APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHP

Academic Supervisors
Name: Erwin Pauws
ICH Programme/Section: DBC/DBBD

Name: David Dunaway
ICH Programme/Section: DBC/SCRM

Clinical Supervisor
Name: Richard Bowman
GOSH department: Ophthalmology

1. Title.
Optimizing ophthalmological surveillance and surgical outcomes in syndromic craniosynostosis

2. Portfolio summary.

Aims
1. To develop an effective non-invasive neuro-ophthalmic screening test for sight threatening intracranial hypertension (ICH) in syndromic craniosynostoses, by performing systematic, detailed clinical, electrophysiological, optical coherence tomography and ultrasound studies of the optic nerve structure and function.
2. To study neuro-ophthalmic phenotypes in mouse model for syndromic craniosynostosis (Crouzon, Apert, Pfeiffer) and determine whether impaired FGF signalling through mutation of the FGFR2 receptor is the primary or secondary cause.
3. To compare clinical outcomes between GOSH and Rotterdam to establish whether delayed cranial vault expansion, dependent on ophthalmological screening (GOSH method), is more or less effective than early cranial vault expansion, independent of ophthalmological screening (Rotterdam method).

Background
GOSH sees 350 new referrals per year for children with craniosynostoses. Syndromic craniosynostoses carry a significant risk of developing ICH, which in turn carries risk of permanent visual loss, and many centres throughout the world perform early cranial vault expansion because of this risk. Direct measurement of intracranial pressure (ICP) with a catheter is invasive, carrying risk of complications and the results can be difficult to interpret, in terms of determining what levels of ICP pose a risk to vision or other neurological functions. GOSH is perhaps unique in delaying vault expansion surgery, relying on intensive ophthalmological surveillance, to seek evidence of ICH through fundoscopy (papilloedema) or reduced visual evoked potential (VEP) responses as a trigger to performing vault expansion. Therefore surgery can be delayed until older in many children compared to other international centres. The results of these different approaches have not been compared. Does delayed surgery lead to fewer complications? Are visual / developmental results worse because of longer periods of subclinical ICH when surgery is delayed?

Neither disc assessment (shown previously by GOSH work to be insensitive in younger children1) nor VEPs directly measure ICP but they have been shown to be useful2 and do have the advantage of assessing the structure and function of the optic nerve which is the organ most at risk from ICH and which we are most concerned with protecting. A few small studies have shown that optical coherence tomography (OCT) may be helpful but this is not proven3. Another non invasive
technique for assessing ICP is ultrasound measurement of optic nerve sheath diameter. The GOSH unit is well placed to look at correlation between OCT, VEP, ultrasound and clinical disc changes in this condition to try and understand the risk of ICH to visual function at different ages and both pre and post surgery.

Mouse models for syndromic craniosyostosis (e.g. Crouzon) have been generated and their craniofacial skeletal phenotype has been studied extensively4. Mice mimick clinical features of Crouzon patients, including ocular proptosis. ICP has not been measured but unpublished observations from the Pauws lab suggest that adult mice develop corneal opacity. Studying the phenotypic and molecular events causing the clinically significant, ocular features of syndromic craniosynostosis in an animal model will increase our understanding of the underlying mechanisms and allow for a potential adjustment of clinical intervention.

**Proposed methodology**

A. **Prospective study**

All consenting children with syndromic craniosynostosis (whether pre or post-operative) will be enrolled in a longitudinal study. They will undergo detailed neuro-ophthalmological assessment at 4 monthly intervals (age 0 to 3yrs) and 6 monthly intervals (age 3 to 8yrs). This will include clinical examination, OCT imaging of the optic nerve, ultrasound and VEP responses. They already undergo disc assessment, visual acuity assessment and electrophysiology as part of our existing clinical protocol (which lacks an evidence base) but do not get regular OCT or ultrasound and therefore our understanding of the pathology is limited. Systematic measurement of all these parameters will enable exploration of the correlation between structural changes (clinical, OCT and ultrasound) and functional changes (visual acuity and electrophysiology and, in more co-operative children, visual field), hence obtaining a more detailed understanding of the pathology, and the changes in ICP associated with these syndromes, and its effect on the optic nerve. It will also form a database which can be used to correlate with later functional outcomes of surgery.

A subgroup of these patients would undergo ICP monitoring as clinically indicated if there is doubt about the significance of changes in clinical signs or vision or headaches.

B. **Animal study**

To further characterise the ocular phenotype of the Crouzon mouse we intend to study the eye at embryonic and postnatal stages using post-mortem uCT, histology and gene expression analysis. In vivo techniques for measuring ICP in mice will be developed using current knowledge of human OCT and/or ultrasound. A Home Office Project License (70/8817) is in place for these experiments.

C. **Retrospective study**

Children with syndromic synostoses who presented to GOSH and Rotterdam between 2010-2012 will have their records examined and compared in terms of age/type of surgery, number of operations, evidence of ICH pre / post-operatively, visual acuity aged 5 years, baseline and follow up airway data, neuropsychological and developmental outcomes.

**Skills to be achieved by PhD trainee**

Generic skills including critical thinking, hypothesis generation, study design, data collection and management and analysis, paper writing and cross disciplinary communication and collaboration.

Specific skills would include a range of ophthalmological investigation and imaging techniques such as ultrasound, OCT and visual electrophysiology.

**Relevance to the area of paediatric surgery**

This study would increase our understanding of the pathophysiology of the optic nerve in these syndromes and this in turn may provide a more accurate understanding of changes in ICP and their
potentially harmful effects. It may change practice in terms of surveillance protocols and timing of surgery.

References


