APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

**Academic Supervisor**
Name: Professor Andrew Copp  
ICH Programme/Section: DBC/Developmental Biology of Birth Defects

**Clinical Supervisor**
Name: Mr Dominic Thompson  
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1. Title.
Chiari II brain malformation: why is it so closely associated with spina bifida?

2. Portfolio summary.

**Aims:**
Open spina bifida (OSB; ‘myelomeningocele’) is a common cause of neurodisability in young children. However, the most life-threatening aspect of OSB is the Chiari II brain malformation, which affects 90% of OSB cases. A recent, randomised control trial of antenatal versus postnatal repair of myelomeningocele, concluded that antenatal repair resulted in a lower incidence of Chiari II malformation compared with conventional postnatal repair [1]. This observation is the most commonly cited indication for antenatal surgery. This project aims to determine why Chiari II so commonly accompanies SB, as this is not understood. The student will test the following hypothesis, which represents the most prevalent view [2] on Chiari II origin: Hypothesis: Chiari II malformation results primarily from persistent cerebrospinal fluid (CSF) leakage from the OSB lesion in utero, leading to a small hindbrain and reduced posterior skull fossa size which, in turn, causes the cerebellar vermis / brain stem to herniate.

**Background:** The Chiari II brain malformation affects around 0.5/1000 pregnancies and involves herniation of the cerebellar vermis, with/without the brain stem, through the foramen magnum into the vertebral canal. Chiari II is the commonest cause of death in children with OSB under 2 years of age [3]. Physical compression of the hindbrain, cranial nerves and spinal cord can cause inspiratory stridor, a medical emergency due to hypoglossal nerve dysfunction/vocal cord paralysis. Posterior fossa surgical decompression may be required. These effects are distinct from the lower body neurological deficit of OSB [4]. It is not clear why Chiari II so often accompanies OSB, as the two lesions affect completely different parts of the CNS. One view is that OSB initiates a sequence of developmental events that directly leads to Chiari II: i.e. the hypothesis to be tested. Alternatively, OSB and Chiari II could result from independent (‘pleiotropic’) effects of a single causative genetic/non-genetic factor, with no pathogenic link between the two defects.

**Proposed methodology to be adopted:**

**Mouse studies.** Using MRI, we detected Chiari II in splotch (Pax3) mutant mouse fetuses with OSB [5]. This provides a system for experimental analysis of Chiari II development. The student will first define the time-course of Chiari II development in the mouse model, to test whether a small hindbrain/posterior skull fossa precedes Chiari II, as predicted by the hypothesis. He/she will then use conditional gene targeting to induce OSB locally, by making only the low spine genetically mutant while the brain/skull is wild-type. According to the hypothesis, Chiari II should still develop, whereas the ‘independent effects’ idea would predict that Chiari II will be absent in this situation.

**Human studies.** The student will analyse existing MRI scans of children treated by the neurosurgeons at GOSH, to test for a role of hydrocephalus or spinal cord tethering in Chiari II. MRI of children with postnatally closed OSB lesions, +/- shunt for hydrocephalus, will be compared to correlate the degree of ventriculomegaly with the severity of Chiari II. Our hypothesis predicts a lack of correlation. MRI of patients whose spinal cord is ‘tethered’ due to OSB or due to ‘closed’ spinal...
lipoma will be compared to determine presence/severity of Chiari II. Our hypothesis predicts Chiari II only in OSB, where CSF leakage occurs.

**Skills to be achieved by the PhD trainee:**
The student will gain skills in the genetics and developmental biology of mouse spina bifida models, including dissection and handling of fetuses. He/she will learn methods for performing mouse fetal MRI and morphometric methods for analysing clinical MRI scans.

**Relevance to the area of paediatric surgery:**
Chiari II is a common cause of morbidity and mortality in spina bifida, with requirements for surgical posterior fossa decompression in severe cases. This project is ideal for a surgical trainee who aims to develop a career in paediatric neurosurgery.

References: