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FULL PAPER

Apparent diffusion coefficient measurements to support a diagnosis of intracranial hypotension

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Objective: Intracranial hypotension (ICH) can be a challenging diagnosis, as cerebrospinal fluid leaks may be difficult to confirm, patients may have other causes for clinical symptoms and imaging findings can be non-specific, particularly in the setting of comorbidities. We investigate the use of brain diffusion measurements [apparent diffusion coefficient (ADC) values] in the assessment of ICH.

Methods: 13 cases of ICH were identified retrospectively based on imaging findings and their clinical histories were compared with 13 control subjects. Regional ADC values and average diffusion constant (D_{av}) from brain slice ADC histograms were measured.

Results: ADC values trended higher in all brain regions in patients with ICH than those in control subjects, with statistically significant differences in frontal white matter, mid-brain and deep grey structures. D_{av} determined by

a single-slice ADC histogram was significantly higher in patients with ICH than in the control group ($p = 0.008$). In two cases followed longitudinally, D_{av} correlated with the patient's symptoms and decreased towards normal value with blood patch. In one case, decreased D_{av} correlated with the formation of subdural collections.

Conclusion: Cerebral oedema as assessed by increased ADC is strongly correlated with ICH (10 of 13 cases). Histogram analysis of ADC values may offer increased accuracy of ADC measurement. ADC value assessment in the determination of ICH may be particularly useful in complex clinical cases, where treatment is followed over time or where gadolinium is not used and meningeal enhancement cannot be assessed.

Advances in knowledge: This article investigates the use of brain diffusion measurements in the assessment of ICH in the clinical setting.

Intracranial hypotension (ICH) can be a difficult diagnosis, and the sensitivity and specificity of cranial imaging for diagnosis of ICH is unknown. Making a diagnosis of ICH can be particularly difficult in complex cases such as patients with craniotomy or shunt, chronic migraine, or systemic disease such as human immunodeficiency virus (HIV) or cancer. Current diagnostic criteria include invasive procedures such as myelography, cerebrospinal fluid (CSF) pressure studies and response to blood patch. Additional imaging hallmarks of ICH may aid in making a more definitive diagnosis non-invasively.

Depletion of CSF results in decreased spinal fluid pressure. As CSF pressure drops, compensatory mechanisms, including venous engorgement and the formation of subdural collections, can occur; phenomena that have been explained by the Monro-Kellie hypothesis.¹ These compensatory phenomena can be seen at imaging as diffuse, smooth dural thickening and enhancement, pituitary engorgement and extra-axial collections and are used to suggest the diagnosis of ICH at imaging. Each of the classic

imaging findings are non-specific, and ICH has even been reported in the absence of imaging findings.^{1,2} Cerebral oedema also occurs in ICH and may result from tissue fluid retention as a consequence of the Monro-Kellie hypothesis, but may also be explained by venous outflow obstruction as a result of brain "sag".³ Diffusivity measurements have been used as a surrogate marker for cerebral oedema.⁴⁻⁶ We aimed to test a hypothesis that ADC value measurements from routine clinical MR scans can be used to measure cerebral oedema in ICH and can be used to support a diagnosis of ICH.

METHODS AND MATERIALS

After institutional review board (UMass Memorial Medical Center Worcester, MA) approval was obtained, a retrospective review of the radiology report database and electronic medical records was performed in patients who underwent brain MRI over a 5-year period at this institution from 1 January 2007 through 31 December 2012. Patients were first identified through the imaging database by searching for the keywords "intracranial hypotension".

Table 1a. Brain apparent diffusion coefficient (ADC) values measured from normal (control) subjects

