Prognostic Significance of Uric Acid Serum Concentration in Patients With Acute Ischemic Stroke

Ángel Chamorro, MD; Victor Obach, MD; Álvaro Cervera, MD; Marian Revilla, MD; Ramón Deulofeu, PhD; John H. Aponte, MD

Background and Purpose—We sought to assess in 881 consecutive patients with acute ischemic stroke the clinical relevance in regard to functional outcome of the natural antioxidant uric acid measured at hospital admission.

Methods—Patients had serum uric acid (mg/dL) measured by standard procedures 18.2±15.5 hours from clinical onset. At hospital discharge (11.0±6.0 days), neurological impairment was classified as moderate/severe (Mathew score ≥75; n=304) or mild/absent (Mathew score >75; n=577). Demographics, atherosclerotic risk factors, history of organ disease, baseline neurological score, stroke subtype, infarction size, renal function, aspirin use before stroke, stroke therapy, diuretic use, and laboratory markers, including erythrocyte sedimentation rate, were analyzed in both outcome groups with the use of backward logistic regression.

Results—Increased uric acid values were found in men, hypertensives, alcohol drinkers, and patients with coronary, pulmonary, or renal diseases. Diabetic patients had lower uric acid levels on admission. Uric acid was directly associated with hematocrit (P<0.001), sodium (P<0.001), creatinine (P=0.001), and triglycerides (P<0.001) and inversely related with nonfasting glucose (P=0.001) levels. Neurological impairment on admission (P=0.001) and final infarction size on CT/MRI (P=0.01) were also inversely associated with uric acid. A logistic regression adjusted for confounders confirmed the following independent (odds ratio, 95% CI) good outcome predictors: age (0.97, 0.96 to 0.99), Mathew score on admission (1.14, 1.12 to 1.17), erythrocyte sedimentation rate (0.98, 0.97 to 0.99), infarction volume (0.98, 0.98 to 0.99), and uric acid (1.12, 1.00 to 1.25).

Conclusions—In patients with acute ischemic stroke, there is a 12% increase in the odds of good clinical outcome for each milligram per deciliter increase of serum uric acid. This finding reinforces the relevance of oxidative damage in ischemic stroke. (Stroke. 2002;33:1048-1052.)

Key Words: antioxidants ■ cerebrovascular disorders ■ outcome ■ uric acid

For many years, uric acid has been used in clinical practice as a marker of several metabolic disturbances, although until recently its antioxidant properties had not been considered. The plasma concentration of uric acid is almost 10-fold higher than other antioxidants, such as vitamin C and vitamin E. Moreover, uric acid has much higher antioxidant capacity. Ischemia and hypoxia result in decreased cellular competence to synthesize ATP. Ischemia also promotes the conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO), as the likely result of increased intracellular calcium, and activation of proteases. Whereas XDH activity does not produce reactive oxygen species, the XO reaction is a major source of free radicals during ischemia/reperfusion injury. Arguing for a role of XO in brain damage are studies in which allopurinol, a XO inhibitor, has been shown to have protective effects against reperfusion injury. Epidemiological studies have suggested a direct relationship between the levels of the natural antioxidant uric acid and the risk of coronary or cerebrovascular ischemic events. However, it is not completely clear whether this association indicates that uric acid is an independent ischemic risk factor or it represents a marker of atherosclerotic disease. Whether the concentration of uric acid at the onset of ischemic symptoms influences the severity of stroke also remains to be elucidated. Assuming the relevance of oxidative stress in patients with brain ischemia and the antioxidant capacity of uric acid, we addressed this question in a large series of patients with acute ischemic stroke.

Subjects and Methods
From July 1992 to January 1997, 881 patients with ischemic stroke were admitted to the Neurology Service within 72 hours from the onset of symptoms (mean±SD admission delay was 18.2±15.5 hours). Our institution is a tertiary hospital that covers an urban area of approximately 500 000 individuals, predominantly whites; with very few exceptions, all patients with stroke are admitted into the Neurology Service. Demographics, baseline characteristics of pa-
tients, main workup findings, in-hospital events, and therapies administered before and during hospitalization were prospectively collected by stroke neurologists as part of the Downtown Barcelona Stroke Registry.18 Neurological impairment was measured at baseline and at hospital discharge or death with the use of the Mathew Stroke Scale16 (normal examination = 100, death = 0), whose specific value has been established.17 Routine blood tests, ECG, and a baseline brain CT scan were performed in all patients on hospital arrival. A follow-up brain CT scan or brain MRI (60% of patients) was also performed before discharge to better delineate the topography and size of the lesion.18 Additional diagnostic tests were performed as appropriate to document whether the suspected cause of stroke was lacunar (n = 160), cardiembolic (n = 280), atherothrombotic (n = 147), or undetermined (n = 294).18 Strokes secondary to spontaneous brain hemorrhage, trauma, neoplasms, coagulation disorders, aneurysms, or arteriovenous malformations were not included in the study. Patients who were taking iron or antioxidant vitamins regularly during the weeks preceding the qualifying event were not included in the study. After the qualifying event, participants in the study did not receive thrombolytic agents, intravenous antithrombotic therapy, or investigational drugs. At the time of the qualifying event, 145 patients were taking aspirin (<325 mg/d). After the qualifying event, therapies included platelet antiaggregants (n = 295), anticoagulants (n = 548), oral hypotensives (including diuretics) (n = 384), oral antidiabetic agents (n = 49), and insulin (n = 133).

