

Post-infectious and post-hemorrhagic hydrocephalus may have a common pathway that triggers ventricular zone disruption

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Background

Hydrocephalus is a neurological condition characterized by abnormal dilatation of the cerebral ventricles. The main etiological factors in neonates are central nervous system infections and hemorrhage, which leads to post-infectious (PIH) and post-hemorrhagic (PHH) hydrocephalus, respectively. We have found that PIH and PHH share common pathophysiological mechanisms such as ventricular zone (VZ) disruption. VZ disruption is implicated in the etiology of neonatal hydrocephalus as a result of N-cadherin (N-cad) cleavage. Adam10 is a metalloproteinase responsible for the regulation of N-cad-dependent cell junctions; increased ADAM10 activity causes VZ disruption by loss of cell junctions. We hypothesize that Adam10-N-cadherin cleavage is a common pathway in PIH and PHH, and its modulation may prevent VZ disruption and other hydrocephalic events.

Materials and Methods

Progenitor cells from newborn mice were cultured as a monolayer of VZ cells that received either blood to mimic PHH or alpha-hemolysin (HI- α), a bacterial toxin released in infections, to mimic PIH. Treatments included: (1) DMSO (vehicle control), (2) syngeneic blood, (3) syngeneic blood + ADAM10 inhibitor (Ad Ih), (4) HI- α , (5) HI- α + Ad Ih. Cell cultures and media, were evaluated with immunohistochemistry, ELISA and western blots.

Results

In vitro treatments were associated with significant disruption of N-cad expression ($p < 0.05$), reduction in the percentage of VZ cells ($p < 0.01$) and increased ADAM10 activity ($p < 0.05$) in PHH and PIH conditions. However, when the cells were pre-treated with ADAM10 inhibitors, cytological structure and N-cad expression were preserved in PHH and PIH conditioned cells; no significant differences were seen when compared to control.

Conclusions

In vitro results indicate that ADAM10 plays a prominent role in the pathogenesis of PHH and PIH and pharmacological modulation of ADAM10 reduces VZ disruption in both cases.