Control subject	Age (years)/sex	Central pons	Central MB	Teg MB	BG	Thal	Fr WM	Par WM	CBM	s-s D_{av}
1	53/F	609	673	710.5	706.0	782.0	781.0	803.5	680.0	747
2	44/F	729	808	633.5	765.5	713.5	815.0	884.5	730.0	716
3	50/F	958	769	626.5	676.0	702.0	753.0	726.5	699.0	700
4	35/F	810	681	584.5	676.0	686.5	720.5	704.5	656.5	723
5	28/M	877	899	669.5	736.0	724.5	706.5	710.0	714.5	733
6	50/M	678	718	767.5	713.0	737.5	710.0	781.5	765.0	731
7	46/F	789	742	631.0	715.0	682.5	765.0	726.5	697.0	736
8	57/M	690	748	655.0	734.5	661.0	757.0	764.0	694.0	732
9	62/M	855	692	753.5	639.0	738.5	764.5	792.0	698.5	735
10	55/M	742	796	725.0	723.5	813.0	762.5	739.0	869.0	731
11	40/M	716	660	587.0	691.0	753.5	701.5	689.0	657.0	711
12	55/M	894	700	624.0	721.5	707.5	751.5	672.0	718.0	731
13	58/F	814	751	826.0	692.5	714.5	655.5	676.0	711.5	726
Mean	48.7	781.6	741.3	676.4	706.9	724.3	741.8	743.8	714.6	727.1
SD	9.8	99.0	66.3	74.3	32.4	41.4	41.4	60.3	54.6	12.2

Table 1b. Brain apparent diffusion coefficient (ADC) values measured from subjects with intracranial hypotension

ICH patient number	Age (years)/sex	Central pons	Central MB	Teg MB	BG	Thal	Fr WM	Par WM	CBM	s-s D_{av}
1	51/M	–	818	831.0	825.5	761.5	704.0	707.0	750.5	728
2	46/M	801	741	758.0	728.5	703.0	777.0	858.5	758.5	750
3	58/F	948	739	749.0	755.0	848.0	828.5	801.0	760.0	937
4	32/M	693	692	712.0	772.0	780.0	770.5	702.0	741.5	748
5	43/M	811	830	790.0	757.5	935.0	765.5	888.5	794.0	834
6	45/M	–	748	766.0	897.5	841.0	805.0	634.5	811.5	778
7	54/F	802	652	663.5	761.0	772.5	829.5	753.5	740.0	774
8	60/F	–	889	824.5	769.0	737.0	873.0	761.5	704.5	825
9	56/M	944	725	633.5	818.0	804.5	897.0	868.0	651.0	811
10	28/F	993	712	697.5	753.0	773.5	750.5	749.5	650.0	753
11	46/M	678	722	779.5	770.0	678.0	716.0	662.0	704.5	699
12	44/F	755	903	662.5	747.5	839.0	723.0	828.5	709.5	741
13	32/F	1077	894	918.0	748.0	748.0	831.5	832.0	702.0	780
Mean	45.8	850.2	774.2	752.7	777.1	786.2	790.1	772.8	729.0	781.4
SD	10.2	133.3	83.1	79.6	45.1	68.1	60.1	81.1	48.5	60.6

BG, basal ganglia; CBM, cerebellum; F, female; Fr WM, frontal white matter; M, male; MB, mid-brain; Par WM, parietal white matter; SD, standard deviation; s-s D_{av} , ADC value taken from single-slice ADC histogram as described in the Single-slice apparent diffusion coefficient histogram generation and analysis section; Teg MB, tegmental mid-brain; Thal, thalamus.

Values not reported where there is image distortion owing to susceptibility effects (two patients).

ADC values given as $\times 10^{-2} \text{ cm}^2 \text{ s}^{-1}$.

Figure 1. 43-year-old man with positional headache. Apparent diffusion coefficient (ADC) map at the level of the lateral ventricles (left). Histogrammic display of pixel ADC value frequency (y-axis) as a function of ADC value (x-axis). Single-slice average diffusion constant is determined by the location of the histogram peak.

Inclusion/exclusion criteria

To be included in the study, a case required MR of the brain with anatomic imaging in each of the three planes, diffusion-weighted imaging (DWI) (in the axial plane) and imaging findings suggestive

of ICH, including dural thickening and meningeal enhancement, and/or subdural collections and/or brain sag.^{7,8} This search yielded 43 patient studies. Clinical records were then reviewed to identify cases with clinical suspicion for ICH. This yielded 14 cases of

Table 2. Clinical summary for patient cases of intracranial hypotension (ICH)

