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MRI findings in children with congenital cytomegalovirus infection retrospectively diagnosed with dried umbilical cord

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Abstract

Purpose Brain MRI provides important information about suspected congenital CMV infection in neonatally underdiagnosed children. This study aimed to describe MRI findings in children in whom congenital CMV infection was not suspected during the neonatal period and was proven retrospectively.

Methods We enrolled 31 children referred to the pediatric neurology clinic with neurological symptoms who were proven to have congenital CMV infection based on dried umbilical cord samples. Upon diagnosis, MR and CT images were assessed using the van der Knaap scoring system integrated with additional variables. Two investigators independently assessed all images.

Results The age at diagnosis was < 12 months in 14, 12–24 months in 11, and > 24 months in 6 patients. The initial symptom triggering clinic referral was delayed development in 22, seizure in 5, deafness in 3, and hemiplegia in 1 patient. Of the 31 children, 30 had a white matter (WM) abnormality predominant in the deep WM of the parietal lobe ($n = 25$). Anterior temporal lesions were observed in 21 children. Cortical lesions were observed in 7 children, suggestive of polymicrogyria. No child had cerebellar or brainstem abnormalities. Brain CT was performed in 22 of 31 children, and 11 showed punctate cerebral calcification in the periventricular and/or deep WM.

Conclusion Patients with congenital CMV infection with delayed neurological symptoms show a relatively uniform pattern of parietal-dominant multifocal WM lesions and anterior temporal lesions, with or without polymicrogyria.

Keywords Cytomegalovirus · MRI · PCR · Umbilical cord · Brain injury

Abbreviations

CMV	Cytomegalovirus
SGA	Small for gestational age

Introduction

Congenital cytomegalovirus (CMV) infection occurs in approximately 0.25–2% of live births [1–4], but approximately 90% of congenital CMV infections are asymptomatic during the neonatal period. Among such neonatally asymptomatic infants, some develop sensorineural hearing loss and/or developmental delay first recognized from late infancy through childhood. However, it is difficult to confirm congenital CMV infection beyond the neonatal period.

MRI plays an important role in the suspicion of congenital CMV infection. Typical MRI findings include white matter (WM) abnormalities, cerebellar hypoplasia, polymicrogyria, and periventricular calcification [5]. However, these MRI findings were reported mainly from symptomatic patients during the neonatal period, and little is known about clinical and radiological characteristics in patients retrospectively diagnosed with congenital CMV infection.

Dried blood spots on Guthrie cards obtained during the first few days of life have been used for the retrospective diagnosis of congenital CMV infection [6, 7]. Additionally, based on a Japanese traditional custom in which umbilical cord is dried and preserved as a birth memorial for all Japanese children,

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several studies from Japan have indicated that CMV-DNA is preserved in the umbilical cord [8, 9].

The aim of this study was to characterize radiological findings of patients who were non-symptomatic or minimally symptomatic during the neonatal period and were shown to have congenital CMV infection based on dried umbilical cord samples.

Methods

Patients

Participants in this study were children referred to our institutions from 2008 to 2018 due to neurological symptoms such as developmental delay or seizure who were retrospectively diagnosed with congenital CMV infection. Congenital CMV infection was defined by the presence of CMV DNA in dried umbilical cord using real-time quantitative PCR, as described previously [9]. This study was approved by the ethics committee of the Nagoya University Graduate School of Medicine. Written informed consent was obtained from the parents for both the study and its publication.

Magnetic resonance imaging

MRI was performed on a 1.5- or 3-T MR scanner using a head coil in each institution. The MRI data comprised axial T1- and T2-weighted, axial FLAIR, coronal T2-weighted, and sagittal T1-weighted images.

Assessment of MRI findings

All MRI images were reviewed by two of the three authors (H.K., H.K., and A.S.) based on the van der Knaap's scoring system [10] integrated with some additional variables. Abnormalities in deep gray matter, cerebellum, and brainstem included any signal or structural abnormalities. Cerebellar hypoplasia was assessed by visual inspection. Dilated lateral ventricles were qualitatively scored as none, mild, moderate, or severe. The presence or absence of ventricular septations were also noted [11]. When performed, CT was assessed by the same investigators if calcification was present or absent. The final consensus was based on discussion.

