Subjects with Elevated CRP Levels and Asymptomatic PAD Prone to Develop Cognitive Impairment

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Abstract:

The CRP is an independent predictor for stroke, ACS, PAD, linked to atherogenesis. Not all patients with elevated CRP levels have cardiovascular or cerebrovascular symptoms. The purpose of this research study is to verify if there is a correlation between the high CRP levels, PAD and cognitive impairment, concluding that subjects with high CRP levels should be evaluated for PAD and cognitive impairment as "a sooner treatment, a better outcome" applies to their condition.

Rezumat:

Proteina C reactivă este un factor independent de risc pentru AVC, sindrom coronarian acut şi boală arterială periferitcă. Nu toţi subiecţii cu nivele plasmatice ridicate de PCR au simptome cardio sau cerebrovasculare. Scopul lucrării de faţă este de a verifica existenţa unei corelaţii între nivelul PCR, prezenţa bolii arteriale periferice şi deficitul cognitiv. Concluzia acestui studiu este că indivizii cu nivel ridicat de PCR trebuie evaluaţi pentru prezenţa BAP, cu măsurarea imediată a indicelui gleznă-braţ, precum şi evaluarea statusului lor cognitiv, pe principiul o depistare precoce, un tratament precoce au un efect mai bun, cel puţin în cazul acestor indivizi expuşi la risc pentru complicaţii severe cardio şi cerebrovasculare.

A sizable series of prospective epidemiologic studies indicates that baseline levels of CRP, especially when measured with high-sensitivity methods (hs-CRP), are associated with increased risk of developing future cardiovascular disease (CVD) events. The relationship is seen even when controlling for usual CVD risk factors. CRP levels are also predictive of incident type 2 diabetes and increase risk of both diabetes and vascular disease when used as an adjunct to definitions of metabolic syndrome. It remains uncertain, however, whether the major role of CRP is as a contributing cause of CVD events, a marker of CVD risk, or a marker of inflammation that is causal for CVD.

In recent years, C-reactive protein has become established as a risk factor for cardiovascular disease. Increased levels of CRP predict future myocardial infarction and stroke independently of other cardiovascular risk factors, and it has been suggested that measurement of CRP, in addition to traditional risk factors, may improve our ability to predict cardiovascular disease.

C-reactive protein (CRP) is a non-specific marker of systemic inflammation, but whether it plays a causal role in atherosclerosis and its complications remains controversial.

Normally the level of plasma CRP should be undetectable. Low risk of developing cardiovascular disease is for CRP levels lower than 1.0mg/L. For average risk of developing cardiovascular disease CRP levels are between 1.0 and 3.0 mg/L and higher than 3.0 mg/L signifies a high risk for cardiovascular disease.

In selected patient groups, CRP levels were positively associated with angiographically established coronary artery disease. In addition, CRP has been related both cross-sectionally and prospectively to peripheral arterial disease (PAD). In the Rotterdam Study, CRP is strongly associated with atherosclerosis measured at various sites in the arterial tree. Several mechanisms have been described by which CRP and other inflammatory mediators may be actively

involved in atherogenesis. However, not all studies found a clear association between CRP and atherosclerosis. Recent data suggest that inflammation is involved in atherogenesis. C-reactive protein (CRP), a major acute-phase protein, has been associated with the presence and severity of atherosclerosis and has been found to predict cardiac events in subjects with and without prevalent cardiovascular disease. Raised concentrations of inflammatory mediators may reflect inflammation in the arterial wall associated with atherosclerosis but may also be causally involved in the disease process. Sources of inflammation include infections and smoking. Moreover, levels of obesity have been shown to be associated with low-grade inflammation.

Findings examining potential direct proatherogenic effects of CRP in vitro and in vivo are mixed. Randomised controlled trials specific to CRP are currently lacking. Several observational studies show high circulating CRP to be associated with increased risk of coronary heart disease (CHD) events and increased carotid intima-media thickness, a subclinical marker of atherosclerosis. These associations may have non-causal explanations as a result of reverse causality or confounding (the association of CRP with atherosclerosis may arise from the common association of the two with other causative factors). Indeed, CRP is related to many other risk factors, such as obesity, smoking and socioeconomic adversity, as well as other “novel” risk factors such as fibrinogen and interleukin-6.

The inflammatory activity within atherosclerotic plaques is one of the main determinants of the vulnerability of plaques to rupture. Because plaque rupture, thrombus formation, and subsequent organization and incorporation of the thrombus in the plaque are thought to be the most important cause of rapid progression of atherosclerotic plaques, CRP may be a good predictor of progression of atherosclerosis.