Number	Age (years)/sex	Clinical	Pachy-meningeal enhancement	Subdural collections	Brain "sag"	Histogram D_{av}
1	51/M	Positional HA	+	+	+	728
2	46/M	Post LP HA	+	+	+	750
3	58/F	Trauma/HA	+	+	±	937
4	32/M	Positional HA	+	—	—	748
5	43/M	Positional HA BP	+	—	+	834
6	45/M	Positional HA, somnolence BP	+	+	++	774
7	54/F	Positional HA BP	+	+	—	774
8	60/F	Positional HA BP	+	—	++	825
9	56/M	Post LP	+	+	—	811
10	28/F	Positional HA post lumbar discectomy-BP	—	—	±	753
11	46/M	Positional HA/leak/BP	+	+	±	699
12	44/F	Positional HA/leak/BP	+	+	+	741
13	32/F	Positional HA/leak/BP	+	±	—	780

—, normal appearance no significant brain sag; ±, questionable brain sag; +, mild brain sag; ++, significant obvious brain sag; BP, blood patch; CSF, cerebrospinal fluid; D_{av} , average diffusion constant; F, female; HA, headache; LP, lumbar puncture; M, male.

In Cases 11–13, CSF leak was confirmed.

All cases with BP had clinical suspicion for CSF leak after being seen by a neurologist.

Cases 1, 4–8, 11–14 are spontaneous.

In Cases 2–4 and 10, HA not reported as positional, though risk for hypotension felt to be high based on recent surgery or LP.

Figure 2. Tukey interleaved box and whiskers plot showing apparent diffusion coefficient (ADC) values determined from ADC maps, using standard region of interest method to assess various brain regions. The final data set is average diffusion constant as determined by single-slice histogram as described in the Methods section. BG, basal ganglia; CBM; cerebellum; Fr WM; frontal white matter; ICH, intracranial hypotension; MB, mid-brain; Par WM; parietal white matter; s-s D_{av} , single-slice average diffusion constant; Teg MB, tegmental mid-brain; Thal, thalamus.

probable ICH based on clinical history and imaging findings. Of these, three cases followed recent lumbar puncture, one case followed trauma and one case followed lumbar spine surgery (Table 1). The remaining nine cases were thought to be spontaneous CSF leaks. One case where intrathecal chemotherapy had been recently administered was excluded from this cohort. This cohort included seven male and six female patients, with an average age of 45.8 years and a standard deviation (SD) of 10.2 years.

Control subjects were randomly selected from the same imaging period and were roughly matched for age and sex. The control subjects underwent contrast-enhanced MRI for clinical symptoms of headache (eight), dizziness (one), vertigo (one), weakness (two) and tinnitus (one) that were thought to be unrelated to ICH. Patients with tumour, hydrocephalus, marked atrophy or significant white matter disease were not included. This resulted in a 'normal' cohort group of five males and eight females and an average age of 49.7 years; SD of 10.1 years.

MRI data acquisition and analysis

All images were obtained from a single 1.5 T scanner (Signa®; GE Healthcare, Milwaukee, WI) equipped with gradients with a maximum slew rate of $120 \text{ mTm}^{-1} \text{ ms}^{-1}$ and a maximum strength of 33 mTm^{-1} . A standard high-definition receive-only multi-element (eight element) surface head coil was used. Axial images were acquired parallel to the anteroposterior commissure line in standard fashion. The imaging protocol consisted of multiplanar T_1 weighted imaging [pre- and post-contrast axial: repetition time (TR)/echo time (TE), 550/13 ms; pre-contrast sagittal: TR/TE, 400/9 ms; post-contrast coronal: TR/TE, 12.8/5.37 ms], axial T_2 weighted imaging (TR/TE, 3150/1000 ms), axial fluid-attenuated inversion recovery (TR/TE, 902/142 ms), axial multiplanar gradient recalled acquisition in steady state (TR/TE, 517/25 ms) and axial spoiled gradient recalled (SPGR) (TE/TR 12.8/5.37 ms). Field of view was $220 \times 220 \text{ mm}$ or $240 \times 240 \text{ mm}$ for all series. Images were acquired at 5-mm slice with 1-mm gap, with the exception of sag T_1 (6 mm, no gap) coronal T_1 (6 mm and 0 mm gap) and SPGR (2 mm and 1 mm gap).

The regions of interest (ROIs) were set as a circle with the area of $71\text{--}84 \text{ mm}^2$ in the central pons, central mid-brain, bilateral tegmental mid-brain, lentiform nuclei, thalami, bilateral frontal white matter (Fr WM) and parietal white matter as had been performed previously. Additional measurements were made in the cerebellar hemispheres. Left and right side measurements were averaged. Measurements were performed using the picture archiving and communication system monitor, and the method was confirmed to be equally as accurate as those made on the dedicated workstation.

