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Research Article

Fetal Cerebral Lamination in Cytomegalovirus-Infected Fetuses

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Abstract

Objectives: This study aimed to assess qualitatively and quantitatively the laminar organization of the cerebral cortex by prenatal ultrasound and MRI in cytomegalovirus-infected fetuses.

Methods: A retrospective study was conducted in 18 fetuses with a positive CMV PCR-analysis of amniotic fluid. All cases underwent serial ultrasound scans and at least one MR study before 28 weeks of gestation. Eleven cases with prenatal ultrasound diagnosis of CMV infection leading to termination were compared with the 7 cases going to term.

MRI detected 2 patterns of abnormal cerebral lamination: focal disruption of lamination and abnormal intermediate zone. On ultrasound, the laminar structure was visible as the interface between the subplate zone and the intermediate zone, quantitatively evaluated by measuring the distances between the different layers.

Results: In the TOP group, MRI showed focal disruption of lamination and abnormal intermediate zone in 3/11 and 11/11 cases respectively. In the TERM group, none of them had a disruption of lamination on MRI, however 3 had an abnormal intermediate zone.

On ultrasound, the posterior horn of the lateral ventricle was significantly larger in the TOP group compared to the TERM group. Measurement of the thickness of the subplate zone relative to the intermediate zone did not significantly differ between both groups.

Conclusion: The lamination pattern of the fetal brain can be evaluated qualitatively on MRI and ultrasound before 28 weeks and may indicate abnormal brain development in CMV-infected fetuses. Quantitative differences in lamination were not demonstrated on ultrasound.

Keywords: *Cytomegalovirus; Lamination; Fetal MRI; Fetal Ultrasound; Brain*

Abbreviations

MRI: Magnetic Resonance Imaging; CMV: Cytomegalovirus; PCR: Polymerase Chain Reaction; TOP: Termination of Pregnancy; VZ: Ventricular Zone; PP: Pre-Plate; MZ: Marginal Zone; SP: Deeper Subplate; CP: Cortical Plate; cCMV: Congenital Cytomegalovirus

Introduction

The presence of normal fetal cerebral lamination reflects normal fetal brain development. Normal cerebral lamination patterns have been described histologically and by MRI [1-3]. Both subplate and intermediate zones in normally developing fetal brains can be depicted reliably on prenatal ultrasound before 28 weeks of gestation. However, their characteristics usually disappear at 34 weeks of gestation [4].

Neuronal precursor cells proliferate, differentiate and migrate to the cortical plate by radial and tangential migration. Migrating neurons are apposed to radial glial cells, which guide them to their final position in the cortex. Some cells take a tangential migratory route, which leads to a wide dispersion of neurons derived from the same precursor.

Neurons of the cerebral cortex arise in the germinal ventricular zone (VZ) at the surface of the lateral ventricles. Newborn neurons migrate towards the cerebral surface to form the primordial plexiform layer or preplate (PP). This zone is then split into the superficial marginal zone (MZ) and the deeper subplate (SP) by the arrival of the cortical plate (CP) cells. Under-migration or over-migration of neurons will lead to cortical abnormalities. Abnormal patterns of cerebral lamination have been associated with abnormal brain development [5].

Congenital Cytomegalovirus infection (cCMV) has become a major healthcare issue far more important than the burden of Down syndrome and neural tube defects [6-12].

Around 30000 cases of CMV-related disabilities are born each year in the USA. A similar number is born in the European Union, with overall mortality and sequelae rates of 0.5% and 17 - 20% respectively [13].

CMV-positive cells are found in neurons, neuroblasts, glia, endothelium, ependyma and meninges. White matter abnormalities include periventricular leukomalacia and deposition of iron and calcium in neurons, axons and dendrites.

Necrosis is also associated with viral inclusions in cells and inflammatory infiltration with T lymphocytes.

Neural stem cells are predominantly affected. These cells differentiate into both glia and neurons. Their damage or loss leads to decreased brain mass and abnormal neuronal migration, leading to abnormal organization. In cytomegalovirus infection, the increased echogenicity and the focal heterogeneity of the intermediate zone precede the development of microcephaly and ventriculomegaly [14]. The neuropathological effects are caused by post-migratory inflammatory and ischemic necrosis [15]. The cells in the ventricular and subventricular zones are primary targets for CMV [16].

