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Ilydio Polachini, MD, died suddenly, June 29, 2001 while on vacation with his wife Bea. He was the medical director of neuroimaging at Kalamazoo Neurologic Institute since 1989. Ilydio was a leader in MR imaging for 15 years and was past president of the American Society of Neuroimaging. He was active at the American Academy of Neurology for 20 years, having served as chairman of the neuroimaging course for 5 years. He appeared on many programs as an expert in various areas of imaging including MRA, spectroscopy, stroke and spine disease. In addition, he has published widely in the field, including two chapters in a successful textbook of neuroimaging.

He devised many protocols for the Phillips Company and helped in the development of their MRA program. He spoke to groups all over the world, including the Brazilian Radiologic Society and other societies in Europe and North and South America. He visited his family in Brazil frequently and was able to send images from Kalamazoo by satellite to his home in Rio Preto, Brazil where he read the studies just after they were done in Kalamazoo.

He was a graduate of Rio de Janeiro State University of Medical Sciences and completed residencies at the Dent Neurological Institute in Buffalo, New York, and at the State University of New York. In 1983, he won the Oldendorf Award for his work on white matter. For the past 3 years, he has written the neuroimaging questions for the American Board of Psychiatry and Neurology.

Ilydio was a great and loyal friend. We spoke on the telephone every week. We often traded jokes, and he had an endearing way of laughing most heartily after he delivered one of his own. He was a gifted and passionate teacher and was always available to explain the intricacies and mystery of the computer.

We gave seminars together with Rob Bakshi all over the country and everyone was amazed at the depth and breadth of his knowledge of physics. He could look at a poor MRI study and tell the technologists that they did not need a new machine; instead he could devise protocols and give suggestions that would make the study beautiful. He understood his machine like nobody else. Some of the country’s top neuroradiologists would express their amazement at his abilities in the technical field. Little did they know that the only formal physics training he had was a night class at Western Michigan State College. He took this course while he directed the Kalamazoo Neuroimaging Institute with his dear friend Dr. Azzam Kanaan. Together, they built a cutting-edge operation with eight scanners servicing the southern half of Michigan.

He was very generous. He recently insisted that I obtain a cable modem so I could tap into his huge database in Michigan for interesting cases. He also set up an MRI center in his hometown, Rio Preto, Brazil, and taught the physicians how to read and overread them. Recently, he participated as faculty in a course in spectroscopy for his friend and mentor, Brian Ross. The participants, all radiologists, voted Ilydio as the best teacher.

He leaves behind a lovely young wife, Bea, 3 wonderful children, and devoted parents and siblings. We are all diminished by his untimely death at the age of 48. A giant has left the stage, but thank God we were there to see and touch him.

—Jack Greenberg, MD
Philadelphia, PA
June 29, 2001
ABSTRACT

The Stroke Prevention in Sickle Cell Disease (STOP) trial used transcranial Doppler (TCD) to screen children with sickle cell disease with no history of stroke. Children (who consented) who had time-averaged mean of the maximum (TAMM) velocities in the middle cerebral artery and/or distal internal carotid artery were randomized to transfusion or standard. Over a slightly more than 20-month average follow-up, there were 11 strokes in the standard care arm and 1 stroke in the transfusion arm. This study has caused a great deal of interest in using TCD to screen children with sickle cell disease. For the STOP TCD data to be applied appropriately, it is necessary for users of TCD to understand how the STOP TCD examinations were performed, how the TCD velocities were measured, and which velocities were used. This article will review the STOP TCD scanning protocol and the reading protocol and review the TAMM velocity and how it differs from other velocity measurements.

Background

Children with sickle cell disease (hemoglobin SS) have a significant risk of developing ischemic stroke, with 11% of HbSS patients suffering a stroke before the age of 20. These strokes are primarily the result of stenosis or occlusion of the anterior intracranial circulation affecting the distal intracranial internal carotid artery (ICA) and/or proximal middle cerebral artery (MCA) and/or the proximal anterior cerebral artery (ACA). Many of these children who develop severe intracranial stenosis also develop moyamoya phenomenon. The stenoses are located in sites that can be readily evaluated by TCD. Based on the original data demonstrating that TCD could identify children at high risk of stroke, the Stroke Prevention in Sickle Cell Disease (STOP) trial was undertaken. In the STOP trial, 130 children identified by TCD as being at high risk of stroke were randomized to receive either transfusion or standard care. These 130 children were entered into the trial based on their having 2 TCD examinations that demonstrated time-averaged mean of the maximum (TAMM) velocities of ≥200 cm/s in one or more of the MCAs or terminal ICAs. Over an average
follow-up of about 20 months, there was 1 stroke in the 63 children randomized to transfusion and 11 strokes in the 67 randomized to standard care, which represented a greater than 90% reduction in stroke incidence in the transfusion population. As a result of the findings of this study, the National Institutes of Health released a clinical alert on September 18, 1997, which stated:

The STOP Trial confirmed that TCD can identify children with sickle cell anemia at high risk for first time stroke. Since the greatest risk of stroke occurs in early childhood, it is recommended that children ages 2-16 receive TCD screening. Screening should be conducted at a site where clinicians have been trained to provide TCDs of comparable quality and information content to those used in the STOP trial and to read them in a manner consistent with what was done in STOP. . . . It is recommended that centers that wish to start screening children with sickle cell anemia for stroke risk do studies to compare their current equipment with STOP trial TCD equipment. . . . Although the optimal timing is not known, re-screening should occur approximately every 6 months.

The TCD velocity criteria used in STOP for classification of stroke risk (Table 1) apply only to children with sickle cell anemia who have not had a previous stroke. Although the clinical alert suggests rescreening every 6 months, we think that those children with normal velocities can be rescreened once a year, those with conditional velocities should be rescreened within 3 to 6 months, and those with an abnormal velocities should undergo repeat screening within the next few weeks (and if the second study is also abnormal, should be offered transfusion therapy at that time).

STOP TCD Examination

The STOP TCD protocol is one that requires attention to detail. It is a focused examination designed to obtain the highest TAMM. The STOP TCD scanning protocol uses an absolute cut point of a TAMM ≥ 200 cm/s in the distal ICA or MCA to determine stroke risk. It became clear early in the study that to obtain the velocities used in this study, the TCD sonographers had to perform meticulous examinations, expending extra effort to identify the highest velocities rather than simply obtaining a Doppler waveform and moving to the next depth.

For the STOP findings to be applied correctly to determine stroke risk in children with sickle cell disease, the TCD interpreters must use the TAMM velocity and not other velocities.

TCD users who wish to use the STOP data to interpret TCD examinations performed on sickle cell patients should always remember that although most Doppler arterial examinations use peak systolic velocity to determine severity of stenosis, the STOP TCD criteria are based on the TAMM velocity. Children with sickle cell disease have higher velocity flows than other children, and significantly higher velocity flows than adults. A child with sickle cell disease who is at low risk of stroke has a TAMM velocity of about 130 cm/s. A peak systolic velocity of 200 cm/s is normal for a child with sickle cell disease; however, a TAMM velocity of 200 cm/s is severely abnormal.

**Table 1. Stroke Prevention in Sickle Cell Disease (STOP) Classification of Transcranial Doppler Results in Children With Sickle Cell Anemia**

<table>
<thead>
<tr>
<th>Classification</th>
<th>TAMM Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>TAMM &lt;170 cm/s</td>
</tr>
<tr>
<td>Conditional</td>
<td>TAMM &gt;170 but &lt; 200 cm/s in the middle cerebral artery and/or distal internal carotid artery</td>
</tr>
<tr>
<td>Abnormal</td>
<td>TAMM &gt;200 cm/s in the middle cerebral artery and/or terminal internal carotid artery</td>
</tr>
<tr>
<td>Inadequate*</td>
<td>Study Was Unable to Be Read.</td>
</tr>
</tbody>
</table>

TAMM = time-averaged mean of the maximum.

*Study Was Unable to Be Read.

**Brief Review of the TAMM**

The use of the TAMM was initially proposed by Aaslid. In the first edition of his book on TCD, Aaslid discussed the topic of choice of velocities:

The most practical Doppler reading of velocity is that of the spectral envelope or outline. This parameter is relatively easy to define even if the signal is barely above the instrument noise. Furthermore, if flow in curved segments is observed, the maximum Doppler shift will correspond to the part of the segment closest to being “in line” with the ultrasonic beam. The outline reading thus has an inherent error minimization when measuring absolute flow velocities.

Aaslid then noted,

Traditionally, systolic, diastolic, and mean values are used to describe pressure, flow and velocity in the arterial system. Of these values, the mean carries the highest physiological significance because it depends less on central cardiovascular factors such as heart rate, contractility, total peripheral resistance and aortic compliance than do systolic or diastolic values. Moreover, the time-mean (of the maximum Doppler shift) velocity correlates better with perfusion than the peak and trough values.

In the second edition of Aaslid’s book, it was noted that...
The mean flow velocity utilized in Transcranial Doppler is referred to as a time mean of the peak velocity envelope, the envelope being a trace of the peak flow velocities as a function of time.

Because almost all TCD reports used TAMM velocity, the TAMM velocity was used in the development of the STOP TCD velocity criteria (Figs 1, 2).

**Fig 1.** Visual measurement of the time-averaged mean of the maximum. A spectral outline of the highest velocities of the waveform is shown. The horizontal cursor is placed so that the area above the line and under the peak of the waveform outline (A) is the same as the area below the line and above the waveform outline (B).

**Fig 2.** Actual spectral trace of Figure 1 demonstrating placement of the cursor on the waveform. The gain has been set so that the waveform follower/envelope is accurately tracking the maximum velocity. On this well-defined waveform, the visual measurement of time-averaged mean of the maximum (TAMM) and the computer measurement of the TAMM are the same, 70 cm/s. The cursor measurement is in the second box from the top on the right side of the screen. The computer-measured TAMM is in the fourth box from the top on the right.
Other Mean Velocities

There has been a great deal of confusion about the term *mean* velocity. On the original TCD equipment, the TAMM was reported simply as the mean. As a result of this, much of the original TCD literature simply used the term mean and did not specify that it was the TAMM. Over the past few years, TCDI has come into use. TCDI can calculate a number of mean velocities that are not the TAMM. None of these other calculated means are the TAMM and, therefore, cannot be applied to the STOP data set.

On some TCDI units, a vertical line can be brought up on the screen and used to measure the highest velocity at a specific point. When this measurement is engaged, at the same time that the highest velocity is measured the computer can calculate the mean velocity by averaging all of the velocities in the spectral profile at that point in time. This measurement is sometimes referred to as the instantaneous mean (see Fig 3).

The computer can summate a series of instantaneous means obtained over the time course of one or more waveforms and develop a time average of the mean of the mean velocities (see Fig 4). Some ultrasound units identify this as the time-averaged mean, so it can potentially be confused with the TAMM. This time-averaged mean of the mean velocity is not the same as the time-averaged mean of the maximum velocity. If the sonographer reviews the image, the mean velocity line that is drawn will track within the body of the waveform and will not follow the peak velocities. This time-averaged mean of the mean velocity is significantly lower than the TAMM.

Yet another mean is the intensity weighted mean across time. This represents the mean of every point of the fast Fourier transform weighted by the intensity of the reflected signal above (or below) the zero line. This velocity is significantly lower than the TAMM.

Many centers have calculated the mean using a formula that adds one third of the peak systolic velocity plus two thirds of the end diastolic velocity. This formula virtually always results in velocities that are slightly lower than the TAMM. In a preliminary study of 20 sickle cell patients, we found that this calculation typically resulted in velocities that were 4% to 10% lower than the TAMM. In some instances, the formula-calculated mean was actually higher than the measured TAMM. We did not pursue the reasons for this difference, but it appeared that the pulsatility index and heart rate affected this calculation. Because this calculation does not reliably give the same TAMM velocity as used in STOP, this calculation should not be used to determine the TAMM.

On the Nicolet TC-2000 TCD unit, which was used in the STOP study, there is a waveform follower (envelope) that tracks the highest velocities of the velocity profile. The computer then averages the highest velocities over time and determines the TAMM. Transcranial color Doppler imaging (TCDI) units use different terms for the same velocity: Acuson calls its highest velocity profile trace the TAMx (time average of the maximum) velocity; ATL calls its version of the TAMM the TAP (time average of the peak) velocity.

**Fig 3.** (Top) Instantaneous mean. The vertical cursor is placed so that it measures the peak velocity. This is displayed on the right side of the screen as 0.57 m/s. Under this number is a mean of 0.20 m/s. This mean represents an average of all the velocities in the waveform that fall along this vertical cursor. (Bottom) Same waveform. The vertical cursor has been moved very slightly to the right of the position in the top image. The peak velocity is still measured as 0.57 m/s, but the mean at this point in time is 0.39 m/s. It can be seen that this mean is not only the same as the time-averaged mean of the maximum but also very sensitive to cursor placement.
Angle of Incidence

The Nicolet TC-2000 TCD unit uses dedicated (or “blind,” since there is no B-mode image data) Doppler. Because the artery cannot be visualized, angle correction cannot be applied. The TCD unit assumes that the kHz shift is obtained at an optimal angle of insonation (0° or 180°) and that the angle of correction is not needed to calculate the velocity. Because all of the STOP velocity data were developed using blind Doppler, angle correction should not be used if an examination is performed using TCDI, since angle correction may potentially result in calculated velocities that are higher than those that would have been obtained using the STOP protocol. Our recent experience comparing TCDI with STOP TCD has been recently published. 9

STOP TCD Scanning Protocol

Children have smaller head diameters than adults. Vessel identification by TCD is based on expected depth of arterial segments, direction of flow, and spatial relationships to other identified vessels. Calipers are used to measure head diameters as the distance between the posterior aspect of one transtemporal window to the posterior aspect of the other transtemporal windows (the calipers are placed so that the caliper tips lie just anterior to each ear, just above the zygomatic arch). Nomograms for different head diameters were developed to provide sonographers with data on expected depths for different landmarks such as the ICA bifurcation and the top of the basilar (Table 2).

Children have thinner skulls than adults and large transtemporal acoustic windows. Adequate power to penetrate the skull is usually easily achieved. The large windows allow the sonographer to manipulate the probe to optimize alignment with the artery to obtain the highest velocity.

Children should be scanned only when clinically stable. Hypoxia, hypercarbia, fever, hypoglycemia, and worsened anemia can all increase cerebral blood flow (CBF) and flow velocity. Sickle chest syndrome, pneumonia, splenic sequestration, hemolytic crisis, hypoglycemia, and potentially other processes can all result in an increase in CBF, and TCD velocities, over the patient’s baseline. Hypocarbia and recent transfusions can decrease CBF and flow velocity. Because of the potential impact of alterations of any of these variables on TCD velocities, the results of TCD scans performed when children with sickle cell are admitted to the hospital for medical illnesses should generally not be used to determine stroke risk.
Children should lie quietly but should not be allowed to go to sleep because the increase in CO2 with sleep can elevate CBF and velocities. Because of the large number of variables that can potentially affect flow velocity, STOP required that a child have 2 abnormal TCDs separated by at least 2 weeks before the child was considered definitely abnormal and could be randomized in this study.

The STOP TCD scanning protocol requires the examiner to meticulously track the arterial segments and optimize the signal at each depth to obtain the highest velocity possible. Because the velocity risk profile for stroke development is based on the highest velocity in the MCA and terminal ICA, the major focus is on identifying the highest velocity in these areas. The MCA should be identified and tracked to as shallow a depth as possible, usually <40 mm. The artery is then tracked in 2 mm depth increments, with the signal optimized and recorded at each depth. The ICA bifurcation is identified, and recordings are made of the ACA and terminal ICA ≥4 mm deeper than the ICA bifurcation. The posterior cerebral arteries are then identified, tracked as shallowly as possible, and tracked and recorded in 2 mm depth increments to the top of the basilar at the midline.

**Signal Optimization**

Signal optimization consists of a combination of efforts used by the sonographer to obtain the highest velocity. The initial goal is to identify a transtemporal window with the best angle of insonation. Children have large temporal windows when compared to adults. Unlike many adults who have only 1 window, children have several windows, and the sonographer has to identify which of several windows is best. The sonographer searches for the window where the sharpest waveforms and highest velocities can be obtained. Once the best window has been identified, the sonographer attempts to obtain the highest velocity by making a series of minor probe manipulations that may involve either minor changes in angulation or sliding of the probe to obtain a better angle of insonation.

Because the highest TAMM predicts stroke risk, it is crucial that the sonographer undertake this painstaking/meticulous search for the highest velocity at each depth. Failure to identify a high velocity may result in incorrect risk prediction for a child. Even when a strong Doppler signal is detected, minor manipulations of the probe will sometimes detect a much higher velocity signal that is “hiding” in the background. The sonographer must also pay close attention to audible clues suggesting the presence of local high velocities: these include turbulence, high-pitched pulsatile hissing in the background (which is not displayed), and sudden cutoff of visual display of the waveform. As the vessel is tracked, the sonographer may have to continue to make minor adjustments of the probe to identify the highest velocity at each depth.

The sonographers are instructed to obtain as clean and sharp a signal as possible, with the best possible signal-to-noise ratio. They are also instructed to obtain the highest velocity, even if that signal is not as crisp and clear as a lower velocity signal at the same depth.

**Measuring the Velocity**

For STOP, all velocities were read off-line using a visual technique. The Nicolet TC-2000 has a computer-based algorithm for tracking the maximum velocities and determining the TAMM. Unfortunately, many TCD recordings have less than optimal signal-to-noise ratios, which caused mistracking of the waveform follower, which in turn results in inaccurate computer-determined measurements (Fig 5). For this reason, we developed a standardized reading protocol that was rigorously tested and found to deliver extremely reproducible measurements. The Nicolet TC-2000 allowed manipulation of the baseline and gain controls. It also provided a horizontal line (cursor) that could be displayed on the screen and positioned at any point on the waveform to help with the measurements. The gain settings and baselines are adjusted to standardized settings prior to reading the velocities.
The gain is adjusted as follows. The gain is increased to the point that the waveform follower first begins to misidentify background noise as signal; when this happens, the gain is then decreased to next highest level. If there is wraparound signal causing the waveform follower to misidentify the wraparound as part of the signal, the baseline is adjusted to remove the wraparound. These adjustments of gain and baseline are performed by every reader prior to reading so that each reader reads velocities measured at the same gain and baseline settings. This standardization results in highly reproducible velocity measurement. When the visually guided readings using the STOP TCD reading protocol are compared to the computer-determined TAMM on waveforms that allow optimal tracking of the maximal velocities by the waveform follower, the velocities are usually within \( \leq 5 \) cm/s of each other (see Fig 6).

In those TCD recordings that have excellent signal-to-noise ratio, the waveform follower will tightly track the highest velocities and will accurately calculate the TAMM. Under situations in which there is poor signal-to-noise ratio, the waveform follower will not accurately track the highest velocities and may overread or underread the TAMM (see Fig 5). The STOP reading protocol allows one to accurately read and record the velocities in those recordings where the waveform is well defined but where the signal-to-noise ratio is poor and the waveform follower cannot accurately track the highest velocities. This visually guided reading technique was standardized as follows. Imagine that the waveforms represent mountain peaks and valleys. Draw a line across the waveforms so that if the peaks of the waveforms/mountains were pushed over, they would fill the valleys (see Figs 1, 2, 6). This represents the TAMM line. This line typically lies at the level of the “shoulder” of the waveform. However, this rule of thumb does not work as well with waveforms with unusually high or low pulsatility. The reader can rapidly calibrate his or her eye by working with sharply defined waveforms with good signal-to-noise ratio and comparing the visually read TAMM with the waveform follower measured TAMM.

**Conclusion**

The STOP study demonstrated that TCD can be used to identify a population of children with sickle cell disease who are at high risk of developing a stroke. The risk determination is based on the TAMM and not on peak systolic or other velocities. To use the STOP TCD criteria, the TCD examinations and readings should be performed in a manner similar to those used in STOP. The TCD examinations performed in STOP were very focused, with the aim of identifying the highest velocity in the MCA and distal ICA. The STOP TCD reading protocol resulted in velocities similar to those obtained by the computer on optimal signal-to-noise ratio signals and allowed accurate measurement of velocities in those recordings where there was adequate signal outline to measure, but where the signal-to-noise ratio was poor and the waveform follower could not track the waveform reliably. When the

**Fig 5.** An example in which the gain has been set too high so that there is a poor signal-to-noise ratio. The waveform follower is unable to accurately track the peak velocities, resulting in the computer overestimating the velocities.
Fig 6. Cursor placement (refer to Fig 1 for definitions of A and B). This series demonstrates visual placement of the cursor. (Top) The horizontal cursor is much too low and the peaks are much too large for the valleys (A is much greater than B), and the resulting velocity of 148 cm/s is less than the true time-averaged mean of the maximum (TAMM). (Middle) The cursor is placed appropriately so that A = B, and the measured velocity, 174 cm/s, is correct. (Bottom) The cursor is placed "too high" so that A is much smaller than B, and the resulting velocity measurement, 205 cm/s, is higher than the correctly measured TAMM.
TCD examinations and readings are performed according to STOP protocol on children with sickle cell disease, those children at high risk for development of stroke can be identified and managed with transfusion to dramatically decrease their risk of stroke.

References

Comparison of Transcranial Color-Coded Sonography and Magnetic Resonance Angiography in Acute Ischemic Stroke

ABSTRACT

Background and Purpose. This study was designed to assess the accuracy of transcranial color-coded sonography (TCCS) as compared to magnetic resonance angiography (MRA) for detecting intracranial arterial stenosis in patients with acute cerebral ischemia. Methods. The authors prospectively identified 120 consecutive patients admitted with acute ischemic stroke and performed both TCCS and MRA with a mean interval of 1 day. TCCS data (sampling depth, peak systolic and end diastolic angle-corrected velocity, mean angle-corrected velocity, and pulsatility index) for middle cerebral arteries (MCAs) were compared to MRA data and classified into 4 grades: normal (grade 1): normal caliber and signal; mild stenosis (grade 2): irregular lumen with reduced signal; severe stenosis (grade 3): absent signal in the stenotic segment (flow gap) and reconstituted distal signal; and possible occlusion (grade 4): absent signal. The cutoffs were chosen to maximize diagnostic accuracy.

Results. Interobserver agreement for MRA grading resulted in a weighted-kappa value of 0.776. The rate of poor temporal window was 37% (89/240). Doppler signals were obtained in 135 vessels, and the angle-corrected velocities (peak systolic, end diastolic, mean) were significantly different (P = .001, P = .006, and P < .001) among the MRA grades: grade 1 (100, 47, 68 cm/s), grade 2 (171, 72, 110 cm/s), grade 3 (226, 79, 134 cm/s), grade 4 (61, 26, 39 cm/s). Additionally, an angle-corrected MCA peak systolic velocity ≥120 cm/s correlates with intracranial stenosis on MRA (grade 2 or worse) with high specificity (90.5%; 95% confidence interval = 78.5%–96.8%) and positive predictive value (93.9%) but relatively low sensitivity (66.7%; 95% confidence interval = 61.2%–69.5%) and negative predictive value (55.1%). Conclusion. Elevated MCA velocities on TCCS correlate with intracranial stenosis detected on MRA. An angle-corrected peak systolic velocity ≥120 cm/s is highly specific for detecting intracranial stenosis as defined by significant MRA abnormality.

Key words: Transcranial color-coded sonography, magnetic resonance angiography, acute ischemic stroke.

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Transcranial color-coded sonography (TCCS) was introduced as a new technique for imaging the basal cerebral arteries. Because TCCS includes both B-mode and color-
coded Doppler capabilities, the vessels can be more easily identified than by conventional blind transcranial Doppler (TCD). The angle of insonation may also be measured and corrected, yielding velocity measurements that might be closer to the true values compared to blind TCD. TCD has already been shown to be an effective tool for detecting middle cerebral artery (MCA) stenosis, but data about the use of TCCS in intracranial stenosis are still limited. Magnetic resonance angiography (MRA) is a non-invasive method to visualize the circle of Willis and has been shown to have a high sensitivity and specificity for detecting intracranial abnormalities compared to conventional digital subtraction angiography. There are limited data with regard to the correlation between TCCS and MRA in detecting intracranial artery stenosis. The present study aims to assess the accuracy of TCCS as compared to MRA in diagnosing intracranial stenosis in the main stem of the MCA in patients with acute ischemic stroke.

Materials and Methods

Patients admitted to Shin Kong WHS Memorial Hospital in Taipei with the clinical diagnosis of acute ischemic stroke from October 1, 1999, to January 31, 2000, were studied prospectively. All except patients in an uncooperative state or with unstable vital signs were evaluated with extracranial carotid duplex (HP5500, 5-7.5 MHz probe) using previously described techniques, TCCS, and MRA during hospitalization. To exclude hemodynamic influence from extracranial vessel disease, patients with more than 50% stenosis of extracranial internal carotid artery were excluded. A total of 120 patients (240 MCAs) were finally included in this study.

Transcranial Color-Coded Sonography

TCCS (HP5500) examinations were performed by the same examiner without knowledge of MRA results. All TCCS studies were done using a 2-MHz pulsed ultrasound transducer. The signals were transferred by fast Fourier transformation spectral analysis. We used the transtemporal approach to study the MCA. Angle-corrected flow velocity measurement was performed for at least 3 points along the course of the MCA at depths of 48 to 60 mm with frequency-based color mode. The profiles of Doppler signals with the highest mean velocity were recorded for each MCA. A neurologist without knowledge of other test findings interpreted the TCCS studies independently. The profiles included depth, peak systolic velocity, end diastolic velocity, mean velocity, and pulsatility index (PI). Poor temporal bone windows were defined as inability to visualize the midbrain structures of the interrogated sides on the B-mode image. We did not attempt to insonate the MCA ipsilateral to the poor window from the contralateral side. A possible occluded MCA was defined by lack of signal on the color display despite visualization of at least 2 other ipsilateral vessels (anterior cerebral artery, internal carotid artery, or posterior cerebral artery) and lack of any signal when interrogated with pulsed-wave Doppler.

Magnetic Resonance Angiography

MRA was performed on a 1.5-T Magneton system (Siemens). Axial 3-dimensional time-of-flight MRA of the circle of Willis was obtained (TR = 36, TE = 7, flip angle = 25°, NEX = 1, 20-cm field of view, 512 × 192 matrix size, 72 sections, 1-mm slice thickness). Both source images and maximum intensity projection renderings were acquired. Two neuroradiologists blind to the clinical and ultrasound findings reviewed each MRA independently, and a consensus was obtained for the final analysis. The MRA data for main stem of the MCA were classified into 4 grades: normal (grade 1): normal caliber and signal (Fig. 1A); mild stenosis (grade 2): irregular lumen with reduced signal (Fig. 1B); severe stenosis (grade 3): absent signal in the stenotic segment (flow gap) and reconstituted distal signal (Fig. 1C); and possible occlusion (grade 4): absent signal (Fig. 1D).

Statistical Analysis

Mean and standard deviations of velocity measures by different MRA grading were summarized descriptively. Doppler velocity measurements and PI obtained with TCCS were compared to the MRA grading groups and evaluated by single-factor analysis of variance. All statistical comparisons were carried out at the 5% level of significance (2-tailed). Receiver-operating characteristic (ROC) curve analysis was applied to compare the overall performance in evaluating intracranial stenosis defined by MRA compared to peak systolic, mean, and end diastolic flow velocities obtained by TCCS. The cutoffs were chosen to maximize diagnostic accuracy. The kappa value was applied to describe agreement of MRA grading between the 2 neuroradiologists.

Results

A total of 120 patients (62 men, 58 women; 65.1 ± 11.9 years of age) were included in the study. The mean time interval between performing MRA and TCCS was 1 ± 2.0 days. In 82 of the patients, MRA was performed prior to TCCS, and in 38 patients, the TCCS was performed prior to MRA. The agreement between MRA grading by 2 neuroradiologists resulted in a weighted-kappa value of 0.776. During TCCS evaluation, poor temporal bone win-
dows were found bilaterally in 37 patients and unilaterally in 15 patients, resulting in nonvisualization of 89 vessels out of 240 (37%). Possible occlusion by TCCS criteria was noted for 16 vessels (6.7%). There were 135 vessels with measurable velocities. The relationship between TCCS (poor window, possible occlusion, or measurable velocity) and MRA grading (normal, mild stenosis, severe stenosis, or possible occlusion) is presented in Table 1. MCA Doppler signals were measurable in 135 vessels, and the velocities (peak systolic, end diastolic, mean) were

Fig 1. Magnetic resonance angiography data for the main stem of the middle cerebral artery was classified into 4 grades: (A) normal (grade 1): normal caliber and signal; (B) mild stenosis (grade 2): irregular lumen with reduced signal; (C) severe stenosis (grade 3): absent signal in the stenotic segment (flow gap) and reconstituted distal signal; and (D) possible occlusion (grade 4): absent signal.
significantly different ($P = .001$, $P = .006$, $P < .001$) among the MRA grades: grade 1 (100, 47, 68 cm/s), grade 2 (171, 72, 110 cm/s), grade 3 (226, 79, 134 cm/s), grade 4 (61, 26, 39 cm/s) (Table 2). However, the PIs of the MCA Doppler signals were not related to the MRA grades ($P = .11$).

A threshold cutoff of the MCA peak systolic velocity $\geq 120$ cm/s correlates with intracranial stenosis on MRA (grade 2 or worse) with high specificity (90.5%; 95% confidence interval = 78.5%–96.8%) and positive predictive value (93.9%) but relatively low sensitivity (66.7%; 95% confidence interval = 61.2%–69.5%) and negative predictive value (55.1%), and the area under the ROC curve is 0.694 (Table 3). A threshold cutoff of the MCA mean velocity $\geq 85$ cm/s has lower sensitivity (59.1%) and negative predictive value (50.6%) but higher specificity (92.9%) and positive predictive value (94.8%) in identifying intracranial stenosis defined by abnormal MRA, and the area under the ROC curve is 0.672 (Table 4). Performance was also assessed for a threshold cutoff of the MCA end diastolic velocity $\geq 60$ cm/s, including sensitivity (52.7%), specificity (90.5%), positive predictive value (92.5%), and negative predictive value (46.3%) in identifying intracranial stenosis defined by abnormal MRA, and the area under the ROC curve is 0.637 (Table 5). A threshold cutoff of the MCA peak systolic velocity $\geq 160$ cm/s was assessed to evaluate the ability to separate mild (grade 2) from severe (grade 3) stenosis on MRA with sensitivity (72.7%), specificity (60.0%), positive predictive value (20.0%), and negative predictive value (90.9%).

