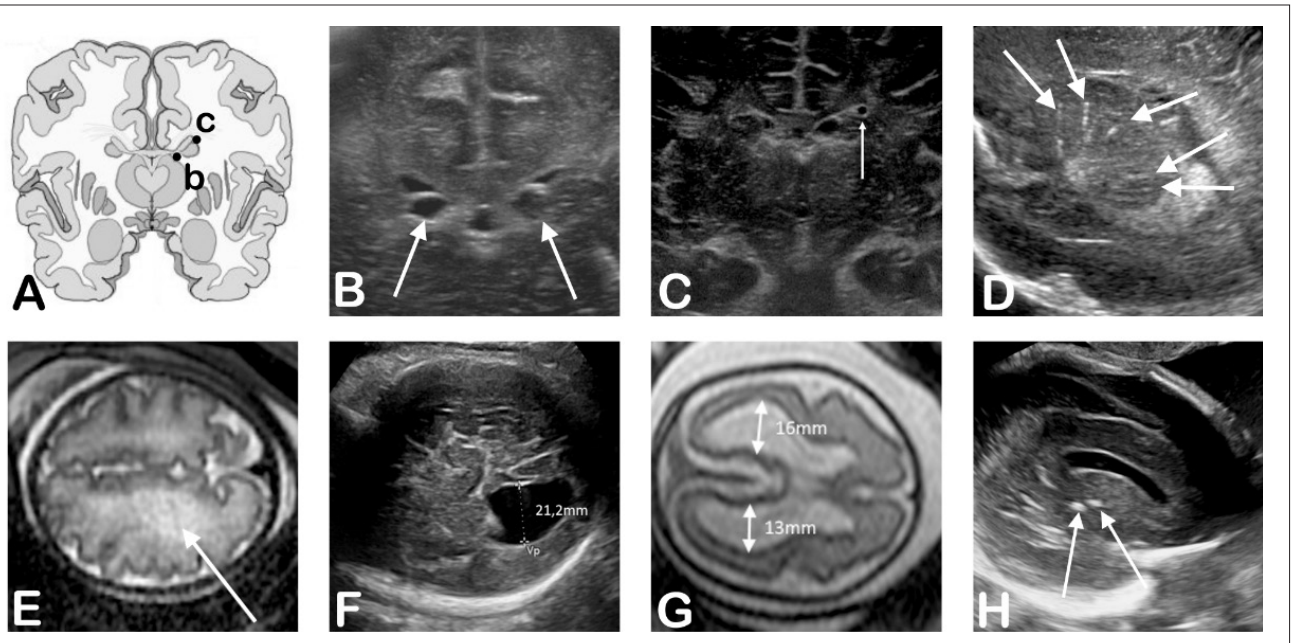
White matter abnormalities (12/25) coexisted always with poor outcomes (PDD±SNHL).

Ventricular size abnormalities (8/25): Outcome was normal for ventricular asymmetry without ventriculomegaly (4/25) when it co-occurred with SEPC and LSV (#6, #13). There was one case (#14) of unilateral severe ventriculomegaly suffering from PDD+SNHL. Cases with bilateral ventriculomegaly (moderate [#4, #8] or severe [#16]) had neurodevelopmental delay.

Cerebral calcifications (8/25): Two children (#1, #10) with microcalcifications had normal outcomes. Case #12 with SEPC, white matter abnormalities and a single calcification spot next to the lateral sulcus developed severe bilateral SNHL, spastic diplegia, language and behavior disorders.

The others (#4, #8, #9, #16, #23) had multiple periventricular or parenchymal calcifications and suffered from cerebral palsy

Figure 2 Cerebral lesions associated with CMV infection (**A**. Periventricular pseudocysts : subependymal (b) and paraventricular (c) pseudocyst. **B**. Subependymal pseudocysts (#20, TCU, day 1 post-natal). **C**. Paraventricular pseudocyst (#24, TCU, day 6 post-natal). **D**. Lenticulostriate vasculopathy (#14, TCU, day 1 post-natal). **E**. Hypersignal T2 white matter (#14, MRI, 32w5d). **F**. Unilateral ventriculomegaly (#14, US, 35w2d). **G**. Bilateral ventriculomegaly (with lissencephaly, microcephaly, calcifications) (#16, MRI, 30w2d). **H**. Cerebral calcifications (#8, US, 28w5d))



#: case number; **MRI**: magnetic resonance imaging; **TCU**: transcranial ultrasound; **US**: ultrasound; **w/d**: week/day of pregnancy

and global developmental delay ±SNHL.

