PLACENTAL PATHOLOGY IN UNDERSTANDING PERINATAL BRAIN INJURY

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Introduction
Static disorders of motor function, such as cerebral palsy (CP), develop within the first two years of life in approximately 2 – 3/1000 children (Himmelmann et al. 2010). Depending on the regional prevalence of premature birth (especially at less than 28 weeks gestation), the proportion of cases related to extreme immaturity may vary from between 25 and 50%. In almost all cohorts the proportion of otherwise unremarkable term infants (> 37 wks) is relatively constant at around 40% – 50%. The remaining cases are a heterogeneous group, including near term infants, markedly growth restricted infants of all gestational ages, infants with undiagnosed genetic or chromosomal disorders and infants with neurotoxic exposures to infectious agents or other toxins in either the prenatal or postnatal period.

Recognized clinical risk factors for CP and related disorders in the extremely preterm infant include earlier gestational age, superimposed fetal growth restriction, a low Apgar score at birth, postnatal hypoxia, overly aggressive ventilation with hyperoxia–hypocarbia, patent ductus arteriosus, postnatal corticosteroid therapy and postnatal inflammatory disorders including necrotizing enterocolitis and late onset sepsis (Babcock et al. 2009). The degree of risk associated with ascending bacterial infections (chorioamnionitis), as discussed below, remains controversial and is considered in Chapter 6. Recognized risk factors for central nervous system (CNS) injury in term infants include a positive family history of neurodevelopmental disorders, fetal growth restriction, abnormal neurological examination in the first days of life (neonatal encephalopathy) and hypothyroidism (Redline 2008a). The degree of risk associated with so-called birth asphyxia (recently defined by several international consensus conferences) is also controversial and will be discussed later in the book. Novel therapies decreasing the susceptibility of neurons to injury, including magnesium sulfate in preterm infants and head cooling in term infants, raise the possibility of attenuating CNS injury associated with acute insults, but may be less efficacious in cases with coexisting placental pathology.

The existing literature on placental pathology and CNS injury suffers from several problems. First, adverse outcomes are rare and often diagnosed years after birth. Other limitations include bias of ascertainment, lack of an appropriate control group, inadequate characterization of placental lesions, use of surrogate short-term outcomes, unmeasurable
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differences in genetic susceptibility to injury and failure to fully account for the effects of gestational age and post birth complications. Nevertheless, contrary to the conclusions of a recent commentary (Nelson and Blair 2011), strong working hypotheses have emerged from the large number of published reports regarding which types of placental lesions are most likely to increase the risk of CNS injury. The focus of this chapter will be to place these pathologic findings in perspective in terms of their ability to cause or alter the threshold for the various manifestations of perinatal brain injury including abnormal neuroimaging, neonatal encephalopathy, ischemic stroke, seizure disorders and later disabilities such as CP and developmental delay in live born infants and neuropathological changes in stillbirths.

Potential placental mechanisms for injury
The placenta is essential for fetal life; constituting its only source for oxygen, water, nutrients and elimination of waste products. So in a sense it is not surprising that placental dysfunction can lead to disordered growth and development or injury to specific organs such as the brain and spinal cord. However, it has been challenging to isolate the particular patterns of placental injury that are most likely to cause damage. Before considering specific placental lesions, the potential pathways by which placental dysfunction could affect fetal brain function will be briefly reviewed.

Paucity of protection
In this scenario the fetus is deprived of specific crucial elements such as essential amino acids, maternal or placental hormones, or minerals and vitamins that are necessary for CNS development or protection from injury (Dammann and Leviton 1999). One simple way this can occur is preterm birth, that is, severing the fetus from its maternal supply line. Other potential mechanisms include genetic or epigenetic abnormalities in placental transporters or growth factor expression and maternal deficiencies in dietary intake or metabolic state. While these pathways may be extremely important, as evidenced by the importance of a positive family history and the known effects of maternal hypothyroidism and phenylketonuria on later childhood CNS function, they have no known structural correlate and cannot be detected by pathological examination.

Dysfunction of core pathways
The supply line between mother and fetus depends on adequate maternal circulating volume and blood pressure; an intact and appropriately remodeled utero-placental vasculature; free circulation through and drainage of the placental intervillous spaces; a short diffusion distance between maternal blood and fetal capillaries; and an intact, non-obstructed feto-placental circulation (see Fig. 1.1). Pathophysiological processes directly affecting these core pathways fall into two categories. The first category includes acute sentinel events such as maternal shock, uterine rupture, abruptio placenta, umbilical cord occlusion and feto-placental hemorrhages. These often result in either fetal death or recovery without CNS sequelae, but in some cases lead to global asphyxia and later CP with major developmental disabilities (Myers 1975). The second category includes chronic sub-lethal processes
leading to gradual loss of function and decreased placental reserve to withstand later injury (i.e. situations where fetal demand exceeds placental supply). Processes associated with decreased placental reserve include maternal malperfusion (MMP), secondary to inadequate maternal vascular remodeling, inadequate placental mass (placental weight less than 10th centile for gestational age) and processes affecting the diffusing capacity across the interhemal membrane (placental maturation defect, perivillous fibrin(oid) deposition and villitis of unknown etiology [VUE]), that is unexplained villus infiltration by maternal T lymphocytes.

