Differential Diagnosis of Normal Pressure Hydrocephalus by MRI Mean Diffusivity Histogram Analysis

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AJNR Am J Neuroradiol 2013, 34 (6) 1168-1174
doi: https://doi.org/10.3174/ajnr.A3368
http://www.ajnr.org/content/34/6/1168
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ABSTRACT

BACKGROUND AND PURPOSE: Accurate diagnosis of normal pressure hydrocephalus is challenging because the clinical symptoms and radiographic appearance of NPH often overlap those of other conditions, including age-related neurodegenerative disorders such as Alzheimer and Parkinson diseases. We hypothesized that radiologic differences between NPH and AD/PD can be characterized by a robust and objective MR imaging DTI technique that does not require intersubject image registration or operator-defined regions of interest, thus avoiding many pitfalls common in DTI methods.

MATERIALS AND METHODS: We collected 3T DTI data from 15 patients with probable NPH and 25 controls with AD, PD, or dementia with Lewy bodies. We developed a parametric model for the shape of intracranial mean diffusivity histograms that separates brain and ventricular components from a third component composed mostly of partial volume voxels. To accurately fit the shape of the third component, we constructed a parametric function named the generalized Voss-Dyke function. We then examined the use of the fitting parameters for the differential diagnosis of NPH from AD, PD, and DLB.

RESULTS: Using parameters for the MD histogram shape, we distinguished clinically probable NPH from the 3 other disorders with 86% sensitivity and 96% specificity. The technique yielded 86% sensitivity and 88% specificity when differentiating NPH from AD only.

CONCLUSIONS: An adequate parametric model for the shape of intracranial MD histograms can distinguish NPH from AD, PD, or DLB with high sensitivity and specificity.

ABBREVIATIONS: AD = Alzheimer disease; DLB = dementia with Lewy bodies; NPH = normal pressure hydrocephalus; MD = mean diffusivity; PD = Parkinson disease

Normal pressure hydrocephalus is a reversible cause of dementia, incontinence, and gait disturbance in the elderly. Accurate and timely diagnosis is essential to its successful treatment. Diagnosis of NPH can be difficult because the clinical symptoms associated with NPH are common in the elderly and can overlap those of age-related neurodegenerative disorders such as Alzheimer and Parkinson diseases. Nonobstructive enlargement of the cerebral ventricles in NPH can be difficult to distinguish from age- and disease-related ex-vacuo ventricular enlargement by conventional CT and MR imaging techniques. Expert clinical evaluations performed in specialized centers can achieve up to 90% accuracy in identifying shunt-responsive patients with NPH; however, diagnosis of NPH in general practice is much less successful. It has been estimated recently that only 10%–20% of patients with NPH get the appropriate specialized treatment. Recognition of NPH in general practice could be improved if more objective and quantitative imaging methods were available for differential diagnostic and prognostic purposes.

Brain imaging is an integral part of NPH diagnosis. To meet the criteria for probable NPH by international consensus guidelines, one must use brain imaging to document an Evans index (the ratio of the widest diameter of the anterior horn of the lateral ventricle to the transverse intracranial diameter) of ≥0.3. Another imaging sign that has been validated recently as an adjunct to the diagnosis of NPH is disproportionate enlargement of the inferior subarachnoid spaces with tight high-convexity subarachnoid spaces. A number of quantitative imaging biomarkers have also been proposed as aids to NPH diagnosis, such as phase-contrast aqueductal flow measurements, aqueductal stroke volume measurements, and the ratios of ventricular volume to cortical...
thickness, increased DTI fractional anisotropy of periventricular white matter and the basal ganglia, CSF and blood flow, and temporal changes in the apparent diffusion coefficient during the cardiac cycle. The use of these techniques has largely been confined to research studies in specialty centers, and none have been proven to improve the diagnosis of NPH in routine clinical practice.

Alterations in brain-water diffusivity in NPH were first reported nearly 20 years ago. It has been recently reported that region-of-interest-based DTI techniques can distinguish shunt-responsive NPH from other dementias with higher specificity than the Evans index (95% versus 80%).

