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ATHEROSCLEROSIS AMONG PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER ROLE OF COLCHICINOTHERAPY

Poster presentation

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Morbidity and mortality from cardiovascular diseases (CVD) is high in developed societies. 50% deaths in all the world occurs because of ischemic heart disease, atherosclerosis and its complications (WHO report).

For early prevention, prophylaxis of CVD important is to reveal endothelial dysfunction in early stages of it's development, as a hallmark for vascular diseases. In last decades among classical Framing CVD risk factors critical role have been considered to a chronic sub acute inflammation as well.

AIM of our study was to reveal role of chronic sub acute inflammation in development of cardiovascular pathology, and the role of anti-inflammatory treatment in its prophylaxes.

We performed our studies among patients with Familial Mediterranean fever (FMF), which is a genetic autosomal recessive rheumatic, chronic inflammatory disease, prevalent among Eastern Mediterranean populations, mainly Armenians, Sephardic Jews, and Arabs. There are 4000 diagnosed patients only in Armenia - Incidence is about 0,1%.

It is clinically characterized by recurrent self-limited attacks of fever, poliserozites - accompanied by intermittent abdominal, chest, joint, cutaneous pain and swelling, occurring at variable intervals.

Main complication of FMF is development of AA histochemical type amyloidosis predominantly affecting perireticular renal tissue, adrenal, liver and spleen.

Amyloidoses is quite frequent in Armenia (about 40%) and is responsible for poor prognosis of the disease.

Diagnosis of FMF first of all is based on evaluation of clinical picture.

The symptoms of FMF are closely related to the FMF gene (MEFV) mutations. MEFV is located at the short arm of 16 chromosome, encoding so called protein marenostrin (meaning Mediterranean sea) or pyrin (the Greek word for fever). So far more than 50 mutations of the disease have been described.

There are five common mutations: four regrouped in exon 10 (V726A, M694V, M694I, M680I) and one in exon 2 (E 148Q).

In our opinion only three important pathological FMF mutations-M694V, V726A and M680I can be distinguished.

Mutation genotypes especially homozygouse state of Met 694Val mutation of FMF gene causes complicated and severe course of disease.

Non-specific markers of inflammation ESR, C-reactive protein (CRP) during the attacks has diagnostic value. As well them are used for evaluation of the efficiency of the treatment.

COLCHICINOTHERAPY

FMF cannot be cured, but it can be controlled with life-long use of colchicine (1 to 2 mg/day). It is an alkaloid isolated from the autumn crocus [***colchicum autumnale***] Its mode of action is unknown but this drug is able to inhibit attacks or prolong intervals between them in about 95% of the patients.

The attacks can usually be prevented

in 60% of patients – completely

in 33% - partially

in about 5% of cases patients are resistant to colchicine.

Colchicine is also able to prevent or delay the appearance of renal complications in 2/3 patients.

If the patient stops taking the drug, the attacks often develop (even after missing only one dose) and the risk of amyloidosis increase.

Pharmacokinetics: Colchicine is absorbed readily after oral administration and reaches peak plasma level within 2 hrs. Its metabolites are excreted in the intestinal tract and urine.

Pharmacodynamics: Colchicine produces its anti-inflammatory effects by binding to the intra-cellular proteins [*tubulin*], thereby preventing its polymerization into micro-tubules and leading to inhibition of leukocyte migration and phagocytosis. It also inhibits the formation of leukotriens B4 and other inflammatory mediators.

Colchicin effecting on chemotaxis of neutrofils and on production of inflammation mediating several factors **prevents endothelial impairment**, inflammatory cellular reactions and by the FMF pathogenetic mechanisms **the lesion of heart vessels and progression of atherosclerosis.**

OTHER INDICATIONS OF COLCHICINE Colchicine is also used for prophylaxis of recurrent episodes of gouty arthritis, Behecet disease, sarcoid arthritis and hepatic cirrhosis.

Adverse effects: The most common side effect is DIARRHEA, others like nausea, vomiting, hair loss, bone marrow suppression, peripheral neuritis and myopathy.

