Recanalization after thrombolysis in stroke patients

Predictors and prognostic implications

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Abstract—*Objective:* To estimate rates, predictors, and prognostic importance of recanalization in an unselected series of patients with stroke treated with IV thrombolysis. *Methods:* We performed a CT angiography or transcranial Doppler (TCD) follow-up examination 24 hours after IV thrombolysis in 64 patients with documented occlusion of the intracranial internal carotid or middle cerebral artery (MCA). Complete recanalization was defined by a rating of 3 on the Thrombolysis in Myocardial Infarction or 4/5 on the Thrombolysis in Brain Ischemia grading scales. Information about risk factors, clinical features, and outcome was prospectively collected by standardized procedures. *Results:* Complete recanalization was achieved in 36 of the 64 patients (56.3%). There was a nonsignificant trend of recanalization rates to decline with a more proximal site of occlusion: 68.4% (M2 segment of MCA), 53.1% (M1 segment), and 46.2% (carotid T) (p for trend = 0.28). Frequencies of vessel reopening were markedly reduced in subjects with diabetes (9.1% vs 66.0% in nondiabetics, $p < 0.001$) and less so in subjects with additional extracranial carotid occlusion ($p = 0.03$). Finally, complete recanalization predicted a favorable stroke outcome at day 90 independently of the information provided by age, NIH Stroke Scale, and onset-to-needle time. *Conclusions:* We found a high rate of vessel recanalization after IV thrombolysis occlusion. However, recanalization was infrequent in patients with diabetes and extracranial carotid occlusion. Information on recanalization was a powerful, early predictor for clinical outcome.

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IV thrombolysis with tissue plasminogen activator (tPA) is the first-choice therapy for ischemic stroke if applicable within 3 hours.[1,2] There is broad consensus that thrombolysis improves clinical outcome by resolving the occlusive clot and restoring adequate blood flow.[2] The rate of successful recanalization after IV tPA, however, is not well established because the large intervention trials have not systematically assessed vessel status before and after therapy. The few data available are from a limited set of stroke databases and case series,[3-20] most of which were comparatively small and from secondary referral centers. Moreover, these studies were partly retrospective in design, and some applied continuous TCD monitoring,[3-6,12,13,15] which, by itself, may affect recanalization.

The current prospective study aims at assessing the frequency of recanalization after IV thrombolysis in a series of 64 consecutive and unselected patients with documented occlusion of the intracranial internal carotid artery (ICA) or middle cerebral artery (MCA). An additional focus will be on the identification of predictors of vessel recanalization and on its prognostic potential.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the January 2 issue to find the title link for this article.

Methods. *Study subjects.* Between 2002 and 2004, 100 patients with anterior circulation stroke were treated with tPA at the stroke unit of the Innsbruck University Hospital (Department of Neurology). During the study period, the Innsbruck University Hospital was the only thrombolysis facility in Northern Tyrol—a survey area of 500,000 inhabitants—and all patients with suspected acute stroke potentially eligible for thrombolysis were referred to the hospital. Accordingly, the study cohort represents an unselected series of thrombolysis patients. tPA was given at the usual dose of 0.9 mg/kg.[2] Standard inclusion and exclusion criteria were applied.[2] As a single exception, patients older than 80 years were treated if otherwise healthy and eligible. As a hospital standard and as part of the protocol, each patient underwent cranial CT, CT angiography (CTA), and CT perfusion scan before and 24 ($\pm$4) hours after treatment. If the CT protocol was not feasible or if reservations about application of contrast agents existed (allergy, renal insufficiency, or hyperthyreosis), noncontrasted CT plus transcranial Doppler (TCD) was performed. In 26 subjects, occlusions of the ICA or MCA (M1/M2 segments) could not be detected. Most of these patients either had occlusions of periph-

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eral branches of the MCA (peripheral perfusion deficits or infarcts on 24-hour CT/MR) or lacunar infarcts (on 24-hour CT/MR). Of the remaining 74 patients, 10 did not have 24-hour follow-up exams. Therefore, 64 patients formed the study population.

Clinical and laboratory assessment. Clinical data were prospectively retrieved for each patient, including demographics, preexisting risk factors for stroke, medication history, admission blood pressure and glucose levels, stroke onset-to-needle and door-to-needle times, and stroke classification, location, and cause. All parameters were assessed according to standardized protocols. Diabetes was coded as present only if prediagnosed by a physician (ascertained by a review of medical records) and treated (diet, drug treatment, or both). Clinical status at baseline was assessed using the NIH Stroke Scale (NIHSS) by NIHSS-certified neurologists. At day 90, the modified Rankin scale (mRS) was obtained to classify clinical outcome. Assessment of outcome was blind to revascularization status and all covariates of interest (G.W.).

