# NEONATAL NEUROLOGICAL OUTCOME OF SMALL FOR GESTATIONAL AGE VERSUS PREMATURE INFANTS

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**Abstract**

*Introduction* Neonates born prematurely or small for gestational age (SGA) as a consequence of intrauterine growth restriction (IUGR) have a higher risk of neurological injury due to fetal hypoxia. Hypoxic ischemic encephalopathy (HIE) and intraventricular hemorrhage (IVH) are the main clinical forms of brain injury. The patterns and underlying mechanisms of neurological injury are interrelated. *Aim of the study* The purpose of the study was to evaluate the neurological outcome of SGA newborns versus neonates born preterm. *Materials and methods* A 3 year randomized case – control study was conducted between the 1st of January 2014 and the 31th of December 2016, at the Emergency County Hospital, Timisoara. 170 SGA newborns and 170 AGA newborns matched 1:1 for gestational age and birth month were included in the study. Patients were divided in 4 subgroups according to gestational age: 101 SGA newborns born at term (SGA-Term) and 69 SGA newborns born preterm (SGA-Preterm), 101 AGA neonates born at term (AGA-Term) and 69 AGA neonates born preterm (AGA-Preterm). *Results and discussions* Preterm neonates had difficulties of early neonatal adaptation, as indicated by a low APGAR score. Preterm neonates irrespective of birth weight, had a higher incidence of both HIE (26.1% SGA Preterm versus 11.8% SGA Term and 11.5% AGA Preterm compared to 0.0% AGA Term ) and IVH (20.3% SGA Preterm versus 7.9% SGA Term and 15.9% AGA Preterm compared to 0.0% AGA Term ). *Conclusions* Neonates born preterm have a poorer neurological outcome compared to term newborns, regardless of birth weight. SGA is an additional, aggravating factor for neurological injury. More extensive studies on the different subgroups of SGA newborns are required in order understand the underlying mechanisms.

**Keywords:** newborn, neurological injury, fetal hypoxia

## Introduction

Preterm and small for gestational age (SGA) births with associated intrauterine growth restriction (IUGR) have been linked to neonatal neurological morbidity [1-5]. These disturbances of intrauterine growth and development are caused by an impaired placental blood flow with subsequent chronic fetal hypoxia [6-9]. Fetal and neonatal brain development is vulnerable to oxidative stress from hypoxic–ischemic injury. Although, disturbances in vascular autoregulation and their effect on the immature vascular supply of the brain represent a common pathway to neurological damage, establishing a causal relationship between type and onset of the neurological insult and specific forms of brain injury is difficult due to the fact that the underlying mechanisms are mulifactorial and overlapping. Hypoxic ischemic encephalopathy (HIE) and intraventricular hemorrhage (IVH) represent the main clinical forms of brain injury that occur as a result of repeated episodes of ischemia-reperfusion during the prenatal, intrapartum or postnatal period [3, 10-12].

## Aim of the study

The purpose of the study was to evaluate the neurological outcome of SGA newborns versus neonates born preterm by evaluating the incidence, risk factors and underlying mechanisms of HIE and IVH in these newborns.

## Material and method

A 3 year randomized case – control study was conducted between the 1st of January 2014 and the 31th of December 2016, at the Neonatology Department of the Clinic of Obstetrics, Gynecology and Neonatology, Emergency County Hospital, Timisoara.

According to the literature, newborns are framed as being SGA if their length and/or height is less than two standard deviations (< -2SD) below the mean for gestational age or less than the 10th percentile (< Perc 10%) of a population-specific birth weight [13, 14]. Likewise, preterm birth is defined as a live birth that occurs prior to 37 weeks of gestation [15, 16].

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Patient data collected form medical records was anonymized and organised into an electronic directory. Medical records of all inborn patients aged between 0-28 days were reviewed. Patient selection was made according to the following exclusion criteria: syndromal, chromosomal or infectious etiology of low birth weight and chronic maternal disease.

