VIA MEDICA
ORIGINAL ARTICLE
Vol. 63, No. 4, pp. 373–376

ISSN 0015–5659
www.fm.viamedica.pl

Acute ischaemic stroke increases the erythrocyte sedimentation rate, which correlates with early brain damage

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[Received 9 June 2004; Revised 24 September 2004; Accepted 24 September 2004]

The acute phase response follows tissue injury and contributes to its exacerbation with pro-inflammatory and pro-thrombotic mechanisms. Acute phase proteins promote erythrocyte aggregation and falling, with the result that the erythrocyte sedimentation rate (ESR) is a measure of the acute phase response.
As the acute phase response accompanies ischaemic brain damage, we studied ESR values in patients within the first 24 hours of ischaemic stroke and evaluated whether these values may be related to the volume of anatomically relevant single hemispheric brain computed tomography (CT) areas observed at the same period, indicating early stroke-related cerebral changes.
We observed an increase in ESR in stroke patients and a positive correlation between the ESR values and the volume of early brain CT hypodense areas.
The results suggest that elevation in ESR values is observed soon after a stroke and may reflect the relationship between the degree of acute phase response in the early phase of ischaemic stroke and the extent of local brain damage.

Key words: stroke, acute phase response, erythrocyte sedimentation rate

INTRODUCTION

The acute phase response is an important mechanism of host reaction to tissue injury, promoting inflammatory/thrombotically-mediated affection of the organ involved.

The response is triggered by cytokines, small proteins produced by activated local and systemic cells, and is characterised by cytokine-induced hepatic synthesis of pro-inflammatory and pro-coagulant acute phase proteins, including globulins and fibrinogen [12]. The globulin C-reactive protein (CRP) and fibrinogen are major acute phase proteins, and their increased plasma concentrations promote the aggregation of erythrocytes, causing them to fall more rapidly [12]. The erythrocyte sedimentation rate (ESR) is the rate of erythrocyte fall in a column of blood and is a measure of the acute phase response [12].

Ischaemic brain damage is also accompanied by the acute phase response [9], and numerous acute phase proteins have been observed to increase in the serum or plasma of acute ischaemic stroke patients [2, 15, 17]. However, the behaviour of ESR following acute stroke is not clearly delineated as the studies to date which report an increase in ESR in ischaemic stroke patients have been performed days after the stroke [16, 19, 20] or have shown ESR to be elevated not earlier than 5–7 days after the disease onset [10].

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A number of authors have indicated that acute phase response is involved in ischaemic brain damage mechanisms, including inflammation and activation of the coagulation system [2, 6, 7, 9, 15, 17].

However, only one study [4] has demonstrated that the higher ESR values observed in patients within 72 hours of ischaemic stroke were associated with larger brain infarcts.

It is therefore reasonable to study ESR values in the early phase of a stroke, along with a direct comparison between these and the size of early ischaemic brain damage.

The study had two aims. The first was to investigate ESR values in ischaemic stroke patients within 24 hours of the disease onset and to compare the results with those of a control group. The second aim was to evaluate whether the ESR values in ischaemic stroke patients within 24 hours of the disease onset may be related to the volume of brain CT (computed tomography) hypodense areas observed at the same period, indicating early ischaemic stroke-related changes.

MATERIAL AND METHODS

Patients

The study involved 23 first-ever ischaemic stroke patients (mean age ± SD: 72.2 ± 10.8 years, 17 women) admitted between the 6th and the 20th hour after the onset of symptoms. Blood samples were collected from each stroke patient within 30 min of admission, and the diagnosis was confirmed by brain CT performed within the next 30 min. The patients had complete ischaemic stroke, defined as clinical symptoms persisting for > 24 h [3] and confined to the territory of the middle or anterior cerebral artery. Of the 23 patients, 12 had hypertension, 5 were smokers, 4 had diabetes mellitus, and 2 had atrial fibrillation. The exclusion criteria consisted of inflammatory, immunological and malignant disease, infection, hyperthermia, major renal or hepatic failure, deep vein thrombosis, tissue injury within the previous year and also immunosuppression and treatment with anti-inflammatory drugs within the previous 6 months.

A total of 15 tension headache subjects (mean age ± SD: 70.1 ± 8.6 years, 11 women) were included as controls. These did not suffer from hypertension, diabetes mellitus, and atrial fibrillation nor were they smokers. The same exclusion criteria were applied to the controls as to the stroke patients. The study was performed on the basis of the informed consent of each patient and the approval of the Ethics Committee of the University School of Medicine in Poznań.

Laboratory procedure

Blood samples from the stroke patients were collected within 24 h of the onset of the disease symptoms, and prior to the administration of any medication. Blood samples from the tension headache patients served as a control group. The samples were taken from intravenous cannulae and ESR measurements (in mm/h) were performed using the standard laboratory method.

Evaluation of the volume of early brain CT hypodense areas

Brain CT was performed within 24 h of stroke. Brain CT scans were carried out parallel to the orbito-meatal line using 10-mm (supratentorial) and 5-mm (infratentorial) slice thicknesses. Each stroke patient, with the exception of one with radiologically invisible changes, presented an anatomically relevant early CT hypodense area localised in the cerebral hemisphere and did not display other CT changes. The volume (given in ccm) of the early brain CT hypodense areas was calculated according to the formula based on length × depth × height (in mm) of the area measurements [14].

