

Markers and mechanisms of abnormal neurovascular development in the preterm infant

Akademisk avhandling

Som för avläggande av medicinsk doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Kammaren, Blå stråket 5, den 10 februari 2023, klockan 09:00

av William Hellström

Fakultetsopponent: Deirdre Murray, Professor, University College Cork, Irland

Avhandlingen baseras på följande delarbeten

- I. Bertan Cakir, William Hellström, Yohei Tomita, Zhongjie Fu, Raffael Liegl, Anna Winberg, Ingrid Hansen-Pupp, David Ley, Ann Hellström, Chatarina Löfqvist, Lois E. H. Smith. IGF-1, serum glucose, and retinopathy of prematurity in extremely preterm infants. *JCI Insight*, 2020, October, Volume 5, Issue 19
- II. Ulrika Sjöbom*, William Hellström* Chatarina Löfqvist, Anders K. Nilsson, Ingrid Pupp, David Ley, Kaj Blennow, Henrik Zetterberg, Karin Sävman, Ann Hellström. Analysis of brain injury biomarker Neurofilament Light and neurodevelopmental outcomes and Retinopathy of Prematurity among preterm infants. *JAMA Network Open*, 2021, April, Volume 4, Issue 4 *delad försteförfattare
- III. William Hellström, Lisa M. Hortensius, Chatarina Löfqvist, Gunnel Hellgren, Maria Luisa Tataranno, David Ley, Manon J.N.L. Benders, Ann Hellström, Isabella M. Björkman-Burtscher, Rolf A. Heckemann, Karin Sävman. Postnatal serum IGF-1 levels associate with brain volumes at term in extremely preterm infants. *Pediatric Research*, 2022, June 9, PMID: 35681088
- IV. William Hellström, Chatarina Löfqvist, Ulrika Sjöbom, Anders K. Nilsson, Gunnel Hellgren, Liv Södermark, Staffan Nilsson, Matteo Bruschetti, David Ley, Henrik Zetterberg, Kaj Blennow, Ann Hellström, Karin Sävman. Neonatal serum levels of insulin-like growth factor (IGF)-1 and brain injury marker neurofilament light (NfL) are associated with autism at early school age in children born extremely preterm. *In manuscript*

SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER



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Abstract

Background: The extremely preterm infant is at risk of lifelong neurodevelopmental impairments due to brain injuries or abnormal neurovascular development. Mechanisms are largely unknown and biomarkers for adverse outcomes are sparse. The growth factor insulin-like growth factor (IGF)-1 is a key regulator of neurovascular developmental processes and endogenous levels are low following preterm birth. **Aim of the thesis:** To investigate the impact of growth factors on neurovascular development, e.g. retinopathy of prematurity (ROP), brain injury, brain volumes measured by magnetic resonance imaging, and neurodevelopmental outcome in preterm infants and in an animal model. In addition to identify possible biomarkers for abnormal neurovascular development in preterm infants. **Materials and Methods:** *Paper I:* Associations between serum glucose levels, serum IGF-1, and ROP were explored in preterm infants (n=117) and in an oxygen-induced retinopathy/hyperglycemia mice model including IGF-1 substitution treatment. *Paper II:* Longitudinal serum Neurofilament Light (NfL, biomarker for axonal injury) levels were evaluated in preterm infants (n=221) as a biomarker for ROP, brain injury, and neurodevelopmental outcome at 2 years of age. *Paper III:* Longitudinal serum growth factor levels were correlated with total and regional brain volumes at term in extremely preterm infants (n=49). *Paper IV:* Longitudinal serum levels of NfL and IGF-1 and the association to neurodevelopmental outcomes at early school age were investigated (n=72). **Results:** *Paper I:* Hyperglycemia was associated with lower IGF-1 levels, increased number of any ROP and with ROP severity. Hyperglycemia decreased endogenous IGF-1 expression, and IGF-1 treatment decreased ROP-associated vascular changes in the mice model. *Paper II:* NfL levels increased after birth and remained high, with increased levels independently associated with ROP development. High NfL levels were associated with unfavorable neurodevelopmental outcomes at 2 years. *Paper III:* Low serum IGF-1 levels were independently associated with reduced total brain, white matter, cortical grey matter, deep grey matter, and cerebellar volumes. *Paper IV:* Unpublished results, see *Paper IV*. **Conclusion:** IGF-1 may have a beneficial role in brain development and may have a protective role in ROP development. NfL may serve as a biomarker for ROP and adverse neurodevelopmental outcome.

Keywords: extremely preterm infant, brain development, brain volume, ROP, neurodevelopment, BSID, IGF-1, NfL

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