Recent data also indicate that the insulin resistance syndrome is accompanied by an increased acute-phase response. A link between the insulin resistance syndrome and the inflammatory state is further suggested by increased levels of the acute-phase proteins plasminogen activator inhibitor-1 (PAI-1) and fibrinogen in the insulin resistance syndrome and by the finding that dyslipidemia in the insulin resistance syndrome and during the acute-phase response shows strong similarities. Obesity, the insulin resistance syndrome, and atherosclerotic disease are closely linked and may all be determinants of an increased acute-phase response. However, it is not clear whether these factors are independently associated with the inflammatory state.

Previous studies on associations between CRP level as a measure of inflammation and cardiovascular risk factors were conducted in middle-aged men and elderly men and women, all of whom are at relatively high risk for atherosclerosis. Atherosclerosis and smoking are potential sources of inflammation and possibly obscure the relation of CRP with other risk factors.

Peripheral arterial disease (PAD), a manifestation of atherosclerosis, has been found to affect approximately 18% of the population aged 55–74 years. Although intermittent claudication is considered the earliest and the most common presenting symptom of PAD, community-based epidemiological studies showed that most people with PAD are asymptomatic.

Upon suspicion of PAD, the first-line study is the ankle brachial pressure index (ABI) which is a measure of the fall

in blood pressure in the arteries supplying the legs. A reduced ABI (less than 0.9) is consistent with PAD. Normal range for ABI: 0.9 > ABI < 1.3.

Abnormal ABI values range as follows below:

ABI < 0.9

0.5< ABI < 0.8 – moderate PAD

ABI <0.5 severe PAD with covert signs and symptoms such as claudication

ABI >1.3

PAD patients, whether symptomatic or asymptomatic, have an increased risk of death and cardiovascular events because of co-existing clinical or subclinical atherosclerosis in the coronary and cerebral arteries, and a decreased ankle brachial index (ABI) of <0.90 is a risk factor for ischemic stroke in the elderly.

Some clinical studies have found cognitive deficits on tests of attention, psychomotor speed, executive function, visuospatial ability and visual memory among patients with symptomatic moderate-to-severe PAD and PAD amputees, who were free of clinical stroke and transient ischemic attacks (TIAs). Two longitudinal cohort studies have also shown in a general stroke-free population that intermittent claudication was associated with poor performance on various cognitive function tests.

Increased levels of CRP have been reported in PAD patients. Evidence from prospective studies shows that CRP is linked to raised risk of stroke in the general population, and are predictive of cardiovascular events, including stroke, in patients with PAD. Furthermore, CRP has been significantly associated to increased risk of cognitive decline and dementia in population-based, cross-sectional and prospective studies.

PURPOSE

The purpose of this paper is io verify if there is a correlation between the high CRP levels, PAD and cognitive impairment.

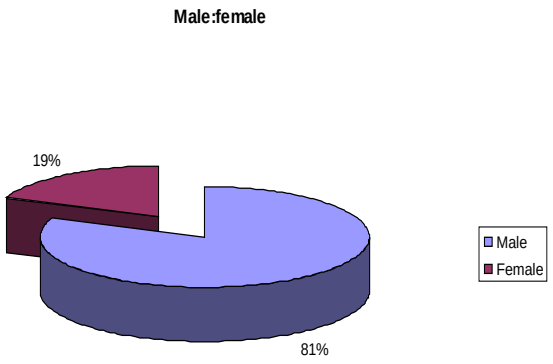
MATERIAL AND METHOD

There were evaluated 32 subjects, aged over 40, with CRP>1g/L admitted in the ER with no history of cardiovascular or cerebrovascular disease, during 2008 – 2009, in the Countz Clinical Hospital of Arad. There were evaluated the CRP levels, the ABI (Doppler measurement) and cognitive status (MMSE).

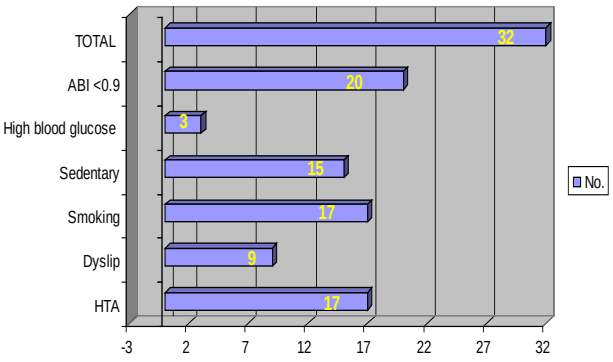
RESULTS

Of the 32 subjects most were men (81%), average age 58.2 yrs. 20 of the patients had an ABI<0.9, meaning a potentially angiographically significant PAD. On the whole sturdy group, the MMSE mean value was 25.3. In the patients that associated PAD with high CRP levels, the MMSE mean score was 21.8. In the 12 patients (37%) that had only CRP>1g/L the MMSE mean value was 28.6. The lowest MMSE score was met in the group with PAD and high CRP levels.