Clinical variables

We collected the following antenatal, perinatal, and postnatal variables: maternal and neonatal histories, chief complaints, and neurodevelopmental status upon diagnosis, including motor, intellectual, and behavioral abnormalities, hearing and visual impairments, and epilepsy. Microcephaly was diagnosed with head circumference > 2 standard deviations below the mean for gestational age and sex. Small for gestational age (SGA) was defined as birth weight below the 10th percentile for gestational age at birth.

Statistics

We used Fisher's exact test for statistical analysis and defined $p < 0.05$ as significant. SPSS was used for statistical analysis.

Results

During the study period, 31 patients were diagnosed with congenital CMV infection. All 31 patients were term or near-term infants without asphyxia, hepatosplenomegaly, petechiae, thrombocytopenia, or microcephaly at birth. Eight infants had SGA without microcephaly, and another 6 had mild jaundice. Neonatal hearing screening was performed in 23 infants, and 11 (48%) required referral, all of whom were later diagnosed with sensorineural hearing loss (Table 1).

The reasons for referral to a pediatric neurology clinic were developmental delay in 22 (71%), seizure in 5 (16%), deafness in 3 (9.7%), and hemiplegia in 1 (3.2%) patient. At diagnosis, two patients had three of the four manifestations (developmental delay, seizure, deafness, and hemiplegia), 15 had two, and 14 had one manifestation. Median (range) age at the initial MRI scan was 12 months (range, 4 months to 13 years). Of the 31 patients, 30 had MR abnormalities, as listed in Table 2. The patient with no MRI abnormality was a 6-

Table 1 Patients' characteristics ($N = 31$)

Variables	$N = 31$
Male sex	17 (55%)
Gestational age	
36 weeks	3 (10%)
37 to 42 weeks	28 (90%)
Perinatal problems	
Small for gestational age	8 (26%)
Mild jaundice	6 (19%)
Refer in neonatal hearing screening	11/23 (48%)
Age at examination	
< 12 m	14 (45%)
12 m ≪ 24 m	11 (35.5%)
24 m≪ 36 m	4 (13%)
> 36 m	2 (6.5%)
Reason referring to pediatric neurology clinic	
Developmental delay	22 (71%)
Seizure	5 (16%)
Deafness	3 (10%)
Hemiplegia	1 (3%)

Table 2 MRI characteristics based on the van der Knaap's scoring system integrated with additional variables

MRI characteristics	$N = 30$
WM abnormalities	30 (100%)
Distribution of lesions, bilateral and multifocal: extensive and confluent: diffuse	18:12:0
Symmetry of lesions, symmetrical: asymmetrical	29:1
No. of lesions, fewer than 10: between 10 and 20: more than 20	17:9:4
Consistency of lesion size, little variation in size: marked variation in size	18:12
Periventricular involvement	15 (50%)
Deep WM involvement	29 (97%)
Arcuate fiber involvement	7 (23%)
Zone predominantly involved, deep WM: others	28 (93%):2 (7%)
Frontal lobe involvement	25
Parietal lobe involvement	29
Occipital lobe involvement	27
Temporal lobe involvement	25
Location of largest lesions, parietal lobe: others[a]	25 (83%):5 (17%)
Myelination, normal: mildly delayed: considerably delayed	28:3:0
Dilated lateral ventricles	16 (53%)
Ventricle wall septums	7 (23%)
Abnormalities of anterior part of temporal lobe	21(70%)
Cortical gyral abnormalities	7 (23%)
Suggestive of polymicrogyria	7
Symmetry, symmetrical: asymmetrical	2:5
Predominant location, lateral aspects of the brain: other	7 : 0
Deep grey matter abnormalities	1 (3%)
Cerebellar abnormalities	0
Brainstem abnormalities	0

[a] Others include frontal, occipital, and temporal lobes or diffuse

month-old boy with a complaint of developmental delay following the results of neonatal hearing screening. Among the 30 patients with MRI abnormalities, bilateral multifocal WM abnormalities, predominantly in the deep WM ($n = 29$) and the parietal lobes ($n = 25$), were the most common findings (Table 2, Fig. 1, and Fig. 2). Seven patients (23%) had a lateral ventricular septum located in the posterior with ($n = 1$) or without ($n = 7$) anterior horns of the lateral ventricles (Fig. 1f). Dilated lateral ventricles were observed in 15 patients (50%; mild in 11, moderate in 4). Additionally, anterior temporal abnormalities were observed in 21 (68%) children (Fig. 3), 18 of whom had a WM abnormality predominant in the parietal lobes (Fig. 2).

