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CSF dynamics disorders: Association of brain MRI and nuclear medicine cisternogram findings

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ABSTRACT

Disproportionately enlarged subarachnoid space hydrocephalus (DESH), characterized by ventriculomegaly, high convexity/midline tight sulci, and enlarged sylvian fissures on brain MRI has been increasingly recognized as a distinct diagnostic imaging entity that falls within the larger category of idiopathic normal pressure hydrocephalus. Normal pressure hydrocephalus has been previously characterized as a CSF dynamics disorder based on abnormalities on nuclear medicine cisternography: radiotracer in the lateral ventricles and absent or delayed ascent of radiotracer over the cerebral convexity. The purpose of this work was to evaluate for differences in nuclear medicine cisternography between patients with vs without DESH and thereby provide support for the concept that DESH is a structural imaging marker of a CSF dynamics disorder. The study included 102 patients (mean age 71 years, range 46–86, 38 females), 58 patients with cisternogram performed to evaluate suspected normal pressure hydrocephalus (mean age 73 years, range 46–86 years, 24 female) and 44 patients evaluated for headache (mean age 68 years, range 60–82 years, 14 female). All patients had an MRI of the brain performed within 13 months of the cisternogram. Cisternogram imaging, typically acquired at 0.5, 1, 2, 4, and 24 h post injection, was evaluated for the time at which radiotracer reached the basal cisterns, presence of persistent radiotracer in the lateral ventricles, time radiotracer first entered the lateral ventricles, presence of radiotracer over the cerebral convexity, and time at which radiotracer was first visualized over the cerebral convexity. MRI features of ventriculomegaly (defined as Evans' index $\geq$ 0.3) and high convexity tight sulci (HCTS) were recorded. Based on the MRI features, patients were grouped according to presence or absence of DESH (ventriculomegaly and HCTS). Those without DESH were separated into groups of ventriculomegaly alone, HCTS alone, and neither ventriculomegaly nor HCTS. Cisternogram metrics were compared between MR-defined groups. Patients with DESH showed a higher frequency of radiotracer in the lateral ventricles and delayed or absent ascent over the cerebral convexity compared to those without DESH, higher frequency of ventricular radioactivity vs those with HCTS alone, and shorter time to ventricular radioactivity compared to those with ventriculomegaly alone. Patients with ventriculomegaly or HCTS alone had a higher frequency of radiotracer in the lateral ventricles and delayed ascent of radiotracer over the cerebral convexity compared to those with neither ventriculomegaly nor HCTS. These findings support DESH and the individual components of ventriculomegaly and HCTS as markers of disordered CSF dynamics.

Abbreviations: DESH, disproportionately enlarged subarachnoid space hydrocephalus; HCTS, high convexity tight sulci; NPH, normal pressure hydrocephalus; NM, nuclear medicine.

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1. Introduction

Disproportionately enlarged subarachnoid space hydrocephalus (DESH), characterized by ventriculomegaly, high convexity/midline tight sulci (HCTS), and enlarged sylvian fissures on brain MRI is thought to result from disordered CSF dynamics (Hashimoto et al., 2010; Kitagaki et al., 1998). In the Japanese population, DESH is often used in the diagnostic criteria for idiopathic normal pressure hydrocephalus (iNPH) (Mori et al., 2012), a condition characterized by the classic clinical triad of cognitive decline, gait impairment, and urinary incontinence (Adams et al., 1965). The DESH imaging features have been shown to correlate with shunt-responsive hydrocephalus in some reports (Hashimoto et al., 2010; Narita et al., 2016) but not all (Ahmed et al., 2018).

While DESH as a subcategory of NPH has been more recently described, NPH has been previously characterized by other imaging markers of abnormal CSF dynamics, including abnormal radiotracer distribution on nuclear medicine (NM) cisternography. NM cisternography in patients with NPH demonstrates persistent radioactivity in the ventricles with absence of the normal ascent of radiotracer over the cerebral convexities on delayed imaging (James et al., 1970; McCullough et al., 1970; Patten and Benson, 1968). These findings on cisternography have also been shown to correlate with shunt-responsive hydrocephalus (Larsson et al., 1990; McCullough et al., 1970).

DESH may be more common than initially realized. Recently, DESH MR features have been assessed in population-based studies (Akiba et al., 2020; Graff-Radford et al., 2019). DESH MRI features were present in approximately 6% of the elderly population and were associated with cognitive impairment. Therefore, determining whether the DESH imaging pattern on MRI is associated with independent indicators of CSF dynamics has clinical relevance. While abnormal radiotracer distribution on NM cisternography is a marker of a CSF dynamics disorder, the correlation between this and MR features of DESH has not been studied; thus the pathophysiology behind DESH features has not been well elucidated.

The objective of this study was to determine if there were differences in radiotracer distribution on NM cisternography between patients with vs without DESH MRI features. We hypothesized that cisternogram metrics of radiotracer in the lateral ventricles and delayed or absent ascent over the cerebral convexity will be seen more often in those patients with DESH vs those without DESH.

2. Methods

2.1. Patients

Patients who had previously undergone nuclear medicine cisternography were retrospectively identified using the Mayo Clinic Medical Record Linkage system. We identified two groups of patients: one group of patients with indication "hydrocephalus" in whom the cisternogram was performed to evaluate suspected NPH; the other group with a clinical presentation of "headache" in whom the cisternogram was performed to evaluate for a possible CSF leak but in whom none was found. The latter group was then intended to serve as a reference point of individuals who were expected to have normal CSF dynamics. The inclusion criteria were cisternogram performed between years 2000 and 2017 and brain MRI within 13 months of the cisternogram. The rationale for this date range was that imaging exams prior to 2000 were not accessible for review, and after 2017 NM cisternography use became more targeted to difficult cases during a period of radiotracer shortage. Due to the relatively large number of cisternograms performed to evaluate headache in young adults, we further limited this search to patients age 60 years and older to better match the age of the patients in the hydrocephalus group. Exclusion criteria were secondary hydrocephalus, prior shunt placement, clinical diagnosis of CSF hypotension, and imaging findings of CSF leak on myelography or cisternogram, per radiology report or on image review for this study.

2.2. Chart review

The medical record was reviewed for demographic and clinical data. Demographic information included sex and age at time of cisternogram. Clinical data included cognitive, gait, or urinary impairment as recorded in the initial neurology consultation note that prompted the cisternogram to be performed. Cognitive impairment was defined as short test of mental status score < 34 on a 38-point scale (Townley et al., 2019). If the short test of mental status exam was not recorded, a clinical diagnosis of mild cognitive impairment or dementia was used as the indicator of cognitive impairment. Gait impairment was determined by any recorded gait abnormality on the neurologic exam or the clinical diagnoses. Urinary impairment was determined via the clinical history and diagnoses.