### Discussion

Many studies have suggested that intracranial stenosis, especially in the MCA, is more prevalent in Asian people than Caucasians. Various noninvasive diagnostic tools have been used to identify such lesions. MRA and TCCS are among the most commonly used methods. One of the major limitations of TCCS is the lack of a suitable imaging window. The reported rate of poor temporal window is

<table>
<thead>
<tr>
<th>Peak Systolic Velocity Cutoff (cm/s)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Overall Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 100$</td>
<td>77.4%</td>
<td>66.7%</td>
<td>83.7%</td>
<td>57.1%</td>
<td>72.1%</td>
</tr>
<tr>
<td>$\geq 110$</td>
<td>71.0%</td>
<td>69.0%</td>
<td>83.5%</td>
<td>51.8%</td>
<td>70.0%</td>
</tr>
<tr>
<td>$\geq 120$</td>
<td>66.7%</td>
<td>90.5%</td>
<td>93.9%</td>
<td>55.1%</td>
<td>78.6%</td>
</tr>
<tr>
<td>$\geq 130$</td>
<td>57.0%</td>
<td>92.9%</td>
<td>94.6%</td>
<td>49.4%</td>
<td>75.0%</td>
</tr>
<tr>
<td>$\geq 140$</td>
<td>49.5%</td>
<td>95.2%</td>
<td>95.8%</td>
<td>46.0%</td>
<td>72.4%</td>
</tr>
</tbody>
</table>

The result chosen to yield maximal diagnostic accuracy is shown in bold type. Area under the receiver-operating characteristic curve = 0.694.
16.3% in a TCCS study in a Caucasian cohort. In our study population, the majority of the patients are older Taiwanese, and the failure rate was 37%, which is much higher than that reported for Caucasians. Only 10 of 240 (4.2%) MCAs had evidence of possible occlusion by MRA in this study, which is somewhat smaller than expected because we exclude patients with uncooperative state or unstable vital signs, which should tend to bias the study toward less severe ischemic stroke patients.

The MCA was assessed between 48 and 60 mm corresponding to M1 segment, which may preclude detection of the proximal M2 MCA and terminal internal carotid artery. Elevated MCA velocities on TCCS correlate well with severity of intracranial stenosis detected on MRA by the grading system used in this study. This MRA grading system also has a good interrater agreement (kappa = 0.776). The mean of MCA peak systolic velocities from patients having normal MRA is 100.3 cm/s, which is similar to previously reported data (107 cm/s). Increasing severity of stenosis according to MRA correlates with increasing velocity by TCCS except in patients with possible occlusion by MRA. Two of 10 patients with possible occlusion by MRA had detectable, but low, velocity by TCCS. This was probably due to the tendency of MRA to exaggerate the degree of a severely stenotic lesion caused by a very sluggish blood flow, which can nevertheless be detected by TCCS. However, a possible occlusion by TCCS was not an accurate predictor of occlusion by MRA in this study either.

An angle-corrected peak systolic velocity of $\geq 120$ cm/s is highly specific (90.5%) but less sensitive (66.7%) for detecting intracranial stenosis as defined by abnormal MRA grades (grade 2 or worse). One possible reason for only modest sensitivity is that MRA grade 2 represents a wide range of stenosis, some of which is undoubtedly not hemodynamically significant. The parameters of end diastolic velocity or mean velocity are not as good as those of peak systolic velocity in terms of overall accuracy and areas under the ROC curve in detecting intracranial stenosis. This likely is a reflection of the fact that increasing systolic velocity is the initial effect of mild stenosis and that elevation of mean or end diastolic velocity occurs with more severe or hemodynamically significant stenosis.

Our data were unable to identify an appropriate velocity cutoff point to separate mild (grade 2) from severe (grade 3) stenosis found on MRA. This is likely due to several factors including the small number (n = 11) of severely stenotic MCAs in our study and the probable broad overlap of degrees of stenosis classified as grade 2 or 3 on MRA, as well as multiple hemodynamic factors such as collateral flow patterns, luxury perfusion, hematocrit, intracranial pressure, or cardiovascular status, all of which may influence velocities in stenotic vessels.

In conclusion, compared to MRA in stroke patients, TCCS has excellent specificity and positive predictive value in the identification of MCA stenosis. Angle-corrected peak systolic velocity criteria of $\geq 120$ cm/s performed the best. Although quite specific for the presence or absence of stenosis, we were not able to accurately identify subcategories of stenosis, at least partly due to the small number of severe stenoses found in our patients. Based on our results, velocities that many operators would consider being only mildly elevated MCA velocities (eg, $\geq 120$ cm/s in peak systolic velocity or $\geq 85$ cm/s in mean velocity) are actually indicative of intracranial stenosis significant enough to be notable on MRA. In addition, Taiwanese stroke patients have a higher rate of inadequate temporal window than Caucasians. In the future, the use of ultrasound contrast agents may overcome this limitation of TCCS.

### Table 4. A Cutoff for Middle Cerebral Artery (MCA) Mean Velocity in Identifying Intracranial Stenosis With Abnormal Magnetic Resonance Angiography (MRA)

<table>
<thead>
<tr>
<th>Mean Velocity Cutoff (cm/s)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Overall Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 75$</td>
<td>67.7%</td>
<td>76.2%</td>
<td>86.3%</td>
<td>51.6%</td>
<td>72.0%</td>
</tr>
<tr>
<td>$\geq 80$</td>
<td>61.3%</td>
<td>88.1%</td>
<td>91.9%</td>
<td>50.7%</td>
<td>74.7%</td>
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<tr>
<td>$\geq 85$</td>
<td>59.1%</td>
<td>92.9%</td>
<td>94.8%</td>
<td>50.6%</td>
<td>76.0%</td>
</tr>
<tr>
<td>$\geq 90$</td>
<td>48.4%</td>
<td>97.6%</td>
<td>97.8%</td>
<td>46.1%</td>
<td>73.0%</td>
</tr>
<tr>
<td>$\geq 95$</td>
<td>46.2%</td>
<td>97.6%</td>
<td>97.7%</td>
<td>45.1%</td>
<td>71.9%</td>
</tr>
</tbody>
</table>

The result chosen to yield maximal diagnostic accuracy is shown in bold type. Area under the receiver-operating characteristic curve = 0.672.

### Table 5. A Cutoff for Middle Cerebral Artery (MCA) End Diastolic Velocity in Identifying Intracranial Stenosis With Abnormal Magnetic Resonance Angiography (MRA)

<table>
<thead>
<tr>
<th>End Diastolic Velocity Cutoff (cm/s)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Overall Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 50$</td>
<td>61.3%</td>
<td>64.3%</td>
<td>79.2%</td>
<td>42.9%</td>
<td>62.8%</td>
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<tr>
<td>$\geq 55$</td>
<td>58.1%</td>
<td>78.6%</td>
<td>85.7%</td>
<td>45.8%</td>
<td>68.4%</td>
</tr>
<tr>
<td>$\geq 60$</td>
<td>52.7%</td>
<td>90.5%</td>
<td>92.5%</td>
<td>46.3%</td>
<td>71.6%</td>
</tr>
<tr>
<td>$\geq 65$</td>
<td>45.2%</td>
<td>95.2%</td>
<td>95.5%</td>
<td>44.0%</td>
<td>70.2%</td>
</tr>
<tr>
<td>$\geq 70$</td>
<td>37.6%</td>
<td>95.2%</td>
<td>94.6%</td>
<td>40.8%</td>
<td>66.4%</td>
</tr>
</tbody>
</table>

The result chosen to yield maximal diagnostic accuracy is shown in bold type. Area under the receiver-operating characteristic curve = 0.637.
The study was supported by a grant from Shin Kong WHS Memorial Hospital [8302-90-2106-01]. Li-Ming Lien is a recipient of the 2001 William M. McKinney Award by the American Society of Neuroimaging for this article, which was presented in part at the 24th annual meeting of the society in Las Vegas, Nevada. The authors thank Ulf Schminke, MD, for his helpful discussions.

References


Diagnostic Value of Apparent Diffusion Coefficient Hyperintensity in Selected Patients With Acute Neurologic Deficits

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R. Gilberto Gonzalez, MD, PhD
George Hunter, MD
Bing Wang, BA
Walter J. Koroshetz, MD
Lee H. Schwamm, MD

ABSTRACT

Background and Purpose. A pattern of decreased intensity on apparent diffusion coefficient (ADC) maps is useful in the early detection of ischemic brain injury. Less information exists with regard to patients with acute neurologic deficits in whom there is abnormal conventional magnetic resonance imaging (MRI) and increased ADC intensity. Methods. The authors identified 13 patients with acute neurologic deficits who underwent diffusion MRI and had calculated ADC maps demonstrating hyper-intensity in regions characterized by computed tomography hypodensity and MRI T2 hyperintensity. The initial and follow-up imaging characteristics and clinical syndromes were recorded. Results. Clinical syndromes included hypertensive encephalopathy, posterior leukoencephalopathy, hyperperfusion following carotid endarterectomy, venous sinus thrombosis, HIV encephalopathy, and brain tumor. Diffusion-weighted imaging (DWI) was hyperintense in 3 of 13 patients, isointense in 4 of 13 patients, heterogeneous in 3 of 13 patients, and hypointense in 3 of 13 patients. The ADC values in these regions were significantly higher than those in control regions (P < .0001). At early follow-up, MRI abnormalities resolved completely in 3 of 13 patients and partially in 9 of 13 patients. MRI abnormalities were unchanged in 1 patient. Conclusions. In the evaluation of patients with acute neurologic deficits, ADC hyperintensity may identify a subset of patients with vasogenic edema of nonischemic etiology. Frequently, these conditions are potentially reversible if appropriately managed. DWI and conventional images alone are not sufficient to identify these neurologic conditions.

Patients with syndromes characterized by vasogenic edema due to nonischemic causes may present with neurologic deficits suggestive of infarction. Clinical evaluation, computed tomography (CT), and conventional magnetic resonance imaging (MRI) at times do not fully differentiate these syndromes from those due to cytotoxic edema of ischemic etiology.

Diffusion imaging supplemented with the review of apparent diffusion coefficient (ADC) maps and calculation of ADC values, however, can differentiate vasogenic (ie, extracellular) edema from cytotoxic edema. Echo planar isotropic diffusion MRI yields diffusion-weighted images. In addition, synthesized ADC maps can be calculated off-line. On diffusion-weighted imaging (DWI), either a decrease in diffusion or an increase in T2 relaxation time can produce hyperintensity. By comparison, only changes in water diffusibility can produce a signal change in ADC maps. Cytotoxic edema due to acute infarction is characterized on early imaging by ADCs that are markedly decreased compared to those of normal brain tissue and produces hyperintensity on DWI and hypointensity on ADC maps. In contrast, purely vasogenic edema is characterized by ADCs that are increased compared to those of normal brain tissue.

Because DWI has both T2 and diffusion components, vasogenic edema may appear hypointense, isointense, slightly hyperintense, or heterogeneous on DWI depending on the extent of the T2 signal contribution. When vasogenic edema produces DWI hyperintensity due to T2 “shine through,” the DWI pattern may resemble that seen...
in acute or subacute infarction. Vasogenic edema, however, usually produces hyperintensity on ADC maps, in contrast to the marked hypointensity that one would expect in early ischemic lesions.

We studied 13 illustrative patients with acute cerebral dysfunction due to vasogenic edema as evidenced by ADC hyperintensity. We review the clinical syndromes and imaging characteristics associated with these conditions and examine the potential influence of ADC maps on clinical management.

Materials and Methods

We identified 13 patients (range, 17-79 years) from October 1995 to October 1997 who presented to the neurology service with acute neurologic deficits suggesting acute stroke as a diagnostic possibility, but in whom another diagnosis was made based on diffusion MRI. Based on in-depth analysis of DWI scans performed from December 1994 to November 1995 and from April 1996 to September 1997, we estimate that during the time period addressed in this article, we scanned approximately 380 patients with diffusion MRI. Of these, 88% of patients were diagnosed with acute stroke or transient ischemic attack and 12% of patients had a final diagnosis other than ischemia (Ramon G. Gonzalez, MD, personal communication, June 15, 1999).

In 11 of 13 patients, unenhanced head CT demonstrated abnormal hypodense regions, which had been reported as abnormal. In 2 of 13 patients, initial head CT had been reported as normal. One was an outside scan of unknown quality, and the other was performed at our institution and was clearly abnormal on subsequent review by the authors. CT and MRI time points were recorded or were estimated from available information retrospectively. In all patients, T2-weighted MRI demonstrated abnormal hyperintense regions and ADC maps demonstrated abnormal hyperintense regions. At the time, echo planar images were produced off-line and ADC maps were not routinely available until the following day. A neuroradiologist (PWS) and neurologist (LHS) reviewed the patient records, and 2 neuroradiologists (PWS, RGG) and 2 neurologists (LHS, WJK) reviewed the brain images. The clinical history, predisposing risk factors, clinical follow-up, CT, fluid-attenuated inversion recovery (FLAIR), T2, DWI, and ADC characteristics on presentation and follow-up were recorded. Nine of 13 patients were personally evaluated (LHS, WJK). We have previously reported 4 of these patients (cases 5, 7, 8, 10) in separate articles.

MRI was performed on a 1.5-T Signa whole-body scanner (General Electric, Waukesha, WI) with echo planar capabilities (Advanced NMR Systems, Wilmington, MA). DWI and ADC maps were obtained using single-shot echo planar imaging [TR = 6000 ms, TE = 118 ms, 40 × 20-cm field of view (FOV), 256 × 128 matrix size, 20 axial slices, 6-mm slice thickness, 1-mm gap]. The effective gradient strength was 14 mT/m, and b values were 1221 mm²/s and 47 mm²/s with 6 gradient directions and 3 signal averages. The trace of the diffusion tensor was calculated to produce isotropic DWI and ADC maps. This methodology has been previously described in detail.

Other routine MRI sequences included sagittal T1-weighted images [TR = 650 ms, TE = 16 ms, 20 × 20-cm FOV, 256 × 192 matrix size, 5-mm slice thickness, 1-mm gap, 1 signal average], fast spin echo proton density weighted images [TR = 2500 ms, TE = 18 ms, 20 × 20-cm FOV, 256 × 256 matrix size, 5-mm slice thickness, 1-mm gap, 1 signal average], fast FLAIR images [TR = 10,002 ms, TE = 141 ms, TI = 2200 ms, 24-cm FOV, 256 × 192 matrix size, 5-mm slice thickness, 1-mm gap, 1 signal average], and fast spin echo T2-weighted images [TR = 4200 ms, TE = 102 ms, 20 × 20-cm FOV, 256 × 256 matrix size, 5-mm slice thickness, 1-mm gap, 1 signal average].

CT of the head was performed on an Advantage helical scanner (General Electric, Waukesha, WI) with 5 mm contiguous axial slices with 140 kVp, 340 mAs, and 1-second scan time.

Mean ADC for a selected region of interest (ROI) was obtained with a commercially available image analysis program (Alice, Parexel, CO). ROIs were sampled from the core of an area of ADC hyperintensity. Control ROIs were taken from a similar region on the contralateral side of the brain when the contralateral side of the brain was of normal signal intensity. Otherwise, control ROIs were taken from the thalamus (for gray-matter lesions) or corpora of the white-matter lesions as appropriate.

Means of lesion ADCs were compared to means of control ADCs with a paired 2-tailed Student t test after an F test was performed to test the equality of variance.

Results

All 13 patients had clearly defined risk factors for ischemic stroke, including atherosclerosis, vasculitis, and potential hypercoagulability. They presented with acute neurologic deficits suggestive of acute ischemic stroke (9 of 13) or suggestive of another diagnosis but with acute ischemic stroke in the differential diagnosis (4 of 13). Demographic details, clinical findings, and imaging findings are presented in Table 1. All patients underwent a noncontrast head CT as the initial imaging study within 24 hours of symptom onset, after which a presumptive diagnosis was
made (Table 1). Head CT scans in 12 of 13 patients demonstrated hypodense regions for which the differential diagnosis included acute infarction. Head CT scan in 1 of 13 patients was performed within 1 hour of symptom onset and was reportedly normal at an outside hospital (ie, still consistent with acute ischemic injury).

In all patients, T2-weighted MRI was performed within a mean of 30.7 hours after symptom onset (range, 1-72 hours) and demonstrated abnormal hyperintense regions. In many cases, these were more extensive than the abnormalities as visualized on CT. Mean of ADC ratios (lesion regions of interest compared with normal contralateral brain) for the entire cohort was 1.84 ± 0.38 (range, 1.31-2.55) (Table 1). On DWI, these regions were hypointense in 3 of 13 patients, isointense in 4 of 13 patients, heterogeneous in 3 of 13 patients, and hyperintense in 3 of 13 patients. On ADC maps, the abnormal regions were characterized by hyperintensity. The mean ADC obtained in each selected ROI characterized by hyperintensity on ADC maps was significantly higher than the mean ADC of the control ROI (P < .0001). These findings confirmed the diagnosis of vasogenic edema and excluded acute infarction as the major underlying pathophysiology. No lesions demonstrated hemorrhagic components on CT or MRI.

Based on initial clinical assessment and head CT, the presumptive diagnosis of stroke was made in 9 of 13 patients. Final diagnoses included posterior leukoencephalopathy (n = 5), glioblastoma multiforme (n = 1), cerebral venous sinus thrombosis (n = 2), and hyperperfusion syndrome following carotid endarterectomy (n = 1). The presumptive diagnosis in 4 of 13 patients was one other than stroke, but it was the neurologist’s concern that ischemic infarction be excluded. Three pregnant patients were initially thought to have posterior leukoencephalopathy secondary to eclampsia. However, the clinical history and distribution of imaging abnormalities raised concern about posterior circulation infarction or venous sinus thrombosis. The final diagnoses were posterior leukoencephalopathy (n = 3). One patient initially thought to have HIV encephalitis or infarction secondary to vasculitis was ultimately diagnosed with HIV encephalitis (n = 1). These findings are summarized in Table 1.

In each patient, the identification of a vasogenic edema pattern changed the presumptive diagnosis or significantly altered patient management. Initial and final diagnoses, clinical management, and patient outcomes are summarized in Table 1. In all patients except case 2, specific stroke treatments were discontinued or not initiated. In this patient, heparin had been started for possible ischemic stroke but was continued for documented venous thrombosis. The treatments included anticoagulation with heparin (cases 1, 3, 4, 5, 6, 7, 8, 10, 11, 13), planned evaluation for a source of embolism (cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10), radiotherapy (case 9), and/or immunosuppression (case 13). In all patients except case 2, new treatments targeted to the cause of the vasogenic edema were initiated. These included metastatic evaluation (case 1), stricter blood pressure control (cases 3, 4, 5, 6, 7, 8, 10), slow sodium correction (case 7), transvenous thrombolysis (case 9), aggressive antiviral therapy (case 12), and treatment to reduce cerebral edema (case 11).

Eight patients had normal neurologic examinations at discharge; 7 of these 8 underwent follow-up MRI that demonstrated complete resolution or marked improvement of vasogenic edema. Two patients (cases 2, 8) had only mild residual neurologic deficits at discharge and had resolution of their vasogenic edema on follow-up MRI. One patient (case 1) had a stable neurologic exam after resection of a glioblastoma with postoperative changes on his follow-up MRI. Two patients (cases 5, 11) had stable neurologic deficits with improvement in their vasogenic edema on early follow-up MRI scans.

Of note, 4 patients (cases 5, 8, 9, 11) had regions of brain consistent with ischemic infarction at follow-up imaging. Two of these patients (cases 8, 9) had small areas of decreased ADC within the larger regions of increased ADC on their initial MRI scans, and these small areas went on to complete infarction as would be expected. The patient in case 9 originally had a transient neurologic event and seizure referable to a CT-hypodense lesion detected in the left parietal lobe. This was felt to be due to tumor or thromboembolism, and MRI was not performed until 10 days later when new symptoms developed that were not referable to the parietal lesion. A diagnosis of venous sinus thrombosis ultimately explains all the lesions and symptoms.

Two other patients (cases 5, 11) ultimately developed infarctions in regions initially characterized only by increased ADC (ie, potentially reversible vasogenic edema). One patient with posterior leukoencephalopathy without severe hypertension developed reversal of ADC from hyperintensity to hypointensity and died of multiorgan failure. This patient was discussed and illustrated in a previous report.12 The other patient with hyperperfusion syndrome following carotid endarterectomy (case 11) initially had near interval resolution of her vasogenic edema with clinical improvement. One month later, however, she developed infarction in the left internal carotid artery territory of unclear etiology and had persistent lower extremity weakness and speech difficulty.
<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Findings</th>
<th>CT Findings</th>
<th>Presumptive Diagnosis</th>
<th>Conventional MRI Findings</th>
<th>Diffusion MRI Findings</th>
<th>Final Diagnosis and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sudden-onset blurred vision, dizziness, apraxia, and motor aphasia in a 79 y/o F with history of atrial fibrillation, transient ischemic attack, and seizures</td>
<td>L posterior parietal cortical and subcortical hypodensity</td>
<td>L MCA stroke</td>
<td>-72 h after sx onset ADC: hyperintense Mean ADC&lt;sub&gt;l&lt;/sub&gt; = 1.63 × 10⁻³; range, 1.30-1.81; ADC&lt;sub&gt;r&lt;/sub&gt; = 2.13 DWI: hypointense</td>
<td>Brain tumor Heparin and embolic w/u discontinued. Metastatic w/u begun. L parietal glioblastoma was resected 2 weeks after initial MRI.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Viral prodrome f/b aphasia, lethargy, L gait ataxia, L hemiparesis, and R gaze preference in a 17 y/o WF on OCP</td>
<td>Bilateral thalamic hypodensity</td>
<td>Basilar stroke</td>
<td>~24 h after sx onset ADC: hyperintense; also noted R thalamic hypointensity Mean ADC&lt;sub&gt;l&lt;/sub&gt; = 4.07 × 10⁻³; range, 3.59-4.74; ADC&lt;sub&gt;r&lt;/sub&gt; = 1.81 DWI: hyperintense; also noted hyperintense R thalamic focus</td>
<td>Deep venous sinus thrombosis Continued on intravenous heparin. No embolic w/u done. Resolution of vasogenic edema w/ marked neurologic improvement at 12 d. Small R thalamic hemorrhage in region of low ADC.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Headache, visual loss, and weakness f/b seizure in a 23 y/o AF 75 d post partum, with HTN, Wegener’s, and renal failure on immunosuppression</td>
<td>Bilateral posterior parietal cortical and subcortical hypodensity</td>
<td>Eclampsia; r/o posterior circulation embolic strokes</td>
<td>~12 h after sx onset ADC: hyperintense Mean ADC&lt;sub&gt;l&lt;/sub&gt; = 1.10 × 10⁻³; range, 0.89-1.27; ADC&lt;sub&gt;r&lt;/sub&gt; = 1.52 DWI: hyperintense</td>
<td>Eclampsia Stricter BP control and treatment for eclampsia. No heparin. No embolic w/u done. Normal neurologic exam at discharge 4 d after symptom onset.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Headache f/b confusion, visual changes, and seizures in a 29 y/o WF 9 m pregnant</td>
<td>Bilateral occipital cortical and subcortical hypodensity</td>
<td>Eclampsia; r/o PCA strokes or venous sinus thrombosis</td>
<td>~24 h after sx onset ADC: hyperintense Mean ADC&lt;sub&gt;l&lt;/sub&gt; = 1.56 × 10⁻³; range, 1.18-1.82; ADC&lt;sub&gt;r&lt;/sub&gt; = 2.40 DWI: heterogeneous</td>
<td>Eclampsia Strict BP control and treatment for eclampsia. No heparin. No embolic w/u done. Normal neurologic exam and markedly improved vasogenic edema on MRI 5 d after symptom onset.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Stupor with R hemiparesis and visual loss in a 55 y/o WF with h/o CAD, HTN, and hyperlipidemia</td>
<td>Bilateral PCA/MCA and L ACA/MCA border-zone cortical and subcortical hypodensity</td>
<td>Border-zone strokes</td>
<td>~48 h after sx onset ADC: hyperintense Mean ADC&lt;sub&gt;l&lt;/sub&gt; = 1.63 × 10⁻³; range, 1.43-1.84; ADC&lt;sub&gt;r&lt;/sub&gt; = 2.13 DWI: hypointense</td>
<td>Posterior leukoencephalopathy Strict BP control. No heparin. No embolic w/u done. Resolving vasogenic edema at 8 d, but new foci of cytotoxic edema at 14 d in regions of initial increased ADC. Death due to multiorgan system failure.</td>
<td></td>
</tr>
<tr>
<td>Case Number</td>
<td>Clinical Presentation</td>
<td>Imaging Findings</td>
<td>Pathology/Additional Information</td>
<td></td>
<td></td>
<td></td>
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<td>-------------</td>
<td>--------------------------------------------------------------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<td></td>
</tr>
</tbody>
</table>
| 6           | Headache, coma, absent pupil and corneal reflexes, and L hemiparesis in a 31 y/o WF 1 d postpartum with acute HTN | Bilateral thalamic, cerebellar, and pontine hypodensity  
Bilateral posterior circulation strokes | T2: bilateral thalamic, cerebellar, pontine, deep white matter and cortical and subcortical hypointensity  
ADC: hyperintense  
Mean ADC_L = 1.10 × 10^-3; range, 0.96-1.28;  
ADC_R = 1.45  
DWI: hypointense | Eclampsia  
Strict BP control and treatment for eclampsia.  
No heparin. No embolic w/u done. Normal neurologic exam at 7 d, and complete resolution of vasogenic edema on f/u MRI at 10 months. |
| 7           | Headache f/b cortical blindness in a 66 y/o WF with h/o CAD, HTN, hyperlipidemia, and pelvic CA | Bilateral occipital and parietal cortical and subcortical hypodensity  
Bilateral posterior circulation embolic strokes | T2: bilateral occipital and parietal cortical and subcortical hypointensity  
ADC: hyperintense  
Mean ADC_L = 0.99 × 10^-3; range, 0.87-1.13;  
ADC_R = 1.41  
DWI: isointense | Posterior Leukoencephalopathy  
Strict BP control. Slow correction of serum sodium. Heparin and embolic w/u discontinued. Normal neurologic exam at discharge and markedly improved vasogenic edema on f/u MRI 2 d after initial exam. |
| 8           | ARDS f/b generalized seizure, R gaze preference, weak L corneal reflex, and L facial droop in a 33 y/o WF 35 d postpartum | Bilateral occipital and parietal cortical and subcortical hypodensity  
Bilateral posterior circulation embolic strokes | T2: bilateral occipital cortical and subcortical hyperintensity  
ADC: hyperintense  
Mean ADC_L = 1.96 × 10^-3; range, 1.73-2.18;  
ADC_R = 2.55; also noted occipital hypointensity  
DWI: heterogeneous; also noted occipital hyperintensity | Posterior leukoencephalopathy  
Strict BP control. No heparin. No embolic w/u done. Complete resolution of vasogenic edema on f/u scan at 6 m w/ small peripheral cortical infarcts in regions of initial low ADC causing mild visual deficits. |
| 9           | TIA w/L hand weakness and numbness f/b seizure in a 30 y/o WF with h/o metastatic CA on chemotherapy | L parietal cortical and subcortical hypodensity  
L MCA embolic stroke; r/o metastatic tumor | T2: L parietal and bilateral deep gray nuclei hyperintensity  
MRV: deep venous sinus thrombosis | Deep venous sinus thrombosis  
No embolic w/u done.  
Tumor radiotherapy discontinued. Transvenous thrombolysis performed. Normal neurologic exam at 7 w. Complete resolution of vasogenic edema and very small R thalamic stroke in region of low ADC on initial MRI. |
| 10          | Severe neck pain f/b seizure in a 30 y/o HF, 9 m pregnant with acute HTN | Bilateral occipital and parietal cortical and subcortical hypodensity  
Eclampsia; r/o bilateral posterior circulation strokes due to vertebral dissection | T2: bilateral occipital, parietal, and frontal cortical and subcortical hyperintensity  
ADC: hyperintense  
Mean ADC_L = 6.16 × 10^-3; range, 5.10-6.93;  
ADC_R = 1.55  
DWI: hypointense | Eclampsia  
Stricter BP control and treatment for eclampsia.  
No heparin. No embolic w/u done. Normal neurologic exam at 5 d. Complete resolution of vasogenic edema on f/u MRI at 4 weeks. |
<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Findings</th>
<th>CT Findings</th>
<th>Presumptive Diagnosis</th>
<th>Conventional MRI Findings</th>
<th>Diffusion MRI Findings</th>
<th>Final Diagnosis and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>R facial twitching f/b status epilepticus in a 79 y/o WF with HTN, diabetes, and 7 d post L CEA</td>
<td>Outside CT reportedly normal.</td>
<td>Seizures due to embolic stroke after recent carotid surgery</td>
<td>T2: L frontal and parietal cortical and subcortical white matter hyperintensity</td>
<td>~48 h after sx onset ADCl = 1.04 x 10⁶; range (0.86-1.24); ADCr = 1.99 DWI: isointense</td>
<td>Post-endarterectomy hyperperfusion syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strict BP control. Heparin discontinued. Treatment to reduce cerebral edema and control seizures. Resolving vasogenic edema at 11 d, but at 6 w MRI w/infarct in the L parietal area that had initial increased ADC. Patient w/ speech difficulty, bilateral leg weakness, and refractory seizures at discharge.</td>
</tr>
<tr>
<td>12</td>
<td>Headache w/ visual loss, f/b apraxia, and L facial droop in a 35 y/o WF with HIV, migraine, and PE on warfarin</td>
<td>Bilateral cerebellar and occipital and parietal cortical and subcortical hypodensity</td>
<td>HIV encephalitis; r/o vasculitic infarctions or PML</td>
<td>T2: bilateral cerebellar, occipitoparietal cortical and subcortical hyperintensity</td>
<td>Postgradolinium T1: no enhancement ADCl = 6.93 x 10⁶; range, 5.77-8.02; ADCr = 1.85 DWI: isointense</td>
<td>HIV encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjuvant aggressive antiviral HIV treatment. Normal neurologic exam at 8 d. Markedly improved vasogenic edema on MRI at 1 w.</td>
</tr>
<tr>
<td>13</td>
<td>Headache and diplopia f/b seizure in a 29 y/o HF with lupus nephritis on immunotherapy</td>
<td>Hypodense lesion in brainstem (official report was “normal”)</td>
<td>Lupus vasculitis w/strokes; r/o cerebritis and venous sinus thrombosis</td>
<td>T2: cerebellar, brainstem, and scattered cortical and subcortical hyperintensity</td>
<td>~48 h after sx onset ADCl = 0.84 x 10⁶; range, 0.71-0.94; ADCr = 1.31 DWI: isointense</td>
<td>Hypertensive Encephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strict BP control. No heparin or high dose immunosuppression. Normal neurologic exam at discharge 4 d after initial MRI. Complete resolution of vasogenic edema on f/u MRI at 3 w.</td>
</tr>
</tbody>
</table>

w/u = workup, y/o = year old, h = hour, m = month, d = day, L = left, R = right, F = female, W = white, H = Hispanic, A = African American, MRI = magnetic resonance imaging, DWI = diffusion-weighted imaging, ADC = apparent diffusion coefficient, ADCl = lesion ADC, ADCr = ADC ratio, BP = blood pressure, MCA = middle cerebral artery, PCA = posterior cerebral artery, ACA = anterior cerebral artery, TIA = transient ischemic attack, sx = symptom, f/b = followed by, PML = progressive multifocal leukoencephalopathy, OCP = oral contraceptive pills, PE = pulmonary embolism, CAD = coronary artery disease, HTN = hypertension, CA = cancer, ARDS = adult respiratory distress syndrome, MRV = magnetic resonance venography, CEA = carotid endarterectomy.
Conventional images, DWI, ADC, and follow-up images of cases 1, 4, 6, and 11 are presented in Figures 1 through 4.

