CHRONIC INFLAMMATORY MARKERS – FACTORS FAVOURING CEREBROVASCULAR DISEASE IN PATIENTS SUFFERING FROM SUBCLINICAL HYPO- OR HYPERTHYROIDISM

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Abstract: *Current studies have shown that elevated C-reactive protein (CRP) promotes atherogenesis and the development of cardiovascular and cerebrovascular diseases. The aim of this study was to investigate the presence of chronic inflammation by measuring serum CRP as atherogenic factor in patients suffering from subclinical hypothyroidism (HoTS) and stroke versus patients with stroke and without HoTS. The study was conducted on 154 patients who had suffered a stroke and a control group consisting of 15 patients with normal thyroid function, without signs and symptoms of stroke. The results have shown that increased levels of CRP have been associated with stroke and HoTS and demonstrate the important role of inflammation in the development of atherosclerosis (ATS) in these patients.*

INTRODUCTION

It is now recognized that moderate and permanent increase of the level of C-reactive protein (CRP) is a risk factor for cardiovascular and cerebrovascular disease.(1) Several studies have shown that elevated CRP may be responsible for atherogenesis.(2,3) CPR is a protein produced by the liver in case of inflammation, as a the response to interleukin-6. CPR is considered a marker of inflammation as its increased level indicates that the patient is suffering from a pathology involving inflammatory mechanisms.

Among nontraditional risk factors for atherosclerosis, determining CRP is a method commonly used. We assumed that subclinical hypothyroidism (HoTS) together with CPR increases the risk of cerebrovascular disease.

PURPOSE

The purpose of this research was to investigate the presence of chronic inflammation by measuring serum CPR as an atherogenic factor in patients suffering from HoTS and stroke versus patients with stroke and without HoTS.

MATERIALS AND METHODS

The study was conducted on 154 patients who had suffered a stroke, hospitalized in Asklepios Neurological Hospital from Schildautal, Germany, between 2013 and 2015 and a control group consisting of 15 patients with normal thyroid function without signs and symptoms of stroke, hospitalized in the Endocrinology Clinic of Sibiu, between 2014 and 2015. The age of the patients included in the study ranged between 60 and 80 years old.

Within the study, there were made up two groups of patients: one group of patients undiagnosed with HoTS previously to stroke, and a control group comprising stroke patients without HoTS. There were no significant differences regarding age between the treatment group and the control one (except for the presence of HoTS in the treatment group).

After applying the inclusion and exclusion criteria, of the 154 stroke patients, there were included in the study a total of 116, aged 65 to 80 years old, of whom 72 were men and 44 were women.

After dosing TSH, FT3 and FT4, there were found eight patients with stroke and HoTS and 13 patients with subclinical hyperthyroidism (HiTS) and stroke, previously undiagnosed with stroke.

For statistical analysis, there were randomly selected among stroke patients without HoTS, a number of 15 patients.

Exclusion criteria were: patients receiving amiodarone treatment, previous diagnosis of hypothyroidism or hyperthyroidism, severe obesity, heart failure, severe systemic disease, chronic renal and hepatic diseases, malignancies, patients with no thyroid hormone dosages.

Euthyroidism was defined by normal values for TSH (0.35-4.94 μU/ml) and FT4 (0.7-1.48 ng/dl). Subclinical hyperthyroidism was defined as TSH below 0.35 μU/ml and normal FT4. Subclinical hypothyroidism was defined as TSH above the normal, with values between 5.00 and 10.00 μU/ml and normal FT4. CPR normal value was considered as 0.5mg / dl.

Stroke diagnosis was made based on clinical and paraclinical signs.

Laboratory examinations performed were: magnetic resonance imaging (MRI), computer tomography (CT) or angioCT angioRMN, Doppler ultrasound, ECG, EEG, chest X-ray, lumbar puncture, oximetry.

For statistical analysis, Student T-test was used.

RESULTS

In the study group, the results showed 8 patients with HoTS and 13 patients with HiTS, and no thyroid dysfunctions in the remaining patients.

Table no. 1. CRP values in mg/dl in the study patients

	CRP (mg/dl) in patients with stroke and HoTS (N=8)	CRP (mg/dl) in patients with stroke and HiTS (N=13)	CRP (mg/dl) in patients with stroke and normal thyroid function (N=15)	CRP (mg/dl) in patients with normal thyroid function without stroke (N=15)
	2.6	0.4	1.6	0.4
	5.3	0.1	0.3	0.5
	6.7	0.1	2.8	0.8
	0.7	0.5	2.4	0.5
	2.0	1.7	1.8	0.4

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	2.3	0.2	1.9	1.2
	4.3	0.5	1.5	0.9
	7.1	0.1	0.5	0.2
		0.2	0.3	1.1
		0.2	0.4	0.3
		0.3	1.0	0.7
		1.5	2.1	0.3
		0.5	0.5	0.7
			0.8	0.3
			1.1	0.3
M±DS (N: <0.5mg/dl)	3.62±2.44	2.73±2.81	1.73±2.12	0.57±1.37

Table no. 2. Mean values for TSH, FT4 and CRP in the study patients

Patients	TSH (M±DS)	FT4 (M±DS)	CRP (M±DS)
Stroke with HoTS N=8	7.27±2.11	1.06±0,19	3.62±2.44
Stroke with HiTS N=13	0.32±0.12	1.26±0.24	2.73±2.81
Stroke with normal thyroid function N=15	2.38±1.61	1.32±024	1,73±2.12
Normal thyroid function without stroke N=15	1.44±3.20	1.17±0.26	0.57±1.37

