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FETAL BRAIN INJURY ASSOCIATED WITH UTERINE HYPERSTIMULATION AND CRANIOCEREBRAL COMPRESSION DURING LABOR

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ABSTRACT

OBJECTIVE: To evaluate neonatal and neuroradiological findings following fetal hypoxic/ischemic injury associated with uterine hyperstimulation during labor.

METHODS: We evaluated 31 singleton, term babies with subsequent cerebral palsy (CP) or other severe neurological handicap. During labor each fetus presented in cephalic presentation with initially reassuring FHR patterns and no evidence of preexisting injury. Each fetus endured prolonged, stimulated labor with excessive uterine activity (>2 hours) and at birth showed no evidence of severe acidosis.

RESULTS:

Obstetrical: Labor, especially the 2nd stage, was prolonged in each patient. Malposition (OP position-12, 35.5%) and need for operative vaginal (9, 29.0%) or cesarean delivery were common (14, 45.2%)- Marked, sustained abnormalities of the fetal heart rate tracing were observed in all fetuses, but rarely suggested severe hypoxemia. The mean duration of excessive uterine activity was 4 hours (range 3-14 hours).

Neonatal: **5**-minute Apgar scores were <4 in 4 (12.9%) and >6 in 11 (35.5%). The umbilical artery pH was >7.0 in all neonates (where available). Marked bruising, molding, cephalohematoma and/or subgaleal hemorrhage were present in (26, 83.9%) and mild anemia (hct < 45%) was present in 11 (35.5%). Twenty-four infants (77.4%) went directly to the NICU; four (12.9%) were admitted after a latency period averaging 11 hours. Three infants (9.7%) were discharged home without going to the NICU. Moderate-severe encephalopathy was present in 24 (77.4%) and seizures were present in 22 (71.0%) usually within the first day,

Neurology / Neuroradiology: Neonatal scans, when performed with sufficient time after injury, showed diverse, supratentorial lesions (limited, focal, multifocal / diffuse, non-focal) compatible with ischemia. Five (16.1%) also showed injury to the basal ganglia / brainstem. Sagittal sinus thrombosis was found in two cases. In seven cases (22.6 %) there was isolated infarction in the distribution of a single major cerebral vessel. Intracranial hemorrhage, (SAH, SDH) was present in 11 (35.5%), sometimes more than one type, but was not generally considered the primary insult.

Long term: Long term outcome was marked by CP in 25 (80.6%**%**), Mental retardation in 21 (67.7%l) and microcephaly in 17 (54.8%) and numerous other handicaps. Neuroradiological findings including atrophy, and encephalomalacia were common.

CONCLUSIONS: These data associate diverse, ischemic and hemorrhagic fetal neurological injury with various mechanical effects on the fetal head during labor, but ***without*** systemic fetal acidemia. The clinical features of prolonged labor, uterine hyperstimulation, occiput posterior position, molding, head trauma/compression and operative vaginal delivery in association with diverse, supratentorial ischemic / hemorrhagic CNS lesions supports a notion of injury that derives from mechanical forces on the fetal head during labor resulting in diminished cerebral perfusion. The neonatal presentations and the severity of the neuroradiological findings varied considerably; no newborn, however, met widely published, "essential criteria" for assigning ischemic injury to the events of labor, [1]

Abbreviation List

CBF	**Cerebral blood flow**
CP	**Cerebral palsy**
CPP	**Cerebral perfusion pressure**
CCIE	**Craniocerebral Compression Ischemic Encephalopathy**
EFM	**Electronic fetal monitoring**
FHR	**Fetal heart rate pattern**
HIE	**Hypoxic-Ischemic Encephalopathy**
ICH	**Intracranial hemorrhage**
ICP	**Intracranial pressure**
IUP	**Intrauterine pressure**
MAP	**Mean arterial pressure**
MC	**Microcephaly**
MR	**Mental retardation**
NCEP	***"Neonatal Encephalopathy and Cerebral Palsy" ACOG/AAP***
SAH	**Subarachnoid hemorrhage**
SDH	**Subdural hemorrhage**
SGH	**Subgaleal hemorrhage**
UA	**Umbilical artery**
UBF	**Uterine blood flow**
UV	**Umbilical vein**

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BACKGROUND

It is widely believed that intrapartum fetal neurological injury results from impaired maternal-fetal-placental exchange, decreased fetal oxygenation, metabolic acidemia, and impaired cardiac function ultimately leading to cerebral ischemia.[2] In turn, impaired brain cell metabolism, exhausted energy sources and cell death [3 4 5 6] lead to later neurologic sequelae including CP. [7 8 9] In such cases it is further believed, that the newborn will present immediately with signs of moderate / severe hypoxic-ischemic encephalopathy (HIE) along with very low Apgar scores, severe metabolic acidosis (UA pH<7.0, BD > 12) and multisystem organ involvement, [10, 1, 11, 12]

Over the years we have observed a large group of neonates whose hypoxic-ischemic neurological injury occurred ***during labor,*** without significant acidemia at birth, but associated with excessive uterine activity and significant head trauma. We present here the neonatal neurological and neuroradiological findings in 31 of these children.

