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Prenatal contributions to epilepsy: lessons from the bedside

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ABSTRACT – While epilepsy can present at any age, this condition often occurs because of adverse events early in life. Pathogenetic mechanisms also cause deleterious consequences to the brain during prenatal life. For the epileptologist to fully appreciate developmental epileptogenesis, one must apply an ontogenetic approach (i.e. "nature-nurture-niche") in order to study the epileptic condition from a fetal neurology perspective. Genetic susceptibility can involve pre-fertilization and post-fertilization mechanisms that dictate the timing and form of major malformations associated with specific epileptic syndromes. Maternal, fetal, and placental disease conditions also contribute to either brain malformations or injuries, depending on events during the first or second half of pregnancy. Sequential stages during prenatal brain development, from embryonic through perinatal periods, specify which gray and white matter structures may be adversely altered, with later expression of seizures in the context of motor, cognitive and behavioral deficits. Translational research from bench to bedside should consider the acquired causes of pediatric and adult epilepsies in the context of the patient's genetic environment.

KEY WORDS: epilepsy, prenatal, maternal diseases, placenta, fetus, neonate

Children and adults can suffer from epileptic conditions that are prenatal in origin [1, 2]. Most investigations have focused on the genetic origins of selected generalized and partial epilepsies [3]. Dramatic advances in genetic markers for specific forms of epilepsy indicate that certain epilepsies are determined at conception, as represented by malformations in cortical development. The most severe anomalies are structurally visible during the embryonic and fetal stages of brain development (i.e. less than 24 weeks after conception).

Advances in magnetic resonance imaging techniques provide the epileptologist with the diagnostic means by which a more strict classification of anomalous brain development can be developed [4]. Such a classification scheme closely reflects the maturational sequences of brain development, from neural tube closure to neuronal differentiation and proliferation, migration, dendritic organization and synaptogenesis, neurotransmitter elaboration and myelination.

Regressive processes incorporating programmed cell death (i.e. apoptosis) and activity-dependent development, remodel neuronal networks in the maturing brain, accelerating during the third trimester, and continuing into the third decade of postnatal life [5, 6]. This process of resculpting also plays a crucial role in epileptogenesis [7-9]. While newer techniques utilizing

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volumetric magnetic resonance imaging offer greater insight concerning specific changes in quantities of gray and white matter that appear during maturation [10, 11], remodeling of brain structure and function at the neural network or cellular levels are not readily detected by present neuroimaging techniques.

Comparatively less attention has focused on pathogenetic mechanisms leading to epileptogenesis during the perinatal stage of brain development that begins at 24 weeks gestational age through to one month of postnatal life. Acquired brain injury from maternal-placental-fetal-neonatal diseases can have profound effects on brain development during this period, contributing to a spectrum of neurological sequelae, which include epilepsy, and cognitive and behavioral sequelae. These disease processes are also more prevalent in fetal/neonatal populations than major brain malformations such as lissencephaly, schizencephaly or holoprosencephaly.

Investigations over several decades have indicated that diseases of the mother, placenta and fetus contribute substantially to developmental disorders ranging from cerebral palsy [12] and mental retardation [13, 14] to learning disabilities and neurobehavioral deficits [15]. Pathogenetic mechanisms leading to acquired brain injury during fetal life include chorioamnionitis, asphyxia and stroke syndromes. These same disease processes may also contribute to the epileptic condition. Our understanding of epilepsy therefore must integrate prenatal mechanisms of brain injury into models of developmental epileptogenesis, to study how inflammatory, asphyxial and thromboocclusive conditions contribute to the genesis of various epilepsies.

Prenatal considerations by the epilepsy consultant

Formulating a differential diagnosis for any medical condition begins with fact finding; such a strategy pertains to both the pediatric and adult epilepsy patient. Consideration of maternal and prenatal histories, as well as cognizance of preconceptional medical risks, family histories and environmental conditions add important perspectives to our understanding of the genesis of the epileptic condition. Epileptologists must frame the clinical neurological profile of the patient in the context of the developmental niche or gestational maturity during which a maturational disorder or acquired disease process occurs which later presents as epilepsy for the patient. Historical data, clinical examination findings, and laboratory information must be placed along a timeline that considers prenatal as well as postnatal time periods when brain damage may have occurred, or was exacerbated in the context of the patient's genetic endowment [16].

Structural and functional descriptors of the epileptic condition are useful and complementary, but not always equivalent for every clinical scenario. Improvements in neuroimaging techniques, particularly magnetic resonance imaging, provide a greater likelihood of detecting certain major anatomical markers that may be associated with epilepsy. However, there will always be limits of resolution using either neuroimaging or neurophysiological monitoring with respect to anatomical and neural network disruptions in brain development, which contribute to epilepsy. Therefore, epileptologists must continue to practice accurate history-taking and clinical examinations to more fully appreciate epilepsy risk, even when test results are inconclusive. Cognizance of the prenatal stages in brain development will help the epilepsy specialist formulate a more comprehensive differential diagnosis for seizures which includes maternal, placental and fetal contributions, while also considering postnatal events such as closed head injury, encephalitis/meningitis and cardiopulmonary arrest, which further lower the threshold for seizure initiation at older ages.

Classifications concerning malformations in cortical development have applied the sequential stages in prenatal brain development to categorize generalized and focal anomalies of the brain by magnetic resonance imaging. This classification scheme applies to both generalized as well as localization-specific epilepsies. Barkovich *et al.,* [4] for example, described malformations that can be broadly classified to represent four general stages in brain development;

1) malformations due to abnormal neuronal/glial proliferation;

2) malformations due to abnormal neuronal migration;

3) and malformations due to abnormal cortical organization;

4) malformations, not otherwise specified. *Table 1* lists the generalized and focal/multifocal anomalies that can be identified by MRI, as later verified by neuropathology at the time of epilepsy surgery or on postmortem examination.

This neuroimaging classification scheme provides the intellectual scaffolding upon which clinicians can better identify patients who have epilepsy with documented cortical malformations. Leventer *et al.,* [17] for example, described 109 children with abnormal of cortical development documented on MRI images from 8 days to 18 years old. Seventy-five percent of these children presented with seizures, an abnormal neurological examination being noted in less than half of this population. Almost two-thirds exhibited developmental delay or mental retardation, and nearly 20% of the patients also had associated non-CNS anomalies. A spectrum of cortical development abnormalities included generalized, hemispheric or multifocal forms for 70% of patients, and involved both cortical and white matter lesions in 60%; noncortical anomalies were also noted in over two-thirds of the patients. The incidence of various abnormalities are listed in *table 1* and

Table 1. Classification scheme for malfomations of cortical development*.