2.3. MRI review

One neurologist (NG-R) with over 30 years of experience in the field of NPH and prior validation of DESH findings (Graff-Radford et al., 2019) performed MRI review blinded to the clinical information and cisternogram findings. The following MRI features were assessed as present or not: ventriculomegaly, high convexity/midline tight sulci, focal sulcal dilation, and sylvian fissure enlargement. Ventriculomegaly was defined as an Evans' index ≥ 0.3 measured on the axial T2-*weighted* FLAIR sequence; the Evans' index is the ratio of the widest width of the frontal horns of the lateral ventricles to the widest width of the inner table of the skull. HCTS was defined as crowding of the sulci near the midline vertex relative to sulci elsewhere. Focal sulcal dilation and sylvian fissure enlargement were defined as sulcal or sylvian fissures that were noticeably larger than adjacent sulci. If a patient had multiple brain MRIs, the MRI performed nearest to the cisternogram and prior to intervention (e.g. shunt placement) was used for evaluation. All available imaging sequences, including sagittal and/or axial T1-*weighted* and axial T2-*weighted* FLAIR, from that exam were reviewed. The MR findings were used to categorize patients as DESH or not DESH, with DESH defined as ventriculomegaly and HCTS (Hashimoto et al., 2010; Kitagaki et al., 1998; Mori et al., 2012). Patients without DESH were categorized as isolated ventriculomegaly, HCTS, or neither. Representative examples are shown in Fig. 1.

2.4. Cisternogram review

The cisternogram acquisition times were at approximately 0.5, 1, 2, 4, and 24 h; some patients also had imaging at approximately 6 and 48 h. Two nuclear medicine radiologists (CHH, DRJ), blinded to the clinical information and MRI, in consensus reviewed images to determine the time of the study at which the radiotracer first reached the basal cisterns, presence of radiotracer in the lateral ventricles, time of the study at which the radiotracer first entered the lateral ventricles, whether or not radiotracer persisted in the lateral ventricles on subsequent time points, presence of radiotracer over the cerebral convexity during the imaging observation period, and the time of the study at which radiotracer was first visualized over the cerebral convexity (Fig. 1). Finally, the readers individually determined if taking these findings together, they would give an overall clinical impression of findings of normal pressure hydrocephalus or not. Disagreement in clinical impression was resolved by consensus review.

2.5. Standard protocol approvals, registrations, and patient consents

The study was approved by the Mayo Clinic Institutional Review Board.

2.6. Statistical analysis

As the goal of this work was to perform an imaging to imaging comparison, the primary analyses assessed for differences in cisternogram metrics among all patients (indication NPH and headache) categorized by MRI findings. First, we evaluated for differences in the above cisternogram metrics between all patients with DESH vs without DESH. The time at which radiotracer first entered the basal cisterns, frequency of persistent radiotracer activity in the lateral ventricles, time at which radiotracer entered the lateral ventricles, frequency of radiotracer over the cerebral convexity, time at which radiotracer was first visualized over the convexity, and frequency of an overall impression of abnormal cisternogram were compared between groups. Only persistent ventricular radioactivity was considered positive for ventricular radioactivity, and the time to ventricular radioactivity was only calculated for patients with persistent ventricular radioactivity, as transient radioactivity may be seen in normal cases (McCullough et al., 1970). Clinical measures of frequency of cognitive, gait, and urinary impairment were also compared between groups. Wilcoxon rank sum tests were used to test for differences between groups on time variables and chi-squared tests were used to assess differences between binary (present/absent) variables. Statistical significance was defined as $p < 0.05$. Similar analyses were performed in the subgroup of patients with DESH to assess for difference in cisternogram metrics between those patients with vs without focal sulcal dilation or enlargement of the sylvian fissures.

To evaluate effects of individual MR features of ventriculomegaly and HCTS, the above cisternogram metrics were compared between patients with DESH, ventriculomegaly alone, HCTS alone, and neither ventriculomegaly nor HCTS. Pairwise group comparisons were performed using Wilcoxon rank sum tests for time variables and chi-squared