MATERIALS AND METHODS

Hypotheses

We hypothesize that persistent uterine hyperstimulation in association with prolonged labor, malposition and excessive pushing produces fetal neurological hypoxic / ischemic injury related to mechanical/ischemic effects for which fetal hypoxia may be absent or mild. In these cases, the presentation of the neonate will be highly variable and often will not meet the "essential criteria" for associating neurological injury with systemic asphyxia during labor. [1]

Patient population

This is a retrospective, descriptive study of 31 singleton, term infants who presented in cephalic presentation during labor without known medical complications. The patients, delivered between 1990 and 2006, derive from either personal consultations or medico-legal evaluations by several of the authors and involve diverse institutions ranging from large academic medical centers with residency programs to small community hospitals with minimal neonatal resources. Each fetus demonstrated a normal FHR pattern at the outset of labor with no evidence of IUGR, fetal anomaly or injury (even in retrospect). All women received oxytocin and / or prostaglandin for induction or augmentation of labor. Each case involved excessive uterine activity (hyperstimulation) as defined in Table I that persisted continuously for more than 2 hours. Irrespective of FHR pattern, urgency or route of delivery, each fetus demonstrated absence of significant acidosis on umbilical cord blood analysis (UA pH >7.0 or BD <-12) or had an

immediate (first 12 hour) neonatal course incompatible with significant acidosis or asphyxia. Each newborn went on to suffer long-term neurological disability (e.g., CP).

For each case, we evaluated over 200 obstetrical, neonatal, neuroradiological and follow up variables Upon coding, the records were de-identified in accordance with HIPAA guidelines. The mother's medical history was evaluated for data that might cast light on the potential for adverse outcome. We determined the features of the entire FHR pattern as well as the timing, indication, route and urgency of delivery. The *1st stage of labor was considered prolonged if the slope of dilatation during active labor was <1 cm / hour. The 2nd stage was considered prolonged if the fetus was undelivered within two hours.* Further obstetrical data are not shown in this paper. We evaluated immediate neonatal outcome in the form of the Apgar scores at 1, 5, 10 minutes and the umbilical cord gases at delivery. We considered pH values <7.2 or BD between -7 and -12 in arterial blood as indicative of moderate acidosis with pH values with pH <7.0 or BD >= 16 as severe acidosis. We further categorized the duration and the efforts of resuscitation, the character and presence of meconium, the indications of trauma (fracture, brachial plexus injury, facial palsy), and evidence of ***significant craniocerebral compression*** (CC) including severe molding (Figures 1 and 2), caput, bruising, fracture, cephalhematoma and subgaleal hemorrhage. We noted the disposition of the newborn to NICU or regular care. Encephalopathy, defined clinically, required the presence of at least two of the following criteria lasting longer than 24 hours: altered level of consciousness, hypotonia, feeding or respiratory difficulty of central origin. [13] [14] Further, we sought information about renal, hepatic, cardiac, sepsis or treatment thereof.

Although classifications of neuroradiological examinations have been proposed, there was little consistency in the descriptions of the neuroradiological examinations. [15] For this study, however, we relied upon the ultrasound, CT, MRI reports provided in the medical records during both the initial hospitalization and on subsequent follow-up studies. Neurological injuries were considered ***hypoxic / ischemic*** when such lesions were specifically identified in the radiographs. These included infarction, "stroke", white matter injury, etc. We assessed the anatomic distribution of these lesions (cerebral cortex, subcortical white matter, periventricular, deep nuclear structures, basal ganglia, and brainstem structures). We classified as "diffuse" those lesions described as **"diffuse"** or involving bilateral supratentorial and occasionally infratentorial ischemic lesions. We classified as **"focal"** those lesions referred to as "focal", infarct, stroke or unilateral. We classified as "**venous stroke" those injuries associated with sagittal or other venous thromboses.**

Injuries were considered ***traumatic*** if there was fracture, or other obvious trauma or contusion (excluding bruising). We have considered as ***hemorrhagic*** those radiographs that evidenced subarachnoid (SAH), subgaleal (SGH), intraventricular (IVH), subdural (SDH), or parenchymal hemorrhage. We also assessed

other abnormalities in the form of mass effect from large hemorrhage, herniation of the tentorium or falx cerebri, and the presence of vasogenic or cytotoxic edema.

Measures of Neonatal Outcome

Follow-up records were evaluated for serious outcomes including any permanent neurological handicap such as seizures, mental retardation, micro or hydrocephaly, developmental delay and cerebral palsy (including hemiplegia, diplegia, quadriplegia).

Follow up neuroradiographs were evaluated for the presence of such factors as encephalomalacia, ventriculomegaly, hydrocephalus, gliosis, calcification, and atrophy.

Statistics

This statistics in this study are descriptive only.

RESULTS

Obstetrical data:

The minimal gestational age was 36 1/7weeks and the oldest was 41 2/7 weeks. The average BWT was 3682 grams; 5 infants (16.1%) weighed over 4000 grams. The majority of cases (25 – 80.6%) were primigravidas in whom labor was being induced with oxytocin or prostaglandins. In the remainder oxytocin was used to augment labor. The majority of labors (92%) were prolonged, frequently in the 1st stage and almost invariably in the 2nd stage. Almost half of the deliveries (14 – 45.2%) were delivered by cesarean usually in the 2nd stage. Vacuum / Forceps were applied in 9 (29.0%) Only 19.4% were delivered spontaneously. The fetal position in the 2nd stage was OP in 12 (38.7%). More detailed obstetrical features of these patients are presented elsewhere.

