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# Neuroimaging in infants with congenital cytomegalovirus infection and its correlation with outcome: emphasis on white matter abnormalities

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## ABSTRACT

**Objective** To evaluate the association between neuroimaging and outcome in infants with congenital cytomegalovirus (cCMV), focusing on qualitative MRI and quantitative diffusion-weighted imaging of white matter abnormalities (WMAs).

**Methods** Multicentre retrospective cohort study of 160 infants with cCMV (103 symptomatic). A four-grade neuroimaging scoring system was applied to cranial ultrasonography and MRI acquired at  $\leq 3$  months. WMAs were categorised as multifocal or diffuse. Temporal-pole WMAs (TPWMAs) consisted of swollen or cystic appearance. Apparent diffusion coefficient (ADC) values were obtained from frontal, parieto-occipital and temporal white matter regions. Available follow-up MRI at  $\geq 6$  months (N=14) was additionally reviewed. Neurodevelopmental assessment included motor function, cognition, behaviour, hearing, vision and epilepsy. Adverse outcome was defined as death or moderate/severe disability.

**Results** Neuroimaging scoring was associated with outcome ( $p < 0.001$ , area under the curve  $0.89 \pm 0.03$ ). Isolated WMAs (IWMAs) were present in 61 infants, and WMAs associated with other lesions in 30. Although TPWMAs and diffuse pattern often coexisted in infants with IWMAs ( $p < 0.001$ ), only TPWMAs were associated with adverse outcomes (OR 7.8; 95% CI 1.4 to 42.8), including severe hearing loss in 20% and hearing loss combined with other moderate/severe disabilities in 15%. Increased ADC values were associated with higher neuroimaging scores, WMAs based on visual assessment and IWMAs with TPWMAs. ADC values were not associated with outcome in infants with IWMAs. Findings suggestive of progression of WMAs on follow-up MRI included gliosis and malacia.

**Conclusions** Categorisation of neuroimaging severity correlates with outcome in cCMV. In infants with IWMAs, TPWMAs provide a guide to prognosis.

## INTRODUCTION

Cranial ultrasonography (cUS) and MRI are complementary in neuroimaging for congenital cytomegalovirus (cCMV) and aid outcome prediction.<sup>1–11</sup> Our neuroimaging scoring system was validated in a small cohort of symptomatic infants.<sup>6</sup> While major lesions correlate with poor outcomes, less is known about white matter abnormalities (WMAs).<sup>1–9</sup> cCMV-related WMAs can be associated with other central nervous system (CNS) lesions or an isolated finding.<sup>5–7 9 12 13</sup> They can be multifocal or diffuse, and a specific pattern of temporal-pole WMAs (TPWMAs) is characteristic.<sup>5–7 9 12–14</sup> The correlation between extent of isolated WMAs (IWMAs) or presence of TPWMAs and outcomes in cCMV has been scarcely studied.<sup>7</sup> Diffusion-weighted imaging (DWI) may provide insight into the neuropathological substrate of WMAs, and apparent diffusion coefficient (ADC) values could serve as quantitative adjunct to qualitative analysis.<sup>15</sup> Lastly, postnatal evolution of WMAs remains poorly understood.<sup>12 16 17</sup>

This study aimed to: (1) examine the predictive ability of neuroimaging categorisation using cUS and MRI in a large cohort of infants with cCMV, both symptomatic and asymptomatic; (2) describe the MRI features of WMAs in infants with cCMV and determine if ADC values can aid in their quantitative characterisation; (3) evaluate the postnatal course of WMAs by comparing early MRI findings with those observed later in childhood; (4) examine the association between IWMAs and neurodevelopmental outcome.

## METHODS

### Patient population

This retrospective cohort study included infants with cCMV born before January 2022 from eight European university hospitals. Inclusion required cUS and MRI within 3 months of postnatal age (PNA) or corrected age (CA) for prematurity. Exclusion criteria were major non-cCMV-related

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Neuroimaging is the best available single predictor of neurological outcome in infants with congenital cytomegalovirus infection. While normal neuroimaging is reassuring, and major destructive lesions or brain developmental derangements imply a poor prognosis, less is known about white matter abnormalities.

**WHAT THIS STUDY ADDS**

⇒ In infants with congenital cytomegalovirus infection and isolated white matter abnormalities, polar temporal lobe involvement was associated with severe hearing loss or hearing loss combined with moderate neurodevelopmental disabilities in 35% of cases. Another 20% of infants with this finding had isolated non-severe hearing loss. The absence of temporal-pole white matter abnormalities was found to have a negative predictive value, indicating a low risk of poor outcomes.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ With improved diagnosis resulting from prenatal and neonatal screening for congenital cytomegalovirus infection, and the increased use of fetal and postnatal MRI, congenital cytomegalovirus-related white matter abnormalities represent a common conundrum today, involving difficult treatment and prognostic dilemmas. Our study results provide a novel guide to prognosis in these infants. Future studies could help develop a more definitive prognostic framework. Additionally, further research is needed to understand the role of antiviral treatment in improving outcomes of infants with congenital cytomegalovirus infection and isolated white matter abnormalities.

malformations, genetic disorders or comorbidities that could affect neurodevelopment.

