Cerebral palsy and criteria implicating intrapartum hypoxia in neonatal encephalopathy – an obstetric perspective for the South African setting

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The science surrounding cerebral palsy (CP) indicates that it is a complex medical condition with multiple contributing variables and factors, and causal pathways are often extremely difficult to delineate. The pathophysiological processes are often juxtaposed on antenatal factors, genetics, toxins, fetal priming, failure of neuroscientific autoregulatory mechanisms, abnormal biochemistry and abnormal metabolic pathways. Placing this primed compromised compensated brain through the stresses of an intrapartum process could be the final straw in the pathway to brain injury and later CP. It is therefore simplistic to base causation of CP on only an intrapartum perspective with radiological 'confirmation', as is often the practice in medico-legal cases in South African courts. The present modalities (magnetic resonance imaging (MRI) and cardiotocography (CTG)), when available, that retrospectively attempt to determine causation in courts are inadequate when used in isolation. Unless a holistic scientific review of the case including all contributing clinical factors (antepartum, intrapartum and neonatal), fetal heart rate monitoring, neonatal MRI if possible (and preferred) or late MRI, and histology (placental histology if performed) is taken into account, success for the plaintiff or defendant currently in a court of law will depend on eloquent legal argument rather than true scientific causality. The 10 criteria set out in this article to implicate intrapartum hypoxia in hypoxic-ischaemic encephalopathy/neonatal encephalopathy serve as a guideline in the medico-legal setting.

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High-value claims against obstetricians in litigation in both the public and private sectors are mostly related to cerebral palsy (CP) cases on the basis of intrapartum hypoxia resulting in hypoxic-ischaemic fetal brain damage and, by extension, invoking 'negligent intrapartum care'. This development has resulted in steep rises in insurance premiums, placing service delivery under serious threat.[1] It is widely assumed that CP is the direct result of an adverse event during birth and that it could have been prevented, yet only 10 - 14% of CP cases have been shown to be caused by intrapartum hypoxia.[2] Clinical epidemiological studies have shown that most cases of CP are not related to intrapartum hypoxia.[3,4] These studies, however, appear to be confined to high-income countries and are unlikely to be applicable to low- and middle-income countries (LMICs). The latest data reported by the Perinatal Problem Identification Programme in the Saving Babies Report show that intrapartum hypoxia makes up 24.3% of all neonatal deaths where the birthweight was >500 g.[5] While accurate figures for intrapartum-related causes of CP in South Africa (SA) are not known, it is likely to follow that, with this large number of deaths owing to intrapartum hypoxia, the number of infants surviving such an insult with neurological damage will probably be substantially higher than in high-income countries. This view is supported by a retrospective study by Mahlaba *et al.*[6] where 144 cases of CP were reviewed, of which 88 had neuroimaging reports and 42% of these showed evidence of hypoxic-ischaemic injury.

Numerous risk factors and causes are associated with CP.[3,4] We need to be careful not to oversimplify CP, which involves complex pathophysiological processes. Contributory variables incorporate failure of neurophysiological autoregulatory mechanisms, abnormal biochemistry and abnormal metabolic pathways. These are often juxtaposed with possible priming of the fetal brain on sometimes undetected antenatal insults such as fetal infection, inflammation and late-onset intrauterine growth restriction (IUGR) where hypoxia with cerebral redistributive mechanisms are already in place.[7] Placing this primed, compromised and compensated brain through the stresses of an intrapartum process could be the final straw in the pathway to brain injury and later CP.

Medico-legal cases involving CP in SA courts are mainly judged on magnetic resonance imaging (MRI) findings and cardiotocography (CTG) to assess causation and liability. Clinical notes are often missing, incomplete or inadequate, and Apgar scores are often inadmissible owing to falsification and late entries notwithstanding incomplete or lost information. Umbilical artery cord pH is generally not available in the State sector while, in the private sector, the BetterObs programme of the South African Society of Obstetricians and Gynaecologists in 2020 recommended umbilical artery cord pH sampling in all deliveries as standard of care to improve postnatal care and assist in causation in the event of hypoxic-ischaemic encephalopathy (HIE). CTG has a false positive rate for

predicting CP of 60 - 99%,[8-10] and often invites biased attempts by expert witnesses at retrospective temporal reconstruction of a fetal condition with the outcome known. The predictive capability of CTG in neonatal encephalopathy (NE) is explored in the present article. Imaging of the brain has become an important tool in the drive to a better understanding of the timing and aetiology behind CP. It has been shown that the morphology of brain damage strongly relates to the stage of brain development at which the insult occurs. Two main patterns of hypoxic-ischaemic injury can be distinguished in the term neonate: these are the so-called acute profound (deep grey matter) and partial prolonged (watershed) lesions. Neuroimaging is further explored later in this supplement.

Neonatal encephalopathy: Evidence for antenatal factors, intrapartum factors, or both