Each FHR pattern on admission was deemed normal. The average duration of *continuous,* excessive uterine activity as defined in Table I was 9 hours with a range of 3-*14 hours.* Despite relentless excessive uterine activity in the 1st stage of labor, there was usually no discernible fetal response (including early decelerations) for at least *4 hours.* Over time there ensued decreasing baseline variability, rising baseline rate and decelerations, almost invariably during the 2nd stage.

Neonatal features (Table II)

The majority of neonates showed at least some depression of the Apgar score (<7) at 1 and 5 minutes 83.9***%*** and 64.5***%*** respectively, only 2 infants had 5 minute Apgar scores less than 4. Umbilical artery gases were available only in 19 (61.3***%)*** of the cases (usually the most obviously depressed). While about half of these values fell below 7.2, all available UA pH and BD values were above 7.0 and BD >11.

Twenty-four infants (77.4%) were transported to the NICU immediately, 4 (12.9%) were transferred there after a latent window of 5 to 13 hours and 3 (9.7%) were discharged without special care. The incidence of anemia, ventilator use, feeding problems, sepsis, multisystem organ involvement are described in **Table** . Ventilator care was required in almost half of the infants (15, 48.4%) – at least transiently. The majority of newborns did not show obvious renal or hepatic problems and elevations of liver enzymes and / or decreased urine output were usually transient or mild. Mild anemia (hematocrit < 45%) was present in 12 newborns (38,7% - range 55 - 39). Four infants required blood transfusion.

In 26 (83.9%) infants there was significant head trauma in the form of molding/bruising irrespective of the route of delivery. (Figures 1 and 2). Cephalohematoma (11, 35.5%) and SGH (4, 12.9%) were all associated with forceps or vacuum-assisted delivery.

Moderate to severe neonatal encephalopathy appeared in 24 (77.4***%***) Seizures with an onset of < 48 hours) in 22 (71.0***%***). Typically, signs of concern (feeding, alertness, etc) were present throughout this

window not only in those referred directly to the NICU but in those transferred in later. In those patients discharged home without special care there were no obvious alerting signs, except perhaps in retrospect*. The average length of stay was 12 days (range 2 - 23)

Neuroradiology (Table III, Figures 3-8)

The majority of the infants received US, CT or MRI during initial admission, but there was considerable variation in the timing and modality (ultrasound, CT, MRI). ***Ischemic injuries*** - Of the 31 newborns, 23 (74.2%) were evaluated by ***MRI/CT or ultrasound during the first week of life. (Figures 2-8) –*** Five scans, obtained on the first or second day of life were either "negative" or showed only edema. Diffuse lesions predominated (Table IV), Injury to the brainstem /deep nuclear injury patterns were seen in 5 (16.1%), but invariably in association with a spectrum of significant cerebral (watershed) injuries. The severity of these lesions varied considerably ranging from lesions confined to the watershed area to those that were more global (cortical and subcortical) in distribution. Even when the lesions were labeled "diffuse", the distribution of the injuries had considerable asymmetry. In no patient was a chronic lesion found that antedated the onset of labor. In 12 cases (38.7%) the lesion was focal – described as "stroke" or "infarction" involving the distribution of a major artery, usually the left middle cerebral. Despite this designation, other areas of the brain were often involved, including the adjacent cortex and the contralateral hemisphere.

Cranial Hemorrhage - There were 12 children (38.7%) who had hemorrhages invariably in association with ischemic lesions. These are listed in the Table III. In some instances there were multiple types of hemorrhage. Except for the 4 cases of SGH with severe extracranial blood loss, these intracranial hemorrhages lesions were rarely severe or life-threatening.

Other findings: (Table III)

Cerebral edema and early scans: First day scans were interpreted as normal or revealing only diffuse edema. On follow up, scans that were originally interpreted as normal revealed ischemic injury. Some revealed poor differentiation of gray / white matter as well as a generalized decreased attenuation through both cerebral hemispheres. Venous thrombosis was found in 2 cases in association with other ischemic injuries.

Follow up (Table IV)

Long-term follow-up of patients revealed evidence of severe supratentorial injury and dysfunction, including: acquired microcephaly (15, 48.4%), mental retardation (16, 51.6%), spasticity (23, 74.2%), developmental delay (%), and abnormal cognitive function (%). Patient thought to have “stroke” generally had a more favorable prognosis.

Discussion

This study documents clear evidence of perinatally acquired, radiologically proven, ischemic and hemorrhagic neurological injuries associated with hyperstimulation and other mechanical forces during labor, but without severe systemic hypoxemia or metabolic acidemia. Alternative causes of brain injury, antenatal injury, and significant intrapartum systemic hypoxia were reasonably excluded. We have termed this constellation of findings as craniocerebral compression ischemic encephalopathy (CCIE)

Mechanical forces during labor from uterine hyperstimulation, prolonged labor and compressive cerebral injuries may readily result in hypoxic-ischemic cerebral injury even without obvious superficial trauma or hemorrhage or severe metabolic acidemia, [16 17 18, 19 20, 21]. These dangers of have been described extensively in the medical literature for centuries [22 23 24 25 26 27 28 22 29] The overall contribution of such factors to ischemic brain injury during labor , however, is difficult to establish, due, in largest part, to the widespread notion that these ischemic injuries are hypoxemic (asphyxial), not mechanical, in origin. [30])