Discussion
Occasionally, in complex clinical scenarios, CT and conventional MRI may not differentiate tissue signal abnormality due to ischemic infarction from that due to vasogenic edema. In this setting, hyperintensity on ADC maps may help identify the subset of patients whose neurologic deficits are due to vasogenic edema. These patients have potentially reversible clinical syndromes that require a different therapeutic approach.

Posterior leukoencephalopathies typically produce vasogenic edema in subcortical white matter but frequently involve overlying cortex. These include hypertensive encephalopathy, eclampsia, cyclosporine toxicity, FK-506, thrombotic thrombocytopenic purpura, and posterior leukoencephalopathies without a known cause. The posterior predilection can sometimes resemble posterior cerebral artery infarction. Edema in the deep white matter, deep gray nuclei, brain stem, and cerebellum can also appear to be in the distribution of.

Fig 1. Case 1. A 79-year-old man with atrial fibrillation and sudden-onset blurred vision, dizziness, apraxia, motor aphasia, transient ischemic attack, and seizures with hypointensity on diffusion-weighted imaging (DWI). The arrow indicates a left parietal occipital lesion that is hypodense on axial computed tomography (A). On magnetic resonance imaging obtained 72 hours after symptom onset, the lesion is hyperintense on axial fluid-attenuated inversion recovery (B), hyperintense on axial T2 (C), hypointense on axial DWI (D), and hyperintense on axial apparent diffusion coefficient (ADC) (E). Within the lesion, the mean ADC₀ = 1.63 × 10⁻³ with ADC ratio 2.13. These findings are consistent with vasogenic edema. A contrast-enhanced axial T1-weighted image at a different angle obtained the following day (F) demonstrates an underlying 2-cm ring-enhancing mass, ultimately diagnosed as a glioblastoma multiforme.
arterial vascular territories. Cerebral cortical vein thrombosis causes vasogenic edema involving gray and white matter that may be confined coincidentally within a defined arterial vascular territory. Also, deep venous thrombosis can produce bilateral thalamic T2 hyperintensity mimicking arterial infarctions in the “top of the basilar” territory. Hyperperfusion syndrome following carotid endarterectomy produces vasogenic edema mimicking internal carotid artery territory infarction. While unusual, tumoral edema can sometimes be mistaken for ischemic infarction on unenhanced images.

Furthermore, patients with vasogenic edema syndromes may present with focal neurologic deficits suggestive of acute ischemic stroke. This was the case in 9 of our reported patients (cases 1, 2, 5, 6, 7, 8, 9, 11, 13). Alternatively, patients with vasogenic edema syndromes may present with clinical deficits such as headache or seizure that are highly suggestive of vasogenic edema (eg, eclampsia) but in whom acute ischemic stroke needs to be excluded. This was the case in 4 of our patients (cases 3, 4, 10, 12). Thus, in complex cases, clinical evaluation and conventional imaging alone may not adequately exclude stroke in patients with new onset focal neurologic deficits.

It has been well documented that as cytotoxic edema develops due to ischemia, the ADCs of affected brain tissue decrease and remain low for 1 to 2 weeks. This effect produces hyperintensity on DWI and hypointensity on ADC maps. The ADC returns to baseline at 1 to 2 weeks and remains elevated thereafter. Conversely, vasogenic edema is characterized by a relative increase in water in the extracellular compartment as compared to the increase in intracellular water seen with cytotoxic edema. Extracellular water is more mobile and results in...
increased ADCs. This effect has been demonstrated in animal models of cerebral edema and in selected patients with gliomas, eclampsia, and hypertensive encephalopathy. Because DWI has both T2 and diffusion components, vasogenic edema may appear hypointense, isointense, hyperintense, or heterogeneous on DWI. When vasogenic edema produces DWI hyperintensity due to T2 “shine through,” the DWI pattern may resemble that seen in acute or subacute infarction. Vasogenic edema, however, always produces hyperintensity on ADC maps, in contrast to the marked hypointensity that one would expect in early ischemic lesions. Thus, whenever hyperintense lesions are visualized on T2-weighted images, DWI should be obtained and postprocessed with ADC map calculation.

At 1 to 2 weeks, the ADCs in ischemic stroke increase to and then exceed the level of the ADCs of normal brain tissue. This most likely reflects the accumulation of extracellular water and development of gliosis as ischemic stroke evolves. Thus, 1 to 2 weeks after symptom onset, ischemic stroke and vasogenic edema syndromes may have similar appearances on DWI and ADC maps. From this time point forward, the images can no longer reliably distinguish between the 2 syndromes. However, the diagnosis of ischemic injury is usually either established or excluded by this time.

Ischemic and vasogenic edema may coexist in an individual patient. Interestingly, as was demonstrated in cases 8 (posterior leukoencephalopathy) and 9 (deep venous sinus thrombosis), DWI and ADC maps are sensitive enough to detect foci of ischemia even within regions of vasogenic edema. In addition, if the vasogenic edema does not respond to treatment, as was seen in cases 5 (posterior leukoencephalopathy) and 11 (hyperperfusion syndrome following carotid endarterectomy), follow-up images may demonstrate new regions of ischemia in areas

Fig 3. Case 6. A 31-year-old woman 1 day postpartum with acute hypertension, headache, coma, absent pupil and corneal reflexes, and left hemiparesis with hyperintensity on diffusion-weighted imaging (DWI). On magnetic resonance imaging obtained 2 hours after symptom onset, the arrows indicate bilateral cerebellar lesions that are hyperintense on axial T2 (A), axial DWI (C), and axial apparent diffusion coefficient (ADC) (D). There is also hyperintensity in the pons on axial T2 (B). These findings are consistent with vasogenic edema. Within the lesion, the mean ADC = 1.10 × 10−3 with ADC ratio 1.45. Axial T2 obtained 10 days later (E) demonstrates that the cerebellar lesions have resolved. A diagnosis of eclampsia was made. The pontine lesion in B also resolved (not shown).
previously characterized by vasogenic edema only, suggesting that even potentially salvageable tissue is vulnerable to permanent injury. The causes of subsequent tissue death are varied and may include compression of vessels due to increased intracranial pressure, hemorrhagic stroke, tissue shifts, and release of cytotoxic materials.

Although we have selected representative cases, a wide variety of syndromes can produce vasogenic edema. The most important factors determining the development of vasogenic edema are hydrostatic forces and increased vascular permeability. In animals, it has been demonstrated that a rapid increase in arterial pressure leads to overdistension of arterioles, mechanical disruption of tight junctions, and movement of fluids and proteins into the interstitium. This mechanism likely accounts for the vasogenic edema observed in patients with hypertensive encephalopathy or with hyperperfusion syndrome following carotid endarterectomy. Furthermore, animal models of venous occlusion have demonstrated increased pressure in the postcapillary venules, opening of tight junctions, and leakage of fluorescein dye. This mechanism is likely responsible for the vasogenic edema observed in patients with venous sinus thrombosis. Both cyclosporine and FK-506 have been associated with the
development of vasogenic edema. Although a direct effect on the cerebrovascular endothelium has not been demonstrated, both drugs have toxic effects on vascular endothelial cells. Ultrastructural studies of malignant brain tumors have demonstrated alterations in capillary endothelium (open intercellular tight junctions, wide gap junctions, abundant endothelial vesicles, and defects in capillary basement membranes) thought to lead to blood brain barrier disruption and edema formation.

Correctly identifying a vasogenic edema syndrome in the acute setting may affect patient management. Misdiagnosis of a vasogenic edema syndrome as acute ischemia could lead to unnecessary pharmacological therapy that increases the risks of systemic and intracranial hemorrhage and the expense of unnecessary diagnostic tests. Failure to correct relative hypertension in vasogenic edema syndromes could result in neurologic worsening due to increased edema. The identification of a vasogenic edema pattern on ADC maps triggers further diagnostic evaluation to establish the correct etiology and therapy. Based on our appreciation of cases such as the ones presented here, ADC maps are now immediately calculated and displayed for clinical interpretation at our institution. We believe that this helps to prevent misdiagnosis and inappropriate therapy and should be the standard methodology for image interpretation. If ADC maps cannot be calculated, then less technically challenging methods such as ratio images or exponential images should be displayed. Currently, several commercial vendors offer ADC and/or exponential imaging capabilities.

In conclusion, in patients with acute neurologic deficits and T2 hyperintense abnormalities, DWI may be confounded by T2 shine-through. Image postprocessing such as the calculation of ADC maps can differentiate the elevated diffusion associated with vasogenic edema from the restricted diffusion associated with cytotoxic edema. This may profoundly effect patient management.

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References


Lack of Relation Between Severity of Stroke and Severity of Extracranial Internal Carotid Artery Lesions in Taiwanese First-Ever Ischemic Stroke Patients

ABSTRACT

Background and Purpose. The authors attempt to determine whether hemodynamically significant extracranial internal carotid artery (ICA) lesions correlate with the severity of first-ever hemispheric ischemic stroke. Methods. Carotid duplex was used to evaluate carotid arteries. The National Institutes of Health Stroke Scale was used to describe the severity of the stroke and was stratified as follows: 1-6 = mild, 7-15 = moderate, >15 = severe. Duplex findings were categorized according to velocity criteria into <50% stenosis if ICA peak systolic velocity (PSV) (cm/s) <140 and >50% stenosis if ICA PSV >140 or ratio of ICA and common carotid artery in PSV >2. No detectable flow at ICA was considered occlusion. Stroke subtype was classified according to TOAST criteria. Results. Two hundred nineteen consecutive patients were enrolled, including 127 with mild, 65 with moderate, and 27 with severe stroke. The prevalence of ICA stenosis >50% in each group was 3.6%, 1.4%, 0.9%, respectively. Two patients in the severe group had total ICA occlusion. The overall prevalence of significant ICA lesions was 6.8%. Conclusions. There is no positive correlation of stroke severity with the severity of duplex findings, which may be due to low prevalence of significant ICA lesions or other stroke mechanisms. Most of the patients had mild stroke, and the majority had ICA stenosis <50%. Small-vessel occlusion tended to have mild severity of stroke. Intracranial artery lesions or other factors causing stroke in Taiwanese should be investigated. Given the low incidence of significant extracranial carotid disease in symptomatic Taiwanese stroke patients, routine screening of symptomatic Taiwanese for extracranial carotid artery disease does not provide enough information to determine stroke mechanism, and transcranial Doppler should be added to the screening tests.

Key words: Internal carotid artery, diameter stenosis, first-ever ischemic stroke, velocity.


The severity of carotid atherosclerosis as evaluated by ultrasonography is a useful indicator of the risk of ischemic stroke in symptomatic patients and is a major risk factor predicting the occurrence of neurologic and other vascular events in asymptomatic patients. It has been shown that mortality increases significantly with the degree of ipsilateral internal carotid artery (ICA) stenosis, but a correlation with stroke severity has not been reported. Although carotid disease can cause lacunar type strokes, it is more likely to cause large, embolic strokes or large hemodynamic “watershed” infarcts. We performed a prospective study using noninvasive duplex methods to evaluate ipsilateral lesions of extracranial ICA to correlate with the severity of the first-ever hemispheric ischemic stroke.

Materials and Methods

Patients admitted to the study hospital’s department of neurology ward during the study period (September 28, 1998, to October 31, 1999) were recruited for this study. First-ever ischemic stroke was defined as acute onset of neurological deficits due to ischemic vascular insult without past history of cerebrovascular disease. All patients had brain computed tomogram to exclude hemorrhage and carotid duplex study to evaluate extracranial carotid artery. The National Institutes of Health Stroke Scale (NIHSS) was used to describe the severity of the stroke. Moderate strokes were defined as having scores between

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7 to 15, whereas scores below this range (1-6) indicated mild stroke and scores above this range (>15) indicated severe stroke. Carotid duplex examination was carried out using Aspen (Acuson) with a 4-MHz transducer. Peak systolic velocity and diastolic velocity were measured in the external carotid artery, ICA, and common carotid artery, and we measured the velocity before, at, and after the maximally stenotic area. Duplex findings were categorized according to velocity criteria into <50% stenosis if ICA peak systolic velocity (PSV) (cm/s) <140 and >50% stenosis if ICA PSV > 140 or ratio of ICA and common carotid artery in PSV >2. No detectable flow at ICA was considered occlusion. Stroke subtype was classified according to TOAST criteria based on clinical features, brain imaging, cardiac imaging (transesophageal and/or transesophageal echocardiography), ultrasonography of extracranial and/or intracranial large arteries, angiography (magnetic resonance or conventional angiography), and other remarkable laboratory findings.

**Statistical Methods**

Chi-square was used for the statistical analysis, and mean (SD) was used to describe the data.

**Results**

Two hundred nineteen consecutive patients were enrolled, including 127 mild, 65 moderate, and 27 severe stroke patients. Characteristics of the patients are shown in Table 1. In the 3 severity groups, there was 6.3% (8/127), 4.6% (3/65), and 7.5% (2/27) ICA stenosis >50%, respectively. Two patients in the severe group had total ICA occlusion (Table 2). The overall prevalence of significant ICA lesions is 6.8% (Table 3). Table 4 shows the number and percentage of stroke subtype in the 3 severity groups. There was no positive correlation of stroke severity with the severity of duplex findings. The prevalence of significant extracranial ICA lesions is low in first-ever Taiwanese ischemic stroke patients. Most of the patients in this study had mild stroke, and a majority had ICA stenosis <50%. Among stroke subtypes, large-artery atherosclerosis and cardioembolism groups tended to have more severe stroke as compared to small-vessel occlusion group. This finding was statistically significant.

**Discussion**

This study demonstrated that there is a low prevalence of significant extracranial ICA lesions in first-ever Taiwanese stroke patients. Additionally, significant ICA stenosis was not related to stroke severity, which may due to the low prevalence of significant ICA lesions and other stroke mechanisms. Among the stroke subtypes, small-vessel occlusion tended to have mild severity of stroke as compared to large-artery atherosclerosis and cardioembolism. There were only 6 patients in the large-artery atherosclerosis group, and 9 patients in the undetermined group had significant ICA lesions. Most of the

<table>
<thead>
<tr>
<th>Stroke Severity*</th>
<th>No.</th>
<th>%</th>
<th>ICA &lt;50%</th>
<th>%</th>
<th>ICA &gt;50%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (1-6)</td>
<td>127</td>
<td>58</td>
<td>119/127</td>
<td>93.7</td>
<td>8/127</td>
<td>6.3</td>
</tr>
<tr>
<td>Moderate (7-15)</td>
<td>65</td>
<td>29.9</td>
<td>62/65</td>
<td>95.4</td>
<td>3/65</td>
<td>4.6</td>
</tr>
<tr>
<td>Severe (&gt;15)</td>
<td>27</td>
<td>12.3</td>
<td>23/27</td>
<td>85</td>
<td>4/27b</td>
<td>15</td>
</tr>
</tbody>
</table>

a. As measured on the National Institutes of Health Stroke Scale.
b. Two patients had ICA occlusion.
stroke patients in this study had mild deficits, and a major-
ty had ICA stenosis <50%.

Extracranial carotid lesions are known to be a major cause of ischemic cerebrovascular disease. Large multi-
center prospective studies such as the North American Symptomatic Carotid Endarterectomy Trial⁵ and the European Carotid Surgery Trial⁶ have shown the etiologic significance of carotid lesions for ischemic stroke events in a symptomatic population, and several researchers have reported that the stroke event rate is closely related to the severity of carotid atherosclerosis,⁷⁻⁹ but a correla-
tion between stroke severity using NIHSS categorization and extracranial ICA lesions has not been studied. Our data showed that stroke severity did not correlate with extracranial ICA lesions but with stroke mechanisms. Previous studies have reported that Chinese stroke patients have more intracranial vessel disease than do white stroke patients, whereas extracranial disease is extremely rare.¹⁰,¹¹ Mori et al,¹² a Japanese study, reported that almost one half of their cases with carotid distribution transient ischemic attack came from intracranial arterial stenosis or occlusion. Feldmann et al¹³ also described that the preponderance of intracranial vascular lesions in Chi-
inese patients is similar to that seen in blacks and Japanese. Caplan et al¹⁴ reported that whites more commonly had disease of the extracranial vessels, particularly the cervical carotid artery.

In conclusion, intracranial artery lesions and other fac-
tors such as cardioembolic mechanism, nonathero-
sclerotic vasculopathies, hypercoagulable states, and hematologic disorders causing stroke in Taiwanese should be investigated. Given the low incidence of significant extracranial carotid disease in symptomatic Taiwanese stroke patients, routine screening of symptomatic Taiwanese only for extracranial carotid artery disease does not provide enough information to determine stroke etiology, and brain magnetic resonance angiography and transcranial Doppler should be added to our screening tests.

Table 3. Prevalence of Significant Internal Carotid Artery (ICA) Lesions

<table>
<thead>
<tr>
<th>Stroke Severity</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (1-6)</td>
<td>8/219</td>
<td>3.60</td>
</tr>
<tr>
<td>Moderate (7-15)</td>
<td>3/219</td>
<td>1.40</td>
</tr>
<tr>
<td>Severe (&gt;15)</td>
<td>4/219</td>
<td>1.80</td>
</tr>
<tr>
<td>Total</td>
<td>15/219</td>
<td>6.80</td>
</tr>
</tbody>
</table>

a. As measured on the National Institutes of Health Stroke Scale.

Table 4. Number and Percentage of Stroke Subtype in 3 Severity Stroke Groups

<table>
<thead>
<tr>
<th>Stroke Severity</th>
<th>Large-Artery Atherosclerosis</th>
<th>Cardioembolism</th>
<th>Small-Vessel Occlusion</th>
<th>Undetermined Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Mild (1-6)</td>
<td>18</td>
<td>38</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>Moderate (7-15)</td>
<td>16</td>
<td>33</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Severe (&gt;15)</td>
<td>14</td>
<td>29</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>100</td>
<td>38</td>
<td>100</td>
</tr>
</tbody>
</table>

a. As measured on the National Institutes of Health Stroke Scale.

References


Interobserver and Intraobserver Reliability of Venous Transcranial Color-Coded Flow Velocity Measurements

ABSTRACT

Background and Purpose. Venous transcranial color-coded duplex sonography is a new technique for noninvasive evaluation of the intracranial venous system. However, the interobserver and intraobserver reliability of this method is unclear. Methods. In 23 healthy volunteers (30 ± 7.3 years of age), the deep middle cerebral vein (dMCV), basal vein (BV), vein of Galen (VG), and straight (SRS), transverse (TS), and superior sagittal (SSS) sinuses in addition to the arterial segments of the circle of Willis were insonated through the temporal bone window on 2 consecutive days by 2 experienced examiners. The examiners were blinded to each other’s results. The interobserver and intraobserver reliability was calculated using a method described by Bland and Altman, resulting in 2-SD confidence intervals. Results. Non-angle-corrected and angle-corrected systolic and end diastolic venous flow velocities (FV) were in good accordance with published normal values, ranging between 8.6 and 19.2 cm/s. The interobserver reliabilities for non–angle-corrected systolic FVs in the dMCV, BV, VG, SRS, and TS were ±1.8, 2.4, 2.6, 3.3, and 4.6 cm/s; for angle-corrected systolic FVs, the interobserver reliabilities were ±2.5, 3.1, 13.9, 11.6, and 7.7 cm/s. The intraobserver reliabilities for non-angle-corrected systolic FVs in the dMCV, BV, VG, SRS, and TS were ±2.9, 3.2, 2.6, 3.2, and 6.1 cm/s; for angle-corrected systolic FVs, the intraobserver reliabilities were 3.2, 3.7, 13.9, 11.6, and 7.5 cm/s. Angle correction was not attempted for the SSS. The interobserver and intraobserver reliabilities for systolic FVs in the SSS were ±3.3 and ±3.3 cm/s, respectively. Conclusions. Intracranial venous FVs can be measured with a high interobserver and intraobserver reliability in healthy human subjects. Intraobserver reliability was higher for cerebral veins than for dural sinuses, predisposing them for follow-up examinations; however, angle correction for venous FVs in the VG and the SRS is not advisable.

Key words: Transcranial color-coded sonography, intracranial veins, dural sinuses, interobserver reliability, intraobserver reliability.

In contrast to the established clinical and scientific applications of transcranial color-coded duplex sonography (TCCS) in the evaluation of the intracranial arterial system, venous TCCS is a new, noninvasive modality for studying intracranial venous hemodynamics in patients with cerebral venous thrombosis, ischemic stroke, and head trauma. Examination protocols and normal venous flow velocities (FVs) have already been established. However, the interpretation of intracranial venous studies is hampered by the fact that the interobserver and intraobserver reliability of the method is unclear. The aim of this study was to provide data on the interobserver and intraobserver reliability of venous TCCS and to answer the following question: for which venous intracranial vessels are angle-corrected FV measurements feasible?

Participants and Methods

Out of 25 volunteers, 23 presumably healthy participants (11 females, 12 males; 30 ± 7.3 years of age) took part in this study. One male and 1 female were excluded because of an insufficient acoustic temporal bone window based on the lack of visibility of the mesencephalon. On 2 consecutive days, venous TCCS was performed by 2 examiners with at least 3 months of training in finding venous flow signals. The examiners were blinded to each other’s results. The order of insonation by the 2 examiners was decided randomly. The examinations were performed at
approximately the same time of day (±3 hours). Prior to each examination, blood pressure and heart rate were recorded.

All examinations were performed in the supine position according to previously published protocols. The ultrasound system was positioned on the right side of the proband’s head. In short, the temporal bone window was insonated using a TCCS system (Hewlett Packard, Sonos 2000) equipped with a 2.0-MHz sector transducer. After optimizing the color program, the different segments of the arterial circle of Willis (M1 segment of the middle cerebral artery [MCA], A1 segment of the anterior cerebral artery [ACA], and P1 and P2 segments of the posterior cerebral artery [PCA]) were insonated and peak systolic flow velocities (PSVs) and end diastolic flow velocities (EDVs) were recorded on both sides. Because angle correction has already been validated for arterial velocities, angle correction was applied in the case of paired vessels. Mean FVs were not registered due to difficulties with the construction of envelope curves around the venous Doppler spectra.

Statistical Analysis

Because the positive identification as well as the unambiguous failure to obtain Doppler signals from a vessel in case of occlusion are of diagnostic importance, we defined interobserver agreement on vessel identification as either the positive agreement of both examiners on the identification of a specific vessel or the failure to do so in contrast with the case of disagreement. In a similar manner, intraobserver agreement on vessel identification was defined as either the positive identification or the failure of depiction of a specific vessel on consecutive measurements by 1 examiner. Interobserver and intraobserver agreement on vessel identification was statistically analyzed using a Fisher exact test.

To assess the interobserver and intraobserver reliability of measurements of venous FVs, in a first step, correlation coefficients were calculated based on a linear regression model to compare the present data with older studies. For this purpose, the individual venous and arterial FV measurements of day 1 and day 2 of a specific examiner were averaged. Then, the averaged FVs of examiner A were correlated with those of examiner B. Correlation coefficients for the day-to-day comparison were calculated in an analogue manner. PSVs and EDVs were treated separately.

In a second step, data were analyzed using a method described by Bland and Altman. This method excludes a systematic bias of the data by relating the differences between corresponding FV measurements of examiner A and B \(D_{A-B}\) or between corresponding FV measurements of 1 examiner on day 1 and day 2 \(D_{1-2}\) to the respective mean of the corresponding data pairs. Based on these differences of FV measurements, 2-SD CIs for interobserver and intraobserver reliability were calculated. This again was performed for the PSVs and EDVs separately. Because side differences could not be excluded a priori, analysis was performed for the total of insonated vessels as well as separately for the left and right side in the case of paired vessels.

The differences of FV measurements in between examiners \(D_{A-B}\) and of consecutive measurements \(D_{1-2}\) were subjected to further statistical analysis. \(D_{A-B}\) and \(D_{1-2}\) values of a specific vessel were compared using a Stu-
dent $t$ test. Differences in the variance of $D_{A-B}$ and $D_{1-2}$ values were examined with a $F$ test. Prior to these procedures, the differences ($D_{A-B}$ and $D_{1-2}$) were tested for normal distribution; this hypothesis could not be rejected.

The means of PSVs and EDVs were calculated for comparison with previously reported data. Furthermore, evaluation for potential side differences was performed using a student $t$ test.

To compare heart rate and blood pressure measurements, a Wilcoxon matched pairs test was performed.

Results

Heart Rate and Blood Pressure Variations and Mean Arterial and Venous Flow Velocities

Neither for the measurements of examiner A and B nor for the consecutive examinations on day 1 and day 2 could significant ($P > .05$) differences be observed for blood pressure and heart rate.

The mean PSVs and EDVs of the examined arteries of the circle of Willis as well of the intracranial veins and sinuses are summarized in Table 1. This table also includes the absolute vessel identification rates reached in this study. To facilitate comparison with previously published data, venous mean flow velocities were calculated with and without angle correction. Significant side differences were observed for the dMCV and the TS ($P < .05$), with higher FV on the left compared to the right side: dMCV PSV 9.0 vs 8.2 cm/s; dMCV EDV 6.2 vs 5.6 cm/s; TS PSV 17.1 vs 15.6 cm/s; TS EDV 12.4 vs 11.0 cm/s. For all other vessels, no side differences could be detected.

Interobserver Reliability

The interobserver correlation coefficients (CIs) (Table 2) were higher for the intracranial veins than for the dural sinuses both for non–angle-corrected and angle-corrected PSVs and EDVs. Correlation coefficients were higher for the PSVs than for the EDVs. The CIs for the different seg-
Table 1. Mean Arterial and Venous Peak Systolic Flow Velocities (PSVs) and End Diastolic Velocities (EDVs)

<table>
<thead>
<tr>
<th>Vessel</th>
<th>No. of Averaged Measurements</th>
<th>Average Identification Rate</th>
<th>PSV (cm/s)</th>
<th>EDV (cm/s)</th>
<th>Median Insonation Angle (degree)</th>
<th>Quantile of Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA</td>
<td>178</td>
<td>96.7%</td>
<td>112.5 ± 20.2</td>
<td>50.8 ± 9.9</td>
<td>26</td>
<td>19-32</td>
</tr>
<tr>
<td>ICA</td>
<td>155</td>
<td>84.2%</td>
<td>86.5 ± 14.2</td>
<td>38.2 ± 7.4</td>
<td>0</td>
<td>0-7</td>
</tr>
<tr>
<td>ACA</td>
<td>165</td>
<td>89.7%</td>
<td>87.9 ± 18.8</td>
<td>41.7 ± 9.5</td>
<td>8</td>
<td>5-13</td>
</tr>
<tr>
<td>P1 PCA</td>
<td>156</td>
<td>84.8%</td>
<td>64.6 ± 11.8</td>
<td>30.0 ± 6.5</td>
<td>7</td>
<td>0-11</td>
</tr>
<tr>
<td>P2 PCA</td>
<td>176</td>
<td>95.7%</td>
<td>59.0 ± 13.6</td>
<td>28.2 ± 7.2</td>
<td>19</td>
<td>16-25</td>
</tr>
<tr>
<td>dMCV</td>
<td>168</td>
<td>91.3%</td>
<td>8.6 ± 1.9</td>
<td>5.9 ± 1.4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>BV</td>
<td>174</td>
<td>94.6%</td>
<td>11.9 ± 2.9</td>
<td>8.7 ± 2.2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>GV</td>
<td>90</td>
<td>97.8%</td>
<td>13.0 ± 3.1</td>
<td>9.6 ± 2.3</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>SRS</td>
<td>76</td>
<td>82.6%</td>
<td>11.6 ± 2.3</td>
<td>7.2 ± 1.8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>125</td>
<td>67.9%</td>
<td>16.4 ± 4.4</td>
<td>11.8 ± 3.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SSS</td>
<td>53</td>
<td>57.6%</td>
<td>12.2 ± 4.1</td>
<td>8.7 ± 3.3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values represent averaged flow velocity (FV) measurements on day 1 and day 2 and of examiner A and examiner B. Flow velocities are listed as mean ± SD. For venous structures, angle-corrected and non-angle-corrected FV measurements were performed; for arteries, only angle-corrected measurements were recorded. MCA = middle cerebral artery, ICA = internal carotid artery, ACA = anterior cerebral artery, PCA = posterior cerebral artery, dMCV = deep middle cerebral vein, BV = basal vein, GV = vein of Galen, SRS = straight sinus, TS = transverse sinus, SSS = superior sagittal sinus.

Table 2. Correlation Coefficients of Venous Interobserver and Intraobserver Reliability

<table>
<thead>
<tr>
<th>Vessel</th>
<th>No Angle Correction</th>
<th>Angle Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interobserver</td>
<td>Intraobserver</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>SD</td>
</tr>
<tr>
<td>dMCV PSV</td>
<td>0.94</td>
<td>0.61</td>
</tr>
<tr>
<td>dMCV EDV</td>
<td>0.88</td>
<td>0.55</td>
</tr>
<tr>
<td>BV PSV</td>
<td>0.94</td>
<td>0.99</td>
</tr>
<tr>
<td>BV EDV</td>
<td>0.92</td>
<td>0.89</td>
</tr>
<tr>
<td>VG PSV</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>VG EDV</td>
<td>0.62</td>
<td>1.24</td>
</tr>
<tr>
<td>SRS PSV</td>
<td>0.66</td>
<td>1.68</td>
</tr>
<tr>
<td>SRS EDV</td>
<td>0.59</td>
<td>1.44</td>
</tr>
<tr>
<td>TS PSV</td>
<td>0.83</td>
<td>1.95</td>
</tr>
<tr>
<td>TS EDV</td>
<td>0.54</td>
<td>2.13</td>
</tr>
<tr>
<td>SSS PSV</td>
<td>0.76</td>
<td>2.75</td>
</tr>
<tr>
<td>SSS EDV</td>
<td>0.75</td>
<td>2.12</td>
</tr>
</tbody>
</table>

n = number of averaged paired examinations, PSV = peak systolic flow velocity, EDV = end diastolic flow velocity, dMCV = deep middle cerebral vein, BV = basal vein, GV = vein of Galen, SRS = straight sinus, TS = transverse sinus, SSS = superior sagittal sinus.
However, for all other venous structures, angle correction resulted in 2-SD CIs of ±6.2 cm/s to 13.9 cm/s. For non-angle-corrected and angle-corrected venous flow velocity measurements, the variance of $D_{A-B}$ values was significantly higher for sinuses than for intracranial veins. Table 5 contains the arterial 2-SD CIs.

