Acta Biomed 2015; Vol. 86, Supplement 1: 36-40

Original article

Late preterm babies and the risk of neurological damage

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Summary. Late preterm infants (born between 34+0 and 36+6 weeks gestation) account for the recent striking increase in premature birth and they carry a higher vulnerability to suffer brain insults compared to term infants. These babies can develop any kind of known brain lesions including those affecting the most premature babies (i.e.an intraventricular haemorrhage) and lesions affecting more typically term babies like asphyxia and stroke. In other words there is not a specific brain lesion characterizing this gestational age group, and there is not a specific maturational landmark although "subplate neurons" are suppose to ultimate their connectivity in this period and the cortical volume is significantly increasing. In addition we should not forget the possibility that "late preterm babies" may present neurological clinical impairments in the absence of recognized morphological brain lesions even with the use of highly sophisticated MR imaging techniques. For these reasons a wider use of more sophisticated neuro radiological studies is not sufficient to better understand why some studies highlight that the risk of developmental delay or disability can reach 36% higher among late preterm infants compared with term infants. We believe we should improve also our skills to identify even those very subtle clinical signs of impairment deserving further investigations although we often admit these babies in the normal post natal nurseries where clinical observation cannot be so appropriate. (www.actabiomedica.it)

Key words: late preterm, neonatal brain, preterm brain

Introduction

Late preterm infants (defined as babies born between 34^{+0} and 36^{+6} weeks gestation) have been grouped together only because they are the most represented premature infants (about 72% of preterm births) in the developed countries, reaching 7-8% of total live-births, and they account for the striking increase in premature birth which occurred in the last two decades (1). There is not a peculiar common pathway to develop certain disease characterizing this peculiar gestational age group, especially for cerebral lesions as between 34 and 36 weeks of gestation there is a continuum between the most important prematurity and what we intend for term babies.

The higher vulnerability of late preterm infants to develop diseases in the early neonatal period, compared to term babies, is well known. Mortality rate shows a 3-fold increase compared to term born controls and morbidity rates approximately doubles for each additional gestational week earlier than 38 weeks (1). Short term morbidities of late preterm infants include temperature instability, respiratory distress syndrome, excessive weight loss and dehydration requiring intravenous infusion, sepsis, hypoglycemia and jaundice requiring phototherapy (2).

Cerebral Magnetic Resonance Imaging (MRI) studies have documented morphological maturational processes such as myelination, cortical folding and progressive involution of germinal matrix (3,4), together with changes in specific functions like visual performances (5,6). There is not another gestational age so arbitrary gathered as there is not a specific landmark of an achieved maturation but only an amalgam of disappearing processes (i.e., involution of the germinal matrix) and maturing one (i.e., myelination) (3,4). One of most characteristic developmental neurological process of this period is perhaps the ultimate maturation

of "subplate neurons" making neuronal connections although cannot be associated to any specific brain lesion in case this process is altered (7).

Cortical volume in the late preterm infant is only 53% of the term volume, with approximately half the volume being attained in the last 6 weeks of gestation. In addition, myelinated white matter is present in minimal quantities in an extremely preterm infant, but increases dramatically as term approaches, with a 5-fold volume increase between 35 and 41 weeks (8). Vulnerability of specific neuronal populations in the late preterm is due to multiple factors but, like white matter vulnerability in the early-preterm brain, excitotoxicity and oxidative stress may play a significant role in late-preterm injury. For example, at that stage there is an over-expression of glutamate receptors in regions like the basal ganglia (9). Those receptors are necessary for long-term potentiation and connectivity, but after an insult, their activity can lead to the production of nitrogen and oxygen free radicals that can injure nearby cells. Basal ganglia and thalami are also recognized as metabolically active zones with increased energy requirements which contribute to their particular vulnerability to acute hypoxic insults.

For these reasons late preterm babies are exposed to a wider spectrum of brain lesions common to both most premature and more mature babies as they can develop not only germinal matrix-intraventricular haemorrhage (GMH-IVH) and cystic periventricular leukomalacia (cPVL) (10) but also arterial/venous stroke (11,12), hypoxic-ischemic encephalopathy (HIE) (13), and those parenchymal injuries following hypoglycaemia. The adding problem is the paucity of the related clinical symptoms compared to more term babies therefore these lesions can remain undiagnosed until later in childhood, and may contribute to explain the increased risk of impaired neurobehavioral outcome reported in the literature.

The wide range of cerebral lesions affecting "late preterm babies"

The peculiar contradiction of the highly unspecific brain vulnerability of babies born between 34 and 36 weeks + 6 days make possible for these babies to develop any kind of known brain lesions including those affecting the most premature babies (i.e.an intraventricular haemorrhage) and lesions affecting more typically term babies like asphyxia and stroke (14). In addition, you can have a variable number of different cerebral lesions affecting the same baby at the same time. A very indicative lesion of this multipotential brain vulnerability is showed in case of venous thrombosis (15). A very late appearance of a mild intraventricular haemorrhage together with periventricular white matter changes is very suspsicious for a venous thrombosis of the deep venous system. At 34 wks'GA is still possible to have an intraventricular bleed from the remaining germinal matrix at the caudo-thalami notch and white matter bilateral lesions due to involvement of the medullary veins mimicking a PVL lesions (15,16,17). This process can be triggered by the increased venous pressure occuring during thrombosis of the deep venous system (i.e, internal cerebral vein,vein of galen or straight sinus) (15,16).

Periventricular leukomalacia

Although the incidence of the most severe cystic forms of PVL has dramatically decreased in very low birth weight babies it is our impression that some unexpected and clinically very subtle forms of PVL are still possible in less premature, like the "late preterm babies". We believe these are those forms potentially linked to chorioamnionitis, a condition very likely to have been over emphasized in the pathogenesis of the almost disappeared PVL (10). Other milder form of PVL, usually referred to as "punctate lesions", predominately linearly organized and bordering the lateral ventricles are likely to be present in late preterm babies although good epidemiological studies are lacking in this field (18).