cCMV was considered symptomatic in case of<sup>18</sup>: thrombocytopenia; petechiae; hepatomegaly; splenomegaly; intrauterine growth restriction<sup>19</sup>; hepatitis or CNS involvement, such as microcephaly,<sup>2 19</sup> characteristic radiographic abnormalities (intracranial calcifications, moderate/severe ventriculomegaly (lateral ventricle width  $\geq 10$  mm on a coronal section at the atria level),<sup>20</sup> brain atrophy, cortical malformation, callosal abnormalities<sup>21 22</sup> or cerebellar hypoplasia<sup>23 24</sup>), abnormal indices or CMV DNA detection in cerebrospinal fluid, chorioretinitis or sensorineural hearing loss (SNHL; threshold  $>30$  dB by auditory brainstem responses). Clinical treatment protocols varied during the study period. From 2003, symptomatic patients with CNS involvement were treated with ganciclovir/valganciclovir for 6 weeks, starting within the first month of birth.<sup>25</sup> From 2015, all symptomatic patients received the same treatment plus 4.5 months of valganciclovir.<sup>26</sup>

**Early neuroimaging**

This included cUS and MRI conducted within 3 months of age. cUS was performed using 5 to 12 MHz probes. MRI at 1.5 or 3 Tesla included sagittal, axial and coronal T1-, T2- and DWI, ADC maps, gradient echo and susceptibility-weighted imaging.

Neuroimaging findings were graded using our scoring system.<sup>6</sup> WMAs (figure 1) were defined as abnormally high signal intensity (SI) on T2-weighted MRI and ADC maps, and low SI on T1- and DWI, and categorised as multifocal (non-confluent frontal,

parieto-occipital and/or temporal) or diffuse (confluent).<sup>12</sup> TPWMAs were defined as swollen or cystic appearance of the anterior temporal lobes.<sup>6 12 13</sup> IWMA were diagnosed when they were the sole neuroimaging finding or associated with lenticulo-striate vasculopathy (LSV); caudothalamic, frontal or temporal germinolytic pseudocysts; occipital horn septations or ventriculomegaly  $\geq 7.5$  mm<sup>20</sup> without other signs of brain atrophy. To determine their prevalence in otherwise asymptomatic infants, IWMA were not included in the definition of symptomatic cCMV.

ADC values were measured from axial DWI ( $b=1000$  s/mm<sup>2</sup>) using circular 0.2 cm<sup>2</sup> regions of interest (ROIs) placed bilaterally in three WM areas: frontal, parieto-occipital and temporal (online supplemental figure 1). To account for the influence of gestational age (GA) and PNA, postmenstrual age (PMA) or CA at acquisition was considered for both preterm and term infants, and only examinations performed within 30 days of CA were included.

In preterm infants, scans performed at or after term-equivalent age (TEA;  $\geq 37$  weeks' PMA) were assessed where available for findings influenced by GA/PMA (WM SI, ADC values, cortical gyration).

Two masked experts per centre reviewed the images independently. Inter-rater intraclass correlation coefficients (ICCs) with 95% CIs were calculated for: total score, presence of WMAs, their extent and presence of TPWMAs. Disagreement was resolved by consensus.

**Follow-up neuroimaging**

Review of MRI from 6 months (or equivalent CA for preterm infants) focused on changes in WMAs (extent, appearance and SI on T1-, T2-, DWI and fluid-attenuated inversion recovery (FLAIR) sequences), volume loss and impaired myelination.<sup>27</sup>

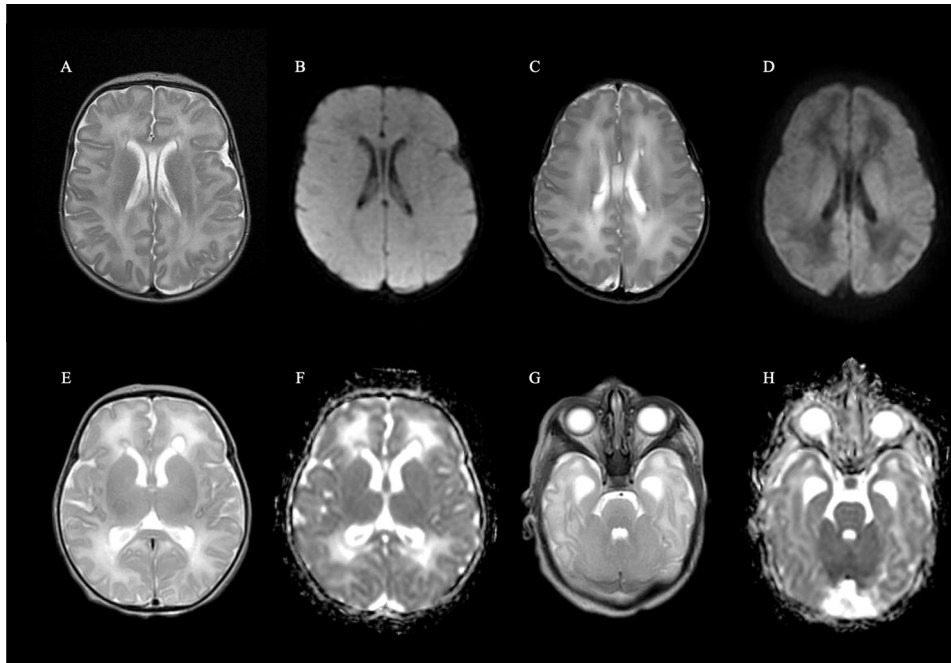
**Neurodevelopmental outcome**

Neurodevelopmental data were recorded for children with follow-up  $\geq 12$  months (or equivalent CA for prematurity). Visits included clinical interview, screening of atypical neurodevelopment, physical and neurological examination. Hearing evaluations consisted of auditory brainstem responses or audiometry. Standardised neurodevelopmental assessments were conducted for children with atypical neurodevelopment. Suspected behavioural disorders were assessed using the Child Behaviour Checklist, defining a disorder as a score  $>97$ th percentile on the Diagnostic and Statistical Manual of Mental Disorders-oriented scales.

