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Original article

The pathology of incipient polymicrogyria

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Abstract

Objective: To characterise the early tissue changes of post encephaloclastic polymicrogyria in the human fetus.

Methods: We identified and reviewed the clinical histories and autopsy pathology of post ischemic fetal cerebral cortical injury at less than 30 weeks gestational age (GA). The histology of local cortical abnormalities was examined with neuronal, glial, microglial and vascular immunohistochemical markers.

Results: We identified eight cases ranging from 18 to 29 weeks GA: 5 cases show full thickness cortical infarcts and 3 show periSylvian post-ischemic necrosis of the cerebral cortex. The maximal age is less than 10 weeks after injury. There are abnormalities in gross fissuration as early as one month after injury. Disruption of the pia limitans was associated with a microglial and glial response and full thickness cortical injury. Macrophages were often seen accumulating deep to abnormal cortex. Hyperplasia of the subpial granular cell layer was universal in perilesional cortex. Cajal Retzius neuron hyperplasia, aggregation, and both superficial and deep displacement were noted. Where there was loss and dispersal of early cortical pyramidal neurons there was usually no pseudolaminar necrosis. Radial glia by 18 weeks GA showed altered growth patterns and lateral branching. Altered migration of primitive elements was often prominent. Particularly prior to 20 weeks GA subadjacent subplate neurons showed striking hypertrophy.

Conclusions: The array of histological changes encompasses all tissue elements of the affected brains, early in the evolution polymicrogyria. Although subpial alterations were ubiquitous, not all changes are referable to alterations in the pia limitans. The role of the necroinflammatory response in the genesis of abnormal cytoarchitecture deserves further study.

Keywords: Polymicrogyria; Fetal; Porencephaly; Schizencephaly; Malformation

1. Introduction

The association between clastic lesions of the cerebral cortex in midgestation and subsequent polymicrogyria is well established [1,2], and the fetal and post-natal histopathology of polymicrogyria in general has been recently the subject of extensive review [3–5]. Polymicrogyria is an etiopathogenically diverse morphology, and can arise as a consequence of a primary malformative process or develop after encephaloclastic insults, usually thought to be in early midgestation [3,6]. Post encephaloclastic lesions comprise a spectrum that includes viral infection, haemorrhage and bland

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ischemic infarction [3,5–7]. However, even within lesions with a putatively similar pathogenesis, the tissue changes leading to polymicrogyria are obscure. Despite the known relationship between fetal brain injury and polymicrogyria, the series of maturational and reactive changes in the affected cortex has not been well defined.

Investigating this evolution is challenging, in that acute or subacute lesions in midgestation can be clinically silent [8,9] and are often only detected during routine surveillance ultrasound, or soon after delivery at term. Moreover, fetal remains are fragile, and artefactual distortion and autolysis can render cytoarchitectural assessment impossible. There is therefore little insight on the early timing and histological evolution of such lesions in midgestation, when the large patterns of cortical folding are normally produced. Pathogenic understanding is further made difficult by the complexity and of human cerebral cortical maturation itself: the process by which normal gyration is achieved is itself somewhat unclear [10]. Finally, the insults that may give rise to the clastic lesions may themselves be clinically obscure, particularly if the systemic autopsy, with particular attention to the placenta, is incomplete, or clinical history lacking [8,9]. Further, final appearances may be affected by insults that may vary in intensity, duration or may be repeated over time [6].

However, given that polymicrogyria is a sequel to midgestation clastic injury to the cerebral cortex, an examination of the early reactions to such injury might refine our understanding of the process. In order to clarify the evolution of early post encephaloclastic cortical malformation, and to attempt to evaluate the pathogenesis of polymicrogyria in this setting, we reviewed a series of brains with established post-encephaloclastic cortical pathologies at autopsy, from midgestation and early third trimester fetuses, when cortical folding is substantially incomplete, and performed clinical pathological correlation using routine histological and immunohistochemical studies. In order to maximize etiopathogenic homogeneity we restricted our study to the cortical and subcortical pathology of bland infarctions and ischemic injury.

2. Materials and methods

Approval was obtained from our institutional review board. We searched our autopsy database for the past 12 years for cases of preterm fetal ischemic and/or haemorrhagic neocortical injury, outside the setting of agonal haematoma. Cases were included if they contained lesions which could be expected to regularly demonstrate polymicrogyria at term, i.e. fetal age at autopsy was less than or at 30 weeks gestation with histologically identified destructive lesions of the cerebral neocortex. We excluded agonal haematomas and small petechial haemorrhages, infants with survival of more than a day postnatally, and cortical lesions associated with complex cerebral malformations (e.g. exencephaly, severe hydrocephalus, encephaloceles, lissencephaly syndromes, primary abnormalities in cortical patterning, aneuploidy, vascular malformations), mitochondrial disease or congenital infections of the brain parenchyma (e.g. *Cytomegalovirus*, *Toxoplasma*) causing primary injury to the substance of the brain. When a case was identified, we reviewed the clinical history and, post mortem radiographs. If growth arrest lines were detected, an approximate dating of the growth arrest episode was attempted [11,12]. This entailed establishing fetal age at time of death from averaged age of fetal long bones (humerus, ulna, femur, and tibia). Subsequently the length between growth arrest lines in the same bones was used to estimate the age at which the significant insult occurred [13].

In our institution, all fetal brains extracted are fixed and hardened intact in 5% formol acetate for 10–14 days, followed by blocking and paraffin embedding according to standard protocols, and sectioned at 6 μm thickness. All histopathology slides of autopsy tissues and the placental examination as well as the cytogenetics reports were reviewed. In addition to routine diagnostic histology, appropriate tissue blocks of brain were stained with antibodies to alpha–Beta crystallin (clone G2JF, Leica Novocastra, dilution = 1:75), Calretinin (clone DAK Calret1, Dakocytomation, 1:100), CD15 (clone MMA, Cell Marque, 1:35), CD68 (clone PG-M1, Dakocytomation, 1:75),Collagen IV (Clone CIV22, Dakocytomation, 1:50), GFAP (Polyclonal, Dakocytomation, Dilution: 1:500), 1:100), nestin (Polyclonal, Millipore, 1:4500), neurofilament light chain (clone DA2, Leica Novocastra, 1:300), OTX1 (Polyclonal, Abcam, 1:100) reelin (clone E5, Santa Cruz, 1:75), synaptophysin (clone 27G12, Leica Novocastra, 1:100) and vimentin (clone V9, Dakocytomation, 1:200).

For the purposes of this study, we defined potentially polymicrogyric cortex as immediately perilesional cortex with distinct lamination abnormalities or with marked irregularity and undulation of the cortical mantle, or as lesional cortex with such irregularity and post necrotic changes (e.g. calcification, rarefaction, macrophage accumulation). We used these criteria because layering at midgestation is poorly defined, and gross gyration in most areas is early or absent. We did not count mere irregularity or tufting [6] of the superficial cortex as lesional. In all cases, the histology of the abnormal neocortex was compared with directly adjacent neocortex with normal architecture on H + E staining.

3. Results

3.1. Clinical findings and systemic pathology

We identified seventeen fetal cases and of these, four cases of porencephaly were rejected because of advanced