Cowan and associates[12] showed that more than 90% of term infants with NE, seizures, or both, but without specific syndromes or major congenital defects, had evidence of perinatally acquired insults, with a low rate of established brain injury acquired before birth. The frequency of risk factors in infants with and without an established brain abnormality did not differ greatly, but the study was not designed to explore antenatal aspects of perinatal brain injury. Their data do not exclude the possibility that antenatal factors could initiate a causal pathway for perinatal brain injury and that they, possibly together with genetic predispositions to hypoxic-ischaemic injury, might make some infants more susceptible than others to the stresses of labour and delivery. Martinez-Biarge *et al*.[13] set out to determine whether antepartum factors alone, intrapartum factors alone, or both in combination, are associated with term neonatal encephalopathy. All cases that met the criteria for perinatal asphyxia had neuroimaging findings consistent with acute hypoxia-ischaemia, and had no evidence for a non-hypoxic-ischaemic cause of their encephalopathy. Controls were neurologically normal born infants. On logistic regression analysis in their study, only **one antepartum factor** (gestation ≥41 weeks) and **seven intrapartum factors** (prolonged membrane rupture, abnormal CTG, thick meconium, sentinel event, shoulder dystocia, tight nuchal cord, failed vacuum) remained independently associated with HIE (overall 6.7% of cases and 43.5% of controls had only antepartum factors; 20% of cases and 5.8% of controls had only intrapartum factors; 69.5% of cases and 31% of controls had antepartum and intrapartum factors; and 3.7% of cases and 19.7% of controls had no identifiable risk factors (p<0.001). The authors concluded that their results did not support the hypothesis that HIE is attributable to antepartum factors alone, but they strongly pointed to the intrapartum period as the necessary factor in the development of this condition. On the other hand, a large study by Badawi and colleagues,[14,15] investigating the presence of antenatal and intrapartum factors in infants with encephalopathy, concluded that, for most infants with this disorder, the causal pathway began before birth. Badawi *et al*.[14,15] reported that, in their distribution of risk factors for neonatal encephalopathy, only 4% related to intrapartum hypoxia only, 69% related to antepartum risk factors only, and in 25% was it related to a combination of antepartum risk factors and intrapartum hypoxia. Note that the Cowan study was not specifically designed to determine the role of antenatal risk factors in neonatal encephalopathy. The results between these two studies may be problematic to compare, owing to differing study populations and case definitions. In Gaffney's study,[16] there was found to be an association between the quality of intrapartum care and CP, but this seems to have a role in only a small proportion of all cases of CP. The authors concluded that the role of adverse antenatal factors in the origin of CP needs further study. Volpe[17] found that where there is early-onset neonatal encephalopathy, the likelihood of intrapartum asphyxia remains high. Volpe comments that the 'neurological syndrome' that accompanies serious peripartum hypoxic-ischaemic cerebral injury is the prototype for neonatal HIE. He adds that in considering the nature and timing of hypoxia-ischaemia as the aetiology of neonatal HIE, three features are deemed to be important: (*i*) evidence of fetal distress and/or fetal risk for hypoxia-ischaemia (e.g. fetal heart rate abnormalities, sentinel event, fetal acidaemia); (*ii*) the need for resuscitation and/or low Apgar scores; and (*iii*) an overt neonatal neurological syndrome in the first hours or day of life.

Fetal priming

Fetal priming may play a leading role in perinatal brain injury. Priming creates a vulnerability and susceptibility to the stresses of the intrapartum process which may be the final straw in the pathway leading to HIE.

Inflammation and neonatal encephalopathy

Most cases of CP (but not necessarily NE) are due to antenatal factors recognised in human epidemiological studies[3,4] which act in synergy with each other to create a disturbance, and often prime the fetal brain for hypoxia, with the intrapartum period being the final straw. The labour process is 'hypoxic-centric' as blood flow to the fetus diminishes with each contraction. A physiologically normal fetus has adequate reserve to overcome this, but with fetal priming this reserve is diminished, exposing the fetus to hypoxic damage. Inflammation and maternal fever caused by chorioamnionitis or urinary tract infections are now well-recognised subacute or acute factors frequently associated with NE at birth and with CP risk in several studies regarding preterm, near-term or full-term infants.[18-22] In a study of full-term newborns who had CP, 38% of spastic quadriplegias were associated with chorioamnionitis.[23] Many studies have linked the close associations between perinatal infections and hypoxic-ischaemic insults to the brain and could convert a minor hypoxic stimulus insult into a seriously damaging event intrapartum in the event of fetal brain priming.[24-27] Recent evidence suggests that inflammatory phenomena play a more significant role in the aetiology of brain lesions common in CP.[24-27] A recent study in Uganda[28] showed that maternal and newborn infection, and inflammation based on blood cultures, molecular assays and placental histology, are independent risk factors for NE. The strongest associations were seen with fetal inflammation (funisitis) and early neonatal bacteraemia, supporting a role in the aetiological pathway of term brain injury. Increasing evidence suggests the critical importance of a sensitising effect of inflammation in the pathogenesis of NE.[29,30] There is also evidence of a protective effect of maternal chorioamnionitis in neonates as regards neonatal brain injury. It is possible in some cases that chorioamnionitis may have had a pre-conditioning effect that protected the neonate against brain injury.[31] There can thus be both a sensitising and protective effect, depending on the interval between the inflammation stimulus and the hypoxic event.

Placental-mediated disease

Placental-mediated disease can result in hypoxia or fetal priming for hypoxia, with some degree of IUGR present when labour starts. Two types of IUGR are recognised – early onset and late onset: at <34 weeks' gestation, the IUGR is regarded as early onset, and after 34 weeks as late onset.[32,33] Placental-mediated disease is due to abnormalities in placental implantation and transformation (degree,

if any, of trophoblastic invasion of the spiral arterioles), and results in a phenotype that will be diagnosed later in pregnancy. The phenotype can encompass multiple conditions including IUGR, pre-eclampsia, combined IUGR and pre-eclampsia, stillbirth or abruptio placentae.[34] The main pathogenesis of the placental maladaptive process is placental arteriolar vasoconstriction that results in perfusion abnormalities leading to placental ischaemia and necrosis. This is generally true for early-onset IUGR where the cascade of cardiovascular deterioration is predictive. In this scenario, fetal adaptation sets in early, resulting in a small fetus and predictable Doppler velocimetry or flow velocity anomalies.[35] However, in late-onset IUGR, the pathogenesis is mostly related to placental diffusion anomalies and, in this scenario, diagnosis can be elusive as the fetuses are not necessarily small and umbilical artery Doppler velocimetry (which is the premier fetal vessel of investigation in IUGR), is often normal. The only method of diagnosing hypoxia in late-onset IUGR fetuses is by the middle cerebral artery Doppler velocimetry, which reveals arterial redistribution.[36] In the presence of fetal hypoxia, the fetus sets into motion fetal redistributive mechanisms as a compensatory measure to protect vital organs including the brain, heart and adrenal glands. Thus, in late-onset IUGR, if one has not investigated the cerebral circulation, hypoxia can be missed and the fetus will enter the intrapartum process primed for hypoxic brain injury. Thus, often irrespective of intrapartum management (which could be optimal), the stressful process of labour will compromise this fetus. Furthermore, the devastating condition of 'unexplained' stillbirth in the late third trimester is often due to undiagnosed late-onset IUGR, and these fetuses which may fall within the normal weight range die owing to severe hypoxia and acidosis as a result of acute placental failure.[7,37] A normally grown fetus with normal metabolic demands that is subjected to acute placental failure and thus acute hypoxia is probably more at risk of a stillbirth/neurological impairment than an early-onset chronic growth-restricted process where fetal adaptation has set in.