Adverse outcome was defined as death or moderate/severe disability. Moderate/severe disability was defined as: cerebral palsy<sup>28</sup>; Griffiths Mental Development Scales (GMDS) developmental quotient (DQ), Bayley Scales of Infant Development II (BSID-II) Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI), Bayley Scales of Infant and Toddler Development third edition (Bayley-III) composite cognitive or motor score or overall IQ  $<-2$  SD; epilepsy; severe SNHL ( $>70$  dB threshold and/or requiring cochlear implants); visual impairment (visual acuity  $<20/40$  or poor fixation behaviour caused by cortical, optic nerve and/or retinal abnormalities) or behavioural disorder.

**Statistical analysis**

Categorical variables were expressed as number (percentage), and continuous variables as mean $\pm$ SD or median (range), depending on data distribution. Categorical variables were



**Figure 1** Spectrum of isolated WMAs on MRI in infants with cCMV. Axial T2-weighted image (A) and DWI (B) of a 1-week-old term infant with homogeneous SI in the WM, considered normal. Axial MRI of a 2-day-old term infant showing abnormally high SI on T2-weighted MRI (C) and low SI on DWI (D) in peritrial white matter and that adjacent to the frontal horns. WMAs were considered multifocal in this case. Axial T2-weighted imaging (E, G) and apparent diffusion coefficient maps (F, H) of a 9-day-old term infant with cCMV and diffuse WMAs involving both deep and subcortical WM. Note the temporal-pole WMAs (G, H). Mild ventriculomegaly and a left frontal germinolytic pseudocyst (E, F) are also observed. cCMV, congenital cytomegalovirus; DWI, diffusion-weighted imaging; SI, signal intensity; WMAs, white matter abnormalities.

compared using the  $\chi^2$  test or Fisher's exact test. Continuous variables were compared using the Student t-test or Mann-Whitney U test. Holm-Bonferroni correction was employed for multiple comparisons. Linear relationship between continuous variables was evaluated using the Pearson ( $r$ ) or Spearman ( $r_s$ ) correlation coefficient. Linear or binomial logistic regression analysis was performed to adjust for confounding factors. ORs and 95% CIs were calculated for risk estimates. Significant variables were assessed using receiver operating characteristic analysis, and the area under the curve (AUC), SE, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% CIs were calculated. Statistical significance was set at  $p < 0.050$ . IBM SPSS Statistics V.29.0.0.0 software was used.

## RESULTS

### Demographics and clinical findings

Out of 165 patients (born between June 1999 and September 2021), 160 were included after excluding 5 with comorbidities. Ninety (56.3%) were girls and 70 (43.8%) were boys. Median GA was 38 weeks (range 28–41 weeks). At birth, 103 (64.4%) infants were symptomatic, 55 (34.4%) asymptomatic and 2 (1.3%) had unknown presentation. **Table 1** presents neonatal and neurodevelopmental characteristics of study patients according to clinical presentation. Median age at latest assessment of the 129 surviving infants with follow-up was 4.0 years (range 1.0–15.3 years). It was 4.3 years (range 1.0–15.3 years) for symptomatic infants, and 3.7 years (range 1.0–9.4 years) for asymptomatic infants ( $p = 0.378$ ). One hundred nine (84.5%) infants were  $\geq 24$  months at follow-up, and 65 (50.4%) were  $\geq 4$  years.

### Early neuroimaging

Out of 41 preterm infants, 30 had  $\geq 1$  MRI between TEA and 3 months of CA (median PMA 39 weeks; range 37–48 weeks). Eleven had only preterm MRI (median PMA 35 weeks; range 29–36 weeks). For term infants, median PNA at MRI was 11 days (range 0–90 days), and 94 (79.0%) scans were performed within 1 month of age. Neuroimaging characteristics based on cCMV presentation are summarised in online supplemental table 1.

### Neuroimaging scoring

All 160 patients had suitable images for scoring. ICC for neuroimaging score was 0.93 (0.88–0.96). **Figure 2** represents the association between scoring and outcome according to cCMV presentation. Scoring had a significant association with outcome in the overall population ( $p < 0.001$ ). The OR for score  $\geq 2$  and adverse outcome was 20.0 (7.14–56.0). AUC was  $0.89 \pm 0.03$ , and predictive values: sensitivity 90.0% (78.2–96.7%); specificity 69.0% (58.1–78.5%); PPV 62.5% (50.3–73.6%) and NPV 92.3% (83.0–97.5%).

### White matter abnormalities

In 156 (97.5%) cases, WMAs could be assessed on T1- and T2-weighted MRI; 145 (92.9%) had DWI available. ICC was 0.96 (0.92–0.99) for presence of WMAs, 0.91 (0.82–0.96) for their extent and 0.99 (0.94–1.00) for TPWMAs. WMAs were found in 91 (58.3%) infants, of whom 30 (33.0%) had other lesions and 61 (67.0%) had IWWMAs.

### Isolated WMAs

**Figure 3** summarises characteristics of infants with IWWMAs. TPWMAs frequently coexisted with diffuse WMAs ( $p < 0.001$ ).

