AJNR

Imaging of carotid artery stenosis: the role of CT angiography.

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AJNR Am J Neuroradiol 1997, 18 (3) 591-593
http://www.ajnr.org/content/18/3/591.citation

LETTERS

Imaging of Carotid Artery Stenosis: The Role of CT Angiography

We read with interest the article on imaging of carotid artery stenosis by Vanninen et al (1) and we agree that actually "ultrasound followed by confirmatory angiography is a cost-effective way to image patients suspected of carotid artery stenosis." Nevertheless, among the different carotid artery imaging methods analyzed in the paper, computed tomographic (CT) angiography was not mentioned. We think that CT angiography should be considered in the imaging protocol of carotid stenosis because the new data acquisition technique with the combined movement of tube and cradle ("helical" or "spiral" CT) can image a volume of tissue in a short period and clearly show vascular structures if intravenous contrast material is used.

The most reproducible and accurate technique for the representation of CT vascular data is not yet established (2, 3): to obtain carotid bifurcation images we use the maximum intensity projection (MIP) algorithm because, in our opinion, it is less operator dependent than three-dimensional shaded-surface display technique. The MIP method also has some disadvantages and limitations: in particular, stenosis is not assessable on MIP images when circumferential calcified plaques are present. For this reason we prefer to measure the vascular lumen on the axial CT images: the level of maximum stenosis is chosen after complete rotation (360°) of the carotid bifurcation MIP image or, when circumferential calcified plaques are present, after evaluation of the one-by-one axial images (A. Saletti, F. Calzolari, S. Ceruti, R. Tamarozzi, "Misura con Angio-TC delle Stenosi della Biforcazione Carotidea: Esperienza Personale," presented at the Premio Marzocco Meeting, Florence, Italy, December 1995).

The degree of carotid stenosis can be determined by using the guidelines of the North American Symptomatic Endarterectomy Trial (NASCET) or of the European Carotid Surgery Trial (ECST) (4). To test the efficacy of CT angiography, we think that at present both methods should be used. In fact, the NASCET method allows a good comparison with intaarterial digital subtraction angiography whereas we think the ECST method permits a better evaluation of the degree of stenosis because residual lumen and true vascular diameter are measured at the same carotid level. Moreover, CT angiography is the only imaging technique applicable to the ECST method (and, in general, a precise measurement of the carotid stenosis), because it permits the exact evaluation of both the true arterial diameter and the residual carotid lumen (Fig 1).

Large multicenter trials are necessary to assess definitively the role of CT angiography in the imaging protocol of carotid bifurcation stenosis. CT angiography can be performed in order to obtain, before endarterectomy, further representation of the carotid bifurcation after ultrasound examination when magnetic resonance (MR) angiography and/or intraarterial digital subtraction angiography are contraindicated or supply doubtful results and, if necessary, to show the plaque morphology or the carotid wall, as in cases of thrombosis in carotid bifurcation aneurysms.

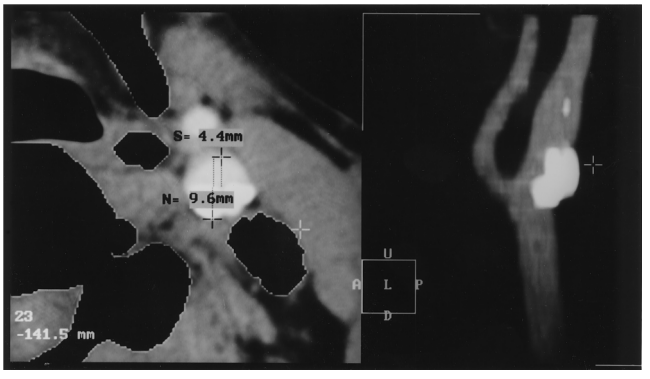

Fig 1. CT angiography of the left carotid bifurcation: calcified plaque of the internal carotid bulb.

The degree of carotid stenosis is determined by using the ECST method. The level of maximum stenosis is chosen with an electronic caliper (+) on the MIP image (right) and/or on the corresponding axial image (left); these are seen simultaneously on the monitor of the CT console. Measurements are made on the axial image. *S* indicates diameter of the residual lumen; *N*, true carotid diameter.

We believe that CT angiography of the carotid bifurcation could replace MR angiography (more expensive) or digital subtraction angiography (more invasive and expensive) only if vascular surgeons will not consider important the main disadvantages of CT angiography (the limited field of view and the doubtful ability to show plaque ulceration) (2, 3). Many authors assert that the presence of carotid siphon stenosis should not influence the decision to perform carotid endarterectomy in patients with the appropriate indications (5); other studies report that plaque ulceration has remained a subject of dispute in making decisions about carotid endarterectomy (6).

