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CLINICAL FACTORS ADVERSELY AFFECTING EARLY OUTCOME AFTER BRAIN INFARCTION

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SUMMARY - *Purpose and methods:* One-hundred-and-nine consecutive patients admitted during the acute phase of a CT-confirmed brain infarction (BI) were studied. Putative adverse influence of demographic and stroke risk factors, previous medical history, clinical presentation, initial and follow-up neurological examination, initial general evaluation, laboratory findings, chest X-ray and electrocardiographic findings, treatment, and topography and etiology of the ischemic insult was analysed. The end-point for assessment was early death (within 30 days). Statistical analysis was performed with univariate analysis and multiple regression. *Results:* The main adverse factors related to an increased death risk during the first 30 days were, in decreasing order of importance: coma 48-72 hours after admission; stroke occuring in already hospitalized patients; Babinski sign on admission; minor degrees of impairment of consciousness 48-72 hours after admission; stroke related to large artery atherothrombosis and to embolism; a history of early impairment of consciousness; cardiac failure on admission. In 53 lucid patients on admission, only a history of congestive heart failure (CHF) was associated with a reduced survival rate. In 56 patients with impaired consciousness, the presence of a Babinski sign increased death risk, but the main factor predicting a high case-fatality rate was the persistence of consciousness disturbances after 48-72 hours. *Conclusions:* The presence of impairment of consciousness, especially coma, 2-3 days after disease onset, and a history of CHF greatly increase the early case fatality rate in patients with acute BI presenting with or without consciousness disturbances at admission, respectively. The use of a prognostic algorythm considering these few variables seems to predict the approximate 30-day fatality rates.

KEY WORDS: cerebral infarction, coma, death, heart failure (congestive), prognosis.

Determinantes clínicos do risco de vida na fase aguda do infarto cerebral

RESUMO - Foram estudados 109 pacientes internados na fase aguda do infarto encefálico. Foi investigada a possível influência prognóstica adversa de diversos aspectos da história epidemiológica e médica, apresentação clínica, exame neurológico de admissão e sequencial, exame clínico geral, exames radiológicos, laboratoriais e eletrocardiograma, tratamento, topografia e mecanismo etiopatogênico da lesão isquêmica sobre o risco de vida nos primeiros 30 dias de doença. Foram feitas análises estatísticas de univariância e regressão múltipla. *Resultados:* Os primeiros fatores prognósticos adversos encontrados foram: coma 48-72 horas após a admissão; infarto intra-hospitalar; sinal de Babinski ao exame inicial; graus menores de depressão da consciência; infarto por aterotrombose de grandes vasos ou por embolização; história de alteração precoce da consciência; falência cardíaca à admissão. Em pacientes lúcidos à internação (53 casos), somente história de insuficiência cardíaca associou-se a aumento da mortalidade. Em 56 casos com alteração da consciência, a presença do sinal de Babinski aumentou o risco de vida, mas o principal fator adverso foi a persistência do distúrbio de consciência após 48-72 horas. *Conclusões:* A presença de depressão da consciência, em especial o coma, 2-3 dias após o início da doença, e história de insuficiência cardíaca aumentam grandemente o risco de vida na fase aguda do infarto cerebral. A utilização de um algoritmo prognóstico simples considerando estas variáveis torna mais objetiva a previsão do risco de vida após o infarto.

PALAVRAS-CHAVE: infarto cerebral, coma, morte, insuficiência cardíaca (congestiva), prognóstico.

Brain infarction (BI) is responsible for most deaths following cerebrovascular disease[6,15,23,36,38]. Case fatality rates after BI vary widely in different studies, and seem to depend mainly on series

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composition- extension of neurological insult, presence and degree of consciousness impairment[8,10,22,28,29,31,37,38]. Few authors stressed the importance of extraneurological factors, especially cardiac comorbidity[7,13,22,23,33], in the determination of fatal outcome.

We studied 109 consecutive patients admitted to the HUCFF-UFRJ in the acute phase of BI, in order to discover the factors that independently affect early survival. In all patients the diagnosis was confirmed by cranial computed tomography (CT).

SUBJECTS AND METHODS

Data from one-hundred-and-nine hospitalized patients older than 20 years of age were consecutively collected along 1986 and 1987. A retrospective study was them carried out. All patients were admitted within one week of onset of disease. Diagnosis of the stroke syndrome followed accepted rigid clinical criteria[4], and was made in the presence of an acute onset (≤ 48 hours) of neurological deficit not associated with trauma or other obvious diagnosis, lasting more than 24 hours or until death, and occurring in the last week. Patients with severe neurological insults are preferentially admited to our hospital. An initial CT was always required for admission to study.

Strokes were classified according to causal mechanisms considering the neurological and medical history, neurological symptoms and signs, CT and, when available, findings from electrocardiogram (ECG), echocardiogram, ultrasound and angiographic studies of cervical arteries. To discriminate large-artery atherothrombosis (ATH) from embolic brain infarction (EMB), we used classification criteria adapted from the National Survey of Stroke (NSS)[38]. CT excluded alternative diagnoses such as intracerebral or subdural hemorrhages, tumours. This eliminated various degrees of diagnostic uncertainty present in the original classification. ATH was diagnosed in the absence of specific criteria for EMB, lacunes (LAC) or other diagnoses. A normal angiogram or the absence of anatomically appropriate extra or intracranial arterial stenosis were considered exclusion criteria for ATH. EMB was diagnosed in the presence of a cardiac source of emboli-cardiac surgery or myocardial infarction within the last six weeks, valvular disease (including mitral valve prolapse), infeccious or marantic endocarditis, dilated congestive cardiomyopathy, atrial fibrillation or other supraventricular tachyarrhythmia, atrial mixoma and right-to-left cardiac shunts. As in the NSS, cases of BI associated with irregular or ulcerated carotid plaques (as assessed by carotid ultrasound or angiogram) were also classified as EMB. Mohr and coworkers[24] suggested that over 20% of BI cases of cardioembolic origin may exhibit a gradual onset. This is in contrast with a large and detailed autopsy study suggesting that such gradual onset is extremely rare, at least in fatal cases. In the absence of routine and early angiographic evaluation, we created a class of "infarctions of undetermined cause" (IUC) composed of patients with a cardiac source of emboli but exhibiting a gradual (>6 hours) onset of symptoms and signs before hospitalization. LAC was diagnosed in the presence of a classical lacunar syndrome and a normal CT or a small (≤ 20 x 20 x 20 mm) pontine or deep hemispheric infarct on CT[12,30]. The OTHER category included arteritis of diverse etiologies, arterial dissection, migraine-related stroke, venous infarctions and other unusual causes of BI.

We studied the univariate influence of the factors listed in Table 1 on the probability of early death (within 30 days of admission). Proportions of patients reaching this end-point were studied by chi-square (χ) or Fisher's exact method.P values ≤ 0.05 were considered significant. Missing data were present in the study of some variables, *e.g.* aphasia or urinary incontinence were only analysed in lucid patients; results of complementary exams were only entered when obtained within 72 hours of admission. All variables were then entered into a proportional hazard model based on backward elimination stepwise regression (Statistical Package for Social Sciences, SPSS[26]), with death within 30 days as the dependent variable. We also studied separately lucid patients on admission and those with any degree of impairment of consciousness with a similar procedure. Our final aim was the construction of a simple prognostic algorythm which could predict the chances of survival in different subgroups of patients.

A detailed description of the entire series of 109 patients may be found elsewhere[3]. In summary, there were 65 (59.6%) white patients; 59 (54.1%) were men. The age on admission for all patients (mean ± 1 sd) was 57±17(men 58±16; women 55±18). There were 18 patients ≤ 40 years old (11 women; 10 EMB). Most patients had associated previous diagnoses: 66 (60.6%) arterial hypertension (AH); 17 (15.6%) diabetes mellitus (DM); 49 (45%) diverse cardiopathies, mostly rheumatic valvar disease and congestive heart failure (CHF) (13 cases each) and ischemic heart disease (12 cases). The BI was recurrent (occurring more than three weeks after an initial stroke[37]) in 14 cases. In 22 the BI followed one or more transient ischemic attacks. Most cases (98) involved the supratentorial (ST) compartment. The final diagnosis was ATH in 50 cases (45.9%); EMB in 40 (36.7%); IUC in 6 (5.5%); LAC in 7 (6.4%); and OTHER in 6 (5.5%)

Table 1. Clinical variables accessed in 109 cases of brain infarction.

1 - DEMOGRAPHIC FACTORS AND PREVIOUS MEDICAL HISTORY

· RACE
· AGE
· SEX
· CARDIAC DISEASE
  - any type
  - congestive
  - hypertensive
  - ischemic
  - rheumatic
  - infectious
  - other

· DIABETE MELLITUS
· ARTERIAL HYPERTENSION
· PREVIOUS STROKE
· TRANSIENT ISCHEMIC ATTACK
  - any type
  - unique vs multiple
  - recent vs remote

· CHRONIC OBSTRUCTIVE PULM. DIS.
· CHRONIC RENAL FAILURE
· ALCOHOLISM

2 - CLINICAL PRESENTATION

· TIME FROM ONSET TO ADMISSION
· PERI-OPERATIVE ONSET
· EARLY LOSS OF CONSCIOUSNESS
· SEIZURES
· HEADACHE
· ONSET
  - gradual (> 6 hours) vs rapid

3 - INITIAL NEUROLOGICAL EXAM

LEVEL OF CONSCIOUSNESS
normal vs altered vs coma

· GLASGOW COMA SCALE +
· PUPILLARY DISFUNCTION +
· RESPIRATORY PATTERN +
· BRAINSTEM REFLEXES +
· CONJUGATE EYE DEVIATION++
· MOTOR DEFICIT ++
  - any degree
  - partial vs massive

· BABINSKI SIGN ++
  - uni or bilateral
  - uni vs bilateral

· WALKING ABILITY +++
· APHASIA +++
· VISUAL FIELD DEFECT +++
· SPHINCTER CONTROL LOSS +++
· SENSORY DISTURBANCE +++
· OTHER FINDINGS

4 - SEQUENCIAL NEUROLOGICAL EXAM

· LEVEL OF CONSCIOUSNESS
· CHANGES OF LEVEL OF CONSCIOUSNESS
· CHANGES OF FOCAL SIGNS

5 - INITIAL CLINICAL EXAM

· BLOOD PRESSURE
  - diastolic
  - systolic

· CARDIAC ARRHYTHMIAS
  - any type
  - rapid supraventricular arrhythmias
  - others

· CONCURRENT ACUTE DISEASES
  - any type
  - pneumonia
  - cardiac failure
  - others

· OTHER CONCURRENT DISEASES
  - peripheral arterial disease
  - carotid artery disease

6 - LABORATORY FINDINGS

· HEMATOCRIT / HEMOGLOBIN
  - both sexes
  - men
  - women

· TOTAL LEUCOCYTE COUNT
· GLYCEMIA
· UREA
· CREATININE
· SODIUM

7 - X-RAY AND ECG FINDINGS

· X-RAY ABNORMALITIES
  - acute pneumonia
  - cardiac disease
  - other

· ECG ABNORMALITIES
  - any type
  - cardiac arrhythmia
  - ischemia
  - conduction block
  - ventricular strain
  - others

8 - FINAL DIAGNOSES

· ETHIOLOGY
  - large artery atherothrombosis
  - cerebral embolism
  - lacunar infarct
  - other
  - undetermined

· TOPOGRAPHY
  - supra vs infratentorial

9 - TREATMENT

· SUPPORTIVE MEASURES
· ANTICOAGULATION
· PROPHYLATIC HEPARIN
· ASPIRIN
· OSMOTIC THERAPY
· CORTICOSTEROIDS

\+ only patients with impaired consciousness on admission
++ all cases and in patients with or without impaired consciousness on admission
+++ only lucid patients on admission

Table 2. Factors increasing early death risk after brain infarct.

