National Centre for the Replacement Refinement & Reduction of Animals in Research

mathematics POEMS healthcare

NC3Rs/POEMS Network Maths Study Group - Applying mathematics to 3Rs problems

Understanding patterns of retinal haemorrhage

Richard Bonshek

Manchester Royal Eye Hospital

Background to the Problem

Patterns of retinal bleeding are important as signatures of injury or disease. Certain patterns of retinal haemorrhage are considered to have significance as a marker for head trauma. In trauma, retinal haemorrhage may occur as a primary result of head injury or as a secondary phenomenon due to raised intracranial pressure, and there is disparity between clinical observations of retinal haemorrhage and most biomechanical approaches to thresholds of retinal vascular damage. Thus approaches based upon considerations of the contribution of raised intracranial pressure and intravascular pressure - and particularly the rate of increase of these quantities - are of importance.

Details of the problem

Retinal bleeding can occur due to elevated intracranial pressure and elevated vascular pressure, with a number of differing but characteristic patterns seen (for example, papilloedema, Terson's syndrome, Valsalva retinopathy and Purtscher retinopathy). Of these patterns, Terson's syndrome, seen in situations of precipitate rise in intracranial pressure (such as due to rupture of an intracranial aneurysm) has the greatest similarity to the retinal haemorhages of paediatric head trauma. On the other hand, Valsalva retinopathy due to raised central venous pressure (as might occur with severe coughing), appears to be very rare in babies and children. Factors that need to be considered in understanding mechanisms of injury include the particular anatomy of the human ophthalmic vascular circuit, optic nerve anatomy and physiology, the effect of the coat of the eye and intraocular pressure and autoregulation of the retinal circulation. In particular, the manner in which the central retinal vein is occluded as it enters the optic nerve is likely to be critical to understanding how the rate of rise of intracranial pressure translates to different patterns of haemorrhage.

Ideas and data for informing possible mathematical models

Some relevant biomechanical data are available in the literature for adult humans and animals; much less are available for infants for obvious ethical reasons. However adult and animal data will provide a framework for estimating parameters appropriate for infants. Some relevant computational bioengineering models of ocular injury are available (see references 4, 5, 6 below).

Questions you would like to see answered

The Study Group is asked to investigate whether mathematical models can provide quantitative support for alternative hypotheses for mechanisms of failure of retinal blood vessels under different loading conditions. In particular, models can be used to address how the rate of rise of intracranial pressure influences the conformation of arterial and venous vessels that are confined within the optic nerve and the impact of such changes on the remainder of the retinal circulation. It is hoped that models will provide new mechanistic insights into distinct patterns of retinal haemorrhage and hence enhance diagnostic procedures.

The potential impact on animal use

Large animal models have been shown to offer advantages over rodent models in replicating specific mechanisms, morphology and maturational stages relevant to age-dependent brain injury responses (Duhaime 2006 Devel. Neurosci. 28, 380). For example, piglets are used to mimic human brain injury due to mechanical trauma via cortical indentation (Duhaime et al. 2000 J Neurosurg 93, 455) or rapid head rotation (Ragupathi et al. 2004 J. Neurotrauma 21, 307; Ibrahim et al. 2010 J Neurotrauma 27, 1021); head rotations in piglets has been shown to lead to retinal haemorrhage (Coats et al. 2010 Inv. Ophth. Vis. Sci. 51, 4792). Rats have been used to test whether hypoxia leads to retinal damage (Kaur et al. 2009 Inv. Ophth. Vis. Sci. 50, 5364). The relevance of these models in predicting the human condition has been questioned. Better proxies for human anatomy and physiology are desperately needed, particularly for infants. Mathematical and computational models complement such approaches by investigating different mechanisms of injury in silico; in the long term, there is potential for such models to provide improved guidance for clinical diagnosis and for legal assessments in cases of potential abuse.

Relevance to medicine and healthcare

Improved understanding of mechanisms of retinal haemorrhage will improve diagnosis and will help enable healthcare professionals to recognise accurately cases of trauma to infants. This has potential implications for child safeguarding and family protection.

References

1. DG Talbert (2005) Med. Hypoth. 64: 8-13
2. JF Geddes & DG Talbert (2006) Neuropath. Appl. Neurobiol. 32: 625-634
3. DG Talbert (2006) Med Hypoth. 66: 691-694
4. AS Hans, SY Bawab & ML Woodhouse (2009) Graefes Arch Clin Exp Ophthalmol 247: 561
5. N Rangarajan, SB Kamalakkannan et al. (2009) J Am Assoc Ped Ophthal Strab 13: 364
6. TJ Harrison, CO Abbasi, TA Khraishi (2011) Invst Ophthalmol Vis Sci 52: 8102