Single-slice apparent diffusion coefficient histogram generation and analysis

Axial ADC maps were sent to a free-standing workstation (ADW; GE Medical Systems, Milwaukee, WI). Single-slice ADC histograms were generated using FuncTool v. 9.4.05a (GE Medical Systems). Whole-brain ROI is placed at the level of the corona radiata/lateral ventricular body, and the "histogram" option is selected in FuncTool, which generates the ADC histogram for the slice image, the histogram representing the pixel frequency for each ADC value (Figure 1). Using this method, a single-slice histogram can be generated in only a few seconds and requires virtually no data manipulation. Single-slice average diffusion constant (s-s D_{av}) values were recorded as the peak value for each case. The histogram is a gaussian distribution as has been noted for whole-brain histographic analysis,^{9–11} and the ADC values determined by this method are in keeping with those previously reported.^{12–14} Histographic display of clinical data of individual patients can show a slightly non-gaussian

Table 3. Summary of statistical significance of cohort data from Table 1, from unpaired samples t -test

	Central pons	Central MB	Tegmental MB	Basal ganglia	Thalamus	Frontal white matter	Parietal white matter	Cerebellum	Histogram
Intracranial hypotension	0.173	0.165	0.015	<0.001	0.009	0.010	0.097	0.307	0.008

MB, mid-brain.

Bold values are significant at $p < 0.05$.

Equality of variance between data sets determined using Levene's test.

Figure 3. 45-year-old man with positional headache and somnolence, with three MRI studies over a 17-day period (intracranial hypotension patient number 6). This patient had significant brain sag with questionable brain stem compression. MRI of the cervical, thoracic and lumbar spine at presentation failed to identify a cerebrospinal fluid leak. Single-slice average diffusion constant ($s-s D_{av}$) values were determined from apparent diffusion coefficient histogram. Arrows mark blood patches. D_{av} declined to normal levels following two blood patches. Symptoms improved following blood patches, and D_{av} returned to below normal levels. Note coincidental evolving subdural collections.

distribution where the peak and the modal values do not strictly coincide. In such cases, the mean tissue pixel value is taken as the mode of the distribution rather than as the absolute peak (Figure 2).

Figure 4. 43-year-old man with positional headache (intracranial hypotension patient number 5), with multiple MRI studies over a 2-year period. Single-slice average diffusion constant ($s-s D_{av}$) values were determined from apparent diffusion coefficient histogram. An opening cerebrospinal fluid pressure of 10 cm was obtained 1 week after the first imaging study (short arrow); radioisotope cisternogram and CT myelogram identified multiple thoracic meningeal diverticula. Arrows mark blood patches. The first blood patch (T12/L1) yielded no relief of symptoms, patient symptoms improved for 2–3 weeks but returned after the second and third patches (T4/T5 and high thoracic). The fourth patch resulted in sustained relief of symptoms (T12/L1 and T6/T7). Only trace subdural collections were seen in this case. D_{av} is seen to be increased on the final study and the patient reported worsening headaches and 'having the old symptoms again'.

Statistical analysis

Tukey box-and-whisker plot was performed using GraphPad Prism® v. 6.0 for Windows (GraphPad Software, Inc., La Jolla, CA; www.graphpad.com). Unpaired samples *t*-tests were performed using statistical software (SPSS® v. 20; SPSS Inc., Chicago, IL). A $p < 0.05$ was considered indicative of a significant difference.