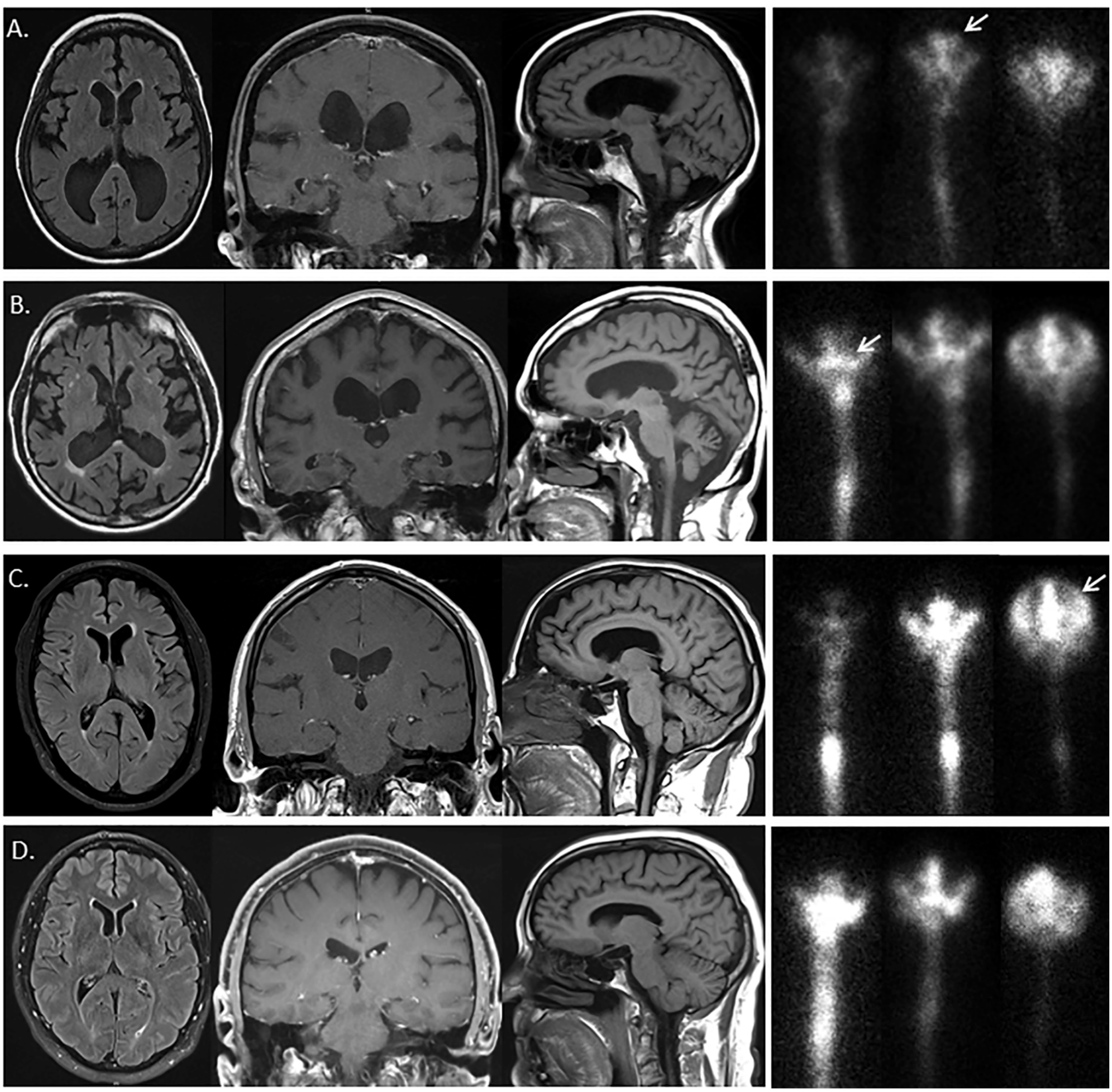

Fig. 1. Representative cases. Images from four patients, shown from left to right: axial T2 FLAIR at the level of the lateral and third ventricles, coronal T1 post-contrast or T2 FLAIR at the level of the posterior commissure, sagittal T1-*weighted* images off midline, and anterior projection cisternogram views of the head and upper spinal canal at 2, 4, and 24 h. (A.) 65-year-old man with DESH. Radiotracer was at the basal cisterns at 2 h, lateral ventricles at 4 h (arrow, A) and did not ascend over the convexity at 24 h. (B.) 78-year-old man with ventriculomegaly but no HCTS. Radiotracer was at the basal cisterns at 2 h (arrow, B), lateral ventricles at 4 h, and ascended over convexity at 24 h. (C.) 70-year-old man with HCTS alone. Radiotracer was at the basal cisterns at 2 and 4 h, transiently entered the lateral ventricles at 6 h (not shown), and ascended over the convexity at 24 h (arrow, C). (D.) 63-year-old man with neither ventriculomegaly nor HCTS. Radiotracer was in the basal cisterns at 2 h, unchanged at 4 h, and ascended over convexity at 24 h; radiotracer did not enter the lateral ventricles.

tests for binary variables.

Analyses were repeated considering only those patients for whom cisternogram was performed to evaluate suspected NPH. Statistical comparisons were not performed between the "no DESH" subgroups due to small sample sizes.

Finally, the percent agreement and Cohen Kappa for overall diagnosis were calculated between the cisternogram readers.

2.7. Secondary analyses

Although the primary goal of this study was to assess the association between cisternogram and MR findings of CSF dynamics disorders, we also assessed for a difference in cisternogram metrics and MR features between the patients undergoing clinical evaluation for suspected NPH vs headache.

3. Results

3.1. Patients

We identified 93 patients with a cisternogram performed to evaluate for "hydrocephalus" and 79 patients with a cisternogram indication of "headache". A total of 70 (41%) patients were excluded for prior shunt placement, secondary hydrocephalus, clinical diagnosis of CSF hypotension, or NM cisternogram findings suggestive of CSF leak. The total number of patients included in further analysis was 102 (mean age 71 years, range 46–86, 38 females), 58 patients with cisternogram performed to evaluate suspected NPH (mean age 73 years, range 46–86 years, 24 female) and 44 patients evaluated for headache (mean age 68 years, range 60–82 years, 14 female). Of the patients who presented with suspected NPH, 34 (59%) had cognitive impairment, 55 (95%) gait impairment, and 35 (60%) urinary impairment. Of the patients who presented with headache, 3 (7%) had cognitive impairment, 7 (16%) gait impairment, and none urinary impairment. Clinical assessment of cognitive, gait, and urinary impairment was missing for two patients in the headache group. The MR was performed on average 2.0 ± 2.9 months prior to the cisternogram (median < 1 month MR prior to cisternogram, range MR 13 months prior to 2 months after the cisternogram).

3.2. MR review

Patient categorization based on MR features is shown in Fig. 2. On MR review, 61/102 (60%) patients had ventriculomegaly based on the Evans' index and 49/61 (80%) of these patients also had HCTS and therefore a designation of DESH. Among the cases without ventriculomegaly by the Evans' index, HCTS was uncommon (6/41, 15%). Focal sulcal or sylvian fissure enlargement was present in 38/49 (78%) of patients with DESH, 4/6 (66%) of patients with HCTS alone, 4/12 (33%) patients with ventriculomegaly alone, and 1/35 (3%) of patients with neither ventriculomegaly nor HCTS.

3.3. Cisternogram review

Among 102 patients, 52 (51%) cisternogram exams were judged to be overall compatible with findings of NPH. A total of 52 (51%) cases showed persistent radiotracer uptake in the lateral ventricles and 16 (16%) lack of ascent over the cerebral convexities. The median time for radiotracer to reach the lateral ventricles was 2 hrs and ascend over the cerebral convexity, 24 hrs.

3.4. Cisternogram ratings

The cisternograms readers agreed on overall impression of normal vs abnormal cisternogram in 96/102 cases giving an interrater agreement of 94% and a Cohen Kappa statistic of 88%.

