Normal and Abnormal Development of the Central Nervous System I

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This paper concerns the excitotoxic cascade throughout early brain development. Excessive amounts of glutamatergic agents at the N-methyl-D-aspartate (NMDA) site induces deleterious calcium influx able to reproduce a broad spectrum of abnormal developmental patterns with cerebral palsy (CP).

During migration of neurones, Ca-influx regulation at the NMDA site controls migration. Cytoarchitectonic patterns resulting from exaggerated or reduced calcium influx mimic periventricular nodular heterotopias, subcortical band heterotopias, and other lissencephalic patterns.

After completion of migration of neurones, glutamatergic agents induce laminar depopulations of neocortical layers V to VIa characteristic of postmigratory polymicrogyrias. Clinicopathological correlations, including sequential ultrasound, from our European multicentre study, confirm that perfusion failures leading to layered polymicrogyrias often happen after the end of neuronal migration and before the peak of gyration (19 to 28 weeks).

When all neocortical neurones became aerobic (after 30 gestational weeks in the human), glutamate produces severe neuronal losses in all neocortical layers (II, III, TV, V and VI), resulting in a whole spectrum of neocortical lesions occurring around term: focal neocortical necroses throughout the whole cortical thickness, ulegyrias, multicystic encephalopathies, and porencephalic cysts.

Furthermore, at the developmental stage corresponding to 25 to 30 gestational weeks in the human, glutamatergic agents induce the formation of white-matter cysts mimicking certain aspects of periventricular leukomalacias (PVLs). New pathophysiological data underlines the need to look further at PVLs. (1) Ultrasound echodense and/or echolucent abnormalities in premature white matter are heterogeneous. Neonatal white-matter damage is pathologically heterogeneous. Oversimplifications of clinical-pathological correlations, omitting this diversity, are risky. (2) Etiology of PVLs seems to be multifactorial including infections with production of cytokines, perfusion failure/hypoxia, preconceptional factors, thyroid hormone and growth factor deficiencies. (3) The developmental stage of occurrence peak of PVLs corresponds to the peak of production of oligodendrogial precursors and of astrocytic precursors for the upper cortex. PVLs may affect both glial subpopulations with functional consequences. (4) An alpha-amino-3-hydroxy-5-methyl-

4-isoxaole-proprionic acid (AMPA)/kainate cascade is able to launch oligodendroglial cell death. An NMDA glutamatergic excitotoxic cascade, distinct from the oligo/AMPA/kainate cascade, also produces PVLs in several animal models.

Pharmacological tools destined to inhibit the 'cascades' have recently been developed and are promising for neonatal 'neuroprotection'.

Glutamate at the NMDA receptor site is one of the key issues for protection of the developing brain against environmental factors carrying risks of CP.

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