Obstetrical Factors

In this study each fetus entered labor behaviorally normal (FHR pattern) without evidence of hypoxia or prior injury (even in retrospect). Numerous risk factors for difficult delivery were present in these cases. The infants tended to be large, labor was invariably prolonged with many hours of excessive uterine activity (>2 hours) stimulated by oxytocin, prostaglandins or both and frequently excessive pushing during the 2nd stage. The incidence of malposition in the form of persistent occiput posterior (OP) was 32% (expected frequency - +/- 5***%),*** The OP position is known to be associated with prolonged labor, increased molding, fetal decelerations and operative delivery and is an independent risk factor for subsequent CP. [13] Molding, invariably present and frequently severe, in turn increases ICP and decreases both venous sinus return and therefore, blood flow to the brain [31-33]. Operative delivery (cesarean / forceps / vacuum) was employed in over 80% of cases. Operative vaginal delivery is a risk factor for mechanical / traumatic / ischemic injury and increased ICP and subsequent ischemic and hemorrhagic injury including SGH. [20, 34]

Fetal factors

Only two fetuses had severe, prolonged decelerations immediately prior to delivery (both had basal ganglia injury, but absent umbilical acidosis). Decelerations, though frequently present, were usually not severe, but invariably associated with absent variability and tachycardia (relative or absolute). Experimentally, as the increased ICP secondary to head compression approaches the MAP, the fetus responds with hypertension and peripheral vasoconstriction (the Cushing response), but decelerations

are uncommon.[35, 36] In experimental animals occlusion of the umbilical cord (associated with peripheral vasoconstriction and fetal hypertension) produces loss of autoregulation in less than five minutes. [37]

Neonatal Factors

These newborns had a high incidence of low Apgar scores, need for resuscitation and a wide spectrum of neonatal neurological dysfunction and developmental disabilities. In addition, there was significant head trauma in the form of severe caput, molding/bruising, cephalohematoma, irrespective of the route of delivery; SGH was confined to those delivered by vacuum. The majority of the newborns were transferred to the NICU immediately. These infants usually presented with a broad range of difficulties in adaptation, respiratory function, etc. However, seven (22,6%) of the newborns were initially thought to be sufficiently robust to be sent to normal newborn care. Of these seven, four were returned to the NICU between 5 and 13 hours of life. Three (9.7%) were discharged home without special care.

Apgar scores in those referred immediately to the NICU were generally depressed, but only 4 had sustained values below 4 at 5 minutes. The four infants returned to the NICU later had higher Apgar scores, but nevertheless, eventually required extensive care and sustained equally severe cerebral injuries. While they showed no obvious stupor or coma, these infants did not “wake up” easily and failed to make normal eye contact or interact or feed normally. It took a number of hours, for these disorders of adaptation to be recognized. Thus in at least seven of these cases, there was poor appreciation of the perinatal brain injury during the immediate neonatal period. In the three sent home without special care, symptoms such as vomiting, although mild, were present – in retrospect. The diagnosis of a neurological problem stemming from birth was made between 6 weeks and almost 3 months of age. There appears to be a wide range of disability in association with perinatal “stroke” and parenthetically to events of labor as a risk factor. [38] [39] [40] [41] We believe that the term “stroke”, as currently used has created considerable ambiguity and confusion when it has not been rigorously confined to a “traditional” single-vessel “stroke”. Rather, patchy areas of hemispheric ischemia, deep gray nuclear involvement and adjacent white matter injury have also been referred to as stroke or infarct and have confounded understanding and research in this area.

Mild to moderate hypoxemia (BD between -11 and -8) was found in about half and mild anemia (Hct <45%) was found in almost one-third of these neonates. To some extent therefore, hypovolemia, and hypoxemia therefore, may be contributing factors further impairing cerebral oxygen delivery in the face of altered cerebral perfusion. Hypoxemia results from the well-known reduction in UBF that is proportional to the duration and amplitude of the contraction. Anemia may result from intra, or extra- cranial hemorrhage. Placental abruption, present in 2 cases, is both a risk factor and a potential consequence of uterine hyperstimulation, but an unlikely cause of fetal blood loss. Thirdly, with predominantly umbilical

vein compression, arterial flow from fetus to placenta is maintained, but return from the placenta is reduced producing hypovolemia. [42]

Perinatal neurological injuries are frequently characterized (clinically and radiologically) as either prolonged partial asphyxia (PPA), or acute, near-total intrapartum asphyxia (ATA), or combinations of the two. These classifications appear to apply both clinically and neuroradiologically. On neuroradiological examination, ATA mainly involves the lateral thalamus, posterior putamen and selected brain stem nuclei. PPA involves mainly the cerebral cortex and subjacent white matter and is associated with later spastic quadriplegia and microcephaly. Cerebral vascular autoregulation tends to protect brainstem structures with their high metabolic demands, at the expense of supratentorial structures [43] which appear more vulnerable to localized pressure increases than infratentorial structures due to anatomic relationships that tend to protect the brainstem.