Placental histological examination may contribute significantly to determining the aetiology of apparent hypoxia-related CP. Placental lesions decrease the threshold for brain injury.[38] Placentas with decreased reserve may be unable to function adequately during labour. Multiple early and late insults can act together to increase the risk of perinatal brain injury. Contributory factors where placental histology can help to focus on the aetiology include findings of chorioamnionitis with severe fetal inflammatory response, diffuse villous oedema and multiple inflammatory placental lesions. Redline produced a placental classification incorporating the 2014 Amsterdam Placental Workshop group criteria.[39] Placental pathologies relevant to CP include: (*i*) sentinel lesions – abruptio placentae, fetal haemorrhage, umbilical cord occlusions; (*ii*) thrombotic or inflammatory lesions of fetal circulation – fetal vascular malperfusion, severe chronic villitis, meconium-associated vascular necrosis, chorioamnionitis with severe fetal vasculitis; (*iii*) decreased placental reserve – maternal vascular malperfusion, diffuse chronic villitis, chronic abruption, chronic fetal vascular malperfusion, massive perivillous fibrin deposition; and (*iv*) adaptive responses in the placenta – increased nucleated red blood cells, villous chorangiosis, and distal villous immaturity.[40]

Diabetes

Another important cause of fetal priming is a metabolically unstable fetus in maternal diabetes. The concept of a pseudo-hypoxic state is based on the fact that fetal hyperinsulinaemia in diabetes results in an increased metabolic rate, leading to increased glucose oxidation and oxygen consumption. The capacity for oxidative metabolism is generally limited in all fetuses owing to low pyruvate dehydrogenase activity and, in a fetus of a diabetic pregnancy, this capacity is further reduced and thus increasing the risk for anaerobic metabolism irrespective of the prevailing levels of oxygen in the fetal circulation, leading to an increased risk for fetal acidosis.[41,42] The high incidence of nucleated red blood cells and polycythaemia (which are markers for hypoxia) in diabetic infants could reflect tissue hypoxia and fits well with the hypothesis of a 'pseudo-hypoxic state' in the fetus.[42,43] These fetuses are primed for hypoxia well before the intrapartum process. Risk factors in these fetuses would be macrosomia, polyhydramnios and abnormal cardiac function.[41,42] These fetuses are at higher risk of delivery complications, hypoglycaemia and acquired brain injury. In late-booked patients (those who first attend antenatal care late in pregnancy), for example, the glucose tolerance status may not be known, yet this fetus could well be primed for a damaging intrapartum hypoxic episode, especially in patients with an increased body mass index.

Toxic factors, maternal factors, postmaturity

Among toxic factors, alcohol is one of the most frequent which could determine brain maldevelopment during the whole pregnancy and later CP in case of severe malformation such as lissencephaly.[44] In animal studies, it was observed that it is an additional factor which aggravates damage induced by an acute ischaemic or excitotoxic event.[45] Other drugs such as cocaine and even tobacco smoking are implicated. An increasing number of drugs such as valproic acid taken by the mother during gestation are shown to interfere with brain energy, transfer of carbon monoxylic acid and carbohydrate and lipid metabolisms. This alteration may not be transitory but can permanently impair neuronal function and contribute to postnatal neurological disease including CP.[46] One could hypothesise fetal brain priming by toxic factors on the basis of altered metabolic pathways making them vulnerable to intrapartum hypoxic brain damage. In post-term birth, placental involution and dysfunction make the brain sensitive to damage.[15] Maternal factors such as maternal thyroid disease have been related to neonatal encephalopathy and CP in full-term infants. Antiphospholipid syndrome and systemic lupus erythematosus on the basis of a vasculopathy can also be implicated.[47]

Implications for liability of healthcare workers

It needs to be accepted that underlying priming antepartum factors may present with intrapartum evidence of fetal hypoxia and should be detectable on monitoring. If a vulnerable fetus is hypoxic on admission, this needs to be detected and dealt with appropriately. Where the underlying factor is undetected and the labour is considered low-risk, standard monitoring with intermittent auscultation should be able to detect decelerations. Decreased baseline variability will, however, be difficult to assess with intermittent auscultation. An underlying vulnerability is not an excuse for healthcare workers who do not follow standard monitoring practice. Nevertheless, the degree of vulnerability and how soon a pregnant woman presents to the labour ward will ultimately determine the severity of the hypoxic-ischaemic process that may already be under way. Irrespective of intrapartum management, subsequent NE/CP may be unavoidable.

