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MR Volume Estimation of Subcortical Brain Lesions and Ventricular Cerebrospinal Fluid: A Simple and Accurate Stereologic Method

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PURPOSE: To describe an MR imaging quantification method for estimation of total volumes of both white and gray matter subcortical lesions and ventricular cerebrospinal fluid (CSF) in the living human brain, and to determine the method's reliability. **METHODS:** In 12 subjects, total subcortical lesion and ventricular CSF volumes were estimated using systematic sampling. Systematic sampling was performed on equidistant MR sections using a counting grid with systematically ordered intersection points. The grid was randomly positioned on each consecutive MR section. Each grid intersection point hitting the structure of interest represents a fixed known volume dependent on grid intersection point distance and the sum of the section thickness and section gap. **RESULTS:** Total volume estimation of subcortical lesion and ventricular CSF takes 15 and 5 minutes per subject, respectively. Coefficients of error of the individual volume estimates ranged from .01 to .13 and are negligible to the coefficients of the group mean (range, .70 to .89). For subcortical lesion volume, the random intraobserver error yielded .04 and for ventricular CSF .02; the random interobserver error amounted to .11 and .04, respectively; and the systematic interobserver error was .15 and .04, respectively. **CONCLUSION:** The method described here for subcortical lesion and ventricular CSF volume estimation is accurate, reliable, valid, and fast.

Index terms: Magnetic resonance, technique; Brain, magnetic resonance; Brain, measurements; Brain, volume

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With the advent of brain magnetic resonance (MR) imaging, subcortical white and gray matter lesions have been identified in healthy subjects and in a variety of neurologic diseases and sequelae of general internal diseases (1). The clinical significance of subcortical lesions is subject to controversies regarding their pathogenesis. Many attempts have been undertaken to quantify the severity of subcortical lesions to clarify this issue. Until now, MR quantification of subcortical lesions has been performed using semiquantitative rating scales (2–7). The main drawbacks of these scoring methods are: (*a*) absence of quantitative data on total volume of subcortical lesions; (*b*) consequently, unreliable information concerning the actual severity of subcortical lesions; and (*c*) moderately poor intraobserver and interobserver agreements of semiquantitative rating scales (6–8).

The purpose of this study is to evaluate an efficient stereologic method for estimating the total volume of subcortical lesions and ventricular cerebrospinal fluid (CSF) volumes in the living human brain and to determine its accuracy and reproducibility.

Methods

Subjects

As part of a larger study toward a refinement of clinical criteria of suspected vascular parkinsonism (unpublished data), three patients with idiopathic Parkinson disease, seven patients suspected of vascular parkinsonism (ie, lower-body parkinsonism, absent response to levodopa, and abundant subcortial lesions on MR), and two hypertensive control patients were randomly selected from a large patient population to assess the accuracy of the volume quantification method.

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Stereologic Quantification Method

An MR examination was performed with a 1.5-T system using MR pulse sequence parameters of 2500/20/2 and 2500/80/2 (repetition time/echo time/excitations). Images were made in the transverse plane, parallel to the intercommissural line, throughout the whole brain. The section thickness was 4 mm with a 0.4-mm intersection gap. Spatial resolution was 0.9 mm, corresponding to a 256 × 256 matrix. All MR scans had an identical field of view of 230 mm.

To determine the interobserver random and systematic error, two investigators (O.J.M.V. and J.C.M.Z.) quantified separately the total volume of subcortical lesions as evident from areas with increased signal intensity on both 2500/20 and 2500/80 images, without knowledge of age, sex, identity, or clinical diagnosis of the patients. Perivascular dilatations (Virchow-Robin spaces) were not taken into account, because they are isointense relative to CSF on spin-echo, proton density–weighted images (9). A hyperintense rim around the tip of the frontal horn was present in all subjects and was considered normal. Actual volume measurements were performed on proton density–weighted images (2500/20).

To determine intraobserver random error, one investigator (J.C.M.Z.) quantified subcortical lesion and ventricular CSF volumes twice with an interval of 4 weeks, again without knowledge of age, sex, identity, or clinical diagnosis.

For volume determination, the digital image information was not transferred onto an image analysis system, nor was the MR section analyzed on the computer screen, because the latter gives erroneous results because of the parallax of the computer screen itself. Instead, the photographic hard copy of each MR section was used. The magnification factor of each hard copy is defined as the actual length of the scale bar of each MR section divided by the representing length of the brain tissue, in this study, 43.48 mm/100 mm = 0.4348.

For subcortical lesion volume determination, each MR section was linearly magnified with a vertical projection system. Optimal focus was reached at a magnification of 2.3 (the scale bar of each MR section representing 100 mm of brain tissue measured at a focus projection level 230 mm). A transparent counting grid with systematically ordered intersection points at a 5-mm distance was randomly placed at the focus level of the projected MR section. For determination of ventricular CSF volumes, the same transparent counting grid was placed directly and randomly on the photographic hard copy of each MR section on an illuminator (Fig 1).