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
A. Decreased proliferation increased apoptosis: microcephalies
1. Microcephaly with normal to thin cortex
2. Microlissencephaly (extreme microcephaly with thick cortex)
3. Microcephaly with polymicrogyria/cortical dysplasia
B. Increased proliferation decreased apoptosis (normal cell types): megalencephalies
C. Abnormal proliferation (abnormal cell types)
1. Non-neoplastic
a. Cortical hamartomas of tuberous sclerosis
b. Cortical dysplasia with balloon cells
c. Hemimegalencephaly (HMEG)
2. Neoplastic (associated with disordered cortex)
a. DNET (dysembryoplastic neuroepithelial tumor)
b. Ganglioglioma
c. Gangliocytoma
II. Malformations due to abnormal neuronal migration
A. Lissencephaly subcortical band heterotopia spectrum
B. Cobblestone complex
1. Congenital muscular dystrophy syndromes
2. Syndromes with no involvement of muscle
C. Heterotopia
1. Subependymal (periventricular)
2. Subcortical (other than band heterotopia)
3. Marginal glioneuronal
III. Malformations due to abnormal cortical organization (including late neuronal migration)
A. Polymicrogyria and schizencephaly
1. Bilateral polymicrogyria syndromes
2. Schizencephaly (polymicrogyria with clefts)
3. Polymicrogyria with other brain malformations or abnormalities
4. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes
B. Cortical dysplasia without balloon cells
C. Microdysgenesis
IV. Malformations of cortical development, not otherwise classified.
A. Malformations secondary to inborn errors of metabolism
1. Mitochondrial and pyruvate metabolic disorders
2. Peroxisomal disorders
B. Other unclassified malformations
1. Sublobar dysplasia
2. Others

* From Barkovich *et al.,* 2001 [4].

range from the more frequently described anomalies such as heterotopic gray matter, developmental polymicrogyria and other cortical development abnormalities, to nonspecific CNS abnormalities such as ventriculomegaly, enlarged extra-axial spaces, agenesis of corpus callosum and delayed myelination. Following Barkovich's suggested neuroimaging classification, Leventer subdivided malformations of cortical development into roughly three types; 37% involving progenitor neuronal proliferation and differentiation, 31% with neuronal migration and 32% with neuronal organization or unclassified development stages. Such descriptions allow the epileptologist to identify malformations of cortical development which occur primarily during embryonic or fetal stages of brain development after the completion of cell migration. Disorders of neuronal organization generally imply events during the third trimester. Nonspecific findings represent anomalies that largely fall below the resolution of MRI and in some instances implicate older gestational ages. During the perinatal period of brain development, more subtle maldevelopment or damage can occur, which contributes to epilepsy, as well as cognitive and behavioral deficits.

Another descriptive study emphasizes the diagnostic contributions of clinical histories with regard to epileptic patients who exhibit specific neuroimaging findings. Palmini *et al.,* [18] described 40 patients with neuronal migrational disorders (NMD), 38 of whom had epilepsy. This group was compared with 40 epileptic controls who had no NMD noted on neuroimaging. Using a standardized questionnaire, the authors differentiated "prenatal" influences such as trauma, medication use, X-ray exposure, intrauterine infection, metabolic abnormalities, family history of congenital malformations and fetal loss from peri- and postnatal adverse events such as asphyxia, prematurity, infection and trauma. The authors assumed that the occurrence of prenatal adverse effects occurred during the period of brain development from 6 to 20 weeks gestation. Note that adverse conditions during the third trimester of pregnancy were not addressed. They reported that for the NMD group, 58% of children presented with these historical risk factors, compared to only 15% of the controls. Conversely, 50% of the control group with epilepsy and without NMD, reported peri- or postnatal complications, such as asphyxia or infection. Interestingly, both groups were similarly affected by genetic contributions to the epileptic condition, (i.e. 13% for NMD and 20% for the control group). This study emphasizes that historical information, when combined with neuroimaging findings, helps to estimate the time periods associated with the development of epilepsy, based on trimester-specific conditions during gestation.

Prenatal historical information can also be important for seizure cohorts other than for epileptic populations. Sidenvall *et al.,* [19] described a population-based study of 75 children, several months to 15 years of age who underwent MRI studies after their first, unprovoked afebrile seizure; only three out of the 75 patients had brain malformations noted on neuroimaging. This case-controlled study included statistical analyses of seven pre- and perinatal risk factors including birth order, vaginal bleeding, hypertension, need for cesarean section, smoking, gestational age at delivery, and Apgar score of ≤ 6. No risk factors were noted for nearly 90% of the control population, while 52% of the seizure population had two or more significant risk factors based on univariate analyses. Several factors also remained significant on multivariate analyses including vaginal bleeding, gestational age, need for caesarean section and smoking. These prenatal risk factors were broadly defined, and failed to specify maternal, placental or fetal diseases in a trimester-specific manner, such as preeclampsia, thrombophilia or asphyxia. The authors also did not adjust for mental retardation, cerebral palsy or CNS anomalies. Nonetheless, their findings emphasize the prenatal contributions of maternal or fetal diseases in children who later present with an unprovoked afebrile seizure. Despite the absence of neuroimaging abnormalities, seizure risk can be ascertained using prenatal histories.

One type of cortical malformation, polymicrogyria, illustrates the diversity of prenatal disease processes that can contribute to epilepsy in children, ascertained simply by prenatal medical histories. Polymicrogyria is not a single pathological entity and at least two forms (unlayered and four-layered) exist that may have different origins, (i.e. migrational in the first instance, and post-migrational destruction in the latter instance). Pascual-Castroviejo *et al.,* [20] described 13 children with cerebral palsy between eight months and ten years of age who later developed epilepsy between three and 14 years of age. All children initially presented, between three and six months of age, with a hemiparesis, and none had suffered peripartum distress at the time of labor and delivery. Ten of the 13 later developed epilepsy, and all had unilateral polymicrogyria documented on MRI. These authors found that spontaneous threatened abortion as described by the mother, or maternal hypertension were noted in five of the 13, while six of the 13 were low birthweight infants (i.e. less than 3 kg). The authors suggested that developmental mechanisms which contribute to polymicrogyria may be fundamental for some children (i.e. from conception), while other, acquired forms of polymicrogyria occur as a consequence of maternal hypertension, chorioamnionitis or conditions of prematurity. Disorders of progenitor neuronal migration or organization leading to polymicrogyria have been reported as a consequence of gestational hypertension, hemorrhagic events or inflammatory changes which contribute to placental hypoperfusion and ischemic injury to the developing fetal brain [21]. Hypoperfusion to the fetus from twin-to-twin transfusion syndrome and hydrops fetalis [22, 23] are cited as examples of prenatal disease conditions that contribute to acquired forms of this cortical migration defect. Multiple maternal-fetal-placental risk factors may contribute to abnormal brain development resulting in different, acquired brain anomalies, as exemplified by polymicrogyria.