3.5. Cisternogram and clinical findings in patients with vs without DESH

When considering all patients, those with DESH showed a higher frequency of persistent radiotracer in the lateral ventricles than those without (41/49, 84% vs 11/53, 21%; $p < 0.001$); when radiotracer did enter the lateral ventricles, the time to first appearance in the lateral ventricles was insignificantly shorter (median (25th, 75th percentile): 2 (1,4) vs 3 (2,5) hrs; $p = 0.23$) (Table 1). Patients with DESH also more frequently lacked normal ascent of radiotracer over the cerebral

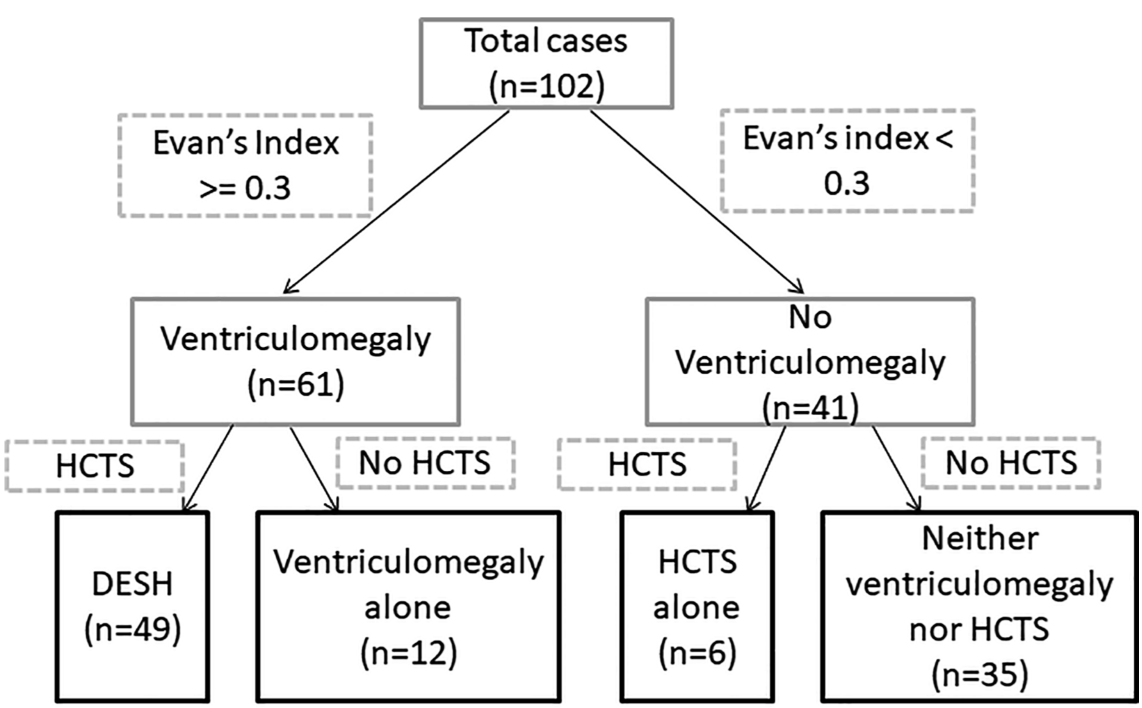

Fig. 2. Patient categorization based on MRI criteria.

Table 1
Comparison of cisternogram and clinical metrics between all patients with vs without DESH and respective p values (columns 1–3); the patients without DESH were further divided into three groups: ventriculomegaly alone (Ventric), high convexity tight sulci (HCTS) alone, and neither ventriculomegaly nor HCTS (columns 4–6). The median and interquartile ranges are reported for the time metrics and number (percentage) for the binary metrics.

All Patients (n = 102)	DESH(n = 49)	No DESH(n = 53)	P value	Ventric.(n = 12)	HCTS(n = 6)	Neither(n = 35)
Demographics and clinical						
Age (years)	74 (68,81)	69 (63,77)	0.03	80 (76,82)	71 (65,79)	67 (62,72)
Cognitive impairment	31 (63%)	6 (11%)	<0.001	4 (33%)	0	2 (6%)
Gait impairment	44 (90%)	18 (34%)	<0.001	8 (67%)	5 (83%)	5 (14%)
Urinary impairment	29 (59%)	6 (11%)	<0.001	3 (25%)	3 (50%)	0
Cisternogram indication NPH	45 (92%)	13 (25%)	<0.001	6 (50%)	5 (83%)	2 (6%)
Cisternogram metrics						
Time to basal cisterns (hr)	2 (1,4)	2 (1,6)	0.26	2 (1,4.5)	2 (1,6)	2 (1,6)
Persistent ventricular radioactivity	41 (84%)	11 (21%)	<0.001	8 (67%)	2 (33%)	1 (3%)
Time to ventricles (hr)*	2 (1,4)	3 (2,5)	0.23	4 (2,6)	2	2
Over convexity	35 (71%)	51 (96%)	0.002	11 (92%)	6 (100%)	34 (97%)
Time to convexity (hr)**	48 (24,48)	24 (24,48)	<0.001	24 (24,48)	24 (24,48)	24 (24,24)
Subjective NPH findings	41 (84%)	11 (21%)	<0.001	8 (67%)	2 (33%)	1 (3%)

* Summary statistic is among those in whom the radiotracer entered the lateral ventricles.
** Summary statistic is among those in whom the radiotracer ascended over the cerebral convexity.

convexity (14/49, 29% vs 2/53, 4%; $p = 0.002$). When radiotracer did ascend over the cerebral convexity it was delayed in the DESH group (48 (24,48) vs 24 (24,48) hrs; $p < 0.001$); the difference in time for radiotracer to reach the convexity remained statistically significant between groups when including patients without radiotracer ascent over the convexity in the Wilcoxon rank sum. Time for radiotracer to reach the basal cisterns was similar between groups (2 (1,4) vs 2 (1,6); $p = 0.26$). Clinically, a majority of the DESH group had cognitive, gait, and urinary impairment, and the symptoms were more than twice as common in those with DESH vs those without ($p < 0.001$). When the DESH group was divided into those with vs without focal sulcal dilation or enlarged sylvian fissures, there was no significant difference in cisternogram or clinical measures between groups (Supplemental Table 1).