Table no. 3. Mean values of CRP in patients with stroke and HoTS or HiTS versus patients with stroke and normal thyroid function

	CPR (M±DS)	P	*p*
Stroke + HoTS	3.62±2.44	<0.00035	<0.05
Stroke + normal thyroid function	1.73±2,12		
Stroke + HiTS	2.73±2.81	<0.0031	<0.05
Stroke + normal thyroid function	1.73±2.12		

Table no. 4. Mean values of CRP in patients with normal thyroid function versus patients with stroke and normal thyroid function, HoTS sau HiTS

	CRP (M±DS)	P	*p*
Normal thyroid function (control group)	1.44±3,20	<0.00232	<0.05
Stroke + Normal thyroid function	1.73±2.12		
Normal thyroid function (control group)	1.44±3.20	<0.0001	<0.05
Stroke+ HoTS	3.62±2.44		
Normal thyroid function (control group)	1.44±3.20	0.291	NS <0.05
Stroke+ HiTS	2.73±2.81		

DISCUSSIONS

Our results indicate that CRP is increased in patients with HoTS, who have suffered a stroke. Mean CRP was significantly increased in patients with HoTS and stroke (3.62 ± 2.44 mg/dl) compared to stroke patients without HoTS (1.73 ± 2.12 mg/dl), the difference was statistically significant (p <0.05).

CRP was significantly increased (p <0.05), both in HiTS and stroke patients (2.73 ± 2.81 mg/dl) versus patients with stroke and without HoTS (1.73 ± 2.12 m /dl).

Comparing the CRP value in patients with HiTS and stroke (2.73 ± 2.81 mg/dl) with the CRP level (1.44 ± 3.20 mg/dl) in patients with normal thyroid function and without stroke, there were found no statistically significant differences (p = NS to < 0.05).

Atherosclerosis is considered a chronic inflammatory disorder where both immune responses, innate and acquired, influence disease progression.(4) Mediators of inflammation in atherosclerosis are mainly the cytokines: interleukin-1 (IL-1), IL-6, tumour necrosis factor-α (TNF-α), C-reactive protein (CRP), interferon-γ (IFN-γ). IL-6 produced from cells of the vascular smooth muscle stimulates the CRP production. CRP favours the passage of lipids in the endothelial space, representing the first step in atherosclerosis.(4-6) It follows that atherosclerosis is associated with a chronic inflammatory process and is the main cause of ischemic stroke.

Comparing CRP level (1.73 ± 2.12) in stroke patients without subclinical thyroid dysfunction with the CRP level (1.44 ± 3.20) in patients with normal thyroid function and without stroke, there is found a statistically significant increase (p <0.05) in the first ones.

Our results have found that subclinical hypothyroidism is associated with elevated levels of CRP. Our results are consistent with previously published results.(7,8)

It was claimed that TSH values above the physiological limit cause endothelial dysfunction by increasing serum concentrations of IL-6, TNF-α, CRP, being thus involved in atherogenesis.(9,10) In our research, TSH values were significantly higher (7.27 ± 2.11 μU/ml), statistically significant (p <0.05) in patients with HoTS and stroke, compared with patients with stroke and without HoTS (2.38 ± 1.61 μU/ml).

CRP is one of the most studied inflammatory markers, being a strong and independent predictor of stroke, with a linear response between plasma concentration and risk increase. With age, CRP level is negatively correlated with thigh diameter, measured at its half. Elderly people with sarcopenia have witnessed higher levels compared with younger age.(11)

Chronic inflammation can initiate and promote atherosclerosis and its complications through adverse effects on vascular endothelium and may be one of the factors contributing to the occurrence and progression of endothelial dysfunction in patients with HoTS.

CRP directly interferes with endothelial function by reducing the formation of NO (which has a vasodilatory effect) and through the increase of the production of endothelin-1 (ET-1), which is a powerful vasoconstrictor.

There are researchers who argue that CRP dosing would be even a better indicator than the dosage of cholesterol in the prevention of ischemic vascular disease.(12)

For CRP levels below 1 mg/l, the risk is reduced. For concentrations between 1 and 3 mg/l, the risk is moderate. The risk for stroke is increased when CRP level exceeds 3 mg/l.

TSH, LDL and CRP level in patients with HoTS and stroke was significantly increased compared to stroke patients without HoTS.

There was a positive correlation between CRP and TSH, cholesterol, LDL and triglycerides.

CRP is a marker of increased risk of recurrence if one year from the occurrence of ischemic stroke the blood has concentrations than 2mg/dl. The high level of CRP at 6 weeks after the stroke may predict future vascular events or death.

CRP is the most widely studied marker of inflammation, because it is an important and independent predictor of cerebrovascular disease risk. There was also proved the association between obesity and increased CRP, as well as the additive effect as a risk marker for stroke. Increased values of CRP are found in obese, sedentary people and in those with subclinical and clinical atherosclerosis. CRP can be associated with cerebrovascular risk independently of the lipid profile altered in the patients suffering from ATS.(13-16)

Our research shows that CRP dosage and TSH allow better supervision of persons at risk of stroke.

Our study has some limitations regarding the small number of subjects studied. Even in these conditions, we can say that HoTS is associated to chronic inflammatory processes with increased risk for cerebrovascular disease.

CONCLUSIONS

- Elevated levels of CRP were associated with stroke and HoTS, and it is plausible that this neuronal and glial marker to predict events preceding and/or following the stroke.
- Elevated CRP may suggest the presence of HoTS, providing useful information for predicting stroke.
- CRP dosage allows better supervision of persons at risk of stroke.
- CRP in patients with elevated HoTS demonstrates the important role of inflammation in worsening ATS in these patients.

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