The concept of "nature-nurture-niche" helps define the epileptic condition

Advances in clinical and basic developmental neuroscience research demand that the epileptologist approach the evaluation of epilepsy in the context of three overlapping influences that form and remodel neurological structure and function, beginning during prenatal life, and continuing into childhood and adulthood; "nature-nurture-niche" [24, 25]. Historical data, clinical findings and laboratory information must be placed along a timeline that considers prenatal time periods during which brain malformation or damage occurs in the context of the child's genetic endowment. Different mechanisms of cellular injury and/or repair can contribute to neuronal or glial cell loss or recovery. Such mechanisms include the destructive pathways of necrosis and apoptosis, as well as

adaptive mechanisms which protect the developing brain by promoting cell survival and activity-dependent development, sometimes with clinicopathological consequences [8, 9]. Understanding maturational aspects of stress to the brain, which promote vulnerability or protection will help create a blueprint for the design of neuroprotective strategies against the development of epilepsy, as well as better anticipation of later neurological morbidities that also result from the conséquences of remodeling, which emerge during early life.

In the following section, prefertilization and postfertilization genetic influences are discussed that help define the epileptic condition.

Genetic contributions to the developmental process of "nature-nurture-niche"

Neuronal migration is a complex ontogenetic process which occurs early during embryonic and fetal development. Genetic control of neuronal migration involves different cell populations. Selective human and rodent genes, as well as other factors, have been linked to multiple neuronal migrational disorders *(table 2)*.

Some of these established or hypothetical links between genes or gene products and migrational disorders help explain how migratory neurons travel past subplate neurons along a migrational pathway to sites initially below layer 1, in an inside-outside pattern, extending from cortical layers II through VI. Three general trajectories include radial migration of neuroblasts along glial-guiding neurons originating from the periventricular germinative zone, secondly, tangential migration in the germinative zone, followed by radial migration along glial guides, and thirdly, tangential migration in the intermediate zone of neurons originating from the ganglionic eminence *(figure 1)*. As reviewed by Gressens [27], these genes or gene products exemplify prefertilization genetic miscodings that are responsible for specific cortical development abnormalities such as the lissencephalies, double-band cortex and X-linked periventricular heterotopias.

Our current understanding of the process of connectivity in the developing neocortex certainly remains incomplete, but other important influences have been impli-

Table 2. Gene and gene products associated with neuronal migration disorders in human and rodent neocortex*.

LIS1 gene, PAF	Miller-Dieker syndrome and some isolated type I lissencephalies
DCX or XLIS gene	X-linked subcortical laminar heterotopia and lissencephaly syndrome (or double cortex syndrome)
Filamin 1 (FLN1)	X-linked dominant periventricular heterotopia
Tish gene	Laminar band heterotopias, double cortex syndrome
Reelin	Inverted cortical layers
p35/cdk5 kinase	Inverted cortical layers
Neurotrophins	Status verrucosus, molecular ectopias, inverted cortical layers
GABAergic system	Neuronal migration disorders
Glutamatergic system	Neuronal heterotopias, molecular ectopias
Peroxysomal apparatus	Zellweger syndrome
Pax6 gene	Abnormalities of radial glia

* Adapted and modified from Gressens, 1998 [26].

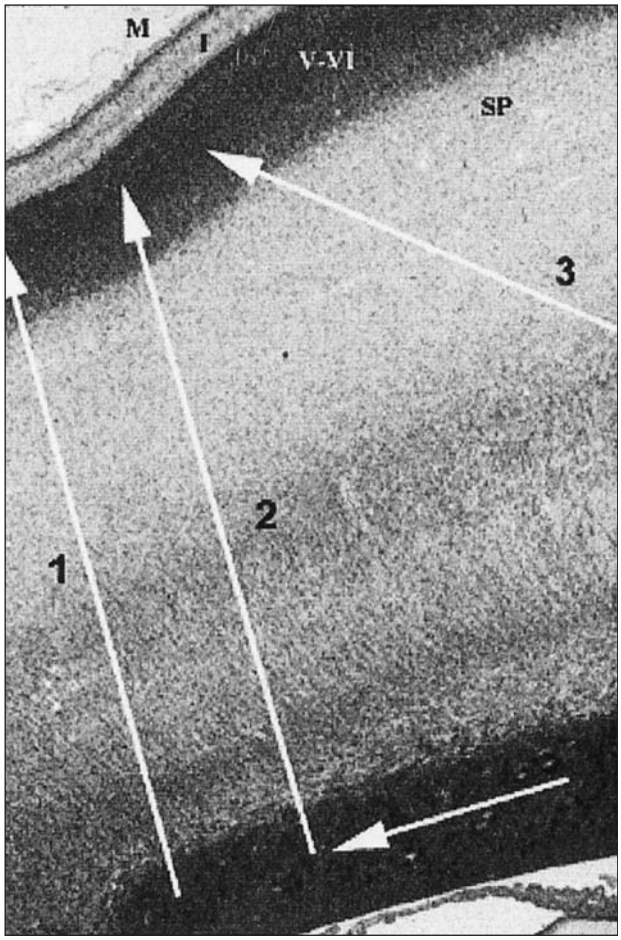

Figure 1. *Coronal neopallium on section at 15-weeks of gestation showing a schematic representation of different migratory pathways adopted by neurons.* **1:** Radial migration along radial glial cells of neurons originating from the periventricular germinative zone **(GZ)**. **2:** Tangential in the germinative zone **(GZ)** followed by a radial migration along glial guides. **3:** Tangential migration in the intermediate zone **(IZ)** of neurons originating from the ganglionic eminence. ML molecular layer; cortical layers V-VI; LD, lateral ventricle. Reprinted with permission Gressens, 2000.

cated. Transient actions of specific neurotransmitters during neocortical development, for example, also appear to be important for neuronal connectivity. Dammerman and Kriegstein [28] argue that pertubations in the time course or extent of these neurotransmitter changes may result in either localized or global cortical malformations. For example, taurine regulates neuronal migration and development early in gestation, while GABA regulates neurogenesis, final neuronal number, and heterosynaptic plasticity including NMDA synthesis. Alterations in this cortical circuitry by genetic miscodings lead to changes in these neurotransmitter pools, which in turn, promote the flawed development of brain circuitry responsible for seizure initiation and propagation.