Genetics

Genetic polymorphisms may increase the risk or severity of neonatal brain injury in NE and should be considered.[48] An increased risk of CP has been observed in some families in a national Swedish database.[49] Gene factors are involved in some

thrombophilias underlying perinatal strokes and secondary CP.[50] Genetic polymorphisms in gene-encoding proteins of inflammation or coagulation or vascular endothelium of the placenta are associated with CP in some children.[50] Recent investigation of genetic causes in a large cohort of singleton CP cases shows that the proportion of the cases carrying plausible genetic mutation is much larger than previously thought. At least 14% of nearly 200 singleton cases with CP studied have been found to have a plausible genetic mutation, *de novo* or inherited.[51] A further 44% had candidate variants that are yet to be resolved in regard to their causation of the CP. The percentage of cases with a genetic mutation is likely to rise as larger cohorts are studied, new CP genes are discovered, and whole genome sequencing is routinely performed. It is also now important to consider possible genetic causes that may directly, or through genetic susceptibility, trigger different pathways to different neuropathologies that share the common clinical trait of a nonprogressive movement disorder diagnosed as CP. In the near future, it will be possible to test for many of the putative or validated genes that have been associated with CP to date. This panel of different pathogenic genetic variations contributing to the CP spectrum is very likely to grow over the next decade, and should open a new direction into the causes of CP and challenge previous medico-legal assumptions about the culpability of the accoucheur.

Neuroimaging

Neonatal MRI can help evaluate brain injury and identify infants at risk for CP, and also assists in establishing timing of the injury depending on when it is performed. Two main patterns of hypoxic-ischaemic injury can be distinguished in the term neonate.[52] These are the so-called acute profound (deep grey matter) and partial prolonged (watershed) lesions. The acute profound injury follows abrupt-onset near-total asphyxia of short duration (sentinel events), where there is no time for compensatory redistribution of blood flow from the cerebral hemispheres to the life-preserving deep grey matter (predominantly basal ganglia and thalamus). Examples of sentinel events resulting in the acute profound injury pattern are ruptured uterus, abruptio placentae, cord prolapse and sudden-onset fetal bradycardia of unknown origin.[53-55] The partial prolonged brain injury pattern involves the vascular watershed zones affecting cerebral white matter and the overlying cortex. This injury follows vascular redistribution with sacrifice of the parasagittal regions and sparing of the deep grey matter in response to ongoing cerebral hypoxia-ischaemia, with the duration of injury measured in hours rather than minutes. Intermediate, combined and other injury patterns are also observed. These injuries are best distinguished in the neonatal period but remain discernible into adulthood, as the effects on the brain are static and permanent. Neonatal MRI is rarely available in low-resource settings, forcing a dependence on MRI in childhood or adolescence where the findings invite retrospective efforts to implicate clinical events and their timing. 'Acute profound' and 'partial prolonged' brain lesions are often used retrospectively to 'diagnose' and implicate clinical events and scenarios. If the MRI is performed beyond three weeks post delivery, it cannot on its own delineate if the injury occurred during labour or within days before labour and delivery.[11] Imaging abnormalities suggestive of hypoxic-ischaemic injury need to be correlated, where possible, with the known sequence of events during pregnancy, childbirth and infancy. These radiological descriptions are probably accurate in describing the neurological ischaemic insult but less accurate in extrapolating this to aetiology, causation and timing. Much of the data describing these lesions are from animal model studies involving vascular occlusion techniques but there are also many human studies that have corroborated these types of lesions in the acute hypoxic setting.[53-55] The evolution of these lesions as described by the radiological findings has merit but it is doubtful that a direct extrapolation to the labouring mother in the maternity ward can always be made. Furthermore, to judge cases from a purely radiological perspective without giving clinical context, diminishes the value and sensitivity of the modality to predict causation. Even if these lesions are seen, they may not necessarily represent events solely in the intrapartum period – in many instances, the intrapartum period is just the final straw on an already hypoxic primed fetus from antenatal factors. The clear distinction between these two descriptions are in many cases in the clinical setting not clear-cut, with a mixed picture described, making aetiological determination difficult.

Although the acute profound injury pattern is linked to a clinical incident or process, namely a sentinel event, the central grey nuclei injury may also occur in the absence of clinically obvious sentinel events and this is well-described in the literature.[53] A single sudden hypoxic event of unknown cause, presenting as an acute onset of fetal bradycardia in a monitored fetus, can result in an 'acute profound picture'.[53,55] Animal experiments involving intermittent so-called sub-threshold hypoxic episodes over several hours have produced similar brain injuries, as reviewed by Gunn and Bennet.[56] However, these repeated episodes of 5 - 10 minutes of profound hypoxia are not plausible proxies for occurrences in normal or abnormal human labour.

Although neuroimaging studies have made significant contributions to our understanding of CP, many are less informative than they might be because of four common problems: (*i*) ascription of aetiology to anatomic findings; (*ii*) inconsistent description of pathological findings; (*iii*) inconsistent anatomical findings and brain timing insult estimates; and (*iv*) studies not based on generalisable samples.[57]

MRI can provide mutual information from diffusion-weighted imaging, conventional imaging, and magnetic resonance spectroscopy, which can inform timing. Information regarding the likely timing is best obtained with early imaging (first 24 - 96 hours of life) with further follow-up imaging to define the full nature of the abnormalities, optimally at 10 days of life (but with an acceptable window between 7 days and 21 days of life, depending on the logistics of acquiring MRI in the clinical setting).

However, even if the MRI has been done long after the event, the information cannot be dismissed. The injury is in any case a one-off and does not progress, and the chronic evolution seen months or years later is well understood and shows typical features on MRI. This evidence, however, has to be interpreted in the context of the sequential clinical data, noting that the fetus was well at onset of labour, and then fetal heart rate anomalies developed, followed by low Apgar scores postnatally and then HIE.

In LMIC settings, we have to accept that the norm would be the late MRI, usually during childhood. Such MRI scans can also be of value. In fact, they can show abnormalities, or normality, not consistent with hypoxic-ischaemic injury. They can show basal ganglia-thalamus-type injuries that suggest sudden-onset injury ('acute profound') that are usually not amenable to obstetric interventions. When they show cerebral watershed injury with or without deep nuclear injury (partial prolonged), a range of explanations will be possible, where correlation with clinical findings is important. Timing of lesions in the late MRI predicting when the insult occurred, will always, however, be an issue. It will be the duty of the obstetrician to correlate the MRI with what happened. Therefore the retention of

good clinical notes reflecting clinical data is crucial in this scenario. It is unacceptable in these cases for the radiological perspective to be viewed in isolation without giving clinical context to the radiological findings. Medico-legal decisions should be based holistically on the clinical data and the radiology, interpreted in the context of the clinical scenario. Otherwise, success of litigated cases will depend on eloquent legal argument rather than a cogent scientific argument. It needs to be noted that lack of accurate reliable documentation and absence of adequate monitoring make apparent practice difficult to defend where, in fact, the care may have been in fact optimal.