DISTURBANCES INVOLVING MULTIPLE DISTINCT PHYSIOLOGIC COMPARTMENTS
Numerous studies have shown that CNS injury is strongly associated with multiple placental lesions (so-called ‘mixed pathology’). These lesions may act synergistically to disrupt a single core pathway or in parallel by blocking both primary and compensatory pathways. They can act either directly by affecting gas exchange or indirectly via the elaboration of harmful circulating mediators including cytokines, pathogen or damage associated molecular patterns (PAMP/DAMP), complement fragments, microparticles, activated coagulation components, vasoactive molecules and reactive oxygen species. It is important to distinguish the finding of multiple independent lesions from multiple abnormalities that all characterize a single pattern of injury (so-called constellation disorders).

PRECONDITIONING INVOLVING PLACENTAL LESIONS OCCURING AT DIFFERENT TIMES
The general hypothesis of preconditioning is that changes of state induced by prior events can either positively or negatively modulate the deleterious effects of a subsequent insult.
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(Hagberg et al. 2004). In the placenta these sequential insults generally involve repeated exposure to hypoxia, circulating inflammatory mediators, or some combination of the two. However, they could also potentially include placental conditions that alter the fetal endocrine or metabolic state. The concept of preconditioning helps to explain the inconsistent association of any single placental lesion with CNS injury. Since preconditioning can also be positive, this may explain why in some studies processes such as chorioamnionitis and mild MMP have actually been found to be neuroprotective.

Placental pathology in CNS injury
Key characteristics of a good pathological study include the use of clearly defined and generally accepted findings that characterize interruption of a specific physiological pathway, incorporation of scaling that distinguishes the intensity (grade), duration (stage), extent and character of these findings and comparison with an appropriate control group. Ideally specific criteria for each finding should be fully described as reproducibility of these findings is an important consideration for clinical application and studies involving multiple different scorers. However this is not a central issue for studies undertaken in a single center or where scoring is done at a central reading center. Unfortunately, few studies have met all of these benchmarks. This, combined, with the logistic issues and clinical confounders mentioned above, contributes to continuing skepticism regarding the validity of placental pathology in helping to explain adverse neurological outcomes.

Patterns associated with CNS injury at all gestational ages
Several types of placental injury have been consistently associated with different types of CNS injury in diverse clinical scenarios at all gestational ages. The identification of more than one placental lesion has been the strongest and most consistent predictor between studies and is the finding least influenced by other risk factors and confounders (Redline and O’Riordan 2000, Viscardi and Sun 2001, Chang et al. 2011). Also, the degree of risk has been shown to increase significantly with each additional placental lesion identified. The most commonly observed combinations are a vascular lesion (either maternal or fetal) with an inflammatory process (either acute or chronic); however combinations of a maternal and fetal vascular lesion or acute and chronic inflammation are also seen.

A second set of findings in diverse types of CNS injury are placental changes indicative of severe MMP, such as villous infarction (Fig. 1.2a). These have been associated with neuronal necrosis in stillborn fetuses, CP and developmental delay in preterm infants and CP in association with neonatal encephalopathy in term infants (Burke and Tannenberg 1995, Redline et al. 2007). A much less common form of maternal perfusion abnormality known as maternal floor infarction has also been associated with both motor disorders and developmental delay at all gestational ages (Adams-Chapman et al. 2002).

Finally, pathological findings suggestive of chronic partial or intermittent umbilical cord obstruction, have also been implicated in several studies of CNS injury (Grafe 1994, Redline 2008b). The biological plausibility for this pattern is supported by neurological follow-up in infants with sonographic evidence of persistent cord entanglements and animal
studies documenting the effects of repetitive episodes of fetal hypoxia and partial prolonged asphyxia (Myers 1975, Clapp et al. 2003). Gross pathological lesions affecting the umbilical cord, such as membranous insertion, excessive length, increased coiling and tight knots can all potentially restrict feto-placental blood flow. When combined with histological indicators, such as scattered small foci of avascular villi, intimal fibrin cushions in stem villous vessels, perivascular edema around stem villous arteries, distal villous immaturity and chorionic/stem villous venous dilation at the cord insertion site, they can cause a physiologically significant reduction in umbilical blood flow, increased placental venous pressure and fetal vascular stasis.

