Condition of artery wall and endothelium function in children with juvenile rheumatoid arthritis

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Due to persistent endothelial dysfunction, the children with juvenile rheumatoid arthritis, even when the underlying disease is inactive, have the risk of vascular lesions. We showed the subclinical vascular lesion in the children with juvenile rheumatoid arthritis in the form of thickening in the common carotid artery intima-media complex, increase in stiffness of carotid arteries and presence of endothelial dysfunction from the results of humeral artery endothelium-dependent vasodilation test.

Keywords: juvenile rheumatoid arthritis, children, endothelial dysfunction

Introduction

Juvenile rheumatoid arthritis (JRA) is a chronic autoimmune disease with debut at the age under 16 years with primary localization of the process in the locomotor apparatus based on dysfunction of immunity system and intense autoagression which result in pathologic immunity responses. General incidence and prevalence of JRA in the world varies from 2 to 20 to 16 to 150 per 100 thousand children respectively (Petty R.E. et al., 2004). According to the 2010 data of the Health Care Ministry of Ukraine, in Ukraine incidence and prevalence of JRA among children aged 0 to 17 years was 0,05 to 0,34 respectively per 1000 of children population.

Investigations of P.J. Nicola et al. (2005) showed that for adult rheumatoid arthritis patients the risk of cardiovascular diseases connected with atherosclerosis (AS) is two times higher than for the population in general. Up to 1990s the AS basis was considered to be the ‘cholesterol theory’ based on detection of traditional AS risk factors established from the results of Freamingham study: hypercholesterolemia, arterial hypertension, sugar diabetes, obesity, cigarette smoking and inactive mode of life. However D.H. Solomon et al. (2003) showed that high probability of cardiovascular pathology development in adult patients with rheumatoid arthritis cannot be fully attributed to presence of classical risk factors only. Further scientific studies of A. Doria et al. (2005) left no doubts that the central atherogenesis link is development of inflammatory process in vascular wall resulting from persistent endothelium activation. In this case systemic or evident local inflammatory process in the organism of the patient which is characteristic for rheumatoid arthritis presents an independent risk factor of AS development due to its ability for activation induction of endothelial cells.

Many studies demonstrated that AS is a long-term process which often debuts in as early age as infantile (Packard R.R., Libby P., 2008). The children with risk factors (obesity, sugar diabetes, arterial hypertension etc.) at the age >8 years during autopsy are often detected initial AS lesions of aorta at the stage of yellow bands, in some cases – small AS plaques in coronary arteries (Stary H.C. et al., 1992). It means that AS detection at early stages already in the infantile age in the persons with risk factors of its early development is important for pediatrics and preventive cardiology.

AS vascular lesion has a staged course. The atherogenesis beginning is endothelial dysfunction. Aggregation of immunity cells, oxidized low density lipoproteins (LDLP) in the vascular wall, migration of smooth myocites into the subendothelial layer, increased synthesis of collagen result first in the vascular stiffness increase and then in uniform wall thickening which histologically corresponds to the stage of yellow bands. As the pathology progresses, AS plaques appear in the most typical locations (aorta, coronary arteries, internal carotid artery bulb). All the described stages with exception of the latter, according to the new views, are related to the AS subclinical stage. It is AS diagnostics at the stage of endothelial dysfunction, increase in stiffness and thickening of vascular wall that is important for prevention of cardiovascular diseases in future (Doria A. et al., 2005).

The generally accepted instrumental diagnostic method for endothelial dysfunction is determination of the humeral artery endothelium-dependent vasodilation using duplex sonography. Thus G. Kerekes et al. (2008) showed significant drop in indications of endothelium-dependent vasodilation, compared to the reference group from among adults, in the rheumatoid arthritis patients which gave evidence of endothelial dysfunction. In literature we found singular studies on the condition of humeral artery endothelium-dependent vasodilation in JRA children. Thus A.P. Vlahos et al. (2011) showed the reliable decrease in test indications in JRA children compared to the reference group, which demonstrated endothelial dysfunctions in the persons of the first group.

Determination of arterial stiffness is a relatively new method in vascular lesion diagnostics. R. Klocke et al. (2003) when studying the arterial stiffness by duplex sonography, detected the reliable increase in vascular wall stiffness index in adult rheumatoid arthritis patients without traditional AS development risk factors (cigarette smoking, obesity, arterial hypertension, sugar diabetes, etc.) and cardiovascular diseases. In the domestic literature we did not find any studies on vascular wall stiffness in JRA children.