However, these methods require operator-defined regions of interest, which are subjective and prone to inter-rater variability issues and or require image registration to normative images. Identifying all registration errors is almost impossible, and registration is especially problematic for conditions with large anatomic deformations such as NPH. Problems with registration of patients with NPH have already been reported.

We hypothesized that radiologic differences between NPH and AD/PD can be captured by a robust and objective DTI technique that does not require intersubject image registration or operator-defined regions of interest. To that end, we developed a parametric fitting model for the shape of a whole-brain mean diffusivity histogram applicable in the differential diagnosis of NPH. Histogram approaches are attractive, compared with other diffusion MR imaging analysis methods because of their robustness and reproducibility. These approaches typically do not depend on intersubject registration of images or tissue segmentation and smoothing. Consequently, they are not susceptible to many of the common pitfalls of DTI analysis. NPH is well-suited for MD and smoothing. Consequently, they are not susceptible to many of these methods require operator-defined regions of interest, which are subjective and prone to inter-rater variability issues and or require image registration to normative images. Identifying all registration errors is almost impossible, and registration is especially problematic for conditions with large anatomic deformations such as NPH. Problems with registration of patients with NPH have already been reported.

We hypothesized that radiologic differences between NPH and AD/PD can be captured by a robust and objective DTI technique that does not require intersubject image registration or operator-defined regions of interest. To that end, we developed a parametric fitting model for the shape of a whole-brain mean diffusivity histogram applicable in the differential diagnosis of NPH. Histogram approaches are attractive, compared with other diffusion MR imaging analysis methods because of their robustness and reproducibility. These approaches typically do not depend on intersubject registration of images or tissue segmentation and smoothing. Consequently, they are not susceptible to many of the common pitfalls of DTI analysis. NPH is well-suited for MD and smoothing. Consequently, they are not susceptible to many of the major features of the DTI histograms is a peak below 1E-3 mm²/s, consisting primarily of voxels in the brain parenchyma.

In subjects with enlarged ventricles, a distinctive second peak appears in the MD region above 3E-3 mm²/s (Fig 1, upper right). We observed that the region between 1E-3 mm²/s and 3E-3 mm²/s frequently has a steeper slope in subjects with NPH compared with patients with NPH. This is a consequence of extracellular water accumulated within white matter of patients with NPH (Fig 2). For the overall MD distribution, see On-line Fig 1. The parametric histogram fitting presented in this article is designed to quantify this difference in the histogram slope.

**Analysis Methods**

The parametric model for fitting of the histograms is a modification of the multicomponent model developed by Dyke et al for analyzing pediatric DTI data. The normalized histograms were fitted by a weighted sum of 3 functions representing the brain, CSF, and the brain-CSF partial volume voxels together with brain voxels with high MD:

\[ P(MD) = f_{brain}(MD) + f_{CSF}(MD) + f_{mix}(MD), \]

where

\[ f_{brain}(MD) = \frac{1}{\sqrt{2\pi\sigma_{brain}}} \exp\left[-\frac{1}{2} \left( \frac{MD - \mu_{brain}}{\sigma_{brain}} \right)^2\right], \]

\[ f_{CSF}(MD) = \frac{1}{\sqrt{2\pi\sigma_{CSF}}} \exp\left[-\frac{1}{2} \left( \frac{MD - \mu_{CSF}}{\sigma_{CSF}} \right)^2\right], \]

\[ f_{mix}(MD) = \frac{1}{\sqrt{2\pi\sigma_{mix}}} \exp\left[-\frac{1}{2} \left( \frac{MD - \mu_{mix}}{\sigma_{mix}} \right)^2\right]. \]
and, here introduced, the generalized Voss-Dyke function:

$$P_{\text{VDS}}(MD) = \int_0^1 \frac{1}{\sqrt{2\pi}\sigma_d(t)} \exp \left\{ -\frac{1}{2} \left( \frac{MD - \mu_d(t)}{\sigma_d(t)} \right)^2 \right\} dt,$$

where \( \mu_d(t) = t^\theta \mu_{\text{brain}} + (1 - t^\theta) \mu_{\text{CSF}} \) and

\[ \sigma_d(t) = \sqrt{t^\theta \sigma_{\text{brain}}^2 + (1 - t^\theta) \sigma_{\text{CSF}}^2} . \]