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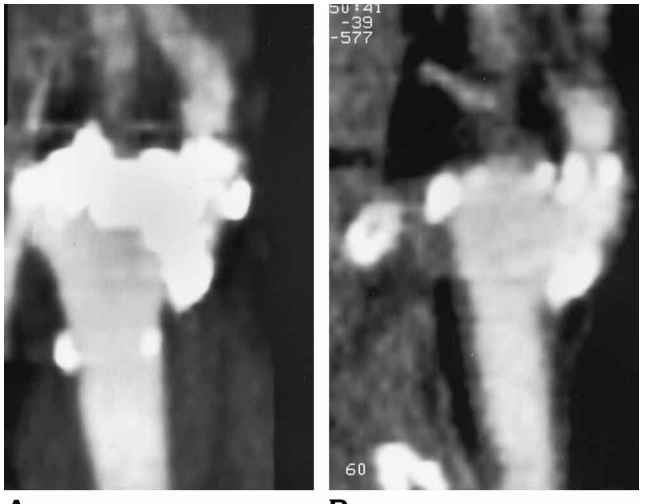
Reply

We appreciate the interest of Dr Calzolari et al in our article. We wrote it almost 2 years ago when the technique of CT angiography was not as sophisticated as it is today. Similarly, the technical quality of MR angiography is continually developing. Even at present, however, relatively small numbers of patients are included in the published studies of diagnostic accuracy of CT angiography in the assessment of carotid bifurcation atherosclerosis (1, 2, 3). Link et al (4) have reported poor correlation in a group with mild stenosis. Comparisons with the other currently available noninvasive modalities in larger series of patients have not been made. We therefore feel that even if CT angiography seems promising, its true potential in the diagnostics of carotid artery stenosis remains to be determined. Because CT angiography is unique in its ability to show calcified plaques in relation to the soft atheroma and vessel wall, it might become especially useful if endovascular treatment such as balloon angioplasty or stent placement are considered.



A **B**

Fig 2. *A*, Dense calcifications prevent the measurement of the exact degree of stenosis in the MIP image.

B, Multiplanar reconstruction image allows the measurement of the residual lumen at the level of maximal stenosis. In addition, it is possible to assess the axis of the internal carotid artery and confirm that the measurement is performed perpendicular to it.

Calzolari et al strongly recommend the use of axial sections for the measurements. However, it should be emphasized that the accuracy of stenosis measurement on axial images depends on the scan plane, which has to be perpendicular to the carotid artery (5, 6). This may not be the case if the proximal part of the internal carotid artery is elongated. In addition to the original axial sections, several types of reconstruction programs, such as MIP, shaded surface display, and multiplanar reconstruction can be used to quantify stenosis degree. Multiplanar reconstruction images can also be useful in calcified bifurcations (Fig 2).

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Editor's note.—*The letter from Calzolari et al and the original article by Vanninen et al were referred to John Huston, whose comments follow.*

Comment

As large multicenter trials have demonstrated the benefit of carotid endarterectomy (1, 2), attention has turned to identifying clinically significant carotid stenosis with noninvasive techniques both to decrease complications resulting from conventional arteriography and to decrease imaging costs. In their letter, Calzolari et al call attention to the developing technique of CT angiography made possible by the recent technical advances of spiral CT scanning.

A consensus for the display technique for measuring stenosis on CT angiography has yet to develop. Standard commercially available reconstruction techniques such as MIP are not routinely capable of separating the calcified portion of atherosclerotic plaques from intraluminal contrast material (3). Even small focal calcified plaques, let alone circumferential plaques, can significantly interfere with measurements based on MIP images. Therefore, the approach by Calzolari et al to measure the degree of stenosis on axial CT images remains the preferred technique, even in the absence of calcified plaques.

The article by Vanninen et al considers several models to arrive at the most cost-effective method to image carotid stenosis before surgery. Their results indicate a high dependence on the calculation of local charges and costs. For instance, in their experience, an overnight stay in the hospital costs less than an unenhanced CT scan and was a fraction of the cost of an MR angiogram. As costs are considered, it is important to adjust for differences among countries resulting from varied health care systems. Also, costs can vary considerably among institutions within the same country. Calzolari et al state that MR angiography is more expensive than CT angiography; however, one could imagine a practice in which an MR angiogram without contrast could equal the cost of a CT angiogram on a new spiral scanner that required nonionic contrast administration.

