Increase of neuronal injury markers Tau and neurofilament light proteins in umbilical blood after intrapartum asphyxia

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Abstract

Introduction

Asphyxia caused by a lack of oxygen or blood flow to the brain around the time of birth affects 1% of infants and 10-20% of these cases develop some degree of hypoxic-ischemic encephalopathy [1,2] in the developed world whereas the occurrence is much higher in underprivileged countries [3].

Today infants suffering from moderate or severe encephalopathy are offered neuroprotective therapy with hypothermia (4) and other therapies are currently being developed (3). Therefore, there is a renewed interest in the development of biomarkers that can predict the risk of brain injury and aid in the selection of cases that should be offered therapy. Previous reports show that MRI/MRS (5) as well as multiple biochemical biomarkers in cerebrospinal fluid or neonatal blood hours to days after birth are elevated after moderate and severe asphyxia at least if there is development of HIE (6-16). However, there is a scarcity of biomarkers detectable in readily accessible body fluids such as umbilical blood early enough to be useful for directing therapy (17).

Generally, cases with asphyxia that do not develop moderate or severe encephalopathy are considered to have a good long-term prognosis (16,18). However, recent studies suggest that there may be a continuum relationship between severity of asphyxia and outcome as cognitive outcome seems affected also in cases with mild encephalopathy (19) and the school performance was suboptimal in children aged 16 born with Apgar <7 at 5 min (20). Utilizing new sensitive analytical assays our aim was to explore whether the axonal brain injury biomarkers tau and neurofilament light (NFL) (Zetterberg H, Blennow K. Nat Rev Neurol. 2016 Oct;12(10):563-74) were elevated in umbilical blood at birth in cases with moderate asphyxia (Apgar $\leq$7, 5 min and metabolic acidosis but not HIE) compared with a non-asphyxiated group of newborns.

Materials and methods

The ethical board of the Västra Götaland approved the study protocol (#...). Informed consent was provided by all study participants.

The asphyxia participants included 12 newborns (6 boys, 6 girls; median gestational age: 39 weeks) with neonatal asphyxia (Apgar $\leq$7 at 5 min and /or umbilical blood acidosis (pH $\leq$ 7.0). The control group comprised 24 newborns (15 boys, 9 girls; mean gestational age 37 weeks) without neonatal asphyxia (Apgar $\geq$8 at 5 min and umbilical cord pH >7.35).

Umbilical artery and vein blood samples were routinely obtained from study

participants through a doubly clamped segment of the umbilical cord and collected into non-heparinized 5 ml syringes. From these samples, we measured acid base and blood gases. After centrifugation,serum samples were collected and frozen and stored at 80^{o}C until the assay was performed.

NFL and tau concentrations were measured using ultrasensitive Single molecule array (Simoa) assays as previously described in detail (refs: Rohrer JD et al., Neurology. 2016 Sep 27;87(13):1329-36; Mattsson N et al., Neurology. 2016 Oct 25;87(17):1827-1835). The measurements were performed by board-certified laboratory technicians who were blinded to clinical information in one round of experiments using one batch of reagents. Lower limits of quantification were around 1 pg/mL and intra-assay coefficients of variation were below 10%.

Results

The asphyxia group had a median Apgar of 3 at 1 min, 7 at 5 min and 8 at 10 min which was significantly lower than in the control group (Table 1). The mean arterial pH was 6.93 and base excess -16.5 in the asphyxia group compared to 7.37 and -1.92, respectively, in controls indicating a significant degree of hypoxia in the asphyxia group. However, none of the asphyxia cases developed any degree of hypoxic-ischemic encephalopathy and there was no mortality in any of the groups (check !!).
The mean serum concentration of tau was 61.8 $\pm$ 22.3 pg/mL ($\pm$ SEM) in the asphyxia group compared to 23.2 $\pm$ 4.3 in the control group (p=0.026). The concentration of NFL amounted to 62.5 $\pm$ 23.0 pg/mL ($\pm$ SEM) in the umbilical blood of the asphyxiated newborns and 25.2 $\pm$ 2.1 in the controls (p=0.028).

Discussion

1. summarize results
2. no one measured TAU and NFL in umbilical blood before but TAU in neonatal serum and NFL in CSF and describe what they found
3, interesting that brain injury markers are sign increased in spite of moderate degree of asphyxia and no HIE supporting that some brain injury may occur even without overt signs of HIE and also interesting that these sensitive assays could detect the low basal levels of these proteins in the serum as well as the moderate increases seen after asphyxia
4. could mean that these markers could be useful for guiding the clinician regarding neuroprotective therapy and in the future these or similar markers could be analyzed in the fetal scalp and if raised could direct the clinician whether the infant should be delivered or not. (maybe not possible to measure in 50 ul of blood ?? and maybe not fast enough to be useful for the obstetrician - but maybe in the future) - one of the problems with the presently used pH and lactate is the limited specificity
5. limitations. relatively limited # of cases and only moderately asphyxiated needs to be reproduced in a larger cohort of infants with and without different degrees of HIE.

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