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Annotation

Perinatal brain damage, post-injury cortical reorganization (acquired cortical dysplasia) and epilepsy

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With improved magnetic resonance neuroimaging, cortical dysplasia is been diagnosed in an increasing number of children with epilepsy. The pathogenesis of cortical dysplasia remains unexplained. The general consensus is that these lesions represent genetic disorders caused by alterations in the normal migration of cortical neurones hence the term 'cortical dysgenesis' is often used. However, not all cortical dysplasias are the result of neuronal migration disorders and the term 'acquired cortical dysplasia may be used to distinguish such lesions from those caused by neuronal migration disorders. Genetic and acquired cortical dysplasias may share similar cytoarchitectural alterations. Probably, the similar pathology observed in these disorders reflects common post-injury repair mechanisms intrinsic to the developing cerebral cortex rather than the nature of the original insult. While the association of cortical dysplasias and epilepsy has been amply demonstrated, the role that these cortical lesions play in its pathogenesis remains essentially unexplained. Detailed study of the brains of infants who survived documented perinatal brain damage suggest that post-injury alterations, rather than the original lesion and/or its subsequent glial scarring, constitute the fundamental underlying mechanism in the pathogenesis of epilepsy and other neurological sequelae (e.g. cerebral palsy, dyslexia, cognitive impairment, and poor school performance) which occur following neonatal brain damage.

Keywords: cortical dysplasia, epilepsy, histopathology, pathogenesis

Introduction

Cortical dysplasia is a neuropathological term used to describe focal, diffuse, and/or generalized cytoarchitectural disorganization of the cerebral cortex with or without glio/neuronal heterotopias. The term was used by Taylor to describe cortical alterations observed in epileptic patients [1]. With improved magnetic resonance neuroimaging, cortical dysplasia is being diagnosed in an increasing number of children with epilepsy [2]. The improve visualization of the size, location and distribution of these cortical lesions have rendered them suitable to surgical excision, often with excellent results in the treatment of intractable epilepsy [2,3].

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Pathogenesis of cortical dysplasia

The pathogenesis of cortical dysplasia remains unexplained. The general consensus is that these lesions represent genetic disorders caused by alterations in the normal migration of cortical neurones [4,5], hence the term 'cortical dysgenesis' is often used [4,6]. However, not all cortical dysplasias are the result of neuronal migration disorders. Cortical dysplasias have been described in neonatal encephalopathies caused by infections, trauma, alcohol, and, particularly, following hypoxic/ischaemic and/or haemorrhagic brain damage [7–11]. I have introduced the term 'acquired cortical dysplasias' to distinguish these lesions from those caused by neuronal migration disorders [10]. Acquired cortical dysplasias are also often associated with neurological sequelae, including epilepsy, cerebral palsy, dyslexia,

neurological delay, cognitive impairment, and poor school performance [7,9,10,12]. Cortical dysplasias have been also induced by a variety of experimental procedures, including X-ray irradiation, freezing, aluminium gel, and surgical trauma [4,6,7]. Cortical development is a complex evolving process during which – under strict genetic constrains and at specific times – neurones, axonic fibres, glial cells and capillaries originate, migrate, differentiate and establish structural and functional renewable interrelationships [10,13]. At any time during development, this process can be interrupted by either genetic and/or acquired injury and, if the infant survives, the subsequent differentiation of the cerebral cortex will invariably and progressively be altered. Genetic and acquired cortical dysplasias may share similar cytoarchitectural alterations. Probably, the similar pathology observed in these disorders reflects common post-injury repair mechanisms intrinsic to the developing cerebral cortex rather than the nature of the original insult.

The clinical significance of cortical dysplasia

While the association of cortical dysplasias and epilepsy has been amply demonstrated, the role that these cortical lesions (genetic and/or acquired) play in its pathogenesis (and in that of other neurological sequelae) remains essentially unexplained. To address this question at least three basic developmental processes must be understood: (i) the nature of the original insult and the resulting cortical damage; (ii) the repair mechanisms of the injured but still developing cerebral cortex; and (iii) the post-injury progressive reorganization (acquired cortical dysplasia) of the cerebral cortex of surviving infants.

The brains of 36 infants who survived documented perinatal brain damage caused by haemorrhagic and/or hypoxic/ischaemic injury and later died for a variety of reasons have served as a basis for detailed study [8–10]. The infants survival time ranged from hours, days, weeks, or months, to several years. Their evolving neuropathology included: acute, subacute (healing), and/or chronic (repaired) stages of various cortical lesions and their subsequent post-injury reorganization (acquired cortical dysplasia). Among the long survival cases, 10 infants developed epilepsy, two developed cerebral palsy, and several were cognitively impaired.

From these studies concerning the pathogenesis of acquired cortical dysplasias, their impact on the development of the infant cerebral cortex, and their possible role in the pathogenesis of epilepsy, the following conclusions have been drawn:

1 Primarily undamaged cortical regions adjacent to any neonatal brain lesion survive, retain their intrinsic vasculature, and are capable of continuing their development. However, their post-injury structural and functional differentiation will invariably and progressively be altered and result in acquired cortical dysplasia.
2 The grey matter overlying white matter lesions, despite partial sensory deprivation and inability to reach functional targets, survives, retains its intrinsic vasculature, and undergoes progressive post injury reorganization. This post-injury reorganization is characterized by progressive cytoarchitectural transformations involving neurones (atrophy and hypertrophy), changes in synaptic profiles, modifications of the intrinsic circuitry, and reactive gliosis.
3 Some axotomized projection neurones overlying white matter lesions survive, despite the loss of their normal functional targets, and, develop new synaptic and intracortical axonal profiles, and become progressively transformed into local circuit neurones; an idea already proposed by Cajal in 1928 [14]
4 Some dendrotomized pyramidal cells underlying subpial haemorrhages survive, develop new synaptic profiles, and become progressively transformed into stellate neurones.
5 Some intrinsic neurones of the grey matter adjacent to an injured site undergo post-injury hypertrophy characterized by large size (meganeurone), new morphological features, dendritic and axonal expansion, strongly positive neurofilament stain, and, possibly, nuclear polyploidy.
6 Both the intrinsic fibres of layer I and some Cajal–Retzius cells survive, even in severe grey matter lesions, and can interconnect adjoining and distant cortical regions that have lost other types of functional connections.
7 Myelinated and strongly neurofilament positive fibres may be capable of interconnecting the dysplastic cortex with other cortical and subcortical regions and of carrying normal as well as abnormal (epileptic) impulses.
8 These post injury neuronal, synaptic, fibrillar, vascular, and glial alterations are not static but ongoing processes that will continue, perhaps

throughout the life of the individual, to affect the structural and functional maturation of the neocortex and influence the neurological and cognitive development of affected children.

9 It is proposed that these post-injury alterations, rather than the original lesion and/or its subsequent glial scarring, constitute the fundamental underlying mechanism in the pathogenesis of epilepsy and other neurological sequelae (e.g. cerebral palsy, dyslexia, cognitive impairment, and poor school performance) which occur following neonatal brain damage.

10 To identify some of these post injury (neuronal, synaptic, fibrillar, vascular, and glial) alterations the combined use of immunohistochemical stainings and, especially, the rapid Golgi method is required.

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