Seven patients (23%) had cortical gyral abnormalities (unilateral $n = 5$, bilateral $n = 2$) (Fig. 4) suggestive of polymicrogyria on MRI. The polymicrogyria was localized in the lateral fronto-parietal lobe in 4 children and in the lateral fronto-parieto-temporal lobes in 3. There are some differences in patient characteristics and MRI findings between cases with and without polymicrogyria on MRI (Table 3). Of the 30 patients with MRI abnormalities, only 1 had deep grey matter signal abnormality located in the left caudal head, and none had brainstem or cerebellar abnormalities.

CT was performed in 14 patients. The median (range) age at CT was 8 months (range, 4 months to 54 months). Five of them (36%) had cerebral calcification scattered only in the periventricular WM or also in the deep WM (Fig. 5).

Discussion

Most published studies on MR imaging characteristics in congenital CMV infection are based on findings from neonatally symptomatic patients or fetuses [5, 12–17]. Here, we report MRI findings of congenital CMV infection in patients who had no or minimal symptoms during the neonatal period and were later diagnosed retrospectively. All but one patient exhibited bilateral, multifocal WM lesions, with the largest lesions in the deep parietal areas (83%), relatively sparing the periventricular and subcortical WM. Lesions of the anterior temporal lobe (70%) and the ventricle wall septum were

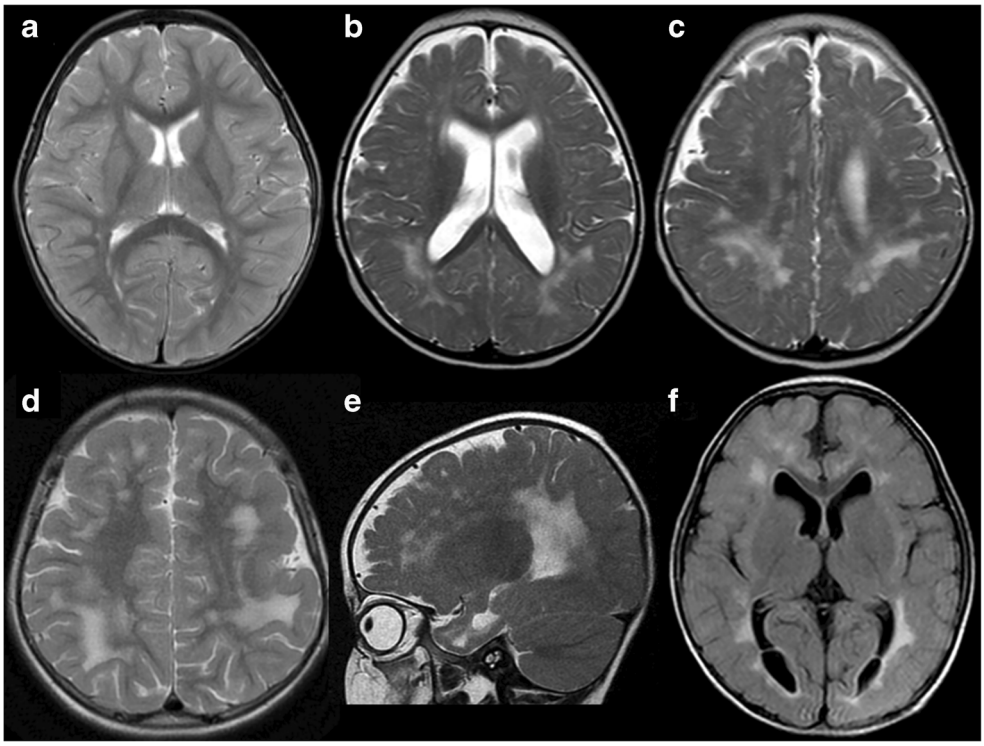

Fig. 1 Representative images of white matter abnormalities. **a** An axial T2-weigted MR image showing "punctate" white matter (WM) abnormalities. **b**–**d** Axial T2-weighted MR images showing bilateral multifocal WM abnormalities with parietal dominance from different patients. **e** A sagittal T2-weighted MR image showing WM abnormalities with parietal dominance. **f** A FLAIR image showing ventricle adhesion in the occipital horns of the lateral ventricles

commonly involved. These results support a previous report by van der Knaap, with a larger sample size [10].