The study group consisted of 170 SGA newborns and the control group of AGA neonates was matched 1:1 for gestational age and birth month. Patients were divided in 4 subgroups according to gestational age: 101 SGA newborns born at term (SGA-Term) and 69 SGA newborns born preterm (SGA-Preterm), 101 AGA neonates born at term (AGA-Term) and 69 AGA neonates born preterm (AGA-Preterm).

Cerebral ultrasound was performed in the first day postpartum in all newborns included in the study. Changes of the cerebral structure consistant with HIE or IVH were noted.

HIE was diagnosed using an ultrasound classification adapted from Ilves (Table 1) [17].

IVH was evaluated by ultrasound and classified according to the grading systems of Papile et al. and Volpe, shown in Table 2 [5, 18].

Table 1. Ultrasound findings in Hypoxic-Ischaemic Encephalopathy adapted from Ilves.

| Form / Method | Mild | Moderate | Severe |
|---|---|---|---|
| **Grey–Scale Sonography** | moderate increase of parenhymal echogenicity; age: 48 -72 h | | moderate/severe increase of parenchymal echogenicity; age: 12 ± 2 h |
| | reversed appearance of hypoechoic grey matter and hyperechoic white matter | | increased echogenicity with central pattern of injury |
| | spared regions: brainstem, cerebellum, deep grey matter structures | | affected regions: deep grey matter structures |
| **Doppler Sonography** | increased mean cerebral blood flow velocity (BFV) in all the cerebral arteries | | severe increase in cerebral BFV |
| | diminished resistive indexes (RI) in the cerebral arteries | | decrease in RI hypovascularity and/or hyperemia in the basal ganglia |

Table 2. Ultrasound grading of Intraventricular Hemorrhage.

| Grade | Papile Criteria | Volpe Criteria |
|---|---|---|
| **I** | unilateral/bilateral germinal matrix hemorrhage | germinal matrix hemorrhage with no IVH or IVH occupying < 10% of the ventricular area on parasagittal view |
| **II** | IVH without ventricular dilatation | IVH occupying 10- 50% of the ventricular area on parasagittal view |
| **III** | IVH with ventricular dilatation | IVH occupying 50% of the ventricular area on parasagittal view ± periventricular echodensities |
| **IV** | IVH extending into adjacent brain parenchyma | periventricular venous hemorrhagic infarction (PVHI); cystic periventricular leukomalacia |

**Results**

Anthropometric characteristics and neonatal adaptation score of the studied groups are shown in Table 3. Difficulties of early neonatal adaptation, as indicated by a low APGAR score, are noticed in preterm neonates in both SGA study group and AGA control group.

Table 3. Anthropometric data and neonatal adaptation score of the studied neonates.

| Group | | n | Gestational Age | Birth Weight | Birth Length | APGAR score |
|---|---|---|---|---|---|---|
| SGA Study Group | Term | 101 | 39.48 ± 1.18 | 2296.46 ± 163.14 | 46.67 ± 1.67 | 8.81 ± 0.70 |
| | Preterm | 69 | 34.49 ± 1.94 | 1706.60 ± 374.56 | 43.00 ± 2.87 | 8.05 ± 1.25 |
| AGA Control Group | Term | 101 | 40.00 ± 1.15 | 3427.17 ± 467.18 | 50.90 ± 0.35 | 9.00 ± 0.56 |
| | Preterm | 69 | 33.44 ± 2.04 | 2282.08 ± 147.12 | 46.34 ± 1.01 | 8.49 ± 0.90 |

AGA – appropriate for gestational age; SGA-small for gestational age.

Figures 1 and 2 show the percentage distribution of HIE and IVH respectively, among newborns included in the study.

Preterm neonates irrespective of birth weight, have a higher incidence of HIE, namely 26.1% SGA Preterm versus 11.8% SGA Term and 11.5% AGA Preterm compared to 0.0% AGA Term. A higher incidence of IVH in both SGA and AGA preterm neonates was also noticed: 20.3% SGA Preterm versus 7.9% SGA Term and 15.9% AGA Preterm compared to 0.0% AGA Term newborns.