The debate circa CTG

The CTG is the cornerstone of intrapartum fetal monitoring, used for the past four decades and is unlikely to be replaced soon. The CTG is also used frequently in the medico-legal setting to pronounce on cases. Owing to its subjective nature and large inter-observer and sometimes intra-observer variability, CTG interpretation has become a contentious issue. The CTG is used retrospectively, with the outcome already known to temporally reconstruct the adverse event and is therefore often open to bias. There are differing strong opinions on each side of the debate for the CTG and we will attempt here to give a balanced view on its use. Current data show that use of the CTG during labour results in no significant differences in rates of CP, infant mortality or other standard measures of neonatal well-being as reviewed by the Cochrane Library,[7] by NICE[58] and FIGO,[59] but has been associated with an increase in caesarean sections and instrumental vaginal births. The CTG is also accepted as having a 60 - 99% false positive rate in predicting CP.[8,9] On the other hand, Witznitzer,[60] Chen *et al*.,[61] and Vintzileos[62] have different opinions. Witznitzer concluded that electronic fetal monitoring has a biologic basis on supporting research (although most studies are underpowered or have not defined appropriate study variables or outcomes), and there is evidence that, when utilised as part of an ongoing quality improvement programme, this results in improved neonatal outcome. Witzniter has also commented that more research is needed to define the use of electronic fetal monitoring in appropriate target populations, in determination of neonatal outcome, in utilisation with other measures of fetal functioning, and in quality improvement and education programmes. Vintzileos proposes that longitudinal fetal heart rate changes rather than a cross-sectional assessment should be used to detect intrapartum hypoxia. Chen *et al*.[61] in a retrospective study, examined the association between electronic fetal heart rate monitoring and neonatal and infant mortality, as well as neonatal morbidity. The primary finding of the study was that electronic fetal monitoring use during labour was associated with a significant decrease in early neonatal and infant mortality. However, the good outcomes may not necessarily be the result of CTGs but of other confounders. Newer studies have linked neonatal acidaemia with intrapartum fetal heart rate patterns. Toomey *et al*.[63] showed that tachycardia in the last two hours of labour was most specific in predicting neonatal acidaemia while total decelerations (variable and late) were most sensitive. They found that acidaemic neonates were more likely to have CTGs having >11 late decelerations, >15 total decelerations and at least 80 minutes of tachycardia in the last 2 hours of labour. Williams *et al*.[64] reported that the most significant intrapartum fetal heart rate parameter to predict development of significant acidaemia is the presence of minimal/absent variability for at least an hour as a solitary abnormal finding. It needs to be stated, however, that the finding of acidaemia does not always equate to CP. They also found that fetuses with normal variability and accelerations even in the presence of late decelerations and/or variable decelerations maintained an umbilical artery pH >7 in more than 97% of cases. Rosenbloom *et al*.[65] reported umbilical arterial lactate levels at birth in a nested case-control study within a prospective cohort of labouring mothers at term who achieved active labour. Neonates with umbilical arterial lactate >4 mmol/L (cases) were matched 1:1 to controls with lactate <4 mmol/L. Electronic fetal heart rate monitoring patterns were then compared by multivariable logistic regression. They reported no differences in electronic fetal monitoring (EFM) parameters in the first 60 minutes after admission. At the beginning of active labour, 13.5% of cases and 26.1% of controls had always normal tracings. Cases were therefore less likely to have an always normal tracing from admission to the active phase. The researchers concluded that elevated umbilical arterial lactate at birth is associated with distinct EFM patterns early in the course of labour. A review of 12 trials (37 000 deliveries) comparing continuous CTG during labour with intermittent fetal heart auscultation found that the relative risk of neonatal seizures in low-risk women was significantly lower in women undergoing continuous monitoring (relative risk (RR) 0.36, 95% confidence interval 0.16 - 0.81) but had no effect on the incidence of paediatric neurological morbidity, CP or perinatal death.[66] This effect seems greater in women with low-risk pregnancies, probably because CTG facilitates earlier detection of fetal distress, thus allowing timely delivery. Others, however, reported some concerns regarding these 12 RCTs, covering 37 000 women. Only 2 of these trials were of high quality and only 3 trials reported data in low-risk women. The combined sample size of 12 RCTs is insufficient to determine whether EFM can significantly lower neonatal mortality or reduce the risk of intrapartum-related CP. Alfirevic *et al*.,[9] noted that to test the hypothesis that continuous monitoring can prevent 1 death in 1 000 births, more than 50 000 need randomisation.

There are polarised views on the use of the CTG intrapartum but we believe that introducing standardised guidelines in interpretation will improve its use and sensitivity to detect hypoxia-ischaemia. Standardised guidelines, for example those by Macones *et al*.,[67] may also ensure fairness in the medico-legal setting, where strong personal expert opinion often wins the day rather than appropriate interpretation according to accepted criteria. It needs to be noted that many cases of NE and CP occur in so-called 'low-risk patients'. However, in the SA setting, according to Department of Health guidelines, CTG is not recommended for low-risk labour but rather intermittent auscultation is recommended before and immediately after contractions. CTG monitoring is not recommended for intrapartum use in community health clinics. CTG is recommended only for high-risk labour, such as previous caesarean section, suspected IUGR, multiple pregnancy, pre-eclampsia, antepartum haemorrhage, premature rupture of membranes, suspected chorioamnionitis, meconium-stained liquor, poor progress in labour and oxytocin infusion.[68] The National Institute for Health and Care Excellence (NICE) recommends that continuous monitoring of the fetal heart with CTG should be restricted to high-risk labour. This is in keeping with most guidelines internationally. We have to accept at the present moment that the CTG, irrespective of the problems and issues, remains the cornerstone of intrapartum monitoring, but we need to understand its usefulness and limitations.