MEDICAL HISTORY		SEQUENCIAL NEUROLOGICAL EXAM	
· Congestive Heart Failure	p=0.053	· Impaired Consciousness	
· Perioperative stroke	p=0.011	- Any degree	p=0.002
· Inhospital stroke	p=0.027	- Coma (vs lesser degrees)	p=0.039
		- Lesser degrees (vs normal)	p=0.022
INITIAL NEUROLOGICAL EXAM		· Deterioration to Coma (in patients with lesser degrees of impairment)	p=0.044
· Impaired Consciousness (any degree)	p=0.03	· Worsening of Motor Deficit to Plegia	p=0.011
- In Patients With Impaired Consciousness		· Appearance of Uncal Herniation	p=0.055
· Brainstem Disfunction	p=0.066		
· Babinski Sign	p=0.033	INITIAL CLINICAL EXAM	
· Bilateral Babinski Sign vs normal	p=0.011	· Arterial Hypotension	p=0.029
- All patients		· Cardiac Arrhythmia (other than supraventricular tachyarrhythmia*)	p=0.053
· Babinski Sign	p=0.009		
· Bilateral Babinski Sign vs unilateral	p=0.09	COMPLEMENTARY EXAMS	
vs normal	p=0.017	· High Hemoglobin Level vs low level	p=0.032
· Unilateral Babinski Sign vs normal	p=0.038	vs normal	p=0.046
		DRUG THERAPY	
		· Corticosteroids	p=0.034

* Frequent ventricular ectopic beats, bi-trigeminism, and one patient with complete atrioventricular block

Most patients (70.6%) were admitted within 24 hours of disease onset (59 cases) or were already hospitalized for other medical/surgical reasons (18 cases, 5 perioperative infarcts; 12 EMB). Eleven patients exhibited motor seizures at onset. An initial blood pressure record of 140/90 mm Hg or more was present in 68 patients (63%), cardiac arrhythmias (especially atrial fibrillation and frequent ventricular ectopic beats) in 31 (28.4%), and CHF in 13 (11.9%). At the first neurological examination, 103 patients (94.5%) exhibited motor deficit (plegia of at least one limb in 46). Fifty-six patients (51.4%) had an altered level of consciousness (including 43 of 77 evaluated in the first 24 hours); nine were comatose, and 47 presented with minor degrees of loss of consciousness (confusional states, delirium, hipersonia or stupor). Twenty of these 56 patients (35.7%) already exhibited altered pupillary function, respiratory patterns or brainstem reflexes, all suggesting additional brainstem dysfunction. Among lucid patients, 33.6% (21) were aphasic, 24.5% (13) had lost sphincter control, and 47.5% (19 of 40 evaluated) could not walk. One patient died on the first day, from massive hemispheric infarction. After 48-72 hours of in-hospital observation, impairment of consciousness was present in 51 patients (47.2%), including 13 in coma. Many patients exhibited worsening of focal signs (19), especially motor deficit, or the development of uncal herniation (7).

RESULTS

Thirty-four patients (31.2%) died during hospitalization, 26 (23.9%) in the first 30 days following admission. Most deaths (18) occurred in the first 15 days. Deaths within 30 days were mainly related to the severity of the neurological insult- 11 cases (10 ST strokes). Eight of these deaths occurred in the first week. Cardiovascular and infectious complications were responsible for 8 and 7 deaths respectively, and were more evenly distributed. All 8 late deaths (> 30 days) were related to infection (4 cases, all from nosocomial pneumonia) or constituted sudden unexpected events (cardiac arrhytmias or massive pulmonary embolism).

Table 2 shows the results of univariate analysis. No demographic or stroke risk factor was statistically important. Women exhibited a slightly higher case-fatality rate (30% *vs.* 18%). EMB was more commonly diagnosed in women (48% *vs* 27.1%, ℵ p 0.039) as well as impairment of consciousness at the first neurological exam (62% *vs* 42.4%, ℵ p 0.064).This suggests that women frequently suffered more serious strokes.

Patients admitted between 3 and 7 days after stroke onset exhibited a low fatality rate (6.3%). Patients with in-hospital strokes fared badly (44.5% early case-fatality rate). Most (11) were admitted for medical or surgical

Table 3. Factors independently related to increased 30-day case fatality rate in 109 cases of acute brain infarction: multiple regression analysis.