Patterns associated with CNS injury in preterm infants

The majority of studies addressing CNS injury in preterm infants have focused on histologic chorioamnionitis (HCA). Although meta-analysis has found HCA to be a significant risk factor for CP, the exact nature of the relationship remains unclear (Shatrov et al. 2010). Several specific problems confound this association: (1) the prevalence of HCA increases dramatically with decreasing gestational age, the strongest predictor of CNS injury in this population; (2) HCA is highly prevalent in this population (over 50%) and often seen with precipitous uncontrolled vaginal deliveries, while other less frequent causes of preterm birth (twins, pre-eclampsia) are often more closely monitored and more likely to undergo elective operative deliveries; (3) HCA-negative comparison groups are enriched for placentas with mild MMP, which may exert a protective effect against CNS injury (see below); (4) HCA predisposes to post-birth neonatal complications that may themselves be the cause of injury; and (5) HCA is a complex mixture of different grades and stages of maternal and fetal inflammation that have not been adequately separated in many studies.
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In placentas with HCA the strongest and most consistent risk factor for CNS injury is acute fetal vasculitis affecting either umbilical (funisitis) or chorionic plate (chorionic vasculitis) vessels. Fetal vasculitis is not a true vasculitis, but rather transmigration of fetally-derived neutrophils toward bacteria in the amniotic fluid. When found in umbilical arteries, compared with the umbilical vein alone, fetal vasculitis has been correlated with elevated levels of fetal cytokines (Rogers et al. 2002). Specific outcomes in preterm infants that have been associated with HCA with or without FV include intraventricular hemorrhage, white matter lesions on early head ultrasound and developmental delay at various periods during childhood (Leviton et al. 1999, Mittendorf et al. 2003). Other studies have shown that increased intensity of FV, recent non-occlusive fetal thrombi and maternal perfusion abnormalities all increase the risk of injury with HCA (Redline et al 1998, Kaukola et al. 2006). However, a few studies have found that HCA is associated with a decreased risk of death and no change in the risk of neurological impairment, illustrating the continuing controversy regarding the exact nature of this relationship (Dexter et al. 2000, Andrews et al. 2008).

Additional placental lesions that have been associated with more than one pattern of CNS injury in preterm infants include diffuse villous edema, severe MMP and two decidual lesions, recent hemorrhage and fibrin and lymphoplasmacytic inflammation (Kumazaki et al. 2002, Mehta et al. 2006, Redline et al. 2007, Maleki et al. 2009, Leviton et al. 2010). Interestingly, mild MMP was associated with a reduced risk of adverse outcomes in one study (Redline et al. 1998).

Patterns associated with CNS injury in term infants
Methodological issues such as the inability to identify infants at risk and a lack of appropriate controls, have made the study of placental pathology and CNS injury in term infants particularly difficult. Observations in specific cohorts such as cases in litigation, infants with neonatal encephalopathy, tertiary care referrals for head cooling and stillbirths with detailed neuropathologic examination provide some insight. Fetal thrombotic vasculopathy (FTV, Fig. 1.2b) and other pathological processes damaging large feto-placental vessels in the umbilical cord and/or chorionic plate (VUE with obliterator fetal vasculopathy, meconium-associated fetal vascular necrosis and HCA with intense fetal vasculitis) have emerged as highly prevalent and strongly significant predictors of CNS injury. In the largest studies, these have been specifically associated with neuronal damage, neonatal encephalopathy and CP (McDonald et al. 2004, Redline 2005, Chang et al. 2011). Although often seen in cases of intrapartum distress, their effects appear to be independent of indicators of birth asphyxia such as low cord pH and 5 minute Apgar score. In term infants referred for head cooling they have been found by some, but not all, investigators to predict a decreased responsiveness to therapy compared with infants showing evidence of birth asphyxia alone (Wintemark et al. 2010, Ernst et al. 2012).

Other pathologic lesions associated with CNS injury in term placentas include heterochronic placental lesions (one present for weeks, the other present for 6 – 12 hours or more), scattered foci of avascular villi suggestive of umbilical cord obstruction and placental infarcts (Redline and O’Riordan 2000, Redline 2008, Nelson and Blair 2011).
In smaller studies, placental maturation defect and FTV were found to be more prevalent in children with perinatal stroke, whilst placental maturation defect and VUE were more prevalent in infants with seizures (Scher et al. 1998, Elbers et al. 2011).

**Pathological approach**
Finally, leaving theoretical and epidemiological considerations aside, I will briefly describe how I, as a pathologist and medico-legal consultant, approach the relationship between specific placental lesions and CNS injury in individual cases. I generally subdivide cases into six categories. These categories are hierarchical in the sense that earlier categories take precedence over later ones. However, the finding of lesions in multiple categories is very common and undoubtedly increases the risk of significant CNS damage.

