The dynamics of brain and CSF growth in normal versus hydrocephalic development in a mouse model

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Introduction: Hydrocephalus has traditionally been clinically quantified by linear measurements of ventricle size, with adjunct use of cortical mantle thickness [1]. However, clinical outcome is related to brain cognitive function, which is more directly related to brain volume than these traditional measures. We sought to quantify the dynamics of brain and ventricular CSF volume growth in normal versus hydrocephalic development in a mouse model using high-field MRI.

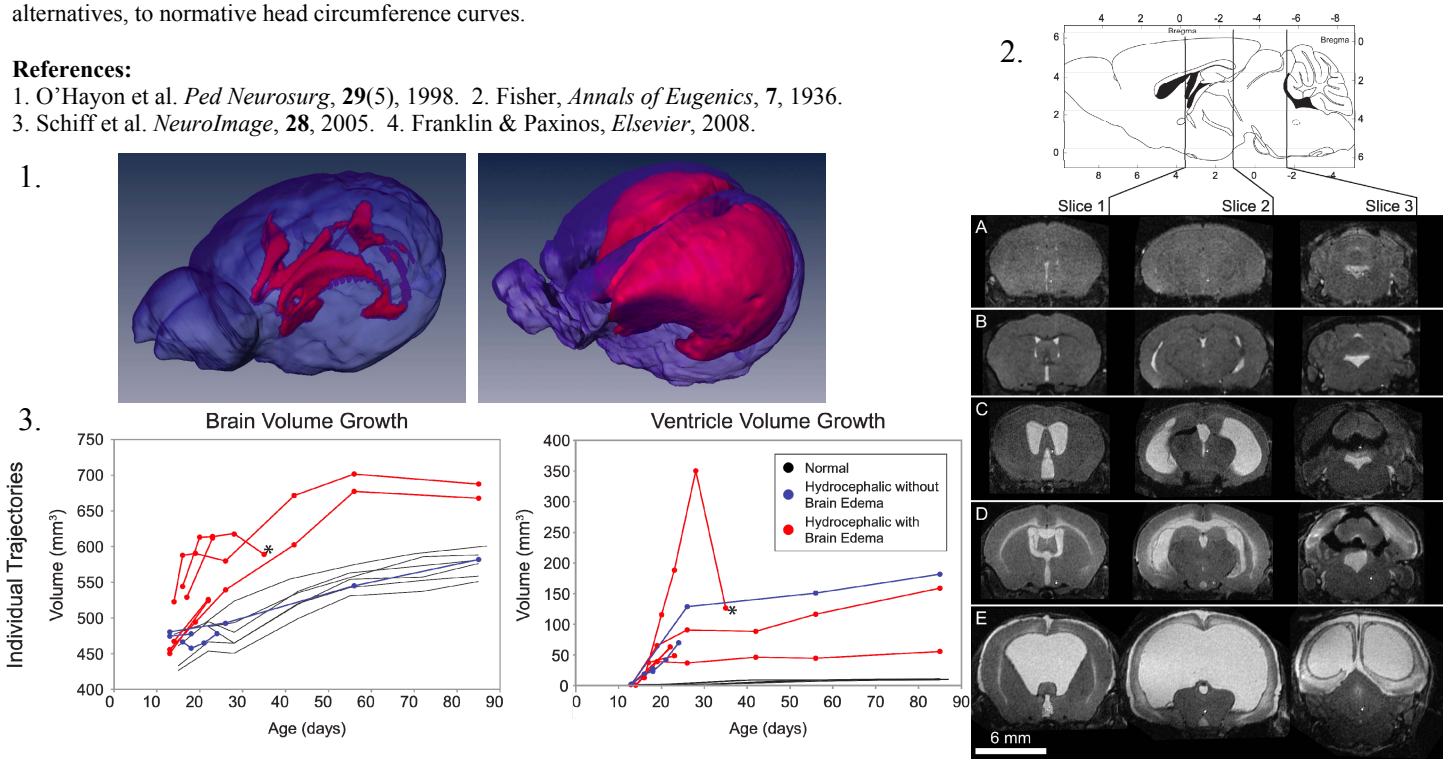
Methods: Hydrocephalus was induced in 14-day-old C57BL/6 mice by percutaneous injection of 10 µl of kaolin solution (250 mg/ml aluminum silicate in 0.9% sterile saline) into the cisterna magna. Anesthetized hydrocephalic (n=9) and normal (n=6) mice were serially imaged from age 2-12 weeks using a custom built surface resonator (2 x 1.7 mm) on a 14.1 tesla MRI system (Varian Inc., Palo Alto, CA). The T2-weighted multi slice (90 slices) spin-echo pulse sequence (TE=30 ms, TR=5 s) comprised an in-plane resolution of 90 µm and a slice thickness of 200 µm. Using 4 averages each experiment took 32 min. Total brain and ventricle volumes were calculated using Amira (Mercury Computer Systems, Inc. Chelmsford, MA), and linear discriminant analysis (LDA) was applied [2,3].

Results: Two very different patters of response were seen in hydrocephalic mice compared with normative growth. In one pattern (n=3), brain growth was normal despite accumulation of CSF and head enlargement, and in the second pattern (n=6) brain growth was faster than normal as CSF volume increased along with parenchymal edema. In this latter pattern, spontaneous rupture of the ventricular system led to a normalization of brain volume, implying edema from trans-mantle pressure gradients. These two patterns of hydrocephalus were significantly discriminable using LDA (Wilks' lambda=0.32, $p<0.01$ by Chi-squared distribution). In contrast, clinically relevant measurements of head circumference or frontal and occipital horn ratios [1] were unable to discriminate between these two patterns of hydrocephalus.

Conclusions: This study is, to our knowledge, the first serial quantification of the growth of brain and ventricle volumes in normal versus hydrocephalic development. Neonatal hydrocephalus can have very different patterns of development, almost impossible to observe with traditional clinical measures. Our findings demonstrate the feasibility of constructing normative curves of brain and fluid growth as compliments, or alternatives, to normative head circumference curves.

References:

1. O'Hayon et al. *Ped Neurosurg*, **29**(5), 1998. 2. Fisher, *Annals of Eugenics*, **7**, 1936.
3. Schiff et al. *NeuroImage*, **28**, 2005. 4. Franklin & Paxinos, *Elsevier*, 2008.



Figures: Panel 1) Volumetric reconstruction of the segmented MR images of a 12-week old normal mouse (left) and a severely hydrocephalic mouse at 4-weeks (right). Blue designates brain and red designates ventricular fluid. **Panel 2)** T2-weighted MR images at locations indicated in the diagram at the top [4]. A normal mouse is shown in rows A & B at 4-weeks and 12-weeks. Row C, D, & E show 4-week-old hydrocephalic mice without edema, with edema in a mild case, and with edema in a severe case, respectively. **Panel 3)** The development of brain (left) and ventricle (right) volumes for all mice individually. Ventricle volumes of all hydrocephalic mice are significantly larger than normal, however, brain volumes are only larger in those hydrocephalic mice with edematous brain. The starred data points show the normalization of volumes of the severely hydrocephalic mouse after spontaneous rupture.