Hyperechogenic ependyma (6/25) appeared with bad outcomes: severe SNHL (#1, #17, #23), limb hypertonicity at 12 months of life (#5 infected during the second trimester) and cerebral palsy (#8, #16, #23).

Gyration *disorders* (4/25) coexisted with at least motor development delay (#8, #14, #16, #23). In case #14, the follow-up was only up to 6 months so it was too early to know how the axial hypotonia would progress.

Temporal horn cysts (5/25) were observed with deafness (#1, #22), hypoacusis (#14), axial hypotonia (#1, #14), cognitive and language delay (#3) and cerebral palsy (#21).

Occipital horn cysts (4/25) accompanied frequently temporal horn cysts (#1, #3, #22). Case #23 developed cerebral palsy, epilepsy and deafness.

Microcephaly (4/25) was associated with PDD (#5, #8, #16, #23). Case #5 was long-lost after 12 months.

Periventricular halo (4/25) co-occurred with severe developmental delay (#3, #4, #16, #23).

Intraventricular septa (3/25): Outcome was always poor, namely, bilateral deafness (#1), hypoacusis (#14), axial hypotonia (#1, #14) and cerebral palsy with epilepsy (#8). Case #1 presented bilateral deafness and axial hypotonia with good evolution with physiotherapy care.

Corpus callosum hypoplasia (2/25) accompanied epilepsy (#8) and cerebral palsy (#8, #21).

Cerebellar hypoplasia (2/25) was seen with cerebral palsy (#8, #16), epilepsy (#8, #16) and mental retardation (#16).

Other cerebral findings were also seen: choroid plexus cyst (#9, #15, #24), septum pellucidum cyst (#16, #20), cavum verge (#20) and hyperechogenic caudate nucleus (#14).