Specific categories of genetic coding define a homeodomain, comprised of transcription factors which activate or repress groups of downstream target genes, which develop large segments of particular organs such as within the brain. The OTX1 gene, for example, has expressive domains characterized in the developing rostral brain of mouse embryos [29]. Studies of epileptic mice lacking the OTX1 gene exemplify how a prefertilization defect in this homeobox gene expression subsequently alters brain circuitry in an age-or trimester-specific fashion. Avanzini *et al.,* [30] demonstrated how the lack of an OTX1 gene results in altered neuronal structure within the ventricular zone at mid-gestation, compared to disordered circuitry within the cortical plates of layers V and VI at older gestational ages. One might speculate how acquired diseases during pregnancy can influence the manifestation of faulty genetic expression; different neuronal populations are uniquely affected, depending on the stage of brain development during which gene products are expressed. For the OTX1 gene, a defect in expression of this homeobox gene will result in excessive excitatory amino acid-mediated synaptic driving, leading to hyperexcitable conditions. At earlier times during gestation, this expression of hyperexcitability is found within the ventricular zone rather than the cortical plate at older gestational ages.

In addition to disorders of gene expression, which are caused by prefertilization defects in brain development, postfertilization disturbances also contribute to disrupted genetic-molecular pathways, as proposed by Knudson [31] to explain carcinogenesis. Postfertilization somatic mutations, presumably due to disease or acquired environmental factors may inactivate the remaining normal copy of an oncogene resulting in increased susceptibility of the organism to the development of a particular cancer. This same hypothesis may explain the loss of heterozygosity in certain genetic neurological disorders, such as tuberous sclerosis [32]. Postfertilization somatic mutations may inactivate the remaining normal copy of a TSC gene, which then leads to a wide range of phenotypic features affecting individuals with TS, including candidate genes which promote epileptogenesis. Somatic mutations occur because of acquired prenatal or postnatal diseases with inactivation of the remaining normal copy of an epilepsy-producing gene. The TS patient, for example, will then demonstrate greater seizure severity as well as an increased risk of malignant transformation of hamartomatous growths.

Recent studies of discordant monozygotic twins also explore the integrated effects of genetic and acquired causes for epilepsy. Briellmann *et al.,* [33] studied 12 monozygotic twins discordant for epilepsy, with respect to major or minor clinical risk factors associated with epileptogenic lesions documented on brain magnetic resonance imaging and quantitative brain volume abnormalities. Acquired neonatal factors included intraventricular hemorrhage, skull fracture, severe birth asphyxia, Apgar scores of 0 to 3 and an umbilical artery pH of less than 7. Postnatal factors included severe postnatal head injury documenting contusion or cerebral hemorrhage, significant cerebral infection, stroke, complicated febrile seizures or craniocerebral trauma. Minor risk factors included prematurity or low birth weight, mild head injuries, uncomplicated febrile seizures. Major risk factors were associated with acquired lesions in four of the 12 twins. MRI lesions without major risk factors were also found in four different twin-pairs; two of these pairs had unilateral malformations of cortical development while one had bilateral periventricular heterotopias or focal atrophy. Significant twin-to-twin differences in MRI volumes, without obvious MRI lesions or major risk factors, were found in two out of 12 twins. The authors conclude that 10 out of 12 pairs had clinical/MRI correlates to explain epilepsy, which suggests that acquired factors during prenatal development contributed to postfertilization genetic processes promoting epilepsy.

Montenegro *et al.,* [34] also explored the interrelationships between genetic susceptibility and prenatal injury in the genesis of specific malformations of cortical development. Seventy-six patients were subdivided into three groups of malformation in cortical development (MCD) (i.e. focal cortical dysplasias, heterotopias/agyria-pachygyria and polymicrogyria/schizencephaly). They concluded that focal cortical dysplasias resulted in more severe epilepsy, but from less important genetic and prenatal events. The group with heterotopias/agyria-pachygyria had a stronger genetic predisposition. Finally, the group with polymicrogyria/schizencephaly were less frequently associated with epilepsy but had stronger associations with both genetic and prenatal events. Prenatal events included in their analyses were reported by the mother or family only during early pregnancy. Adverse events during the third trimester from maternal, placental or fetal diseases were not considered in this study, which may have also contributed to post-migrational forms of these three groups of cortical anomalies.

Maternal-placental-fetal diseases and epilepsy risk

Specific developmental anomalies and adverse prenatal conditions during the first half of gestation have been the major focus of research to explain specific epileptic syndromes. Comparatively less attention has been devoted to maternal-placental-fetal diseases during the later half of pregnancy or during parturition and neonatal life. Four topics will be discussed which illustrate how adverse events, particularly during the perinatal period (i.e. 24 weeks gestation to one month postnatal life) contribute to the genesis of epilepsy; white matter necrosis or periventricular leukomalacia (PVL), maternal thrombophilia, placental diseases and the harmful consequences of neonatal brain disorders associated with neonatal seizures.

White matter necrosis and epilepsy risk – maternal/placental diseases

Cerebral palsy (CP) is the general neurological disability of motor tone and posture in children who may have genetic or acquired conditions to explain this spectrum of disabilities [12]. There is evidence associating motor deficits in some children and exposure to maternal infection during prenatal life. The presence of chorioamnionitis has been associated with brain injury as a result of the brain's inflammatory response to infection [35-37]. Cytokines are the principal mediators commonly expressed after inflammation, and brain injury may result not only from direct effects of pathogens and their toxins but also the effects of neuroinflammatory mediators which are released to preserve brain structure and function [38]. Some argue that prooligodendrocytes are the primary sites of damage, while others argue that white matter damage may involve both axons and oligodendrocytes in a manner that extend injury to oligodendroglial axonal fibers, as well microgliosis and/or astrogliosis, sometimes called periventricular leukomalacia (PVL) [39].