The prevalence of risk factors and the history of preceding medical disorders were prospectively recorded in all subjects and categorized as previously established. The record of risk factors included the following: arterial hypertension (treated or blood pressure values >160 mm Hg systolic or >90 mm Hg diastolic on repeated measures), diabetes (treated or fasting glucose >110 mg/dL at least in 2 separate analyses), dyslipidemia (treated or ≥240 mg/dL), coronary heart disease (history of angina, myocardial infarction, or congestive heart failure), smoking (>5 cigarettes per day), alcohol intake (>2 drinks per day), intermittent claudication, and prior stroke or transient ischemic attack.

### Laboratory Assessment of Uric Acid

All study participants had blood samples taken the first day of admission and uric acid measured by standard laboratory procedures with urate oxidase reagent on a Dax analyzer (Bayer-Technichon). External quality control program showed an interassay coefficient of variation <3.5%

#### Statistical Analyses

The χ² test, t test, and Wilcoxon rank sum test were used as appropriate. A nonparametric Mann-Whitney test was used to analyze levels of uric acid. Neurological impairment or death at hospital discharge (11.0 ± 6.0 days) was analyzed by stepwise logistic regression with an inclusion criterion of P < 0.10. Neurological impairment was dichotomized as moderate/severe (Mathew score ≤75) or mild/absent (Mathew score >75). The level of significance was set at P < 0.05.

### Results

#### Univariate Determinants of Clinical Outcome

A good outcome at hospital discharge (Mathew >75) was scored in 577 patients (65%), and poor neurological outcome was scored in 304 (35%), including 45 patients (5.1%) who died during hospitalization but after uric acid had been measured. The demographic and clinical characteristics of the population and main therapies administered to the 2 outcome groups are shown in Table 1. On univariate analysis, poor functional outcome at discharge was associated with older age, female sex, atrial fibrillation, congestive heart failure, and smoking.

As shown in Table 2, patients with poor outcome at discharge had statistically significantly higher values of
As illustrated in Table 3, a statistically significantly higher concentration of uric acid was associated with male sex, arterial hypertension, alcohol, and past symptoms of cardiovascular, pulmonary, or renal diseases. Continuous variables also directly associated with uric acid were Mathew score on admission \((P=0.001)\), hematocrit \((P=0.001)\), sodium \((P=0.0001)\), creatinine \((P=0.0001)\), and triglycerides \((P=0.0001)\). As indicated in Table 4, patients with small-vessel disease had statistically significantly higher uric acid values than other stroke subtypes.

Diabetic patients had lower uric acid values (Table 3). Uric acid, mg/dL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>5.45±1.77</td>
<td>4.72±1.70</td>
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<td>Hypertension</td>
<td>5.35±1.88</td>
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<tr>
<td>Alcohol</td>
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<td>5.10±1.79</td>
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</tr>
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<td>5.21±1.70</td>
<td>5.11±1.81</td>
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<tr>
<td>Aspirin before stroke</td>
<td>5.11±1.85</td>
<td>5.15±1.77</td>
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<tr>
<td>Prior TIA/stroke</td>
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TIA indicates transient ischemic attack. Values are mean±SD, expressed in milligrams per deciliter.

*Nonparametric \(P^*\) values (Mann-Whitney).

Uric acid, mg/dL

As expected, other independent stroke outcome variables that did not remain in the model were sex, hypertension, use of hypotensive agents after stroke, diabetes, nonfasting glucose, coronary artery disease, atrial fibrillation, congestive heart failure, intermittent claudication, dyslipidemia, chronic pulmonary disease, smoking, chronic renal disease, aspirin use before stroke, stroke subtype, creatinine, sodium, nonfasting glucose, hematocrit, cholesterol, and triglycerides.