**Intraobserver Reliability**

Similar to the results of the linear regression analysis of interobserver reliability, regression coefficients for intraobserver reliability (Table 2 and 5) were higher for venous and arterial PSVs than for EDVs, and higher for intracranial veins than for dural sinuses.

The results of the venous 2-SD CIs for intraobserver reliability are summarized in Table 3. Two-SD CIs were higher for the dural sinuses than for intracranial veins. For non-angle-corrected FV measurements, the 2-SD CIs were lower than ±3.2 cm/s for the cerebral veins and ranged from ±3.2 to 6.1 cm/s for the dural sinuses. Here, lowest 2-SD CIs were found in the SRS. Angle correction resulted in 2-SD CIs of less than ±3.7 cm/s in the dMCV and BV. However, for all other venous structures examined in this study, 2-SD CIs for angle-corrected FV measurements ranged from ±6.1 to 13.9 cm/s. Here again, the variance of $D_{1-2}$ values was significantly higher for sinuses than for intracranial veins. The intraobserver 2-SD CIs for the arterial system are summarized in Table 4.
Figures 2 and 3 graphically summarize the results of the venous interobserver and intraobserver reliability and demonstrate the anatomy of the venous vessels insonated in this study.

**Interobserver and Intraobserver Agreement on Vessel Identification**

The interobserver agreement on vessel identification of intracranial veins and sinuses decreased in the following order: BV 99.9%, dMCV 97.8%, GV 97.8%, SRS 91.3%, TS 80.4%, SSS 78.3%. The agreement was higher for intracranial veins than for dural sinuses ($P < .05$). A positive identification by both examiners was possible for the venous vessels in 97.8% for the BV, in 95.7% for the GV, in 93.5% for the dMCV, in 73.9% for the SRS, in 60.9% for the TS, and in 50.0% for the SSS. Intraobserver agreement was again significantly higher for intracranial veins than for dural sinuses ($P < .05$). For the arteries, the following intraobserver agreements on vessel identification were reached (positive agreement in parentheses): ICA 100% (100%), M1 MCA 100% (95.7%), A1 ACA 96.6% (89.1%), P2 PCA 94.6% (96.7%), P1 PCA 92.4% (83.7%).

**Discussion**

TCCS has been widely used for the evaluation of the intracranial arterial system. Venous TCCS is a new technique for the assessment of the hemodynamics of the intracranial venous circulation. The method has been used for diagnosis and follow-up of patients with cerebral venous thrombosis and for the evaluation of venous hemodynamics in patients with space-occupying stroke and head trauma. Simultaneous arterial and venous measurements may offer more insight in cerebral auto-regulation processes and the cerebral microcirculation. However, a shortcoming of these studies is the lack of in-
formation on the interobserver and intraobserver reliability of venous TCCS. This is a prerequisite for any studies on the physiology and pathophysiology of the intracranial venous system and holds especially true for follow-up examinations.

Previously published protocols for examination of the intracranial arterial and venous system have been applied in this study.\textsuperscript{1,3,7,8} Mean PSVs and EDVs for the arteries of the circle of Willis and for the intracranial veins and sinuses in this study comply well with data for the same age group.\textsuperscript{10,13,14} In this study, we observed a statistically significant side difference for the dMCV and the TS, with higher flow velocities on the left side. The side difference in the transverse sinus finds its explanation in usually smaller diameters of the left transverse sinus compared to the right side. A further explanation is the summation of small differences by calculating the mean over all measurements in this study.

This study was designed to evaluate the interobserver and intraobserver reliability of angle-corrected and non-angle-corrected venous TCCS flow velocity measurements in a setting that resembles a normal clinical situation.

The interobserver and intraobserver agreement on the identification of venous vessels ranged from 80% to 99% and was higher overall for intracranial veins than for dural sinuses. Agreement on vessel identification for the cerebral veins was nearly as high as for cerebral arteries. Although agreement on vessel identification was lower for dural sinuses, it is still sufficient for clinical use and can be increased by application of echocontrast agents.

For assessment of the interobserver and intraobserver reliability of venous FV measurements, 2-SD CIs as well as correlation coefficients were calculated, since correlation coefficients, although routinely used, are not a particularly adequate parameter. Interobserver and intraobserver reliabilities were again higher for intracranial veins than for dural sinuses, predisposing them for follow-up examinations. Agreement on vessel identification of the cerebral veins was comparable to the cerebral arteries. Unlike the arterial system, the insonation of the VG and the dural sinuses suffers from unfavorable insonation angles, resulting in higher 2-SD CIs for the interobserver and intraobserver reliability and a lower agreement on vessel identification at least for the dural sinuses.

Based on our results, angle correction is advised only for the dMCV and BV; for all other venous vessels, angle correction resulted in high inaccuracies. However, as far as follow-up examinations are concerned, non-angle-corrected FV measurements of the dMCV, BV, VG, and SRS are sufficiently accurate for clinical and scientific purposes. Of course, our results apply only to venous FVs within the normal or physiological range, whereas in case of pathology, far higher or lower FVs may be expected (ie, due to changes in venous vessel diameter).

CIs of arterial measurements are reported in this study for 2 reasons: first, only 1 study\textsuperscript{8} has reported CIs on the reproducibility of angle-corrected flow velocity measurements. Second, the arterial interobserver and intraobserver reliability may be used to gauge the overall precision of this study based on previously reported results. The findings in this study comply well with data from the literature. Correlation coefficients of the reproducibility of angle-corrected flow velocity measurements have been reported for the MCA at 0.68 to 0.93, for the ACA at 0.75 to 0.94, and for the PCA at 0.63 to 0.94.\textsuperscript{8,11} In particular, our results are in excellent agreement with the CIs for the reproducibility of TCCS measurements reported by Baumgartner and colleagues.\textsuperscript{8}

References

Brain Volume Changes on Longitudinal Magnetic Resonance Imaging in Normal Older People

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ABSTRACT

Background and Purpose. The purpose of this study is to investigate the longitudinal age-related changes in human brain volume using stereological methods. Methods. Sixty-six older participants (34 men, 32 women, age [mean ± SD] 78.9 ± 3.3 years, range 74-87 years) with normal baseline and follow-up examinations underwent 2 MRIs (magnetic resonance imaging) of the brain on average 4.4 years apart. The volumes of the cerebrum (defined as cortex, basal ganglia, thalamus, and white matter), lateral ventricles, and cerebellum were estimated on the 2 MRIs using an unbiased stereological method (Cavalieri principle). Results. The annual decrease (mean ± SD) of the cerebral volume was 2.1% ± 1.6% (P < .001). The average volume of the lateral ventricles on the second MRI was increased by 5.6% ± 3.6% per year (P < .001). The average volume of the cerebellum on the second MRI was decreased by 1.2% ± 2.2% per year (P < .001). Even though the average cerebral volume was significantly different between men and women on initial MRI and second MRI, the percentage change of the age-related cerebral volume decrease in male and female brains between initial MRI and second MRI were identical. Conclusions. The findings showed that there was age-related atrophy of cerebrum and cerebellum and age-related disproportional enlargement of lateral ventricles in normal older men and women.

Key words: Brain volume, aging, longitudinal, magnetic resonance imaging, stereology.

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with severe subcortical white matter hyperintensity on the second MRI (3 with early dementia), and 2 with subclinical infarcts on the second MRI were excluded, leaving a total of 66 normal individuals (mean age at the time of the initial MRI 78.9 ± 3.4 years, range 74-87 years). To be considered normal, the participants had to have normal balance and normal cognitive function on neurological examination. None developed clinical dementia, and all maintained a normal MMSE score (≥ 26) and a normal total Tinetti score (≥ 24) through the time of the second MRI scan. Participants had no history of clinical stroke or transient ischemic attacks. None had a history of myocardial infarction, severe cardiomyopathy, or renal failure. Moreover, none had clinically important peripheral neuropathy, severe arthritis, or severe musculoskeletal disease. All participants were living at home in the west Los Angeles area, and all were functioning independently. The racial demographics were as follows: white non-Hispanic = 50, Hispanic = 9, African American = 5, and Asian = 2.

**MRI**

MRI of the brain was performed at baseline and after a follow-up period of 4.4 years (range 3-5 years). All MRIs were performed with a magnetic field strength of 1.5 T (Signal General Electric, Milwaukee, WI). The GE scanner was upgraded (hardware and software) in January 1995 and in October 1998. But we could find no evidence for a systematic change in our volume measurements associated with these upgrades. For the purpose of this study, we used T2-weighted images in the axial plane with a slice thickness of 5 mm and 1.5-mm gap between slices. The images covered the entire brain from the vertex to the foramen magnum. All of the first and second images were obtained as follows: field of view 220 mm, matrix 256 × 256, TR = 3000 ms, TE = 96 ms. The same processor was used to produce the hard copies (baseline and follow-up) for analysis. The magnification bar was accurately printed on each hard copy of MRI.

**Stereology Background**

The Cavalieri method is named after the Italian mathematician Buonaventura Cavalieri, a pupil of Galileo. It has recently been refined and applied in a series of studies involving invasive and noninvasive scanning. According to Cavalieri’s principle, the volume of arbitrarily complex structures can be estimated from the sum of parallel areas separated by a known distance provided the set of sections is positioned at random on the chosen axis. Profile areas are most efficiently estimated by point counting. The Cavalieri method consists of the following steps:

1. Scan or physically cut the object in a series of parallel planes a distance \( T \) apart, the first plane starting randomly in the interval 0 to \( T \).

2. The sectional area of the object cut can be efficiently estimated with the point counting method. The point-counting method consists of superimposing randomly on each slice a test lattice overlay bearing a systematic arrangement of test points. Counting points that fall on the profiles of the object provides an unbiased estimate of the areas of the object profiles. If the areal equivalent of each test point is known, then the total area \( (A) \) of the object profiles on all slices, in \( \text{cm}^2 \), is estimated from the total number of test points, \( \sum P \), using

\[
\sum A := a(\rho) \times \sum P,
\]

where \( := \) indicates that the result is an estimated value rather than the true value and \( a(\rho) \) represents the area associated with each test point at the brain scale (i.e., with the magnification of MRI taken into account), which is the distance between test points squared after correction for magnification.

3. From these area estimates with the point-counting method and the mean distance between slices, \( T \), the unbiased volume \( \langle V \rangle \) estimator, becomes

\[
V := T \times \sum A := T \times a(\rho) \times \sum P := T \times a(\rho) \times (P_1 + P_2 + \ldots + P_m),
\]

where \( P_1, P_2, \ldots, P_m \) denote the points counted in \( m \) slices.

In the case of noncontiguous slices, \( T \) equals the slice thickness plus the interslice gap, which is the case in the present study. Note that this simple volume estimator requires absolutely no assumptions about the shape or spatial arrangement of the object itself.

**Practical Implementation**

The brain structures were evaluated in every slice between the vertex and skull base (approximately 18 to 21 slices per individual). The volume was measured on each MRI slice where the specified brain structure (cerebrum, cerebellum, and lateral ventricles) was seen. The MRI films were placed in turn on a light box. On each MRI scan, a transparent counting grid was randomly overlaid, and all points hitting the cerebrum (defined as cortex, white matter, basal ganglia, and thalamus), lateral ventricles, and cerebellum were counted and recorded separately (Figs 1, 2, 3). The cerebellar volume represents the sum of the right and left cerebellar hemispheres and includes the vermis and deep nuclei. The boundaries of the cerebellum were defined according to the rules described previously by Aylward et al. To remove the influence of line thickness, a test point is defined as the true point of in-
intersection between the upper edge of the horizontal line of a cross and the right-hand side edge of the vertical line of that cross. The density of crosses on the counting grid varied with the structures being quantified. In Figure 1, the circled crosses (10 mm apart) were used to estimate the volume of the cerebrum, whereas all crosses (5 mm apart) were used to estimate the cerebellum in Figure 2. In Figure 3, all crosses (2.5 mm apart) were used to estimate the volume of the lateral ventricles. The area associated with each point had to be corrected for the magnification of the MRI that was obtained from the magnification bar printed on each hard copy. On average, 126 points were counted per brain for the volume estimation of the cerebrum, 187 points for the volume estimation of the lateral ventricles, and 80 points for the volume estimation of the cerebellum. The volumes of the cerebrum, lateral ventricles, and cerebellum were then estimated using the Cavalieri principle described above (formula (2)).

Reproducibility

Cerebrum volume was measured twice in 20 participants using the present stereological technique, resulting in an intrarater correlation coefficient of 0.94. Another study also found high repeatability and precision for this stereological technique (an interrater correlation coefficient of 0.95 for 3 raters and intrarater correlation coefficients of 0.95 to 0.98). 22

Statistics

Group means were compared using Student’s t Test for paired observation. The group means between men and women were compared using Student’s t Test for unpaired observation. A P value < .05 was adopted as significant throughout.

Fig 1. Magnetic resonance imaging of the brain from a participant with test points overlaid at random. Circled crosses (10 mm apart) were used to estimate the volume of cerebrum. Points hitting the cerebrum were counted.

Fig 2. Magnetic resonance imaging of the brain from a participant with test points overlaid at random. All crosses (5 mm apart) were used to estimate the volume of cerebellum. Points hitting the cerebellum were counted.

Fig 3. Magnetic resonance imaging of the brain from a participant with test points overlaid at random. All crosses (2.5 mm apart) were used to estimate the volume of lateral ventricles. Points hitting the lateral ventricles were counted.
Results

The mean volumes of the cerebrum, lateral ventricles, and cerebellum on initial MRI and second MRI are shown in Table 1. Individual values at the time of the initial MRI and the annual rate of change of these measurements (%) are shown in Figure 4. The annual rate of change was calculated by subtracting the second from the initial volume in each individual, dividing by the initial volume and by the number of years between MRIs in that individual, and multiplying by 100. The annual decrease (mean ± SD) of cerebral volume in men and women was 2.1% ± 1.7% and 2.1% ± 1.5%, respectively. The annual increase in lateral ventricular volume in men and women was 5% ± 2.7% and 6.3% ± 4.2%, respectively. The average decrease in cerebellar volume in men and women was 1.3% ± 2.1% and 1.1% ± 2.4%, respectively. There did not appear to be any distinct subpopulations but rather a continuum with the majority of participants in the middle (Fig 4A). There was marked variability in the cerebral, ventricular and cerebellar volume measurements at each age, with women usually having smaller volumes than men (Fig 4B). Average cerebral volume was significantly less in women than in men on both initial MRI and second MRI (P<.005) (Table 1).

Despite the fact that there was a highly significant annual rate of change in cerebral, cerebellar, and ventricular volumes, we did not find significant correlations between age and cerebral volume, cerebellar volume, or ventricular volume on either initial MRI or second MRI. This apparent discrepancy in the data can best be explained by the marked variability in brain and ventricular size in the participants of all ages and the narrow range of the participants’ ages.

Discussion

The Cavalieri estimator of volume is independent of both shape and orientation of the objects being investigated. However, the object must be properly defined and identifiable on each scan: this is an essential prerequisite. To reduce the “partial voluming” (ie, the observation that the boundary trace of the brain structure on the real MRI slice tends not to coincide with that of a hypothetical midplane in the corresponding slice), one should reduce scan thickness as much as technically possible. Although thinner slices would have been preferable (ie, 3 mm or less), 5-mm-thick slices were standard when this longitudinal study began almost 10 years ago. Follow-up studies include thinner slices using the gradient echo technique, but it will be several more years before enough of these new scans are available for comparison. Although partial voluming due to thick slices might lead to a slight overestimation of the volume measurements, it could not explain the observed decrease in volume from the first to second scans because slice thickness was the same for both scans.

In this longitudinal study of nondemented older people, we found a surprisingly high annual rate of brain shrinkage, 2.1% per year on average. Numerous prior cross-sectional studies have also identified evidence of brain shrinkage with age but at a lesser rate (1% or less per year).\textsuperscript{2,3} However, most of these cross-sectional studies have included relatively few participants older than 75 years. Although rates of brain shrinkage are typically calculated using a linear model, two cross-sectional studies that included a broad range of ages suggested an exponential loss of brain volume as a function of age. Takeda and Matsuzawa\textsuperscript{24} measured a brain atrophy index (BAI) using computed tomography in 301 normal individuals with an age range over 8 decades. The BAI was defined as the cerebrospinal fluid space volume divided by the cranial cavity volume × 100. They found a relatively modest increase in the BAI up until approximately the age of 70, but after the age of 70 there was a rapid increase in the BAI with marked subject-to-subject variability. Using an exponential model, they calculated that the doubling time for the BAI was 22.5 years in men and 17.2 years in women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial Magnetic Resonance Imaging Group</th>
<th>Second Magnetic Resonance Imaging Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N = 66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>78.9 (3.3)</td>
<td>83.3 (3.4)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cerebral volume (cm\textsuperscript{3})</td>
<td>657 (71)</td>
<td>594 (59)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Lateral ventricular volume (cm\textsuperscript{3})</td>
<td>48 (19)</td>
<td>60 (24)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cerebellar volume (cm\textsuperscript{3})</td>
<td>98 (11)</td>
<td>92 (12)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Men (n = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>79.0 (3.0)</td>
<td>84.0 (3.0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cerebral volume (cm\textsuperscript{3})</td>
<td>680 (74)</td>
<td>614 (58)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Lateral ventricular volume (cm\textsuperscript{3})</td>
<td>49 (17)</td>
<td>60 (22)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cerebellar volume (cm\textsuperscript{3})</td>
<td>98 (14)</td>
<td>92 (14)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Women (n = 32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>78.5 (3.4)</td>
<td>82.8 (3.6)</td>
<td>&lt; .001</td>
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<tr>
<td>Cerebral volume (cm\textsuperscript{3})</td>
<td>632 (59)</td>
<td>575 (53)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Lateral ventricular volume (cm\textsuperscript{3})</td>
<td>47 (21)</td>
<td>59 (26)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cerebellar volume (cm\textsuperscript{3})</td>
<td>97 (8)</td>
<td>92 (9)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Standard deviations are in parentheses.
Fig 4. (A) Rate of cerebral volume loss (\% per year) derived from 66 participants. Diamond = men, triangle = women. Annual change (\% per year) = \[\left(\frac{\text{value on second MRI} - \text{value on initial MRI}}{\text{value on initial MRI}}\right) \times \frac{\text{number of years between 2 MRIs}}{\text{number of years between 2 MRIs}}\times 100.\] (B) Scatter plots of the age of participants on the initial MRI versus the volume estimates of the cerebrum (defined as cortex and white matter).
Guttmann et al\textsuperscript{25} used an MRI segmentation technique to identify age-related changes in gray and white matter. They found relatively little change in gray matter with age but an exponential decrease in the volume of white matter with age, again with the most dramatic fall in white matter volume after the age of 70. If age-related changes in brain volume follow an exponential model rather than a linear model, then the difference between our finding of a 2.1\% rate of shrinkage per year in individuals mostly in the ninth decade compared with prior cross-sectional studies that found less than 1\% shrinkage per year could be explained by the fact that we studied an older population that was on a steeper part of the age versus shrinkage curve.

To our knowledge, there have been only 4 previous longitudinal studies assessing brain volume changes associated with normal aging, and only 1 of these (Mueller et al) allows direct comparisons with our data. Fox and Freeborough\textsuperscript{26} performed serial MRI scans on 19 normal individuals and 9 patients with Alzheimer’s disease with a mean age of 50.3 \pm 7.9 years and 54.3 \pm 8.2 years, respectively. The controls had no complaints of cognitive problems and no evidence of memory deficit on formal testing. They found an annual rate of brain atrophy in the controls of 0.24\% compared with 2.78\% in the patients with Alzheimer’s disease. Intervals between the first and last scans ranged from 6 to 30 months. They used the brain boundary shift integral (BBSI) as a measure of brain atrophy. Considering the low annual rate of brain atrophy in their relatively young controls, they concluded that measurements of BBSI might be useful for the early diagnosis of Alzheimer’s disease. Jack et al\textsuperscript{27} measured the volume of the hippocampi and temporal horns in 24 cognitively normal older individuals aged 70 to 89 years who were individually matched with respect to gender and age with 24 patients with Alzheimer’s disease. The mean annual rate of hippocampal volume loss in the controls was 1.6\% \pm 1.4\%, and the temporal horns increased in volume by 6.2\% \pm 7.7\% per year (values similar to our cerebrum and lateral ventricle values). By contrast, the rates of change in these structures in the patients with Alzheimer’s disease were 4.0\% \pm 1.9\% per year and 14.2\% \pm 8.5\% per year, respectively. Wahlund et al\textsuperscript{28} performed longitudinal MRI studies of the brain in a small group of 24 normal older individuals followed for approximately 5 years on average (age range at outset 75-85 years). Volumes of the lateral ventricles and the frontal cerebrospinal fluid spaces increased significantly during the period of observation. Neuropsychological tests remained unchanged over the same time period.

Mueller et al\textsuperscript{29} performed serial MRIs (4-mm-thick coronal scans with 2.5-mm gaps between scans) during 3 to 9 years of follow-up on 3 groups of older normal individuals: young old (age range 67-74), middle old (age range 76-85), and oldest old (age range 85-93). Participants were followed with yearly MMSEs, neuropsychological tests, and neurological examinations. Of note, of the 37 oldest old individuals initially entered into the study who had 3 or more MRIs available for analysis, 44\% showed changes consistent with early dementia and were excluded from the analysis. After these exclusions, the oldest old group contained 20 individuals, the middle old group 15, and the young old group 11. Brain volumetric measurements were determined using a computer-assisted segmentation technique. On cross-sectional comparison, there were significant differences between groups in total brain, left and right hemisphere, temporal lobe, basilar-subcortical region, and hippocampus volumes, with the oldest old individuals showing the smallest volumes followed by middle old and young old individuals. Mean lateral ventricular size, however, was not significantly different in the 3 groups. The longitudinal measurements showed an approximately 0.5\% annual decrease in total brain volume but with no difference in the rate of brain volume loss in the young old, middle old, and oldest old groups. Lateral ventricular size also increased with an annual rate of about 0.5\%, again with an approximately equal rate of increase in the 3 groups. Because their middle old and oldest old normal groups covered approximately the same age range as our older normal participants, how do we explain the different annual rate of brain volume loss and ventricular enlargement found in the 2 studies?

Could technical issues associated with data acquisition and analysis explain the differences in age-related loss of cerebral volume in the 2 studies? Although longitudinal studies reduce the problem of secular bias, they raise other problems such as the likelihood that the serial acquisitions will differ in some systematic fashion that will bias the data. Small changes in software or hardware introduced during the longitudinal study could potentially bias the results. Mueller et al\textsuperscript{30} noted some changes in MRI protocol used during their longitudinal MRI study but, on assessing the data, could find no evidence that these changes in MRI protocol systematically influenced their data. Although 2 upgrades of our MRI scanner were made during the course of the longitudinal study, all studies were obtained with the same protocol, the same processor was used to produce hard copies, and the magnifi-
cognition bar was accurately printed on the MRI copies. The fact that we found an annual rate of approximately 2% cerebral volume loss yet did not find a significant correlation between cerebral volume and age on either first MRI or second MRI is not so surprising when one considers the narrow age range of our population (about 1 decade) and the marked variability in cerebral volume measurements from participant to participant (Fig 4). Indeed, this finding further reinforces the importance of longitudinal comparisons when searching for age-related cerebral volume effects.

It is unlikely that the differences in analysis techniques—segmentation versus stereology—could explain the differences in findings between the two studies. Several prior studies that have compared these 2 analysis techniques, both on postmortem specimens and MRI, have found a remarkably high correlation in the results of the 2 techniques ($>0.95$). The different analysis techniques could explain the difference in absolute values in cerebral and ventricular volumes between prior studies and ours but could not explain the differing rate of change in these measurements over time.

The most likely explanation for the differing findings on age-related changes in brain and ventricular volume in our study and the study by Mueller et al is the different definitions of “normal” older individuals. Both studies excluded clinically demented individuals and followed individuals with yearly MMSEs and neurological examinations. Mueller et al defined a normal MMSE as $\geq 24$; we defined a normal MMSE as $\geq 26$. Mueller et al performed yearly neuropsychological testing, whereas we focused on other aspects of the neurological examination. Mueller et al excluded 44% of their oldest old participants because they developed cognitive impairment consistent with early dementia on their serial exams. We excluded 14% of our older participants based on clinical and/or MRI findings, 9% having developed signs of dementia on clinical examination. Thus, Mueller et al were more rigid in their exclusion criteria, with the main difference being their rate of exclusion of patients with early dementia. Presumably, this higher rate of detection of early dementia was based on patients’ neuropsychological testing (which we did not include).

Issues not addressed in the Mueller et al article were how early dementia was defined and whether the participants who were excluded for dementia had or developed Alzheimer’s disease. This is not a trivial issue, since it can be very difficult to separate neuropsychological changes that occur with normal aging from those that represent early Alzheimer’s disease. Studies have clearly shown that older individuals with mild memory or other cognitive impairment are more likely to go on to develop dementia compared with their peers with normal memory and cognitive skills. However, it is not clear how many of these individuals with mild memory and cognitive deficits will go on to develop the neuropathological characteristics of Alzheimer’s disease. It is possible that the normal distribution of memory scores in a population of older individuals is related to variation in overall brain volume. The distribution of cerebral volume measurements and the annual rate of cerebral volume change in our patients appear to be a continuum without any subgroups. The key issue is whether our participants with the highest rate of cerebral volume loss will go on to develop Alzheimer’s disease or other clearly defined types of dementia. The length of follow-up since the second MRI scan is still too brief to answer this question. However, we are continuing to follow these individuals with yearly examinations and ultimately, when possible, with postmortem examination. Presumably, the oldest old individuals in the Mueller et al study that were excluded because of development of early dementia had a higher annual rate of cerebral volume loss than the individuals who remained in the study. As in our study, it would be of great interest to know whether these older individuals go on to develop Alzheimer’s disease.

In conclusion, we found a higher rate of age-related cerebral volume loss and ventricular enlargement in very old normal individuals compared with most prior reports. Comparison with prior cross-sectional studies is difficult because most of these prior studies included only a small number of individuals in this very old age range and used a linear model as opposed to an exponential model to relate age to cerebral volume change. There is only 1 prior longitudinal study that allows direct comparison with our data, and this study found a much lower rate of annual change in cerebral volume in normal older individuals in the same age range as our participants (0.5% vs 2.1%). However, this other longitudinal study was much more aggressive in excluding older individuals with what the researchers considered to be early signs of dementia. The key question yet to be answered is whether older individuals with a high annual rate of change in cerebral volume and poorer performance on neuropsychological testing represent part of the continuum of the normal population or the early stages of a definite dementia syndrome such as Alzheimer’s disease.

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References


Cerebrovascular reserve can be estimated by measuring the change in cerebral blood flow velocity at the proximal middle cerebral artery (MCA) that occurs in response to a vasodilatory stimulus such as CO₂ or intravenous acetazolamide.¹² Measurement of this cerebrovascular reactivity helps to identify patients with reduced cerebral perfusion, quantifies the hemodynamic impact of extracranial carotid artery stenosis or occlusion,³–⁵ and predicts the clinical outcome in some clinical settings such as carotid endarterectomy,⁶–⁸ extracranial-intracranial arterial bypass,⁹–¹⁰ severe intracranial hematoma,¹¹ and ischemia after traumatic brain injury.¹² Good correlation between changes in regional cerebral blood flow measured by single photon emission computed tomography and changes in flow velocity in the MCA obtained by transcranial Doppler (TCD) sonography during cerebral vasoreactivity testing has been reported.¹³–¹⁵

During changes in arterial CO₂ concentration, cerebrovascular resistance changes occur at the microcirculatory level whereas the diameter of large conduit vessels such as the MCA shows little or no change.³,¹⁶,¹⁷ Thus, the relationship between blood flow velocity and flow volume within the MCA is linear as long as CO₂ does not affect the diameter. It is well known that MCA mean velocity (Vm) increases during hypercapnia and decreases during hypocapnia. Expected changes in MCA flow velocity due to changes in CO₂, increases of 2.5% to 5% in MCA velocity per mm Hg increase in CO₂,³,¹⁷ are established and are commonly used parameters to evaluate cerebral vasoreactivity. Changes of common carotid artery (CCA) volume flow rate (VFR) after CO₂ inhalation, which may be an alternative method of cerebral vasoreactivity testing, have not been extensively reported. We conducted this study to evaluate the relationship between MCA Vm, CCA VFR, and end-expiratory flow rate.

tory CO₂ (EE-CO₂). The relationship between MCA Vm and CCA VFR was also analyzed.

**Materials and Method**

Following informed consent, 10 normal individuals without either cerebrovascular disease or significant hemodynamic changes in extracranial carotid arteries demonstrated by carotid duplex sonography and with CCA lumen diameter of more than 3.0 mm were prospectively studied. CCA VFR was obtained by Color Velocity Imaging Quantification (CVI-Q) using a Philips SD-800 Color Velocity Imaging System with a 7.5-MHz linear transducer (Philips Ultrasound International, Irvine, CA), and ipsilateral MCA Vm, identified by standard TCD methods, was continuously monitored using a Muller headband and an EME TC 2000 TCD machine (Nicolet, Madison, WI), with the data recorded on videotape for a precise off-line computer-assisted determination of MCA Vm. A sequence of at least 20 cardiac cycles of MCA Vm was recorded. Each side was studied with each participant supine and instructed to rest comfortably. One measurement of blood pressure and 1 measurement of pulse rate were obtained at the same time the CCA VFR and MCA Vm were studied, including measurements at 5 minutes before CO₂ inhalation, after 2.5 minutes of CO₂ inhalation, and at 5 minutes after cessation of CO₂ inhalation. The gas mixture used was 5% CO₂ and 95% oxygen. EE-CO₂ was monitored by infrared capnometer (Nellcor ULTRÁ CAPN-6000). Differences were tested with *t* tests and Pearson’s Correlation Coefficient.