CT examinations were done on 4- and 16-row multidetector systems (Siemens Volume Zoom and Sensation, Erlangen, Germany). Precontrast CT was performed with orbitomeatal coverage from skull base to vertex (4-mm slice thickness). Slice orientation of CT-perfusion was chosen individually with 10-mm slice thickness using 40-mL (4 mL/s) nonionic contrast agent (Ultravist, Schering, Berlin, Germany), whereas CTA covered the carotid bifurcation to the superior sagittal sinus (60-mL contrast agent [3 mL/s]).

We used the Thrombolysis in Myocardial Infarction (TIMI) and the Thrombolysis in Brain Ischemia (TIBI)[7,21] flow grade–derived scales to ascertain recanalization with CTA and TCD. Complete recanalization was defined by TIMI 3 (unimpeded perfusion of the distal vasculature and normal clearance of contrast agents regardless of residual stenosis or focal flow gap) or TIBI 4 or 5 (low-resistance flow with or without focal velocity increase compared with the normal side). Partial recanalization was diagnosed in cases of TIMI 1 or 2 (minimal or incomplete flow signal beyond the occlusion site) or TIBI 1 to 3.[7,21] TCD was performed by an experienced sonographer using a single-channel 2-MHz pulsed wave TCD probe (DWL Multi-Dop X2). TIBI flow grade was determined via a transtemporal window at a depth of 50 to 65 mm. The TIBI classification has been validated against angiographic TIMI scores with a high degree of accordance.[21] For TIMI grades, CTA source images and projections were evaluated by experienced neuroradiologists (K.G., T.G., S.F.). In our study, 15 patients had both CTA and TCD to confirm accordance between both modalities in the routine setting. CT and TCD were performed while waiting for the results of blood tests, especially the complete blood and platelet counts, and thus caused no delay in tPA administration. All examinations were well tolerated.

Statistical analysis. Statistical analysis was performed using the SPSS 12.0.1 software. Categoric variables were compared using the χ^2 test and Fisher exact test as appropriate. Predictors of vessel recanalization and of good clinical outcome were identified by forward stepwise logistic regression analysis, allowing for all variables listed above and presented in table 1. Goodness of fit for the logistic regression model was confirmed by the Hosmer and Lemeshow statistics. A two-sided p value <0.05 was regarded significant.

Results. We evaluated 64 consecutive patients (36 female, 28 male) with anterior circulation stroke treated with IV tPA. Demographic factors, risk profiles, and baseline clinical findings are summarized in table 1. Mean age was 65.7 years, and median baseline NIHSS was 18 compared with 14 (National Institute of Neurological Disorders and Stroke), 13 (European Cooperative Acute Stroke Study [ECASS] I), 11 (ECASS II), and 9 (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS]).[1]

Twenty-four hours after administration of IV tPA, complete recanalization was achieved in 36 patients (56.3%), whereas partial or no recanalization was observed in 10 (15.6%) and 18 patients (28.1%). Classifications based on CTA and TCD were in close agreement (κ coefficient = 0.84), and recanalization rates were identical irrespective of ascertainment by CTA or TCD.

Table 1 *Clinical characteristics of the study population (n = 64)*

Variable	Mean ± SD or n (%)
Age	65.7 ± 13.8
Male	28 (44%)
Baseline NIHSS score	18 (16–21)*
Side of occlusion—left MCA/ICA	37 (58%)
Site of vessel occlusion	
MCA M2 segment	19 (30%)
MCA M1 segment	32 (50%)
Intracranial distal ICA	13 (20%)
Additional cervical ICA occlusion	16 (25%)
Cause	
Cardioembolic	28 (44%)
Large artery disease	27 (42%)
Unknown	9 (14%)
Stroke-to-needle time, min	132 ± 33
Door-to-needle time, min	57 ± 20
Antiplatelets	19 (30%)
Risk factors	
Hypertension	39 (61%)
Diabetes mellitus	11 (17%)
Tobacco	10 (16%)
Atrial fibrillation	24 (38%)
Hyperlipidemia	13 (20%)
Systolic BP on admission, mm Hg	154 ± 23
Diastolic BP on admission, mm Hg	87 ± 15
Glucose level on admission, mmol/L	7.19 ± 2.66

* Median (interquartile range). NIHSS, NIH Stroke Scale; MCA = middle cerebral artery; ICA = internal carotid artery; BP = blood pressure.