CMV first infects the periventricular zone leading in cell proliferating resulting in microcephaly. Later the virus is simply infecting the glial cell of the periventricular zone, leading to disturbances in the migration and causing multiple disorders such as lissencephaly, schizencephaly, pachygyria, and polymicrogyria. CMV can also infect neuronal cells and lead to later neurological dysfunction [17].

Only one paper addressed the qualitative lamination disorders in CMV-infected fetuses (6 out of 68 cases), describing two distinct cerebral patterns: (A) loss of a normal laminar pattern and thinning of the cortex, associated with cysts, focal haemorrhage, calcifications and ventriculomegaly; and (B) increased echogenicity of the intermediate zone and abnormally prominent laminar pattern with focal areas of heterogeneity which subsequent calcification. In two cases, abnormalities of the intermediate zone were the earliest indication of CMV infection, predating the development of microcephaly, ventriculomegaly and intracranial calcification [4].

Objectives of the Study

Fetal cerebral lamination patterns can be used as a marker of normal brain development before 28 weeks of gestation. This study aimed to assess quantitatively the laminar organization of the cerebral cortex by prenatal ultrasound and to perform a qualitative analysis by MRI in Cytomegalovirus (CMV) infected fetuses.

Materials and Methods

A retrospective study was conducted in 18 fetuses between 21 - 27 week's gestation with a positive CMV PCR-analysis of amniotic fluid. All cases underwent serial ultrasound scans and at least one MR study before 28 weeks of gestation.

All ultrasound procedures were performed with a GE Voluson E6, E8 or V730 ultrasound system (GE Healthcare, GE Medical System Europe, Zipf, Austria) and two-dimensional probes (3,5-5 MHz curvilinear abdominal). Skills required from the operators were those of performing an extended neurosonogram. MR imaging was performed on a 3Tesla system (Siemens, Erlangen, Germany) using a combined six-channel phased-array body coil together with a spine coil. Patients were positioned supine or in a left lateral decubitus. No breath hold was used. T2-weighted imaging of the brain was done with a half-Fourier acquired single-shot turbo spin-echo sequence in a transverse, coronal and sagittal plane (with respect to the fetal head). Sequence parameters of T2 weighted images were as follows: repetition time 1000 ms, echo time 133 ms, slice thickness 3 mm, field of view 380 x 380 mm (with an in-plane resolution of 1.5 mm x 1.5 mm). Additional scanning was performed as part of the routine protocol, including gradient echo sequences, T1-weighted imaging and diffusion-weighted imaging of the fetal head and body. The mean examination time of the entire clinical protocol was 25 - 30 minutes. The routine MRI protocol did not include three-dimensional acquisitions.

The laminar structure is depicted as the interface between the subplate zone and the intermediate zone. Evaluation by ultrasound standardized axial planes at the section of the biparietal diameter provides optimal visualization of the subplate-intermediate zone interface. The subplate zone is sharply delineated from the more superficial cortical plate and the deeper intermediate zone below. Quantitatively evaluation is performed by measuring (a) the posterior horn of the lateral ventricle at the level of the sulcus occipito-parietalis medialis, (b) the distance between the posterior horn and the subplate-intermediate zone interface and (c) the distance between the subplate-intermediate zone interface and cortical plate (Figure 1).

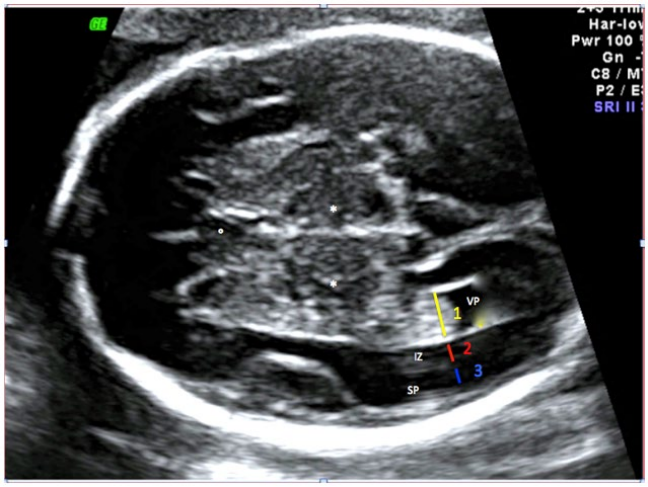

Figure 1: *Axial plane of the fetal head representing the different landmarks and the applied measurements.*