**Table 1** Characteristics of 158 children born with symptomatic or asymptomatic cCMV

| Characteristics  | Presentation at birth |                     | P value |
|--|-----------------------|---------------------|---------|
|  | Symptomatic (N=103)   | Asymptomatic (N=55) |         |
| <b>Neonatal characteristics</b>  |                       |                     |         |
| Sex, n (%)   |                       |                     | 0.044   |
| Male   | 39 (37.9)             | 30 (54.5)           |         |
| Female   | 64 (62.1)             | 25 (45.5)           |         |
| GA, weeks, median (range)  | 38 (28–41)            | 38 (28–41)          | 0.996   |
| Prematurity ( $\leq 37$ weeks), n (%)  | 25 (24.3)             | 15 (27.3)           | 0.679   |
| Intrauterine growth restriction (weight $< -2$ SD), n (%)  | 25 (24.3)             | N/A                 | N/A     |
| Antiviral treatment, n/total (%)*  | 70/96 (72.9)          | 26/52 (50.0)        | 0.005   |
| <b>Outcome data</b>  |                       |                     |         |
| Moderate or severe disability, n/total (%)†  | 38/83 (45.8)          | 3/45 (6.7)          | <0.001‡ |
| Cerebral palsy, n/total (%)†   | 23/83 (27.7)          | 0                   | <0.001‡ |
| Moderate or severe cognitive deficit§, n/total (%)†  | 17/83 (20.5)          | 1/45 (2.2)          | 0.005   |
| Behaviour disorder, n/total (%)†   | 6/83 (7.2)¶           | 2/45 (4.4)¶         | 0.712   |
| Epilepsy requiring antiepileptic medication, n/total (%)†  | 14/83 (16.9)          | 0                   | .002‡   |
| Severe or non-isolated SNHL, n/total (%)†  | 30/83 (36.1)          | 1/45 (2.2)          | <0.001‡ |
| Severe SNHL, n/total (%)†  | 23/83 (27.7)          | 1/45 (2.2)          | <0.001‡ |
| SNHL in association with other moderate or severe disabilities, n/total (%)†   | 20/83 (24.1)          | 0                   | <0.001‡ |
| Visual impairment, n/total (%)†  | 6/83 (7.2)            | 0                   | 0.090   |
| More than one moderate or severe disability, n/total (%)†  | 25/83 (30.1)          | 1/45 (2.2)          | <0.001‡ |
| Death, n (%)   | 8 (7.8)               | 0                   | 0.051   |
| Combined adverse outcome, n/total (%)*   | 46/91 (50.5)          | 3/45 (6.7)          | <0.001‡ |
| Mild disability, n/total (%)†  | 9/83 (10.8)           | 3/45 (6.7)          | 0.539   |
| Non-severe SNHL without other moderate or severe disabilities, n/total (%)†  | 9/83 (10.8)           | 1/45 (2.2)          | 0.098   |
| Mild cognitive deficit**, n/total (%)†   | 1/83 (1.2)            | 2/45 (4.4)          | 0.282   |
| Any disability, n/total (%)†   | 47/83 (56.6)          | 6/45 (13.3)         | <0.001‡ |
| Lost to follow-up before 12 months (or equivalent CA for prematurity), n/total of surviving patients (%)   | 12/95 (12.6)          | 10/55 (18.2)        | 0.354   |
| *N of the total number of patients for whom the variable was available.  |                       |                     |         |
| †N of the total number of surviving patients for whom the variable was available.  |                       |                     |         |
| ‡Statistically significant with the use of Holm-Bonferroni correction for multiple comparisons.  |                       |                     |         |
| §GMDS DQ, BSID-II MDI, Bayley-III composite cognitive score or global IQ $< -2$ SD.  |                       |                     |         |
| ¶Behavioural problems in children born with symptomatic cCMV included attention deficit/hyperactivity (n=3) and pervasive developmental problems (n=1); one child had a combination of oppositional defiant problems, affective problems and anxiety. Behavioural problems seen in children born asymptomatic included pervasive developmental problems (in addition to cognitive impairment) in one case and affective problems in another. |                       |                     |         |
| **GMDS DQ, BSID-II MDI, Bayley-III composite cognitive score or global IQ between $-1$ and $-2$ SD.  |                       |                     |         |
| BSID-II, Bayley Scales of Infant Development II; CA, corrected age; cCMV, congenital cytomegalovirus; DQ, developmental quotient; GA, gestational age; GMDS, Griffiths Mental Development Scales; MDI, Mental Developmental Index; N/A, not applicable; SNHL, sensorineural hearing loss.  |                       |                     |         |

However, only TPWMAs, and not extent of WMAs, were associated with moderate/severe disability (OR 7.8; 1.4–42.8), specifically severe SNHL or SNHL combined with other moderate/severe disabilities (OR 16.2; 1.8–144.9). TPWMAs had a sensitivity of 77.8% (40.0–97.2%); specificity of 69.1% (52.9–82.4%); PPV of 35.0% (15.4–59.2%) and NPV of 93.5% (78.6–99.2%) for moderate/severe disability (AUC 0.73 $\pm$ 0.09). AUC of TPWMAs and diffuse pattern combined was 0.67 $\pm$ 0.11. Outcome of IWWMAs was no different according to antiviral treatment.

### White matter ADC values

ADC values were measured from 103 MRI scans. An inverse correlation was observed between PMA/CA at MRI and ADC values in parieto-occipital and temporal ROIs ( $p < 0.050$ ). Online supplemental table 2 shows the association between ADC values, qualitative neuroimaging and outcome. After controlling for neuroimaging score, the relation between ADC values and outcome remained only for the right frontal lobe ( $p = 0.011$ ).