In their letter, Calzolari et al touch on the controversy surrounding the best method to measure carotid stenosis (4, 5). This debate might never be satisfactorily concluded. What must be remembered is that large studies, including NASCET and ECST, show benefit for surgical intervention using a specific method for determining carotid stenosis. The letter raises the intriguing possibility that CT angiography could determine the cross-sectional area of stenosis better than conventional angiography. Appropriate validation with a large trial or adequate comparison with conventional angiography would be required before adopting such an alternative technique.

Calzolari et al have appropriately called attention to the growing potential of CT angiography for the noninvasive evaluation of carotid stenosis. Continued technical developments will allow CT angiography to extend its field of view such that it will exceed that of ultrasound and potentially equal that of MR angiography. Further, the authors are correct that additional trials will be necessary to determine the most appropriate role for CT angiography in evaluating carotid atherosclerotic disease.

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Age and Sex Do Not Affect Cerebellar Volume in Humans

With MR-based 3-D volumetry (1), we quantified the size of the cerebellum and the total intracranial volume (= brain + cerebrospinal fluid) in a group of 31 neurologically healthy subjects (nonalcoholics) of age 19 to 73 years (19 men with mean age of 40.6 years; 12 women with mean age of 41.6 years) after obtaining informed consent (Fig 3). The intracranial volume tended to decrease slightly (correlation factor = $-.36$; $P < .05$) with age in both men and women. The decline in volume of the bony skull may reflect the demographically taller population in present generations rather than an individual reduction in size. The male intracranial volume was significantly larger than the female ($P < .0005$) and might reflect the differences in skeletal architecture between the sexes.

The quotient of cerebellar and intracranial volume showed no correlation with age. These results agree with a study of Escalona et al (2), who used a stereologic technique to quantify cerebellar volume. While the loss of cell mass in the cerebrum is evident on the macroscopic level as the widening of cerebral sulci and the enlargement of the ventricular system, the cerebellum seems to sustain its size. The reason for this discrepancy remains uncertain, particularly with the known loss of cerebellar neurons shown in postmortem studies (3). Notably, pathologic degeneration of the cerebellum compared to the cerebrum differs in course and pathogenesis: whereas cerebral atro-

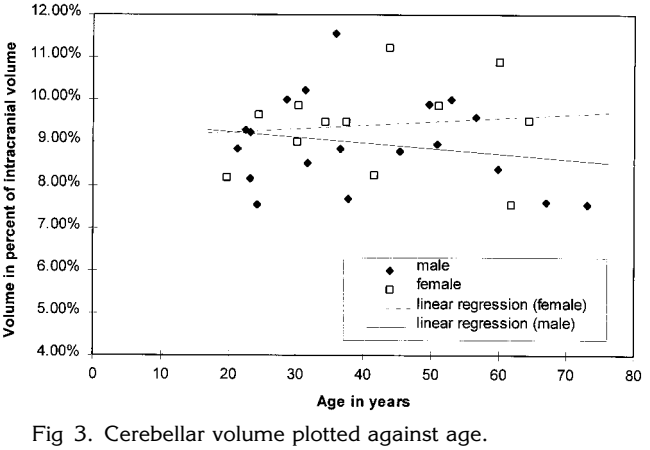

Fig 3. Cerebellar volume plotted against age.

phy (eg, in Alzheimer disease) resembles normal aging in many morphologic and histologic features and affects the cortex in a more homogenous way, cerebellar degeneration (eg, in olivopontocerebellar atrophy) is mostly familiar and exhibits circumscribed patterns of atrophy in subcortical structures. The mechanisms of the loss of neurons might therefore be different.

Likewise, we did not observe a correlation between sex and cerebellar volume ($P = .41$, t test), if we considered the difference in intracranial volume of men and women by calculating the ratio of cerebellar and skull volumes. Without such normalization of the absolute size, the differences were significant ($P < .01$); this effect probably accounts for the discordant results of Escalona et al (2), who compared absolute volumes. Besides, differences between the sexes would be difficult to understand without any structural or clinical correlation.

In conclusion, the cerebellum seems to follow a different individual evolution than the cerebrum. The facts about cerebellar volume related to sex and age might be important in the evaluation of the numerous disorders that produce subcortical degeneration evident in morphologic imaging.

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Comment

Age-related loss of cerebellar tissue was documented in a postmortem investigation by Ellis in (1920) (1). Along with Luft et al's findings, the results of some recent in vivo MR studies (2) seem to contradict Ellis's conclusion, whereas other studies support his findings (3) (J. H. Dupuis, C. McGavran, N. Raz, S. D. Briggs, J. D. Acker, "Aging of the Cerebellar Hemispheres and Vermis Observed In Vivo," and M. P. Sullivan, L De Toledo-Morrell, and F. Morrell, "MRI-Detected Cerebellar Atrophy during Aging," both presented at the 25th Annual Meeting of the Society for Neuroscience, San Diego, Calif, November 1995). Can this discrepancy be reconciled?