Determination of common carotid artery intima-media complex (CCA IMC) thickness by duplex sonography is considered a golden standard of instrumental diagnostics for AS subclinical stage and stratification of cardiovascular disease development risk in adults. P.N. Tyrrell et al. (2010) made meta-analysis of 60 CCA IMC investigations by duplex sonography involving 3761 adult patients with rheumatologic diseases, 37% of whom had rheumatoid arthritis. In the latter the significant CCA IMC thickening was detected compared to the healthy patients. E. Pietrewicz and M. Urban (2007) detected the reliable thickening of CCA IMC in JRA children compared to the reference group (0,43 mm against 0,4 mm respectively), and in the
children with polyarthritis CCA IMC was reliably thicker than in the children with oligoarthritis (0.46 mm against 0.43 mm respectively). However in the domestic literature we found no data on CCA IMC thickness in JRA children.

Resulting from the analysis of the literature data described, the purpose of our investigation lay in the study of condition of vascular wall and endothelium function in JRA children.

Object and methods of investigation

Under our observation we had 93 children with JRA and 21 children without rheumatic diseases and cardiovascular pathology development risk factors. Among JRA patients, 43 (46.2%) were boys and 50 (53.8%) girls. The average age of the patients was 11.5+/-0.4 years.

JRA diagnose and classification criteria were performed according the International League of Rheumatologic Associations (Petty et al., 2004). Distribution of the patients depending on the disease form is given in Table 1.

The average disease duration in JRA children was 67.3+/-4.7 months. The main disease-modifying anti-rheumatic agent in JRA children was methotrexate in dosage of 15 mg/m2 of the body surface area per week together with single time peroral 5mg folic acid the day after methotrexate administration. The average duration of methotrexate administration was 47.5+/-7.3 months. Two children with articular form of JRA were administered hydroxychloroquine in dosage of 6 mg/kg of body mass per day. Glucocorticoids were administered to 18 (54.5%) children with systemic JRA and 5 (8.3%) children with the articular form of JRA. The average cumulative dose of glucocorticoids was 13.7+/-2.7 g. From the results of clinical-laboratory examination in JRA patients the disease activity score was determined in accordance with the generally accepted method. The disease was considered inactive in case it met the criteria of the American Board of Rheumatologists for clinical-laboratory JRA remission (Wallace C.A. et al., 2011). Distribution of the patients depending on the disease activity score is given in Table 2.

All the JRA patients and reference group children underwent determination of thickness of CCA IMC and CCA stiffness index, and in 37 JRA patients (17 [45.9%] had systemic JRA and 20 [54.1%] had articular form of JRA) indications of humeral artery endothelium-dependent vasodilation were determined using duplex sonography on the Philips EnVisor C (Philips, Netherlands) ultrasonic scanner. All the measurements were performed in accordance with the method of the American Heart Association (Urbina et al., 2004).

Results and discussion

Average values of IMC ofmagistral arteries and CCA stiffness index in the children with various forms of JRA depending on duration of the disease as well as in the children of the reference group are given in Table 3.

The average indications of CCA IMC in the patients with JRA articular form with the disease duration >8 years are reliably different from the indications in the patients with JRA articular form with the disease term <2 years and 2 to 8 years (p<0.01 in both cases). The average indications of CCA IMC in the systemic JRA patients with the disease term 2 to 8 years and >8 years were reliably higher than the relevant indications of the same groups of patients with JRA articular form (p<0.001 and p<0.01 respectively). The reliable difference of the average CCA IMC indications in JRA articular form patients from the reference group was observed after 8 years of the disease (p<0.001), and in case of systemic JRA – after 2 years of the disease (p<0.001). The CCA IMC thickness in the patients with JRA articular form had a medium direct correlation with the disease term (r=0.63; p<0.01), term of methotrexate administration (r=0.53; p<0.01) and number of the articulations involved (r=0.51; p<0.01). We found the medium direct correlation between CCA IMC thickness in the children with systemic JRA and the disease duration (r=0.65; p<0.01), term of glucocorticoid administration (r=0.64; p<0.05), total glucocorticoid dose (r=0.55; p<0.05) and term of methotrexate administration (r=0.52; p<0.05). We did not find any correlation of CCA IMC thickness in JRA patients depending on the activity score.