RESULTS

Regional study of brain ADC values in ICH trended higher for all measured brain regions, as illustrated in Table 2 and Figure 2. Statistically significant differences between ADC values of control subjects and patients with probable ICH are shown in Table 3 and were seen in the tegmental mid-brain ($p = 0.015$), basal ganglia (BG) ($p < 0.001$), thalamus (Thal) ($p = 0.009$) and Fr WM ($p = 0.010$). Using a histographic method for determining average diffusion constant (D_{av}) of a whole-brain slice, D_{av} of the ICH group was statistically significantly different from the control group ($p = 0.008$). Case 3 presented following trauma, where it could be possible that brain oedema occurs at least in part from direct brain trauma, rather than from CSF leaks. The case in question had a documented dural tear with accepted signs of ICH with pachymeningeal enhancement (PME), small and symmetric subdural collections and borderline brain sag without evidence of brain contusion, haemorrhage, or diffuse axonal injury. Clinical notes were in agreement with dural tear and CSF leak rather than brain swelling as a consequence of trauma. Tukey box-and-whisker plots are designed to reveal such outliers and were used for this reason, and the dot above the box-and-whiskers for $s-s D_{av}$ (Figure 2) is the trauma case. If this case is excluded from the analysis, and an unpaired Student's *t*-test is again performed for the remaining data, statistically significant differences between ADC values of the control subjects and patients with probable ICH are again noted and were seen in the tegmental mid-brain ($p = 0.024$), BG ($p < 0.001$), Thal ($p = 0.019$) and Fr WM ($p = 0.047$). Using the histographic method for determining D_{av} of a whole brain slice, D_{av} of the ICH group was statistically significantly different than that of the control group ($p = 0.005$).

Figure 5. 54-year-old woman with positional headache and with multiple MRI studies over a 3-month period (intracranial hypotension patient number 7). Single-slice average diffusion constant (D_{av}) values were determined from apparent diffusion coefficient histogram. In this case a large decrease in D_{av} was noted, with D_{av} being even lower than what is seen for normal control subjects. MRI images at this time (b) show that the patient developed subdural fluid collects between the first MRI (a) and the MRI 10 days later (b). The collections decreased in size MRI (c and d).

Two cases followed with several MRI studies through the course of the condition served to illustrate changes in D_{av} correlated with patient symptoms and with blood patch treatment (Figures 3 and 4). One case followed with several MRI studies showed a sharp decline in D_{av} with the development of subdural collection and a return to normal values when the collections resolved (Figure 6).

There was no significant correlation between the size of the subdural collections and D_{av} and no significant correlation between D_{av} and the extent of brain sag in this small cohort.

DISCUSSION

ICH can be spontaneous, or secondary to a known event such as lumbar puncture. ICH typically presents as orthostatic headache, although non-postural or even exertional headaches have been reported.¹⁵ In addition to headaches, symptoms include

neck stiffness, tinnitus, hyperacusia, photophobia and nausea, as well as a wide variety of cranial nerve symptoms. Occasionally, one or more of these additional symptoms dominate the presentation and the patient may even deny headache.^{15–17} In patients with multiple comorbidities or cranial or spinal surgeries, chronic migraine or systemic disease such as cancer or HIV, ICH may go undiagnosed by clinical findings.

Diagnostic criteria for spontaneous ICH [spontaneous intracranial hypotension (SIH)] in the 2004 International Classification of Headache Disorders-2 is based on clinical presentation together with CSF opening pressure <6 cm water, observation of CSF leakage on an imaging study or MRI features of SIH.⁸ Other criteria may include symptomatic relief with blood patch.⁷ To further the diagnostic complexity, CSF opening pressures are not always obtained or may not be completely reliable in ICH patients, and blood patch may not be successful, particularly if the sight of leak is not known, and multiple blood patches may be needed to achieve relief from symptoms.^{16,18} A recent study reports high success with identification of CSF leaks with MR contrast myelography,¹⁹ but MR contrast is not currently approved by the federal food and Drug Administration for intrathecal administration in the USA, and most facilities hesitate to use MR contrast for this purpose. Myelography, CSF pressure studies and blood patch are invasive procedures that should ideally be reserved for treatment rather than diagnostic purposes. For this reason, more non-invasive diagnostic imaging criteria for ICH are needed.

Figure 6. 37-year-old man with headache following intrathecal chemotherapy. Here the meningeal enhancement (right) may be due to chemotherapy [19], and this patient is therefore not included in the intracranial hypotension group. Thin bilateral subdural collections and average diffusion constant of 763 suggest hypotension, likely secondary to lumbar puncture.