The three-tier fetal heart rate interpretation (as presented by the National Institute of Child Health and Human Development Workshop Report[67] (http://samj.org.za/public/sup/15399-1.pdf)) is helpful and which the authors accept should be used for conformity and consistency, i.e. Grade 1 is normal, Grade II is indeterminate and Grade III is abnormal. It is the grade II CTGs which are indeterminate

and account for >80% of cases[67] and that are difficult to predict fetal acid-base status at observation as they are quite variable ,from most benign to most threatening, but are also very subjective, especially interpretation of FHR variability. An advance in this regard is the Vintzileos proposition[62] to recategorise some grade II tracings where any pattern of decelerations that cause compensatory tachycardia should be included in the list of clinically significant decelerations. Grade I CTG, i.e. the normal CTG, is useful in that it is strongly predictive of normal acid-base balance at the time of observation. Grade III CTG is abnormal, showing a sinusoidal pattern or absent variability with recurrent late decelerations, recurrent variable decelerations, or bradycardia. This is strongly predictive of abnormal fetal-acid base status at the time of observation. Depending on the clinical situation, efforts to expeditiously resolve the underlying cause of the abnormal fetal heart rate pattern should be made. In such cases, regardless of variability, there is correlation between severity and duration of bradycardia and fetal acidaemia at birth with time to delivery thresholds being 25, 13, 8, 6 and 5 minutes for bradycardias at 80, 70, 60, 50 and 40 bpm, respectively.[69] Vintzileos[62] also states, in keeping with the concept of priming, that fetuses with reduced fetal reserve should be taken into consideration especially in the interpretation of category II fetal heart patterns, where antenatal factors play a significant role in reducing thresholds for brain injury intrapartum.

Criteria for implicating intrapartum hypoxia in neonatal encephalopathy

The Cerebral Palsy Expert Task Force comprising the American College of Obstetrics and Gynecologists and the American Academy of Pediatrics in the first edition of their report outlined criteria which they regarded essential to trying to establish a causal link between intrapartum hypoxic events and CP. Depending on the nature and timing of the brain injury, it is now known that there are multiple potential pathways that can lead to CP in term infants, and the signs and symptoms of NE may range from mild to severe. Consequently a revision in 2014[11,70] of the criteria set out in 2003, took into account a broader perspective. It is also acknowledged that there are knowledge gaps which may still preclude a definitive set or set of markers that accurately identify with high sensitivity and specificity an infant in whom NE is attributable to an intrapartum event. Distal risk factors (DRFs) and proximal risk factors (PRFs) are described in their causal pathways. DRF implies a pathogenic effect exerted on fetal brain development which begins at a time remote from the onset of irreversible brain injury, e.g. some placental anomalies, genetic anomalies, and environmental and sociodemographic factors. PRF implies a pathogenic effect on the fetal brain development at a time that closely predates or coincides with the onset of irreversible brain injury, e.g. acute chorioamnionitis and abruptio placentae. Interestingly, it has also been noted that both DRF and PRF factors can occur in the same patient, leading to NE. NE may or may not be seen after birth when the brain injury or anomaly occurs at a time remote from the delivery process. It is also noted that a brain insult may occur at multiple points during gestation. The neonatal period may also be susceptible to brain injury following a predisposing distal risk factor. So there can be many permutations in the causality of an acute hypoxic brain insult. A revised version by the Cerebral Palsy Expert Task Force proposed that a multidimensional, comprehensive and holistic assessment be performed of the neonatal status and all potential contributing factors. These must include maternal medical history, antenatal risk factors, and intrapartum factors (including fetal heart rate monitoring results and factors relating to the delivery itself) in order to establish the likelihood that an acute hypoxic-ischaemic event occurred within close temporal proximity to labour and delivery which could have contributed to NE.

Most neonates with HIE develop fetal distress without a sentinel event. There could be a combination of causes in an individual neonate (variables not always completely understood) but the clinical response must be to act accordingly in those fetuses deemed to be at risk of injury to prevent this, based on either antepartum risk factors and/or intrapartum factors, e.g. abnormalities in the fetal heart rate monitoring and/or delays in progession of the intrapartum process. A fetus can have several factors that make it susceptible to injury but appropriate management may prevent that from happening. In this regard, Bothma and Buchmann[71] stated that there appears to be a failure to detect or respond to evidence of fetal distress even in facilities with skilled staff and available resources. In SA, the incidence of fresh stillbirths weighing 2 500 g or more seems to be unacceptably high, even in secondary and tertiary referral institutions. Fresh stillbirths in this birthweight category should be rare, but 35% of fresh stillbirths in SA are in this category, with the leading primary obstetric cause of death being intrapartum asphyxia and birth trauma.[71] The root of the problem seems to be a failure to detect evidence of fetal distress, especially in labours that appear uncomplicated. This leads one to conclude that there is a significant role for improving labour-related care and ability to timeously detect compromise during labour, whatever the causal pathway. Buchmann and Velaphi[72] wrote that there has been a general decline in rates of intrapartum hypoxia and its consequences, especially in developed countries. However, a large enquiry may be an important vehicle for providing information to help prevent HIE and intrapartum-related perinatal death in the local setting. Although antenatal factors may play a role in pathogenesis of NE, optimal intrapartum care would in many instances avoid hypoxic brain injury.

