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"Valutazione prenatale seriale della risonanza magnetica nei feti infetti da CMV trattati con valaciclovir rispetto a quelli non trattati"

"Serial prenatal MR imaging evaluation in valacyclovir-treated vs untreated CMV-infected fetuses"

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INTRODUCTION

Congenital cytomegalovirus (cCMV) infection remains the leading cause of non-genetic sensorineural hearing loss and neurodevelopmental impairment worldwide. The prevalence of cCMV is approximately 0.5–2% of all live births, with significant geographical variation depending on maternal seroprevalence [1]. While the majority of infected fetuses are asymptomatic at birth, up to 10–15% may develop long-term sequelae, even in the absence of overt clinical signs during the neonatal period [2]. Fetal MRI has become an essential tool in the prenatal evaluation of CMV-infected fetuses. It provides superior contrast resolution compared to ultrasound and can detect subtle brain abnormalities, including isolated "minor" lesions—typically represented by temporal pole T2 hyperintensity and small cystic changes. Although often underestimated, these abnormalities have been associated with subsequent sensorineural hearing loss, unilateral auditory pathway dysfunction, and mild cognitive or behavioral impairment [3]. Therapeutic strategies aimed at mitigating the impact of CMV infection in utero have been investigated for more than two decades. Oral valacyclovir, a prodrug of acyclovir with increased bioavailability, can achieve higher maternal and fetal plasma concentrations and has been proposed as an antiviral intervention during pregnancy. Previous studies suggested that maternal treatment with high-dose valacyclovir (8 g/day) may reduce viral replication, decrease the risk of severe symptomatic infection at birth, and potentially improve neurological outcome [4, 5]. However, radiological correlates of these effects, especially on subtle "minor" lesions, remain underexplored.

The present study compares serial prenatal MRI findings between valacyclovir-treated and untreated fetuses with confirmed cCMV infection, focusing on the occurrence and progression of isolated "minor" lesions.

MATERIALS AND METHODS

Study population and design

This was a retrospective single-center cohort study performed on fetuses with confirmed congenital CMV infection who underwent serial brain MRI. All cases were identified from our institutional fetal MRI database. Maternal CMV infection was documented by seroconversion between the periconceptional period and 18 weeks' gestational age, and fetal infection was confirmed by PCR or viral isolation from amniotic fluid. The candidates were recruited as clinical cases with ethical approval for retrospective review of clinical notes and MRI by the Milano Area 1 Ethics Committee (n. 27757/2022). Informed consent to the research and to publication of the results was obtained.

Patients were selected based on well-defined criteria. Specifically, the availability of at least two serial fetal brain MRI examinations was required for each case. In addition, no major brain malformations had to be present at the time of the initial assessment. Finally, inclusion required the availability of complete clinical data regarding maternal therapy.

In this regard, we have provided a flowchart illustrating the selection of our cohort divided into group A (untreated patients: controls) and group B (treated patients: cases) as shown in Figure 1.