CVI-Q makes use of timing data (time domain) contained in the gray-scale B-mode scan lines rather than Doppler frequency shifts to obtain flow velocity information, and a mathematical technique called cross-correlation is used to determine the echo arrival time shift between subsequent pulses. To measure VFR, CVI-Q integrates the time-varying flow profile in a vessel with cross-sectional measurements derived from M-mode color display sampling across the vessel diameter. Criteria for obtaining reliable measurement of VFR with CVI-Q are straight portion of vessel, vessel greater than 3 mm in diameter, angle of insonation greater than 30° but less than 70°, optimum color gain control, center of vessel, accurate measurement of angle of insonation, and satisfactory velocity and flow pattern. CVI-Q is an accurate and reproducible method of assessing volume flow in the vessels, and measurements should be repeated at least 3 times to ensure accuracy. We obtained 5 VFR readings with CVI-Q in each CCA and chose the median value for analysis. We measured CCA VFR at 1.5 cm below the bifurcation of CCA, and the criteria to obtain accurate CVI-Q results were followed.

**Results**

Four women and 6 men with a mean age of 36 years (38 years for women and 34 years for men) were included. In 1 participant, EE-CO₂ data during CO₂ inhalation were missing because of technical error. Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, EE-CO₂, CCA VFR, and MCA Vm showed significant changes when comparing before and during, and during and after breathing CO₂ using a paired *t* test (*P* < .05). There was no statistically significant difference between the parameters before and after CO₂ inhalation. Tables 1 and 2 summarize the parameter differences data. The only statistically significant difference between right and left side was a slightly higher increase in CCA VFR during breathing CO₂ on the right (*P* = .04). We used Pearson’s Correlation Coefficient to determine the relationship between MCA Vm, CCA VFR, and EE-CO₂ and found statistically significant correlations (*P* < .01) between MCA Vm and EE-CO₂ (*P* = .0001, *r* = 0.616, Fig 1), CCA VFR and EE-CO₂ (*P* = .0001, *r* = 0.527, Fig 2), and MCA Vm and CCA VFR (*P* = .0008, *r* = 0.422). The

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>During</th>
<th>Change</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<td>127.5 (14.8)</td>
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<td>Diastolic blood pressure (mm Hg)</td>
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<td>78.5 (8.1)</td>
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<td>.0001</td>
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<td>Pulse rate (/min)</td>
<td>66.0 (9.8)</td>
<td>74.7 (8.5)</td>
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<tr>
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<td>46.2 (3.7)</td>
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<td>.0001</td>
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<tr>
<td>Common carotid artery volume flow rate (ml/min)</td>
<td>354.9 (85.9)</td>
<td>450.0 (99.6)</td>
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<tr>
<td>Middle cerebral artery mean velocity (cm/s)</td>
<td>58.7 (11.4)</td>
<td>80.1 (16.9)</td>
<td>36.6</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Table 1. Mean Parameter Differences and Ranges Before and During Breathing CO₂ in 10 Participants

Standard deviations are in parentheses.
change in MCA Vm was correlated with the changes in SBP and DBP ($P = .05$, $r = 0.36$ and $P = .01$, $r = 0.43$, respectively) after correction for multiple comparison. There was no statistically significant correlation between the change in CCA VFR and either SBP or DBP. MCA Vm and CCA VFR increased 5.2% and 4.3%, respectively, per mm Hg increase in EE-CO$_2$. MCA Vm increased 0.3 cm/s for each ml/min increase in CCA VFR.

Discussion

In normal individuals, MCA flow velocity shows CO$_2$ reactivity of 3.4 ± 0.8%/mm Hg, which is very close to 4.1 ± 1% CO$_2$ reactivity of cerebral blood flow determined by the xenon clearance technique. These data suggest that MCA flow velocity may provide a good correlation with MCA flow volume. Observations on MCA Vm using TCD and ipsilateral internal carotid artery (ICA) flow volume using an electromagnetic flow meter in patients undergoing carotid endarterectomy have shown a linear relation between MCA Vm and ICA flow volume. Given that the ipsilateral MCA receives a constant proportion of the ICA flow volume during CO$_2$ inhalation, and in the absence of cerebral artery stenosis either extracranially or intracranially, relative changes in ICA flow volume reflect relative changes in MCA flow volume. Although of potential clinical interest, we are not aware of any prior studies using CCA VFR with CO$_2$ reactivity to assess cerebrovascular reserve in patients with ICA disease. Such an approach would be expected to yield results similar to the current use of MCA Vm with CO$_2$, with results varying depending not only on the severity of ipsilateral ICA stenosis but on the severity of contralateral ICA stenosis or posterior circulation disease, and the available collateral pathways. CCA flow volume has been investigated with ultrasound techniques to estimate cerebral blood flow, and in normal participants the sum of ICA and external carotid artery flow volumes correlate well with CCA flow volume measurement, although CCA flow volume appears to be slightly higher. Therefore, the measurement of CCA VFR should correlate with the flow velocity and the flow volume in MCA, which represent the distal regional per-

Table 2. Mean Parameter Difference and Ranges During and After Breathing CO$_2$ in 10 Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>During</th>
<th>Change</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>127.5 (14.8)</td>
<td>108.3 (11.8)</td>
<td>14.8</td>
<td>.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78.5 (8.1)</td>
<td>69.9 (8.6)</td>
<td>10.6</td>
<td>.0001</td>
</tr>
<tr>
<td>Pulse rate (/min)</td>
<td>74.7 (8.5)</td>
<td>66.3 (9.2)</td>
<td>12.2</td>
<td>.0001</td>
</tr>
<tr>
<td>Common carotid artery volume flow rate (ml/min)</td>
<td>450.0 (99.6)</td>
<td>340 (55.5)</td>
<td>22.0</td>
<td>.0001</td>
</tr>
<tr>
<td>Middle cerebral artery mean velocity (cm/s)</td>
<td>80.1 (16.9)</td>
<td>55.6 (9.6)</td>
<td>29.6</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Standard deviations are in parentheses.
fusion territory, in individuals without significant carotid and MCA stenosis.

Previous studies have shown a relative increase of 48% in blood flow velocity within the CCA and a 47% increase within the ICA of individuals breathing 5% or 6.8% CO₂. Regional cerebral blood flow changes 3% to 5% per unit change in PaCO₂. MCA flow velocity increases by as much as 52.5% during hypercapnia. In healthy volunteers, a study measuring simultaneous changes in CCA volume flow and ipsilateral MCA velocity showed increases of 30% in MCA velocity and 40% in CCA volume flow with CO₂, and increases of 39% in MCA velocity and 49% in CCA volume flow with acetazolamide. Concentrations of CO₂ higher than the 5% used in this study, or longer periods of inhalation, might result in greater increases in CCA VFR or MCA Vm. Similar changes would be expected if acetazolamide were used as the stimulus rather than CO₂ inhalation.

We demonstrated a statistically significant (P < 0.05) increase of 36.6% and 31.6% in MCA Vm and CCA VFR, respectively, during 5% CO₂ inhalation. The percentage increase in MCA Vm during breathing CO₂ in our study is consistent with previous studies and is the expected response in normal individuals. One study showed no change in the external carotid artery flow volume after acetazolamide injection in the patients who had ipsilateral ICA occlusion without evidence of collateralization through the ipsilateral ophthalmic artery. However another study showed increased blood flow of 34% in the external carotid artery induced by acetazolamide as measured by cutaneous facial blood flow. The studies used different methods of measurement, which may have led to the contradictory results. The lower percentage increase in CCA VFR compared with the increase in MCA Vm may reflect the contribution of flow to the external carotid artery, which does not respond to changes in CO₂. Therefore, changes in CCA VFR should be less than the increase in MCA Vm. We identified a direct correlation between MCA Vm and EE-CO₂ and a significant correlation between MCA Vm and CCA VFR before, during, and after CO₂ inhalation in normal individuals without significant extracranial-intracranial cerebral artery stenosis. TCD is widely performed to evaluate cerebral vasoreactivity, but a major limitation is the absence of adequate temporal windows of which the prevalence is 15%. The measurement of CCA VFR changes may be useful as an alternative method to evaluate cerebral vasoreactivity, especially in patients whose MCA flow velocity cannot be obtained owing to the absent or inadequate acoustic temporal windows. These data also support the hypothesis that changes in MCA velocity during cerebral vasoreactivity testing reflect changes in volume flow in a conduit vessel.

We wish to express our appreciation to Sandy Brim, RRT, from respiratory care at the North Carolina Baptist Hospital in Winston-Salem for his technical support on monitoring CO₂.

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ABSTRACT

Background and Purpose. Wernicke encephalopathy (WE) is an acute phase of Wernicke-Korsakoff syndrome. Pathologic findings change between acute and chronic phases. Only a few magnetic resonance imaging (MRI) studies have been done to date. Methods. To correlate the MRI findings in acute and chronic stages of WE with the known pathologic information, 15 consecutive patients with WE were examined with MRI: 3 before thiamine treatment, 7 within 24 hours of thiamine treatment, 4 between the second and sixth day after thiamine treatment, and 1 fifty-five days after thiamine treatment. Nine of the patients had follow-up MRI between 2 days and 33 months. T1-weighted, proton, and T2-weighted axial images were obtained with additional 5-mm-thick T1-weighted sagittal and coronal images to better visualize the mammillary bodies. Results. In the acute WE, MRI showed high signal intensity on T2-weighted images in periaqueduct and medial thalamic regions. In a few patients with alcoholism, vermian and mammillary body atrophies and third ventricular enlargements were noted. In the chronic phase of WE, T2 hyperintensity disappeared but mammillary bodies and cerebellar vermis became atrophic and third ventricular enlargements were evident. High signal intensity on T2-weighted images disappeared as early as 2 days, and atrophic changes appeared as early as 1 week. Conclusion. MRI is useful for in vivo monitoring and reflects the pathological evolution in acute and chronic phases of WE.

Key words: Wernicke encephalopathy, magnetic resonance imaging, Korsakoff psychosis, high signal intensity, pathologic evolution.


Wernicke encephalopathy (WE) is a neurologic emergency caused by thiamine deficiency and presents with ophthalmoplegia, confusion, and ataxia. The most common cause of thiamine deficiency is chronic alcoholism, but hyperemesis gravidarum, fasting, hemodialysis, uremia, hyperalimentation, and gastric plication for obesity control had also been implicated. Korsakoff psychosis is a residual neurological deficit of acute WE in the spectrum of 1 disease process.

Pathologic findings change between the acute and chronic phases. During the acute phase of WE, there are variable degrees of necrosis, vascular proliferation, astroglial and microglial proliferation, and petechial hemorrhages in the medial thalami, mammillary bodies, periaqueduct, floor of the fourth ventricle, and superior vermis. In the chronic phase, petechial hemorrhage becomes reabsorbed and reorganized, and atrophy becomes prominent in the affected areas. Vascular and astroglial proliferation may progress to some degree. Atrophy of the medial thalamus is an important cause of memory defect in Korsakoff psychosis, and the mammillary bodies are always involved, regardless of memory defects. However, the pathological studies do not address the chronological evolution clearly, or are limited due to its nature.

With the development of neuroimaging techniques, in vivo imaging of the pathology became possible. Computed tomography (CT) shows low density in the periaqueductal area and the bilateral medial thalami. Magnetic resonance imaging (MRI) enables us to make examinations in more detail, and a small number of MRI studies in the acute phase of WE have been reported. Some images taken during follow-up have shown dilation of the third ventricle and aqueduct and a reduction in the size or disappearance of mammillary bodies. However, most of these findings were obtained from isolated cases or studies involving small numbers of participants. Thus, studies that have been conducted to specifically examine the evolution of the process are limited. The purpose of our study was to obtain acute and chronic imaging in patients with WE and, indirectly, information about the in vivo changes associated with WE and compare our findings with known pathologic information.

Methods

Patients

Fifteen consecutive patients with WE were examined by MRI. The clinical diagnosis of acute WE was made by presentation with ophthalmoplegia, confusion, or ataxia
and with history of nutritional deficiency. A good response to thiamine was required to confirm the diagnosis. The chronic stage of WE was determined by the disappearance of acute symptoms or by the clinical feature of Korsakoff psychosis. Neurologic evaluation was performed by 3 different experienced neurologists. All patients but 1 were men and had a mean age of 46.5, with ages ranging from 32 to 61 years. Twelve of the patients were chronic alcoholics, and the others had a history of hyperemesis gravidarum, postjejunostomy, or prolonged voluntary starvation. Informed consent was obtained from each patient.

**Imaging Procedures**

MRI was performed at Seoul National University Hospital using a Goldstar Spectro 20,000 (2.0 T magnetic field strength). A standard protocol of T1-weighted (TR = 500 ms, TE = 30 ms), proton (TR = 2000 ms, TE = 80 ms), and T2-weighted (TR = 2000 ms, TE = 30 ms) axial images with 10-mm-thick slices were obtained. To better visualize the mammillary body, additional 5-mm-thick T1-weighted sagittal and coronal images were obtained. Measurements of the mammillary body or estimations of ventricle size were not made. Seven patients had MRI within 24 hours of thiamine treatment, 4 between the second and the sixth day after thiamine treatment, and 1 fifty-five days after thiamine treatment. Three patients had MRI before thiamine treatment. Nine of 15 patients had follow-up MRIs between 2 days and 33 months from the time thiamine treatment began. MRI findings were evaluated by a radiologist who was blind to the diagnosis.

**Results**

**Summary of Clinical Findings**

Abrupt changes such as confusion, inappropriate response, or gait disturbance were the main reasons for hospital admission. Most patients (except patients 1, 9, and 12) were chronic alcoholics. All the patients (except 9) had ataxia. Eight patients showed confusion. Abnormal ocular signs were shown in 13 patients, ranging from mild gaze-evoked nystagmus to complete ophthalmoplegia (see Table 1). Presentation of confusion without any other signs delayed diagnosis in patient 9.

Thiamine improved all of the patients. Most of the acute neurological signs resolved, but memory defect and nystagmus on extreme gaze remained in some patients. Patients 3, 5, and 6 had a previous admission history due to WE. Seven patients (1, 3, 4, 5, 9, 13, and 15) were left with severe memory defect such that they could not remember time and place.

**Patient 1**

A 35-year-old man with duodenal ulcer and pyloric stenosis underwent bilateral vagotomy, antrectomy, and E-loop jejunostomy. He was unable to eat for 2 weeks because of persistent vomiting. Suddenly, he developed difficulty in maintaining posture and made inappropriate responses to questions. Examination showed unsteadiness of stance and gait, ophthalmoparesis, and nystagmus. Under the impression of WE, thiamine was given and the ophthalmoparesis started to improve in 2 hours. MRI showed high signal intensity on T2-weighted images in the periaqueductal area (including the superior colliculi) and bilateral medial thalami. Mammillary bodies were seen in the T1 sagittal image. He recovered but remained with severe memory defect. Follow-up MRI showed vermic atrophy and enlargement of the third ventricle. High signal intensity on T2-weighted images disappeared; however, mammillary bodies were not visualized (Fig 1).

**Patient 5**

A 58-year-old chronic alcoholic had vomited for several days and was brought to the emergency room due to confusion and abdominal distension. He showed complete lateral gaze palsies and ataxia. Thiamine was given, and an MRI was taken 30 hours after admission, which showed T2 hyperintensity in the periaqueductal and the medial thalamic area. In addition, abnormal hyperintensity in the splenium of the corpus callosum, a characteristic feature of Marchiafava-Bignami disease, was also observed. A second MRI was taken 3 weeks after admission. High signal intensity on T2-weighted images disappeared from the periaqueductal region and medial thalamus but remained in the splenium. Nystagmus on extreme gaze persisted.

After discharge, the patient kept drinking for 1 year. Sudden development of ophthalmoplegia, ataxia, and confusion brought him to the hospital again. MRI taken 1 hour after thiamine treatment showed high signal intensity on T2-weighted images in the periaqueductal and medial thalamic areas. Follow-up MRI in 3 weeks showed a further enlargement of the third ventricle (Fig 2). He recovered, but severe memory defect persisted.

**Summary of MRI Findings**

Table 2 presents a summary of the MRI findings. During the acute phase of WE, 11 magnetic resonance images were obtained. High signal intensity on T2-weighted images in the periaqueductal area was observed in all cases. T2 high signal intensity in the medial thalami regions was present in 7 of 11 images (2 nonalcoholics and 5 out of 9 alcoholics). Four alcoholics did not show abnormal signal
changes in the medial thalami. Mammillary bodies were seen in 2 nonalcoholics; however, the 7 images taken from alcoholics did not reveal mammillary bodies. Superior vermian atrophies and third ventricular enlargement were observed in 3 alcoholic patients.

Twelve scans were performed during the chronic stage of WE. Previous high signal intensity on T2-weighted images disappeared. Mammillary bodies were not in evidence. In nonalcoholics, third ventricular enlargement and vermian atrophy were noted, although 1 patient did not reveal vermian atrophy and 4 of 8 patients did not show third ventricular enlargement.

Seven patients (2 nonalcoholics and 5 alcoholics) had follow-up MRIs. The disappearance of high signal intensity on T2-weighted images and progressive atrophic changes were seen. In the case of patient 5, progressive enlargement of the third ventricle and vermian atrophies were noted. T2 hyperintensity disappeared as early as 2 days after thiamine treatment, and vermian atrophy or third ventricular enlargement appeared as early as 1 week.

**Discussion**

The pathology in WE commonly affects the medial thalami, the periaqueductal area, the mammillary body, the floor of the fourth ventricle, and the superior vermian. Pathologic findings in the acute phase are necrosis and edema. Vascular proliferation, increased astroglial and microglial cells, hemorrhage, and disruption of brain-blood-barrier have been described. High signal intensity on T2-weighted images were mostly distributed in the mesencephalic and diencephalic regions. Involvement of these regions is consistent with known pathologic findings. Furthermore, continuation of T2 high signal intensity from the medial thalami to the periaqueductal area and the floor of the fourth ventricle in patient 2 (data not shown), or the extension of T2 high signal intensity into the superior colliculi, suggests that these anatomic structures share a common pathologic process. This MRI finding has not been described in previously reported cases. However, the involvement of colliculi is a well-known pathologic finding, and we confirm this in our study. Nevertheless, T2 hyperintensity did not last more than 2 days when the appropriate treatments had been given. This disappearance of T2 high signal intensity cannot be explained by known pathologic information. To determine the nature of this finding, further investigations involving diffusion-weighted imaging would be informative, since it would differentiate vasogenic and cytotoxic edema.

In acute phase scans in nonalcoholics, circumscribed high signal intensity in T2-weighted images in mesencephalic and diencephalic areas were observed. In acute phase scans from alcoholics, the distribution of T2 hyperintensity was similar to that of nonalcoholics. However, unlike the nonalcoholics, a number of the patients with alcoholism showed atrophy in the cerebellar vermian or the mammillary bodies. The reason may be that the nonalcoholics were patients without a history of previous WE attacks. Therefore, MRI studies among nonalcoholics likely represented the evolution of pathologic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Etiology</th>
<th>Neurologic Findings</th>
<th>T2 Hyperintensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute</td>
</tr>
<tr>
<td>1</td>
<td>35/M</td>
<td>Jejunostomy</td>
<td>Ophthalmoplegia, confusion, ataxia</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>48/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, confusion, ataxia</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>45/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, ataxia</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>58/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, confusion</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>58/M</td>
<td>Alcoholic</td>
<td>1. Ophthalmoplegia, confusion, ataxia</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Ophthalmoplegia, confusion, ataxia</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46/M</td>
<td>Alcoholic</td>
<td>Nystagmus, ataxia</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>50/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, ataxia</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>40/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, ataxia</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>36/F</td>
<td>Hyperemesis gravidum</td>
<td>Confusion</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>39/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, confusion, ataxia</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>45/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, ataxia</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>59/M</td>
<td>Fasting</td>
<td>Ophthalmoplegia, confusion, ataxia</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>61/M</td>
<td>Alcoholic</td>
<td>Nystagmus, ataxia</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>43/M</td>
<td>Alcoholic</td>
<td>Ophthalmoplegia, confusion, ataxia</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>39/M</td>
<td>Alcoholic</td>
<td>Memory defect</td>
<td>–</td>
</tr>
</tbody>
</table>

a. Patient 5 had 2 episodes of Wernicke encephalopathy.
findings in a first attack of WE. However, the alcoholics might have had attacks before; thus, MRI findings in the acute stage were contaminated by previous injury. In the acute phase of WE, enhancement of mammillary bodies was reported using gadolinium. Unfortunately, we could not perform MRI enhancement in our study. Lack of MRI evidence of hemorrhagic foci, as described in the pathology literature, is probably due to their presence in only a small percentage of cases (20%). When hemorrhage was present, much of it appeared to be agonal.

The MRI findings in the chronic phase did not appear to be different among alcoholics and nonalcoholics. Nonvisualization of mammillary bodies, vermian atrophies, or third ventricular enlargements was a common finding. Atrophic changes of mammillary bodies and superior vermis, as well as third ventricular enlargement, have been described in the pathology, and pathology in mammillary bodies is described in all cases with WE. In our study, 4 out of 11 acute MRI scans did not show mammillary body shrinkage, which is similar to previously reported findings in which the prevalence of mammillary body shrinkage was 40% in acute WE. However, 4 patients with normal mammillary bodies during the acute phase of WE showed mammillary body shrinkage during follow-up. Consistent with pathologic information, involvement of mammillary bodies was noted in all patients with chronic WE in our study. Ongoing atrophic changes in MRI were noted as early as 1 week after thiamine treatment. This information is unobtainable from pathologic study.
In summary, the appearance and gradual disappearance of the characteristic T2 high signals with ongoing atrophic changes were noted over time. Findings obtained from MRI in our study are largely consistent with known pathologic information. In common with the pathologic changes from the acute to the chronic stage of WE, MRI findings changed with the disease process. The direct evidence of lesions provided by MRI allows for the monitoring of the disease process and reflects the evolution of the acute and chronic phases of WE.

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References

### Table 2. Magnetic Resonance Imaging (MRI) Findings and MRI Scan Time

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mammillary Body</th>
<th>Periaqueduct</th>
<th>Medial Thalamus</th>
<th>Third Ventricle</th>
<th>Superior Vermis</th>
<th>Corpus Callosum</th>
<th>Initial</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>– → +</td>
<td>+ → –</td>
<td>– → –</td>
<td>– → –</td>
<td>– → +</td>
<td>–</td>
<td>20 hours</td>
<td>10 weeks</td>
</tr>
<tr>
<td>9</td>
<td>– → +</td>
<td>+ → –</td>
<td>+ → –</td>
<td>– → +</td>
<td>–</td>
<td>1 week</td>
<td>before</td>
<td>1 week</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>142 hours</td>
<td>25 days</td>
</tr>
<tr>
<td>4</td>
<td>– → +</td>
<td>+ → –</td>
<td>– → –</td>
<td>– → –</td>
<td>–</td>
<td>–</td>
<td>6 hours</td>
<td>1 week</td>
</tr>
<tr>
<td>5</td>
<td>+ → +</td>
<td>+ → –</td>
<td>+ → –</td>
<td>+ → ++</td>
<td>+</td>
<td>+</td>
<td>30 hours</td>
<td>3 weeks</td>
</tr>
<tr>
<td>10</td>
<td>+ → +</td>
<td>+ → –</td>
<td>+ → –</td>
<td>+ → ++</td>
<td>+</td>
<td>1 hour</td>
<td>3 weeks</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>– → +</td>
<td>+ → –</td>
<td>– → –</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>before</td>
<td>12 days</td>
</tr>
<tr>
<td>13</td>
<td>+ → +</td>
<td>+ → –</td>
<td>– → –</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>before</td>
<td>33 months</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>9 hours</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>22 hours</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>94 hours</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>58 hours</td>
<td>–</td>
<td></td>
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<tr>
<td>8</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>56 hours</td>
<td>–</td>
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</tr>
<tr>
<td>14</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>23 hours</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>55 days</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

"Before" indicates that MRI was taken before thiamine treatment. For mammillary body and superior vermis, + = atrophy; for corpus callosum, periaqueduct, and medial thalamus, + = T2 hyperintensity; for third ventricle, + = dilation. + → ++ indicates a further dilation on follow-up. + or – is marked in the front (within 48 hours) or back (after 48 hours).

a. Patient 5 had 2 episodes of Wernicke encephalopathy.


ABSTRACT

Background and Purpose. The authors compared the reproducibility of a manual and a semiautomated technique for the quantitation of white-matter lesions in magnetic resonance imaging (MRI). Methods. Volumes of white-matter lesions were determined using fluid-attenuated inversion recovery MRI in 23 AIDS patients with progressive multifocal leukoencephalopathy. Manual outlining was compared to an automated method based on region growing and adaptive thresholding. Results. Lesion volumes from the 2 methods correlated well (61 lesions, \( r = 0.99, P < 10^{-4} \)), although the volumes differed substantially (12.8% ± 13.7%). Interscan, intrasubject reproducibility was better for the automated than the manual method (2.9% ± 3.2% vs 12.4% ± 16.2% volume difference, \( P = .02 \)). Conclusion. The automated algorithm appeared more reproducible, which renders it superior to the manual method for longitudinal studies.

Key words: White-matter lesion, progressive multifocal leukoencephalopathy, segmentation, magnetic resonance imaging, fluid-attenuated inversion recovery.
Manual Segmentation

The manual method consisted of outlining the edges of the lesions on all slices using a mouse pointer. Dedicated software allowed an experienced operator to draw and edit polygonal lines on the magnified FLAIR images. All of the displaying and drawing guidelines proposed by Filippi et al.\textsuperscript{5} were applied.

Automated Segmentation

Lesions appeared as hyperintense regions in the white matter\textsuperscript{6,7} surrounded by relatively uniform, lower intensity normal tissue. From a manually selected starting point (seed), a lesion was extracted by 3-dimensional (3D) flooding into neighboring volume elements (voxels) with intensities higher than a given threshold \( t \). The flooding process is a 3D extension of the “bucket paint” algorithms present in most graphics manipulation software. It consists of growing the region, from the seed point, into adjacent voxels on the same slice as well as on adjacent slices (Fig 2). The region grows only into those neighboring voxels whose intensity is above \( t \), and the process is recursively applied until all voxels above \( t \) that are connected to the initial seed point have been flooded. Because of its 3D nature, this algorithm requires the operator to only seed each lesion on 1 slice where it is visible, since the algorithm will spread into adjacent slices as required.

Subjective and technical segmentation variabilities were reduced through the automatic and adaptive determination of the appropriate threshold for each lesion: Starting from the intensity at the seed point, approximated by its closest multiple of a constant \( a (a=5 \text{ intensity units in our implementation}) \), the threshold was progressively decreased by the discrete amount \( a \). For every threshold value \( t \), flooded lesion volume and its ratio \( r \) to the volume obtained with the previous threshold \((t+a)\) were computed. The algorithm ceased to calculate for the next smaller \( t \) value when the ratio \( r \) exploded (i.e., \( r \) was greater than a constant \( b = 6 \)), as flooding began to spread into normal brain tissue or large extents of the extracranial structures. The constant \( b \) was determined empirically under 2 competing constraints: with small values for \( b \), the algorithm would only detect lesions with uniform intensity (which typically is not the case), whereas using larger values for \( b \) presents the risk that flooding would extend into normal white matter when the transition between lesion and white matter is smooth. The final threshold for segmentation was the value of \( t \) at which the explosion occurred, plus an increment \( d (d=7 \text{ in our implementation}) \). \( d \) determined the tolerance of the algorithm with respect to partial volume effects at lesion boundaries; with smaller values, more voxels with partial lesion volume were included in the segmentation. The value \( d = 7 \) was determined empirically.

Fig 1. Automated extraction of a medium-sized lesion in 2 scans acquired consecutively with 2 head orientations (top: first scan; bottom: second scan). Crosses on the left indicate several manually selected seed points, which, given individually as input to the automated algorithm, all yielded the segmented result shown on the right.
By construction, this algorithm yielded exactly reproducible segmentation from a given seed point. In addition, segmentation proved largely independent of the choice of the seed location (Fig 1). Although manual editing of the segmentation results was possible, it was not used in this study.

Results

Manual drawing correlated well with automated extraction (Fig 3A) for all 61 lesions (17 of which were from the repeat scans with different orientations). However, lesion volumes from the 2 methods differed substantially (up to 59% in absolute value for the smallest lesions and 12.8% ± 13.7% on average) (Fig 3B). Better agreement was found for larger lesions; for instance, the difference was 6.8% ± 4% for lesions larger than 9 cc.

The automated method proved more reproducible than the manual method with respect to different patient orientation (Figs 3C, 3D, 3E). For the 17 lesions evaluated from 2 consecutive scans, good correlations were found between the volumes measured in the first and second scan, both with manual drawing (\( r = 0.989, P < 10^{-4} \)) and with the automated method (\( r = 0.999, P < 10^{-8} \)). However, paired \( t \) tests showed significantly different relative volume differences in the 2 orientations for the manual versus the automated method (\( P = .02 \)). This is due to the smaller volume differences for the automated method compared to manual drawing. For all 17 lesions, the volume difference was 12.4% ± 16.2% for the manual method and only 2.9% ± 3.2% for the automated method. For the 14 larger lesions with volumes above 2 cc, average and maximum volume differences were 11.6% and 47.5% for the manual method and only 1.8% and 5.4% for the automatic method.

Discussion

We found substantial discrepancies between the manual and automated methods, especially for the smaller lesions. The major sources of discrepancies are imaging artifacts, uncertain 3D shape coherence, shape irregularities, and inconsistent drawing rules (Fig 4).

1. Imaging artifacts. The FLAIR sequence presents obvious advantages over the regular T2-weighted sequences.\(^4,8,9\) However, it suffers from the presence of artifactual hyperintensities at the interface between tissues and surrounding cerebrospinal fluid.\(^10\) These artifacts are easily misclassified by automated methods, whereas human observers have less difficulty identifying them. Improved
FLAIR sequences may, however, improve the performance of the automated method.

2. **Uncertain 3D shape coherence.** Even when adjacent slices are available, human observers experience difficulties in identifying the 3D shape of a lesion. The most common manual misclassification in this study was the omission of small, isolated regions, which were disconnected from the main lesion in the slice plane but were connected to the lesion in an adjacent slice. The 3D automated method did not suffer from this problem.