Criteria used to implicate acute intrapartum hypoxia in NE by the American College of Obstetricians and Gynecologists (ACOG) Task Force on Neonatal Encephalopathy and Neurological Outcome (2014)[11,70] are accepted by the present authors and are enumerated below, but we have added comments after each criterion to reflect the SA experience and make them more relevant to our setting, and a 10th criterion, that of placental histology, has also been added. We consider any intrapartum hypoxic event, whether sentinel or more prolonged, to be 'acute' as used in the wording of the ACOG Task Force. A summary of the criteria is presented in Fig. 1. If most of the criteria are met, this will implicate intrapartum hypoxia as causative of the HIE; however, if most of the criteria are not met then it would be unlikely that intrapartum hypoxia can be implicated in the HIE.

Summary of criteria to implicate intrapartum hypoxia in NE[11,70]

1. **Case definition:** NE is a clinically defined syndrome of disturbed neurological function in the earliest days of life in an infant born at or beyond 35 weeks' gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes.
   Comment: Accepted as is.
2. **Apgar score:** Low Apgar scores at 5 minutes and 10 minutes clearly confer an increased RR of CP. The degree of Apgar abnormality at 5 minutes and 10 minutes correlates with the risk of CP. However, most infants with low Apgar scores will not develop CP. There are many potential causes for low Apgar scores. If the Apgar score at

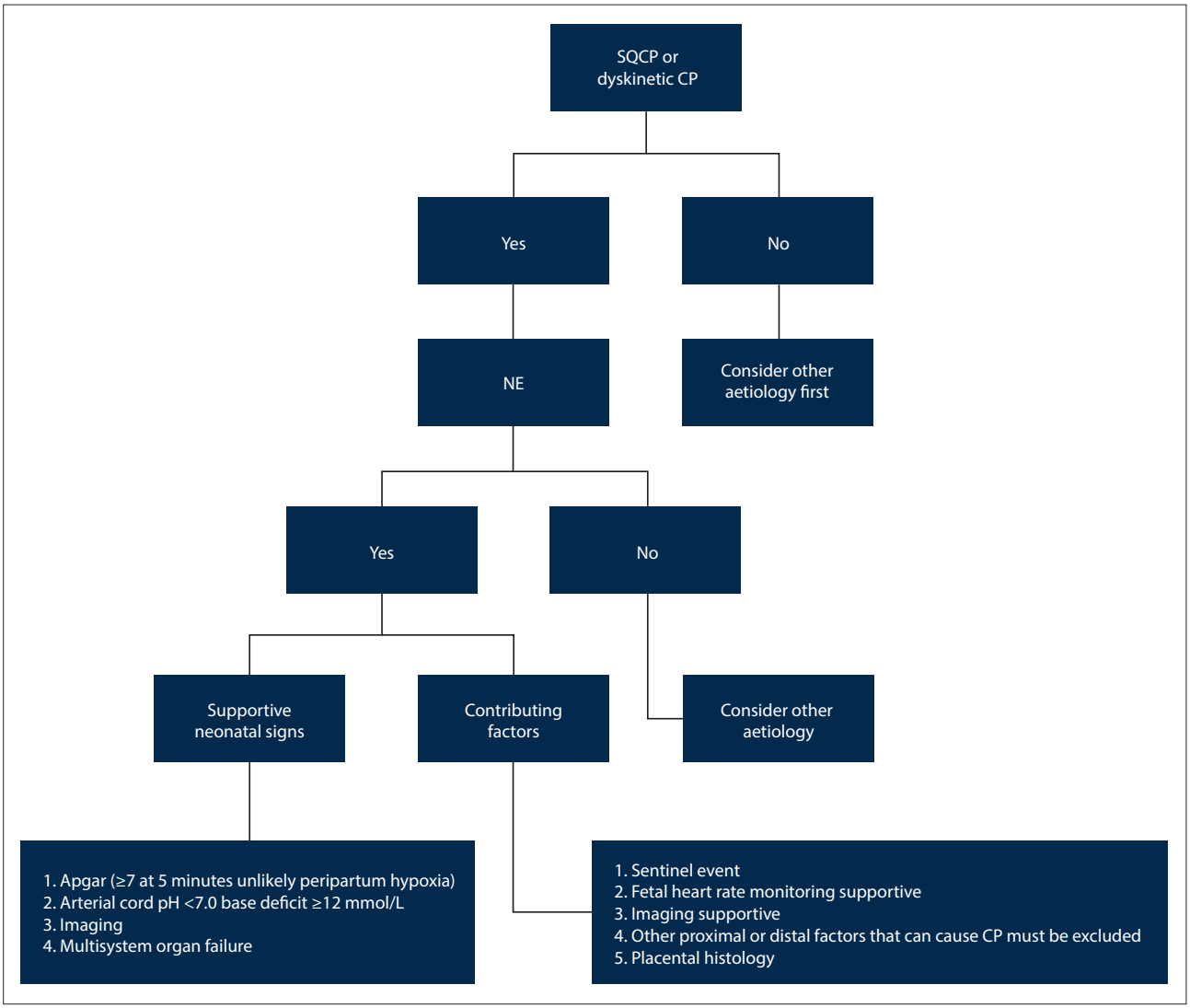

Fig. 1. Algorithm to determine if spastic quadriplegic or dyskinetic cerebral palsy may be the result of an in trapartum hypoxic-ischaemic event. (SQCP = spastic quadriplegic cerebral palsy; CP = cerebral palsy; NE = neonatal encephalopathy.)

5 minutes is ≥7, it is unlikely that peripartum hypoxia-ischaemia played a major role in causing NE.

Comment: This is a subjective assessment and can often be shown to be incorrect retrospectively based on the clinical markers entered in the case notes. Unfortunately, it is also known that falsification of Apgar scores occurs, leading to their inadmissibility. Also, most infants with low Apgar scores will not develop CP.

