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# Biochemical parameters of patients with clinically silent cerebral lesions depend on gender – a preliminary study

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**A** – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

**Summary** **Background.** As the availability and quality of imaging techniques improve, more and more patients are identified with no history of transient ischaemic attack or stroke in whom imaging shows brain infarcts. Clinical silent vascular cerebral lesions (CSVCL) include asymptomatic brain infarction, white matter hyperintensities and brain atrophy. The impact of CSVCL as cerebrovascular risk factors on brain injury increases the likelihood of later life dementia. Cerebrovascular risk factors of stroke, such as hypertension, heart disease, diabetes, eating habits, obesity, smoking and alcoholism, are obvious in medical practise. CSVCL also increases the risk of stroke. The blood's properties are responsible for proper tissue perfusion of the brain.
**Objectives.** Analysis of the different biochemical parameters of blood in women and men with CSVCL.
**Material and methods.** 45 patients were evaluated. CSVCL was diagnosed by means of magnetic resonance imaging. All patients had blood count, blood sugar, urea, creatine serum, thyroid tests, liver tests, lipid profile, fibrinogen, IgM, IgG, IgA and albumin/globulin ratio (A/G) performed. The control group (39 people) had no such symptoms in the central nervous system. Biochemical tests of blood were perform according to routine procedures – automatic analysis in a hospital laboratory.
**Results.** There were observed lower values of haematocrit and IgA, and higher of ERS and IgM were observed more in the group of women than men, as well as there being a higher value of IgA and a lower albumin/globulin indicator in women with CSVCL.
**Conclusions.** The analysis of the results collected for women and men indicates the existence of different mechanisms of CSVCL occurrence.
**Key words:** stroke, cerebrovascular disorders, brain ischemia.

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## Background

As the availability and quality of imaging techniques improve, more and more patients are identified with no history of transient ischaemic attack or stroke in whom imaging shows brain infarcts or vascular cerebral lesions. The brain constitutes only 2% of body weight, but it is supplied by 15% of the total blood volume and consumes 20% oxygen at rest. It has a high metabolic activity, which is possible thanks to the intensive localised blood flow. Proper blood perfusion protect the central nervous system against injury. Blood flow disorders of cerebral circulation underlie the pathophysiology of vascular diseases of the brain [1, 2]. These include ischemic stroke, transient ischemic attack and, recently, more frequently diagnosed, clinically silent vascular cerebral lesions (CSVCL) or asymptomatic cerebrovascular brain injury, which have been recognised as an important problem in neurology [2–4]. Most silent infarcts are lacunes, of which hypertensive small-vessel disease is thought to be the main cause. Although silent infarcts, by definition, lack clinically overt stroke-like symptoms, they are associated with subtle deficits in physical and cognitive function that commonly go unnoticed. Moreover, the presence of silent infarcts increases the risk of subsequent stroke and dementia [1, 5]. The blood's properties are responsible for proper tissue perfusion of the brain. Pathological levels of the blood morphological components can change blood flow [6, 7]. Blood flow is also associated with abnormalities of blood biochemical parameters [8–12]. Many studies have highlighted the prognostic importance of various laboratory parameters and gender in vascular lesions of the central nervous system [13–15].

## Objectives

The aim of the study was the analysis of the different biochemical parameters of the blood in women and men with CSVCL.

## Material and methods

This was a single-centre retrospective study of adult patients of the neurological ward hospitalised due to problems related to the nervous system. 84 patients were evaluated and divided into 2 groups:

- 45 (24 women, 21 men, aged 37–78 years) with ischemic changes – silent vascular cerebral lesions which were diagnosed by means of MRI. The selection criteria included: no history of psychiatric or neurologi-

cal diseases, including transient ischemic attack and stroke, silent brain infarcts in MRI defined as focal T2 hyperintensities ≥ 3 mm without corresponding focal symptoms,

- 39 (19 women, 20 men, aged 36–75) who did not have any ischemic lesions of the brain in the central nervous system (CNS) in MRI – control group. The other selection criteria were the same as for the study group.

The blood parameters and rheological values can be affected by many extra factors. To minimalise incorrect outcomes, the exclusion criteria for both groups were defined as follows:

- acute or chronic infections and neuroinfections (e.g. sinusitis, inflammation of the urinary tract, hepatitis, borreliosis),
- implanted artificial valves or implantable cardioverter defibrillator (ICD),
- any history of transient ischemic attack (TIA) or cerebrovascular accident (CVA),
- ischemic lesions possibly resulting from iatrogenic causes (i.e. diagnostic or interventional angiography, carotid endarterectomy, stenting or cardiac surgery),
- severe cardiac problem (atrial fibrillation, myocardial infarction, endocarditis, cardiomyopathy).