While white matter necrosis or PVL may result from maternal infection, other pathological processes associated with maternal, fetal, neonatal or placental diseases can also harm developing vasculature and neuronal populations. Marín-Padilla, [21] described the harmful effects of white matter necrosis on cortical vasculature from diverse etiologies, with post-injury reorganization of the cortical mantle. The authors cite associations with prematurity, cardiopulmonary difficulties during parturition or neonatal life, monozygotic twinning with fetal transfusion syndrome, congenital/neonatal infections, and trauma. Multifactorial pathogenetic pathways involving maternal-fetal-placental-neonatal entities cannot always be easily differentiated.

Thirty-five infants, from 21 weeks gestational age to term, who died at neonatal to adolescent ages, were investigated using detailed histological examinations on post-mortem neuropathological studies [21]. A number of significant cytoarchitectural alterations were noted in the cortical mantle in association with underlying white matter damage *(figure 2).* Neuronal displacement and disorientations such as heterotopias within layer 1 or the subpial regions were cited. Alterations of neuronal circuitry were demonstrated, including synaptic reorganization and transformation of long projective circuits into local isolated circuits. Neuronal atrophy or hypertrophy of particular cell types were also noted with the altered functional circuitry. Mechanisms resulting in PVL promote the formation of gray matter heterotopias, either within the white matter or throughout any of the cortical layers including layer 1, and are later responsible for the genesis of epilepsy

Figure 2. *Mosaic of camera lucida drawings from rapid Golgi preparations. A 34-week infant who died at 18 days of age suffered prenatal white matter damage with resultant extensive leptomeningeal heterotopias. The disruption site of the external glial-limiting membrane are marked by thick arrows and in the leptomeningeal space, dysplastic lesions are noted containing a variety of displaced neuronal glial fibrillary and vascular elements. Small arrows indicate displaced neurons. Large hypertrophic neurons (*) have long dendrites reaching into the leptomeningeal heterotopia from Marìn-Padilla* et al. *[21] with permission.*

later in life, sometimes in the context of other neurological sequelae.

Epileptologists must recognize the heterogeneity of malformations of cortical development (MCD) in association with white matter lesions, and with respect to the timing of the defect during the developmental process, the anatomical location, and etiology. For example, there is a clinicopathological spectrum of cortical dysplasia in childhood [40]. Classifications are repeatedly being revised, based on new neuropathological and neuroimaging findings [41, 42], including associations with white matter necrosis and/or altered myelination. Leventer [17] described white matter lesions in association with MCD on conventional MRI studies. Newer neuroimaging techniques such as diffusion tractography from MRI images can better document connectivity of heterotopic gray matter by following aberrant white matter tracts, as seen in band heterotopias [43].

Since surgical outcomes are far less optimal for children with MCD, preoperative investigative protocols need constant revision to reflect the gestational age-specific timing of the insult, as well as the harmful neuroplasticity that results, based on etiology and extent of the lesion, in part influenced by white matter injury. All of these factors ultimately limit surgical success for seizure control [44]. The epileptogenic region in MCD may not be discrete, even when focal lesions are documented. Hemispheric laterality of the MCD [45], extratemporal foci [46] and white matter necrosis [47, 48] are three possible factors which influence surgical success. Comparative outcomes between cohorts with congenital lesions that occur earlier during gestation, and acquired lesions which tend to occur later during pregnancy have not been systematically examined. Descriptive case reports such as those by Inder *et al.,* [49] suggest that post-migrational development of polymicrogyria can occur, as noted in a preterm infant who previously suffered PVL, documented by MRI during neonatal life. Similarly, pathogenetic mechanisms during the third trimester of prenatal life may also be responsible for a variety of migrational defects in surviving children, whether born at preterm or fullterm.

White matter necrosis or PVL has been documented in patients with epilepsy, particularly in association with other neurological deficits. Gurses *et al.,* [50] for example, studied two epilepsy populations; one cohort had been referred to a cerebral palsy clinic, while the other group was treated in an epilepsy center. MRI documentation of PVL with or without abnormal cortex was described. When PVL was associated with motor disabilities (i.e. noted for the CP cohort), 47% of the children also suffered intractable epilepsy. These epileptic patients had multiple seizure types, with complex partial seizures being the most common. A single patient had intracranial EEG monitoring demonstrating a multifocal epileptic process with occipital-temporal predominance, which is one site in the cortical mantle over which PVL may occur in the central white matter. In contrast to the cohort with cerebral palsy, patients evaluated in an epilepsy center, presumably without cerebral palsy, had a lower incidence of PVL (2%). While PVL alone may not always predict epilepsy, some children have an increased vulnerability for developing epilepsy if damage or alteration of ascending or descending neuronal pathways result, contributing to other neurological sequelae such as cerebral palsy. One must also recognize selection bias when studying the association of PVL with epilepsy. For example pediatric neurologists evaluate and follow children with seizure disorders who remain in comparatively better control, and consequently do not require evaluations in an epilepsy center; this collective may include children with white matter necrosis or PVL. Secondly, seizures in children with PVL may also first present along a variable timeline throughout childhood and adolescence, with lower epilepsy rates reported at younger age ranges.

Intrauterine vasculopathies and risk for epilepsy

Congenital or acquired causes of thrombophilia have been associated with cerebral palsy [36], and may also contribute to the epileptic condition for some patients. Perinatal stroke from intravascular occlusion is a more common occurrence than past estimates have suggested, with an incidence of one in 4 000 live births [51]. Stroke syndromes during this broad time period are difficult to recognize. Specific diseases of the mother, fetus or the placenta can predispose the child to fetal cerebral infarction [52]. Some children will present in the neonatal period with seizures while others present later during infancy with hemiparesis and developmental delay. Golomb [53] for example, described 22 children with arterial stroke who presented with unilateral weakness as infants; all infants presented after two months of life. An MRI scan documented cerebral infarction presumably during the antepartum period since labor, delivery and neonatal periods were reportedly uneventful. In 18 of the 22 children, gestational complications were noted, which ranged from maternal preeclampsia or diabetes, to prematurity. Fourteen of the 22 had transient coagulation abnormalities associated with a positive family history of thrombophilia, with elevated anticardiolipin antibodies as the most common coagulation abnormalities in 11 of 22 children. Six of the 22 children presented with epilepsy after 6 month to 17-year follow-up. Longer follow-up intervals for some of these children may allow more individuals to express recurrent seizures.