3.6. Cisternogram findings in the four different MR defined groups

When all 102 patients in the study were further divided into groups of DESH, ventriculomegaly alone, HCTS alone, and neither ventriculomegaly nor HCTS, the largest difference in cisternogram measures was between the patients with DESH and those with neither ventriculomegaly nor HCTS (Table 1). Compared to patients with neither ventriculomegaly nor HCTS, patients with DESH showed a much higher frequency of persistent radiotracer in the lateral ventricles (41/49, 84% vs 1/35, 3%; $p < 0.001$), less frequent radiotracer over the convexity (35/49, 71% vs 34/35, 97%; $p = 0.006$), delayed ascent over the convexity when present (48 (24,48) vs 24 (24,48) hrs; $p < 0.001$), and overall much greater frequency of a subjectively abnormal cisternogram (41/49, 84% vs 1/35, 3%; $p < 0.001$). Compared to patients with ventriculomegaly alone, patients with DESH appeared to show a shorter time to radiotracer in the lateral ventricles (2 (1,4) vs 4 (2,6) hrs; $p = 0.06$). Compared to those with HCTS alone, patients with DESH had a higher frequency of persistent radiotracer in the lateral ventricles and a subjectively abnormal cisternogram (41/49, 84% vs 2/6, 33%; $p = 0.02$). Compared to those with neither ventriculomegaly nor HCTS, patients with ventriculomegaly alone had a higher frequency of persistent radiotracer in the lateral ventricles (8/12, 67% vs 1/35, 3%; $p < 0.001$), delayed ascent of radiotracer over the cerebral convexity (24 (24,48) vs 24 (24,24) hrs; $p < 0.001$), and higher frequency of a subjectively abnormal cisternogram (8/12, 67% vs 1/35, 3%; $p < 0.001$). Patients with HCTS alone similarly had delayed radiotracer over the convexity (24, (24,48) vs 24 (24,24) hrs; $p < 0.001$) compared to those with neither ventriculomegaly nor HCTS; frequency of persistent radiotracer in the lateral ventricles (2/6, 33% vs 1/35, 3%; $p = 0.07$) and subjectively abnormal cisternogram (2/6, 33% vs 1/35, 3%; $p = 0.07$) were also higher in patients with HCTS though did not reach statistical significance. The time metrics are summarized in Figs. 3–5A.

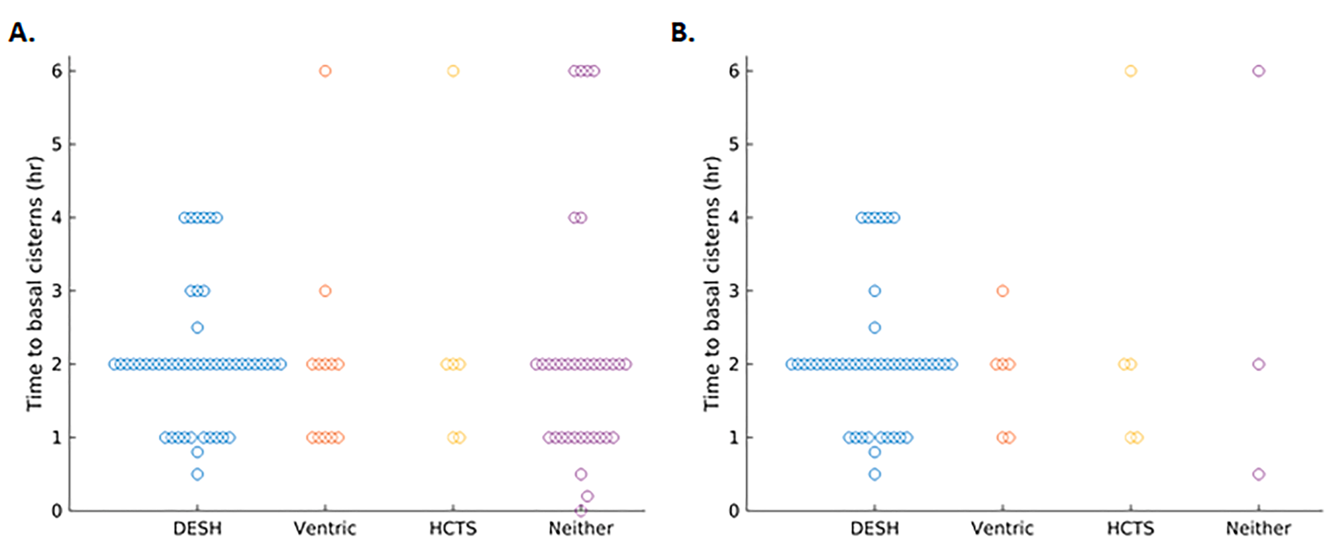

Fig. 3. Dot plots of time for radiotracer to reach the basal cisterns for (A) all patients and (B) patients evaluated for suspected NPH. There was no significant difference in time to the basal cisterns among patients with DESH, ventriculomegaly (ventric), high convexity tight sulci (HCTS), and neither; median time to the basal cisterns was 2 h for all groups.

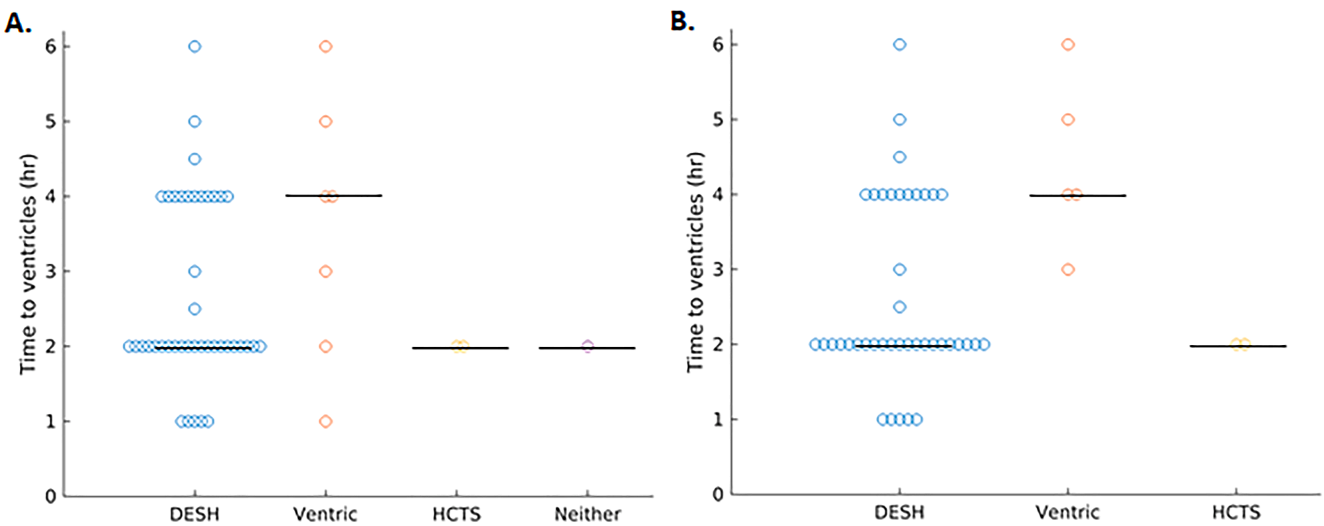

Fig. 4. Dot plots of time for radiotracer to reach the lateral ventricles in patients with abnormal persistent radiotracer in the lateral ventricles for (A) all patients and (B) those with suspected NPH. In (A) one patient with ventriculomegaly alone with time to ventricular radioactivity of 24 h is not displayed. Median values are denoted by the black lines. Patients with ventriculomegaly had a longer median time for radiotracer to reach the ventricles compared to other groups, though comparisons did not reach statistical significance.