The main features and findings of MR studies on age and sex differences in the volume of the cerebellum are summarized in the Table. The effect size (d) for sex differences is presented in a common metric used to compare effects across studies regardless of the original statistics reported. When descriptive statistics are reported, d is computed as the difference between the means normalized by pooled standard deviation; otherwise it is computed from the reported inferential statistics, or is estimated from the P values (3). The common measure of effect size for age-related declines summarized in the Table is either Pearson's correlation (r) or its nonparametric counterpart, Spearman's ρ. The summary of Luft et al's findings reflects additional data kindly provided by Dr Luft (personal communication, August 1996).

The Table shows that despite methodologic differences among the studies conducted at different times in different laboratories, there is relatively little discrepancy in the findings. The root of the contradiction lies in interpretative problems. Escalona et al (2) reported that "age was not a significant predictor of cerebellar volume" (p 928). This is correct if the dichotomous logic of statistical inference is taken on its face value, and an arbitrary and customary .05 level of significance is treated as a fundamental constant. However, power analysis illustrates the weakness of such logic. For a two-tailed test with a probability of type I error (α) = .05, the power to uncover a significant effect of the magnitude reported by Escalona et al is only .37. This value is considerably smaller than a conventional (albeit arbitrary) target value of .80 (4). At such a low level of statistical power, the probability of type II error (β) is .63; that is, the investigators are more likely to miss the effect than to discover it. Moreover, the scatterplot of Escalona et al (p 928) shows a number of influential outliers that reduce the strength of association between age and cerebellar volume. Spearman's ρ values (in parentheses in the Table) computed from these plotted data suggest a somewhat stronger volume-age association than indicated by the parametric statistics sensitive to outliers.

All four studies reveal negative effects of age on cerebellar volume (median $r = -.42$). The difference between the studies in the magnitude of the age effects is not apparent before correction for head size. Thus, the discrepancy in the magnitude (not in the direction) of age effects stems from differences among the samples in the strength of association between age and head size, and cerebellar volume and head size. The stronger these associations (ie, the greater the common variance shared by age, cerebellum, and cranium), the weaker the relationship between age and cerebellar volume. To summarize, the results of the MR studies (Table 1) converge on the assertion that older individuals have smaller cerebellums than their younger peers; sometimes they have smaller craniums as well.

In studying differences between the sexes in cerebellar volume, sexual dimorphism in body size calls for statistical correction. On average, men are taller then women; they also have bigger heads. When no correction for body size is applied, men evidence moderately (Dupuis et al) to

Studies of age and gender differences in cerebellar volume

Study	n	M:F Ratio	Age Range, y	MR Sequence	Plane	Section Thickness, mm	Intersection Gap, mm	Volume, cm^3	r	r, F	r, M	r_{adj}	r_{adj}, F	r_{adj}, M	d	d_{adj}
Escalona et al (2)	37	.76	24–79	Spin-echo	Axial	5	2.5	111.8 ± 12.9	−.27	(−.26)	(−.37)	. . .	. . .	. . .	1.36	. . .
Dupuis et al	93	.94	19–77	SPGR	Coronal	.86	1.5	114.2 ± 15.2	−.42	−.43	−.49	−.34	−.35	−.47	.49	.22
Sullivan et al	64	. . .	22–84	. . .	Sagittal	5	0	. . .	−.56	. . .	. . .	−.45	. . .	. . .	. . .	. . .
Luft et al	41	1.16	19–73	FLASH	Sagittal	.90	0	134.3 ± 14.9	−.41	−.31	−.50	−.10	.10	−.26	.75	.56
Median	53	.94	21–78	. . .	. . .	. . .	. . .	114.2	−.42	−.31	−.49	−.34	−.13	−.37	.75	.39

Note.—r indicates correlation between cerebellar volume and age; r_{adj}, correlation between age and cerebellar volume adjusted by controlling for head size via statistical partialling or ratio normalization; d, effect size for gender differences in volume; and d_{adj}, same effect with the volumes adjusted for head size. Correlations in parentheses are Spearman's ρ computed from Escalona et al's scatterplot (2). SPGR indicates spoiled gradient-echo; FLASH, fast low-angle shot.

substantially (2) greater cerebellar volume. When body size is controlled by partialling out height or dividing cerebellar volume by cranial volume, the sex differences are greatly, but not completely, attenuated. In all three studies that reported relevant data, male subjects tended to show greater age-related declines in cerebellar volume than female subjects, although this interaction was not statistically significant. In sum, the evidence of greater cerebellar volumes and steeper age-related cerebellar volume declines in male subjects is very weak. However, these small but consistent effects merit further investigation.