The frequency of recanalization in various subgroups is summarized in figure E-1 on the *Neurology* Web site (www.neurology.org). Significant differences were found between subjects with and without diabetes ($p < 0.001$) and with and without coexisting extracranial carotid occlusions ($p = 0.03$) (figure 1). Moreover, the probability of vessel reopening decreased with advancing age, higher baseline NIHSS score, and a more proximal site of vessel occlusion. Neither of these trends, however, reached significance. Reopening was obtained in 62.5% (10 of 16) of the occluded extracranial carotid arteries.

Complications of IV tPA were rare, and symptomatic intracerebral bleeding occurred in a single case with persistent vessel occlusion 24 hours after therapy. Six patients developed large MCA infarcts and died within 10 days after thrombolysis.

At day 90, median mRS was 3.0 (range, 0 to 6). A total of 23 of the 64 patients (36%) became functionally independent (mRS ≤ 2). Clinical outcome was substantially better in patients with complete vessel recanalization than in

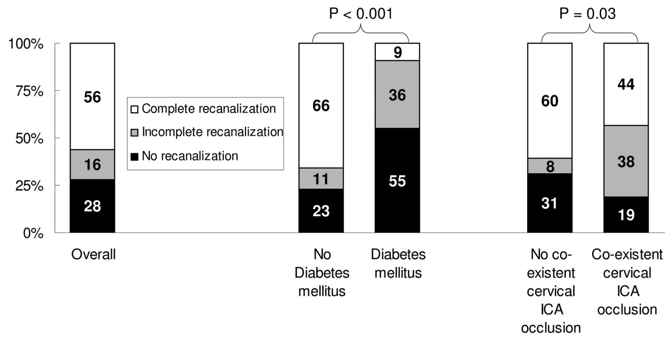

Figure 1. Frequency of recanalization in the overall study population and in subgroups with significant differences in recanalization rates. Values are percentages. ICA = internal carotid artery.

those with partial or no recanalization (figure 2). Further univariate predictors of a favorable clinical outcome were younger age ($p = 0.007$), low NIHSS ($p = 0.003$), and absence of diabetes ($p = 0.005$). A multivariate logistic regression analysis allowing for all variables identified five independent predictors (figure 3). Vessel recanalization, age, and NIHSS maintained significance, diabetes fell short of significance because of its strong association with recanalization, and aspirin pretreatment and onset-to-needle time newly entered the model. Predictive significance of the latter variable was masked in the univariate analysis by its strong association with NIHSS score and age.

Discussion. The rate of recanalization achievable by standard IV thrombolysis of anterior circulation stroke is not well established, mainly because the large trials that qualified thrombolysis as a first-choice treatment for stroke did not systematically assess vessel status before and after intervention. Recently, a number of studies focusing on the concept of continuous TCD-enhanced thrombolysis[3-6,12,13,15] reported recanalization rates of 30% to 56% (complete recanalization) and 60% to 71% (any recanalization) occurring within 2 to 6 hours after thrombolysis (table 2). These data, however, are not easily transferred to standard stroke patients because of trial-specific inclusion and exclusion criteria and putative effects of continuous ultrasound on recanalization. Only a few comparatively small studies have assessed recanalization rates after thrombolysis in the

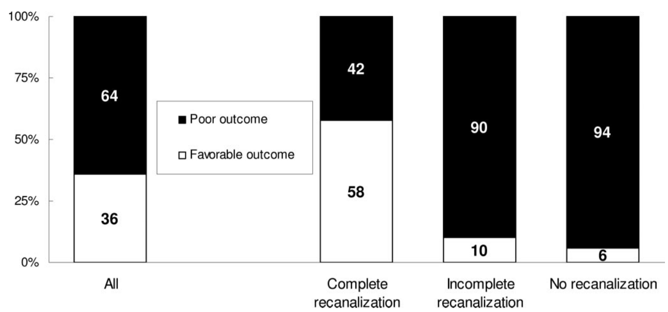

Figure 2. Probability of a favorable clinical outcome (modified Rankin score [mRS] ≤ 2) in patients with complete, partial, and no recanalization. Values are percentages.