Volume estimations were based on Cavalieri's principle (10): the volume of any object may be estimated from randomized and parallel sections separated by a known distance by summing up the areas of all cross-sections of the object and multiplying this sum by the known distance. Images were randomized, because the first section hitting the subcortical lesion or ventricular CSF fell randomly, followed by systematic equidistant sections with a known distance equal to the section thickness plus the section gap. The total area of all cross-sections may be estimated by a stereologic point-counting method (11). A systematic array of grid intersection points is superimposed on each MR section. Giving random positioning of the test array on each MR section, the total number of grid intersection points (P) hitting the object of interest affords an unbiased estimator of the total area. The grid intersection point was defined as the inner corner of the right upper quadrant of each intersection (Fig 1).

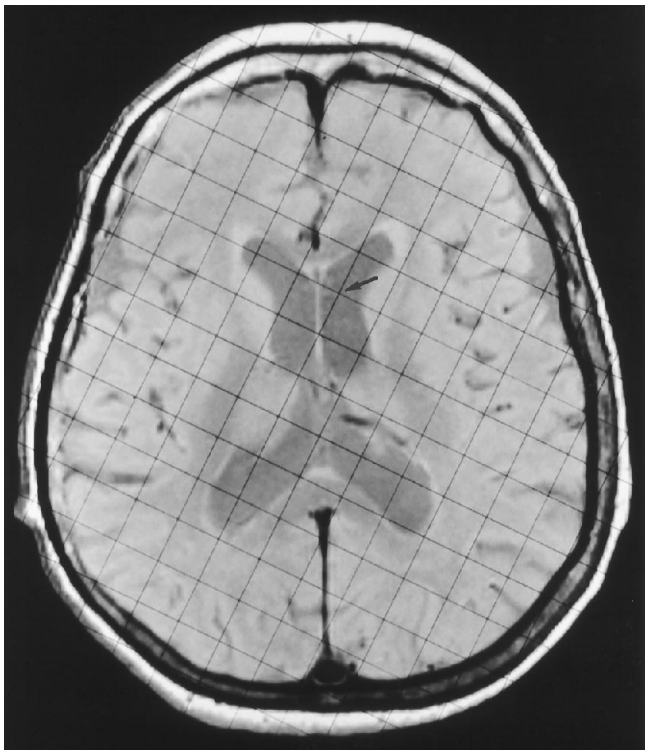

Fig 1. A randomly placed counting grid with systematically ordered intersection points at a 5-mm distance to determine ventricular CSF volume on a 2500/20 MR section. The inner corner of the right upper quadrant of each intersection is the actual sampling point (*arrow*).

The total area of all subcortical lesions (A_{SCL}) on all MR sections can be estimated by the following equation:

$$A_{SCL}\ (mm^2) = P \times a(p)\ (mm^2),$$

where P is the total number of grid intersection points overlying the subcortical lesion, and a(p) is the areal equivalent of one grid point.

$$a(p)\ (mm^2) = 5 \times 5\ (mm^2)/(\text{magnification}^2)$$

$$= 25/(2.3^2)$$

$$= 4.7259\ (mm^2)\ .$$

The total volume of subcortical lesion (V_{SCL}) is then given by:

$$V_{SCL}\ (mm^3) = A_{SCL}\ (mm^2) \times (\text{section thickness} + \text{section gap})$$
$$= P \times a(p) \times 4.4\ (mm^3)$$
$$= P \times 4.7259 \times 4.4\ (mm^3)$$
$$= P \times 20.79\ (mm^3)\ .$$

The same holds true for the estimation of ventricular CSF volume (V_{VCSF}):

$$V_{VCSF}\ (mm^3) = A_{VCSF}\ (mm^2) \times 4.4\ (mm)$$
$$A_{VCSF}\ (mm^2) = P \times a(p)\ (mm^2)$$
$$a(p)\ (mm^2) = 5 \times 5/(\text{magnification}^2)\ (mm^2)$$
$$= 25/(43.48/100)^2$$
$$= 132.25\ (mm^2)$$
$$V_{VCSF}\ (mm^3) = P \times 132.25 \times 4.4\ (mm^3)$$
$$= P \times 581.9\ (mm^3)\ .$$

Statistics

Statistical methods for validation of the stereologic volume estimation method included: (*a*) the determination of the coefficient of error of the individual estimate of each subcortical lesion and ventricular CSF volume (11) compared with the determination of the coefficient of variation of the group mean; (*b*) the random intraobserver and interobserver error; and (*c*) the systematic interobserver error.

The coefficient of error of the estimate of each individual subcortical lesion volume declines in direct proportion to the total number of MR planes and to the total number of grid intersection points (P) (11). Generally, a coefficient of error of less than .05 is obtained if the number of MR planes used is 10 or more, and the number of grid intersection points is 50 or more (11). The mean number of MR planes in this study hitting subcortical lesions and through ventricular CSF was always more than the minimum number of 10, and the mean number of grid intersection points was almost always more than 50. In quantification studies, a coefficient of error of about .1 or less of the individual estimate seems appropriate with regard to precision, because the coefficient of variation of the group mean is always much higher mainly because of the large contribution of the biological variance to the coefficient of variation (12). The coefficient of error of the individual estimates was estimated using the quadratic approximation formula (11).