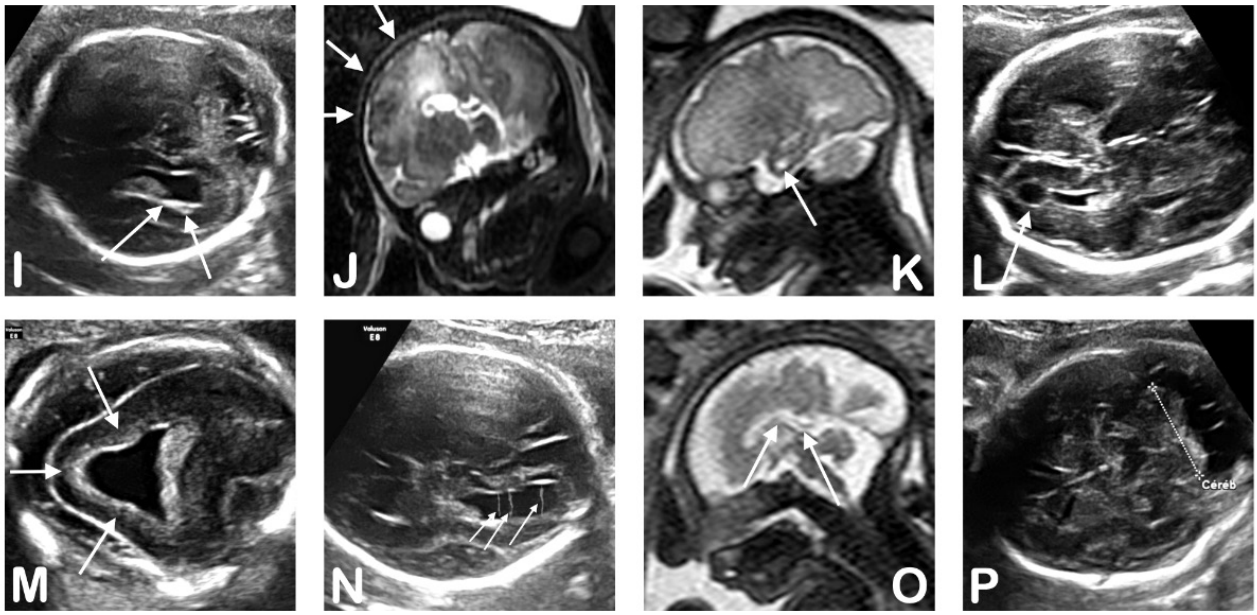
Discussion

CMV may affect fetuses 6 to 8 weeks after maternal infection [9,18,24,25]. Cerebral injuries are caused by tissue destruction, inflammatory response and stem cell vulnerability during critical early stages of brain development [26,28]. This vulnerable period explains that poor outcomes mainly follow infections in the beginning of the pregnancy [5,6,11,29-32], even if the rate of maternal fetal transmission increases with gestational age [17,20,31,33,34]. The case (#5) with second trimester seroconversion and microcephaly was born in 2002. Because the serological test at the end of the first trimester was performed in an external small laboratory, we wonder if the quality of the test was sufficient and if it is a true second trimester infection. With the recent study from Leruez-Ville there is a ray of hope to prevent CMV sequelae with the administration of valaciclovir during pregnancy [35].

Ancora *et al*. [36] found that cerebral lesions in symptomatic neonates are associated with >90% risk of at least one sequela or neonatal death. The review of Hui and Wood [11] suggests that prenatal cerebral abnormalities may carry up to 90% risk of abnormal outcome. However, a third of the children in our study had normal outcomes, confirming Noyola *et al*. observation [37]. Nevertheless, outcome worsens when the number of cerebral lesions increases and these may appear throughout the pregnancy.

MRI enhances the positive and negative predictive value of US for the diagnosis of fetal brain abnormalities [6,28,38,39]; although a normal target prenatal US has the best negative predictive value (>90%) [13,40]. Isolated lesions suspected on MRI alone should be considered with caution [11,16] because of the risk of MRI false positive findings [41]. Besides, the risk of

Figure 3 Cerebral lesions associated with CMV infection. (**I**. Hyperechogenic ependyma (#8, US, 26w5d). **J**. Gyral abnormalities (#14, MRI, 32w5d). **K**. Temporal horn cyst (#1, MRI, 32w0d). **L**. Occipital horn cyst (#1, US, 29w0d). **M**. Periventricular halo (Obstetrics Department's archive). **N**. Intraventricular septa (#8, US, 28w5d). **O**. Corpus callosal hypoplasia (#8, MRI, 35w0d). **P**. Cerebellar hypoplasia (#8, US, 28w5d)



#: case number; **MRI**: magnetic resonance imaging; **TCU**: transcranial ultrasound; **US**: ultrasound; **w/d**: week/day of pregnancy

SNHL remains high until three years of life even if cerebral examination appears normal [8,12,13,30,41,42].

Subependymal pseudocysts develop in the periventricular subependymal area, which contains germinal cells, the main target of CMV [43-45]. As the germinal matrix moves during gestation, their location may indicate the timing of infection [44]. They are found in the caudothalamic groove, below the superolateral angle of the lateral ventricles and posterior to the foramen of Monro [23,46-49].

We confirm that isolated SEPC have good neurodevelopmental outcome [6,44,45,47,49,50].

Paraventricular pseudocysts are located at or just below the superolateral angle of the frontal horns or body of the lateral ventricles, and mainly anterior to the foramen of Monro [23,48-51]. They are normal variants or appear after germinolysis [50-52]. Their prognosis is good [6,15,46,49-52].

Cooper *et al*. [49] have described normal outcomes in cases of SEPC/PVPC combined with mild/moderate ventriculomegaly, ventricular asymmetry or MRI white matter abnormal signal. We found closely similar results, as when accompanying LSV.

Lenticulostriate vasculopathy remains a subjective diagnosis rather similar to the shadow of thin echogenic vessels of normal neonates [53,54]. We found a good outcome for isolated LSV [53-55].