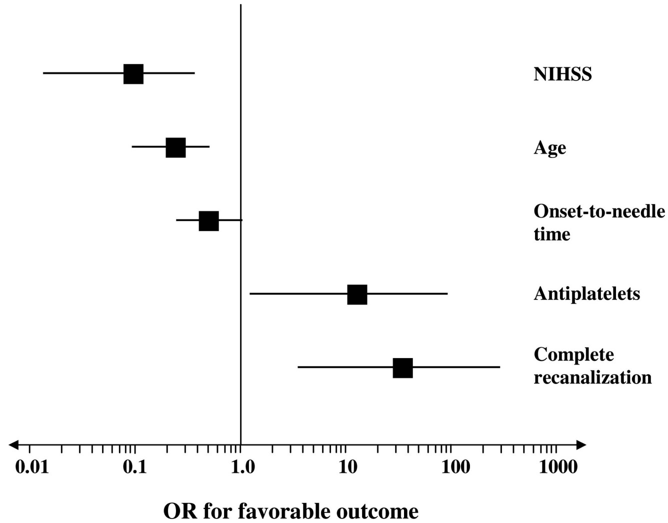

Figure 3. Predictors for a favorable clinical outcome (modified Rankin score [mRS] ≤ 2) derived from a multivariate logistic regression analysis. Odds ratios and 95% CIs were calculated for a 5-point increase in the NIH Stroke Scale (NIHSS), a 10-year increase in age, and a 30-minute increase in the onset-to-needle time. Patients with partial and no recanalization were combined and compared against patients with complete recanalization.

clinical routine setting.[7-11,16-19] Table 2 gives a summary of these evaluations, part of which were retrospective in design and conducted in secondary referral centers. Rates ranged from 17% to 46% for complete recanalization and 31% to 92% for any recanalization. Our prospective study included 64 consecutive thrombolysis patients with documented occlusion of MCA, ICA, or both, yielding a 24-hour rate (95% CI) of complete recanalization of 56.3% (44.1% to 68.5%). In a previous prospective multicenter study, partial or complete recanalization after IV tPA was observed in 34.4% of the 93 patients enrolled. The low rate compared with our study may be explained by the design (dose escalation), mode of drug administration (no bolus), an onset-to-needle time clearly beyond the 3-hour window (mean, 5.4 hours), and assessment of vessel reopening 1 hour after therapy.[20]

In our study, the probability of recanalization decreased with a more proximal site of vessel occlusion. This tendency, however, was not significant, and rates for carotid T occlusion still amounted at 46.2%. In keeping with our findings, two recent studies suggested that patients with carotid T occlusion and IV thrombolysis have a better outcome and more frequent vessel reopening than assumed previously.[8,19] Little information is currently available on how often occlusions of the extracranial carotid artery recanalize after IV thrombolysis.[20] The frequency in our series was high, at 62.5% (10 of 16 patients). However, in most instances high-grade stenosis persisted, and no effect on clinical outcome was found.

Our study identified two independent predictors of recanalization. First, the rate of intracranial vessel