1: **Lesions sufficient alone to explain CNS injury**
These are the so-called ‘sentinel events’ such as abruptio placenta, uterine rupture, fetal hemorrhage, or complete umbilical cord obstruction. Since these lesions cause critical hypoxia they are almost by definition acute, occurring within a period of minutes to hours before birth. Placental findings consistent with sentinel events are generally identified at gross examination and include large retroplacental hematomas, torn fetal vessels, or tight umbilical cord knots. Microscopic examination is generally supplementary to the clinical history and gross examination in these situations. Placental evaluation can sometimes change the clinical diagnosis of a sentinel event by failing to substantiate the clinical impression and/or by identifying alternative explanations.

2: **Lesions sufficient alone to explain CNS injury, but usually seen in combination with intrapartum distress**
The main diagnoses in this category are the thrombotic and inflammatory lesions that affect large fetal placental blood vessels including FTV, VUE with obliterative fetal vasculopathy and prolonged meconium exposure with vascular necrosis. Another inflammatory lesion, chorioamnionitis with an intense fetal vasculitis, has been reported as a risk factor in some studies, particularly when combined with recent non-occlusive chorionic vessel thrombi in preterm infants. These types of lesions not only affect placental function, but can also compromise fetal circulatory physiology and directly cause fetal organ damage via the effects of circulating mediators such as cytokines, microparticles and activated coagulation components.

3: **Lesions sufficient to cause injury, but of lower specificity**
These lesions are also highly prevalent in cases of CNS injury, but overlap with findings observed in placentas submitted for other reasons. Three lesions in this category are chronic partial/intermittent umbilical cord obstruction, marked MMP and diffuse villous edema. The first two are so-called ‘constellation disorders’ that depend on the identification of multiple related findings. In these processes it can be difficult to decide which combinations of findings are most specific for significant placental dysfunction. Further studies are needed to dissect patterns and severities that allow more accurate prediction. One finding
that can assist in assessing the degree of associated hypoxia is an elevation in the number of immature red blood cell precursors in the fetal placental circulation (see below). The third lesion in this category, diffuse villous edema, is only seen in the placentas of extremely low gestational age preterm infants. There is some ambiguity related to this lesion since it is somewhat subjective and an exaggeration of a normal developmental pattern seen in late second trimester placentas. Nevertheless, it has been a strong predictor across studies and is independent of gestational age by multivariate analysis.

4: Lesions usually not sufficient alone to cause injury, but synergistic with intrapartum stress

Lesions in this category decrease the placental reserve by compromising the efficiency of placental function. While not directly causal, they can decrease the threshold for comparatively minor episodes of perinatal stress to compromise CNS function. Most cases of MMP, distal villous immaturity/placental maturation defect, VUE without obliterative vasculopathy, chronic abruption and perivillous fibrinoid deposition without maternal floor infarction fall within this category.

5: Non-causal adaptive lesions indicative of antenatal stress

There are two lesions in this category: villous chorangiosis and increased circulating fetal nucleated red blood cells (NRBC). Chorangiosis reflects increased villous angiogenesis developing over weeks in response to decreased maternal oxygen tension with normal maternal perfusion. Recognized associations include maternal anemia, smoking and pregnancy at high altitudes (Ogino and Redline 2000). Significantly increased circulating NRBC (more than one per high power field, corresponding to a neonatal count of greater than 2500/mm3) represent a physiologic response to decreased fetal oxygen tension with mobilization of immature red blood cell precursors from intramedullary and extramedullary sources (Redline 2008b). Significantly elevated NRBC counts are believed to develop after a period of at least 6–12 hours of significant tissue hypoxia.

6. No identifiable placental lesion

This final category is heterogeneous. Explanations to consider when placentas show no significant lesions include unrecognized clinical sentinel events, birth trauma, inadequate placental examination and intrinsic CNS susceptibility due to genetic or epigenetic abnormalities. The latter explanation is most plausible when a positive family history of neurodevelopmental disorders exists.

Conclusions

Extrinsic factors aside, a unifying hypothesis to account for the relationship between the placenta and CNS injury is that, between 23 and 39 weeks’ gestation there exists a critical period for brain development and resilience to injury that requires a fully functioning placenta. Birth before this stage (paucity of protection) and placental dysfunction during this stage (decreased reserve and preconditioning) can decrease the threshold for problems in the perinatal period. These placental processes also interact with inherent variations in the
set point for CNS injury, a variable that is likely to be influenced by poorly understood genetic and epigenetic factors. Together with better understanding of relevant physiology and genetics and better epidemiological studies, the development of antenatal screening tests to identify fetuses and placentas at risk is a major goal for the prevention, early diagnosis and prompt treatment of perinatal brain damage.

REFERENCES


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