### Follow-up neuroimaging

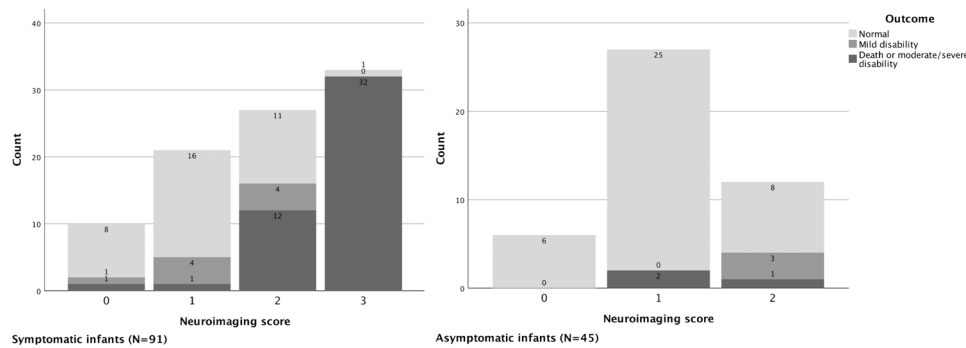
Fourteen patients had repeat MRI at  $\geq 6$  months (mean 2.9 years, range 6 months to 9.9 years). Three children with initial

neuroimaging scores of 0–1 and 1 with a score of 2 had unremarkable follow-up MRI. The remaining 10 children had an early score of 2–3. In all 10, WMAs became more confined and patchier on follow-up MRI, although persisting in multiple areas and lobes bilaterally but asymmetrically (figure 4). Frontal and parieto-occipital lesions showed increased SI on FLAIR imaging, suggesting gliosis. In contrast, TPWMAs showed low SI on FLAIR imaging, in keeping with malacia. Two cases presented multicystic appearance of the temporal WM. Some apparently spared fibre tracts were seen within WMAs. Atrophy and delayed myelination were present in all 10 cases.

### DISCUSSION

This study adds to previous validation of our neuroimaging scoring system, which combines cUS and MRI to include the entire spectrum of cCMV-related brain abnormalities.<sup>6</sup> Our categories align with fetal brain MRI classification, allowing follow-up from fetal to postnatal life.<sup>7</sup>

IWWMAs were common in both symptomatic and asymptomatic cases, consistent with previous studies.<sup>5 8 9 11 13 14</sup> TPWMAs and diffuse pattern often coexisted, with TPWMAs showing the highest ICC. TPWMAs were associated with severe/combined SNHL in 35% of cases and isolated non-severe SNHL in 20%.



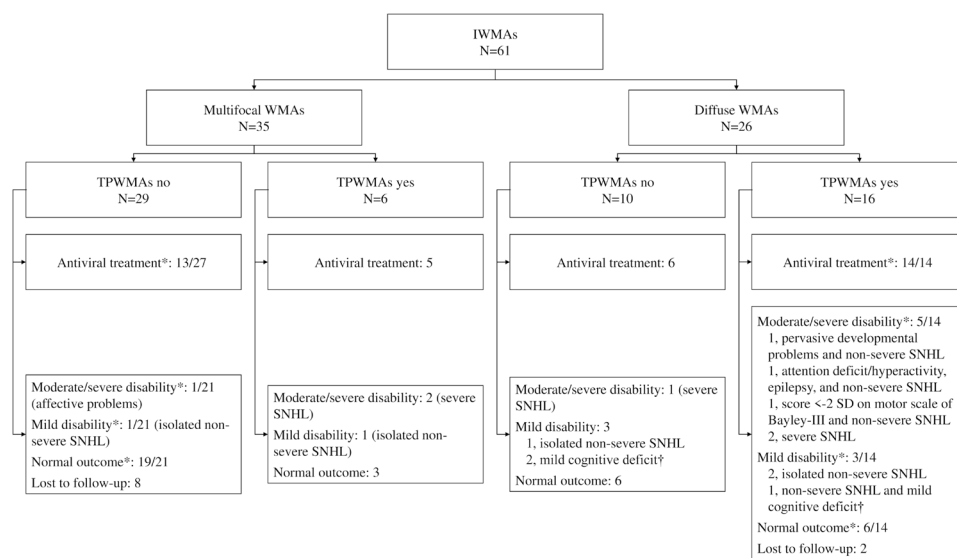
**Figure 2** Outcome according to neuroimaging score in 136 infants with symptomatic or asymptomatic cCMV. Patients for whom neuroimaging scoring did not accurately predict outcome were as follows. Two symptomatic patients with a score of 0–1 developed late-onset unilateral severe SNHL despite having received antiviral treatment. One symptomatic patient with a score of 3 based on signs of atrophy, paraventricular germinolytic pseudocysts, occipital horn septations and WMAs received antiviral treatment and had a normal outcome at 13 months. An infant born 28 weeks preterm, otherwise asymptomatic, had mild ventriculomegaly as the only finding and a neuroimaging score of 1. He did not receive antiviral treatment. Outcome was adverse, consisting of cognitive deficit and pervasive developmental problems. An asymptomatic patient with multifocal WMAs without TPWMAs who did not receive antiviral treatment showed affective problems within the clinical range at 6 years of age. Last, a patient with missing information regarding symptoms and treatment at birth (not represented in the figure) was categorised as 1 based on caudothalamic germinolysis. Her outcome was unfavourable, consisting of epilepsy. cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss; TPWMAs, temporal-pole WMAs; WMAs, white matter abnormalities.

Cannie *et al*<sup>7</sup> found that MRI grades 3–4 were linked with SNHL in 34% of cases and neurological impairment in 12%. Similar to our findings, absence of TPWMAs had high NPV for adverse outcome. The exact reasons for temporal lobe tropism in cCMV are not well understood. However, any part of the auditory neural pathway can be affected, and the virus can spread between the inner ear and the brain.<sup>29</sup> TPWMAs-associated SNHL could arise from either viral replication/inflammation in the inner ear or involvement of the auditory cortex.<sup>7,29</sup>