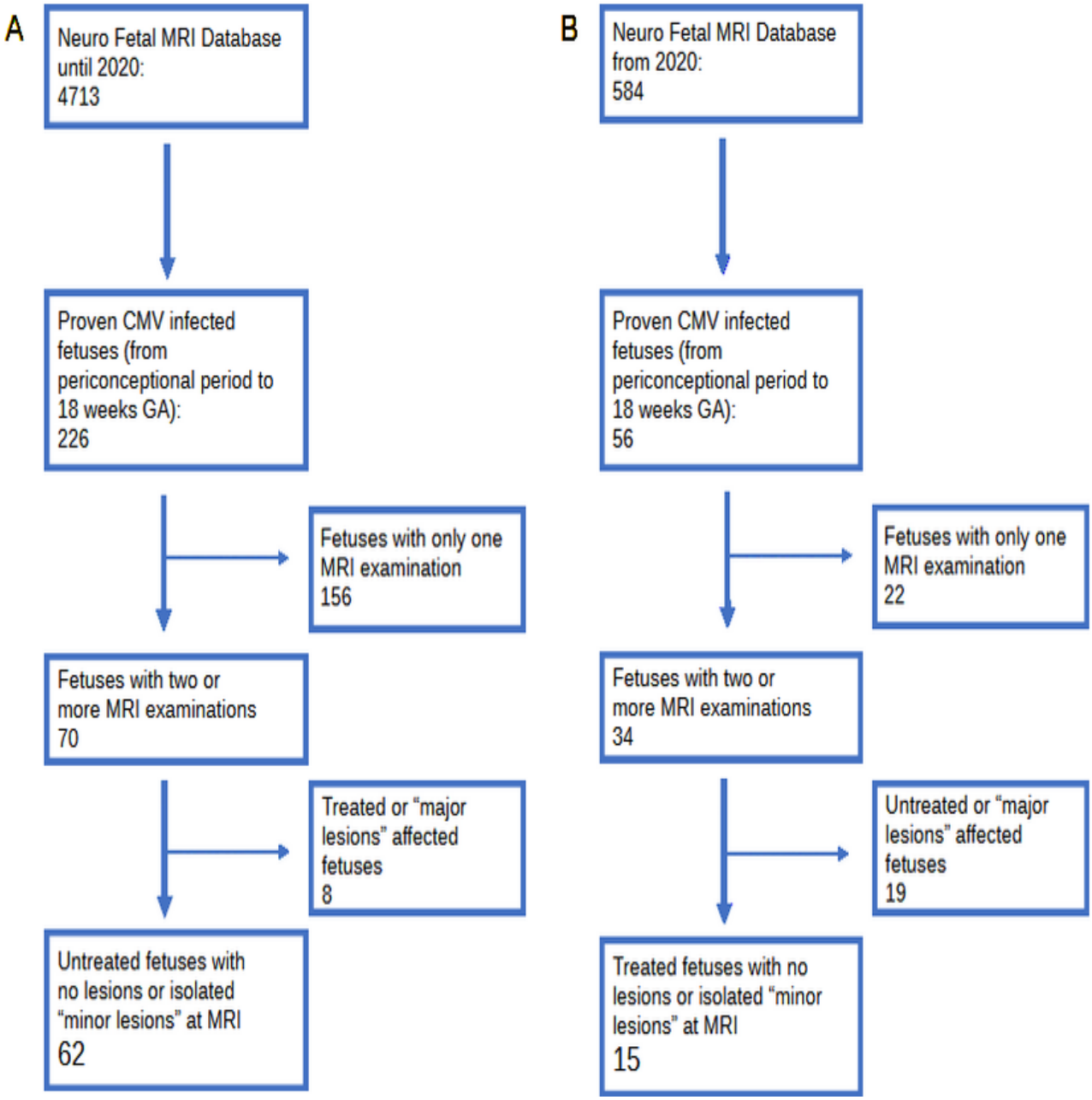

Figure 1: cohort selection flowchart.

Group A: Untreated

From a database of 4,700 fetal MRIs performed between 2005 and 2024, 226 cases were carried out for suspected or confirmed prenatal CMV infection. After exclusion of 156 with only a single MRI or with major lesions at first exam, 70 fetuses with at least two MRIs remained. Eight were further excluded because of immunoglobulin treatment or due to the presence of MR major lesions. The final untreated group consisted of 62 fetuses.

Group B: Treated with valacyclovir

From 56 MRIs performed between 2020 and 2024 in pregnancies with confirmed CMV, 22 were excluded due to single MRI, 12 due to non-adherence to therapy, and 7 due to the presence of major lesions or because loss at follow-up. The final treated cohort consisted of 15 fetuses with at least two MRIs, confirmed maternal seroconversion, and adherence to oral valacyclovir (8 g/day) from diagnosis until delivery.

This rigorous selection ensured comparability between groups.

MRI protocol

Examinations were performed using 1.5T or 3T scanners with maternal phased-array coils. Standard protocol included multiplanar single-shot T2-weighted sequences, steady-state free precession sequences, DWI and T1-weighted gradient-echo imaging.

Image review

Two senior neuroradiologists with >10 years' experience in fetal neuroimaging reviewed all cases in consensus. The primary outcome measure was the presence of "minor" brain lesions, defined as temporal pole T2 hyperintensity, focal temporal horns dilation or small cysts without associated major malformations.

Lesion onset was categorized as:

- absent (both MRIs negative),
- late (lesions appearing only on 2nd MRI),
- early (lesions already visible on 1st MRI).

Statistical analysis

Binary comparisons (absence vs presence of signs) were assessed with Fisher's exact test. Distribution among three categories (none/late/early) was tested with χ^2. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

A total of 77 fetuses were included: 62 untreated and 15 treated with valacyclovir (Table 1).

Characteristic	Untreated (n=62)	Treated (n=15)	p value
Mean maternal age (years)	31.4 ± 4.6	32.1 ± 3.9	0.54
Mean GA at 1st MRI (weeks)	21.5 ± 2.1	21.8 ± 2.0	0.63
Mean GA at 2nd MRI (weeks)	32.6 ± 2.8	32.3 ± 3.0	0.71
Fetal sex (M/F)	34/28	8/7	0.92
Adherence to valacyclovir (8 g/d)	–	100%	–

Table 1. Demographic and baseline characteristics of the two cohorts.