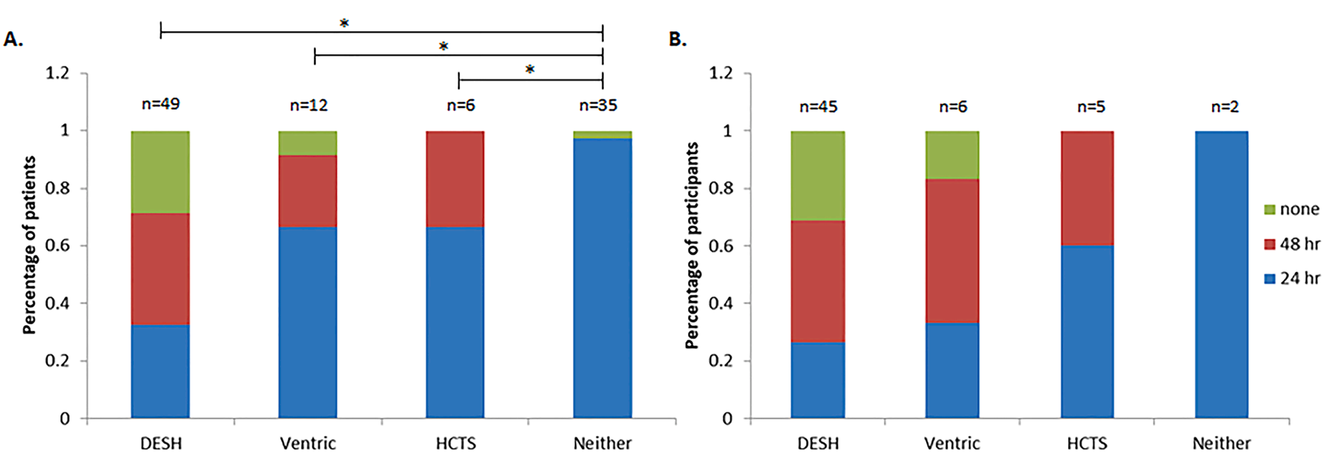

Fig. 5. Distribution of time for radiotracer to ascend over the cerebral convexity in (A) all patients and (B) patients with suspected NPH. A time of 24 h is considered normal, 48 h delayed, and radiotracer not visualized over the convexity at 24 or 48 h (none) abnormal. Ventric = ventriculomegaly. HCTS = high convexity tight sulci. * $p < 0.05$.

3.7. *Clinical findings in the four different MR defined groups*

Among all patients in the study, clinical metrics were also different between the four MR defined groups. Compared to those with neither ventriculomegaly nor HCTS, patients with DESH were older (74 (68,81) vs 67 (62,72) years; p = 0.03) and had a much higher frequency of cognitive, gait, and urinary impairment ($p < 0.001$). Compared to those with HCTS alone, patients with DESH had a higher frequency of cognitive impairment (31/49, 63% vs 0%; p = 0.01). Those with ventriculomegaly alone and HCTS alone showed a higher frequency of gait and urinary impairment compared to patients with neither ($p < 0.001$ to p = 0.02).

3.8. *Cisternogram and clinical findings among only patients with suspected NPH*

Considering only those patients for whom cisternogram was performed to evaluate for suspected NPH, cisternogram findings differed between patients with DESH (n = 45) and without DESH (n = 13) in a similar fashion as described for all patients. However, clinical parameters showed fewer differences between MR defined groups. Compared to patients without DESH, those with DESH showed a higher frequency of persistent radiotracer in the lateral ventricles (41/45, 91% vs 7/13, 54%; p = 0.007) and there was a higher frequency of a subjectively abnormal cisternogram (41/45, 91% vs 7/13, 54%; p = 0.007) (Table 2). Time for radiotracer to reach the lateral ventricles and frequency of radiotracer ascent over the cerebral convexity also differed between those with and without DESH but did not reach statistical significance (time to ventricles 2 (1,4) vs 4 (2,6) hrs; p = 0.07 and frequency of radiotracer over the convexity 31/45, 69% vs 12/13, 92%, p = 0.18, DESH vs without DESH). Those with DESH had a higher frequency of urinary impairment compared to those without DESH (29/45, 64% vs 6/13, 46%; p = 0.007) and trended toward more frequent cognitive impairment (30/45, 67% vs 4/13, 31%; p = 0.05).

When the patients with suspected NPH and without DESH were divided into subgroups of ventriculomegaly alone, HCTS alone, and neither, formal statistical comparisons were not performed due to low numbers. Compared to patients with ventriculomegaly alone, those with DESH appeared to have a shorter time for radiotracer to enter the lateral ventricles when ventricular radioactivity was present (2 (1,4) vs 4 (3,6)

Table 2
Comparison of cisternogram and clinical metrics in patients with suspected NPH, with vs without DESH and respective p values (columns 1–3); patients without DESH were further divided into three groups: ventriculomegaly alone, HCTS alone, and neither ventriculomegaly nor HCTS (columns 4–6). The median and interquartile ranges are reported for the time metrics and number (percentage) for the binary metrics.

Suspected NPH (n = 58)	DESH(n = 45)	No DESH(n = 13)	P value	Ventric.(n = 6)	HCTS(n = 5)	Neither(n = 2)
Demographics and clinical						
Age (years)	74 (68,81)	78 (70,82)	0.43	80 (78,83)	71 (63,82)	70 (69,71)
Cognitive impairment	30 (67%)	4 (31%)	0.05	3 (50%)	0	1 (50%)
Gait impairment	43 (96%)	12 (92%)	0.81	6 (100%)	5 (100%)	1 (50%)
Urinary impairment	29 (64%)	6 (46%)	0.007	3 (50%)	3 (60%)	0
Cisternogram metrics						
Time to basal cisterns (hr)	2 (1,4)	2 (1,5)	0.43	2 (1,3)	2 (1,6)	1 (1,2)
Persistent ventricular radioactivity	41 (91%)	7 (54%)	0.007	5 (83%)	2 (40%)	0
Time to ventricles (hr)*	2 (1,4)	4 (2,6)	0.07	4 (3,6)	2	–
Over convexity	31 (69%)	12 (92%)	0.18	5 (83%)	5 (100%)	2 (100%)
Time to convexity (hr)**	48 (24,48)	24 (24,48)	0.26	48 (24,48)	24 (24,24)	24 (24,24)
Subjective NPH findings	41 (91%)	7 (54%)	0.007	5 (83%)	2 (40%)	0

* Summary statistic is among those in whom the radiotracer entered the lateral ventricles.
** Summary statistic is among those in whom the radiotracer ascended over the cerebral convexity.

hrs). Compared to patients with HCTS alone, those with DESH appeared to have a higher frequency of persistent ventricular radioactivity (41/45, 91% vs 2/5, 40%). Patients with DESH had a higher frequency of cognitive impairment than those with HCTS alone and higher frequency of gait and urinary impairment compared to those with neither ventriculomegaly nor HCTS.