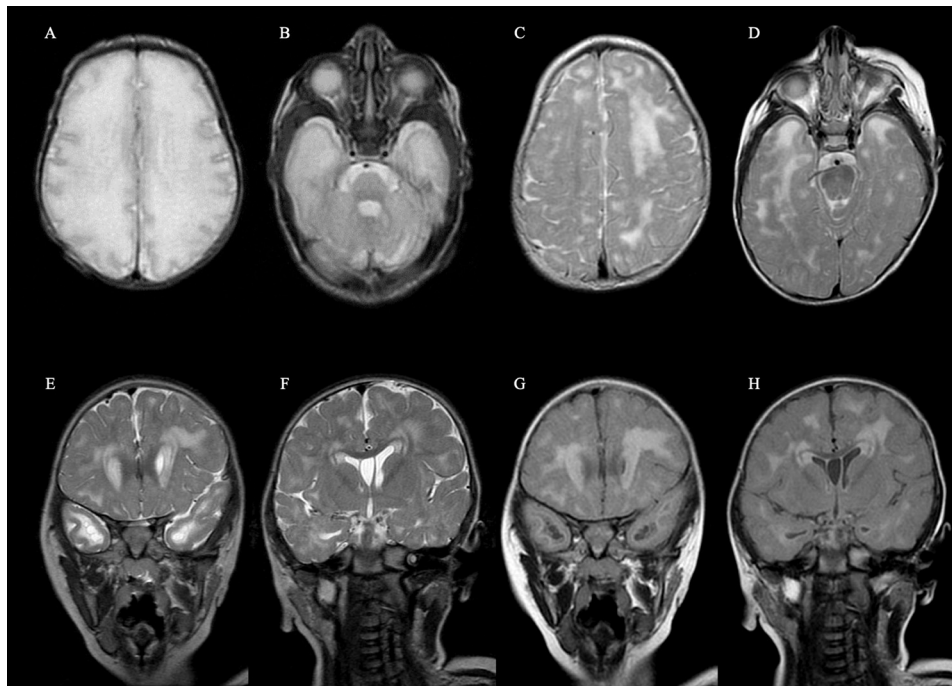
Antiviral treatment is recommended for symptomatic cCMV.<sup>18,25,26</sup> No studies have allocated treatment based on neuroimaging severity. Significant CNS lesions fall within treatment criteria. Antivirals would not be invariably recommended for asymptomatic cases with normal/mild neuroimaging (ie, LSV, caudothalamic germinolysis, mild ventriculomegaly). Limited

knowledge exists about treatment for IWMA, although these may represent ongoing disease, potentially susceptible to antivirals. Treatment rates varied but were generally high in our cases with IWMA. Our observational study could not ascertain treatment effectiveness in this population. New controlled trials or analysis of neuroimaging data from trials of antiviral treatment for infants with mildly symptomatic cCMV or isolated SNHL could shed further light on this question.<sup>30</sup>

van der Voorn *et al*<sup>15</sup> found comparably increased ADC values in WMAs of five children with cCMV and six with periventricular leukomalacia, suggesting shared neuropathological features of axonal loss, premyelinating oligodendrocyte disruption and astrogliosis. Our study is the first to examine WM ADC measurements in a large cohort of infants with cCMV. Recent studies in fetuses showed mixed results. Kotovich *et al*<sup>31</sup> found



**Figure 3** Flowchart showing patterns of WMAs, treatment and outcomes of 61 infants with congenital cytomegalovirus and IWMA (51 with available follow-up data). \*N of the total number of patients for whom the variable was available. †GMDS DQ, BSID-II MDI, Bayley-III composite cognitive score or global IQ between  $-1$  and  $-2$  SD. IWMA, isolated WMAs; SNHL, sensorineural hearing loss; TPWMAs, temporal-pole WMAs; WMAs, white matter abnormalities.



**Figure 4** MRI appearances of an infant girl born at 37 weeks with cCMV, illustrating the postnatal course of WMAs on MRI. (A, B) Axial T2-weighted images of brain MRI performed at 1 week of PNA, showing increased SI of the entire WM and polar temporal lobe abnormalities. There is a simplified gyral pattern. (C–H) Images of follow-up MRI performed at 19 months of age. (C, D) Axial T2-weighted images showing extensive WMAs and volume loss. Coronal T2-weighted (E, F) and FLAIR imaging (G, H) show appearances of established frontal and temporal WM lesions. Frontal lesions show increased SI on both T2-weighted and FLAIR imaging, while TPWMAs show increased SI on T2-weighted imaging and low SI on FLAIR imaging. This suggests a different pathological substrate between both regions (frontal gliosis and temporal malacia). There are multiple small cysts in the WM of the most rostral part of the temporal lobes (E, G). As regards frontal WM injury, there is apparent sparing of some fibre tracts, including commissural fibers and parts of the corona radiata and the anterior limb of the internal capsule (F, H). cCMV, congenital cytomegalovirus; FLAIR, fluid-attenuated inversion recovery; PNA, postnatal age; SI, signal intensity; TPWMAs, temporal-pole WMAs; WM, white matter; WMAs, white matter abnormalities.

reduced ADC values in various brain areas of 90 fetuses with CMV infection and unremarkable MRI. In line with our study, Aertsen *et al*<sup>32</sup> described increased ADC values in 45 MRI examinations of fetuses with first-trimester CMV infection. Differences in timing of imaging during pregnancy may partly explain these disparities.

We found that higher neuroimaging scores and WMAs identified through visual assessment were linked to increased ADC measurements in most regions. TPWMAs were associated with higher values in the parieto-occipital and right temporal regions. Like Kotovich *et al*,<sup>31</sup> we did not find an association between ADC measurements alone and outcome, implying that while ADC values support neuroimaging severity categorisation and qualitative assessment of WMAs, they are not an independent prognostic indicator.