An unusual characteristic of the present study was that none of the infants had cerebellar abnormalities, including cerebellar hypoplasia, dysplasia, or cysts [18], whereas previous studies have shown cerebellar hypoplasia in 40–70% of symptomatic CMV infants [19, 20]. The difference in incidence likely depends on the degree of brain injury and the timing of the injury. Infants with congenital CMV infection who are infected during the first trimester are at increased risk of symptomatic presentation, with severe brain abnormalities including agyria or lissencephaly, marked ventriculomegaly, diffuse WM abnormalities, and cerebellar hypoplasia. Those infected between 18 and 24 weeks of gestation have more typical polymicrogyria, less ventricular dilatation, and less consistent cerebellar hypoplasia. Those infected in the third trimester have no symptoms or only mild symptoms at birth and have normal gyral patterns and damaged periventricular WM [13]. Based on previous reports, our neonatally non-symptomatic or minimally symptomatic series appears to include more children who were infected by CMV midway in the second trimester or later. Differences in images may also be due to the type of brain cells damaged. CMV-immune-labeled cells can be found ubiquitously distributed in the ventricular zone, subventricular zone, and cortical plate in the brains of congenitally infected fetuses [21]. Although CMV can target different cell types in the brains of congenitally infected fetuses, it shows higher tropism to neural progenitor cells. Therefore, CMV infection affects neural progenitor cell proliferation and differentiation at different fetus ages, although the pathogenesis of CMV infection of brain tissue during fetal development remains unclear. Moreover, CMV infection leads to placental dysfunction and fetal hypoxia, which indirectly affects encephalon development. Differences in susceptibility to hypoxia affect brain images [22].

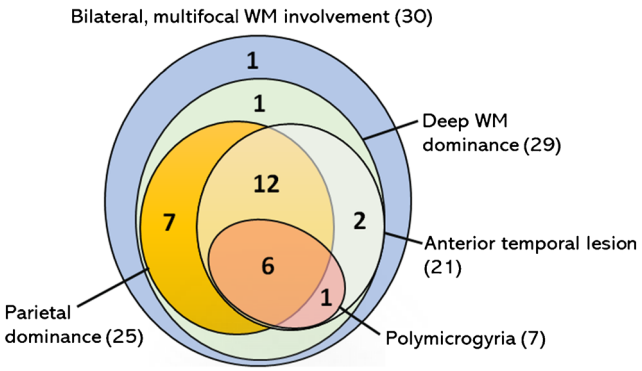

Fig. 2 A Venn diagram showing the relationships among MRI characteristics. The 30 patients with MRI abnormalities had bilateral, multifocal white matter (WM) involvement. The circles indicate whether WM lesions had deep WM or parietal dominance, an anterior temporal lesion was involved, and polymicrogyria was present. Among the 30 patients with MRI abnormalities, deep WM dominance was observed in 29, parietal dominance in 25 (83%), and an anterior temporal lesion was detected in 21 patients. Thus, 18 patients (60%) had anterior temporal lesions with parietal and deep WM dominant lesions. Note that most patients had more than one MRI finding

Our result shows that multifocal, deep white matter involvement is the most common MRI finding in children with congenital CMV infection. Although the pathogenesis of

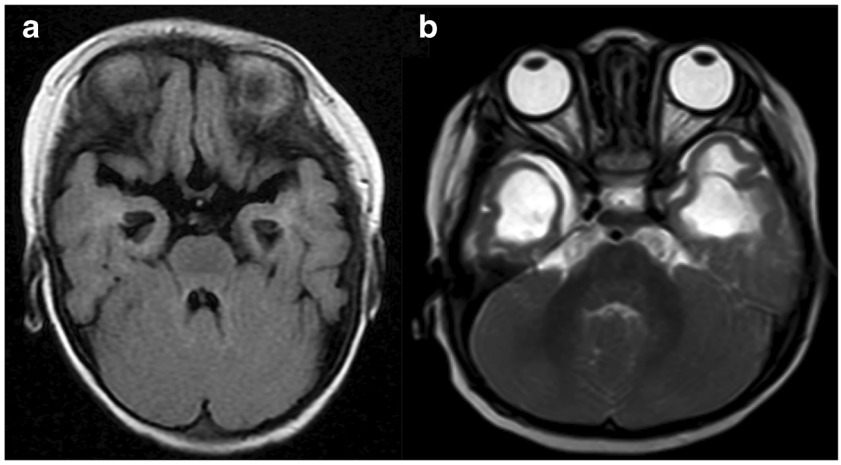

Fig. 3 Anterior temporal lesions. Dilatated inferior horn of the lateral ventricles with a "balloon" appearance and/or white matter signal abnormality (**a** an axial FLAIR) or cysts (**b** axial T2) adjacent to the ventricles