3. **Shape irregularities.** The manual segmentation results typically had smoother shape than the automated results. When lesion boundaries were uncertain, the observer approximated them with a straight line segment. This was particularly true for larger lesions, which required drawing of numerous long polygonal contours. Although this source of subjective variability is less problematic in diseases with smaller and smooth lesions, it was more apparent with the larger, highly irregularly shaped PML lesions. Containing no smoothness constraint, the automated algorithm yielded more objective delineation of lesion boundaries.

4. **Inconsistent drawing rules.** Finally, the major source of interscan variability was the inconsistency of manual drawing rules. Although the operator always tried to include the same amount of partial volume around each lesion, manually drawn outlines were more conservative in some regions than in others. It could be argued that this constitutes an advantage for the manual method, which is guided by expert knowledge of certain technical imaging irregularities. For sequential scans, however, accurate absolute volume quantitation is less important than interscan, intrasubject reproducibility. In this respect, the automated method was superior to the manual method for longitudinal studies.

Overall, the automated algorithm extracted lesions rapidly and with high reproducibility. The particular technique proposed here has the advantage of being largely independent of the manually chosen seed point (Fig 1),
Fig 4. Major sources of discrepancies between the automated (top) and manual (bottom) methods. (A) Imaging artifacts: hyperintensities at the brain-fluid interface are ambiguous for the automated algorithm. (B) Uncertain 3-dimensional shape coherence: here, the human observer omitted a small island connected to the main body of the lesion in another slice. (C) Small shape irregularities: the manual drawing smoothed out the exact shape of the lesion, which was correctly followed by the automated algorithm. (D) Inconsistent drawing rules in the manual method were more conservative in some regions (left arrow) than in others (right arrow).
whereas such dependence has been pointed out as an important weakness of automated procedures. Although it is still possible to obtain a small number of different segmentation outcomes with our algorithm based on different seed locations, these outcomes are usually so dissimilar that only 1 is acceptable.

In principle, the algorithm can be applied directly to any type of lesion and any imaging sequence under the condition that lesions should appear significantly more intense than surrounding normal tissue. Hence, standard T2-weighted sequences would be appropriate for the detection of small lesions deep into the white matter; however, they would pose problems if lesions were adjacent to the ventricles or other fluid-filled spaces (which appear as hyperintense in T2-weighted imaging) because the flooding algorithm would spread from the lesion into the ventricles. The algorithm is also directly applicable to the detection of abnormalities seen in diffusion-weighted imaging, especially when they are small or when their irregular shape renders them difficult to manually delineate.

**Conclusion**

PML lesions are often large and irregularly shaped; hence, they pose different quantitation challenges from many other white-matter diseases. We found that 3 of the 4 major sources of quantitation variability—uncertain 3D shape coherence, shape irregularities, and inconsistent drawing rules—could be minimized using an automated segmentation procedure. The fourth source of error, imaging artifacts with the FLAIR sequence, was more easily identified by manual drawing. However, with improved FLAIR sequences, this problem may no longer exist. Our study demonstrates that an automated approach, coupled with careful inspection and possible interactive editing, is more reliable and efficient than manual drawing. Therefore, automated segmentation of lesion volume provides an objective measure for monitoring disease progression.

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**References**

Increased Incidence of a Midline Brain Anomaly in Patients With Nonsyndromic Clefts of the Lip and/or Palate

ABSTRACT

Background and Purpose. Nonsyndromic clefts of the lip and palate (CLP) are developmental craniofacial abnormalities that are often associated with cognitive dysfunction. This study was designed to evaluate, in patients with CLP, the presence of a specific midline brain anomaly (enlarged cavum septi pellucidi [CSP]) that has been shown in other developmental syndromes to be related to poor cognitive function. Methods. Brain images were obtained using magnetic resonance imaging on 49 adult men with CLP and 75 healthy controls. Size of CSP was measured using consecutive coronal images. Results. The incidence of large CSP in the CLP group was 8% (4 of 49), significantly higher than that found in the control group. In 2 of these 4 subjects, the anomaly was complete nonfusion of the septal leaflets, known as a combined CSP and cavum vergae. Furthermore, there was a significant inverse relationship of IQ and CSP in CLP patients that was not present in controls. That is, in individuals with CLP, the larger the CSP, the lower the IQ. Conclusions. Adult men with CLP have an increased prevalence of enlarged CSP. Moreover, this anomaly is directly related to cognitive deficits. This study provides further evidence that the development of the face and the development of the brain are intimately related and that defects in craniofacial development are most likely associated with defects in brain development.

Key words: Cleft lip/palate, cavum septi pellucidi, neurodevelopment, brain, magnetic resonance imaging.


The septum pellucidum is a thin plate of 2 laminae that forms the medial wall of the lateral ventricles. In early fetal life, the septum pellucidum is a solid structure that is then cleaved to form a fluid-filled cavity along its entire length. This cavity is known as a cavum septi pellucidi (CSP), or “fifth ventricle.” In normal fetal development, the 2 leaflets fuse in a posterior to anterior fashion. This fusion is often not complete, leaving a small cavity of less than .5 cm in length. Thus, a small CSP is considered to be a normal variant of anatomy and is seen in up to 60% of the normal population. When the fusion process is aberrant, the resulting cavity is larger. An enlarged CSP is considered a developmental anomaly and is seen in a variety of developmental disorders including fetal alcohol syndrome, Apert’s syndrome, and schizophrenia. In addition, enlarged CSP has been associated with cognitive dysfunction in heterogeneous pediatric groups showing neurologic abnormalities, mental retardation, and developmental delay. More recently, our laboratory reported a direct inverse relationship between the size of CSP and cognitive function in patients with schizophrenia—the larger the CSP, the lower the full-scale IQ (FSIQ).

Nonsyndromic clefts of the lip and palate (CLP) are developmental craniofacial abnormalities that are manifested as an isolated anomaly and, therefore, are not a part of a genetic syndrome. In addition to the facial defect, patients have been documented to have cognitive difficulties. Specifically, children with isolated clefts of the lip and/or palate have been shown to have a lower IQ compared to matched controls. In addition to this generalized deficit, many patients have abnormalities in language function. This language deficit is severe enough to be designated as a specific reading disability in as much as...
35% of this population. Because the development of the craniofacial structures is intimately related to development of the brain, it seems likely that developmental abnormalities of the brain may accompany facial clefts. However, no study to date has assessed the presence of brain abnormalities in patients with nonsyndromic CLP. This study was designed to evaluate, in patients with CLP, the presence of a specific midline brain anomaly, enlarged CSP. We hypothesize that patients with nonsyndromic CLP will have an increased incidence of enlarged CSP and that the severity of the anomaly will be related to cognitive dysfunction.

Methods

Patients

Patients were recruited from the Cleft Lip and Palate Service at the University of Iowa, which maintains the CLP registry. The Cleft Lip and Palate Registry is a large database of individuals with facial clefts, all of whom were seen and evaluated at the University of Iowa. The study group was limited to adult men (to minimize the confound of gender and age on brain morphology) with isolated clefts of the lip and/or palate. Through the registry, a sample of men currently older than 18 years and having an isolated facial cleft was identified and a letter was mailed inviting them to participate in the study. The protocol for this study was approved by the university institutional review board. All patients signed informed consent forms prior to study enrollment.

Forty-nine men with CLP were studied. The average age was 30.3 years. All were Caucasian. Medical records for each patient were reviewed to verify and document cleft status including cleft region (lip only, cleft lip and palate, or palate only), side of the cleft (right, left, median, or bilateral), and the degree of clefting (complete, partial, or microform). All patients had been previously examined by a trained pediatric geneticist to rule out congenital syndromes. This was done by conducting a thorough physical examination to identify major and minor physical anomalies that would suggest the presence of a congenital syndrome. The group consisted of 34 patients with CLP and 15 patients with clefts of the palate only (CPO). Three patients had lip pits in addition to their cleft lip and/or palate and were clinically diagnosed by a medical geneticist as having Van der Woude syndrome. Van der Woude syndrome is an autosomal dominant, single-gene disorder that is manifested in isolated clefts of the lip and/or palate along with lip pits. Although this condition is indeed considered a “syndrome” based on the genetic findings, clinically the only difference between isolated cleft lip and/or palate and Van der Woude syndrome is the presence of lip pits. There are no other associated physical anomalies. Therefore, these patients were included in the current study.

The control group used for this study consisted of a sample of healthy volunteers previously obtained and used in a magnetic resonance imaging (MRI) study of the incidence of CSP in patients with schizophrenia versus healthy controls. The sample consisted of 39 men and 36 women. The volunteers were recruited from the community through newspaper advertising. Patients and/or controls were excluded if they had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or recent, heavy psychoactive drug use or abuse. Average age of the control group was 27.3, somewhat younger than that of the CLP group.

Cognitive assessment was performed on both groups using a comprehensive battery designed to test a wide variety of functions. For the current study, general measures of overall cognitive function, verbal ability, and nonverbal ability were assessed. The measures used were the Wechsler Adult Intelligence Scale–Revised (WAIS-R) Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ). A study reporting the comprehensive analysis of CLP patients’ cognitive performance compared to an age- and sex-matched sample has been completed and submitted for publication.

Magnetic Resonance Acquisition and Analysis

Magnetic resonance scans were obtained with a T1-weighted 3-dimensional spoiled-grass sequence on a 1.5-T General Electric Signa scanner (TE = 5, TR = 24, flip angle = 40°, NEX = 2, 26-cm field of view, 256 × 192 matrix size) using the coronal plane, yielding 124 contiguous slices 1.5-mm thick.

Rating of CSP

Control Sample. For the previously analyzed control group, hard copies of the MRI films were visually inspected (coronal sections). All control and patient films were combined in random order and visually inspected by 2 raters who were blinded to the clinical status of the patients.

The size of the cavum was measured by its appearance in consecutive coronal 1-mm slices.

A simple rating scale for assessment of CSP was used: 0 represented absence, 1 represented a cavum seen on only 1 slice of brain, 2 represented a cavum seen on 2 slices, 3 represented a cavum seen on 3 slices, and so on. Rating reliability was performed by 2 raters who independently
quantified the size of the CSP on a separate sample of 100 scans using the above scale. Percentage agreement in ratings or size of CSP was high at 79%. Of those scans in which the 2 ratters did not agree, the difference in ratings was never more than 1 point (or 1 mm).

CLP Sample. For the CLP sample, ratings of CSP were performed on the MRI images displayed on a Silicon Graphics computer. All postacquisition processing was done using a locally developed family of software called BRAINS. Details of the image analysis are published elsewhere. The magnetic resonance data were converted to a 3-dimensional data set, and the images can be viewed in all 3 planes simultaneously. The brains were then resampled in 1-mm slices.

Prior to rating the study sample, the rater for this study (SB) conducted a reliability study with a separate sample of scans. Once again, percentage agreement was high (88%), and the difference in ratings was never more than 1 point. The scale was the same as that in the previous study, measuring the size of the cavum by its appearance in consecutive coronal 1-mm slices.

The hard-copy films used in the control sample are 1.5 mm thick contiguous with no gaps, and the resampled images used for the CLP sample are 1 mm without gaps. Thus, the quantitative basis of the rating scale represents the actual anterior to posterior length of the cavum, although partial volumning renders this an approximation only. For example, a rating for the control group of 4 would represent a CSP that was approximately 6 mm long (4 slices at 1.5 mm each). There is a more direct relationship for the CLP sample because the images are 1 mm thick; thus, a CSP with a rating of 6 would be approximately 6 mm long. Although the ratings for the CLP sample may be somewhat more “accurate” based on having 1-mm-thick slices rather than 1.5-mm-thick slices, the rating scales are comparable. Also, any differences in ratings (based on slice thickness) between the 2 groups would be very small (ie, .5 to 1 mm).

**Determination of Enlargement of the CSP**

A small CSP is common in a large proportion of healthy controls and is therefore considered to be a normal variant. Determination of how large a CSP needs to be in order to reflect pathology is not known exactly, although it is clear that an overly conservative estimate may erroneously include CSPs that are in the upper range of the normal variant. The best estimate of size of normal variant cavum is approximately 1 to 4 mm. To allow some room for partial volume effects and to eliminate “borderline” CSP, we defined enlargement of the CSP as greater than 6 mm in length. This corresponds to a rating of greater than 4 for the controls and greater than 6 for the CLP patients. All ratings were then collapsed into 2 groups: those who had CSP enlargement and those who did not.

**Statistical Analysis**

For comparison of incidence of enlarged CSP between the 2 groups, chi-square analysis (or the Fisher exact test when expected group sizes were < 5) was used. Because the a priori hypothesis is that an increased incidence of enlarged CSP is expected in the CLP group, 1-tailed tests were used.

To evaluate the relationship between size of CSP and cognitive measures, Spearman’s correlations were calculated. Nonparametric tests were used because the size of CSP was not normally distributed. Therefore, the use of nonparametric tests will be resistant to the influences of outliers. For all analyses, statistical significance was determined at the \( P < .05 \) level.

**Results**

Table 1 indicates the frequency of CSP in both groups. The incidence of “any” CSP (a rating of equal to or greater than 1) was common in both groups: 44 of 75 or 59% of the controls and 31 of 49 or 63% of the patients with CLP. This was not statistically different \((\chi^2 = 0.26, df = 1, P = .60)\).

However, when incidence of CSP was limited to “pathological” CSP, or CSP defined as “enlarged,” a difference between the 2 groups emerged. Only 1 of 75 controls had an enlarged CSP with a rating of 5. In the CLP group, 4 patients had enlarged CSP. This incidence of enlarged CSP was significantly different between the 2 groups (Fisher exact test, \( df = 1, P = .039 \)).

The severity of enlargement in the CLP group is noteworthy in that 2 of the 4 patients who had enlarged CSP had complete nonunion of the septal leaflets. This is an anomaly known as a combined CSP and cavum vergae (CV) and represents a more severe developmental anomaly. For illustration of various sizes of CSP, see Figure 1.

Because the threshold for enlarged CSP is an estimate only, the same analysis was done using a lower threshold: CSP of 3 or greater in the controls and CSP of 5 or greater in the patients. The results remained the same: 6 of 75 or 8% of controls had an enlarged CSP whereas 9 of 49 or 18.4% of CLP patients had an enlarged CSP. This difference was statistically significant (Fisher exact test, \( df = 1, P = .048 \)).

**CSP and Type of Clefting**

With regard to type of clefting, there did not appear to be any pattern related to enlarged CSP. With the conservative threshold of CSP greater than 6, 1 patient was CPO
(CSP = 42; the patient also had Van der Woude syndrome), 2 patients had bilateral cleft lip and palate, and 1 patient had unilateral cleft lip and palate. Using the more liberal definition of CSP enlargement (rating of greater than 5), the additional 5 patients included 1 CPO, 2 bilateral CLP, and 2 unilateral CLP.

**Relationship Between IQ and Size of CSP**

Mean IQ ($SD$) for the control group was as follows: FSIQ 114.2 (11.6), PIQ 114.6 (11.8), and VIQ 111.1 (12.3). Although the control group has mean IQs above average, these levels are normal for the Iowa population, which generally has an average IQ around 110.\(^25\) For the CLP patients, these values were as follows: FSIQ 96.9 (15.4), PIQ 99.2 (13.2), and VIQ 96.0 (12.1). As mentioned previously, a separate analysis of the cognitive function in this group of adult men with oral clefts compared to an age- and sex-matched control group has been completed and submitted for publication.\(^21\) Table 2 shows the correlations between size of CSP (equal to or greater than 1) and cognitive function. In the control group, there was no correlation between size of CSP and any of the 3 cognitive measures (FSIQ, PIQ, or VIQ). However, for the patients, there was a robust and inverse correlation between the size of the CSP and all 3 measures of IQ—FSIQ ($r = 0.53$, $P = .002$), PIQ ($r = 0.47$, $P = .006$), and VIQ ($r = 0.45$, $P = .01$)—which indicates that the greater the severity of the anomaly, the greater the cognitive deficit. All 3 variables were correlated, suggesting that this anomaly is related not to specific cognitive domains but to more overall cognitive function. As would be expected from the correlations, the average FSIQ scores for the 4 cleft patients with enlarged CSP (1 patient with a score of 81, 2 patients with a score of 84, and 1 patient with a score of 88; average = 84.25, $SD = 2.87$) was significantly below the average score of the remaining group of patients with cleft but no enlarged CSP ($n = 45$, mean = 98.1, $SD = 12.3$): $t = 2.22$, $P = .03$. The 2 patients with the combined CSP and CV had FSIQ scores of 81 and 84.

**Table 1. Frequency of Cavum Septi Pellucidi (CSP) in Healthy Controls and Adult Men With Nonsyndromic Clefts of the Lip and/or Palate**

<table>
<thead>
<tr>
<th>Size of CSP (no. of slices)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4*</th>
<th>5</th>
<th>6*</th>
<th>7</th>
<th>24</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls ($n = 75$)</td>
<td>31</td>
<td>14</td>
<td>24</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients ($n = 49$)</td>
<td>18</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Threshold used for enlarged CSP in controls.
  b. Threshold used for enlarged CSP in patients with clefts of the lip and palate.

![Fig 1. Axial sections illustrating various sizes of the cavum septi pellucidi (CSP). On the left is an example of no CSP (rating of 0) or total fusion of the septal leaflets. In the middle is an example of a small CSP (rating of 5). On the right is an example of a combined CSP and cavum vergae, which represents the most severe form—complete lack of fusion of the septal leaflets (white arrows).](image-url)
Spearman Correlations Between Size of Cavum Septi Pellucidi (CSP) and Cognitive Function

<table>
<thead>
<tr>
<th></th>
<th>FSIQ</th>
<th></th>
<th>PIQ</th>
<th></th>
<th>VIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>0.04</td>
<td>.70</td>
<td>0.01</td>
<td>.87</td>
<td>0.02</td>
</tr>
<tr>
<td>PIQ</td>
<td>-0.53</td>
<td>.002</td>
<td>-0.47</td>
<td>.006</td>
<td>-0.45</td>
</tr>
<tr>
<td>VIQ</td>
<td></td>
<td></td>
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</tbody>
</table>

FSIQ = Full-Scale IQ, PIQ = Performance IQ, VIQ = Verbal IQ (Wechsler Adult Intelligence Scale–Revised).

a. Number of people in each group with a CSP greater than 0.

**Relationship Between Age, Gender, and CSP**

Because the 2 study groups differed in mean age, Pearson’s correlation was calculated between size of CSP and age. There was no significant correlation (r = -0.04, P = .65). Additionally, the 2 groups were uneven in gender composition: the control group was composed of men and women whereas the CLP group was composed of men only. In the control group, there was no significant difference in incidence of any size CSP between the women and men (χ² = 0.99, df = 1, P = .31). These results indicate that the difference in age and gender composition between the 2 groups does not account for the findings of increased incidence of large CSP in the clefting group.

**Discussion**

**Aberrant Brain Development**

This study indicates that adult men with nonsyndromic clefts of the lip and/or palate have an increased incidence of a midline developmental brain anomaly—enlarged CSP. As a group, CLP patients had an 8% incidence of enlarged CSP compared to 1% for the healthy control population. However, the severity of the enlargement is worthy of note. In the control group, 1 individual had enlarged CSP; however, it was just over the threshold, with a CSP size of 5. In the CLP group, 1 patient was just over the threshold (CSP = 7); however, the remaining 3 had very large CSPs, with ratings of 24, 27, and 42. The ratings of 24 and 27 represent a CSP that spans almost half the length of the septum. The largest rating of 42 represents combined anomalies of CSP and CV or complete nonfusion of the septal leaflets. Whereas an enlargement of CSP reflects an arrest of the normal fusion process of the leaflets of the septum pellucidum, a combined CSP and CV (CSP-CV) reflects not an arrest but rather a total lack of any fusion process, a more severe anomaly. Thus, not only does this anomaly occur at a higher incidence in individuals with nonsyndromic CLP, but when it does, it is often representative of significant developmental disturbance.

Enlarged CSP is not at all specific to individuals with nonsyndromic CLP. Rather, the incidence of enlarged CSP is increased in a variety of neurodevelopmental disorders such as Apert’s syndrome, fetal alcohol syndrome, Soto’s syndrome, and schizophrenia. Several studies by Bodensteiner and colleagues have repeatedly documented the association of large CSP and a broad range of developmental problems including mental retardation, developmental delay, seizures, macro/microcephaly, and others. Their work clearly indicates that an enlarged CSP is an important marker for increased risk of disturbed brain development.

The fact that individuals with facial clefts would also have concomitant brain abnormalities can be predicted by the well-known observation that the development of the face and the development of the brain are intimately related, in both normal and abnormal conditions. In fact, preliminary analysis of quantitative brain morphology on the current CLP sample indicates that these patients have significantly abnormal brain morphology with larger than normal frontal lobes and smaller than normal temporal lobes and cerebellum volume.

What is the possible mechanism for lack of septal leaflet fusion resulting in enlarged CSP? Fusion of the 2 leaflets depends on a variety of other surrounding structures developing normally, namely, medial temporal structures such as the hippocampus, midline structures such as the corpus callosum and thalamus, and the cerebral hemispheres. Therefore, a disturbance of any or all of the possible surrounding structures may lead to an enlarged CSP. If these other brain regions are also abnormally developed, more widespread functional deficit may be expected when the leaflets of the septum fail to fuse properly.

Although midline brain anomalies have been, in case and case-series reports, associated with facial clefting, it has always been in the context of a syndrome with multiple anomalies. In this population, the patients have isolated or nonsyndromic clefting—no other congenital anomalies are present. This suggests that the brain abnormality may be specifically related to the facial cleft.

**Relationship to Cognitive Dysfunction**

Not only did individuals with nonsyndromic CLP have increased incidence of enlarged CSP, but the severity of this anomaly was directly related to cognitive dysfunction; that is, the more severe the anomaly, the greater the cognitive deficit. Like the incidence of CSP in developmental syndromes, this phenomenon is also not unique to CLP individuals. In a study of Apert’s syndrome patients,
Renier et al. reported that of the 3 brain abnormalities studied (abnormalities in the corpus callosum, septum pellucidum, or size of the ventricles), only septum pellucidum abnormalities were correlated with cognitive dysfunction. Moreover, in a recent study in our laboratory, we found a robust and inverse relationship between size of CSP and cognitive function in patients with schizophrenia—a finding strikingly similar to the current study. Although the impaired cognitive function of children with nonsyndromic clefts has been documented for some time, it has often been theorized as “secondary” to other factors such as poor hearing or psychological factors. More recent evidence suggests that the cognitive dysfunction seen in nonsyndromic clefting is more likely a primary brain problem. Although the number of individuals with CLP and enlarged CSP is relatively small, this study is strong support for the notion that cognitive deficit in this subgroup is not a secondary phenomenon but, rather, is directly related to abnormal brain development.

Future directions for study include evaluation of brain structure and function in adult women with clefts of the lip and/or palate to investigate whether there are any potential interactions between clefting, brain abnormalities, cognitive dysfunction, and gender. In addition, further studies should explore potential environmental factors such as maternal alcohol ingestion or maternal smoking that may contribute to cognitive dysfunction, clefting, or both.

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References


Venous Infarction of Brainstem and Cerebellum

ABSTRACT

The authors describe 2 cases of posterior fossa venous infarction. A 56-year-old woman with essential thrombocytopenia presented with fluctuating complaints of headache, nausea, vomiting, left-sided numbness-weakness, and dizziness and became progressively stuporous. Cranial magnetic resonance imaging (MRI) showed bilateral parasagittal frontoparietal and left cerebellar contrast-enhancing hemorrhagic lesions. On magnetic resonance venography, the left transverse and sigmoid sinuses were occluded. The second patient, a 39-year-old woman, presented with acute onset of diplopia, numbness of the tongue, vertigo, and right-sided weakness following a gestational age stillbirth. MRI revealed lesions in the right half of midbrain and pons and in the superior part of the right cerebellar hemisphere. Digital subtraction angiography showed right transverse and sigmoid sinus occlusion. The authors suggest that one should investigate the possibility of venous infarction in the presence of posterior fossa lesions that are often hemorrhagic and are not within any arterial territory distribution but respect a known venous drainage pattern. Recognition of the observed clinical and neuroimaging features can lead to earlier diagnosis and, potentially, more effective management.

Key words: Cerebellar infarction, brainstem infarction, dural sinus thrombosis, venous infarction.

Brainstem or cerebellar involvement due to spontaneous cerebral venous thrombosis is extremely rare, probably because of abundant venous collateral drainage of this region. The clinical characteristics of the few reported cases are highly variable, and the neuroradiologic features can easily be misleading. Consequently, the correct diagnosis is generally delayed. We studied 2 patients. The first patient was referred to us for probable multiple hemispheric and cerebellar hemorrhagic metastases. The second patient was referred for an arterial ischemic stroke involving the brainstem and cerebellum. The patients subsequently proved to have occlusion of dural sinuses. Clinical and radiological characteristics of these cases will be reported.

Case 1

A 56-year-old woman had fluctuating complaints of headache, nausea, vomiting, left-sided numbness-weakness, and dizziness since 1 week ago. She was seen in another hospital, where a cranial computed tomography (CT) demonstrated a hemorrhagic lesion in the right frontoparietal parasagittal region. Routine admission laboratory tests were normal apart from a thrombocytosis of 922,000/mm³. She then became progressively stuporous, and cranial magnetic resonance imaging (MRI) revealed multiple bilateral frontoparietal parasagittal lesions and a lesion in the left cerebellar hemisphere and inferior vermis (Fig 1A). All lesions except the cerebellar one had hemorrhagic components, and some of the supratentorial lesions were enhanced after injection of Gd-DTPA. These findings were considered to be compatible with intracerebral metastases, and the patient was referred to the oncology department of our faculty. There, a detailed workup for a primary malignancy was negative. Repeat hemograms showed a thrombocyte count above 600,000/mm³. During the course of her hospital stay in the oncology department, the patient was found to have deep venous thrombosis of the right leg after the development of pulmonary embolism. Transthoracic and transesophageal echocardiography were considered to be normal. The patient was then referred to us. Neurological examination performed 36 days after her initial presentation revealed bilateral papilledema, bilateral extensor plantar responses, and truncal
ataxia. A repeat cranial MRI was done. On gradient echo sequences, all the supratentorial lesions were hemorrhagic (Fig 1B). The cerebellar lesion was now hemorrhagic (Fig 1C) and enhanced by Gd-DTPA injection. Left transverse and sigmoid sinuses were hyperintense on T1-weighted images on both first and repeat MRIs (Figs 1A, 1C). There was a high signal in the mastoid air cells, indicating a mastoiditis (Figs 1A, 1C). Magnetic resonance venography showed occlusion of the left transverse and sigmoid sinuses (Fig 1D), but the superior sagittal sinus had a normal appearance. Detailed etiological evaluation revealed essential thrombocytemia. The patient recovered completely after a follow-up period of 1 year under combined myelosuppressive therapy and anticoagulant treatment with full-dose heparin that was followed by warfarin for 6 months.
Case 2

A 39-year-old woman presented with acute onset of diplopia, numbness of the tongue, dizziness, and right-sided hemiparesis 20 days after a gestational age stillbirth. She was seen at another hospital, and a cranial MRI revealed hyperintensities in T2-weighted images, which were located in the right pons and mesencephalon and in the superior part of the right cerebellar hemisphere. She was then referred to us with the probable diagnosis of posterior circulation ischemic stroke. On examination, she had left hemiparesis, right appendicular ataxia, left hemisensory loss, and right Horner’s syndrome. Laboratory examination disclosed high erythrocyte sedimentation rate, iron deficiency anemia, and slightly elevated thrombocyte count. Cerebrospinal fluid examination was normal. On MRI, the lesion extended from rostral mesencephalon to caudal pons (Fig 2A). On transverse sections, right mesencephalon was involved from the level of crus cerebri to superior colliculi and a large lesion was seen in the basis and tegmentum of the right pons extending to right cerebellar hemisphere (Fig 2B). The right transverse and sigmoid sinuses were hyperintense on T1-weighted and T2-weighted images. Four-vessel angiography

Fig 2. (A) Coronal T2-weighted image shows a hyperintense lesion extending from the rostral mesencephalon to caudal pons (arrow). (B) Axial T2-weighted image shows a large lesion in the basis and tegmentum of the right pons extending to the right cerebellar hemisphere (arrow). (C) Digital subtraction angiography demonstrated no visualization of the right transverse and sigmoid sinuses. (D) Follow-up magnetic resonance imaging 1 year later: the T2-weighted axial section shows a minimal residual infarct in the right brachium pontis (arrow).
failed to reveal any arterial abnormalities and confirmed the occlusion of right transverse and sigmoid sinuses (Fig 2C). The search for a hereditary or acquired hypercoagulable state was negative. Clinical and laboratory evaluation for vasculitic, connective tissue, or granulomatous disorders and Behçet's disease revealed no abnormalities. Anticoagulation with full-dose heparin followed by warfarin for 3 months was instituted. The patient recovered completely after a follow-up of 1 month. A follow-up cranial MRI and magnetic resonance venography performed 1 year after discharge showed minimal residual infarct in basis pontis, tegmentum, and brachium pontis (Fig 2D) and restoration of flow in the sigmoid sinus.

Discussion

The rarity of reports dealing with spontaneous venous occlusive disease of brainstem and cerebellum is presumably due not only to the abundant venous collateral drainage of this region but also to the difficulty of establishing the diagnosis. Recognition of the observed neuroimaging features largely depends on knowledge of the various venous drainage pattern of brainstem and cerebellum. This task is rendered more difficult by the known variability of the posterior fossa venous anatomy. The cerebellar veins are placed on the surface of the cerebellum and are drained regionally into adjacent large veins or sinuses. Three groups of cerebellar veins can be distinguished: superior, anterior, and inferior. The major cerebellar venous collectors are vein of Galen, petrosal sinuses, straight sinus, torcular, and transverse sinus. The superior and inferior groups are more likely to be connected to the midline collectors; vein of Galen, straight sinus, or torcular. In many instances, they open first into the superior or inferior vermian vein before their dural collector or vein of Galen. Some of the superior cerebellar veins run laterally to the transverse sigmoid sinus and superior petrosal sinus. Some of the inferior cerebellar veins open to transverse sigmoid and inferior petrosal sinuses. The anterior cerebellar group of veins joins the petrosal vein that drains primarily into the superior petrosal sinus and includes tributaries from the precentral fissure, tributaries related to cerebellar hemisphere, and tributaries related to cerebellomedullary fissure, which include medial tonsillar veins and veins in the posterolateral fissure vein of the lateral recess of the fourth ventricle. The veins of the brainstem form a superficial venous plexus deep to the arteries and constitute a superior or Galenic group, an anterior or petrosal group, and a posterior or tentorial group. The superior group receives blood from the midbrain via the tectal veins, lateral and posterior mesencephalic veins, and anterior pontomesencephalic vein. The petrosal group drains the anterior aspect of the midbrain and pons via the anterior and lateral pontomesencephalic veins, the peduncular vein, and the pontine veins, which tend to form over the pons a lateral channel on each side that may drain into the petrosal sinuses.

