

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

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2. Oowler, 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.
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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
EI	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) 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.