Here \( f_{\text{brain}}, f_{\text{CSF}} \) and \( f_{\text{mix}} \) correspond to histogram fractions of brain parenchyma, CSF, and mixed voxels respectively; \( \mu_{\text{brain}} \) and \( \sigma_{\text{brain}} \) and \( \mu_{\text{CSF}} \) and \( \sigma_{\text{CSF}} \) are the mean and SD of the brain (CSF) Gaussian. The parameter \( \theta \) did not exist in the original Voss-Dyke equation\(^ {17} \) and is introduced here. This parameter encodes the slope of the generalized Voss-Dyke function, as explained below.

The integral on the unit interval in the definition of the generalized Voss-Dyke function, \( P_{\text{VDS}}(MD) \), was approximated by a Gaussian quadrature on 100 points. This integral can be thought of as a sum of 100 Gaussian distributions representing a homotopy from the Gaussian function \( P_{\text{Gauss}}(MD) \) to the Gaussian function \( P_{\text{brain}}(MD) \). Smaller values of \( \theta \) indicate a higher percentage of voxels with MD values close to those of the brain. This parameter creates the possibility of achieving unequal partial volume voxel distributions. In the original Voss-Dyke function, all fractions of partial volume voxels are necessarily equally likely (Fig 3).

Note that patients with NPH have a disproportionately high number of voxels with elevated MD values (but lower than that of the free water in the CSF compartment).\(^ {6,18,20} \) Patients with AD and PD, on the other hand, have an increased number of partial volume voxels (higher \( f_{\text{mix}} \)) and a more proportional distribution of those voxels (higher \( \theta \)). This results in a steeper slope of the middle part of the histogram fit for patients with NPH compared with those with AD and PD (Fig 1) and makes it possible to distinguish patients with NPH from those with AD and PD.

The form of the function \( P_{\text{VDS}}(MD) \) was chosen so that the function \( P(MD) \) is differentiable with respect to \( \theta \), because it is with respect to the other fitting parameters, so the Jacobian is defined. The total number of optimization parameters was \( 8: f_{\text{brain}}, f_{\text{CSF}}, f_{\text{mix}}, \mu_{\text{brain}}, \mu_{\text{CSF}}, \sigma_{\text{brain}}, \sigma_{\text{CSF}}, \theta \). Histogram fitting was performed by in-house-developed software based on the Levenberg-Marquardt algorithm implemented in C.\(^ {29} \) The Levenberg-Marquardt algorithm was iterated until the difference in fitted curves between 2 consecutive iterations was \(<0.1\%\), and it considered fitting adequate (successful) if the absolute difference between a subject’s measured histogram and fitted curve was \(<5\%\) of the total measured data. We initially experimented with modeling the MD histogram by a 9-parameter model consisting of 3 Gaussian functions (one component for brain parenchyma, a second for partial volume voxels, and a third for the CSF compartment),\(^ {20,30} \) but this model failed to adequately model the partial volume component in most patients with NPH. The original Voss-Dyke model\(^ {11} \) improves over the 3-Gaussian model but does not fully capture the shape of the partial volume voxels in adults with NPH (Fig 1, upper right). The effects of the generalization of the Voss-Dyke fitting method in a subject with NPH is shown in the bottom right of Fig 1.