The average indications of CCA stiffness index in the patients with both JRA forms after 8 years of the disease were reliably different from the indications in the patients with the disease term <8 years (in case of JRA articular form p<0.001 – when compared to the disease term <2 years and p<0.01 – when compared to the disease term 2 to 8 years; in case of systemic JRA – p<0.001 in both cases). In addition the average indications of CCA stiffness index in the patients with systemic JRA with the disease term 2 to 8 years and >8 years were reliably higher than the relevant indications of the same groups of patients with JRA articular form (p<0.001 and p<0.05 respectively). The reliable difference in the average indications of CCA stiffness index in the persons with JRA articular form from the reference group was observed after 2 years of the disease (p<0.05) and after 8 years of the disease (p<0.001), in case of systemic JRA – after 2 and after 8 years of the disease (p<0.001). The medium direct correlation was found between CCA stiffness index and the duration of JRA articular form disease (r=0.67; p<0.01) as well as between CCA stiffness index and duration of methotrexate therapy (r=0.61; p<0.05), number of the articulations involved in case of JRA articular form (r=0.58; p<0.05). We obtained the medium direct correlation with the disease duration (r=0.63; p<0.01), duration of glucocorticoid administration (r=0.68; p<0.01), duration of methotrexate therapy (r=0.63; p<0.01) and total glucocorticoid dose (r=0.415; p<0.05). No correlation was established between CCA stiffness index and the disease activity score in the JRA children.

The test results for humeral artery endothelium-dependent vasodilation are given in Table 4. As it is evident from the table, the indications of humeral artery endothelium-dependent vasodilation in peak speed and humeral artery diastolic diameter were reliably lower in the children with systemic JRA and articular form JRA compared to the reference group (p<0.001). And the average indications of the children with systemic JRA were reliably lower compared to JRA articular form (p<0.01 for ∆V and p<0.001 for ∆D). It is worth attention that although the indications of the humeral artery endothelium-dependent vasodilation in the children with systemic JRA and articular form JRA had strong and medium reverse correlations with the...
The endothelial function impairment rate in JRA children, as derived from the indications of the humeral artery endothelium-dependent vasodilation, is mostly correlated with the activity score per the moment of investigation. It is attributed to the fact that in case of JRA the endothelium function impairment is mainly caused by effect of cytokines and inflammation acute phase proteins (interleukin (IL)-1, IL-6, C-reactive protein) on the endothelial cells, and the level of these substances in blood serum depends on the disease activity. But we also detected the reliable endothelial function impairment in JRA children with inactive disease according to the data of clinical-laboratory examination. It testifies of persistence of endothelial activation even during inactive phase of the disease, which presents a risk factor for early development of AS lesion of vessels in this patient category (Packard R.R., Libby P., 2008).

The recommendations of the American Society of Echocardiographers define four causes of IMC thickening in magistral arteries and their stiffness increase: age, professional sports, subclinical AS and vasculitis(Stein J.H. et al., 2008). The first two factors are of no significance in JRA children because till the age of 20 CCA IMC practically does not change (Glass C.K., Witztum J. L., 2001) and professional sports is excluded for the JRA children due to functional inability. Contrary to the vasculitis nature of vascular wall thickening is the absence in correlation between IMC thickening rate and stiffness increase of magistral arteries on the one hand, and the disease activity score per the moment of investigation on the other. In addition, in JRA patients no increase in the level of circulating immunity complexes is observed which is characteristic for vasculitis. All the data mentioned contradict the vasculitis nature of vascular changes in JRA patients. Therefore the most probable their cause left is AS nature of vessel lesion.

The endothelial dysfunction is the acknowledged factor entailing AS lesion of vessels (Packard R.R., Libby P., 2008). The instrumental indications of endothelial dysfunction are detected in the children with both articular form and systemic JRA, and they are correlated with the disease activity score per the moment of investigation. This confirms the data of other scientists concerning the effect of circulating cytokineson endothelium as a factor which provokes the endothelial dysfunction. On the other hand, it is evident that the vascular wall change rate in JRA patients depends on the exposure to the endothelial dysfunction. This is confirmed by the correlation of magistral vessels IMC and their stiffness in JRA children with the disease duration, duration of glucocorticoid and methotrexate therapy. However due to the fact that the laboratory-instrumental signs of endothelium impairment are reliably lower compared to the reference group, and among the patients themselves they are reliably lower in the children with systemic JRA compared to the articular form JRA.