Our cases demonstrate several potential features of posterior fossa venous thromboses. In our first patient, who exhibited a subacute and fluctuating course with multiple supratentorial and infratentorial lesions, the original diagnosis was multiple cerebral metastases. Another possibility was multiple supratentorial and infratentorial arterial infarctions secondary to essential thrombocytosis. In fact, the cerebellar lesion may well be interpreted as a postero-inferior cerebellar artery territory infarction. In this case, lateral sinus thrombosis should be viewed as an isolated finding due to local infection (ie, mastoiditis or a concomitant venous involvement due to thrombocytosis and unrelated to ipsilateral cerebellar lesion). This hypothesis could clearly explain the multiple supratentorial hemorrhagic lesions in the absence of associated superior sagittal sinus involvement. The absence of symptoms or signs in favor of acute mastoiditis was against the hypothesis of an infectious thrombophlebitis of lateral sinus, and the occurrence of a peripheral deep venous thrombosis and pulmonary emboli together with dural sinus thrombosis suggested a primary involvement of the venous system. The cerebellar lesion was located in the inferior vermis, infero-medial cerebellar hemisphere, and tonsil. In the usual situation, these areas will drain via the inferior vermian vein that has a backward and a superior course and open into the straight or transverse sinus, which was occluded in our case. In this affected territory, only the tonsillar region has a dual drainage pattern. The posterior and lateral aspects of the cerebellar tonsils are drained via the superior and inferior retrotonsillar veins and lateral tonsillar veins that open into the inferior vermian vein and than into the straight or transverse sinus. The anteromedial aspect of the cerebellar tonsil is drained by the medial tonsillar veins that are usually not prominent and converge to join anteriorly the vein of the lateral recess of the fourth ventricle and thence the petrosal vein, which open into the superior petrosal sinus. Alternatively, these veins may also run backward to open into a medial tonsillar tributary of the inferior vermian vein. Overall, the cerebellar lesion was consistent with a hemorrhagic venous infarct due to transverse and sigmoid sinus occlusion, and cerebral venous thrombosis was considered as the most likely cause of at least the clinical and radiological features of posterior fossa involvement in our patient.

In the second case, the rather atypical appearance of the brainstem lesion, involving nearly the entire right mesencephalon and pons, made the differential diagnosis perplexing. The topography of the lesion was not in favor of an arterial origin. A meningoencephalitic, vasculitic, or granulomatous illness with a preferential involvement of brainstem seemed plausible, but cerebrospinal fluid examination did not disclose any abnormalities, and all other laboratory diagnostic procedures were negative. The patient did not have Behçet’s disease, which is endemic in our area. Finally, angiography revealed ipsilateral occluded transverse and sigmoid sinuses. This case was fairly typical of thrombosis of the lateral petrosal vein, which drains into the superior petrosal sinus and, hence, into the thrombosed transverse and sigmoid sinus. The late follow-up magnetic resonance venography showed recanalization of sigmoid sinus and minimal residual pontine infarction. In retrospective analysis, the large lesion in the brainstem and cerebellum was thought to represent mostly edema secondary to venous congestion rather than infarction.

Anticoagulant treatment with heparin and warfarin were instituted in both cases. Under this treatment, the patients did not suffer any further infarction or hemorrhage and the outcome was good. Although it is difficult to explain these good outcomes solely on the basis of anticoagulation, heparin is shown to be effective in patients with cerebral venous thrombosis.

We found only 9 previously reported cases in the English-language literature between 1960 and 2000. The clinical and radiological features of the previously reported cases and of our patients are reviewed in Table 1. In all of those cases, the cerebellum is primarily affected but the brainstem can also be involved. The clinical symptoms are typically of acute onset, rapidly
<table>
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<tr>
<th>Study</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Occluded Sinus</th>
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<th>Infarct Localization</th>
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<tr>
<td>Stevens and Ammerman 13</td>
<td>22/F</td>
<td>Headache, nausea, gait disorder (subacute)</td>
<td>R cerebellar ataxia, L CN 6 deficit, R Babinski</td>
<td>R transverse</td>
<td>Ventrilography, angiography, surgery</td>
<td>Surgery: R cerebellar + hydrocephalus</td>
<td>Pregnancy</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Bousser et al 11</td>
<td>46/M</td>
<td>Headache (acute)</td>
<td>None</td>
<td>Cerebellar veins + L transverse (partial)</td>
<td>CT, angiography</td>
<td>Cerebellar</td>
<td>AT III deficiency</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Bousser et al 11</td>
<td>42/F</td>
<td>Multiple cranial nerve palsies and ataxia (chronic)</td>
<td>Superior sagittal sinus + L transverse + cortical veins + cerebellar veins</td>
<td>CT, angiography</td>
<td>Supratentorial and cerebellar hemorrhagic infarcts + hydrocephalus</td>
<td>Idiopathic</td>
<td>Partial recovery</td>
<td></td>
</tr>
<tr>
<td>Chilvers and Rudge 9</td>
<td>30/F</td>
<td>Loss of consciousness following headache and nausea (acute)</td>
<td>Coma, forced deviation of the eyes, flexor response to pain, bilateral Babinski</td>
<td>Multiple</td>
<td>CT, necropsy</td>
<td>Early CT: normal; necropsy: brain stem and cerebellar</td>
<td>Oral contraceptive</td>
<td>Died</td>
</tr>
<tr>
<td>Rousseaux et al 12</td>
<td>60/M</td>
<td>Headache, nausea, and unilateral ataxia (subacute)</td>
<td>Findings of increased intracranial pressure and unilateral cerebellarvestibular involvement</td>
<td>Transverse</td>
<td>CT</td>
<td>Contrast-enhancing unilateral L cerebellar lesion + hydrocephalus</td>
<td>Idiopathic</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Eng et al 2</td>
<td>57/M</td>
<td>Diabetic hyperosmolar coma and dehydration (acute)</td>
<td>Deep coma, horizontal and rotary nystagmus, extensor response to pain</td>
<td>Straight</td>
<td>CT, necropsy</td>
<td>CT: bilateral cerebellar and L posterior parietal hemorrhage; necropsy: diffuse cerebellar infarct</td>
<td>Dehydration</td>
<td>Died</td>
</tr>
<tr>
<td>Nayak et al 15</td>
<td>20/M</td>
<td>Otitis media, headache, and nausea (acute)</td>
<td>L cerebellar ataxia, dysarthria, nystagmus, titubation</td>
<td>L sigmoid</td>
<td>CT, MRI, angiography</td>
<td>L cerebellar + hydrocephalus</td>
<td>Chronic suppurative otitis media</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Bakaç and Wardlaw 30</td>
<td>64/M</td>
<td>Chest pain and atrial fibrillation, right-sided weakness, drowsiness (acute)</td>
<td>Right hemiparesis, dysphasia, drowsiness</td>
<td>L transverse and sigmoid</td>
<td>CT, necropsy</td>
<td>L temporoparietal and L cerebellar hemorrhagic lesions with mass effect</td>
<td>Unknown</td>
<td>Died</td>
</tr>
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Table 1  Continued

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Kellett et al&quot;14</td>
<td>46/M</td>
<td>Headache, vomiting, dizziness (subacute)</td>
<td>Fluctuation of consciousness, grand mal seizure</td>
<td>Superior sagittal sinus, straight, both transverse and sigmoid</td>
<td>CT, MRI,</td>
<td>L parietal and bilateral cerebellar</td>
<td>Heterozygote 20210A mutation of prothrombin gene</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Current study, case¹³</td>
<td>56/F</td>
<td>Headache, nausea, vomiting, left-sided numbness and weakness, somnolence following dizziness (subacute)</td>
<td>Truncal ataxia, bilateral papilledema, bilateral Babinski</td>
<td>L transverse and sigmoid</td>
<td>CT, MRI, magnetic resonance angiography</td>
<td>Bilateral parietal + L cerebellar</td>
<td>Essential thrombocytosis</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Current study, case²</td>
<td>39/F</td>
<td>Diplopia, numbness of the tongue, dizziness, left-sided weakness (subacute)</td>
<td>R hemiparesis, R cerebellar findings, L hemihypoaesthesia, R Horner’s sign</td>
<td>R transverse and sigmoid</td>
<td>CT, MRI, angiography</td>
<td>R half of the mesencephalon pons and the superior cerebellum</td>
<td>Postpartum period</td>
<td>Complete recovery</td>
</tr>
</tbody>
</table>

L = left, R = right, CN = cranial nerve, CT = computed tomography, MRI = magnetic resonance imaging.
evolving to coma and death, but can be subacute or chronic. Symptoms and signs of elevation of intracranial pressure are common to all patients. Early obstruction of cerebrospinal fluid circulation leading to hydrocephalus is frequent but does not preclude a good prognosis. Vestibular and cerebellar signs are the predominant findings on neurologic examination. On imaging studies, cerebellar infarction can be unilateral or bilateral. It is frequently hemorrhagic and edematous and can sometimes be misleading by having the appearance of a contrast-enhancing mass lesion. Cerebellar involvement may be an isolated finding or associated with supratentorial infarcts. Cerebellar infarction probably follows thrombosis of the surface veins of the cerebellum draining into different sinuses. In the reported cases, these veins were not affected in isolation and concomitant thrombosis of the transverse, sigmoid, or straight sinuses or involvement of multiple sinuses was found. Absence of isolated cerebellar vein thrombosis in the reported cases may be due to difficulties in diagnosis. The overall outcome can be relatively good, with complete recovery in 4 and partial recovery in 2 of 9 reported cases. Causes of posterior fossa venous thrombosis are the same as those observed in other locations. These include pregnancy, postpartum period, oral contraceptive use, dehydration, infections-like chronic supplicative otitis media, and hereditary hypercoagulable states such as antithrombin III deficiency and heterozygote 20210A mutation of prothrombin gene. Essential thrombocytemia, which was the probable etiology in our first patient, is well known for its potential to lead to arterial or venous thrombosis and can be added to this list.

Cerebellar and brainstem venous infarctions, which were formerly thought difficult to recognize during life, are much more easily detected with the advent of MRI, which has revolutionized the imaging of the posterior fossa structures. The diagnosis of venous infarction of posterior fossa structures should be considered in the presence of lesions that are often hemorrhagic and are not within any arterial territory distribution but respect a known venous drainage pattern. Recognition of the observed clinical and neuroimaging features of posterior fossa venous thrombosis can lead to earlier diagnosis and, potentially, more effective management.

References

Cerebral Infarction in Conjunction With Patent Foramen Ovale and May-Thurner Syndrome

ABSTRACT

Stroke patients with paradoxical emboli mandate a search for deep venous thrombosis (DVT) in the lower extremities. Iliac vein compression, or May-Thurner syndrome, places certain patients at risk for development of DVT. The authors present 3 stroke patients with patent foramen ovale and paradoxical cerebral embolism, with demonstrated iliac vein compression as the presumed source of their embolus. May-Thurner syndrome should be considered a potential source of clot, as definitive therapy of this disorder can be curative.

Key words: Stroke, May-Thurner, patent foramen ovale, iliac compression.

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In 1956, May and Thurner1 described a syndrome wherein the left common iliac artery, compressing the right common iliac vein, caused a deep venous thrombosis (DVT). These patients are typically young, present with isolated painful swelling of the left leg, and are often highly athletic individuals with relatively increased muscle bulk. A patent foramen ovale (PFO) is a factor in cerebral infarction as a presumed embolic phenomenon.2-5 The coexistence of PFO and May-Thurner anomaly places patients at increased risk of recurrent cerebral infarction. We present 3 illustrative cases in which this combination was felt to be the cause of cerebral infarction.

Case 1

A 24-year-old man presented with the acute onset of global aphasia and right hemiparesis. Angiography revealed a patent middle cerebral artery but poor filling of multiple branches of the superior division of the left middle cerebral artery; there was no dissection. Past medical history was unremarkable. He was very physically active, playing multiple contact sports, from which he sustained occasional head/neck trauma, but none in the past several years. His only medications were occasional β-agonist inhalers for exercise-induced asthma. He smoked cigarettes rarely and drank beer socially. He denied the use of any recreational drugs.

General physical exam was unremarkable without peripheral embolic stigmata. Neurologically, he was alert but globally aphasic, with a dense right hemiparesis. He was treated with induced hypertension and heparin anticoagulation. Over the next several weeks, his examination improved to a mild motor aphasia and no weakness.

Head computed tomography (CT) confirmed an infarct in the left parietal insular cortex. Hypercoagulability panel was normal (protein S, protein C, antithrombin III, activated protein C resistance screen), as were anticardiolipin IgG and IgM titers. Antinuclear antibody was negative at a 1:40 dilution. Electrocardiogram was remarkable for an unusual P axis and slight notching of the R wave in leads III and AVF (“crochetage”). Carotid ultrasonography was unremarkable. Twenty-four-hour Holter monitoring revealed no arrhythmias but unusual P wave morphologies with a questionable junctional rhythm.

Transcranial and transesophageal echocardiography revealed a normal ejection fraction without wall motion abnormalities and a PFO on contrast study (agitated saline via brachial route). Bidirectional flow across the PFO was seen without Valsalva maneuver. Triplex ultrasound of the lower extremities was negative for DVT. Pelvic MR venogram (MRV) suggested left external iliac vein thrombosis. Pelvic CT scan with contrast was inconclusive, with flow artifact in the left external iliac vein. Left femoro-iliac venogram (see Fig 1) revealed partial obstruction to antegrade flow in the left common iliac vein, the external iliac vein was abnormally small, and there was generous backflow by reflux into the internal iliac veins. There was no substantial gradient at rest between the IVC and the left external iliac vein (2-4 mm Hg); however, with Valsalva maneuver, the IVC pressure went from 14 to 60 mm Hg and the left external iliac vein pressure went from 17 to 30 mm Hg. (The venous system, valveless, is a continuous system without pressure gradient between the IVC and external iliac vein in normal individuals with Valsalva maneuver.) This vascular abnormality is known as the iliac compression syndrome, or May-Thurner syndrome. Although no thrombus was seen on this study at the time, it was felt nevertheless to be the most likely source of the patient’s paradoxical embolus to the left middle cerebral artery via a PFO.

The patient later underwent a transcatheter PFO closure procedure with a Sideris device. The PFO was 3 cm in diameter as measured by balloon passage during catheterization. The Sideris device unfortunately became partially dislodged after several months, necessitating transluminal pericardial patch closure of the patient’s secundum atrial septal defect; he tolerated this procedure well and has had no further neurological events at 2-year follow-up.
Case 2

A 23-year-old athletic college student developed confusion, right facial numbness and tingling paresthesia, dysarthria, and blurry vision. She denied frank head or neck trauma, headache, or neck pain. A head CT 4 days after symptom onset revealed a hypodensity in the left thalamus, verified on magnetic resonance imaging (MRI); no other lesions were seen on MRI.

Her past medical history was unremarkable, including an negative history for migraines, oral contraceptive use, and smoking.

On examination, she had no bruits or murmurs. Neurological examination revealed deficits in short-term memory. She was concrete and echolalic, displaying much difficulty with abstraction. She had no abnormalities of fluency, naming, comprehension, reading, or writing but had some difficulty repeating lengthy sentences and could name only 8 “F” words in 60 seconds. She drew a clock well but could not place the hands correctly. She had slight left lower facial weakness. Her clinical findings were felt to be secondary to her unilateral thalamic lesion as a thalamic disconnection syndrome. She returned to neurological baseline after 6 weeks.

Head and neck magnetic resonance angiography was normal, without evidence of dissection. Twenty-four-hour Holter monitoring was normal. A hypercoagulability panel was normal, as were anticardiolipin IgG and IgM titers. Transthoracic echocardiography revealed a PFO with right-to-left shunting with Valsalva maneuver. Pelvic MRV (Fig 2) revealed a May-Thurner anomaly. The patient was discharged on Coumadin. She later underwent PFO closure with a Sideris device. Her PFO was 5 mm in diameter as measured during catheterization. She has had no further neurological events over the subsequent year.

Discussion

The presence of PFO in the 3 patients here provoked a search for venous disease below the heart as the source of embolus. PFO by itself is not emboligenic and can be present in up to 30% of the normal healthy population. However, when no other source of infarction is found in an otherwise healthy young adult, it is necessary to investigate whether there is a conduit for embolus through the heart from a peripheral venous thrombosis. In addition, engaging in Valsalva maneuver would increase the amount of right-to-left shunting through a PFO, thereby increasing the chance of paradoxical embolism. It is unknown
whether any of the 3 patients in this report were engaging in Valsalva maneuver just prior to their strokes.

A series of 29 patients reported by Cockett and Thomas further characterized the iliac vein compression syndrome initially described by May and Thurner. Classically, the abnormality lies within the left common iliac vein at the point where the right common iliac artery crosses it. This congenital abnormality caused obstruction at this level by adherence of the anterior and posterior wall. This adherence had the gross appearance of a “lateral flap, a central band, or an almost occlusive but perforated membrane.” Later studies subdivided the abnormalities into 5 categories: “central spurs, adhesions, bridges, bands and valves.” The process of adhesion is felt to be secondary to a reactive process “induced by compression of the vein between the lumbosacral spine and the right iliac artery, the intimate contact between vein and artery and the systolic pulse causing chronic trauma, irritation and tissue reaction.” Alternatively, a congenital origin may be to blame: the right common iliac vein originates from the right sacral cardinal vein, whereas the left originates from the combination of the right and left sacrocardinal veins, frequently divided into 2 or more channels; persistent endovenous structures theoretically could result from incomplete dissolution of these channels.

The exact incidence of the iliac compression syndrome is unknown, but it is estimated to be 14% to 32% in postmortem studies. The abnormality is estimated to be 5 times more common in women. The percentage of patients with the abnormality who develop a complication (DVT or pulmonary embolism) is unknown. The iliac vein compression syndrome is most frequently associated with DVT of the left leg and pulmonary embolism in the nonanticoagulated patient. However, in patients with cerebral infarction with PFO, it should also be considered as a potential source of paradoxical embolism. Treatment for this disorder has traditionally been via open surgical vascular procedure, but more recently endovascular techniques and self-expanding metallic endoprostheses have been employed with good initial results. There are no data with regard to potential medical treatments of this condition.

The patients presented here had several striking similarities in their evaluations for cerebral infarction. Echocardiography demonstrated a PFO with right-to-left shunting on agitated-saline contrast study. In patients 1 and 3, right-to-left shunting was seen without Valsalva maneuver, whereas Valsalva was required in patient 2. Nevertheless, we were unable to elicit a clear history of Valsalva maneuver from any patient immediately prior to their stroke.

Second, all 3 patients had a presumed pelvic or lower extremity thrombosis along with radiological findings suggestive of iliac compression syndrome. In case 1, the abnormality was suggested by pelvic MRV and later verified by direct pelvic venography. In cases 2 and 3, a pelvic MRV showed the characteristic anomaly, although no definite evidence for thrombus was seen. Interestingly, all 3 patients were highly athletic individuals—one an avid hockey player, the second an active runner, the third a competitor in national field hockey. They were well-developed musculyly, raising the question of whether their muscular development in the lower extremities added to the development of, or produced, the vascular abnormality secondary to increased external compression.

In summary, our cases illustrate the necessity of fastidious evaluation in young stroke patients. Aside from standard investigations of cerebral vasculature and cardiac rhythm monitoring, these patients should be evaluated for PFO by agitated-saline contrast echocardiography. When a PFO is detected, pelvic or lower extremity thrombosis should be sought—especially in young athletes—and the iliac vein compression syndrome should be recognized as a source of paradoxical embolus.

References

Bilateral Cerebellar Infarctions
Caused by a Stenosis of a
Congenitally Unpaired Posterior
Inferior Cerebellar Artery

ABSTRACT

Bilateral symmetrical cerebellar infarcts in the territory supplied by the medial posterior inferior cerebellar artery (PICA) branches are extremely rare. In the few cases published, it has not been possible to clearly pinpoint the cause of this infarct pattern. The authors present the case history of a 58-year-old man who had acute headaches accompanied by pronounced rotatory vertigo with nausea and vomiting. The neurological examination revealed bilateral cerebellar signs. Cranial magnetic resonance imaging showed bilateral, nearly symmetrical infarcts in the territory of the medial branches of both PICAs. These bilateral PICA infarctions were caused by a stenosis of an unpaired PICA originating from the left vertebral artery supplying both cerebellar hemispheres.

Keywords: Bilateral cerebellar infarction, congenitally unpaired posterior inferior cerebellar artery.

Case

A 58-year-old man was admitted to our stroke unit after the onset of severe occipital headaches accompanied by sweating and rotatory vertigo, nausea, and vomiting. The clinical-neurological examination revealed the following pathological signs: an upward gaze-evoked nystagmus, dysphonia, gait ataxia with a nondirected tendency to fall, and a bilateral limb ataxia. No Babinski’s sign was present. No impairment of strength or sensory function was found.

Cranial magnetic resonance imaging (MRI) conducted immediately upon admission (Fig 1) showed bilateral, nearly symmetrical infarctions in the area supplied by the medial branches of the PICA. In cranial MRI angiography, the PICA could not be adequately assessed on either side. Continuous wave Doppler sonography showed normal extra- and intracranial brain-supplying vessels. Computed tomography angiography (CTA) and digital subtraction angiography (DSA) (Fig 2) both showed a vessel variation of the PICA: it distally originated from the left vertebral artery as a unique large-caliber vessel and diverged into 2 symmetrical branches, each supplying 1 cerebellar hemisphere. Approximately 2 cm from the origin, DSA and CTA (Fig 3) revealed a well-demarcated stenosis. Transesophageal echocardiography (TEE) and sinus rhythm in the electrocardiogram (ECG) (including Holter ECG) revealed no evidence of a cardiac source of embolism. Furthermore, hypercholesteremia existed with a reduction in high-density lipoprotein cholesterol and an increase in low-density lipoprotein cholesterol. There was no indication of vasculitis or coagulopathy. With physiotherapy and early mobilization, the gait ataxia proved reversible. The patient was discharged 15 days after the onset of stroke and still showed a slight gaze-evoked nystagmus and ataxia.

Discussion

Because of the excellent intracranial collateralization system, simultaneous bilateral infarctions are very rare. They can occur as a consequence of bilateral, pathological vascular processes (including, cardiac embolism, coagulopathy) or as the sequel of a
venous thrombosis, for instance, the superior sagittal sinus. They can also occur if both vessels originate from an unpaired trunk. Occlusion of those single arteries results in well-characterized bilateral infarctions such as bilateral paramedian thalamic infarcts caused by an occlusion of an unpaired thalamoperforating artery—a vessel variation that has been found in 30% of the individuals with this type of infarction. Another example is bilateral infarctions in the anterior cerebral artery territory, which can be caused by either a singular vessel (0.3%) or a joint exit of both vessels. These vessel variations are found in around 18% of the normal population. Even in the rare cases of bilaterally symmetrical cerebellar PICA infarctions, such a mechanism has been postulated. In general, the vascular territory of the PICA is highly variable. Thus, in hypoplasia or the absence of either the anterior inferior cerebellar artery (AICA) or the PICA, usually the ipsilateral remaining artery preserves the blood supply in this territory. Additionally, in approximately 15% of the angiograms of the vertebral artery, the PICA is missing.

Tada et al reported a patient with a bilaterally symmetrical PICA infarction involving the medial PICA branches in which one side presented a primarily hypoplastic and the other side a normal PICA. However, it was not possible to determine definitively whether the PICA had supplied the contralateral side with blood. In similar case reports, neither Brusa et al nor Sorenson et al was able to clarify the mechanism of bilateral PICA infarctions. Among a series of 12 patients with bilateral PICA infarcts recently published by Kang et al, a more or less symmetric infarction pattern of the medial PICA territory was seen in 6 patients. The most possible underlying cause was an occluded unpaired PICA in 2 cases, atherosclerotic disease of 1 or both vertebral arteries in 3 cases, and a stenotic dominant PICA in 1 case. Our present case history offers the first angiographic proof of an unpaired PICA supplying both cerebellar hemispheres. Both DSA and CTA proved a proximal stenosis of the common PICA trunk as the cause of the bilateral infarction. Most likely, the infarction was limited to the medial PICA territory because of an AICA dominant supply of the cerebellum that reduces the infarction to a territory that is exclusively supplied by the PICA. The absence of any other atherosclerotic lesions in the large extracranial vessels leads to the assumption that the present PICA stenosis is more likely caused by thromboembolism and is less likely to be of atherosclerotic origin. However, despite an extensive examination including TEE and Holter ECG, no potential cardiac or aortic source of embolism was found. The described condition,

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**Fig 1.** Magnetic resonance imaging of the infarct 2 days after stroke onset (T2 weighted). The infarct remains strictly within the boundaries of the medial posterior inferior cerebellar artery territory. No hemorrhagic components are present.

**Fig 2.** Digital subtraction angiography of the right (A) and left (B) vertebral arteries in anterior-posterior view shows a stenosis (arrow) of the proximal trunk of an unpaired posterior inferior cerebellar artery originating from the left vertebral artery and supplying both cerebellar hemispheres (ltVA = left vertebral artery, rtVA = right vertebral artery, rtPCA = right posterior cerebral artery, ltPCA = left posterior cerebral artery).

**Fig 3.** Computed tomography angiography of the posterior inferior cerebellar artery depicts an unpaired vessel with a high-grade stenosis proximal to its bifurcation into the branches supplying the left and the right cerebellar hemispheres (STEN = stenosis, PICA = posterior inferior cerebellar artery, VERTEBRAL A = vertebral artery).
however, must be differentiated from bilaterally symmetrical cerebellar infarctions associated with venous thrombosis in the posterior cranial fossa. These bilateral cerebellar lesions are due to an excessive collateralization of the venous efference. This is quite rare and differs from the present infarction pattern because it is not symmetrical and because there is no clear delimitation of the infarct area to the PICA territory. Additionally, it has a greater tendency to hemorrhagic transformation.

References

Transient Crossed Cerebellar Diaschisis Following Thalamic Hemorrhage

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ABSTRACT

This report concerns a 65-year-old right-handed woman with cerebral hemorrhage who presented with mild right-sided hemiparesis. Computed tomography (CT) revealed hematoma in the left thalamus and compression of the posterior limb of the internal capsule by a brain edema surrounding the lesion. 99mTc-hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) images obtained 4 days after onset showed hypoperfusion in the left thalamus containing a hematoma as well as contralateral cerebellar hypoperfusion to the supratentorial lesion, which is well recognized as crossed cerebellar diaschisis (CCD) after stroke. CT 14 days after the onset revealed reduction of the brain edema of the posterior limb of the internal capsule accompanied by gradual neurological improvement. SPECT obtained 14 and 28 days later showed that CCD had disappeared. In this case report, the authors discuss the disappearance of CCD due to transient edematous compression of the internal capsule following thalamic hemorrhage on serial 99mTc-HMPAO SPECT scans.

Key words: Brain hemorrhage, crossed cerebellar diaschisis, 99mTc-hexamethylpropyleneamine oxime, single photon emission computed tomography.

Baron et al. first identified contralateral cereellar hypoperfusion, termed crossed cerebellar diaschisis (CCD), in patients with supratentorial infarction using a noninvasive 15O continuous inhalation technique coupled with positron emission tomography. This phenomenon develops not only after infarct but also in association with hemorrhage, tumors, and other disorders. Previous single photon emission computed tomography (SPECT) studies demonstrated that infarcts in the basal ganglia or pons cause CCD, presumably via interruption of the cerebropontocerebellar pathway. Furthermore, results obtained with technetium-ethyl cysteinate dimer SPECT and Xe-133 inhalational SPECT have led to speculation that intracranial hematomas in the basal ganglia cause CCD. To the best of our knowledge, however, there have been no reports on serial changes in CCD following intracerebral hemorrhage or on the relationship between these changes and clinical symptoms detected by 99mTc-hexamethylpropyleneamine oxime (HMPAO) SPECT. We report a unique case of thalamic hemorrhage, showing transient CCD on serial 99mTc-HMPAO SPECT scans.

Case

A 65-year-old right-handed woman presented with mild weakness involving the right side of her body. Hypertension had been diagnosed at age 50. Although she was advised to undergo treatment, she refused and had taken no medication.

She was admitted to our hospital 2 days after the onset. The pertinent findings on general physical examination consisted of a blood pressure of 190/100 mm Hg and regular pulse rate of 70 bpm. Neurological examination on admission revealed right hemiparesis, acalculia, and aproslexia. Emergent computed tomography (CT) revealed an abnormal high-density area in the thalamus and compression of the posterior limb of the internal capsule by a brain edema surrounding the lesion (Fig 1, upper row). Informed consent to participate in this study was obtained from the patient and her family.

The SPECT apparatus was a high-performance, 4-headed gamma camera system equipped with a low-energy, high

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resolution, parallel-hole collimator (SPECT 2000H, Hitachi Medical Company, Tokyo). Ten minutes after intravenous injection of 740 MBq $^{99m}$Tc-HMPAO, SPECT acquisition started in 20-second steps, 64 steps per camera, at 360° and with a 64-pixel format. The projection data were prefiltered with a Butterworth filter, and Chang’s attenuation correction was applied to the reconstructed images.

SPECT images obtained 4 days after onset showed hypoperfusion in the left thalamus with the hematoma (Fig 2, upper row, arrowheads), and CCD was clearly demonstrated (Fig 2, upper row, arrows). Symmetrical regions of interest were manually placed on the left (affected-lesion side) and right cerebellar hemispheres, and the lesion-to-contralateral radioactivity ratio (L/C ratio) was 1.1.

Three days after onset, gradual improvement in neurological signs and symptoms became evident. Finally, 7 days after onset, both right hemiparesis and acalculia had completely disappeared and only slight aproslexia remained.

CT 14 days after the onset revealed amelioration of the brain edema in the posterior limb of the internal capsule following hematoma evacuation (Fig 1, middle row). Eventual clinical improvement appeared to reflect these serial changes seen on CT.

On SPECT 14 and 28 days later, the tracer distribution in the right cerebellar hemisphere had increased in comparison with that on the first SPECT and the right-to-left difference had disappeared, with an L/C ratio of 1.0 in the cerebellum (Fig 2, middle and lower rows).

Follow-up magnetic resonance imaging 30 days after the onset showed a small residual hematoma strictly confined to the left thalamus and complete disappearance on T1-weighted and T2-weighted images of the compression by the hematoma in the posterior limb of the internal capsule (lower row).