Diffuse excessive high SI in the WM appears at TEA in many very preterm infants.<sup>33</sup> In our preterm cases, examinations performed at TEA or beyond were evaluated where available. Rates of WMAs were comparable among infants scanned pre-TEA, at TEA or later, and term infants. However, a potential role of prematurity in WMAs cannot be completely dismissed. An expected inverse correlation between ADC values and PMA/CA was observed, and regression analysis was performed to control for this.<sup>34 35</sup>

Follow-up MRI is infrequently performed in infants with cCMV and was available in only 14 children. All except 3 cases scanned at 6 months had their late examination past 18 months, allowing assessment of established WMAs.<sup>12 17 27</sup> In a study of

16 children with cCMV who underwent follow-up MRI after baseline MRI at  $\leq 4$  months, WMAs also became patchier over time, accompanied by reduced WM volume.<sup>17</sup> Evolving appearances of WMAs could be partly due to continued brain developmental changes, namely myelination progression.<sup>12 17</sup> However, late findings in our study included gliosis and malacia. Our results support that brain lesions in infants with cCMV consist of a combination of static and progressive features.<sup>12 16</sup> Ours and other studies on evolution of brain MRI features in cCMV are retrospective and biased towards more severe cases, where repeat or late MRI is prompted by neurosensory sequelae.<sup>12 17</sup> Repeating MRI without clinical concern is not recommended outside a research setting.

The study included a large number of infants, but has limitations due to its retrospective observational nature. Prenatal serological CMV screening was routine in only three institutions, resulting in insufficient information on maternal infection type and timing. Symptomatic cases outnumbered asymptomatic ones. Outcome data (available in 85% of cases) came from routine follow-up. Longer follow-up would have improved detection of late SNHL, behavioural and developmental disorders. Neuroimaging protocols and equipment varied between centres and throughout the study period. Nevertheless, all images were reviewed specifically for this study in a standardised manner by pairs of blinded independent experts. Lastly, there were no age-matched controls, and late MRI availability was limited for less severe cases.

In conclusion, combining cUS and brain MRI can help predict outcomes in infants with cCMV. DWI is a valuable complement

to conventional MRI for assessing WMAs. In infants with IWMA, TPWMA point to a higher risk of moderate/severe disabilities, which are present in approximately one-third of cases. As prenatal and neonatal cCMV screening become more widespread, it is essential to determine how brain MRI can guide treatment and follow-up decisions for affected infants.

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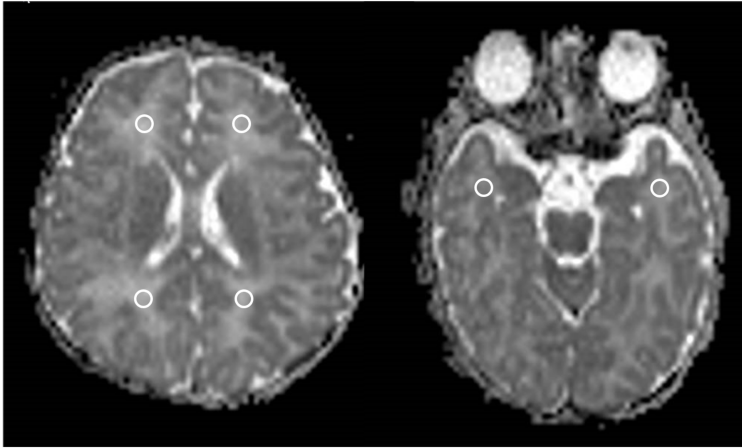
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**Online supplemental figure 1.** Axial ADC images of an infant with cCMV. Circular ROIs to measure ADC values in three WM areas (all of them on both sides, right and left). Frontal and parieto-occipital ROIs were placed on a section at the level of the atria. Temporal ROIs were positioned on a section at the level of the temporal lobes.

**Online supplemental table 1.** Neuroimaging characteristics of 158 infants with symptomatic or asymptomatic cCMV.

| Neuroimaging findings                        | Presentation at birth |                     |        |
|--|-----------------------|---------------------|--------|
|  | Symptomatic (N=103)   | Asymptomatic (N=55) | P      |
| At least one neuroimaging abnormality, n (%) | 90 (87.4)             | 47 (85.5)           | .734   |
| Normal cUS, abnormal MRI, n (%)              | 2 (1.9)*              | 5 (9.1)*            | .050   |
| Abnormal cUS, normal MRI, n (%)              | 6 (5.8)†              | 15 (27.3)†          | <.001# |
| Abnormal cUS, abnormal MRI, n (%)            | 82 (79.6)             | 27 (49.1)           | <.001# |
| LSV, n (%)                                   | 54 (52.4)             | 27 (49.1)           | .689   |
| Caudothalamic germinolysis, n (%)            | 65 (63.1)             | 29 (52.7)           | .205   |
| Ventriculomegaly‡, n (%)                     | 43 (41.7)             | 7 (12.7)            | <.001# |
| Periventricular calcification, n (%)         | 22 (21.4)             | N/A                 | N/A    |
| Frontal or temporal pseudocysts, n (%)       | 23 (22.3)             | 6 (10.9)            | .077   |
| Occipital horn septations, n (%)             | 13 (12.6)             | 2 (3.6)             | .066   |
| WMAs, n/total (%)§                           | 66/99 (66.7)          | 25/55 (45.5)        | .010   |
| IWMA, n/total (%)§                           | 36/99 (36.4)          | 25/55 (45.5)        | .269   |
| Diffuse IWMA, n/total IWMA (%)§              | 18/36 (50.0)          | 8/25 (32.0)         | .162   |
| IWMA with TPWMA, n/total IWMA (%)§           | 19/36 (52.8)          | 3/25 (12.0)         | .001#  |
| Cortical malformation, n (%)                 | 25 (24.3)¶            | N/A                 | N/A    |
| Cerebellar hypoplasia, n (%)                 | 11 (10.7)             | N/A                 | N/A    |

N/A, not applicable.