Prevalence of coagulation disorders in epilepsy populations is largely unstudied, but may be an important entity for a specific subset of patients. A recent study by Cimaz *et al.,* [54] reported the prevalence of anticardiolipin antibeta$_2$ glycoprotein I and antiprothrombin antibodies in

142 young patients with epilepsy. Forty-one children, with a mean age of ten years, had positive antibody findings and a high percentage of ischemic lesions noted on magnetic resonance imaging. Intravascular occlusive disease may have occurred during prenatal life in at least 29% of this cohort, which could have contributed to the epilepsy.

Pregnancy also predisposes the mother and fetus to relative hypercoagulability. For example, protein S and antiphospholipid antibody ratios decrease, while thrombin generation, protein C and fibrinogen levels rise [55]. Acquired maternal/placental diseases can further expose the fetus to more sustained and severe hypercoagulability with resultant cerebral infarction, including autoimmune diseases such as systemic lupus erythematosis [56], hypertensive disorders of pregnancy (especially preeclampsia) [57-62] and genetic forms of thrombophilia to mother and/or fetus [63-65]. These conditions may act independently or cumulatively with injuries in the placenta which contribute to the stroke syndrome in the fetus or neonate [66-78].

Placental disorders and risk of epilepsy

It may be difficult to differentiate maternal from placental disease entities which secondarily harm fetal brain. Thromboses on the maternal side of the placenta can result from, for example, hypertensive disorders of pregnancy (eg. preeclampsia), resulting in intrauterine growth restriction, miscarriage or fetal death. Hypoperfusion, may be one circulatory effect with or without accompanying hypercoagulability, which can lead to brain injury. Thrombosis on the fetal side of the placenta predisposes the fetus to emboli which bypass the pulmonary/hepatic circulations and lodge within the fetal cerebral vasculature causing cerebral infarction, as well as promoting hypoperfusion-induced brain injuries.

Specific pathological findings in the fetal circulation of the placenta include thrombi formation which occur with relative frequency and possibly evolve days to weeks before delivery [79-81]. Placental disease from vascular occlusive mechanisms contribute to neonatal disorders, and most likely later neurological sequelae including epilepsy [52] *(figure 3).* Placental lesions include endothelial cushions, [82, 83, 79] hemorrhagic and endovasculitis [84, 85] fetal stem thrombosis [86, 87] and fetal thrombotic vasculopathy [88]. More recently Kraus *et al.,* [89] identified 16 neonates among 84 perinatal autopsies, with fetal thrombotic vasculopathy in the placenta that was associated with stillbirths as well as intrapartum or neonatal deaths. Two liveborn infants had evidence of systemic as well as cerebral infarctions.

While specific studies discuss the association of placental disease with brain injury, none specifically focus on epilepsy. Surviving children may suffer from various neurological deficits, as a result in part of placental disorders, ranging from cerebral palsy to cognitive/behavioral problems, sometimes in association with epilepsy [90].

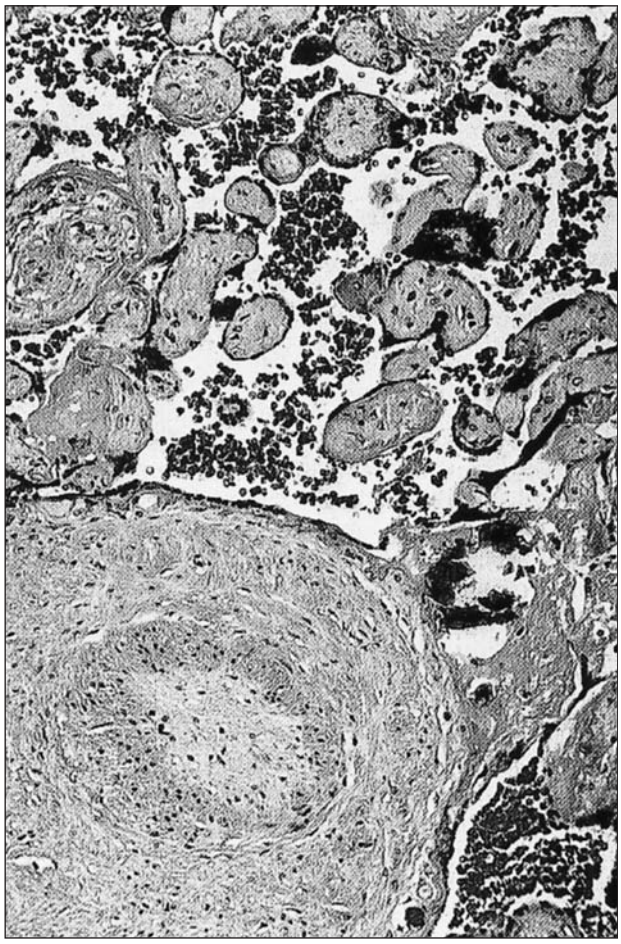

Figure 3. *Microscopic findings characteristic of fetal thrombotic vasculopathy, including a fibrotic obliterated stem vessel at the bottom, with avascular villi at the top. Reprinted with permission Kraus, 1999.*

Prenatal contributions to neonatal brain disorders and epilepsy risk

Epilepsy risk and neonatal encephalopathy

Prenatal brain injury can be expressed clinically during the neonatal period as an encephalopathy. The clinician may find it difficult to distinguish the encephalopathic newborn with altered arousal, hypotonia and seizures due to preexisting fetal brain injuries from the child with new or additional injury during the intrapartum or neonatal periods [16, 91]. One study estimated that at least 25% of encephalopathic newborns had prenatal brain anomalies that could explain the encephalopathic presentation, 36%

of whom also had CNS malformations [92]. An historical cohort study of 371 fullterm newborns with an acute neurological disorder was compared to a control cohort of 362 healthy neonates [93]. The encephalopathic group had a 5.1 times greater risk of epilepsy. Causes for "perinatal hypoxia" were cited, and maternal-placental-fetal diseases accounted for nearly 70% of the suggested clinicopathological mechanisms associated with the presentation of neonatal encephalopathy.

Subsequent epilepsy in premature neonates is also reported to be elevated compared to the general pediatric population. For example, Ishikawa *et al.,* [94] followed 197 survivors of 290 very low birth weight (VLBW < 1 500 g) to a mean follow-up age of 10.5 years. Eight children had epilepsy, which was 3.1 times greater than the general Japanese pediatric population. Clinical risk factors, which explained an increased epilepsy risk, included a gestational age < 27 weeks, birth weight < 1 000 g, severe neonatal encephalopathy and prolonged ventilatory care. Interestingly, 4 out of the 8 preterm neonates had maternal-fetal-placental disease conditions (i.e. preeclampsia, congenital infections, fetal intracranial hemorrhage and twin-to-twin transfusion syndrome), which were cited as the specific prenatal complications associated with epilepsy risk.