In the radiological studies of these patients, the specific ischemic injuries were consistent with either PPA (watershed) or a combination of PPA and ATA (basal ganglia) (Figures 3-8). The injuries, moreover, were both focal and diffuse, occasionally multifocal (and occasionally in the distribution of a major cerebral vessel (usually the MCA). While a “stroke” was identified in seven cases, there seemed no consistency in the use of the term. In several cases, usually involving early CT or ultrasound scans, the initial scan in was interpreted as either normal or showing edema. The majority ultimately revealed primarily supratentorial lesions with cerebral and deeper hypoxic/ischemic injuries that typically progressed to atrophy on follow-up. Such lesions are considered characteristic of PPA – an appellation entirely consistent with the prolonged exposure to uterine hyperstimulation. Nevertheless, the severity and the distribution of the brain injury (the areas of impaired flow) appear highly variable in both distribution and asymmetry within the cortex and white matter including the watershed areas. In those with neuronal necrosis in the basal ganglia and thalamus, lesions were invariably superimposed upon the lesions associated with PPA. There were no isolated brainstem / deep nuclear injury patterns whether on clinical presentation (e.g., EFM criteria / sentinel event) or neuroradiological data. This may be related to the prolonged exposure to excessive uterine activity, variations in pushing effort, descent of the presenting part, molding, position of the fetal head, duration of exposure, etc. along with the variable contribution of mild hypoxia / hypovolemia. In two patients (6.5%) there was also occlusion of the superior sagittal vein.

The seven ‘strokes’ is compatible with a “typical” hypoxic-ischemic insult, but here again, might be related to mechanical effects directly on a single vessel as a result of the angulation / deflection of the fetal head. Most of these were not obtained in the early neonatal period, so that it is not possible to determine if these cases had diffuse edema.

PVL (1) and multifocal injury (3) and isolated white matter injuries (3) are not considered "typical" hypoxic / ischemic lesions. The single case of PVL occurred in the youngest fetus in the group (37 weeks). These findings may be uniquely related to head compression and magnified effects in focal areas in patients with mechanical contributors to ischemia.

Accounting for the variable distribution and severity of the lesions, Sorbe pointed out that the region of the brain in greatest jeopardy is determined by the spatial orientations of the head as it descends through the maternal pelvis. [27] It deserves emphasis that even with a so-called "sentinel event" markedly different patterns of injury may be found. In a study of brain injury in 48 fetuses suffering a sentinel event during delivery Okereafor *et. al* found diverse patterns of injury involving a combination of basal ganglia / thalamic injury with varying amounts of white matter damage. They also found isolated thalamic injury or isolated mild / moderate white matter damage - or even normal findings; the pH in these catastrophic events was less than 7.00 in two-thirds. [44] Each of the patients in this study was deemed normal at the outset and none suffered a so-called "sentinel event."

Shah [14] and Perlman correlated obstetrical features, neonatal characteristics and adverse outcome rates of term infants with moderate to severe HIE secondary to intrapartum asphyxia following PPA, ATA or a combination of both - without reference to neuroradiological scans, an independent review of the EFM tracings or the acid-base characteristics of umbilical cord blood. Nor could they exclude neurological injury prior to labor. Nevertheless, 60% of the infants in their study with "prolonged partial asphyxia" on clinical grounds suffered severe adverse outcomes (death or disability). Additional similarities between the two studies include the highly variable neonatal time course despite devastating subsequent course.

The cases in our study are quite similar to a group of patients reported by Murray et al who reported the intrapartum FHR patterns of 35 infants with variable evidence of HIE at birth (17 mild, 12 moderate, 6 severe). Almost 70% of tracings were normal on admission, but invariably became "nonreassuring" prior to delivery. Of these, the majority (57%) showed gradual deterioration over a median time of 145 minutes with a range of 81- 221 minutes. These authors also found no correlation between duration of pathological fetal tracing and degree of encephalopathy (R = 0.09, P = 0.63) or neurological outcome (P = 0.75) [45]. Issues of hyperstimulation were not discussed.

Intracranial (SAH, SDH) and extra cranial hemorrhage including SGH invariably accompanied ischemic lesions. There were no cases with isolated intracranial hemorrhage. They were occasionally multiple. These hemorrhages, SGH excepted, were rarely severe and generally were not considered the cause of the neurological handicap, but rather the consequences of ischemia and the increased shear forces associated with molding and perhaps operative deliveries. Govaert et al have postulated that ischemia may be secondary to vasospasm induced by hemorrhage. [26]

Lastly, some of the scan findings obtained shortly after birth reveal evidence of small ventricles, small subarachnoid space and what we believe represents vasogenic, not cytotoxic, brain swelling. Normally, cytotoxic edema representing cell injury and generally begins to appear only 24 hours after hypoxic-ischemic injury. These cases of very early edema, if confirmed, may represent edema as a facet of trauma and autoregulatory loss or perhaps cell damage and may appear within 24 hours of birth.

Follow up

Follow up clinical studies revealed significant disability in all infants. The majority had obvious CP, microcephaly, mental retardation, and motor handicaps. Those with combined lesions (ATA and PPA) had more severe outcomes while those with the classical pattern of "stroke" or without thalamic / brainstem involvement appeared to have a more benign course initially. Those with "true" isolated "strokes" had more benign outcomes. These findings, in general are consistent with those of others. [15, 46] Follow up neuroradiological imaging, when available, revealed microcephaly and volume loss, consistent with significant subcortical injury.