HIE and IVH classification according to severity are illustrated in Figures 3 and 4. As shown in Figures 3 and 4, SGA-Preterm neonates have the most severe degree of impairment of both HIE and IVH: 22.2% severe HIE and 6.6% grade IV IVH respectively.

Figure 5 displays a significant correlation between metabolic acidosis and HIE. It can be mentioned that there was no such correlation noted between metabolic acidosis and IVH.

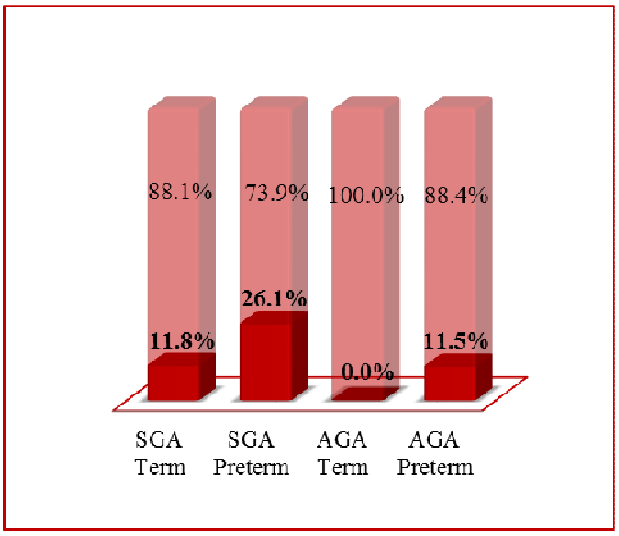


Fig.1: Incidence of HIE among studied neonates.

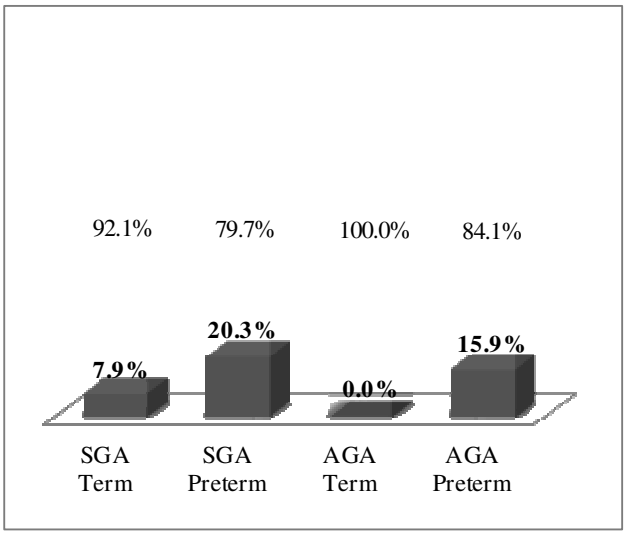


Fig.2: Incidence of IVH among studied newborns.

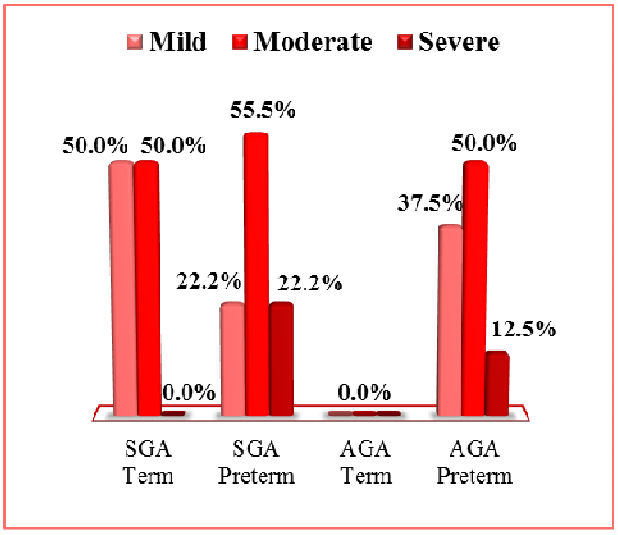


Fig.3: HIE severity classification in the studied groups.