*°: Cavum Septum Pellucidum; *: Thalamus; IZ: Intermediate Zone; SP: Subplate; (1): Posterior horn of lateral ventricle; (2): Distance between posterior horn and subplate-intermediate zone interface; (3): Distance between subplate-intermediate zone interface and cortical plate.*

On MRI, a qualitative analysis of three possible patterns of abnormal cerebral lamination was performed in serial axial planes before 28 weeks: (a) focal disruption of lamination (Figure 2), (b) an abnormal intermediate zone (Figure 3) and (c) diffuse absence of the subplate-intermediate zone interface. Data from the eleven cases with severe CMV-related brain abnormalities on prenatal imaging that underwent termination of pregnancy (TOP group), and were compared to the 7 other cases that were delivered at term (TERM group).

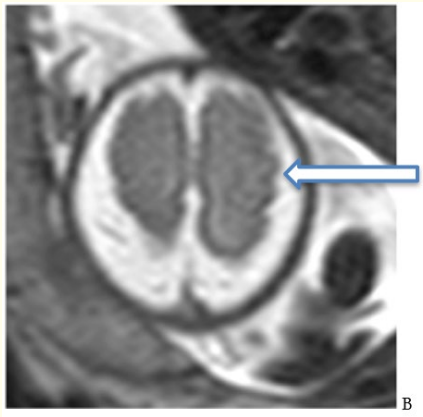

Figure 2: *Legend: Focal disruption of lamination: A: Heterotopic grey matte foci, B: Polymicrogyria.*

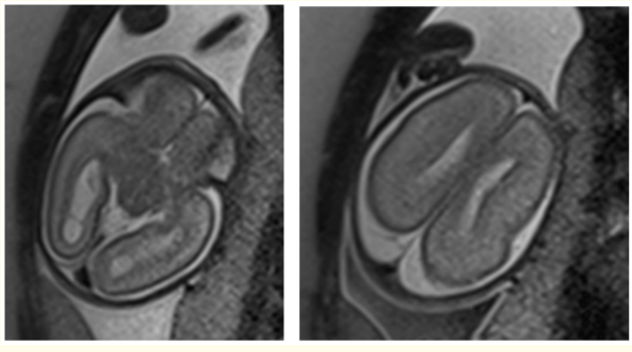

Figure 3: *Abnormal intermediate zone: e.g. abnormal signal, volume loss, destructive lesions. Picture: White matter signal alterations.*

Results

In the study period, we analyzed 253 patients with a primary CMV seroconversion in the periconceptional period or the first trimester of pregnancy. After amniocentesis at 21 weeks of gestation, 68 were CMV PCR positive of whom 18 had serial ultrasound and at least 1 MRI before 28 weeks of pregnancy. Eleven cases had severe CMV-related brain anomalies and the parents opted to terminate the pregnancy (TOP group), while 7 other patients delivered at term (TERM group) (Table 1).

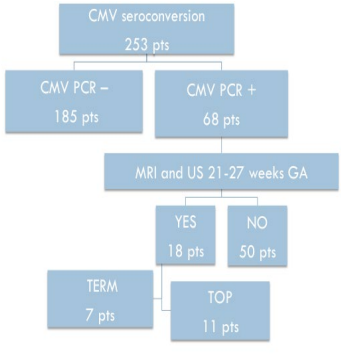

Table 1: *Flowchart of the patients.*

Critical brain lesions were present on ultrasound in all cases in the TOP group. The median posterior horn diameter of the lateral ventricle was significantly larger in the TOP group (mean 0.64 cm; SD 0.12) compared to the TERM group (mean 0.47 cm; SD 0.12) (P < 0.01). The median distances of the subplate zone relative to the intermediate zone did not significantly differ between both groups (Table 2).