MRI is the imaging modality of choice for evaluation of ICH, and MRI features include pachymeningeal thickening and enhancement, subdural fluid collections, pituitary engorgement and brain sag.^{15,16,20,21} PME and subdural fluid collections are explained by the Monro–Kellie hypothesis, which states that the volume in the intracranial compartment is fixed and the intracranial pressure is constant, such that a drop in CSF volume results in compensatory enlargement of venous and arterial structures, and formation of subdural collections imaging findings

Figure 7. 33-year-old-woman presented with headache returned 11 months later with acute onset positional headache with neck stiffness, nausea, photophobia and blurred vision. The second visit was confirmed spinal fluid leak (patient number 13). Note the subtle narrowing of the ventricular system and effacement of the gyri and sulci relative to the prior study, consistent with diffuse cerebral edema. No significant brain sag was seen in this case.

in ICH are non-specific as each imaging feature can be seen in other intracranial pathologies (e.g. Figure 6), and up to 20% of spontaneous ICH has been reported in the absence of imaging features. Diffuse PME is the most common imaging feature and is generally the feature that causes the radiologist to entertain the diagnosis of ICH; however, PME can be seen in a wide variety of other conditions, including infection, neoplastic disease and dural fibrosis from chronic shunting,²² and may even be absent in ICH.²³ Brain sag is seen in more severe cases of ICH, although the imaging appearance of brain sag can be confused with Chiari 1 malformation.^{24–27}

Signs of brain swelling have been previously noted on imaging studies of ICH, with decreased ventricular size and subtle effacement of the sulci^{16,21,28} (Figure 7). These findings may go unrecognized, particularly in young patients and patients without previous imaging studies for comparison. Cerebral oedema may be explained by the Monro-Kellie hypothesis, but may also be the result of decreased venous drainage because of alterations in venous anatomy due to brain sag.³ Savoirdo et al³ studied a specific subset of ICH patients, those with brain sag and without subdural effusions, to observe a correlation between the absence of meningeal enhancement and deep brain swelling as measured by diffusion MRI, to support a hypothesis that deep brain swelling may be caused by a functional stenosis of venous outflow due to central herniation. That study not only demonstrated statistically significant increases in ADC value in deep brain structures of SIH patients with brain sag but also a consistent trend of higher ADC values in all brain regions in ICH patients without brain sag, greater in the deep grey matter, when compared with normal subjects. They suggest that there may be two mechanisms for oedema formation in ICH: (1) oedema owing to venous stagnation compensating for the loss of CSF volume in all ICH patients and (2) oedema owing to functional stenosis of venous outflow in patients with significant brain sag. Failure to achieve statistical significance for diffusion measurements in ICH patients without brain sag in that study may be owing to measurement technique or the small size of the patient cohort.

DWI has the ability to quantitatively assess the molecular movement of water in tissue, and it has been well established that diffusion-weighted images can be used to identify oedema in brain. Unlike conventional imaging, DWI can be used to distinguish between cytotoxic and vasogenic oedema.^{4,5} Because diffusion weighted (DW) images have both T_2 and diffusion components, vasogenic oedema may appear hypo-intense, iso-intense or slightly hyperintense on DW images but is always characterized by increased diffusion values on ADC maps.^{5,6,29} Quantitative assessment of ADC values has been used to measure vasogenic oedema in animal models of cerebral oedema⁴ and in selected patients with gliomas,³⁰ hypertensive encephalopathy³¹ and sinus thrombosis.²⁹ More recently, this approach has been used to characterize cerebral oedema in cases of acute mountain sickness,³² hepatic encephalopathy³³ and diabetic ketoacidosis.³⁴

We aimed to investigate the use of brain ADC values to aid in the diagnosis and monitoring of ICH. Using the ROI method of analysis, we found that routine clinical diffusion-weighted images can suffer from significant distortion in the mid-brain and brainstem that can limit the accuracy of ADC measurements in these regions; however, we find an overall pattern of ADC abnormality in ICH similar to that found by Savoirdo et al,³ with oedema greater in the deep brain structures. Although others have reported that ROI methods can be used to reliably and quantitatively assess diffusion,^{13,14} the ROI method suffers from operator-dependent placement of ROI on ADC maps of low anatomic detail together with averaging over the area of the ROI, generally limiting reproducibility of this method. Histogrammic methods of ADC assessment have been proposed to be more accurate and reproducible, as they evaluate a larger data set than standard ROI methods and do not suffer from operator-dependent placement of ROI.¹² The single-slice histogrammic assessment of D_{av} as we describe requires minimal data transfer or post processing. We have employed this method of assessment of D_{av} from an entire brain slice in order to achieve a more accurate and reproducible measure of D_{av} in ICH.