The interplay between the genetic substrate and environmental stress also influences the risk of epilepsy, as illustrated by a study using a strain of mice with a genetic susceptibility to epilepsy when exposed to environmental stress (i.e. increased handling), [95]. One can speculate for human neonatal populations that effects of stress during critical stages of brain development (i.e. either prenatal or postnatal in timing) significantly influence the risk of epilepsy in later life. Stress may take various forms including adverse prenatal influences from maternal-fetal-placental diseases, as well as postnatal stresses from conditions of prematurity, neonatal encephalopathies, or childhood craniocerebral trauma and CNS infection.

Newborns with inherited metabolic disorders occasionally present with neurological depression, hypotonia and seizures which resemble asphyxial encephalopathy [96]. Inborn errors of metabolism are causes of abnormal brain development, ranging from neural tube defects and holoprosencephaly to migrational disorders and myelination disorders [97], which may later present as epilepsy.

Neonatal seizure recognition and epilepsy risk

A neonatal seizure can be a predominant feature of neonatal encephalopathies. Neonatal seizures also increase the likelihood of neurological sequelae such as epilepsy, with incidence rates ranging from 20 to 55% [98-100]. Suspected clinical seizures however need to be confirmed with EEG documentation to avoid the misdiagnosis of nonepileptic paroxysmal disorders as seizures [101]. Pathological myoclonus, tremors and dystonia/dyskinesias are examples of abnormal motor patterns which are expressed in the absence of coincident electrographic seizures. No systematic evaluation of neonatal nonepileptic movement disorders has been performed to determine if higher risks exist for childhood epilepsy in this population.

Epilepsy risk, neonatal seizures and timing of brain injury

Even when electrographic seizures are confirmed in the neonate, brain injury may have occurred before labor and delivery in a percentage of patients [16]. One study suggested that clinical seizures after asphyxia were associated with elevated nucleated red blood cell counts, which reflects a bone marrow response to asphyxia, possibly associated with neurological injury that occurred in the antepartum period [102]. Another retrospective study emphasized the association of EEG-confirmed seizures and chronic placental lesions, suggesting that a chronic placental disease process can be associated with a neonatal encephalopathy with seizures [103]. Seventy-one neonates, between 23 and 42 weeks of age were compared with respect to EEG-confirmed seizures and placental lesions. A statistically significant association of seizures with chronic placental disease, was noted with or without acute lesions. These placental lesions included thrombolytic, infectious, inflammatory or dysmature features of placental structures. By contrast, no association between exclusively acute placental disease and the encephalopathic newborn with seizures could be established by statistical comparisons.

Epilepsy risk and duration of neonatal seizures

There are situations leading to the underdiagnosis of neonatal seizures that may promote brain injury, particularly when status epilepticus or recurrent seizures result. Neonates may have expressed electrographic seizures without clinical correlates in almost half of one neonatal cohort [104]. In another study, one-third of fullterm infants with electrically-confirmed seizures satisfied a definition of status epilepticus (i.e. 30 minutes of continuous electrographic seizures) [104], with or without clinical expression. Scher *et al.,* [105] recently reported that at least 25% of children who initially presented with electroclinical seizures continued to express continuous or recurrent electrographic seizures without clinical accompaniments, after antiepileptic drug administration. This phenomenon of electroclinical uncoupling may mask SE or recurrent seizures. Finally, electrographic expressions of seizures may go undetected after pharmacological paralysis for ventilatory control involving neonates with severe cardiopulmonary disease *(figure 4a and b).* Given each of these four scenarios, which promote the underdiagnosis of

seizure detection, the risk of seizure-induced brain injury becomes greater if status epilepticus results. Specific models of epileptogenesis in developing animals underscore the harmful consequences of recurrent or prolonged seizures, with short and long term consequences to brain structure and function [8, 9, 106].

Epilepsy risk and the etiology for neonatal seizures

Seizure-induced brain damage may occur in the context of etiologies which directly damage the brain and contribute to neurological sequelae. Children with neonatal seizures can suffer from stroke, cerebral dysgenesis or meningitis, and later suffer neurological deficits on the basis of the underlying etiology rather than the presence, timing and/or severity of neonatal seizures. Pathogenetic pathways which culminate in epilepsy, may originate from "dual pathology" caused by both prenatal events and postnatal injuries from recurrent seizures [107-109]. This has been described for older children, for example, who previously experienced febrile status epilepticus, a postulated reason for mesial temporal sclerosis. Mesial temporal sclerosis is the most common histopathological finding in patients who undergo temporal lobe resection for intractable seizures. Mesial temporal sclerosis and congenital brain anomalies were described in one cohort which later presented with intractable epilepsy requiring surgical intervention [109]. Hippocampal sclerosis was documented in this pediatric cohort in patients as young as four years of age and who later expressed temporal lobe epilepsy; 79% had dual pathology, consisting of mild to moderate cortical dysplasia, in addition to the hippocampal sclerosis, documented on magnetic resonance imaging. Cortical dysplasia clearly originated from prenatal life, superimposed on mesial temporal sclerosis, possibly as a result of febrile status epilepticus during postnatal life. The specific malformations in cortical development cited in this report, however, suggested altered brain maturation before 24 weeks gestation. Acquired MCD, as described by [21] may also be associated with hippocampal sclerosis, caused by events after the start of the third trimester.

Fetal and neonatal patients may also present with brain disorders represented by dual pathology, which implicates cortical injury during the perinatal period, parturition or the neonatal period. Some patients do not exhibit neonatal brain disorders, and later present with childhood epilepsy, as reported for fourteen patients who had congenital porencephaly and hippocampal sclerosis [110]. Prenatal stroke syndromes from maternal-fetal-placental diseases could account for the destructive mechanisms during prenatal life for this cohort *(figure 5)*. Postnatal conditions such as prolonged febrile seizures, or injuries from meningitis/encephalitis or trauma may further increase the likelihood that intractable epilepsy may subsequently result during childhood, adolescence or adulthood [111].