3. **Umbilical artery cord pH:** Fetal umbilical artery cord pH <7.0, or base deficit ≥12 mmol/L, or both, increases the probability that NE, if present, was as a result of an intrapartum hypoxic event; lesser degrees of acidaemia decrease that likelihood. Umbilical venous (UV) blood gas values differ from umbilical artery (UA) values, more closely resembling adult arterial blood than umbilical arterial blood (UA pH ranges: 7.12 - 7.35 and UV pH range 7.23 - 7.44; base deficit ranges: 9.3 to -1.5 for UA and -8.3 to -2.6 for UV).

Comment**:** In LMICs, a fetal umbilical artery cord pH result may not be available.

4. **Presence of multisystem organ failure consistent with hypoxic-ischaemic encephalopathy**: Although the presence of organ dysfunction increases the risk of hypoxic-ischaemic encephalopathy in the setting of NE, the severity of brain injury seen on neuroimaging does not always correlate with the degree of injury to other organ systems.

Comment: Multisystem organ failure as a criterion for NE is important as part of the muldimensional and holistic approach to establish the likelihood of an acute hypoxic-ischaemic event.

5. **Type and timing of contributing factors that are consistent with a peripartum or intrapartum event:** A sentinel hypoxic or ischaemic event occurring immediately before or during labour and delivery will include a ruptured uterus, severe abruptio placentae, umbilical cord prolapse, amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxaemia, maternal cardiovascular collapse and fetal exsanguination from a ruptured vasa previa resulting in a massive fetal haemorrhage.

Comment: A sudden hypoxic event of unknown cause, presenting as an acute onset of fetal bradycardia in a monitored fetus can result in an 'acute profound picture' on MRI.

6. **Fetal heart rate monitor patterns consistent with a peripartum or intrapartum event:** A Grade I or Grade II fetal heart rate tracing[67] when associated with Apgar scores ≥7 at 5 minutes, normal umbilical arterial and venous cord pH, or both, makes it unlikely that an acute hypoxic-ischaemic event occurred. It is important

to make the distinction between a patient who initially presents with an abnormal fetal heart rate pattern and one who develops an abnormal fetal heart rate pattern during labour. Category III fetal heart tracings are predictive of abnormal fetal acid-base status at the time of observation.[67]

Comment: In grade II CTGs, which are indeterminate and account for >80% of cases, it is difficult to predict fetal acid-base status at observation as they are variable from benign to threatening and their interpretation is also subjective, especially with regard to FHR variability.[67] A grade II CTG should not be interpreted in isolation but in the context of other clinical parameters. If not, it can lend itself to biased interpretation by experts owing to its subjective nature, especially as it is often interpreted retrospectively to reconstruct the adverse event.

7. **Neuroimaging studies – MRI:** There are distinct patterns of neuroimaging abnormalities recognised in hypoxic-ischaemic cerebral injury in the infant born at or beyond 35 weeks of gestation which have prognostic value in predicting later neurodevelopmental impairments. Despite advances in neuroimaging, the ability to precisely time the occurrence of a hypoxic-ischaemic event is still limited, depending also on when the MRI is performed.

Comment: As most MRIs for CP are performed late in childhood in LMICs, it is unacceptable in these cases for the radiological perspective to be viewed in isolation without giving clinical context to the radiological findings. Medico-legal decisions should be based holistically on the clinical data (antepartum, intrapartum (including fetal heart rate anomalies) and neonatal risk factors) and the radiology should be interpreted in the context of the clinical scenario.

8. **No evidence of other proximal or distal factors that could be contributing factors:** In the presence of other significant risk factors – such as abnormal fetal growth, maternal infection, fetomaternal haemorrhage, neonatal sepsis, and chronic placental lesions – an intrapartum event as the sole underlying pathogenesis of NE becomes much less likely.

Comment: There is enough evidence that antenatal factors could initiate a causal pathway for perinatal brain injury and that they, possibly together with genetic predispositions to hypoxic-ischaemic injury, might make some infants more susceptible than others to the stresses of labour and delivery. Fetal priming may play a leading role in perinatal brain injury. Priming creates a vulnerability down the line and the stresses of the intrapartum process may be the final straw in the pathway leading to HIE.

9. **Developmental outcome is spastic quadriplegia or dyskinetic CP**

Comment: Accepted as is.

10. **Placental histology, where available, should be interpreted in the clinical context:** Histological findings of chorioamnionitis with severe fetal inflammatory response, sentinel lesions (abruptio placentae, fetal haemorrhage, umbilical cord occlusions), thrombotic or inflammatory lesions of fetal circulation including fetal vascular malperfusion, decreased placental reserve and adaptive responses in the placenta, could be significant and provide an aetiological basis if interpreted in the overall clinical scenario.

Conclusion

1. CP is a complex medical condition with multiple contributing variables and factors involving antenatal factors, intrapartum factors, neonatal factors, genetics, toxins, fetal priming, failure of neuroscientific autoregulatory mechanisms, abnormal biochemistry and abnormal metabolic pathways. Causal pathways are often extremely difficult to delineate.
2. It is simplistic to base causation of CP on only an intrapartum perspective with a late or childhood radiological 'confirmation' using MRI, as is often the practice in medico-legal cases in South African courts.
3. The MRI and CTG modalities that retrospectively attempt to determine causation in courts are inadequate when used in isolation. Unless a holistic and comprehensive scientific review of the case including all contributing factors is taken into account, success for plaintiff or defendant currently in a court of law will depend on eloquent legal argument rather than true scientific causality.
4. For the present, it is imperative for obstetricians and midwives to strive for optimal intrapartum care – appropriate clinical practice and monitoring, with careful and complete note-keeping including contemporaneous maternal clinical documentation, fetal monitoring records and neonatal case records; not doing this provides ammunition to attorneys for emotive scenarios in a court of law.
5. Not being able to exclude other causes owing to unavailable clinical data does not mean that the aetiology for the CP should be defaulted to intrapartum hypoxia. Furthermore, negligent intrapartum care, although unfortunate and requiring correction, does not equate to causation.
6. Medico-legal decisions implicating intrapartum hypoxia in NE and CP should be based on specific criteria as alluded to above.

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