### Classifying Methods

Fitting parameters \( \theta \) and \( f_{\text{mix}} \) were used to construct 2D linear classifiers, one comparing NPH with AD only (group 1: NPH; group 2: AD) and another comparing NPH with all other conditions (group 1: NPH; group 2: AD, PD, DLB). Receiver operating characteristic analysis was performed with a publicly available Matlab package (MathWorks, Natick, Massachusetts).\(^ {31} \) The re-
RESULTS

Generalized Voss-Dyke fitting was successful for all subjects (ie, the absolute difference between the subject’s measured histogram and fitted curve was <5% of the total measured histogram). The basic statistics on all of the fitting parameters and average MD (over the whole histograms) are shown in Table 1.

Classification Power

We compared 2 variants of binary classifiers: comparing patients with NPH with patients with AD only,1 and comparing patients with NPH with all other patient groups jointly (group 1: NPH; group 2: AD, PD, DLB).2 The 2 patients diagnosed both with NPH and AD appear at the top right corner of Fig 4. These patients have a relatively flat distribution of MD values, coming from a combined effect of cerebral atrophy and high MD within the brain parenchyma.

Outliers

The patient with NPH in the top left corner of the Fig 3, misclassified by our method, is an 82-year-old man with a small

![Graph showing the comparison of different classifiers and indices for NPH, AD, and DLB groups.](image)
hemorrhagic infarct in the left thalamus and an atrophic left hippocampus. The other misclassified patient with NPH was a relatively young (63 years of age) female patient with extensive microvascular ischemic disease. The patient with AD within the NPH region in Fig 4 is the oldest one in the patients with AD cohort: an 85-year-old woman with comorbid cerebrovascular disease.

Other Fitting Parameters

The most conspicuous parameter of the MD histograms, location of the raw data histogram peak, was, on average, at the same position for the patients with NPH (mean, 8.05E-4/11006 2.5E-5 mm2/s), AD (mean, 8.02E-4 3.0E-5 mm2/s), and PD/LBD (mean, 8.08E-4 3.5E-5 mm2/s) and did not yield specificity in distinguishing NPH.

Parameter fCSF was elevated in NPH and AD compared with patients with PD/LBD (Table 1). This parameter alone yielded relatively good results in differentiating NPH from all the other conditions (sensitivity, 87%; specificity, 68%) but was not a particularly good indicator of NPH compared with AD (sensitivity, 73%; specificity, 56%). This is in line with results reported in Klassen and Ahlskog, in which a more detailed analysis of ventricle size was performed, and it was argued that the ratio of ventricular volume to cortical thickness is required to distinguish ventricular enlargement in NPH from ex-vacuo expansion in AD.

Parameter μCSF had a mean value of 3.1E-3 ± 1.6E-4 mm2/s over the entire subject population. This corresponds to the well-known MD value for unrestricted water. We found no relationship between the patient diagnoses and μCSF (Table 1).

DISCUSSION

The pathophysiology of NPH includes alterations in the distribution of water between and within the brain parenchymal and CSF compartments. Increased transependymal movement of CSF from the ventricles into the interstitial spaces of the brain may account for the alterations of white matter MD previously reported, as well as the changes in the MD histogram observed in the present study. Other contributors may include increased intraparenchymal CSF production and decreased cerebral perfusion or physical distortion of brain tissue secondary to ventriculomegaly. Further studies are needed to better understand the origins of altered intracerebral water diffusivity in NPH.

MD Histogram Fitting

An often-cited downside of the MD histogram approaches is CSF “contamination,” (ie, inadvertent inclusion into histograms of partial volume voxels with variable amounts of parenchymal and CSF contributions). However, this is actually valuable information for NPH diagnostics because cerebral atrophy and the abnormal intermingling of free water and brain parenchyma occurs to a pathologic degree in NPH. This can be readily appreciated from a comparison of the MD histograms of a healthy control, a patient with NPH, and a patient with AD (Fig 1).

As explained in the “Materials and Methods” section, the original Voss-Dyke method operates under the assumption that all partial volume fractions are possible and equally likely. This adequately modeled MD data from children with late infantile neuronal lipofuscinosis, in whom ventricle size is actually larger (relative to the brain size) than that in the NPH population. Furthermore, in the case of patients with NPH, there are voxels fully within white matter with elevated MD values, but still closer to the MD values for the rest of parenchyma than to the MD values of unrestricted water (Fig 2). This situation is better modeled with the generalized form of the Voss-Dyke function.