The pathogenesis of neurological injury with uterine hyperstimulation

The "pure" model of hypoxic injury as set forth in NECP requires that "trauma" (undefined) be excluded. In general, only about 20% of infants injured during labor meet NECP criteria. [47] [48] Our data and those of [49] [50] [51] others suggest that perinatally acquired neuroradiological injury may be observed irrespective of the clinical appearance of the child at delivery and abundant experimental studies show that ischemic injury may be produced without severe acidemia or a comatose neonate at the time of birth [52] or, by contrast, after blunt abdominal trauma to the pregnant mother. [53] [54-56],[57] [58]. Indeed, it appears that ischemia, not acidemia, is the prerequisite to injury. In the setting of normal systemic oxygenation (and acid-base balance), it has been estimated to occur when cerebral blood flow has been reduced by at least two-thirds. [59] Abetting such reductions in CBF are numerous factors involving excessive uterine contractions, molding, prolonged labor and excessive pushing which act on the fetal head without significantly interfering with fetal-placental gas exchange. [60] [61, 62] [63, 64] [65]

In contrast to the "pure" NECP model, we propose that injury results from reduced CBF as a result of intermittent, but critical increases in ICP, unrelated to systemic fetal hypoxia and acidemia. Physiologically, the ICP always exceeds the IUP, the differential increasing considerably in the 2nd stage of labor where maternal pushing may increase the ICP to 2 to 4 times the IUP. [66] The fetus, however, has multiple compensatory mechanisms to avoid injury from excessive ICP. These take the form of enhanced cardiac output (tachycardia) and elevations of blood pressure (perhaps with decelerations) to provide preferential distribution of fetal cardiac output to the heart, brain, adrenals and placenta (the Cushing Response). [35] [67] [68]. The normal fetal blood pressure is 60/40 (MAP +/- 50). To maintain CBF

and CPP during periods of elevated ICP the fetus must elevate its MAP to about 20-50 mmHg greater than ICP. Thus, an average IUP peak in the 2nd stage of labor of about 75 mmHg, lasting 10-15 seconds at the peak requires a transient elevation of MAP to perhaps 100 mmHg or 125 mmHg, even if only briefly. Even if the fetus could not respond to this level, at least the exposure is short-lived. Sustained pushing along with very frequent contractions may dramatically increase IUP above 100 mmHg and with sustained pushing embarrass even the most resilient fetus because intracranial pressures of this magnitude obviously do no permit adequate cerebral perfusion [30] p 453

Further, it is reasonable to anticipate that these recurrent events will also compromise fetal autoregulation leading to unchecked blood flow. Impaired autoregulation appears within 4 minutes of sustained cord occlusion [37]. Impaired autoregulation may also result from impaired venous outflow and may lead to flow reduction in the face of pressures where otherwise flow might be preserved.

Thus, craniocerebral compression, perhaps abetted by mild acidemia / hypoxemia, vasospasm, abnormal clotting and / or hypovolemia and mechanical shear forces promotes both a variety of hemorrhagic as well as ischemic injuries. Superficial manifestations of these mechanical problems appear in the forms of marked molding caput, obvious bruising along with blood loss associated with cephalohematoma, subgaleal, subdural and subarachnoid hemorrhages. Other problems include sagittal sinus thrombosis and early appearance of cerebral edema. This model does not exclude, minimize or protect against hypoxic / ischemic effects of cord compression or systemic hypoxemic effects of excessive contractions.

For the purposes of this study we have not included patients with prolonged hyperstimulation in whom severe neonatal asphyxia was also present, It will be important in future studies to undertake an evaluation of the role of CCIE in those in whom less prolonged derangements in uterine activity or pushing and / or more significant metabolic acidosis may also be present. While prolonged hyperstimulation certainly abets fetal hypoxia and metabolic acidosis, mechanical / ischemic effects may indeed be the more important link to ischemic injury and prevention.

The strengths of this study include the consistent analysis of the objective obstetrical and neonatal data, including FHR tracings, labor curves, and the biological plausibility of the findings. The limitations of the study include the inconsistencies of obstetrical and neonatal management and in the diverse modalities and interpreters providing the initial neuroradiological information.

Conclusions

The newborns presented in this small, descriptive study demonstrate varied hypoxic / ischemic injuries during prolonged labor in association with prolonged, excessive uterine activity and pushing, certain FHR patterns, and craniocerebral compression (marked molding, malposition, cephalohematoma, and modest

degrees of intracranial hemorrhage). They newborns had diverse clinical presentations consistent with either PPA or combined PPA / APA and diverse neuroradiological findings of ischemia ranging from isolated “stroke”, to limited watershed infarction, to massive, diffuse ischemic injury and, variably, brainstem / basal ganglia ischemic lesions. In some cerebral edema began less than 24 hours after EFM-documented hypoxic-ischemic insults during labor. Follow up clinical studies revealed significant disability including CP (motor handicaps), microcephaly, seizures or treatment thereof and mental retardation. These findings, in aggregate, do not fit the model of hypoxia/ischemia from acidemia and cardiac decompensation, required by some,to assign hypoxic/ischemic injury to the events of labor and delivery. If confirmed, these observations have important implications for understanding the timing and prevention of injury and the selection of candidates for neuroprotection.

LEGENDS

Figure 1
Photograph of infant at birth with severe head molding after prolonged uterine hyperstimulation.

Figure 2
Graphic illustration of marked molding consistent with Figure 1. Notice reduction in suboccipito-bregmatc diameter (green line) and marked increase in occipito-mental diameter (red line).

Figure 3
Axial unenhanced CT at age 22 hrs at level of basal ganglia demonstrating slit-like ventricles with normal appearing deep gray nuclei at this time.