The comparisons of time for radiotracer to reach the basal cisterns, lateral ventricles, and ascend over the cerebral convexity for patients with DESH, ventriculomegaly alone, HCTS alone, and neither ventriculomegaly nor HCTS are summarized in Fig. 3B-5B, respectively.

3.9. *Cisternogram, MRI, and clinical findings in patients with suspected NPH vs headache*

Patients with suspected NPH had more frequent findings of disordered CSF dynamics on cisternography and MRI than patients with a clinical presentation of headache (Supplemental Table 2). Patients with suspected NPH also had a higher frequency of cognitive impairment, gait impairment, and incontinence compared to patients with a clinical presentation of headache who were, on average, younger.

4. Discussion

We performed an imaging to imaging comparison between NM cisternogram and MRI features thought to indicate disordered CSF dynamics in a group of patients with suspected idiopathic NPH and similarly aged patients without NPH. The key findings of the study were: (i) patients with DESH showed abnormal radiotracer distribution (radiotracer in the lateral ventricles and absent or delayed ascent of radiotracer over the cerebral convexity) compared to those without DESH; (ii) among the group of patients with suspected NPH, those with DESH had a higher frequency of abnormal radiotracer distribution compared to those without; (iii) patients with DESH showed more abnormal radiotracer distribution compared to those with ventriculomegaly or HCTS alone; and (iv) patients with ventriculomegaly or HCTS alone showed abnormalities in radiotracer distribution compared to those with neither.

Patients with vs without DESH had a higher frequency of radiotracer in the lateral ventricles, lower frequency of radiotracer over the cerebral convexity, and longer time for radiotracer to ascend over the convexity when it did so. Conceptually, this set of cisternogram findings can be thought of as the result of a mechanical block to the normal flow of CSF over the convexity. This CSF dynamics disorder, documented by cisternography, matches the MR finding of HCTS in DESH – i.e. the high convexity CSF spaces are narrowed with locally increased pressure. Thus an anatomic-functional linkage can be inferred. The differences in cisternogram findings between those with and without DESH were anticipated findings that correspond with prior NM cisternography and more recent MR cisternography studies showing tracer in the lateral ventricles and delayed or absent ascent over the cerebral convexity in patients with NPH (James et al., 1970; Ringstad et al., 2017), as those with DESH had a higher frequency of clinical symptoms of NPH (cognitive, gait, and urinary impairment). There were similar expected differences in radiotracer distribution as well as MRI features of a CSF dynamics disorder in the patients imaged for suspected NPH vs the reference headache group. Nonetheless, it is important to verify the functional assumptions about disordered CSF dynamics underlying the DESH MRI features. As DESH has emerged as an imaging marker associated with cognitive dysfunction in the general population, independent from the classic NPH clinical triad, establishing its association with disordered CSF dynamics has implication outside the field of NPH.

Subgroup analyses provide further support for DESH as a marker of a CSF dynamics disorder. Within the subgroup of patients with suspected NPH, similar differences in cisternogram metrics were found between patients with vs without DESH, though some comparisons did not reach statistical significance likely due to the relatively small number of patients in the group without DESH. These findings support the MR features of DESH to be a marker of disordered CSF dynamics even within the clinical syndrome of NPH.

Patients with DESH also had more abnormal radiotracer distribution than those with ventriculomegaly or HCTS alone. In addition to more frequent ventricular radioactivity and less frequency ascent of radiotracer over the convexity, patients with DESH trended toward a shorter time for radiotracer to enter the ventricles. The time for radiotracer to reach the ventricles has not been previously studied with respect to clinical outcomes. In this study early radiotracer in the lateral ventricles occurred along with established abnormal cisternogram findings and is hypothesized to indicate more perturbed CSF dynamics. One may hypothesize that HCTS alone would be primarily associated with absent/delayed radiotracer ascent over the cerebral convexity and ventriculomegaly with abnormal radiotracer in the ventricles. However, both ventriculomegaly and HCTS alone were associated with abnormal radiotracer in the ventricles and delayed ascent, and the abnormal cisternogram findings were more frequent in patients with DESH.

The abnormalities in radiotracer distribution associated with isolated ventriculomegaly or HCTS were further demonstrated in the comparison of these patients to those with neither ventriculomegaly nor HCTS. Patients with ventriculomegaly alone and HCTS alone had a higher frequency of persistent radiotracer in the lateral ventricles and delayed ascent of radiotracer over the cerebral convexity compared to those with neither ventriculomegaly nor HCTS. These findings support DESH as well as individual MRI features of ventriculomegaly and HCTS as markers of disordered CSF dynamics, in the absence of secondary hydrocephalus (i.e. a focal obstructing lesion).

Focal sulcal or sylvian fissure enlargement, imaging features attributed to extra-ventricular hydrocephalus, was present in most, though not all, patients with DESH and was not associated with differences in cisternogram metrics. On MR review, about half of the DESH patients without focal sulcal or sylvian fissure enlargement had been noted to have features suggestive of long-standing overt ventriculomegaly in adults (LOVA) (Graff-Radford and Jones, 2019; Oi et al., 2000). Although the presence or absence of focal sulcal or sylvian fissure enlargement may indicate different etiologies of disordered CSF dynamics, such as impaired resorption vs LOVA, respectively, cisternogram metrics were similar between these groups.