\*The finding observed in all 7 cases with normal cUS and abnormal MRI consisted of WMAs. One of them also had temporal germinolytic pseudocysts.

†cUS abnormalities in the group of 21 infants with abnormal cUS and normal MRI were LSV in 10, caudothalamic germinolytic pseudocysts in 5, and a combination of LSV and caudothalamic germinolysis in 6.

‡Ventriculomegaly was defined as lateral ventricle width  $\geq 7.5$  mm on a coronal section at the level of the atria.

§N of the total number of patients for whom the variable was available.

¶Cortical malformations consisted of polymicrogyria in 14 cases, a simplified gyral pattern in 6, and a combination of scarce gyration and polymicrogyria in 5.

#Statistically significant with the use of Holm-Bonferroni correction for multiple comparisons.

**Online supplemental table 2.** ADC values in different WM regions in infants with cCMV according to neuroimaging characteristics and outcome measures.

| Characteristics  | WM region                                  |  |  |  |  |  |
|--|--|--|--|--|--|--|
|  | Frontal R                                  | Frontal L                                  | Parieto-occipital R                        | Parieto-occipital L                        | Temporal R                                 | Temporal L                                 |
| Abnormal neuroimaging<br>No (score=0; N=15)<br>Yes (score=1-3; N=88)<br><i>P</i>   | 1753.60±226.67<br>1868.95±235.08<br>.081   | 1689.73±213.19<br>1851.38±242.54<br>.016   | 1614.27±293.71<br>1756.94±267.36<br>.062   | 1618.73±323.98<br>1766.95±285.02<br>.071   | 1476.93±192.94<br>1712.20±360.77<br>.014   | 1488.67±226.03<br>1724.11±358.28<br>.013   |
| Neuroimaging score<br>0-1 (N=58)<br>2-3 (N=45)<br><i>P</i>   | 1793.78±206.21<br>1927.40±253.23<br>.008   | 1765.66±231.91<br>1907.98±238.85<br>.006   | 1643.21±226.18<br>1855.98±287.00<br><.001* | 1645.97±236.85<br>1873.49±312.95<br><.001* | 1517.47±241.76<br>1884.78±363.19<br><.001* | 1548.83±280.82<br>1871.56±352.24<br><.001* |
| WMAs based on visual assessment<br>No (N=40)<br>Yes (N=63)<br><i>P</i>   | 1732.63±187.37<br>1928.05±233.97<br><.001* | 1693.60±194.38<br>1913.06±235.45<br><.001* | 1634.15±228.49<br>1800.94±283.15<br>.005   | 1642.58±234.40<br>1810.63±310.69<br>.009   | 1455.20±170.44<br>1819.36±363.15<br><.001* | 1461.25±208.35<br>1834.95±347.42<br><.001* |
| IWMAs versus WMAs associated with other brain lesions<br>Isolated (N=47)<br>Associated with concomitant lesions (N=16)<br><i>P</i> | 1866.04±219.55<br>2110.19±176.11<br><.001* | 1869.98±224.69<br>2039.63±226.78<br>.017   | 1751.85±266.04<br>1945.13±290.88<br>.034   | 1762.30±295.42<br>1952.63±320.18<br>.065   | 1713.80±330.67<br>2129.44±268.92<br><.001* | 1756.87±338.58<br>2064.31±268.57<br>.003   |
| IWMAs according to extent<br>Multifocal (N=27)<br>Diffuse (N=20)<br><i>P</i>   | 1877.89±241.29<br>1850.05±191.52<br>.672   | 1876.22±263.68<br>1861.55±164.16<br>.828   | 1717.94±241.54<br>1798.85±295.76<br>.302   | 1720.44±255.07<br>1818.80±341.21<br>.264   | 1685.15±299.25<br>1752.50±373.41<br>.496   | 1739.11±317.72<br>1780.85±371.96<br>.681   |
| IWMAs according to the presence of TPWMAs<br>No (N=33)<br>Yes (N=14)<br><i>P</i>   | 1839.70±216.88<br>1928.14±221.05<br>.210   | 1830.79±241.71<br>1962.36±147.43<br>.066   | 1659.48±205.18<br>1969.57±272.24<br><.001* | 1647.21±235.38<br>2033.57±244.07<br><.001* | 1605.88±304.88<br>1968.21±242.52<br><.001* | 1661.12±312.39<br>1982.57±295.45<br>.002   |
| Adverse outcome, all infants<br>No (N=65)<br>Yes (N=23)<br><i>P</i>  | 1781.72±191.24<br>2024.35±254.55<br><.001* | 1769.68±200.27<br>1967.13±272.04<br><.001* | 1682.82±266.54<br>1867.48±289.28<br>.010   | 1678.31±277.97<br>1919.26±286.12<br>.001*  | 1592.51±316.35<br>1967.91±338.05<br><.001* | 1603.78±324.48<br>1944.78±361.52<br><.001* |
| Adverse outcome, only infants with IWMAs<br>No (N=35)<br>Yes (N=5)<br><i>P</i>   | 1806.51±181.55<br>2021.20±209.10<br>.010   | 1816.40±187.94<br>1964.20±176.39<br>.106   | 1750.60±277.18<br>1675.20±230.42<br>.566   | 1744.40±301.11<br>1796.80±307.58<br>.718   | 1699.94±343.06<br>1761.60±284.38<br>.704   | 1742.17±333.26<br>1790.20±468.49<br>.776   |

R, right; L, left.

Data are given as mean±SD. For factors that were significant on univariate analysis, adjusted *P* values are given resulting from linear regression to control for PMA/CA at MRI.

\*Statistically significant with the use of Holm-Bonferroni correction for multiple comparisons.