Cerebral viscoelasticity in normal pressure hydrocephalus: Disorder and softening of the mechanical matrix of the brain and its reorganization after shunt treatment.

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Background: Normal pressure hydrocephalus (NPH) represents an epidemiologically important disease with an incidence of 5.5 per 100,000 and a prevalence of 21.9 per 100,000 [1]. The syndrome is characterized by i) a slowly progressive gait disorder, ii) symptomatic dementia and iii) urinary incontinence. Neuroradiological markers are related to the enlargement of the ventricles. While cerebrospinal fluid (CSF) pressures in NPH patients are within normal ranges, drainage of CSF by spinal tap or by shunt operations leads to a transient improvement of the clinical symptoms.
Problem: To date, the underlying mechanism that transmits relatively small CSF pressure peaks into a significant, irreversible ventricular enlargement remains obscure. Several mechanisms have been postulated such as pressure differences between the ventricles and the subarachnoid space of the cerebral convexity, abnormalities of the periventricular brain parenchyma [2] and diminished vascular compliance [3].
Objective: Considering the current theories of NPH, altered mechanical tissue properties seem to play an important role in its pathogenesis. MR elastography (MRE) uniquely allows the measurement of in vivo viscoelastic properties of brain tissue without intervention [4]. Multifrequency vibration MRE can measure the dispersion of the complex shear modulus in a wider dynamic range and therewith reveal structural information related to the micromechanical network of neuronal tissue [5]. First results of MRE in NPH clearly indicate a disease related softening of brain tissue [6].

Methods *Groups*: 19 patients (mean age 70.5 ± 9.5 [SD] years, 11 females) with idopathic NPH were investigated by cerebral multifrequency MRE at two different time points: i) 2-4 days pre-shunt operation and ii) three months after intervention. 25 healthy volunteers (mean age 62.1 ± 7.0 years, 15 females) were recruited as age-matched control group ***Mechanical head stimulation*:** Superposed low-frequency harmonic vibrations of 25, 37.5, 50 and 62.5 Hz were induced by a head cradle connected to a remote vibration generator as introduced in [7]. ***Imaging:*** Experiments were run on a standard 1.5T clinical MRI scanner (Siemens, Erlangen, Germany). 64 transverse phase images were acquired using a single-shot echo-planar imaging sequence sensitized to motion by a sinusoidal gradient in the direction of slice-selection which was composed by four gradient cycles at a center frequency of 60 Hz. On each second scan the polarity of the motion encoding gradient was toggled and the time delay between start of vibration and imaging was increased so that an entire vibration cycle was captured by 32 phase-difference wave images $u(x,y,t)$. ***Image processing:*** Four complex wave images at driving frequency $U(x,y,\omega)$ ($\omega / 2\pi = 25$, 37.5, 50 and 62.5 Hz) where derived from 32 $u(x,y,t)$-images by temporal Fourier decomposition. Complex modulus images were obtained by wave inversion ($G^*(x,y,\omega)=-\rho\omega^2 U/\Delta U$) and spatial averaging. The resulting global modulus function was fitted by the springpot model function $G^*(\omega)=\kappa(i\omega)^\alpha$ with κ and α as variables. κ was transformed to a parameter related to shear elasticity μ taking η = 3.7 Pas as the mean viscosity in healthy brain according to [5]. α is related to the slope of the G^*-dispersion which increases with the degree of freedoms in the micromechanical network [8]. It is thus referred to as micromechanical order parameter.

Results: Due to NPH shear elasticity μ decreased with 0.59 kPa (-21%) from 2.84 kPa to 2.25 kPa. The micromechanical order α decreased about 0.025 (-9%) from 0.287 to 0.258. The decrease of μ was even more pronounced in the periventricular region of the brain ($\Delta\mu$ = -1.2 kPa [-42.4%]). Three month after shunt treatment, shear elasticity μ = 2.27 kPa was still 0.57 kPa (-20%) lower than in controls whereas α significantly increased to 0.279, which is not significantly (p = 0.279) different from α in healthy brain. Figure 1a summarizes the observed NPH-related change of viscoelasticity parameters of brain tissue.