Statistical analysis

The Mann-Whitney U test was applied to compare ESR values in the stroke patients with those in the controls. Spearman's rank-order correlation test was used to calculate the correlation between ESR values in the stroke patients and the volumes of early brain CT hypodense areas. The results presented as mean ± SD. $P < 0.05$ were considered statistically significant.

RESULTS

Erythrocyte sedimentation rate values in patients within 24 h of ischaemic stroke

The ischaemic stroke patients displayed significantly higher ESR values compared with the control group (26.8 ± 11.7 mm/h v. 7.6 ± 4.8 mm/h; $p < 0.00001$).

The highest value of ESR in the ischaemic stroke patient group was 42.0 mm/h, with the lowest being 5.0 mm/h. The highest value of ESR in the control group was 18.0 mm/h, whereas the lowest was 2.0 mm/h.

The volume of early brain CT hypodense areas in patients within 24 h of ischaemic stroke

Brain CT analysis revealed that the average hypodense area volume was 10.0 ± 10.7 ccm. The largest volume of a hypodense area was 37.5 ccm, whereas the smallest was 0.6 ccm.

Correlation between ESR values and the volume of early brain CT hypodense areas in patients within 24 h of ischaemic stroke

Erythrocyte sedimentation rate values in the ischaemic stroke patient group correlated positively with the volume of early brain CT hypodense areas ($r = 0.95$; $p < 0.000001$). The correlation (r) is shown in Figure 1.

DISCUSSION

An increase in ESR values in ischaemic stroke patients is in agreement with other works [10, 16, 19, 20], although the ESR increment seen here within 24 h of stroke is earlier than those previously demonstrated within 48 h [19, 20] or 72 h [16] of the stroke and is considerable earlier than those reported several days after the stroke [10]. Such a result, indicating the appearance of increased ESR values in the early phase of ischaemic stroke, could be expected from studies reporting elevated plasma levels of acute phase proteins, including CRP and fibrinogen, within hours of the onset of a stroke [7, 10].

We suggest that the increase in ESR values observed in our study is, at least in part, a consequence of the acute phase response to the ischaemic stroke event. This is supported by the study of Szikszai et al. [16], which demonstrated that ESR values were elevated in patients with ischaemic stroke but not in those with transient ischaemic attack. Moreover, a tissue injury as serious a cerebral infarct is a potent inducer of the acute phase response [9, 16]. The suggestion that the ESR increment occurs in response to stroke is also strengthened by the study of Emsley et al. [10], who have shown an increase in ESR values in stroke patients in comparison with those in non-stroke patients with atherosclerosis, the most common pathological condition in ischaemic stroke. Atherosclerosis is an inflammatory disease [13], and vascular risk factors influence concentrations of CRP and inflammation-sensitive proteins [5, 11]. Since the stroke patients under study displayed risk factors for atherosclerosis such as hypertension, diabetes mellitus, and smoking, it is possible that they presented a pre-existing pro-inflammatory/pro-coagulant condition, which may, at least in part, contribute to the increase in ESR values soon after the stroke.

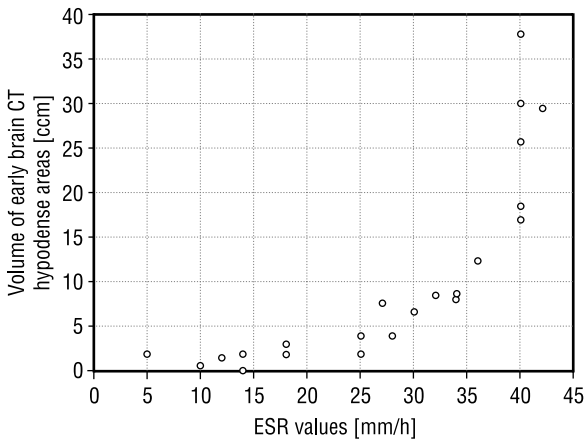

Figure 1. The correlation (r) between ESR values [mm/h] in stroke patients and the volume of early brain CT hypodense areas [ccm].

Acute phase proteins participate in multiple mechanisms promoting a decrement in the survival of neurons subjected to ischaemia. These include an intracerebral influx of leukocytes, the propagation of an intravascular thrombus, and a reduction in blood flow, as well as formation of oedema in the perilesional area [8, 9, 16, 18]. CT hypodense areas evidenced in the cerebral hemispheres within 24 h of stroke represent early ischaemic brain damage [21] along with its extension with leukocyte infiltration [9] and brain local swelling [1, 9, 21]. Thus the positive correlation presented between ESR values and the volume of early brain CT hypodense areas indirectly indicates that the intensity of the acute phase response, as measured by ESR, is related to the early evolution of ischaemic brain damage. This is supported by previous studies demonstrating that the levels of CRP and fibrinogen [6, 7] and higher ESR values in stroke patients were associated with more extensive brain infarcts [4].

To conclude, the data presented suggest that an elevation in ESR values is observed soon after a stroke and may indirectly reflect the relationship between the degree of acute phase response in the early phase of ischaemic stroke and the extent of the local brain damage.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Lucyna Kramer from the Department of Statistics and Information Sciences, University School of Medicine, Poznań for her kind assistance in the preparation of the statistical data.

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