Pathophysiology of
Normal Pressure Hydrocephalus

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Statement of Authenticity

This thesis contains a record of original research performed by the author at the Academic Neurosurgery Unit, Addenbrooke's Hospital, Cambridge, United Kingdom, the Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, United Kingdom, the Department of Neurosurgery, Royal Prince Alfred Hospital, Sydney Australia and the Department of Surgery, University of Sydney, Sydney, Australia.

In all sections of the thesis, the author was primarily responsible for the conduct and direction of the research, study design and the analysis of results. This work has not been submitted for consideration of an award, diploma or degree at any institution previously.

Research was conducted with approval of the Cambridge Regional Ethics Committee when applicable in accordance with the Declaration of Helsinki as amended in September, 2000.

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Publications arising from thesis material

Publications in Peer Reviewed Journals

1. Owler B. K. and Pickard J.D. (2001) Cerebral Blood Flow and Normal Pressure Hydrocephalus. A Review. *Acta Neurologica Scandanavica* 104: 325-342.

2. Owler, B. K., Jacobson, E. E. and Johnston, I. H. (2001) Low Pressure Hydrocephalus Syndrome. Report of 5 cases.. *British Journal of Neurosurgery* 15(4): 353-359.

3. Owler, B. K., Fung, K. Czosnyka, Z. (2001) Importance of ICP monitoring in CSF circulation disorders. *British Journal of Neurosurgery* 15(5): 439-440.

4. Owler, B.K., Momjian, S., Péna, A., Harris, N., Czosnyka, Z., Czosnyka, M., Fryer, T., Smielewski, P., Donovan, T., Coles, J. and Pickard, J.D. (2003) Global & regional CBF in patients with normal pressure hydrocephalus. *Journal of Cerebral Blood Flow and Metabolism* 24: 17-23.

5. Owler, B.K., Péna, A., Momjian, S., Harris, N., Czosnyka, Z., Czosnyka, M., Fryer, T., Smielewski, P., Donovan, T., and Pickard, J.D. (2004) Changes in Cerebral Blood Flow during CSF Pressure Manipulation in Patients with Normal Pressure Hydrocephalus. *Journal of Cerebral Blood Flow and Metabolism* (accepted)

Abstracts in Conference Proceedings

1. Owler, B.K., Péna, A., Momjian, S., Harris, N., Czosnyka, Z., Czosnyka, M., Fryer, T., Smielewski, P., Donovan, T., and Pickard, J.D. (2003). Changes in Cerebral Blood Flow during CSF Pressure Manipulation in Patients with Normal Pressure Hydrocephalus. Proceedings of the Neurosurgical Society of Australasia's Annual Scientific Meeting, Queenstown, New Zealand.

2. Momjian, S., Owler, BK., Czosnyka, Z., Czosnyka, M., Péna, A., Pickard, JD. (2003). Pattern of regional white matter CBF in normal pressure hydrocephalus. Brain 03. Proceedings of the International Society for the Study of Cerebral Blood Flow and Metabolism. Calvary, Canada.

3. Owler, B.K., Pena, A., Harris, N., Czosnyka, Z., Czosnyka, M., Fryer, T., Smielewski, P., Donovan, T., Coles, J. and Pickard, J.D. (2002). Global & regional CBF in patients with normal pressure hydrocephalus. Proceedings of the Neurosurgical Society of Australasia's Annual Scientific Meeting, Broome, Australia.

4. Green, H.A.L., Pena, A., Price, S.P., Owler, B.K., Gillard, J., Pickard, J. D., Carpenter, T. A. Partial Volume effects on Diffusion Tensor Images at 3T. RANZCR. Melbourne, Australia.

5. Owler, B.K., Pena, A., Harris, N., Green, H., Papadakis, N., Martin, K., Donovan, T., Carpenter, A. and Pickard, J.D. (2001). A study of normal

pressure hydrocephalus using diffusion tensor imaging. World Congress of Neurological Surgeons. Sydney, Australia.

6. Owler, B.K., Pena, A., Harris, N., Czosnyka, Z., Czosnyka, M., Fryer, T., Smielewski, P., Donovan, T., Coles, J. and Pickard, J.D. (2001). Global & regional CBF changes in patients with normal pressure hydrocephalus with changes in ICP. Brain 01. Proceedings of the International Society for the Study of Cerebral Blood Flow and Metabolism. Taipei, Taiwan.