Classification

The misclassified patients were at the extremes of their patient group age range, suggesting that age should be considered
as a predictor variable. It has been argued recently, in several large studies, that effects of aging on MD obey a quadratic law ($MD = \alpha + \beta_1 \cdot age + \beta_2 \cdot age^2$), with MD decreasing from birth to approximately 40 years of age and then increasing after 40 years of age. Although our data sample was too small for a rigorous age- and sex-matched analysis, we performed multivariate first order $\theta_{\text{AD}} = \alpha + \beta_1 \cdot f_{\text{mix}} + \beta_2 \cdot age + \beta_3 \cdot age^2$ regression analysis to test for possible dependence of $\theta$ on patient ages and $f_{\text{mix}}$ as independent predictors. As expected, these models did not achieve the necessary $P$ value (.05) to justify introduction of age and age$^2$ as predictor variables. With linear regression, the coefficients for the NPH group were $\theta_{\text{MIBH}} = -0.25 + 1.37 \cdot f_{\text{VD}} + 0.002 \cdot age$, and for AD $\theta_{\text{AD}} = -0.68 + 1.91 \cdot f_{\text{mix}} + 0.006 \cdot age$, indicating potentially stronger dependence on age in patients with AD.

One limitation of this study is that it did not include age-matched healthy subjects or patients with certain other disorders that could affect MD (stroke, uncontrolled hypertension, chronic kidney disease, and so forth). Studying a larger set of healthy and disease controls will allow developing a regression model for the effects of aging. A prospective validation study is needed to rigorously determine the positive and negative predictive values of this method. The effects of different magnetic field strengths and other acquisition parameters remain to be studied but are unlikely to alter the fundamental findings. It is quite likely that method accuracy can be further improved with a more sophisticated classification model that would include other proposed NPH biomarkers obtainable from diffusion MR imaging and T1 MR imaging data. However, higher model sophistication also leads to higher probability of undetected processing errors. Note that the proposed method is fully programmable and does not require user intervention. Most of the previously proposed quantitative NPH imaging biomarkers are operator-dependent and/or have less classification power than is obtained with the generalized Voss-Dyke function.

**CONCLUSIONS**

We developed a novel parametric model for the DTI MD histogram fitting, named the generalized Voss-Dyke function, which is highly successful in segregating patients with NPH from potential confounders without reliance on operator-dependent region-of-interest analyses or intersubject registration. While additional prospective validation is needed and some of the important confounders such as advanced vascular disease have to be considered separately, the presented results provide considerable cause for optimism that this technique can be used to summarize diffusivity changes in NPH and help distinguish NPH from neurodegenerative disorders and other potential diagnostic confounders.

**Disclosures:** Milos Ivkovic—RELATED: Grant: National Institutes of Health, National Institute of Neurological Disorders and Stroke. Comments: F32 fellowship. Fayeza Ahmed—RELATED: Grant: Leon Levy Foundation.* Dana Moore—RELATED: Grant: Hydrocephalus Association Young Mentor Investigator Award.* Comments: I am the primary investigator on this grant. Norman Relkin—RELATED: The Leon Levy Foundation,* Comments: I was principal investigator on a grant from the Leon Levy Foundation for development of new biologic and imaging-based markers of normal pressure hydrocephalus. The work described in this article was supported by that grant. UNRELATED: Consultancy: I am advisor to Eisa Research and Kyowa Kirin Pharma. Comments: My consultancies are unrelated to this manuscript; Grants/Grants Pending: Baxter,* National Institute on Aging,* Payment for Lectures (including service on Speakers Bureaus): American Austria Foundation, European College of Neuropsychopharmacology. Comments: I have received payment for invited lectures unrelated to the present manuscript.* Money paid to the institution.

**REFERENCES**