white matter involvement is unclear, it may involve a combination of disturbed and delayed myelination [13]. Indeed, some white matter signal abnormalities can disappear over a period of years, indicating delayed myelination, but the presence of a dilated lateral ventricle indicates impaired white matter development.

In this study, we showed that PMG is likely to be accompanied by dilated lateral ventricles and anterior temporal abnormalities. Although we did not evaluate the associations with neurological outcomes, MRI scoring systems are reportedly valuable for predicting outcomes [5, 17]. In those scoring systems, the presence of PMG is indicative of the highest severity grade and is associated with the most severe outcomes. By contrast, a punctate WM lesion is likely to be associated with better outcomes.

Using a similar retrospective PCR analysis of dried umbilical cord with limited MRI assessment, Uematsu et al. [23] reported similar proportions of WM abnormalities (100%) and intracranial calcification on CT (48%), but showed a higher proportion of cortical malformations on MRI (50%) compared with our report. This difference may result from differences in the study populations, although the inclusion criteria and time of MRI scans were similar. Another source of differences may be access to testing for CMV DNA in our research institute, which led to the enrollment of more patients with milder neuroradiological characteristics and without cortical malformation. Although the present study included fewer patients with polymicrogyria, the important clinical point is that CMV infection should be considered later in infancy in the presence of polymicrogyria with an unknown etiology, even if the neonatal period was unremarkable.

Anterior temporal lesions are reportedly an important finding for the diagnosis of congenital CMV infection. The present study had a high prevalence at 70%. Similarly, van der Knaap et al. [10] reported that 75% of patients had abnormalities in the anterior part of the temporal lobe and that this finding was specific to CMV infection. However, leukoencephalopathy with temporal lobe cysts are also seen in early onset genetic leukoencephalopathies including Aicardi–Goutières syndrome, a ribonuclease T2 (*RNASET2*) deficiency, and are required for meiotic nuclear division 1 (*RMND1*)-related encephalopathy [24]. Therefore, a combination of anterior temporal abnormality with parietal-dominant multifocal WM abnormality is required for suspicion of

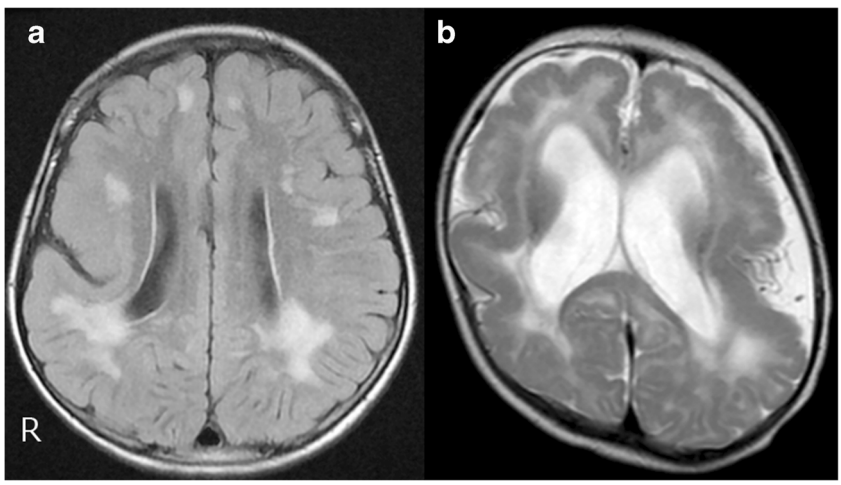

Fig. 4 Cortical gyral abnormality. Gyral abnormalities suggesting unilateral right fronto–parieto–temporal (**a**) and bilateral (**b**) polymicrogyria