	TOP group	TERM group	P-Value
Mean VP	0.64 (SD 0.11)	0.47 (SD 0.11)	0.01
Mean VP to SP-IZ interface	0.18 (SD 0.04)	0.21 (SD 0.03)	0.06
Mean CP to SP-IZ interface	0.45 (SD 0.11)	0.51 (SD 0.12)	0.12

Table 2

In the TOP group, prenatal MRI showed focal disruption of lamination and an abnormal intermediate zone in 3/11 and 11/11 cases respectively. In the TERM group, none had a disruption of lamination on MRI; however, 3 had an abnormal intermediate zone. None of the fetuses had a total diffuse absence of the laminar pattern before 28 weeks (Table 3).

Focal dikruption of lamination	TOP group (n=11)	Term group (n=7)
Normal	3	7
Polymicrogyria	4	0
Heterotopia	1	0
Polymicrogyria + heterotopia	1	0
Destructive lesions	2	0
Abnormal intermediate zone		
Normal	0	4
Signal abnormalities	1	2
Signal abnormalities + thinning	3	1
Signal abnormalities + destructive lesions	3	0
Signal abnormalities + thinning + destructive lesions	4	0

Table 3

Discussion

The presence of a normal fetal cerebral lamination of the brain parenchyma can be used as a marker of normal fetal cerebral development. Fetal cerebral lamination can be evaluated qualitatively on prenatal MRI and ultrasound before 28 week's gestation and may reflect abnormal brain development in CMV-infected fetuses.

Cerebral cortical lamination involves a complex series of genetically regulated steps to generate the laminated structure [18]. Exposure to infections, interruption of blood supply or exposure to teratogens may lead to microcephaly due to increased cell death or reduced neuronal production [19]. Only one paper addressed the qualitative lamination abnormality in CMV-infected fetuses (6 out of 68 fetuses). There were two distinct cerebral patterns: (A) a loss of normal laminar pattern and thinning of the cortex, associated with cysts, focal haemorrhage, calcifications and ventriculomegaly and (B) increased echogenicity of the intermediate zone and abnormally prominent laminar pattern with focal areas of heterogeneity with subsequent calcification [4]. Limitations of that study [4] are the retrospectives approach in which ultrasound findings of normal versus abnormal lamination patterns were compared. Secondly, features of CMV infection are only descriptive, and neither the timing of infection, nor results of amniocentesis are reported. In our study, all the patients had a positive CMV PCR analysis, subsequent ultrasound scans and at least one MR study before 28 weeks of gestation.

Quantitative sonographic measurements of the lamination pattern were not significantly different between the fetuses without or with minor versus severe imaging CMV-related abnormalities of the brain. We could not demonstrate a significant difference between the posterior horn and the subplate-intermediate zone interface and the distance between the subplate-intermediate zone interface and the cortical plate in patients with signs of CMV infection compared to patients without CMV lesions.

The strength of the study is a confirmed diagnosis of CMV for all 18 fetuses. Limitations of this study are the small study population and the sonographic quantitative analysis being performed in the axial plane whereas CMV-related lesions could be picked up in several planes. Parasagittal and coronal planes would be more thorough for evaluation appropriate the laminar pattern. Unfortunately, in this retrospective study, insufficient images of these planes were available to make a proper evaluation The quantitative measurement does not discriminate CMV-related TOP brains from TERM ones. The impact of cCMV is not measurable by the thickness of the cortex alone.

Caution is needed in interpreting the intermediate zone by MRI since white matter signal abnormalities are picked up in both TOP and TERM groups. These are common incidental findings on neuroimaging but can be linked to cerebrovascular dysfunction.

This retrospective study also lacks histopathologic correlation for the terminated pregnancies and no postnatal MRI studies to confirm the abnormalities observed prenatally.

New techniques of screening for malformations of cortical development by ultrasonography require the use of additional imaging by MRI, and cytogenetic and laboratory assessment to confirm the sonographic findings and suspected prenatal diagnosis.

New screening techniques need to be proven by prospective studies of quantitative assessment of lamination by MRI and US. Until then, the diagnosis of abnormal cerebral lamination should be undertaken with caution and appropriate referral to multidisciplinary centres specialized in prenatal neurologic diagnosis is recommended.

Conclusion

The lamination pattern of the fetal brain can be evaluated qualitatively on MRI and ultrasound before 28 weeks and may indicate abnormal brain development in CMV-infected fetuses. Quantitative differences in lamination were not demonstrated on ultrasound.

Conflicts of Interest

None.

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