The screening system included a medical and neurological examination, head MRI scans and blood tests. A detailed history of symptoms of stroke or TIA in the past were also taken. All MRI scans were done on a Siemens Magnetom Vision 1.5-T whole-body MR scanner. T1- and T2-weighted (T1W, T2W) imaging and fluid-attenuated inversion recovery (FLAIR), spin echo (SE), fast spin echo (FSE) and turbo spin echo (TSE) sequence MRI were performer. The magnetic resonance images were analysed by a radiologist blinded to the clinical data. Blood investigations included haemoglobin, total leukocyte count, platelet count, Erythrocyte sedimentation rate (ESR, called also OB), glucose, urea, creatinine, sodium, potassium, serum cholesterol, cholesterol, fibrinogen, bilirubin, aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), albumin, as well as globulin, albumin/globulin ratio (A/G), IgM, IgG, IgA. Biochemical values were separately analysed in all subgroups of men and women. The haematological and biochemical investigations were carried out in the laboratories of the hospital according to routine procedure, using standard commercial reagent kits. Statistical analysis included a comparison of the mean results of chosen biochemical parameters. The mean values were analysed using the *t*-test between men and women with CSVCL, as well as between women and men from the control group and the study group separately. All results can be found in Tables 1, 2 and 3.

The studies were approved by the Bioethics Committee of Poznan University of Medical Sciences (No. 1012-1009).

## Results

The results of the measurements are different in the different subgroups depending on the gender. The comparisons of the biochemical parameters obtained in the groups of men and women are presented in Table 1.

There were observed differences between the group of women and men in haematocrit ($p < 0.001$). Other differences between these two subgroups were observed in the values of some biochemical parameters: fibrinogen, IgM and IgA level, ESR ($p < 0.028$, $p < 0.001$ and $p < 0.016$, respectively). The IgM levels were also different between the group of the control men and men with CSVCL ($p < 0.004$). ESR was on the borderline ($p = 0.05$). The biochemical parameter values in the group of women from the control group and women or men with clinically silent vascular cerebral lesions are presented in Table 2 and 3 respectively.

**Table 1. Comparison of the biochemical values between men and women with clinically silent vascular cerebral lesions**

| Parameter | Group of women *n* = 24 | Group of men *n* = 21 | *p* |
|---|---|---|---|
| Fibrinogen (mmol/l) | 3.44 ± 0.12 | 4.06 ± 0.27 | 0.028 |
| IgM | 1.13 ± 0.09 | 0.71 ± 0.07 | 0.001 |
| IgG | 9.5 ± 0.4 | 9.3 ± 0.3 | – |
| IgA | 2.2 ± 0.1 | 2.7 ± 0.2 | 0.016 |
| ESR | 12 ± 1 | 8 ± 2 | 0.05 |
| Albumin/globulin | 1.56 ± 0.05 | 1.58 ± 0.06 | – |
| Glucose (mmol/l) | 5.45 ± 0.3 | 5.85 ± 0.3 | – |
| Cholesterol (mmol/l) | 5.4 ± 0.2 | 4.9 ± 0.2 | – |
| Hct | 41.50 ± 0.3 | 44.7 ± 0.7 | 0.00001 |

**Table 2. Biochemical parameter values in the group of women from the control group and women with clinically silent vascular cerebral lesions**

| Parameter | Group of control women *n* = 19 | Group of women *n* = 24 | *p* |
|---|---|---|---|
| Fibrinogen (mmol/l) | 3.1 ± 0.4 | 3.44 ± 0.12 | – |
| IgM | 1.4 ± 0.1 | 1.12 ± 0.08 | – |
| IgG | 8.9 ± 0.5 | 10.5 ± 0.4 | – |
| IgA | 1.8 ± 0.1 | 2,2 ± 0.1 | 0.06 |
| OB (ESR) | 11 ± 2 | 13 ± 1 | – |
| Albumin/globulin | 1.8 ± 0.1 | 1.56 ± 0.04 | 0.01 |
| Glucose (mmol/l) | 5.2 ± 0.1 | 5.4 ± 0.2 | – |
| Cholesterol (mmol/l) | 5.3 ± 0.2 | 5.3 ± 0.2 | – |
| Hct | 41.0 ± 0.5 | 41.50 ± 0.3 | – |

**Table 3. Biochemical parameter values in the group of men from the control group and women with clinically silent vascular cerebral lesions**

| Parameter | Group of control men *n* = 20 | Group of men *n* = 21 | *p* |
|---|---|---|---|
| Fibrinogen (mmol/l) | 3.9 ± 0.7 | 4.05 ± 0.28 | – |
| IgM | 1.4 ± 0.1 | 0.70 ± 0.06 | 0.004 |
| IgG | 10 ± 1 | 10.3 ± 0.6 | – |
| IgA | 2.8 ± 0.1 | 2.7 ± 0.2 | – |
| ESR | 9 ± 2 | 9 ± 2 | – |
| Albumin/globulin | 1.5 ± 0.1 | 1.58 ± 0.05 | – |
| Glucose (mmol/l) | 5.05 ± 0.09 | 5.3 ± 0.1 | – |
| Cholesterol (mmol/l) | 5.2 ± 0.1 | 5.8 ± 0.2 | – |
| Hct | 44.61 ± 0.45 | 44.7 ± 0.7 | – |