ROI method shows significant increases in ADC values in the tegmental mid-brain, BG and Thal, as well as white matter of the frontal lobe. Histogrammic display of ADC data provides a more reliable means of determining D_{av} . $s-sD_{av}$ strongly correlated with ICH ($p = 0.008$). Our study of $s-sD_{av}$ of 13 control subjects yielded an average $s-sD_{av}$ of $727 \times 10^{-2} \text{ cm}^2 \text{ s}^{-1}$ with a SD of 12.17, and a maximum individual value of $747 \times 10^{-2} \text{ cm}^2 \text{ s}^{-1}$. If we set maximum normal D_{av} at $750 \times 10^{-2} \text{ cm}^2 \text{ s}^{-1}$, 10 of 13 (77%) cases of ICH demonstrated D_{av} to be above normal (Table 1). Taken as a data set, elevated D_{av} did not correlate with the presence or absence of subdural collections or the degree of brain sag, although such correlations might be made in individual cases when follow-up data is available (Figures 3 and 5).

3 of the 13 cases identified retrospectively had multiple MRI studies, permitting longitudinal assessment of D_{av} . In all three cases (Figures 3–5), decline in D_{av} correlated with improved symptoms. In the first two cases a sharp decline in D_{av} correlated with blood patch. In the first case (Figure 4), the first three blood patches did not result in sustained relief of symptoms; the fourth patch correlated with symptom improvement and decline in D_{av} .

The final D_{av} measurement is recorded at a higher level, and the patient reported worsening headaches and “having the old symptoms again”. The second case (Figure 5) shows final D_{av} at below normal levels, which may correlate with the formation or evolution of the subdural collection. The third case (Figure 6) shows instability of D_{av} measurements that appear to correlate with the appearance and disappearance of subdural collections. Although this is only correlative, the observation may be explained by the Monroe–Kellie hypothesis, where subdural collections contribute intracranial fluid volume and brain oedema is consequently reduced; when subdural collections resolve, brain oedema returns.

One case identified at imaging and with clinical suspicion for ICH was not included in the study cohort because it may be argued that meningeal enhancement is secondary to intrathecal rather than ICH and therefore may not meet diagnostic criteria for ICH (Figure 7). This case serves to illustrate that elevated ADC may aid in making the diagnosis of ICH in more complex clinical scenarios.

The incidence of ICH has been increasing over the last decade, largely owing to increased recognition of the condition with MRI, yet remains a frequently missed diagnosis.²⁴ Cases often fail to meet a confirmatory “gold standard”, and the condition remains incompletely understood and likely underdiagnosed.^{16,20,24} Although advances in imaging appear to be responsible for the increased incidence of ICH, cases may go undiagnosed because of a lack of imaging findings,¹⁵ and the imaging findings may not reflect the severity of the clinical condition.³⁵ It is apparent that no one clinical or imaging finding has a high sensitivity or specificity in making the diagnosis of ICH. Our study finds increases in ADC in the majority of ICH cases. Such a quantitative marker of cerebral oedema may aid in diagnosing and

monitoring ICH. We show that, when compared with an ROI approach, a histographic measurement of D_{av} results in decreased measurement error such that increases in D_{av} can be reliably measured in ICH.

Study limitations

As a pilot study, our cohort size is large enough to achieve statistical significance with ADC measurements using the single-slice histographic approach, and statistical significance is achieved when conventional ROI approaches are used in certain brain regions. Significance may increase and extend to the remaining brain regions if the cohort size was increased. Correlation of diffusion measurements with specific features of ICH, such as subdural effusions, brain sag or following blood patch would require larger cohorts with a greater number of cases, which include some of these specific features. All cases were identified through the radiological archiving system and therefore are bias for abnormal imaging findings. All cases that were performed with contrast demonstrated PME, which may reflect the radiologist’s hesitance to suggest ICH in the absence of PME. Images are of routine diagnostic standard of this institution at the time of acquisition and are obtained at 1.5 T. Routine clinical DWI series suffer from artefacts owing to susceptibility and motion that may be reduced through techniques such as parallel imaging, faster imaging with higher field or the use of diffusion tensor imaging data to generate the ADC trace,³⁶ which are topics for future investigation.

CONCLUSIONS

The majority of ICH cases demonstrate cerebral oedema, which can be measured by MRI. Brain D_{av} is significantly elevated in cases of ICH identified at imaging. In the proper clinical setting, ADC measurements may aid in making the diagnosis of ICH and may prove useful in evaluating response to treatment.

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