Dosage: The prophylactic initial dose of colchicine is 0.6 mg 1-3 times daily. If in current dosage patient is having FMF attack, dosage must be increased by 0.6 mg till patient will not have any attack. Total daily dose should not exceed 6 mg.

- It is important to mention, that in reliably about 30% diagnosed FMF cases mutations can not be revealed. In these cases continuous colchicinotherapy within 6 months will determine the diagnosis. It is probable that patients who do not have inflammatory attacks on colchicine suffer from FMF.

ENDOTHELIAL DYSFUNCTION

It is the main predictor marker of early development of atherosclerosis and is characterized by a reduction of the bioavailability of vasodilators, in particular, nitric oxide (NO), whereas endothelium-derived contracting factors (EDCF) - endothelin-1 etc. are increased. This imbalance leads to an impairment of endothelium - dependent vasodilation, which represents the functional characteristic of endothelial dysfunction.

Material and methods of our study

We studied endothelial dysfunction among 50 Familial Mediterranean Fever (FMF) patients, as well as role of cholchicinotherapy in prophylaxis and prevention of atherosclerosis.

From 50 patients 30 were on non-regular colchicinotherapy, 20 were on regular colchicinotherapy.

We performed our studies before and after colchicinotherapy (6 month and 1 year) and compared our data with those who were receiving regular treatment from the beginning, as well as with control group, were 30 healthy people have been involved.

In all groups we studied level of non-specific markers of inflammation ESR, C-reactive protein (CRP), among FMF patients during the attacks, before and after colchicinotherapy for evaluation of it's efficiency.

For the detection and evaluation of endothelial function we used non-invasive dopplerographic method – by which we studied endothelial-dependent flow-mediated vasodilatation of brachial artery (Celemajer D.S.). As well as we performed ECHO-CG.

Results

- Our own preliminary data show that among middle aged Armenian patients suffering from FMF, and not regularly taking anti-inflammatory treatment by colchicine, endothelial dysfunction is more expressed, and it's progression may be prevented by regular at least within 6 months colchicinotherapy.

- The persistence of the inflammation in the attack-free periods in FMF provides a strong argument for uninterrupted life-long colchicine use in this disease.

- Among middle aged Armenian men suffering from FMF, and not regularly taking colchicin anti-inflammatory treatment, the risk of MI increases as compared with the first generation relatives.

- Basing on our own experience we have revealed that regular colchicin therapy within 6 months in FMF patients at preamyloidal and early amyloidal stages leads to the correction of parameters of diastolic function of both ventricles of heart, particularly to the increase of diastolic reserve measured as $\Delta E/A$ in % and velocity of end-diastolic filling of both ventricles during handgrip (isometric) stress test.

- These findings can be interpreted from position of anti-inflammatory and antiatherogenic affect of colchicine on myocardium and vessels which were relatively untouched by amyloidosis in examined patients.

In addition to our result it is important to mention that MI incidence data obtained from 4167 FMF patients (2490, 60% males and 1677, 40% females) has been retrospectively studied in Armenia /Nazaretyan E.Ye., Ajvazyan A.A., Gasparyan A.Yu./. None of these patients were treated regularly with colchicine. 135 events of MI observed among 108 patients (2,4%; 77%, 86males and 23%, 22 females). It is interesting that 31% of these patients had earlier developed nephropathic amyloidosis while 65% had no signs of amyloidosis. The latter supports the speculation that the main cause of MI in FMF is atherosclerotic rather than amyloid lesion of coronary arteries.

Russian scientists proved that in rheumatic patients ischaemic heart disease (IHD) is manifested 5-10 years earlier, and probability of MI is 50 times higher than in general population. In the treatment scheme it is suggested to include statins, which have a powerful antiinflammatory pleotrop effect

Discussion

Our findings can be interpreted from position of anti-inflammatory and antiatherogenic affect of colchicine on myocardium and vessels.

Conclusion

- To prevent atherosclerosis and reduce intensity of CVD risk factors in patients with chronic inflammatory disorders, appropriate anti-inflammatory treatment should be administered alone or in combination with cardiovascular preparations.

- Early diagnosis and struggle against inflammation as a CVD risk factor among FMF patients is urgent.

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