**Title:** **The impact of neonatal hypoxia – ischemia on oligodendrocyte progenitor cell's fate and effect on myelination in developing brain**

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## Abstract:

One of the main reasons for neurodevelopmental disorders is neonatal hypoxia-ischemia. Depending on the severity of the injury, it induces disruption in growth of neural tissue or cause fatal damage. The typical results in brain MRI of survived babies are areas with hypomyelination, caused by impaired or delayed formation of myelin sheaths around the axons of neurons in CNS. Myelin is produced by oligodendrocytes which originate from oligodendrocyte progenitor cells (OPCs). These cells start to massively differentiate and mature in the perinatal period, thus the temporal lack of oxygen and nutrients supply, characteristic for hypoxic-ischemic insult (HI), may then contribute to significant changes in the biology of oligodendrocytes for the further brain development. To date, the processes initiated by HI remain unclear, hampering the ability to develop adequate preventions.

In the study we analysed the impact of hypoxia-ischemia on the proliferation and maturation of OPCs in rat model of perinatal asphyxia. The injury was induced in 7-day old Wistar rats and it was based on dissection of the left common carotid artery followed by exposition of animals to 7.5% oxygen for 60 min. In selected timepoints after the injury, we collected brains to perform quantitative analyses of proteins and microscopic examination of oligodendrocytes.

The analysis of brain sections collected 3 days after the injury revealed the increase in proliferation of oligodendrocyte progenitors in selected regions (cortex and striatum) and the significant decrease in the number of Olig2+ cells in corpus callosum. After 4 weeks from the injury the expression of main myelin proteins was measured and it revealed the increase in the concentration of MBP, PLP and MAG. After all, in coronal brain sections of adult animals we could characterize typical macroscopic changes, like the hypoplastic hippocampus, reduced striatum and thinness of corpus callosum. Further immunofluorescent staining of myelin, indicated the reduced myelination in cortex (30% reduction; $p<0,001$), striatum (17%; $p<0,05$) and CA3 of hippocampus (21%; $p<0,05$). There was no change in PLP immunoreactivity in the main white matter tract (the corpus callosum) although in this brain region there was decrease in the number of oligodendrocyte progenitor cells (labelled with anti-Olig2) within 3 days after the injury ($p<0,0001$), which was not observed in other analysed areas.

In conclusion, it seems that that hypoxia-ischemia alters programme of oligodendrocyte differentiation and maturation. Although it does not inhibit the synthesis of myelin proteins, the mature oligodendrocyte seem to fail myelination protocol in several brain areas, which results in development of the white matter disorders and neurological deficits observed in babies affected by the injury.

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