MRI findings (Table 2)

Group A – Untreated (n = 62):

- Always negative: 23 (37.1%)
- Lesions only at 2nd MRI: 32 (51.6%)
- Lesions already at 1st MRI: 7 (11.3%)

Group B – Treated (n = 15):

- Always negative: 11 (73.3%)
- Lesions only at 2nd MRI: 4 (26.7%)
- Lesions already at 1st MRI: 0 (0%)

MRI finding	**Untreated (n=62)**	**Treated (n=15)**
Always negative	23 (37.1%)	11 (73.3%)
Lesions only at 2nd MRI (late)	32 (51.6%)	4 (26.7%)
Lesions already at 1st MRI (early)	7 (11.3%)	0 (0%)

Table 2. Distribution of MRI findings between groups.

Three fetal cases exemplifying the possible different evolution of CMV related “minor” lesions on serial fetal MR imaging examinations are illustrated in Figure 2.

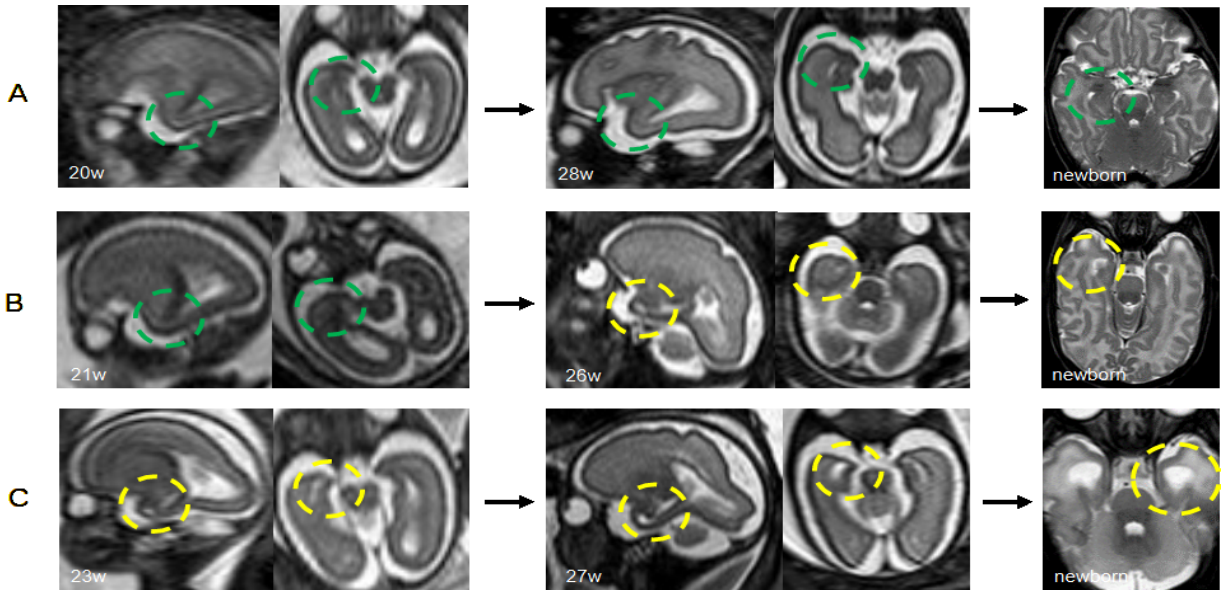

Figure 2: Figure illustrates three fetal cases that exemplify the possible different evolution of CMV-related "minor" lesions (T2W hyperintensities of the temporal poles) in serial fetal MRI examinations. Specifically, we observe case A (top line) in which no minor lesions were ever detected on fetal MRI scans at 20 and 28 weeks or on MRI after birth; in case B (middle line), we observe the appearance of minor lesions on the second MRI scan at 28 weeks, confirmed on MRI after birth; in case C, however, we observe a patient with the appearance of minor lesions already on the first MRI scan at 23 weeks, confirmed on the second at 27 weeks and after birth.