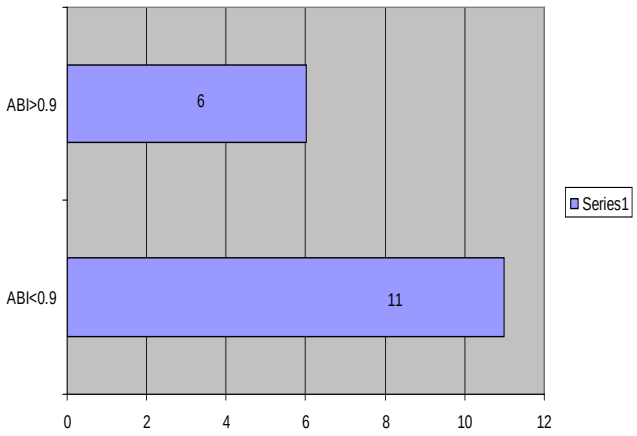
Further data are presented in the tables below and later on discussed in the Discussions chapter.



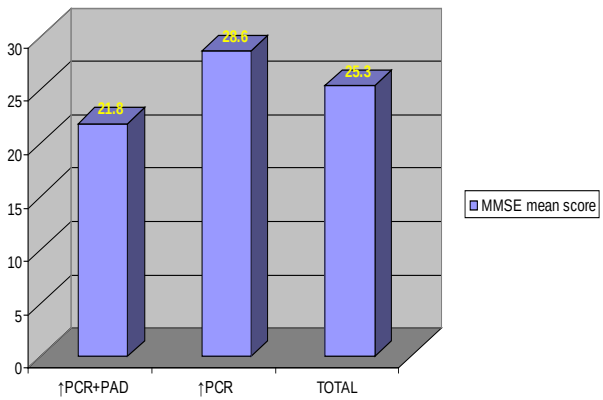
Individual risk factors in the group



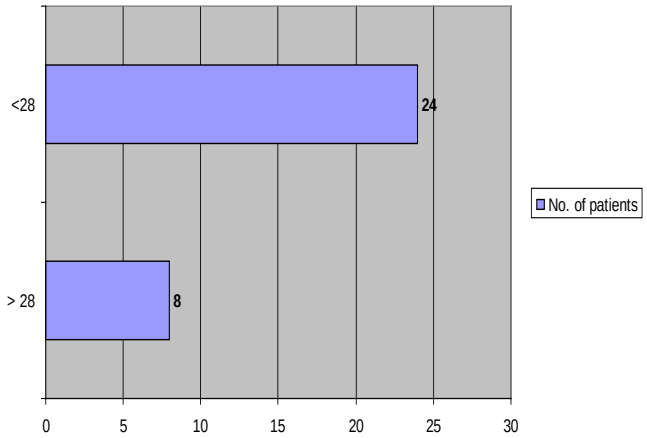
Smoking correlated to PAD



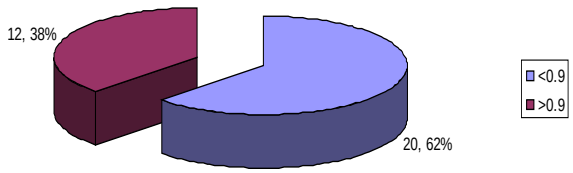
MMSE mean score



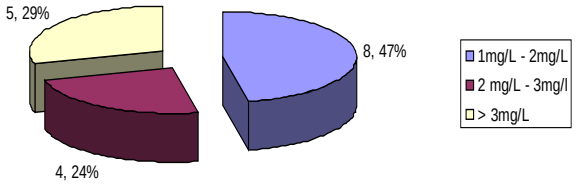
Subjects distribute upon MMSE range above/below 28 points



Distribution of the subjects according to ABI value



Smoking and CRP



DISCUSSIONS

High CRP levels, cognitive impairment and asymptomatic PAD are related due to subclinical atherosclerosis developed on a diffuse inflammatory status in the brain and periphery. The production of inflammatory cytokines (IL-1, TNF-α) due to complement activation and excess coagulation secondary to tissue factor over-expression in the monocytes secondary to elevated CRP levels exacerbates the brain's atherosclerotic and ischemic damage. CRP levels correlated with the presence of dyslipidemia. PAD was more frequent in sedentary individuals (80% had ABI<0.9). No subject had a MMSE score lower than 21. High CRP levels, cognitive impairment and asymptomatic PAD are related due to subclinical atherosclerosis developed on a diffuse inflammatory status in the brain and periphery. The production of inflammatory cytokines (IL-1, TNF-α) due to complement activation and excess coagulation secondary to tissue factor over-expression in the monocytes secondary to elevated CRP levels exacerbates the brain's atherosclerotic and ischemic damage.

CONCLUSION

Subjects with high CRP levels should be evaluated for PAD and cognitive impairment as "a sooner treatment, a better outcome" applies to their condition.

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