Figure 4
Axial unenhanced CT at 48 hrs through the plane of the basal ganglia demonstrating mild decrease in attenuation of the lentiform nuclei consistent with hypoxic-ischemic injury. There remains a slit-like supratentorial ventricular system consistent with a degree of cerebral edema

Figure 5
Left parasagittal unenhanced T1-w Figure from MRI exam at age 4 days demonstrating abnormal T1 hyperintensity in a parasagittal gyriform pattern of distribution as well as T1 hyperintensity returned from the thalami, consistent with ischemic injury. Also note Cephalohematoma at vertex.

Figure 6
Axial DWI (Diffusion Weighted Figure) at age 4 days at the level of the deep gray nuclei demonstrating restricted diffusion abnormality returned from the bilateral thalami (bright on DWI) consistent with a severe hypoxic ischemic injury.

Figure 7
Matching ADC (apparent diffusion coefficient) map at age 4 days at the level of the deep gray nuclei demonstrating restricted diffusion abnormality returned from the bilateral thalami (dark on ADC) consistent with a severe hypoxic ischemic injury.

Figure 8
ADC map through the plane of the occipital poles at age 4 days demonstrating restricted diffusion abnormality returned from the left occipital lobe in a posterior watershed type pattern consistent with an hypoxic-ischemic / hypotensive injury.

TABLE I
Measuring Uterine Activity

Parameter	**Average**	**Excessive – ANY***
Contraction Frequency	2 – 4.5 / 10 min.	>5 / 10 min. **
Contraction Intensity (Amplitude)	25 – 75 mmHg	Not defined!
Duration	60 – 90 sec.	>90 sec.
Resting Tone	15 – 20 mmHg	>25 mmHg
Interval		
(peak-peak)	>2 – 4 min.	<120 sec
(end-beginning)	1 -2 min	< 60 sec
Duty cycle***	< 50 %	> 50%

****Must persist, alone or in combination, continuously for at least 2 hours***

** Called “tachysystole”

The percentage of time that the uterus is contracting.

, **TABLE II**
OBSTETRICAL FEATURES (n=31)

Parameter	*Mean*	*Range*
EGA (weeks)	**38 5/7**	**37 1/7 - 41 2/7**
BWT (grams)	***3682***	***2689 - 4985***
Hyperstimulation (hours)	***9.1***	***2 - 14***

Parameter	*No.*	*Percent (of total)*
Primigravida	***23***	***74.2%***
BWT > 4000	**4**	***12.9%***
Induced labor	***17***	***54.8%***
Oxytocin / PG	***31***	***100%***
Protracted labor	***31***	***100%***
1st stage		
2nd stage		
OP position (late labor)	**12**	***38.7%***
Cesarean	***13***	***41.9%***
Vacuum	***6***	***19.4%***
Spontaneous Vaginal delivery	12	***38.7%***

TABLE III
Neonatal Parameters

	No.	%	
Apgar 1 <4	**12**	**38.7**	
<7	**27**	**87.1**	
Apgar 5 <4	**2**	**6.5**	
<7	**20**	**64.5**	
UA pH (n=19)			
	No.	%(31)	%(19)
7.01 – 7.25	**8**	**25.8**	42.0
>7.25	**11**	**35.5**	58.0
NICU			
Immediate	**24**	**77.4**	
Delayed	**4**	**12.9**	
Not admitted	**3**	**9.7**	
Seizures (onset < 48 hours)	**21**	**67.7**	
Encephalopathy	**22**	**71.0**	
Evidence of trauma*	**24**	**77.4**	
Ventilator assistance	**18**	**58.1**	
Anemia (<12 grams)	**12**	**38.7**	
	Average	**Range**	
Length of stay	**9**	**4 – 23 days**	

***marked bruising, molding, caput, facial asymmetry,**

Neonatal Neuroradiological Examinations

TABLE IV

	No.	% (31)	% (25)
Number scanned (CT/MRI)	25	80.6	100.0
Hemorrhage			
ICH – (SAH, SDH)	11	35.5	44.0
SGH – (clinical)	4	6.5	
Cephalohematoma (Clinical)	11	35.5	
Ischemia			
Watershed – Diffuse	13	41.9	52.0
Watershed – Focal, incl. "stroke", "infarct"	7	22.6	28.0
"Stroke" Single Vessel	3	9.7	12.0
Watershed + basal ganglia	3	9.7	12.0
Watershed + venous thrombosis	2	6.5	8.0
Very early scans			
Edema	3	9.7	12.0
Normal	3	9.7	12.0

Table V
Follow-up
(n=31)

	No.	%
Cerebral Palsy	**23**	74.2
Other Neurological findings*	**6**	19.4
Mental Retardation	**16**	51.6
Microcephaly	**15**	48.4
Developmental Delay	***22***	71.0

*hemiplegia, etc.