Statistical outcomes (Table 3)

In our patient cohort, two groups were distinguished: an untreated group (n=62) and a treated group (n=15). In the untreated group, 23 subjects never showed signs of disease, 32 developed abnormalities only at the second MRI, and 7 were already positive at the first MRI. In the treated group, 8 patients never showed signs of disease, 7 developed abnormalities only at the second MRI, and none were positive at the first MRI. A global analysis, considering the three categories (no abnormalities, late positivity, early positivity) and all types of minor lesions (including endoventricular septa and thalamo-caudate sulcus cysts), did not reveal statistically significant differences between the two

groups ($\chi^2 = 2.54$, $p = 0.28$). Similarly, the dichotomous evaluation (never positive vs. at least once positive) was not statistically significant: 37.1% of the untreated group remained negative compared to 53.3% of the treated group ($\chi^2 = 0.73$, $p = 0.39$; Fisher = 0.38). Although not significant, a trend in favor of treatment was observed, with a higher proportion of patients remaining negative and an odds ratio <1. Finally, the analysis focusing on the time of disease onset (early vs. late positivity) showed that 17.9% of untreated patients were already positive at the first MRI, while no early cases were recorded in the treated group. However, this difference also did not reach statistical significance. In summary, in the initial analysis the observed differences—namely, a higher proportion of always-negative patients and the absence of early positivity in the treated group—did not reach statistical significance, likely due to the limited sample size.

When the analysis was restricted to polar temporal lesions, different results emerged. In this scenario, among untreated patients, 23 showed no alterations, 32 developed abnormalities only at the second MRI, and 7 were already positive at the first. In the treated group, 11 patients remained negative, 4 developed late abnormalities, and none were positive at the first MRI.

The binary comparison between patients who developed abnormalities and those who did not showed a significant difference: 73.3% of treated patients remained negative compared with 37.1% of untreated patients (Fisher $p < 0.05$), with an odds ratio of 4.67 (95% CI 1.29–16.9). This indicates that treated patients had an approximately fivefold higher likelihood of remaining free of radiological abnormalities compared to untreated patients. The more granular three-category analysis also confirmed statistical significance (χ^2, $p = 0.02$): treated patients showed fewer progressions and no early abnormalities. In conclusion, while the preliminary analyses did not reach statistical significance, the focused approach on polar temporal lesions highlighted a clear benefit of treatment, with a significantly higher probability of remaining free of infection-signs and of the absence of early positivity.

Analysis	Untreated	Treated	Test	p value	OR (95% CI)
Always negative vs any lesions	23/62	11/15	Fisher	0.018	4.67 (1.29–16.9)
3-category distribution (none/late/early)	–	–	χ^2	0.02	–

Table 3. Summary of statistical analyses.

DISCUSSION

Principal findings

This study provides evidence that maternal valacyclovir therapy is associated with a higher proportion of fetuses remaining MRI-negative during pregnancy, and with absence of early "minor" brain lesions. The protective effect was statistically significant, despite the relatively small number of treated cases, suggesting a robust signal.

Review of the literature on valacyclovir therapy

Clinical outcomes

The first randomized controlled trial by Leruez-Ville and colleagues [5] demonstrated that maternal valacyclovir significantly reduced the risk of fetal infection when administered early after maternal primary infection. Faure-Bardon et al. [6] extended these findings, reporting a higher proportion of asymptomatic neonates and reduced viral load in treated pregnancies.

More recently, observational studies and meta-analyses have confirmed a modest but consistent benefit in terms of reducing symptomatic disease at birth and improving perinatal outcomes.

However, most of these studies focused on clinical endpoints such as hepatosplenomegaly, intrauterine growth restriction, or hearing loss, rather than neuroimaging correlates [7-8].

Radiological outcomes

Few studies have directly addressed the impact of therapy on fetal brain imaging. In small cohorts, valacyclovir was associated with reduced progression of ventricular dilation and delayed onset of parenchymal abnormalities, although statistical significance was rarely reached [9-10]. Our study adds to this limited body of evidence by systematically analyzing serial MRI findings with a focus on subtle lesions.

The prognostic role of "minor" temporal pole lesions

Temporal pole T2 hyperintensity are increasingly recognized as the most frequent subtle imaging features of cCMV. Although once considered benign, accumulating evidence — including our previous work — indicates that these lesions may predict unilateral sensorineural hearing loss or mild cognitive impairment. In that study of 36 fetuses, the frequency of minor lesions increased with gestational age, and 57% of children developed mild/moderate sequelae at long-term follow-up, including 34% with unilateral hearing loss [11]. Thus, reducing or preventing the occurrence of temporal pole lesions should not be regarded merely as a radiological achievement, but rather as a possible indicator of a milder overall cerebral involvement. This condition may, in turn, translate into a lower risk of long-term neurodevelopmental sequelae, including auditory dysfunction. Although human cytomegalovirus (CMV) demonstrates a well-documented tropism for the temporal lobes, hippocampus, and auditory pathways [12–14], current evidence suggests that CMV-related hearing loss primarily results from direct viral and immune-mediated injury to the cochlear sensory epithelium and spiral ganglion neurons, rather than from cortical or subcortical lesions [15–17]. Therefore, the observed association between minor brain abnormalities and hearing impairment is

more likely to reflect the overall burden of congenital infection than a direct causal effect of temporal lobe involvement.