The issue of correction for body-size differences is important in regards to age- and sex-related differences in the volume of cerebral structures. The use of head size as a correction factor presupposes primacy of the cranial volume over the volume of its contents. Such an assumption is unwarranted. The relationship between growth rates of the skull and the brain is not unidirectional and is, most likely, reciprocal. Not only do bigger skulls allow for development of bigger brains, but bigger and faster-growing brains (and their parts) result in bigger skulls at the early stages of development. Thus, correcting cerebellar volume for head size may be as logical as correcting cranial volumes for cerebellar size. When the concern is with differences in body size, the correction factor must be associated with these differences (eg, height), not with variables strongly influenced by the indexes that are being corrected.

Finally, a practical question is whether age and sex differences in cerebellar volume are large enough to be meaningful for a clinical neuroradiologist. Clinical judgment of relative size of a given structure on the MR image develops in a lengthy process of largely implicit perceptual learning. In estimating the cerebellar size, observers might be using the outlines of the cranium and the posterior fossa on a specific image as their frame of reference, rather than referring to previously observed brains. If indeed there is a tendency for within-patient rather than between-patient comparison, the observations of age and sex differences summarized here may have little impact on clinical judgment.

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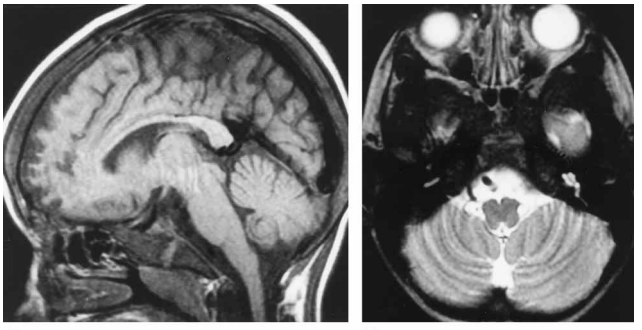

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Fig 4. Sagittal T1-weighted MR image of a 7-year-old child shows diffuse low signal in the clivus and calvarium.

Fig 5. Axial T2-weighted MR image of a 9-year-old child shows markedly low signal in the marrow space of the skull base bones.

Skull Abnormalities on MR of Children with Sickle Cell Disease

Moser et al (1) recently reported the results of a multicenter study that characterized the spectrum of MR abnormalities present in the brain of children with sickle cell disease. The population of children with sickle cell disease that we follow in our own practice is small. It has been our experience, and that of others, that in addition to brain atrophy, hemorrhage, and infarction, there are typical signal changes in the calvarium and skull base in this population. These findings, characterized by low signal in the diploe of the skull on T1-weighted (Fig 4) and T2-weighted (Fig 5) images, are most striking in the clivus and in the sphenoid bones.

Sebes et al (2) reported that among 194 patients with sickle cell disease age 4 months to 55 years, skull radiographs revealed vertical striations (termed a "hair-on-end" appearance) in 5%. This appearance was not seen before the age of 5. In a postmortem study, Williams et al (3) found that the radiolucent areas between the trabeculae corresponded to areas of marrow hyperplasia. Such marrow hyperplasia can be seen in the skull, mandible, and orbit. Facial bones are rarely involved (4). Biparietal and bifrontal bone infarcts have also been described (5). To differentiate between hematologic marrow hyperplasia and iron deposition as a cause for marrow space low signal intensity, Kaneko et al (6) studied sickle cell disease patients with fat saturated T1- and T2-weighted MR sequences. They concluded that the main cause of low signal intensity was iron deposition caused by repeated transfusion rather than red marrow hyperplasia. Although the above pattern of brain parenchymal alteration, so nicely demonstrated by Moser et al (1), appears to be characteristic of sickle cell disease, the recognition of the low signal intensity in the diploe of the sphenoid and clivus heightens one's index of suspicion when definitive diagnosis of sickle cell disease is not included in the clinical history on the MR requisition.

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Reply

We appreciate the interest in our study. The changes in the skull have been well documented, as referenced by Dr Murphy. As part of our data collection we recorded the changes in the skull as observed on MR. We did observe similar findings. We decided not to include this information in our initial paper and to focus on the changes in the brain. The bone findings will be the subject of a subsequent report.

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