White matter abnormalities were associated with poor outcomes in our study but were never isolated. In cases of isolated white matter abnormalities, Capretti *et al*. [12] have described mild cognitive delay and late-onset SNHL while several studies report completely normal outcomes after CMV infection [6,7,11,13,30,37]. When cerebral US examination appears normal, the nature and significance of isolated white matter MRI signal abnormalities are unclear: they may represent a possible delayed myelination in late CMV infection, or a false positive finding [6,41]. Therefore, the probability of neurodevelopmental impairment is low for isolated abnormal white matter signal [13,16,41].

Ventricular size abnormalities: The larger the ventricular dilatation gets, the poorer the neurodevelopmental prognosis becomes [6,56-59]. Pisapia *et al*. [60] have estimated the overall risk of disability in mild ventriculomegaly to be around 10-36%, regardless of its etiology. However, Guerra *et al*. [61] have described cases of normal neurological outcome in isolated CMV-associated ventriculomegaly. We support the idea that isolated ventricular asymmetry [49,62] or mild ventriculomegaly (≤12mm) are not related to poor outcome.

Cerebral calcifications: A single punctate calcification is not associated with poor outcomes according to Noyola *et al*. [37]. Conversely, multiple periventricular or parenchymal calcifications are associated with abnormalities of cortical development and mental retardation [37,63,64]. The clinical manifestations depend on their location, including for example seizures and motor disabilities [65]. Two cases with small punctate calcifications developed normally, others with multiple calcifications or a single calcification spot suffered from psychomotor delay.

Hyperechogenic ependyma: Hyperechogenicity of the ventricular ependyma is a subjective sign, with no specific references except in relation to periventricular halo. Based on our study, we could not establish a close relationship between them. The outcome of our cases varies from severe SNHL to cerebral palsy.

Gyral abnormalities have poor neurodevelopment prognosis. Brain injuries before 16-18 weeks of gestation give lissencephaly, a neuronal cell migration disorder, and between 18-24 weeks polymicrogyria, a cortical organization disorder [9,28,39,66,67]. Polymicrogyria produce a wide spectrum of clinical manifestations including seizures, cognitive delay, hypertonicity, ataxia and hemiparesis [27,68].

***Temporal horn* cysts** are considered to follow damages to the amygdaloid, parahippocampal and temporal subventricular germinal zones [26,43], which are better seen on MRI than on US [6,63]. Our cases had poor outcomes.

Occipital horn cysts, another lesion of the germinal subventricular zone, seem to appear following the natural progression of hyperechogenic periventricular halo. They may be specific signs of congenital CMV infection [14,43,63]. Our cases accompanied frequently temporal horn cysts and presented poor outcomes.

Microcephaly means that head circumference is below three standard deviations [69]. This suggests brain injuries before 25 gestational weeks, before the ending of neurogenesis and neuronal migration [26]. In our study, all children with microcephaly had PDD. Indeed, microcephaly is the most specific predictor for severe neurological sequelae [7]. It has 100% specificity and positive predictive value for the development of mental retardation and 92% specificity for the prediction of major motor deficits [37,70].

Periventricular halo is defined as bilateral areas of homogeneous increased echogenicity of the white matter parenchyma surrounding the ventricular margins, with well-defined borders [63,71]. There seems to be a continuum between the inflammatory process of the periventricular halo and the development of (pseudo)cysts due to germinal necrosis [63,72], as the halo decreases when the periventricular (pseudo)cysts appear during the second trimester [73]. Picone *et al*. [43] have suggested that periventricular echogenicity progressing to posterior occipital horn cysts is one of the most characteristic features of CMV infection. Malinger *et al*. [14] found it in all CMV-infected fetuses and never as an isolated feature [63].

In our study, all cases with periventricular halo presented severe developmental delay. According to Simonazzi *et al*. [71], periventricular halo's histopathologic aspect is well correlated with telencephalic leukoencephalopathy, a diffuse white matter ischemia known to be related to cerebral palsy. However, Cannie *et al*. [38] have described good neurological prognosis for isolated periventricular MRI T2-weighted hyperintensity: this should be linked with the reassuring prognosis of isolated white matter abnormalities discussed above.