**Discussion**

CT on admission showed a thalamic hematoma and compression of the internal capsule by edema around the hematoma. Normally, the cerebropontine fibers descend through the corona radiata and internal capsule and terminate on the pontine nuclei. The pontine nuclei give rise to the transverse fibers of the pons, which cross the midline and enter the opposite cerebellar hemisphere as the middle cerebellar peduncle. In our case, one
possible mechanism accounting for the CCD seen on the first SPECT is interruption of the cerebropontocerebellar tract due to compression of the posterior limb of the internal capsule by the anatomically adjacent thalamic hematoma and edema. Furthermore, CT obtained 14 days after admission showed reduction of this internal capsule compression with improvement of hemiparesis. SPECT conducted at the same time indicated that CCD had disappeared. These results suggest that the posterior limb of the internal capsule is one of the principal lesions inducing CCD via the cerebropontocerebellar pathway. Pappata et al\(^9\) demonstrated that lesions involving the internal capsule tended to produce more significant CCD than those without such involvement. Their results support our hypothesis for the mechanism of transient CCD in our patient. Kanaya et al\(^6\) used Xe-133 inhalational SPECT to examine the cerebral blood flow in 16 patients who had experienced thalamic hemorrhage and reported that neither the 4 cases examined within 3 weeks following the thalamic hemorrhage nor the 12 cases whose hemorrhage was more than 5 weeks old showed significant CCD. The absence of CCD on SPECT at 14 and 28 days in our case is consistent with their results. It is thus reasonable to speculate that acute thalamic hemorrhage involving the internal capsule or putamen induced the transient CCD in the acute stage.

In thalamic hematoma cases, there are 2 other anatomical pathways that may possibly be associated with CCD. The first is interruption of the efferent pathway from the cerebellum.\(^5,9\) The finding that thalamic lesions resulted in retrograde contralateral dentate nucleus atrophy in previous human postmortem studies appears to support the possibility of development of CCD through this pathway.\(^9\) The second possibility is that hypoperfusion of the cerebral cortex through thalamocortical diaschisis leads to CCD.\(^7\)

Our observations strongly support the hypothesis that the lesion, confined to the posterior limb of the internal capsule consisting anatomically of the cerebropontocerebellar pathway, is likely the cause of transient CCD observed in the acute stage of the thalamic hemorrhage.

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References

Magnetic Resonance Imaging Detection of a Lesion Compatible With Central Pontine Myelinolysis in a Pregnant Patient With Recurrent Vomiting and Confusion

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Central pontine myelinolysis (CPM) has traditionally been observed in patients with chronic alcohol abuse and other patients with rapid correction of serum hyponatremia. The neurological deficit can be severe and life threatening. Initial reports suggested a mortality approaching 100%. However, not all cases that fit the imaging criteria of CPM fall into this category. In a recent report, at least 72% survived and 11 of the 32 known survivors recovered completely. Furthermore, the clinical manifestations can be subtle or even absent. This is based on the recently recognized sensitivity of magnetic resonance imaging (MRI) brain scan in the detection of lesions compatible with CPM. It has also been recognized that fluctuations in serum osmolality, such as in burn patients, can produce lesions compatible with CPM, and there has been an increasing array of other disorders, not necessarily associated with hyponatremia, that can be associated with a CPM-type lesion on MRI brain scan.

There have been 3 recent reports of women presenting with hyperemesis gravidarum and secondary dehydration who were found to have lesions on MRI compatible with CPM. Two of these patients had manifestations of Wernicke’s encephalopathy, including 1 with associated thiamine deficiency and 1 with hypernatremia, hypokalemia, and aminotransferase elevation. The third patient had rapid correction of hyponatremia and presented with generalized weakness and extrapyramidal signs. We report a patient with presumptive hyperemesis gravidarum, along with hypokalemia and aminotransferase elevation, but with a Korsakoff’s type of psychosis. Despite evolution of MRI findings compatible with CPM, our patient spontaneously improved, and she underscores the varied manifestations that can be primarily neurobehavioral in nature. Perhaps related to recent success in preventing rapid correction of hyponatremia, CPM-type lesions on MRI may now be reflective of a less specific clinical presentation.

Case
A 24-year-old right-handed African American woman presented with recurrent vomiting with secondary dehydration, confusion, and sinus tachycardia. She had a low serum potassium level of 2.6 mmol/L, a serum sodium of 146 mmol/L, an elevated white blood cell count of 15,500 K/ul, and an elevated serum amylase level of 215 U/L, which was felt to be consistent with pancreatitis. She was also found to have an abnormal liver profile, with an elevated aspartate aminotransferase of 56 U/L and an elevated alanine aminotransferase of 65 U/L, but her total bilirubin was normal at 0.4 mg/dl and her ammonia level was normal at 18 µmol/L. She had undergone laparoscopic cholecystectomy for acalculus cholecystitis 1 week prior to presentation but continued to experience nausea and vomiting for several weeks. She was under treatment with sertraline, 50 mg per day, for depression related to her pregnancy. Her human immuno deficiency virus and rapid plasma reagin tests were both negative.

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negative, as was her antinuclear antibody. She had a normal complete blood cell count and platelet count as well as normal creatinine, calcium, magnesium, phosphate, glucose, thyroid profile, and B12 levels. Her serum osmolality was borderline high at 303 mOsm/kg, and her urine osmolality was normal at 876 mOsm/kg. A noncontrast computed tomography brain scan, performed on day 3 of admission, was normal. Electroencephalograms obtained 2 days and 2 weeks following admission were both normal. An MRI brain scan performed 3 days following admission was normal. The study was repeated 12 days later (Fig 1) because of persistent altered mental status. A lumbar puncture was recommended, but the patient refused. She was started on haloperidol at a dose of 1 mg tid on November 22 because of psychosis with formed visual hallucinations. Sertraline was held, since it was felt that it might have been contributing to her nausea and vomiting. She also received intravenous thiamine supplementation. Her nausea and vomiting resolved during her 3-week hospital course.

Her examination 2 weeks following admission revealed her to be afebrile with a resting pulse of 118 per minute. She was normotensive and alert with no specific complaints. She was fully oriented and could name the 2 most recent presidents. Of note, she is a college graduate and reported that she had a degree in law enforcement. She misidentified the examiner as someone she had previously seen on television and misidentified her nurse as someone she frequently said hello to at the local WalMart store. She communicated without difficulty and could name and repeat well. She had a limited general fund of knowledge and was unable to recall any of 3 objects over several minutes. She scored 25 out of 30 on the Mini-Mental State Exam. She had no dysarthria or nystagmus, and her cranial nerve examination was unremarkable.

She displayed good tone and strength throughout, although she had diminished foot tapping and heel-to-shin testing on the left. She had a broad-based, unsteady gait and required minimal assistance in ambulating. No sensory disturbance was detected. Deep tendon reflexes were 3+ in both upper extremities, with increased finger flexors and a bilateral positive Hoffman’s sign. Deep tendon reflexes were 3/4 at both knees and 3–/4 at both ankles. The Babinski response was positive bilaterally, and the jaw jerk was 2/4.

She was reevaluated 1 month following her admission. She was improved and was no longer on haloperidol. She scored 27 out of 30 on the Mini-Mental State Evaluation. There was still a tendency to confabulate. Her gait ataxia and subtle motor findings had resolved, and her hyperreflexia was less prominent.

**Discussion**

CPM was originally reported to have the clinical hallmarks of quadriparesis, pseudobulbar palsy, and alteration of consciousness. This condition can rapidly evolve into a locked-in state or to progressive coma, but there is an increasing array of clinical variants including neurobehavioral symptoms, extrapyramidal signs, and ataxia.

Furthermore, it has recently been recognized that patients can have typical findings of CPM on MRI brain scan without associated clinical findings. The MRI brain scan may initially be normal, and MRI findings do not necessarily correlate with the clinical presentation.

Imitators of CPM on
MRI include infarction, metastasis, glioma, multiple sclerosis, encephalitis, and changes related to radiation therapy and/or chemotherapy. There is also an entity termed reversible posterior leukoencephalopathy that can be confined to the brain stem and could have similar findings on MRI. Thus, without pathological confirmation, we cannot be sure that our patient did not have some other disease process to explain her condition.

Our patient illustrates that recurrent vomiting, perhaps related to hyperemesis gravidarum, can result in alteration of fluid and electrolyte balance to the extent that osmotic demyelination of the brain stem can occur. Similar to a number of previously reported cases of CPM, our patient had hypokalemia at the time of presentation. Furthermore, she demonstrated improvement in her neurological exam despite evolution of the MRI scan findings.

The increasing number of disorders that can be associated with CPM-type lesions on brain imaging and the variety of clinical signs and symptoms including an asymptomatic state raise questions about the true significance of central pontine demyelination. It is reported to be most commonly associated with severe electrolyte disturbance and can have a characteristic clinical presentation. However, typical lesions can evolve on MRI brain scan irrespective of the clinical course of the patient. Thus, the finding of a CPM-type lesion on MRI brain scan can help to explain the clinical findings for a particular afflicted individual, but this finding does not necessarily help in case management or provide prognostic information.

References

Continuous Arterial Spin Labeling Perfusion Magnetic Resonance Imaging Findings in Postpartum Vasculopathy

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ABSTRACT

Postpartum vasculopathy (PPV) is a rare heterogeneous nonatherosclerotic vasculopathy that occurs in the puerperium. It occurs spontaneously but may be triggered by vasoconstrictor substances. The angiographic findings vary and include narrowing of the intracranial arteries and vasospasm. The angiographic findings and the occurrence of ischemic infarcts suggest that cerebral blood flow (CBF) is impaired in PPV. The purpose of this study is to determine CBF in patients with PPV. The authors conducted a case study of 3 patients with clinical and laboratory criteria for PPV examined during a 2-year period. Clinical examination, computed tomography imaging, structural magnetic resonance imaging (MRI), cerebral angiography, and continuous arterial spin labeling perfusion (CASL-PI) MRI were performed in all patients. Mean global CBF was determined, and perfusion maps were visually inspected. The CBF values and perfusion maps were correlated with the clinical symptoms and the neuroimaging findings. Three women were studied (22, 34, and 36 years old). The median time of presentation was 4 days postpartum. One presented with intracranial hemorrhage and diffuse arterial narrowing, the other 2 with stroke-like lesions, encephalopathy, and segmental narrowing mainly in the posterior circulation. CASL-PI was performed within 1 week of symptom onset in all 3 patients. Global mean CBF values were 51.8, 39.3, and 41.8 cc/100 g/min. Although global CBF was mildly diminished, it was above ischemic levels. Visual inspection of the CASL-PI perfusion maps did not reveal areas of focal hypoperfusion or hyperperfusion. In this series of patients with PPV, CBF was close to normal. Although angiography often reveals diffuse arterial narrowing, the CBF values encountered in this study do not support a state of generalized or focal oligemia. Vasomotor tone may change intermittently in patients with PPV.

Key words: Cerebral blood flow, vasculopathy, postpartum, stroke.


Postpartum vasculopathy (PPV) is an arteriopathy of undetermined cause that occurs in previously healthy puerperal women. The constellation of presenting symptoms includes headache, encephalopathy, seizures, focal ischemic deficits, and intracranial hemorrhage. It is often triggered by the use of ergot derivatives or sympathomimetic agents but may occur without any predisposing factors. Some authors believe that PPV is a variant of eclampsia, but PPV is known to occur in normotensive persons and in individuals without proteinuria or edema. Angiographic examination reveals widespread segmental vasoconstriction often alternating with areas of vascular dilatation. The changes are similar to those seen in eclampsia and in the vasculopathy seen in association with amphetamine abuse or ergot compounds. Transcranial Doppler (TCD) examination in PPV reveals elevated velocities suggestive of vasospasm or hyperemia. An abnormal vasomotor tone as a response to either a transient increase in blood pressure or an intrinsic exaggerated vasospastic response to exogenous agents has been imputed.

Because the angiographic features, the inciting factors, and the pathological findings described in PPV suggest that cerebral blood flow (CBF) is compromised, we sought to determine CBF in patients with PPV2. We performed continuous arterial spin labeling perfusion (CASL-PI) magnetic resonance imaging (MRI) in 3 patients with PPV. We describe the clinical, angiographic, and CASL-PI findings in 3 consecutive patients with PPV.

Materials and Method

This is a case study from the Stroke Center of the Hospital of the University of Pennsylvania. PPV was diagnosed in 3 puerperal women who presented with headache, seizures, encephalopathy, sudden focal deficits, or intracranial hemorrhage. Complete physical and neurological examination, autoimmune panel (antinuclear antibodies, complement levels, sedimentation rate, and antiphospholipid antibodies), TCD, computed tomography (CT) scan of the head, conventional MRI, and 4-vessel cerebral angiogram were obtained in all patients. Cerebral angiography revealed focal or diffuse vessel narrowing in all 3 patients. No systemic disorder other than PPV that could explain the clinical and angiographic findings was present. A complete laboratory examination including urine screening for proteinuria, liver function tests, platelet count, and uric acid level tests was performed to rule out eclampsia.

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CBF was measured using the previously described CASL-PI technique. All CASL-PI studies were performed in a GE Horizon Echospeed 1.5-T scanner. With the use of a 6-minute imaging protocol, CASL-PI was measured at 1.5 T in 8-mm contiguous supratentorial slices with 3.75-mm in-plane resolution. Concomitant structural diffusion-weighted imaging and fluid attenuated inversion recovery (FLAIR) images were obtained. Global CBF was determined using an automated method, and visual inspection of the perfusion maps was done to determine areas of focal hypoperfusion.

Results

Three women were studied in a 2-year period. Patient 1 was a 34-year-old woman who presented with headache, confusion, and a left hemiparesis 4 days postpartum. She had used pseudoephedrine for a cold. Her CT showed a right frontal lobar hemorrhage that required evacuation. TCD examination showed diffusely elevated velocities. Cerebral angiogram performed 2 days after the onset of symptoms showed diffuse vascular narrowing (Fig 1). Patient 2 was a 36-year-old woman who 7 days postpartum developed headache, confusion, right field cut, and a mild left hemiparesis. An MRI showed hyperintensities in the left periatrial region and right caudate. Cerebral angiogram showed basilar artery and bilateral posterior cerebral artery narrowing. Patient 3 was a 22-year-old woman with delayed postpartum eclampsia who presented on day 4 postpartum with headache, confusion, field cut, and seizures. MRI showed a left occipital hyperintense lesion. Cerebral angiogram showed bilateral posterior cerebral artery narrowing. All 3 patients made complete recovery, but patient 1 developed poststroke epilepsy. CASL-PI imaging was performed on day 3 in patient 1 and on day 2 in patients 2 and 3. Cerebral angiogram was performed within 1 week of symptom onset in all 3 patients. Visual inspection of the perfusion maps did not reveal any areas of focal hypoperfusion or hyperperfusion except for focal hypoperfusion in the area where the hematoma was evacuated in patient 1. The global CBF values obtained were 51.8, 39.3, and 41.8 mL/100 g/min, respectively.

Discussion

Postpartum cerebral angiopathy is poorly characterized in the literature. Autopsy findings in a woman dying of “fatal puerperal vasospasm” in the absence of toxemia included thinning of the vessel caliber, intimal thickening, and focal disruption of the elastic lamina. The cerebral angiogram showed diffuse vasospasm and normal venous drainage. TCD examination in postpartum vasculopathy often reveals elevated blood flow velocities suggestive of vasospasm or stenosis. In addition, the entity may be triggered by the use of ergot alkaloid derivatives and sympathomimetic drugs that are known to change vascular tone, reduce vascular lumen, and cause cerebral and systemic ischemia. Although CBF studies in patients with PPV have not been reported, the clinical, angiographic, and autopsy features described previously suggest that CBF might be reduced as according to the Hagen-Poiseuille equation in which elevated blood flow velocity is inversely proportional to the cross-sectional diameter of the conducting tube. Nevertheless, in our small study, we found CBF values close to normal and above the values correlated with ischemia.

Several explanations may account for our findings. It is conceivable that in PPV, the vascular tone changes intermittently in response to hormonal or exogenous influences, and we may have performed our studies in a phase of relative vasodilatation yielding normal CBF values. Abnormal vascular response due to prostaglandin deficiency or acute endothelial dysfunction has been invoked as a possible mechanism in delayed peripartum vasculopathy. If PPV shares pathophysiological features with
postpartum eclampsia, it is possible that abnormal vasomotor tone rather than fixed arteriopathy explains the clinical and imaging findings. Our findings are consistent with the CBF findings in patients with eclampsia, a condition in many aspects akin to PPV. Using TCD, normal to increased flow was seen in patients with eclampsia and parieto-occipital lesions, challenging the vasospasm theory.10 Our findings are consistent with the CBF findings in patients with bona fide eclampsia, an entity in which segmental vascular narrowing is also present.11 Although the imaging findings in eclampsia could be the result of passive dilatation of cerebral arteries with fluid extravasation, several studies have failed to reveal increased perfusion, including this study of 3 patients with PPV.11

CBF may be normal even in the presence of significant vascular stenosis due to robust collateral circulatory pathways, increased cerebral perfusion pressure, changes in blood rheology, and changes in local metabolic demands. Averaging global CBF has some limitations, since CBF values may change from region to region in the brain. Nevertheless, visual inspection of the perfusion maps failed to reveal any areas of focal hypoperfusion. The CASL-PI technique has been used in patients with acute stroke, rendering CBF values that are in agreement with those in the literature. In addition, a good correlation has been found between the presenting clinical syndrome, the perfusion map findings, and the CBF values.14 Thus, our CBF findings and perfusion map results reflect a state of relatively preserved perfusion in this small study of patients with PPV. The normal CBF findings may explain the good outcome encountered in this and other studies.14 Because acquired diffusion coefficient was not determined, we cannot attest to the ischemic nature of the lesions. Similar, nonischemic lesions have been described in eclampsia.

It is conceivable the CBF determination was performed too late after the onset of the vasculopathy when autoregulatory mechanisms had restored perfusion to previously ischemic areas. However, we performed CASL-PI imaging within 1 week of symptom onset, when the patients were still symptomatic and shortly after the angiogram that attested to the presence of arteriopathy was performed. Furthermore, prior case reports have suggested that the vasculopathy may persist for several weeks even though clinical improvement occurs early.9

In this study of patients with PPV, mean global CBF as determined by CASL-PI was above the ischemic threshold, and there was no evidence of focal hypoperfusion. Our findings may have implications in the way blood pressure and volume replacement are managed in PPV. Further studies including a larger sample and serial imaging are required to confirm our findings.

References

Massive Cerebral Edema After Recanalization Post-Thrombolysis

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ABSTRACT

Background. Intravenous thrombolysis with tissue plasminogen activator is an approved and effective therapy for acute ischemic stroke within the first 3 hours from onset. In addition to the risk of hemorrhage, there is a risk of postrecanalization cerebral edema. The authors present the case of a patient with an ischemic stroke treated successfully with intra-arterial thrombolysis who subsequently developed massive brain edema in the face of clinical improvement. Case. An 81-year-old man presented within 1 hour of developing a full right middle cerebral artery (MCA) syndrome. Computed tomography (CT) was normal. A cerebral angiogram demonstrated an occlusion of the M1 segment of the right MCA. The patient was treated with intra-arterial urokinase 750,000 units. He recovered during the procedure. Serial CT scans demonstrated progressive edema with mass effect in the right MCA distribution. The patient remained asymptomatic except for a mild sensory deficit. Discussion. Postrecanalization cerebral edema is an uncommon but potentially lethal complication of thrombolysis. It is postulated that the edema is due to ischemic injury aggravated by reperfusion with vasogenic edema. The presence of this massive edema is usually associated with clinical worsening. The present case illustrates that this disorder can be associated with good outcome.

Key words: Stroke, reperfusion, ischemic brain edema, cerebral ischemia, blood-brain barrier.

Cruz-Flores S, Thompson DW, Boiser JR.
Massive cerebral edema after recanalization post-thrombolysis.

Tissue plasminogen activator (t-PA) intravenously is an approved therapy for acute ischemic stroke within 3 hours from onset. Intra-arterial thrombolysis is a promising treatment for intracranial large-vessel occlusion. A recent clinical trial showed benefit for selected patients with middle cerebral artery (MCA) occlusion treated up to 6 hours from symptom onset. The risk of hemorrhage is well known. There are also cases of brain edema following thrombolytic therapy, some of which have resulted in death. Although it is argued that the edema is secondary to ischemia, vasogenic edema has been reported in patients with cerebral infarction after spontaneous and induced recanalization. This complication is typically associated with clinical worsening. We present the case of a patient with a right MCA occlusion treated successfully with intra-arterial thrombolysis who had a good outcome despite developing massive hemispheric brain edema.

Case Presentation

An 81-year-old man presented to the hospital within 1 hour of developing signs and symptoms consistent with a full right MCA syndrome. On his initial exam, he was awake and oriented. He was dysarthric. He had a forced right gaze deviation, left homonymous hemianopia, left facial weakness, left hemiplegia, left sensory loss, and left hemineglect. Computed tomography (CT) was normal. A cerebral angiogram demonstrated an occlusion of the M1 segment of the right MCA (Fig 1A). At that time, intravenous t-PA was not an approved therapy. It was decided to proceed with an infusion of urokinase 750,000 units intra-arterially. The treatment started 2 hours from symptom onset. Complete recanalization was achieved at 3 hours from symptom onset (Fig 1B). During the procedure, the patient recovered all neurological function except for a mild left hemisensory deficit. A CT scan immediately post-thrombolysis demonstrated a contrast blush in the region of the right basal ganglia (Fig 2). Serial CT scans at day 5 (Fig 3A), day 11 (Fig 3B), and day 21 (Fig 3C) post-thrombolysis revealed progressive edema with mass effect in the right MCA distribution that improved in the last scan.

Discussion

Space-occupying cerebral edema is the most important cause of death in the first days after an acute ischemic stroke in the MCA distribution. The incidence of this complication in patients with a stroke in the MCA territory has been reported to be between 5% and 43% and seems directly related to the volume of the ischemic tissue involved. Thrombolysis increases the probability of arterial recanalization and tissue reperfusion and limits ischemic injury; therefore, it may decrease disability and/or death. The National Institute of Neurological Diseases and Stroke trial on intravenous thrombolysis demonstrated a lower disability in the treated group compared to placebo. As a result, intravenous thrombolysis with t-PA was approved for its use in patients with acute ischemic stroke presenting within 3 hours from symptom onset.

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onset. More recently, a clinical trial of intra-arterial thrombolysis with prourokinase demonstrated benefit in patients with MCA occlusion treated up to 6 hours from symptom onset. In this trial, recanalization was associated with a better outcome.

Although the more worrisome complication of thrombolysis for acute ischemic stroke is intracranial hemorrhage, the development of postrecanalization brain edema is another risk that has not been studied. In the European Cooperative Acute Stroke Study, the most frequent cause of death within the first 7 days was brain edema with transtentorial herniation. It is argued that this space-occupying cerebral edema might be the result of ischemic injury, or it might be due to or aggravated by reperfusion injury triggered by thrombolytic therapy.

Although early recanalization of MCA trunk occlusion is seldom associated with brain edema or hemorrhagic transformation, there is in fact evidence showing that recanalization can...
be harmful to the brain tissue. Irino et al\textsuperscript{1} showed that 17 of 45 patients with an ischemic stroke and angiography-proven spontaneous recanalization developed “capillary blush” and cerebral edema. They hypothesized that the edema was due to hyperemia and, therefore, that hyperemia was a poor prognostic factor. Rudolf et al\textsuperscript{1} treated 51 patients with intravenous thrombolysis within 3 hours from onset. Sixteen percent of these patients developed massive cerebral edema with clinical deterioration; most of them died. Koudstaal et al\textsuperscript{3} reported 2 cases of fatal massive cerebral edema after thrombolytic therapy and
hypothesized that reperfusion was the culprit of the complication.

Experimental models suggest that the extent of tissue damage caused by focal ischemia correlates closely with the level of blood flow during the ischemic episode and its duration. However, there is also some evidence showing that reperfusion can produce further tissue damage. The mechanisms of the “reperfusion injury” are multifactorial and involve chemical and cellular responses that lead to endothelial leakage and capillary bed occlusion (non-reflow phenomenon).

Animal models suggest that after recanalization there is a biphasic opening of the blood-brain barrier (BBB). The first opening occurs shortly after reperfusion and is probably secondary to hyperemia with loss of autoregulation. The second opening of the BBB occurs as late as 72 hours postrecanalization and is caused by tissue infarct. These findings have not been proven in humans. Kuroiwa et al showed in the cat model that recanalization worsens edema by allowing the leakage of proteins into the extracellular space.

Neuropathological studies in animals reveal that severe edema occurs only when there is evidence of vascular and astrocytic ischemic injury. These neuropathological changes in the territory of a temporarily occluded vessel were more severe when the occlusion was caused by a thrombus than when it was caused by a clip. These findings suggest that a significant ischemic injury, affecting neural and endothelial tissue, is a prerequisite for the development of severe edema. Furthermore, the disintegration of an occlusive thrombus may in fact alter the microcirculation and play a role.

Cerebral blood flow (CBF) measurements with xenon-enhanced CT in patients with acute ischemic stroke show that severe edema and herniation occur more often in patients with a CBF lower than 15 cc/100g/min. These findings support the experimental evidence that edema and herniation are associated with severe ischemic injury.

Although the incidence of space-occupying cerebral edema secondary to recanalization may be as high as 16%, its incidence might be much lower. In fact, in the Intra-Arterial Prourokinase for Acute Ischemic Stroke trial, the volume of the infarct and edema by CT scan was smaller in those patients that received prourokinase and had arterial recanalization than in those patients treated with heparin only and did not have arterial recanalization.

Summarizing all the evidence from neuropathological studies on experimental models as well as that from human studies, it seems that edema is due to irreversible ischemic injury and not recanalization and reperfusion.

Marchal et al reviewed the literature on early postischemic hyperperfusion studied by positron emission tomography (PET). They concluded that although experimental evidence suggested that early reperfusion was associated with tissue injury and edema, the PET studies on cats, baboons, and human subjects with a cerebral infarct support the idea that early hyperperfusion after an ischemic stroke is harmless and is associated with clinical recovery and a small or absent infarct in the tissue.

In contrast with those reports of very poor outcome and high mortality associated with space-occupying edema post-recanalization, our case shows that an excellent outcome can be achieved despite the development of severe cerebral edema following intra-arterial thrombolysis. The widespread use of intravenous thrombolysis within 3 hours and the probable extension of the therapeutic window up to 6 hours for intra-arterial thrombolysis might increase the number of patients who develop this complication.

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Letter to the Editor

Several days before I read the article by Levine et al,1 I had cared for a patient with 90% petrous carotid stenosis documented by catheter angiography. He had undergone stenting for a 75% extracranial carotid stenosis in a center with a documented mortality and morbidity of less than 1%. The plan was for stenting of the petrous carotid stenosis at a later date. The issue of surgery versus stenting for extracranial carotid disease is now being debated in the literature.2,3 However, for carotid disease that is not surgically accessible (eg, petrous carotid) in approximately selected centers with a documented low complication rate, stenting is safer than warfarin, which carries a 1% to 2% annual risk of serious complications. I therefore wonder why the 4 patients described by Levine et al were not referred for stenting or angioplasty4 as a safer alternative to warfarin.

Sincerely,
Joseph S. Jeret, MD

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In Response

Thank you for asking us to respond to the brief letter that Dr. Jeret wrote concerning our recent manuscript.1 We remain, however, unenlightened and unaware of authoritative studies that have convincingly shown that angioplasty or stenting is necessarily safer or more effective than best-medical therapy in patients with symptomatic, surgically inaccessible intracranial carotid occlusive disease.

Marks et al, in a manuscript concerning 23 patients with symptomatic intracranial stenoses who continued to have TIAs despite anticoagulant and/or antiplatelet therapy, reported an annual stroke rate of 3.2% for strokes in the territory appropriate to the site of angioplasty, an annual rate of 4.8% for all strokes, 1 periprocedural death due to vessel rupture during angioplasty, and 1 patient whose stenosis “could not be safely crossed.”2 Thus, in 2 of 23 (4.4%) patients angioplasty attempts were unsuccessful. And of their 7 patients with intracranial carotid stenosis, with lesions potentially comparable to those in our patients,1 5 remained on Warfarin plus aspirin despite undergoing angioplasty.3 Dr. Jeret references Marks et al2 “as a safer alternative to Warfarin”—we just don’t see how this has been proven to date.

Golledge et al, in a systematic comparison of 33 studies (13 angioplasty and 20 carotid endarterectomy) of the 30-day outcome of angioplasty with or without stenting and endarterectomy for symptomatic carotid artery disease reported in single-center studies, reported that the risk of stroke was significantly greater with angioplasty than carotid endarterectomy.3 Their significant results included, but were not necessarily limited to, the following: carotid stents were deployed in 44% of angioplasty patients; a stroke rate of 7.1% for angioplasty and 3.3% for endarterectomy (OR 2.22, p < 0.0001); a risk of fatal or disabling stroke of 3.2% for angioplasty and 1.6% for endarterectomy (OR 2.09, p < 0.01); a risk of stroke or death of 7.8% for angioplasty and 4.0% for endarterectomy (OR 2.02, p < 0.001); and a disabling stroke or death rate of 3.9% after angioplasty and 2.2% after endarterectomy (OR 1.86, p < 0.01). Dr. Jeret references Golledge et al3 and his own letter to the editor4 in stating that “the issue of surgery versus stenting . . . is now being debated in the literature”—we just don’t see how these data necessarily apply to patients with symptomatic intracranial carotid disease.

At the time we submitted our manuscript in question,1 our small group of patients remained symptom- and side effect–free for a mean of 24 months. On the day we drafted this response, our patients continue to do well (3 on Warfarin plus aspirin, 1 on aspirin plus careful position changes to avoid orthostatic-induced symptoms) at a mean of 33 months from their last TIA. While we remain poised to consider implementing whatever therapies necessary should any of our patients redevelop cerebrovascular symptoms, we remain unconvinced that our patients should, as Dr. Jeret suggests, be “referred for angioplasty or stenting” at this time.

We currently follow between 600 to 700 unique patients in chronic Warfarin therapy at the William S.
Middleton Veterans Affairs Hospital, with a < 1% annual rate for major bleeding and an even smaller recurrent embolism rate (personal communication, Dr. Christine Sorkness, April 16, 2001). We also anxiously await results from both the WASID study, as this should enlighten us about the optimal medical therapy for patients with symptomatic intracranial stenosis, as well as any carefully designed study that concerns angioplasty or stenting versus best-medical-therapy.

—Ross L. Levine, MD, for the authors
University of Wisconsin Stroke Program
Madison, WI

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