The exact sequence of how disordered CSF dynamics develops is currently unknown. The abnormal cisternogram findings in patients with ventriculomegaly and HCTS alone, greater in frequency with DESH, suggest that patients with ventriculomegaly, HCTS, and DESH may be on a continuum of disordered CSF dynamics. Although ventriculomegaly is generally gradually progressive in patients with hydrocephalus and can be measured with the Evans' index as a continuous variable, we used the accepted threshold of 0.3 to define ventriculomegaly. Some of the patients with HCTS alone had an Evans' index just<0.3 and focal sulcal or sylvian fissure enlargement, features suggestive of early DESH. Despite potentially subtle differences in MRI findings between some patients defined as HCTS alone vs DESH for the purposes of this analysis, the higher frequency of cisternogram abnormalities on average in those with DESH further support the continuum of disordered CSF dynamics. Of note, sylvian fissure enlargement was also present in some patients with ventriculomegaly alone and in those cases appeared to be at least in part due to atrophy. Future quantification of DESH features and study of the continuum of CSF dynamics disorders may be improved by the use of ventricular volumes, as they have been shown to be a better predictor of cognitive and gait abnormalities than the Evans' index (Crook et al., 2020).

In the comparison of MR and cisternogram findings between patients evaluated for NPH vs headache, most patients evaluated for a clinical indication of NPH fell into one of the three abnormal MR groups, whereas most people in the headache group did not have ventriculomegaly or HCTS. Patients with suspected NPH also had a higher frequency of abnormal cisternogram findings. The patients undergoing evaluation for headache were included to assess the full disease spectrum of CSF dynamics disorders. Patients with DESH are at far end of the disease spectrum, and patients who had a cisternogram performed for an entity other than NPH, and thought not to have a CSF dynamics disorder, are at the normal end of the spectrum.

Early NM cisternogram studies in NPH included patients with both secondary and idiopathic NPH and considered radiotracer in the ventricles and absent ascent over the convexity to result from obstruction at the level of the cortical subarachnoid space preventing normal CSF absorption; ventricular radioactivity alone was thought to represent partial obstruction and both ventricular radioactivity and absent ascent over the convexity a more complete obstruction (Bannister et al., 1967; Patten and Benson, 1968). This hypothesis was based on the assumption that CSF is primarily produced in the choroid plexus, enters the subarachnoid space through the foramen of Luschka and Magendie, flows over the cerebral convexity, and exits the subarachnoid space through arachnoid villi to enter the superior sagittal sinus. Since these early cisternogram studies, multiple new hypotheses have been proposed regarding CSF transit: lymphatic drainage through the cribriform plate and spinal canal; glymphatic drainage of CSF along perivascular spaces to the interstitial fluid; and continuous fluid exchange between CSF, blood, interstitial fluid, and parenchyma (Bothwell et al., 2019; Jessen et al., 2015). Given these proposed alternative methods for CSF movement, the etiology of the abnormal radiotracer distribution on NM cisternogram and associated structural abnormalities on MR is likely multifactorial and more complex than initially thought.

The further support of DESH MRI features as indicators of disordered CSF dynamics in this work has implications for clinical practice. The ability to infer disordered CSF dynamics based on the MRI exam, in combination with other minimally invasive imaging studies such FDG PET/CT (Townley et al., 2018), may reduce the need for the more invasive NM cisternography exam in diagnostic evaluation. Although other factors contributed to decreased use of NM cisternography for evaluation of suspected NPH in our clinical practice over the past few years, the use of alternative imaging markers of disordered CSF dynamics have allowed for cisternography to be reserved for complex cases.

There are limitations to this study. The patient group is limited by the retrospective nature of the study and the availability of clinical data. This resulted in low numbers in some of our subgroups. Patients with headache and suspected CSF leak is an imperfect comparison group, as these patients may also have disordered CSF dynamics; however, our exclusion of patients with a clinical diagnosis of CSF hypotension and/or cisternogram findings suggestive of CSF leak should have removed patients with potential confounding factors. Cisternogram images are acquired at discrete set time-points, which inherently limit the ability to observe and quantify distribution of radiotracer. Additionally, images may be acquired a slightly different time points from one patient to another. However, despite measurement challenges, our time-based measures and present/absent categorizations showed similar patterns and pointed to clear differences between the groups. Quantitative assessment of radioactivity would be ideal, though was not feasible in this retrospective study of clinical NM cisternography data. Finally, the level of detail in which intracranial CSF dynamics may be studied with NM cisternography is limited by its spatial resolution. SPECT/CT could be applied to improve spatial resolution (Thut et al., 2014). However, due to radiation dose considerations, SPECT/CT or CT cisternography would not be widely applicable for imaging at multiple time points. More recently applied, MR cisternography may provide improved spatial resolution though involves additional safety considerations (Ringstad et al., 2017).

5. Conclusions

In this study of patients with and without clinical features of NPH, we found that patients with DESH had abnormal CSF dynamics documented on NM cisternogram (radiotracer in the lateral ventricles and absent or delayed ascent of radiotracer over the cerebral convexity) compared to those without DESH. Additionally, frequency and degree of abnormal radiotracer distribution occurred on a spectrum: patients with DESH > patients with ventriculomegaly or HCTS alone > patients with neither ventriculomegaly nor HCTS. These findings suggest that in patients without a focal obstructive lesion or other etiology for secondary hydrocephalus, the structural abnormalities of ventriculomegaly and HCTS are individually associated with functional abnormalities in CSF dynamics and that CSF dynamics disorders occur on a continuum. When both ventriculomegaly and HCTS are present in DESH, there are greater disturbances in CSF dynamics. Because DESH occurs in approximately 6% of the general population $\geq$ 50 years of age (Graff-Radford et al., 2019), these findings suggest that disordered CSF dynamics are a phenomenon associated with aging that should be more widely appreciated among clinicians.

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Declaration of interest

Dr. Elder is the site PI for a clinical trial for SI-Bone, and an academic editor for PLoS One.

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CRediT authorship contribution statement

Petrice M. Cogswell: Investigation, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Jonathan Graff-Radford:** Conceptualization, Methodology, Resources, Writing - review & editing. **Lincoln I. Wurtz:** Investigation, Writing - review & editing. **Neill R. Graff-Radford:** Validation, Investigation, Writing - review & editing. **Derek R. Johnson:** Investigation, Writing - review & editing. **Christopher H. Hunt:** Investigation, Writing - review & editing. **Jeffrey L. Gunter:** Methodology, Writing - review & editing. **Jeremy K. Cutsforth-Gregory:** Resources, Writing - review & editing. **David T. Jones:** Resources, Writing - review & editing. **Benjamin D. Elder:** Resources, Writing - review & editing. **John Huston III:** Validation, Writing - review & editing, Supervision. **Clifford R. Jack Jr:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102481.

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