How therapy may influence lesion development

The beneficial effect of valacyclovir on the development of brain lesions in fetuses with congenital CMV infection is probably mediated through multiple, partially overlapping mechanisms [18]. First, by inhibiting viral replication, valacyclovir reduces the overall viral burden both at the placental level and in the fetus. This decreased viral load limits the amount of virus that can reach the developing brain, thereby reducing the probability and extent of direct viral injury to neural tissue [8].

Second, suppression of viral activity may influence the timing of lesion appearance. By delaying or attenuating viral aggression during critical periods of brain maturation—such as neuronal migration and cortical organization—the drug may postpone the onset of parenchymal damage beyond the most vulnerable developmental windows. This temporal shift could translate into a substantial reduction in the severity of long-term neurological sequelae [5].

Third, therapy may act indirectly by modulating the host immune response. CMV-related injury is not exclusively the result of direct viral cytopathic effects but is also amplified by secondary inflammatory cascades. By lowering viral replication, valacyclovir likely decreases the magnitude of the maternal and fetal inflammatory response, thereby limiting immune-mediated tissue damage. This effect may be particularly relevant in regions that appear highly susceptible to inflammation, such as the temporal poles, where focal lesions are often observed [19].

Taken together, these mechanisms suggest that the impact of valacyclovir is not limited to simple viral suppression but extends to the modulation of both the timing and the pathophysiological processes underlying lesion formation, with potential long-term benefits for neurodevelopmental outcomes.

Broader implications: linking minor lesions and hearing outcome

Sensorineural hearing loss (SNHL) is the most frequent long-term consequence of cCMV. Even in children born asymptomatic, the risk of delayed-onset SNHL remains significant (up to 15%) [20]. Minor MRI lesions, especially temporal pole abnormalities, may serve as early surrogate markers for auditory involvement [11]. Preventing these lesions through therapy could therefore reduce not only radiological abnormalities but also the incidence of hearing loss.

Indeed, studies correlating MRI findings with audiological outcomes have shown that children with minor polar lesions are more likely to present unilateral hearing loss during follow-up. Our findings of absent early lesions in the treated group provide encouraging indirect evidence that valacyclovir may protect also auditory structures. Further studies considering auditory outcomes in valacyclovir treated patients are needed to confirm this hypothesis.

Clinical and counseling perspectives

From a clinical standpoint, the results support the integration of MRI into prenatal monitoring of treated pregnancies. Serial imaging allows detection of late-onset lesions, refining counseling for parents. The finding that 73% of treated fetuses remained lesion-free emphasizes the potential for improved prognostic reassurance [21-22]. Furthermore, highlighting the absence of early lesions may be critical during prenatal counseling, as early positivity often indicates higher risk for neurodevelopmental sequelae.

Limitations

The main limitation is the relatively small number of treated cases, reflecting the recent introduction of valacyclovir into clinical practice and the strict inclusion criteria. Retrospective design and heterogeneity of imaging platforms represent additional constraints. Nevertheless, the statistically significant findings despite limited numbers strengthen the clinical relevance of the observed trends.

Future directions

Future research should focus on multicenter, prospective trials to further clarify the role of valacyclovir in congenital CMV infection. Such studies are needed to confirm the protective effect of the therapy on MRI outcomes, to better understand the relationship between dosage and treatment duration, and to determine the optimal therapeutic regimen.

Additionally, it will be important to correlate imaging findings with long-term clinical outcomes, including both audiological and neurocognitive development, in order to establish the clinical relevance of observed brain changes. Finally, identifying reliable biomarkers—such as viral load measurements or immunological markers—may help predict the evolution of brain lesions and guide individualized treatment strategies.

CONCLUSION

Prenatal valacyclovir therapy in fetuses with confirmed CMV infection was associated with a significantly higher rate of persistently negative MRI findings and complete absence of early-onset minor brain lesions. Given the known association between temporal pole abnormalities and subsequent sensorineural hearing loss and cognitive impairment, these findings suggest that maternal therapy may not only modify radiological trajectories but also reduce the risk of long-term auditory and neurological sequelae. Larger, prospective studies are warranted to validate these results and establish imaging as a surrogate marker of therapeutic efficacy.

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