Table 3 Comparison between patients with and without polymicrogyria

	With PMG $N = 7$	Without PMG $N = 23$	P value
Male sex	3 (43%)	13 (57%)	0.675
Reason referring to pediatric neurology clinic			0.030
Developmental delay	3 (43%)	18 (78%)	
Deafness	0	3 (13%)	
Seizure	3 (43%)	2 (8.7%)	
Hemiparesis	1 (14%)	0	
Perinatal problems			
SGA	3 (43%)	5 (22%)	0.373
Refer in neonatal hearing screening	1/5 (20%)	9/16 (56%)	0.590
Jaundice	2 (29%)	4 (17%)	0.603
MRI age, median (range)	12 m (5 m to 55 m)	12 m (4 m to 13 y)	0.883
WM abnormality			
Bilateral and multifocal: extensive and confluent:	3:4	15:8	0.290
Dilated lateral ventricles	6 (86%) mild 3, moderate 3	9 (39%) mild 8, moderate 1	0.031
Abnormalities of anterior part of temporal lobe	7 (100%)	14 (61%)	0.048
Ventricle wall septums	3 (43%)	4 (17%)	0.163

PMG polymicrogyria, *SGA* small for gestational age, *WM* white matter, *m* month, *y* year

congenital CMV infection. In addition, clinicians should expand their differential diagnosis when retrospective PCR tests for CMV are negative.

The present study has some limitations. First, most of the subjects had one or more of developmental delay, hearing loss, and/or seizure. Investigation of a cohort with different manifestations might yield different MRI findings and a different frequency of positive MRI findings. Second, the sensitivity of the PCR test using umbilical cord was unclear. With dried blood spots, the sensitivity varied from 40 to 100% [6, 7, 25]. Our method may also lack sensitivity and specificity for routine diagnosis of congenital CMV infection. Third, cerebellar hypoplasia was diagnosed by visual inspection. The lack of objective assessment may explain the variability in the incidence of cerebellar hypoplasia among extant studies. Finally, our series included 11 infants who were referred after neonatal hearing screening. These infants should have received a screening for congenital CMV infection within the first 2–3 weeks of life because early treatment with valganciclovir for CMV infection can lead to better outcomes [26].

Conclusions

This study shows MRI characteristics in 31 children with congenital CMV infection who had no apparent perinatal history but later had neurological signs and symptoms. Most patients

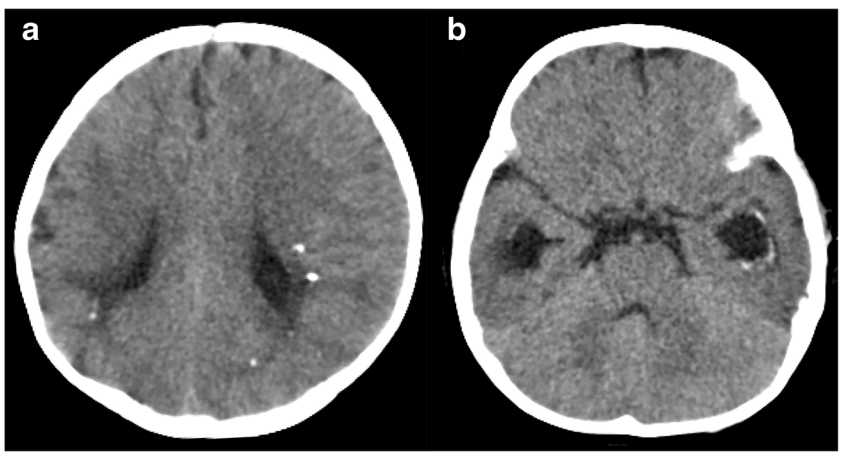

Fig. 5 Calcification on CT. Punctate calcifications are observed in the deep (**a**) and/or periventricular white matter (**b**) on axial non-contrast CT images

had bilateral, multifocal WM lesions, with the largest lesions in the deep parietal area, relatively sparing the periventricular and subcortical WM, with or without polymicrogyria. Additionally, anterior temporal lesions were common but not specific for CMV infection, whereas deep gray matter and cerebellar abnormalities were uncommon. Understanding these characteristic brain MRI findings can support a clinical suspicion of congenital CMV infection because retrospective diagnosis is not generally feasible.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Contributions H.K. wrote the first draft and all authors reviewed the final version of the manuscript. H.K. and Y.I. have been principal investigators, and all authors collected the data presented in this paper.

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