Adverse Factor	Beta	p Value
Coma After 48-72 hours	0.50533	p=0.0003
Inhospital Stroke	0.26543	p=0.014
Bilateral Babinski Sign	0.31767	p=0.0326
Uni or Bilateral Babinski Sign	0.16488	p=0.033
Minor Degrees of Impairment of Consciousness After 48-72 Hours	0.1973	p=0.0396
Large-artery Atherothrombosis	0.20498	p=0.0528
Cerebral Embolism	0.19577	p=0.0724
Early Loss of Consciousness	0.16941	p=0.073
Cardiac Failure	0.19738	p=0.0976

MULTIPLE R=0.55019; F VALUE=4.77527; SIGNIF F=0.0001; (FURTHER STATISTICAL DATA ARE AVAILABLE UPON REQUEST)

treatment of diverse cardiopathies and symptomatic carotid stenosis. Early impairment of consciousness in 13 cases (72.2%). Most deaths in this group (6 of 8) were directly related to progressive neurological deterioration (PND).

Massive motor deficit (no displacement of any segment of one or more limbs)and the presence of the Babinski sign were associated with a worse outcome. A low fatality rate was observed in lucid patients with flexor plantar responses (7.7%) or with dimidiated hyposthesia (4.8% *vs* 28.4%, ℵ p 0.045).

Predictions based on the level of consciousness were more reliable when made 48-72 hours after admission. At that time, any degree of disturbance was associated with a fourfold reduction of the chances of survival. The fatality rate of comatose patients was significantly different from that of patients with lesser degrees of disturbance (such differences were not so obvious on admission). Patients who recovered from initial depression of the level of consciousness fared well (7.7% early fatality rate), as well as those 19 who exhibited partial regression of motor deficit (no deaths).

Hyperglycemia in nondiabetic patients was associated with a nonsignificant reduction of survival rates. We could not directly evaluate its possible adverse effects in diabetic patients, as all had hyperglycemia on admission. Myocardial injury on admission through ECG (3 cases) was always associated with early death. Four other patients with acute myocardial infarct had a good initial evolution, however. The use of dexamethasone was associated with death in 5 of 9 cases.

The multiple regression procedure for all patients (Table 3) again revealed the level of consciousness after 48-72 hours as the main prognostic predictor.Extensor plantar reflexes had an independent adverse effect. BI during hospitalization for other causes was highly predictive of a bad evolution. Although not evident on univariate analysis, the potential impact of cardiac failure on admission was now demonstrated.

We analysed patients with any degree of loss of consciousness on admission (Table 4A). The presence of coma after the second day of hospitalization and the finding of the Babinski sign had important prognostic impact. In lucid patients on admission (Table 4B) a history of CHF was the only factor predicting an increased early fatality rate.

The main prognostic factors after BI are, therefore, quite different in patients who are or not lucid on admission (Table 4, Figure 1). The former usually have high hospital survival rates, except in the presence of CHF. In patients with depressed sensorium, the algorythm stresses the importance of their level of consciousness by the third day after admission.

COMMENTS

The high case fatality rate detected in this and some other studies is probably a reflexion of the initial clinical status of our patients, as suggested by Térent and Andersson[37]. The time course of hospital deaths and the proportion of patients dying from PND, cardiovascular and infectious complications were comparable to reported

Table 4. Factors independently related to increased 30-day case fatality rate in acute brain infarction in patients with or without impairment of consciousness on admission: multiple regression analysis.

Adverse Factor	Beta	p Value
A. Impaired Consciousness on Admission (N=56)		
Coma After 48-72 Hours	0.34397	p=0.0152
Unilateral Babinski Sign	0.46209	p=0.0269
MULTIPLE R=0.44513; F VALUE=6.54834; SIGNIF F=0.0029		
B. Lucid Patients (N=53)		
History of Congestive Heart Failure	0.37755	p=0.0434
MULTIPLE R=0.27858; F VALUE=4.29101; SIGNIF F=0.0434; (OTHER STATISTICAL DATA ARE AVAIABLE UPON REQUEST)		

