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|  |  | **Developmental time course (prenatal)** | **Developmental time course (postnatal)** | **Roles after IVH/PHH** | **References** |
| Extracellular iron transporters and scavengers identified in the neonatal brain |  |  |  |  |  |
|  | Transferrin | CSF: peaks at 18 weeks’ gestation.\*\*\* | Peaks at birth and declines over postnatal weeks 2-3. Stabilizes at postnatal day 24 to stay constant through life.\*\*, \*\*\*  BCECs: Expressed throughout development.  CSF: Decreases from birth to postnatal day 10\*\*\*  Oligodendrocytes: Onset and increase of transferrin synthesis during postnatal days 10-25.\*\*\* | Longitudinal increases in CSF transferrin after human neonatal IVH-PHH are associated with improved cognitive outcomes at 2 years of age.  No significant differences in CSF transferrin after low- and high-grade IVH compared to human neonates without IVH. | [1–11] |
|  | Haptoglobin | Neurons: Expressed at 6-8 weeks’ gestation. Decreases to variable levels at 9-22 weeks. Rises at 25-36 weeks.\*  BCECs: variable expression at 6-10 weeks’ gestation. No expression after 14 weeks.\* | Low compared to fetal development.\* | Intraventricular haptoglobin after IVH in rabbits attenuates hemoglobin-induced inflammation, cytotoxicity, and structural damage.  No significant differences in CSF haptoglobin between human neonates with and without IVH or PHH. | [12–15] |
|  | Hemopexin | Neurons: Expressed from 3-36 weeks’ gestation.\* |  | CSF hemopexin is not elevated after IVH-PHH in human neonates.  Only iron scavenger that is increased between temporary and permanent CSF diversion after IVH-PHH in human neonates.  Ventricle size after IVH in human neonates is inversely correlated with CSF hemopexin levels. | [1,14] |
|  | Ceruloplasmin | Neurons: Expressed from 14-18 weeks’ gestation, but not at 25 weeks.\*  Glia: Expressed weakly from 14-22 weeks’ gestation.\*  Anchored form is expressed at embryonic day 12.5, while diffusible form is not expressed until embryonic day 17.5.\*\* | Increasing expression from postnatal day 1 to postnatal day 7, before subsequently decreasing.\*\*  Astrocytes: expressed at postnatal day 3.\*\*\* | No significant differences in CSF ceruloplasmin after neonatal IVH-PHH in humans.  No significant differences in CSF ceruloplasmin between temporary and permanent CSF diversion. | [1,13,14,16] |
| Membrane iron transporters and scavengers identified in the neonatal brain |  |  |  |  |  |
|  | Transferrin  receptor (TfR) |  | BCECs: Expression peaks in postnatal week 2 between postnatal days 10 and 21.\*\*\*  Neurons: Weak expression seen at postnatal day 5, but robust expression is not observed until postnatal day 15, with a peak at postnatal weeks 3-4.\*\*\*  ChP ependymal cells: Little to no expression at postnatal days 5-10, but robust expression by postnatal day 15.\*\*\* | Not well understood. | [17,18] |
|  | Divalent metal transporter 1 (DMT1) |  | mRNA expression at postnatal day 3, with additional increasing expression in the cortex, hippocampus, striatum, and substantia nigra from postnatal weeks 1-3.\*\*\*  ChP ependymal cells, glia, and neurons: Variable expression from postnatal days 5-10, which increases to robust expression by postnatal day 15.\*\*\* | Not well understood. | [18–21] |
|  | Ferroportin 1 (FPN1) | Expression across the central nervous system was previously reported\*\*\* | BCECs: expressed at postnatal day 0, with decreasing expression from postnatal days 1-8.\*\*\*  Parenchyma: Increase with age, with the lowest expression seen at postnatal week 1. Increasing expression from postnatal weeks 1-9, with subsequent decrease from postnatal weeks 10-28. | Not well understood. | [22–24] |
|  | Low-density lipoprotein receptor-related protein 1 (LRP1) | Radial glia: Expressed at embryonic days 13.5-18.\*\* | Brain expression peaks during postnatal development. Stable expression in glia, neuroblasts, and neurons through development and adulthood.\*\*  Oligodendrocyte precursor cells: Percentage of oligodendrocyte precursor cells expressing Lrp1 increases across embryonic and postnatal development, with nearly ubiquitous expression in adulthood.\*\* | Not well understood. | [25,26] |
| Intracellular iron transporters and scavengers identified in the neonatal brain |  |  |  |  |  |
|  | Ferritin | Glia: expressed from 6-36 weeks’ gestation, with increasing levels from 19-22 weeks’ gestation.\* | Brain expression initially peaks at postnatal day 2 and decreases over postnatal weeks 1-2. Levels begin to rise again at postnatal day 17, and stabilizes at levels similar to those seen at postnatal day 2 by postnatal week 11.\*\*\* | Longitudinal decreases in CSF ferritin between temporary and permanent CSF diversion after PHH in human neonates are associated with improved scores on cognitive and motor aspects of the Bayley III examination at 2 years of age.  Larger ventricle size at the time of permanent CSF diversion is associated with higher levels of CSF ferritin in human neonates.  Elevated levels of CSF ferritin associated with early and severe ventriculomegaly after IVH in human neonates.  Increase in number of ferritin-positive cells in periventricular areas and hippocampus after IVH in mice. | [1,2,13,14,27–29] |
|  | Heme oxygenase 1 (HMOX-1) |  | mRNA and protein levels are high at postnatal days 1 and 3 and decline out to adulthood.\*\*\* | Increase in hippocampus, cortex, and periventricular expression after neonatal GMH-IVH in mice. | [30,31] |
| Related proteins important in neonatal brain iron homeostasis |  |  |  |  |  |
|  | Iron regulatory protein 1 (IRP1) | Low mRNA expression (relative to iron regulatory protein 2).\* | Variable expression from postnatal days 5-10, before increasing at postnatal day 15.\*\*\* | Not well understood.  No change after GMH-IVH in rodents. | [18]  [18,32] |
|  | Iron regulatory protein 2 (IRP2) | High mRNA expression (relative to iron regulatory protein 1).\* | Variable expression from postnatal days 5-10, before increasing at postnatal day 15.\*\*\* | Decrease in expression 1-5 days after neonatal GMH-IVH in postnatal day 7 rodents. | [18,32] |
|  | Amyloid precursor protein (APP) | Protein expression across embryonic days 8.5-13.5, with increasing expression from embryonic days 10.5-13.5\*\* | mRNA expression that increases from embryonic day 12 to postnatal day 10.\*\* | Significantly elevated in the CSF after neonatal IVH in humans.  CSF APP levels associated with ventricular size after neonatal IVH. | [33–36] |

Supplementary Table 1. Pre- and post-natal developmental expression of iron-handling and iron-related proteins in the brain. \* indicates findings derived from experiments using human tissue, \*\* mouse tissue, and \*\*\* rat tissue. CD163, STEAP, TIM, and hepcidin were excluded from the table because their developmental expression profiles are not as well-understood. Abbreviation: CSF, cerebrospinal fluid; IVH, intraventricular hemorrhage; PHH, posthemorrhagic hydrocephalus.

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