Figure 1

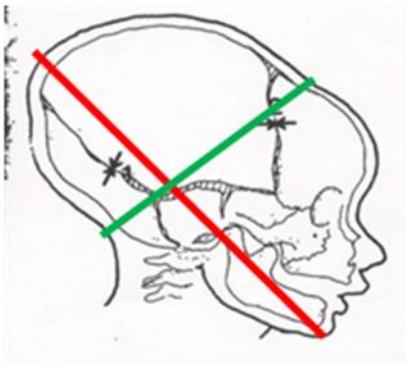

Figure 2

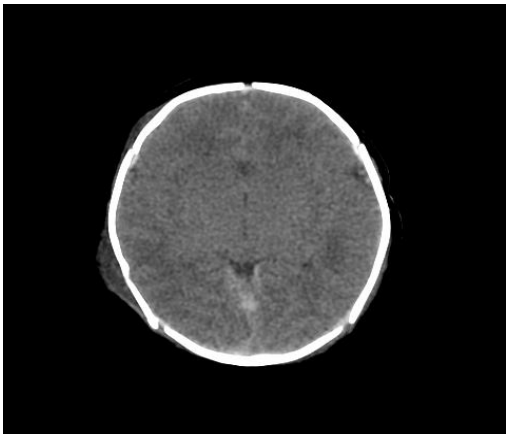

Figure 3

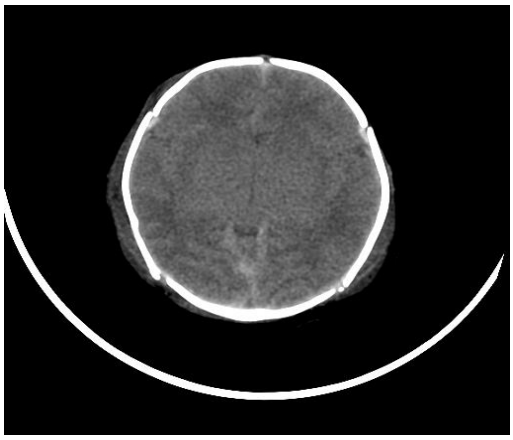

Figure 4

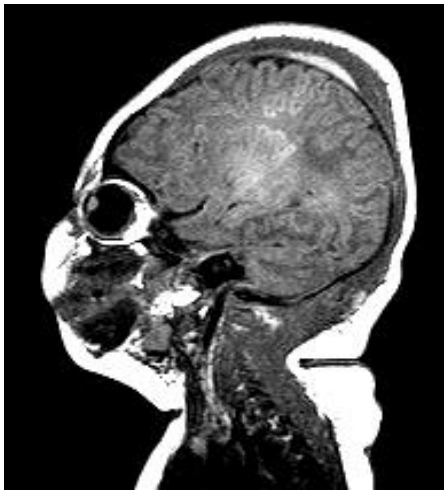

Figure 5

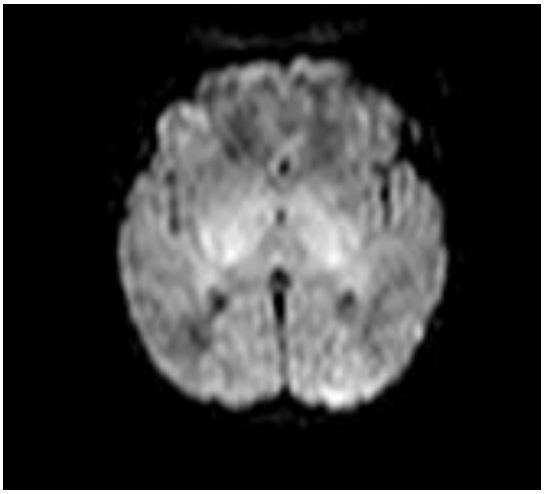

Figure 6

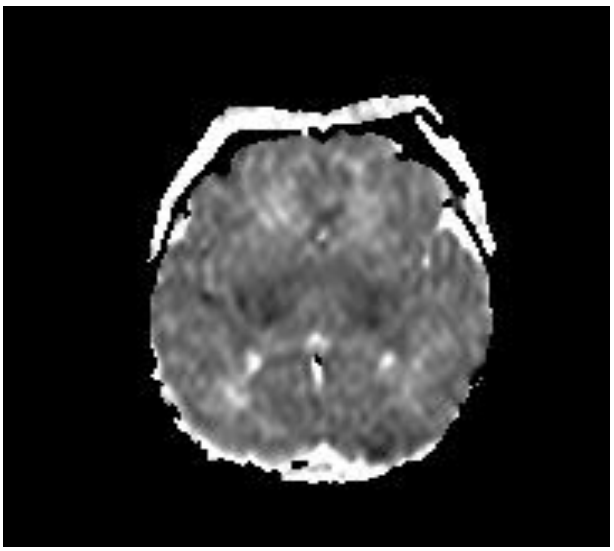

Figure 7

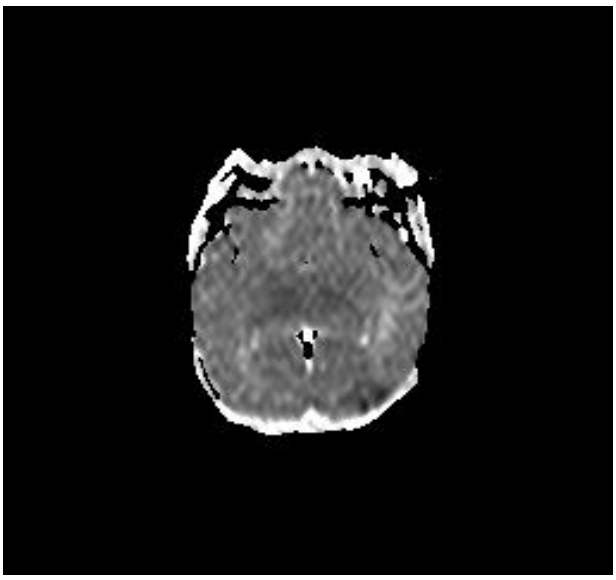

Figure 8

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