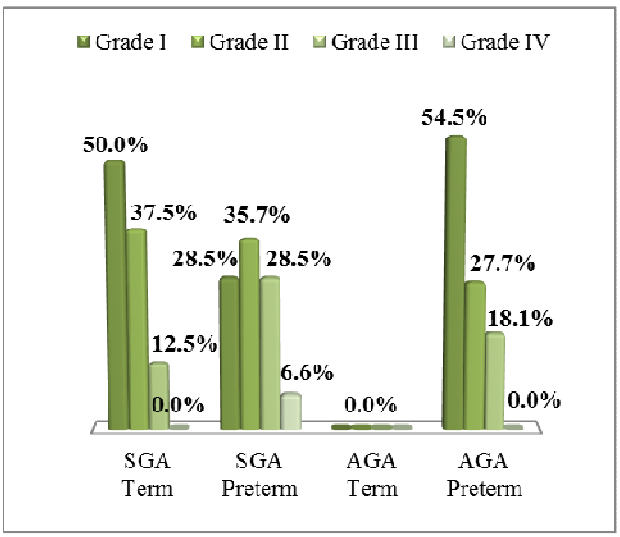


Fig.4: IVH severity distribution in the studied groups.

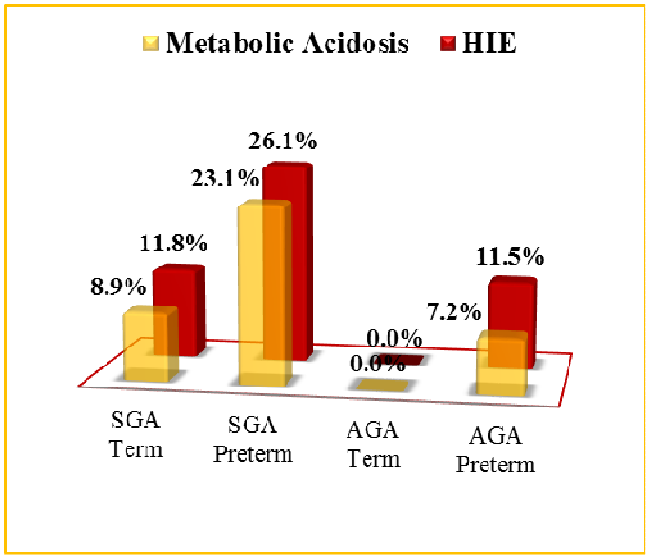


Fig.5: Metabolic acidosis and HIE overlap in the study groups.

**Discussions**

HIE and IVH are believed to be pathologically interrelated [19-21]. This is also supported by results of the current study which underline similar patterns regarding percentage distribution of both HIE and IVH.

While data from literature support a strong correlation between preterm birth and HIE [4, 22, 23] the link between prematurity and IVH continues to be debated [5, 18, 24]. In this study both HIE and IVH had a higher incidence among premature neonates regardless of birth weight, suggesting that the potential underlying mechanism might be explained as a hypoxic injury affecting immature cerebral structures.

Impaired cerebral blood flow and oxygen delivery to the immature brain are possible processes linking premature birth and hypoxic-ischemic neurological injury [10, 25]. This could explain why prematurity and superimposed SGA are stronger correlated to HIE and IVH compared to SGA alone.

**Conclusions**

Premature birth appears to be directly linked to neurological morbidity in neonates irrespective of birth weight.

The incidence of HIE and IVH was higher in SGA Preterm neonates, which leads to the conclusion that SGA is an additional, aggravating factor for neurological injury.

Further studies comparing the effect of preterm birth versus SGA as a consequence of IUGR on neonatal neurological outcome are needed in order to fully understand the underlying mechanisms.

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