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Increased ɣ -Glutamyl Transpeptidase and ɣ-Glutamyl Transpeptidase/Platelet Ratio: Biological Markers of Severe Brain Damage in Cytomegalovirus Infected and Uninfected Fetuses

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Objective

Gamma-glutamyl-transpeptidase (ɣ-GT) is an enzyme with considerable redox activity in biliary epithelial cells, the kidney, pancreas, and brain (microglial/endothelial-cells). In a previous study we observed that increased ɣ-GT levels were related to severe-brain-damage (SBD) in cytomegalovirus (CMV)-infected fetuses irrespective of gestational age. Moreover, thrombocytopenia in CMV-infected fetuses, especially in the second trimester, has been associated with brain damage. Recently, ɣ-GT/platelets ratio (GPR) has been proposed as a new inflammatory biomarker associated with neurological deficit due to hypoxic-anoxic ischemic brain injury in coronary artery disease and other comorbidities. The clinical significance of these biomarkers in CMV-infected and uninfected fetuses is unknown. The main objective of this study was to evaluate the association of ɣ-GT with SBD in CMV- infected and uninfected fetuses and examine whether this biomarker differs between groups. Our secondary aim was to assess whether implementing the use of GPR would increase the detection rate for SBD in CMV-infected and uninfected fetuses.

Methods

ɣ-GT-levels and platelets count were analyzed in fetal blood samples in consecutive cases of CMV-infection (severity neuroimaging findings were classified according to Leruez-Ville et al), and in a cohort of uninfected fetuses with neurological, cardiac, or other abnormalities. GPR was calculated by the following formula: ɣ-GT (IU/L)/platelet count (109/L) x 10. Severity of neurological findings was determined by prenatal neuroimaging in alive newborns, and by postmortem in cases of TOP. ɣ-GT, platelet count, and GPR levels were compared according to brain-damage severity and CMV-infection status. Logistic regression, Receiver-Operator Curve (ROC) analysis, and test of equality of ROC areas were performed.

Results

Twenty-six CMV-infected (20 SBD and 6 mild/no brain lesions) and 35 uninfected-fetuses (14 SBD and 21 mild/no brain lesions) were included. Median (IQR) gestational age (GA) at cardio/cordocentesis was 25.1(22.6-29.6) weeks with no difference between groups. Table-1. Median (IQR) ɣ-GT-level was significantly higher among fetuses with SBD than those with mild/no brain-damage: 266 IU/L (109-667) vs 73 IU/L (42-107), p<0.001. ɣ-GT-levels ≥ 183 IU/l, adjusted for GA at cardio/cordocentesis, were associated with SBD with an OR of 17 (95%CI: 3.9-72) in both groups. When adjusted for GA at cardio/cordocentesis significantly higher ɣ-GT-level values were observed in SBD-CMV-infected-fetuses compared to SBD-uninfected ones, median (IQR): 423 IU/L (110-816) vs.160 IU/L (109-266), p=0.024. For SBD prediction in the uninfected group ɣ-GT ≥187 IU/L achieved 50% sensitivity (Se), 95% specificity (Sp), 10.5 positive and 0.52 negative likelihood ratios (LHR) (AUC: 0.85). Regarding CMV-infected fetuses, prediction was higher, as previously published by our group, with a detection rate of 70% and 83% Sp for a ɣ-GT cut-off ≥183 IU/L. Median (IQR) platelet count was significantly lower among CMV-infected fetuses vs. uninfected ones: 100 (27-155) x103 /mm3 vs. 204 (137-245) x103 /mm3, p<0.001. This difference remained when SBD fetuses were compared according to infection status. We did not observe variations in platelet levels regardless of the severity of brain damage in the uninfected group, p=0.40. Median (IQR) GPR was significantly higher among fetuses with SBD than those with mild/no brain-damage: 2.8 IU (1.0-6.5) vs 0.4 IU (0.3-0.7), p<0.001. As expected, however, we observed significantly higher median (IQR) GPR levels among SBD CMV-infected fetuses than SBD uninfected ones: 4.9 IU (2.3-25.7) vs 1.0 IU (0.8-1.9), p=0.002. GPR adjusted for GA at cardio/cordocentesis was associated with SBD with an OR of 3.10 (95% CI: 1.30-7.45) per every 10 IU increase of GPR in the CMV-infected group. When compared to ɣ-GT levels alone, we found a tendency towards an increased performance for SBD prediction in the CMV-infected group with a GPR≥12 achieving 84% Se, 83% Sp, 5.1 positive and 0.19 negative LHR (AUC: 0.92), p=0.07. Neither did we observe an increase or improvement in the performance for SPD prediction with the GPR compared to the ɣ-GT levels in the uninfected group, p=0.47.

Conclusion

Increased ɣ-GT levels were associated with severe brain damage in CMV-infected and uninfected fetuses. Nevertheless, infection may play a role since the increase was significantly higher among the infected ones. Due to the lower platelet count in CMV-infected fetuses, GPR may improve the detection rate of SBD in this group.