Table 2 *Studies of recanalization after stroke lysis*

Ref.	Procedure and time window	N	Occlusion site	Type and setting of the study	Baseline exam	Follow-up exam	Follow-up interval	Recanalization (complete + partial)	Recanalization (complete)
10	tPA < 3 h	36	MCA or ICA	Prospective stroke database	MRA/CTA	TCD or CTA or MRA	24–72 h	MCA: 88%; ICA + MCA: 31%	n/a
17	tPA < 6 h	39	MCA or ICA	Prospective stroke database	MRA/CTA	TCD or CTA or MRA	< 72 h	74%	46%
19	tPA < 6 h	15	Carotid T	Series of consecutive patients	TCD	TCD	24 h	53%	20%
8	tPA < 3 h	18	Carotid T	Series of consecutive patients	TCD ± MRA	TCD	24–36 h	67%	n/a
18	tPA < 3 h	44	MCA or ICA + MCA	Case series	MRA	MRA	24 h	50%	n/a
9	tPA < 3 h	42	MCA or ICA	Case series	MRA	MRA	48–72 h	74%	n/a
14	tPA < 6 h	52	MCA M1 segment	Multicenter stroke database	MRA	MRA	24 h	71%	17%
16	tPA < 6 h	71	MCA or ICA	Multicenter stroke database	MRA	MRA	24 h	66%	13%
11	tPA < 3 h	24	MCA	Series of consecutive patients with embolic stroke	TCD	TCD	48 h	92%	33% (at 6 h)
7	tPA < 3 h	53	All cerebral vessels	Series of consecutive patients	TCD	TCD	Several hours	85%	40%
20	tPA < 8 h	93	All cerebral vessels	Open-label dose-escalation study	Angiography	Angiography	60 min	34%	11%
5	tPA < 3 h	63	MCA	RCT—control arm	TCD	TCD	2 h	51%	13%
15	tPA < 3 h	39	MCA	RCT—control arm	TCD	TCD	<24 h	n/a	37%
13	tPA < 3 h	36	MCA	RCT—control arm	TCD	TCD	2 h	39%	24%
6	tPA < 6 h*	40	MCA or ICA	Case series	TCD	TCD	6 h	70%	30%
3	tPA < 6 h*	43	MCA or ICA	Case series	TCD	TCD	2 h	66%	37%
5	tPA < 3 h*	63	MCA	RCT—cTCDm arm	TCD	TCD	2 h	n/a	38%
4	tPA < 6 h*	55	MCA	Case series	TCD	TCD	2 h	n/a	36%
15	tPA < 3 h*	39	MCA	RCT—cTCDm arm (±ECA)	TCD	TCD	<24 h	n/a	55% (cTCDm); 56% (cTCDm + ECA)
13	tPA < 3 h*	75	MCA	RCT—cTCDm arm (±ECA)	TCD	TCD	2 h	68% (cTCDm) 71% (cTCDm + ECA)	41% (cTCDm); 54% (cTCDm + ECA)

This table includes serial publications from the same groups. Accordingly, a large number of patients were included in more than one study. N = number of patients with intravenous thrombolysis who had a definite intracranial vessel occlusion at baseline; tPA = tissue plasminogen activator; ICA = internal carotid artery; MCA = middle cerebral artery; CTA = CT angiography; MRA = MR angiography; TCD = transcranial Doppler; cTCD = continuous transcranial Doppler; cTCDm = continuous transcranial Doppler monitoring; ECA = echo contrast agents; RCT = randomized controlled trial; n/a = data not available.

* Application of tPA plus continuous transcranial Doppler.

reopening was lower in patients with a coexisting extracranial carotid occlusion. Secondly, and most importantly, IV thrombolysis did not work well among stroke patients with diabetes. Actually, rates of complete recanalization were as low as 9.1% as opposed to 66.0% in nondiabetics ($p < 0.001$). This finding may partly explain the worse clinical outcome in this group of patients[12,22] and is in close agreement with a previous investigation suggesting a low efficiency of thrombolysis among diabetics with ST elevation myocardial infarction.[23] There are various potential clues of explanation for this phenomenon, but it is tempting to speculate about a central role of plasminogen activator inhibitor (PAI). Levels of PAI are substantially elevated in diabetic patients, and this abnormality is not reversed by standard therapy.[24] Actually, baseline levels of PAI have been shown to be inversely related to clinical outcome in thrombolysis patients,[25] and high PAI may cause thrombolysis failure.[26] Inhibitory effects of PAI on tPA action have consistently been shown in experimental and in vivo (animal) studies.[17,25,26] It should also be mentioned that diabetes impairs the benefit of primary coronary angioplasty on long-term clinical outcome in ST-segment elevation myocardial infarction patients with diabetes,[27,28] and diabetes and even baseline hyperglycemia in the absence of diabetes generally are unfavorable predictors of clinical outcome in stroke patients.

The low recanalization rate among diabetics in our study must be interpreted in light of the limited number of patients with diabetes and, thus, awaits confirmation in larger studies. Provided that this alarming observation holds true in future research, improvement of thrombolysis efficacy in the large segment of diabetics may be viewed as an urgent challenge in acute stroke therapy. Recent advances in thrombolysis potentially relevant to this particular issue are the development of new thrombolytics and an enhancement of standard therapy by novel techniques such as sonothrombolysis, combined intra-arterial thrombolysis, and mechanical clot fragmentation.

