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A MATHEMATICAL ANALYSIS OF PHYSIOLOGICAL AND MOLECULAR MECHANISMS THAT MODULATE PRESSURE GRADIENTS AND FACILITATE VENTRICULAR EXPANSION IN HYDROCEPHALUS

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Abstract. Perhaps the greatest paradox in the hydrocephalus field is the failure of researchers to consistently measure transmantle pressure gradients (ventricle to subarachnoid space) in either human or animal models of the communicating form of the disorder. Without such a gradient, conceptualization of how ventricular distention occurs is difficult. Based on evidence from both a mathematical model [35] and experiments in skin [51], we observed that the intraventricular injection of anti-β_1 integrin antibodies in rat brains results in a reduction of periventricular pressures to values below those monitored in the ventricles. In addition, many of these animals developed hydrocephalus [30]. We conclude that the dissociation of β_1 integrins from the surrounding matrix fibers generates pressure gradients favouring ventricular expansion suggesting a novel mechanism for hydrocephalus development. Several issues, however, need further clarification. If hydrostatic pressure declines in the periventricular tissues then fluid absorption must occur. Aquaporin-4 (AQP4) is a likely candidate for this absorption as it is the predominant water channel in the brain. Indeed, when capillary function is negated, periventricular interstitial fluid pressures increase after anti-β_1 integrin antibody administration. This suggests that capillary absorption of parenchymal water may play a pivotal role in the generation of pressure gradients in our hydrocephalus model. Focusing on these issues, we present two poroelastic models to investigate the role of intramantle pressure gradients in ventriculomegaly and to determine if integrin-matrix disassociation represents a complete causative mechanism for hydrocephalus development.

Key words. Hydrocephalus, β_1 Integrins, Aquaporin-4, Brain Biomechanics, Poroelasticity.

1. Introduction

The term hydrocephalus represents a family of disorders characterized by expansion of the ventricles within the brain. In obstructive hydrocephalus, an observable blockage within the cerebrospinal fluid (CSF) system impairs CSF flow leading to ventriculomegaly. In communicating hydrocephalus however, there is no obvious impediment to CSF movement and the reason for ventricular expansion is unknown. Hydrocephalus can be caused by a wide variety of developmental abnormalities or injuries. Genetic factors are believed to contribute to the development of congenital hydrocephalus and as of 2006, more than 40 mutants and 9 genes have been identified in animal models and humans [54]. Most of the gene products are the cytokines and growth factors involved in brain development. In humans, however, only one hydrocephalus gene has been identified (X-linked) encoding for the cell adhesion molecule L1 [14]. Additionally, there are many cases of hydrocephalus that occur as part of complex syndromes that are difficult to interpret. In contrast to the congenital form, acquired hydrocephalus occurs after development of the brain and can be due to many causes such as trauma, hemorrhage, infection, and tumors.

Hydrocephalus afflicts people of all ages. The incidence of infantile hydrocephalus is approximately one in every 500 live births, making it one of the most

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common birth defects [16, 45]. In children, this condition is especially damaging as up to 78% of children with treated hydrocephalus still suffer debilitating neurological deficits [6, 18]. Additionally, the increasing numbers of aging patients with Normal Pressure Hydrocephalus (NPH), further substantiate the need for better management of this disorder [38]. Gait disturbance, urinary incontinence and dementia in conjunction with expanded ventricles define idiopathic NPH usually in the sixth or seventh decade of life [25]. Secondary NPH is thought to occur from subarachnoid hemorrhage, meningitis, head trauma or stroke and can affect individuals at all ages.

Treatment of hydrocephalus involves the insertion of a catheter called a shunt into a brain ventricle with diversion of CSF to another site of absorption in the body (usually the abdominal cavity). Alternatively, the endoscopic third ventriculostomy technique is used in which a channel in the floor of the third ventricle is opened surgically. This allows CSF flow to the basal cisterns of the brain. Unfortunately, half a century of research has produced little improvement in shunt survival [11]. Approximately 40% of shunts fail and require further surgery within a year, and 60% fail by two years [45]. The overall cost for shunt treatments has been estimated at 1 billion per year in the United States and shunt malfunctions represent at least half of this expense [9, 5, 33]. It is clear that fresh approaches are needed to understand the causes and therapeutic potential of this disorder [4, 49].

2. Physiological and Molecular Mechanisms in the Brain Interstitium

In this section we discuss some existing theories for hydrocephalus development as well as a promising new theory based on a molecular mechanism in the brain interstitium.

2.1. Does a CSF absorption deficit cause hydrocephalus? It would seem intuitively obvious that pressures within the ventricular system would have to be greater than those in the subarachnoid space for ventricular enlargement to occur and yet, some investigators have failed to measure suitable gradients in various models or have measured gradients that were very small [36, 42, 44]. Others have postulated that some factor (possibly a change in compliance) causes the ventricular pulse pressure amplitude to exceed the amplitude of the pulsation in the subarachnoid space (SAS), thus initiating a transmantle pulse pressure gradient and ventricular dilation [12]. The mathematical principles on which this idea is based have been disputed [47] and the idea seems to be falling out of favour. Historically, hydrocephalus has been viewed as a 'plumbing problem' representing (in the communicating type) an imbalance between CSF production and absorption. Since overproduction of CSF is relatively rare [26], many have assumed that an impediment to CSF absorption through the arachnoid projections or extracranial lymphatic vessels increases ventricular pressure and causes ventricular enlargement. This concept, however, is problematic.

In the communicating hydrocephalus model we use, the ventricular and subarachnoid compartments are in communication with one another and thus, pressure would likely increase in both compartments equally if CSF outflow is obstructed. It is, of course, possible that very small transmantle pressure gradients (1 mm Hg or less) induced by some impediment to CSF flow are capable of expanding the ventricles as postulated by Levine [22] and mathematically analyzed in the case of infant hydrocephalus by Wilkie *et al.* [52]. Levine argued that diminutive gradients exist since pressures are diminished towards the periphery of the brain due to the absorption of interstitial fluid into the brain capillaries. The capillary absorption of