Arterial stroke

In most cases, like for arterial stroke affecting term babies, arterial stroke results from placental emboli passing through the patent foramen ovale into the aorta, where the branching of the left common carotid

offers the easiest anatomical path. The left middle cerebral artery, in fact, is the most commonly involved vessel. Injury usually involves both the white matter and the cortex, with the posterior white matter being involved more frequently than the anterior regions (11,12,19). These injuries also affect the brain of premature babies of gestational age above 32 weeks with a similar pattern of lesions involving major branches of arteries, while involvement of the smaller lenticulostriate branches seems to be more common in preterm infants with GA of 28–32 weeks. It remains difficult to identify a specific pathogenesis for arterial infarctions in the minor arterial branches. These younger babies are most often the ones receiving intensive care, and small air bubbles which might pass through the heart via the foramen ovale after insertion of an umbilical venous catheter have been reported as a potential pathogenetic mechanism (19). However, only twin-to-twin transfusion syndrome, foetal heart rate abnormality and hypoglycaemia have been found to be significant and independent risk factors for developing arterial infarctions in the entire population of preterm babies (20,21). No maternal risk factors have been identified. With regard to neurodevelopmental outcome, infants with a main branch arterial infarction are at greater risk of motor/cognitive impairment compared to those with lenticulostriate branches. Preterm compared to term babies have more language problems at 2 years of post-conceptional age (20,21).

Asphyxia

Studies of hypoxic-ischaemic encephalopathy (HIE) in late preterm infants demonstrate that in this category hypoxic insult mainly affects the grey matter, but the sites may differ compared to the more mature term brain. Basal ganglia are most frequently involved, particularly the ventro-lateral thalami and posterior putamen, as occurs in term babies (13). Late preterm infants are more likely to show brainstem lesions compared to term infants, indicating an increased susceptibility of the brain stem at these slightly younger gestational ages. Less frequently, injury may also occur to the hippocampus, the cerebral cortex and the subcortical white matter, particularly the perirolandic region. It is interesting to note that the late preterm infant does not often show cortical abnormalities around the central sulcus, which is, on the contrary, a frequent finding in-term infants. It is likely that this region becomes more vulnerable at term due to its active myelination during the very last weeks of gestation (13). This observation confirms that the metabolic demands of myelination may compound the increased vulnerability of cortical neurons and brainstem, respectively, at more and less mature gestational ages. Ischaemic lesions of the basal ganglia and thalami are associated with cerebral palsy and cognitive impairment. In the case of a severe insult, these lesions can be accompanied by abnormalities in specific cortical regions and in the adjacent subcortical white matter, exacerbating the cognitive deficit. Coexisting abnormal MRI signal intensity in the posterior limb of the internal capsule is a powerful predictor of motor outcome severity (13).

Cerebral palsy in late preterm and intrauterine growth retardation

Two thirds of cerebral palsy arises in the 97% of singletons born at or after 35 weeks of gestation (22). The current impression is that the prevalence of cerebral palsy in these relatively mature neonates, unlike that of survivors of very preterm birth, has not fallen in recent decades. In very recent and convincing studies in which the contribution of potentially asphyxial birth events, inflammation, fetal growth restriction, and birth defects recognized by age 6 years to each of these outcomes was evaluated it emerged that foetal growth restriction and birth defects recognized by age 6 years were more substantial contributors to cerebral palsy and neonatal death than potentially asphyxial birth events and inflammation (22).

The long-term neurological impairment frequently seen in children who showed intrauterine growth retardation (IUGR) cannot be attributed to the presence of overt brain lesions (23). Conventional MR imaging has failed to show even more subtle lesions in IUGR babies, while the number of DTI studies are booming in the search for a common pattern of developmental abnormality. Whatever sophisticated neurological techniques may be used to study brain development,

the risk of brain damage in IUGR neonates could reflect both the liabilities of intrauterine compromise and, in minor entity, the penalties of prematurity. In addition, the exact pathogenetic meaning of "brain sparing", which is not always a guarantee of the full protection of brain development during intrauterine life, needs to be better understood, as in our experience this was associated to an impairment of myelination (24).

Conclusion

An exact knowledge of the specific contribution of each risk factor for brain vulnerability of late preterm babies is far from being understood as large studies with epidemiological insights are very difficult to be performed. It is likely that gestational ages at birth with occurrence of neonatal comorbidities are the most important risk factors for detecting brain lesions in late preterm population especially in those born at 34 weeks more than at 36 weeks of gestation (25).

In addition to difficulties in diagnosing minor brain lesions and correlating these to specific minor neurological impairment we should not forget the possibility that "late preterm babies" may present neurological clinical impairments in the absence of recognized morphological lesions even with use of MRI imaging (25). The problem is further compounded by the fact that we are less aware of the pathogenetic mechanisms causing neurological impairments in late preterm babies since we can only postulate the likely areas of vulnerability that would seem to be subcortically located, and that particularly affect the subplate neurons.

Understanding early human brain development is of great clinical importance, as many neurological and neurobehavioral disorders have their origin in early structural and functional cerebral organization and maturation. Technological advances in neonatal brain imaging are progressively giving more insights for the understanding of disorders of neonatal brain. In these population of preterm babies the need for always more sophisticated neuro radiological studies has to be accompanied by improved skills in identifying even those very subtle clinical signs of impairment deserving further investigations. In this way we may hope to better understand why some studies highlight that the risk of developmental delay or disability was 36% higher among late preterm infants compared with term infants (26).

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