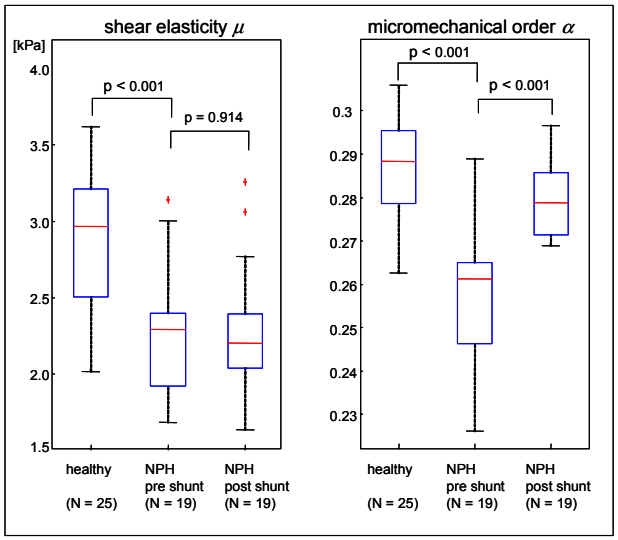

Fig.1: Influence of Normal pressure hydrocephalus (NPH) to brain's mechanical constitution. Elasticity and viscosity of brain parenchyma are given in terms of the parameters μ and α according to the springpot model. NPH is associated with a clear decrease in both shear elasticity and micromechanical order parameter. Tissue rehabilitation is seen in a re-increasing order parameter α while shear elasticity μ remains lower than observed in healthy age-matched controls.

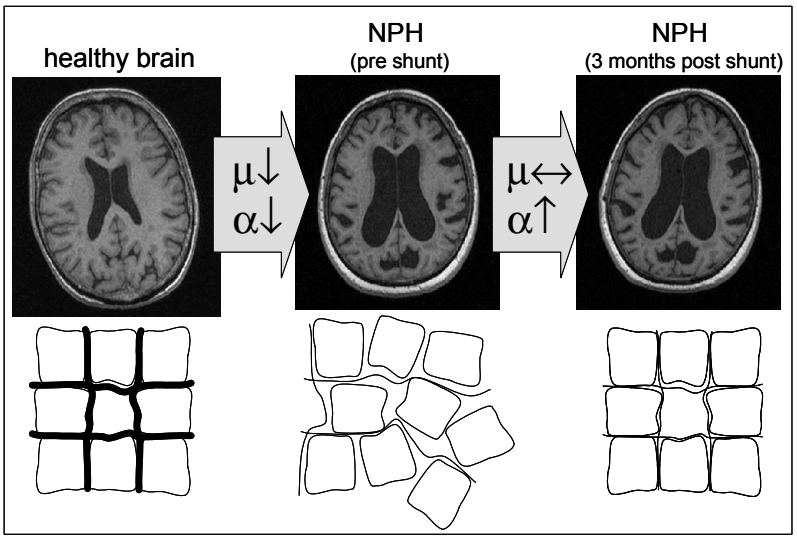

Fig.2: Cerebral imaging in NPH typically shows an enlargement of all ventricles. Our results indicate a degradation of tissue structure that is pronounced in periventricular regions. Since α is related to the geometry of the microstructure, we interpret the observed decrease in α by an increasing disorder in brain tissue in patients prior to shunt treatment. This effect is reversed during tissue repair after shunt placement; however, the tissue remains soft – most presumably since the alignment of the mechanical matrix has reorganized without reestablishing the initial level of cell adhesion and connectivity as present in normal brain tissue.

Discussion: This is the first report of in vivo viscoelastic parameters of the brain in patients suffering from NPH prior and after shunt placement. Our data reveal that NPH affects the mechanical integrity of brain tissue determined by decreased tissue connectivity (μ) and micromechanical order (α). Re-increasing α three month after shunt operation indicates structural re-ordering of brain tissue which is not accessible by morphology-based neuroradiological methods. It remains to be determined to what an extend viscoelasticity markers in NPH can predict functional deficits or therapy outcome.

Literature: [1] Shprecher et al. Current neurology and neuroscience reports 2008;8:371-376. [2] Edwards et al. Brain pathology 2004;14:325-336. [3] Greitz Neurosurgical review 2004;27:145-165; [4] Kruse et al. Neuroimage 2008;39:231-237. [5] Sack et al. Neuroimage 2009;46:652-657. [6] Streitberger et al. NMR in Biomedicine 2010; DOI: 10.1002/nbm.1602. [7] Sack et al. NMR Biomed. 2008;21:265-71. [8] Gurtovenko et al. Advances in Polymer Science 2005;182:171-282.