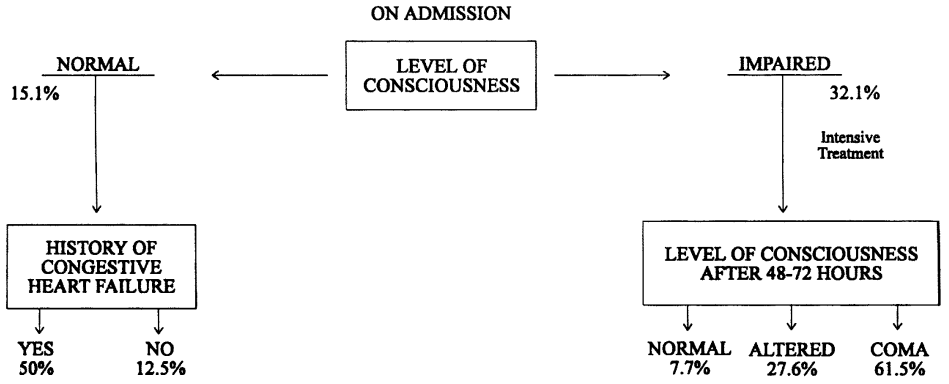

Fig 1. Prognostic algorythm for patients with acute brain infarction.

studies[5,36]. Some deaths related to clinical complications should be considered as terminal events in already critically ill patients[36].

Our case fatality rate for patients ≤ 40 years (23.9) is higher than shown in previous reports on children[35] or young adults[16]. It probably reflects a close association between BI and serious cardiac diseases. Ten patients suffered EMB strokes. This has been related to greater lesion extension, hemorrhagic changes, early reperfusion and other factors leading to increased mass effect[9,17,20,27]. Accordingly, 3 of the 5 deaths in this group were due to PND, the others being related to acute bacterial endocarditis (one immediatly after emergency surgery).

Our finding of a nonsignificant difference in outcome between patients with EMB and ATH is in contrast with previous reports[15,39]. EMB is frequently associated with greater neurological lesions. This probably explains why the independent predictive value of the diagnosis of EMB partially vanishes when variables directly assessing severity are included in the multiple regression analysis.

The close association between disturbances of the level of consciousness, especially coma, and outcome of acute stroke has long been recognized[11,22,31] and continues to be demonstrated in recent years[1,10,14,28,29]. The high fatality rate associated with such disturbances is closely related to the extension and critical topography of the neurological insult and to the development of massive cerebral edema. However, extraneurological factors, such as reduced cardiac output and metabolic derangements, may contribute or entirely explain the impairment of consciousness. In our study, recovery within 48-72 hours was not rare and was associated with increased survival rates. Clearly, early correction of extraneurological factors and anti-edema therapy in selected cases are necessary.

The analysis of the level of consciousness after two or three days of admission has a high predictive value in respect to the clinical outcome. The close association between prolonged and deep coma and the outcome after stroke has been suggested by Gowers (cited by Marquadsen[22]) as early as in 1886, and was later confirmed[31]. Carter, cited by Robinson and cowokers[34], found a fatality rate of 44% after 24 hours of coma, and of almost 90% after more than 48 hours. After this period, most reversible associated factors will be corrected, and most patients who are still obtunded or comatose have suffered extensive neurological lesions.

The adverse prognostic influence of CHF has been described previously[23,33,34], but is not an uniform finding[2,28]. Our results indicate that an admission X-ray suggesting CHF or cardiomegaly is also important: early death in 29.6% (8/27) *vs* 13% (6/46). Aside the possible association with an embolic etiology of stroke and a higher risk of development of fatal arrhythmias and pulmonary embolism, the increased death risk in patients with CHF is probably related to the reduction of

cardiac output and cerebral blood flow. This reduction, even in the absence of an acute neurological insult, may lead to a decreased level of consciousness[32] and focal brain damage[19].

Cardiovascular complications are a common cause of death in the acute phase of stroke[5,21], even in patients with small functional deficits[22,36]. Detection of diverse arrhythmias on admission has been related to increased fatality rates in some[19,23,25,36] but not all[2,37] studies. In our series, most deaths in patients with ventricular ectopic beats were related to PND. In patients with severe neurological insults, ectopic beats may reflect marked sympathetic stimulation. On the other hand, two patients in this group suffered sudden deaths. Acute pulmonary embolism could not be excluded in these cases. However, ventricular extrasystolic beats even without classical ECG warning patterns (frequent or multifocal beats, R on T phenomenon, runs of ventricular tachycardia) may well constitute a warning sign for lethal cardiac arrhytmias in the context of acute stroke.

In summary, the present study suggests that the death risk following acute BI may be predicted by the analysis of some easily assessed clinical variables. Patients without cardiac failure who are lucid three days after admission probably do not benefit from further hospitalization.

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