Adequate recanalization was among the strongest predictors of a favorable clinical outcome at day 90 after stroke (58.3% vs 10.0% and 5.6% in subjects with partial or no recanalization, $p < 0.001$). This finding fits very well to the penumbra concept and proves that the advantage of reperfusion is not offset by a higher risk of bleeding. Actually, none of the patients with documented vessel recanalization developed a symptomatic intracerebral hematoma. Of note, successful recanalization 24 hours after therapy predicts a favorable outcome on top of the information provided by the variables of age, NIHSS, and onset-to-needle time.[3,6,11,29]

Our study has several strengths, including the prospective design, standardized collection of data, and the fact that the whole survey area was served by a single stroke unit. The latter issue is very important because it provides a safeguard against the usual selection in secondary referral centers. There are potential limitations as well. First, both CTA and TCD were used to assess vessel occlusion and recanalization. In cases in whom both modalities were performed, however, there was adequate accordance, as has been reported previously.[21] Second, we could not obtain 24-hour follow-up vessel images in 10 patients. Six of these patients died. In the other four, 24-hour TCD or CTA were obtained more than 24 hours after thrombolysis and documented successful vessel reopening in all of them. Third, the study design did not allow definition of the exact time to recanalization, which may be relevant to individual prognosis.[3,6,11,29] The fact that onset-to-treatment time had no apparent effect on the overall rate of recanalization but emerged as a predictor of clinical outcome strongly suggests that the time of recanalization and subsequent salvage of the penumbra made the difference. Finally, the number of patients studied is comparatively small for complex analyses. Accordingly, in the multivariate logistic regression analysis focusing on risk predictors for a favorable clinical outcome, confidence intervals of risk estimates were broad, and the power to detect associations was limited. A low number of subjects relative to the number of variables tested may also give rise to chance findings.

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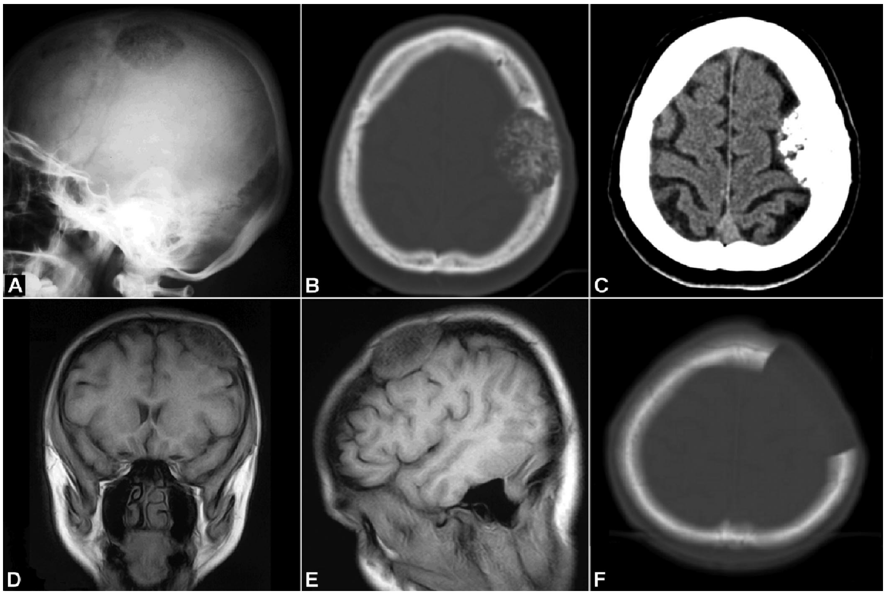

Figure. Lateral X-ray of the skull (A), CT of the head with bone window (B), and cerebral window (C) show large inhomogeneous lesion of honeycomb appearance in the anterior part of the left parietal bone with intracranial extension. MR postcontrast T1-weighted images in the coronal (D) and sagittal (E) planes provide good visualization of the compression of the brain by the bone lesion, slightly enhanced after contrast medium injection. Follow-up CT scan with bone window (F) shows postoperative bone defect with no hematoma visible and no compression of the brain.

Intraosseous hemangioma in parietal bone

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A 35-year-old woman, with headaches for 6 years, was admitted to our Department of Neurology. X-ray showed an osteolytic lesion in the parietal bone, suggesting the presence of hemangioma. CT and MRI (figure) confirmed the tumor, of honeycomb-like internal structure, pressing the adjacent cortex. Neurosurgery of the tumor involved total resection and cranioplasty; the brain compression resolved and the headaches improved. Immunohistochemical examination revealed the presence of endothelial cells expressing CD34 and vimentin.

This case is representative of 0.2% of benign cranium tumors occurring more often in women and with no chromosomal disturbances and no specific neurologic symptoms.[1,2]

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