7. Pena, A., Harris, N.G., Owler B.K. and Pickard, J.D. (2001) The biomechanics of steady-state ventricular dilatation in normal pressure hydrocephalus. 3rd International Hydrocephalus Workshop, Kos, Greece.

8. Czosnyka, M., Czosnyka, Z.H., Owler B.K., Piechnik, S.K., Smielewski, P. and Pickard, J.D. (2001) Testing of cerebrospinal compensatory reserve in shunted and non-shunted patients (an update). 3rd International Hydrocephalus Workshop, Kos, Greece.

9. Owler, B.K., Pena, A., Harris, N., Czosnyka, Z., Czosnyka, M., Fryer, T., Smielewski, P., Donovan, T., Coles, J. and Pickard, J.D. (2001). Global & regional CBF changes in patients with normal pressure hydrocephalus with changes in ICP. Proceedings of the Royal Society of Medicine, London, UK.

10. Owler, B.K., Pena, A., Harris, N., Czosnyka, Z., Czosnyka, M., and Pickard, J.D. (2000) Response of global CBF to changes in ICP in patients with hydrocephalus – an observational study. ICP 2000, Cambridge, UK.

Abbreviations

AR	Autoregulation
AMP_{beg}	CSF pulse amplitude - baseline
AMP_{end}	CSF pulse amplitude - equilibrium
CBF	Cerebral blood flow
CC	Corpus callosum
CCx	Calcarine cortex
CO_2	Carbon dioxide
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
CVR	Cerebrovascular reactivity
D	Mean diffusion
DAT	Dementia of the Alzheimer's type
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
EAM	External acoustic meatus
El	Elastance
EPI	Echo planar imaging
FA	Fractional anisotropy
gCBF	Global cerebral blood flow
GE	Gradient echo
IC	Internal capsule
ICP	Intracranial pressure
ICP_{beg}	Intracranial pressure - baseline

ICP_{end}	Intracranial pressure - equilibrium
i.v.	Intravenous
mmHg	Millimetres of mercury
mmHg/ml/min	Millimetres of mercury per millilitre per minute
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NMR	Nuclear magnetic resonance
NPH	Normal pressure hydrocephalus
OER	Oxygen extraction rate
P	Isotropic component of diffusion tensor
PET	Positron emission tomography
PVI	Pressure-volume index
PVL	Periventricular lucency
Q	Deviatoric component of diffusion tensor
RA	Relative anisotropy
rCBF	Regional cerebral blood flow
R_{csf}	Resistance to CSF absorption
RF	Radiofrequency
sAR	Static Autoregulation parameter
sARi	Static Autoregulation index
SPECT	Single photon emission computed tomography
TE	Echo time
Xe	Xenon

Summary

Normal pressure hydrocephalus (NPH), a CSF circulation disorder, is important as a reversible cause of gait and cognitive disturbance in an aging population. The inconsistent response to CSF shunting is usually attributed to difficulties in differential diagnosis or co-morbidity. Improving outcome depends on an increased understanding of the pathophysiology of NPH. Specifically, this thesis examines the contribution of, and inter-relationship between, the brain parenchyma and CSF circulation in the pathophysiology of NPH.

Of the four core studies of the thesis, the first quantifies the characteristics of the CSF circulation and parenchyma in NPH using CSF infusion studies to measure the resistance to CSF absorption and brain compliance. The second study assesses cerebral blood flow (CBF) was using O^{15}-labelled positron emission tomography (PET) with MR co-registration. By performing CSF infusion studies in the PET scanner, CBF at baseline CSF pressure and at a higher equilibrium pressure is measured. Regional changes and autoregulatory capacity are assessed. The final study examines the microstructural integrity of the parenchyma using MR diffusion tensor imaging.

These studies confirm the importance of the inter-relationship of the brain parenchyma and CSF circulation. NPH symptomatology and its relationship to the observed regional CBF reductions in the basal ganglia and thalamus are discussed. Regional CBF reductions with increased CSF pressure and the implications for autoregulatory capacity in NPH are considered. The reduction in CBF when CSF was increased was most striking in the periventricular regions. In addition, periventricular

structures demonstrated increased diffusivity and decreased anisotropy. The relationship between these changes and mechanisms such as transependymal CSF passage are reviewed.

The findings of this thesis support a role of both the CSF circulation and the brain parenchyma in the pathophysiology of NPH. The results have implications for the approach to the management of patients with NPH.