## Discussion

CSVCL, or silent brain infarcts, are detected in 20% of healthy elderly people and up to 50% of patients in a selected series. Most of such lesions are lacunes, of which cerebral small-vessel disease is thought to be the main cause. Apart from lacunar infarcts, CSVCL is also characterised by white matter lesions, enlarged perivascular spaces and cerebral microbleeds [5]. In spite of a lack of clinically overt stroke-like symptoms, silence infarcts are associated with subtle deficits in physical and cognitive function that commonly go unnoticed. Therefore, in patients with CSVCL, carefully monitoring and treating risk factors (hypertension and others) may provide a benefit by preventing not

only stroke, but also cognitive impairment [16]. Moreover, the presence of CSVCL more than doubles the risk of subsequent stroke and dementia. Awareness related to the risk factors, particularly the modifiable ones, is of crucial importance in general practice and may improve early and long-term prognosis. The general practitioner may play an important role in the prevention of ischemic stroke by informing the patient about the presence of CSVCL [17]. Disorders of blood flow in the blood vessels of the brain lead to clinically silent ischemic lesions of the brain [3]. Blood flow is associated with blood physicochemical parameters and some biochemical parameters [6–10]. It is a subject of hemorheology, which is more and more often becoming interesting to researchers studying impairments related to blood flow disturbances. Abnormalities of blood flow depend on the properties of plasma, the blood morphological components and biochemical parameters [6, 7].

The haematocrit value is one of the parameters which determined the blood viscosity [8, 9, 18]. It caused higher blood viscosity for all shear rates in the group of men. A comparison between the groups of men and women shows a lower value of haematocrit in the group of women. Such a result is compatible with the influence of the haematocrit value on blood viscosity [12]. Changes in haematological parameters at the onset of stroke play an important role in altering the cerebral blood flow. Członkowska and Bhatia demonstrated the importance of haematocrit as a predictive factor for 30-day fatality [19, 20]. From the comparison of biochemical parameters between groups of men and women (Table 1), blood viscosity was significantly correlated with fibrinogen levels. Blood viscosity elevation associated with an increased fibrinogen level was more pronounced in the high haematocrit group [21]. Plasma-fibrinogen concentrations were significantly higher in men. Elevation of haematocrits was found to be more important in the elevation of blood viscosity than an increase in fibrinogen levels. The normal concentration of glucose is 3.9 to 5.5 mmol/L. In the study, the levels of glucose were similar, but it is known that an elevated blood glucose concentration has been implicated as a poor prognostic factor for cerebral ischemia and haemorrhaging [20]. In diabetics, ischemic strokes are often associated with large infarct size and poor outcome due to decreased autoregulation and changes in blood coagulability. Even in non-diabetic patients with hyperglycaemia, the size of the lesion and neurological deficit are worse [22]. Therefore, it is worth evaluating this parameter in patients, especially those with CSVCL. What is important is an easy test for general practitioners to carry out. We could not observe any differences of electrolyte estimations, creatinine or urea, but high creatinine usually significantly affects blood flow in the vessels of the brain. Woo et al. have demonstrated that higher plasma urea and creatinine levels are associated with more severe stroke [23]. Liver function and globulin levels were found to be significantly associated with vessel changes in the brain. It is known that a low albumin/globulin ratio can predispose recurrent strokes [24]. In the group of women, albumin/globulin levels were lower. Such a result is compatible with literature [20, 25], where it was shown that a lower level of the albumin/globulin parameter is a risk factor for the occurrence of CSVCL.

Serum lipids have been linked to a higher risk of ischemic stroke [20]. An inverse association exists for total cholesterol and cerebral haemorrhaging. In a study, cholesterol levels were seen to be similar in men and women. It is known that large protein molecules, such as immunoglobulins, increase blood viscosity. It was found that the IgM value was lower in the group of men. Lower values of IgA and higher levels of the ESD parameter were also observed in the group of women ($p < 0.05$). The high immunoglobulin level, as well as fibrinogen level, correspond with the aggregation of erythrocytes [23]. Another interesting observation is the higher value of IgA and the lower value of the fibrinogen level and albumin/globulin indicator in the group of women with CSVCL (Table 3). Such a result could be very interesting for interpretation of the higher inclination to aggregation in the group of women (Table 1).

Limitations that can affect the study include bias in subject selection. Coexisting diseases, such as migraine, cardiovascular disease, autoimmune diseases – *Lupus erythematosus,* metabolic syndrome, as well as higher rates of smoking and alcohol consumption, could be associated with CSVCL, but the mentioned factors were not analysed [26]. The study group was small, so it is difficult to draw wide and reliable conclusions. As a result, further studies are obviously needed for more detailed conclusions.

## Conclusions

The results of this study indicate that the group of men was characterised by a higher blood viscosity value, which is related to a higher haematocrit value. In the group of women, a higher tendency of erythrocytes aggregation was found.

The analysis of the results collected for the groups of women and men showed different levels of the biochemical parameters of blood and might indicate the existence of different mechanisms of CSVCL occurrence in these two groups, but more studies are needed in order to confirm the results from the study.

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