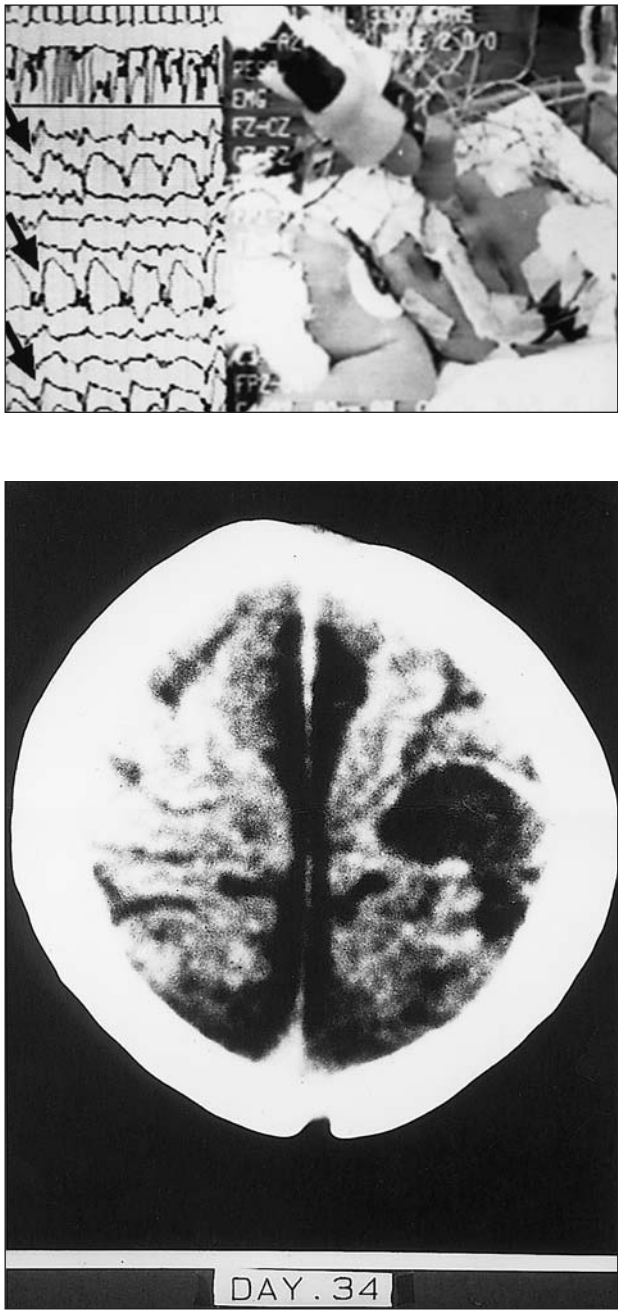

Figure 4a. *Segment of a video EEG for a fullterm infant born to a 45-year-old prima gravida female who suffered severe preeclampsia. No thrombophilia was documented, although significant placental infarction was noted. The child presented with a neonatal encephalopathy, including seizures. This EEG segment documents persistent electrical seizures without clinical signs (arrows), despite multiple antiepileptic medications, while the patient was pharmacologically paralyzed for ventilatory control. 4b: CT scan of brain for the patient in 4a, documenting multifocal infarctions, as a result of both presumed thrombophilia, which also caused placental infarction as well as hypoperfusion-induced injuries from asphyxia, secondary to maternal preeclampsia.*

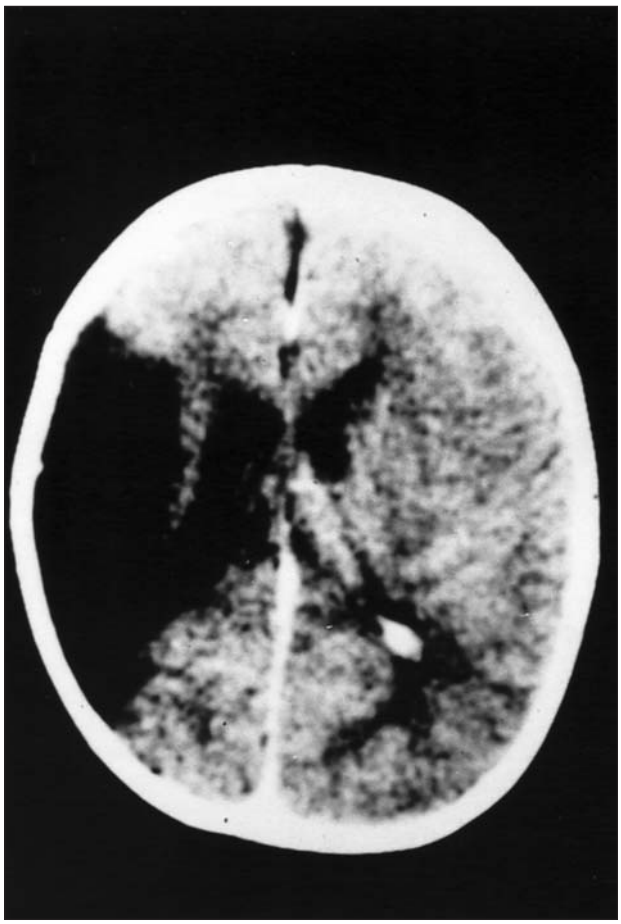

Figure 5. *MRI of the brain of a two-day-old, fullterm neonate, documenting a right middle cerebral artery occlusion. The child presented with seizures in the absence of an accompanying encephalopathy. Maternal preeclampsia with Leiden Factor V deficiency was diagnosed for this newborn.*

Translational research that addresses prenatal origins of epilepsy

Fascinating models of epileptogenesis have been developed over the last two decades which help elucidate the process of epileptogenesis and seizure expression at cellular, membrane, molecular and genetic levels [112-114]. Experimental models, however, need to also address the pathogenetic mechanisms that may occur in specific human fetal or neonatal cohorts, which promote acquired dysgenesis or damage leading to epilepsy, particularly during the second half of pregnancy and into the neonatal period. Perinatal models of brain injury must be applied to epilepsy research, such as occlusion of fetal cerebral arteries [115], manipulation of placental vasculature to induce asphyxia [116, 117], or introduction of maternal infection or inflammatory mediators [118]. Clinical epidemiological studies are also needed to extend the reported associations between cerebral palsy and thrombophilias, for example, to specific maternal-fetal-placental disease states, which can also promote the conditions for epilepsy. This translational research will also provide greater insight into effective neuroprotective strategies of the brain which will counteract the harmful effects of asphyxial, inflammatory and thrombotic diseases, thus reducing the risk for neurological sequelae including epilepsy.

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