Intraventricular septa are imaging aspects resulting from the fusion of adjacent pseudocysts. According to Malinger *et al*. [63] this is a CMV pathognomonic sign corresponding to the separation of the ependyma from the adjacent tissue after substantial germinal damage. This is usually found in the occipital horns but may appear in the temporal horns [63]. We found it in only three cases presenting PDD or deafness.

Corpus callosum hypoplasia follows CMV infection and other multiple conditions. Guibaud *et al*. [69] have observed that

it could also result from severe microcephaly alone owing to major neuronal and commissural axon loss. Its prognosis varies from mild to severe neurological deficits [74]: our two cases suffered from cerebral palsy.

Cerebellar hypoplasia was found with PDD. Massoud *et al*.[75] have described a case of CMV-associated unilateral cerebellar hypoplasia and severe developmental delay.

To **summarize** (Table II), SEPC/PVPC and LSV are very common unspecific findings related to good outcomes. Mild ventriculomegaly or ventricular asymmetry have good neurodevelopmental prognosis, even if associated to SEPC/PVPC/LSV. White matter abnormalities are very frequent and present reassuring outcomes if they are isolated on MRI. Neurodevelopmental prognosis seems poor for calcifications but can be reassuring for punctate calcifications. Hyperechogenic ependyma and particularly gyral abnormalities are associated with cerebral palsy. Microcephaly is the most specific predictor for severe neurological sequelae. Periventricular halo, temporal and occipital horn cysts and intraventricular septa are all related. They are specific infrequent findings following injuries to the subventricular germinal zones and have poor prognosis. Corpus callosum and cerebellar hypoplasia are rare unspecific abnormalities with poor outcomes. It should be clear that the prognosis worsens with the combination of several cerebral lesions.

Limitations

This study is a detailed analysis of the outcome of CMV-associated cerebral damage and, to our knowledge, the largest of its kind. The cases were well documented and the children were followed up for 6 months to 15 years (median 4.3 years). However, it has some limitations because it is a retrospective descriptive study with a small number of cases. The diagnosis, treatment and follow-up of the patients were organized in numerous hospitals and therefore without standardization. Besides, we cannot exclude the confounding effects of the used treatments. Furthermore, as the cerebral findings mainly co-occurred, it is difficult to precisely isolate the prognosis of each one. Large prospective studies are needed to ascertain the correlation between these abnormalities and the long-term outcomes.

Conclusion

CMV infected fetuses are at risk of SNHL and severe developmental delay. Even though the risk of SNHL remains high with an appearing normal cerebral examination, the neurodevelopmental prognosis mainly depends on the type and number of cerebral lesions and is better when CMV infection occurs after the first trimester. In our study, a third of the children with cerebral findings developed normally. This corresponds mainly to cases with SEPC, PVPC, LSV, ventricular asymmetry and mild ventriculomegaly. Table 2 summarizes the significance of the CMV-associated cerebral lesions, which may appear until the end of pregnancy. A multidisciplinary approach is necessary to provide the most accurate counseling to parents. Since some brain lesions do not necessarily have a poor prognosis, antiviral treatments may be an alternative to termination of pregnancy.

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Table 2 Summary of CMV-associated cerebral lesions

Cerebral Lesions	Frequency	Specificity	Severity	Significance
Subependymal pseudocyst	+++	-	-	Good outcome if isolated
Paraventricular pseudocyst	+	-	-	Good outcome if isolated
Lenticulostriate vasculopathy	+++	-	-	Good outcome if isolated
Ventriculomegaly	++	-	-/+	Good outcome if mild and isolated
White matter abnormalities	+++	+	-/++	Good outcome if only lesion on MRI; otherwise bad
Calcifications Hyperechogenic ependyma	++	++	+++	Poor outcome
Gyral abnormalities Microcephaly	+	++	+++	Poor outcome
Temporal horn cyst Occipital horn cyst Periventricular halo Intraventricular septa	+	+++	+++	Poor outcome
Corpus callosal hypoplasia Cerebellar abnormalities	-	-	+++	Poor outcome

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