Results

Data on total number of grid intersection points (P) of subcortical lesions and ventricular CSF for both observers are shown in the Table. The range of coefficients of error of the individual estimates is .026 to .134 for subcortical lesions and .011 to .068 for ventricular CSF. The range of the coefficients of variation of the group mean is .873 to .894 for subcortical lesions and .699 to .717 for ventricular CSF. The random intraobserver and interobserver errors are low for ventricular CSF (respectively, .022 and .043) and for subcortical lesions (.043 and .116). The systematic interobserver error is .043 for ventricular CSF and .155 for subcortical lesions.

Total number of hits (P) on subcortical lesions and ventricular CSF

	Subcortical Lesions			Ventricular CSF		
Observer:	1a	1b	2	1a	1b	2
SVP	359	346	384	325	325	341
HTC	1108	1153	1005	63	65	74
SVP	589	575	427	181	181	180
IPD	105	117	112	113	123	120
SVP	71	57	91	53	53	58
SVP	891	883	873	97	100	103
IPD	97	91	66	152	157	155
SVP	195	213	121	160	161	169
IPD	472	503	489	30	31	29
HTC	32	39	52	71	72	75
SVP	509	458	495	43	46	46
SVP	245	236	242	85	88	86

Note.—1a indicates observer 1 at time point 0; 1b, observer 1 at time point 4 weeks; 2, observer 2; SVP, suspected vascular parkinsonism; IPD, idiopathic Parkinson disease; and HTC, hypertensive control. Subcortical lesion volume = P × 20.79 (mm^3), and ventricular CSF volume = P × 581.9 (mm^3) (see "Stereological Quantification Method").

Discussion

Until now, only semiquantitative rating scales (2–7) were available for the assessment of signal hyperintensities on MR in which the severity of subcortical lesions was expressed as a sum score of points awarded to subjective criterialike focal, multifocal, and confluent lesions (2, 3, 7), or punctate, nodular, and patchy (5).

This study presents an accurate stereologic method to quantify total volumes of subcortical lesions. This method has recently also been applied to estimate the volume of cerebral ventricles in hydrocephalic patients on brain computed tomographic scans (13) and to estimate the volume of several brain structures in Down syndrome on MR scans (14). The sampling procedure of the volume data is largely unbiased, inasmuch as randomness combined with sys-

tematic sampling has been guaranteed: (*a*) the first MR section hits the subcortical lesion or ventricular CSF randomly, followed by systematic sections with a known distance; and (*b*) the set of systematic grid intersection points is placed randomly onto the (projected) MR section.

However, the sampling procedure of the volume data is not fully unbiased: (*a*) each MR section has a certain thickness, and because it is not infinitely thin, it will always bear the risk of partial volume effects; subjective assessment to the boundaries of the lesions and even the presence or absence of some subtle lesions cannot be ruled out completely; and (*b*) each grid intersection point has a certain area, and because it is not infinitely small, there is a theoretical chance of overestimating the number of hits; to overcome this risk, the definition of the grid intersection point was made as the inner corner of the right upper quadrant of each intersection.

The stereologic method is sufficiently accurate, because the individual coefficients of error are relatively negligible to the coefficient of variation of the group mean, constituting only a minor contribution to the total variation of the group mean.

The intraobserver systematic error was not determined, because it was very low and negligible. The method is reproducible, inasmuch as interobserver and intraobserver random and systematic errors are low, especially when compared with the semiquantitative rating scales that yielded Cohen's κ coefficient values in the range of poor to fair interobserver and intraobserver agreements (6, 7).

The method described is fast, because point counting of subcortical lesions and ventricular CSF is carried out within 15 and 5 minutes per patient, respectively. The method is inexpensive, because expensive computerized image analysis systems are not necessary. Moreover, at any chosen gray level, such image analysis systems may overestimate results, because they cannot differentiate pathologic white matter hyperintensities from other high-signal foci of normal structures such as Virchow-Robin spaces, deep gyri, and the rim around the tip of the frontal horn. Therefore, expert analysis remains necessary.

The reproducibility (interobserver and intraobserver random and systematic errors) of the stereologic method is dependent on the brain structure under investigation, because reproducibility appears to be better for ventricular CSF than for subcortical lesions. Apparently, the reproducibility of the chosen gray level of the human eye for determining the subcortical lesion is dependent on the observer and on the moment of investigation. One possible solution to this problem is to minimize the MR section thickness to reduce partial volume effects and enable unambiguous identification of subcortical lesions, which is in fact a general requirement for volume quantification of any object (15).

In conclusion, the present study describes a simple stereologic method that can be applied on routine MR scans in which the total volume of subcortical lesions is to be estimated. It is inexpensive, and preliminary results indicate that it is precise and reliable and, thus, constitutes a new tool in volume measurement of subcortical lesions and potentially of any brain structure of interest.

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