### Relationship Between Uric Acid and Other Laboratory and Clinicoradiologic Findings

To our knowledge, this is the first study describing in a large series of patients the relationship between blood concentration of uric acid and neurological severity of ischemic stroke. The main new finding of the study was that in patients with ischemic stroke there was a 12% increase in the odds of good clinical outcome for each milligram per deciliter increase of uric acid. As expected, other independent stroke outcome predictors were age, degree of neurological impairment at clinical presentation, infarction size on neuroimaging, and ESR, the latter a sensitive marker of the magnitude of the acute phase response. In this study, sex, atrial fibrillation, congestive heart failure, smoking, stroke subtype, nonfasting glucose, and ESR showed significant correlations with uric acid levels.

### Table 3. Uric Acid Concentration on Admission in Relation to Demographics and Risk Factors

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*Nonparametric \(P^*\) values (Mann-Whitney).
glucose, hematocrit, cholesterol, and triglycerides were not independent outcome predictors when multivariate analysis was performed.

However, because this was not the main aim of the study, we cannot exclude the prognostic influence of these factors had they been evaluated by another methodology.

In a small series of subjects, Cherubini and colleagues found lower acid uric levels on admission in patients with ischemic stroke than in healthy controls. In apparent dispute with our findings, patients who died or experienced the greatest functional decline also had higher uric acid plasma levels than patients who remained functionally stable. However, unlike in our study, Cherubini and colleagues did not control for important prognostic confounders that intervene in the setting of acute stroke.

Several studies have provided conflicting results about the clinical significance of elevated uric acid in patients with cardiovascular or cerebrovascular disease. Serum uric acid was found to be an independent predictor of stroke or excess mortality in patients with non-insulin-dependent diabetes mellitus, isolated systolic hypertension, or essential hypertension. The Atherosclerosis Risk in Communities (ARIC) Study observed that the level of uric acid was directly proportional to carotid intimal-medial thickness. The Framingham Heart Study did not find uric acid to be an independent risk factor for cardiovascular disease. Therefore, it has been argued that hyperuricemia could be a compensatory mechanism to counteract oxidative damage related to atherosclerosis and aging in humans. Our findings give further credit to this protective notion of uric acid and spread its effects to the setting of acute ischemic stroke, suggesting that increased uric acid concentration provided a more efficient antioxidant capacity that lessened the clinical repercussion of brain ischemia.

There are experimental data supporting these findings since marked increases in uric acid concentrations have been described in rat models of focal ischemia. These increments have been attributed to the conversion of XDH to XO within the ischemic tissue or within endothelial cells. Uric acid also protected cultured rat hippocampal neurons against cell death induced by glutamate. In these studies, treated neurons suppressed oxyradical accumulation, stabilized calcium homeostasis, and preserved mitochondrial functions. In other studies, uric acid was very effective in suppressing the Fenton reaction and in detoxifying both OH⁻ and peroxynitrite, suggesting an important role in suppressing membrane lipid peroxidation. Low total peroxyl radical trapping potential of plasma was also associated in patients with stroke with greater lesion volumes on MRI and greater neurological impairment.

A few characteristics of the study deserve mention. Clinical outcome was assessed at discharge (or death) rather than at a fixed time. Although the standard deviation of the days of outcome assessment was very narrow (6 days), the degree of this flaw cannot easily be estimated. The variation in concentration of uric acid between individuals might be related in some instances to fluid balance and renal function. To control for these potential confounders, we forced into the logistic regression model variables such as creatinine, sodium, history of renal disease, and use of diuretics. Furthermore, uric acid was measured on admission, before its concentration could be confounded by the intensity of fluid replacement or the heterogeneous administration of medical therapies. Additionally, it could be argued that an excessive delay in admission might have resulted in immobilization/rhabdomyolysis in some patients. However, although we restricted the study to patients with symptoms lasting <72 hours, 80% and 95% of patients were admitted within the first 24 or 48 hours from clinical onset, respectively. We were reassured to note that the levels of uric acid were not related to the delay in admission.

In conclusion, the allegedly greater risk of cardiovascular events or death attributable to hyperuricemia in some studies challenges the antioxidant properties shown by this molecule under different experimental conditions. The results obtained in our study provide strong support for the view that the antioxidant capacity of uric acid is an independent factor that ameliorates the clinical prognosis of patients with acute ischemic stroke. The practical application of this conclusion deserves some thought.

While in some ancient cultures drinking urine was advocated as a healthy practice, it is harder to envision the success of this recommendation in modern societies. However, our study encourages the search of antioxidant therapies in patients with acute ischemic stroke.

References


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