### Table 1 Distribution of JRA children depending on the disease form

<table>
<thead>
<tr>
<th>Form</th>
<th>Articular form (n=60)</th>
<th>Systemic form (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarthritis</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Without arthritis</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*In one child with systemic JRA during the observation period no arthritis developed but the child had arthralgia, intermittent fever, erythema eruptions and was ascribed to the patients with JRA systemic form with delayed articular syndrome

### Table 2 Distribution of JRA children depending on disease activity score per moment of examination

<table>
<thead>
<tr>
<th>Activity score</th>
<th>JRA articular form (n=60)</th>
<th>JRA systemic form (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3 Average indications which define condition of vascular wall in reference group children and in children with various JRA forms depending on disease duration

<table>
<thead>
<tr>
<th>Indication</th>
<th>JRA articular form (n=60)</th>
<th>JRA systemic form (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA IMC, mm</td>
<td>0.42 +/- 0.010</td>
<td>0.47 +/- 0.007</td>
</tr>
<tr>
<td>Stiffness index β, units</td>
<td>3.01 +/- 0.100</td>
<td>3.14 +/- 0.100</td>
</tr>
</tbody>
</table>

I: mainly articular form of JRA; II: systemic form of JRA

### Table 4 Average values of indications of humeral artery endothelium-dependent vasodilation in JRA children and reference group children

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>∆V,%*</th>
<th>∆D,%**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with JRA (n=37)</td>
<td>7.7 +/- 0.7</td>
<td>8.3 +/- 0.7</td>
</tr>
<tr>
<td>Systemic JRA (n=17)</td>
<td>10.9 +/- 0.76</td>
<td>11.8 +/- 0.78</td>
</tr>
<tr>
<td>Reference group (n=21)</td>
<td>18.4 +/- 1.4</td>
<td>18.6 +/- 1.2</td>
</tr>
</tbody>
</table>

* ∆V: change of blood flow linear speed in humeral artery after the test compared to the quiescent state, %
** ∆D: change of diameter of humeral artery after the test compared to the quiescent state, %

### Reference group

The recommendations of the American Society of Echocardiographers define four causes of IMC thickening in magistral arteries and their stiffness increase: age, professional sports, subclinical AS and vasculitis(Stein J.H. et al., 2008). The first two factors are of no significance in JRA children because till the age of 20 CCA IMC practically does not change (Glass C.K., Witztum J. L., 2001) and professional sports is excluded for the JRA children due to functional inability. Contrary to the vasculitis nature of vascular wall thickening is the absence in correlation between IMC thickening rate and stiffness increase of magistral arteries on the one hand, and the disease activity score per the moment of investigation on the other. In addition, in JRA patients no increase in the level of circulating immunity complexes is observed which is characteristic for vasculitis. All the data mentioned contradict the vasculitis nature of vascular changes in JRA patients. Therefore the most probable their cause left is AS nature of vessel lesion.

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activation and dysfunction are observed in the JRA children even in case of zero disease activity, this category of children stays in the risk group concerning early AS lesion of vessels even during remission of the underlying disease.

Conclusions

The investigation results established the reliable CCA IMC thickening, compared to healthy children, in the patients with JRA articular form and JRA duration >8 years, in the patients with JRA systemic form and JRA duration >2 years; the reliable increase in CCA stiffness in the JRA patients with the disease duration >2 years. The changes are more evident in case of the disease systemic form compared to the articular form. The direct correlation was found between CCA IMC thickening, increase in their stiffness and disease duration, glucocorticoid, methotrexate therapy duration in case of both JRA forms. In the JRA children the indications of the humeral artery endothelium-dependent vasodilation are reliably lower compared to healthy children, and are reliably lower in case of JRA systemic form.

Bibliography


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Summary. Children with juvenile idiopathic arthritis as a result of persistent endothelial dysfunction are at risk for vascular lesions, even in a period of inactivity of the underlying disease. We have shown subclinical vascular damage in children with juvenile idiopathic arthritis: thickening of the intima-media complex of the common carotid arteries, increasing of their stiffness and the presence of endothelial dysfunction due to results of flow-mediated dilation test.

Key words: juvenile idiopathic arthritis, children, endothelial dysfunction.

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