Significance of pentraxin-3 levels in patients with juvenile scleroderma

Sirs,

Juvenile scleroderma (JScl) is a rare chronic connective tissue disorder divided into two main disease forms: systemic and localised (1-3). Although extremely rare, juvenile systemic sclerosis (JSS) has worse prognosis with multi-organ involvement and possible life-threatening complications (1-4). Its main pathophysiological characteristics include microvascular abnormalities and excessive fibrosis of the skin, subcutaneous tissues and internal organs due to fibroblast dysfunction (1, 3).

Pentraxin 3 (PTX3) is a multifunctional protein produced at the inflammation site by macrophages, dendritic cells, endothelial cells, smooth muscle cells and fibroblasts (5, 6). Previously studies reported an increased level of PTX3 among adults with scleroderma (5-7).

As far as we know, study among juvenile patients has not been provided yet.

We aimed to measure the level of PTX3 in JS patients comparing to juvenile dermatomyositis (JDM) and healthy children (HC). We investigated correlation of serum PTX3 concentrations with extent of skin fibrosis and with presence of various organ involvements.

A total of 44 patients with JScl (24 with JSS and 20 with localised disease form), 19 patients with JDM and 41 HC were assessed. Patients with JSS met the classification criteria for JSS (8). Demographic and clinical characteristics of study groups are summarised in Table I.

Table I. Demographic and clinical characteristics of patients with juvenile systemic sclerosis, juvenile localised scleroderma, juvenile dermatomyositis and healthy controls.

	Juvenile systemic sclerosis n=24	Juvenile localised scleroderma n=20	Juvenile dermatomyositis n=19	Healthy controls n=41
Female N (%)	23 (95%)	14 (70%)	14 (73%)	33 (80%)
Mean age at disease onset (mean±SD)	10.25±3.99 years	7.92±3.89 years	6.07±4.09 years	
Mean age at diagnosis (mean±SD)	11.93±3.30 years	9.28±3.39 years	6.6±4.07 years	
Mean age at the investigation (mean±SD)	15.76±3.16 years	12.44±3.63 years	11.56+4.03 years	14.33±3.48 years
Mean disease duration (mean±SD)	5.21±4.48 years	5.67±4.21 years	3.5±1.1 years	
Modified Rodnan skin score	19.95±11.09			
Raynaud's phenomenon N (%)	17 (70%)	4 (20%)	0 (0%)	
Digital ulcer N (%)	2 (8%)	0 (0%)	0 (0%)	
Interstitial lung disease N (%)	6 (25%)	0 (0%)	0 (0%)	
Pulmonaryhypertension N (%)	2 (8%)	0 (0%)	0 (0%)	
Heart involvement N (%)	1 (4%)	0 (0%)	0 (0%)	
Gastro-intestinal involvement N (%)	4 (17%)	0 (0%)	0 (0%)	
Renal involvement N (%)	0 (0%)	0 (0%)	0 (0%)	
Anti–topoisomerase I positivity N (%)	4 (17%)	0 (0%)	0 (0%)	
ANA* positivity N (%)	24 (100%)	15 (75%)	10 (53%)	
Median PTX3¶level±SD	10.63 ± 8.61 ng/ml	11.75 ± 9.11 ng/ml	2.96±0.88 ng/ml	2.76 ± 1.338 ng/ml
No treatment N (%)	0 (0%)	4 (20%)	0 (0%)	
Only MTX‖ N (%)	1 (4%)	9 (37%)	0 (0%)	
MTX+steroid N (%)	1 (4%)	10 (50%)	6 (31%)	
MTX+steroid +vasoactive agent N (%)	17 (70%)	0 (0%)	0 (0%)	
MTX+steroid +CYC-A** N (%)	0 (0%)	0 (0%)	13 (68%)	
MTX+steroid +vasoactive agent +CYC*** N (%)	3 (12%)	0 (0%)	0 (0%)	
Biological agent N (%)	3 (12%)	0 (0%)	0 (0%)	

*ANA: antinuclear antibody; **CYC-A: cyclosporine A; ***CYC: cyclophosphamide; ‖MTX: methotrexate; ¶PTX3: pentraxin 3.

In both JSS and JLS patients PTX3 level was significantly higher comparing to patients with JDM and HC ($p<0.001$).

PTX3 level was found to be in positive correlation with modified Rodnan skin score (mRSS) (Rho=0.497, $p=0.030$).

ROC curve analysis revealed that PTX3 could be considered a significant test for JScl (AUC: 0.907, $p<0.001$ for JSS and 0.830, $p<0.001$ for JLS).

Estimated cut off value for PTX3 between JSS and HC was 2.157 ng/ml (sensitivity 96%, specificity 73%) and 3.50 ng/ml (sensitivity 88%, specificity 70%) between JSS and JDM. Cut off of PTX3 between JLS and HC was 2.279 ng/ml (sensitivity 80%, specificity 68%) and 3.5 ng/ml (sensitivity 78%, specificity 78%) between JLS and JDM.

In a study by Shirai *et al*. (4), the level of PTX3 was significantly higher in adult systemic sclerosis patients comparing to healthy controls. PTX3 level was also significantly higher in our both JSS and JLS patients, comparing to JDM and HC ($p<0.001$). Significantly elevated PTX levels in patients with connective tissue disorders (systemic sclerosis, systemic lupus erythematosus) with prominent vascular manifestations (e.g. Raynaud phenomenon, digital ulcerations) has been reported (5, 7, 9). We didn't find significant association between PTX3 and vascular changes, possibly due to its low frequency in our cohort comparing to data reported in the literature (Table I) (10).

While Shirai *et al*. (5) didn't find association between PTX3 level and fibrosis, Iwata *et al*. (6) found correlations between PTX3 level and various fibrotic aspects of the disease. We also found a significant correlation between PTX3 level and mRSS, which represents a relevant measurement of the skin thickening and fibrosis.

As a disease control group, we used patients with JDM. These two disease share common auto-immune nature but the fibrosis of the skin and internal organs is the exclusively characteristic of scleroderma. This could explain the higher level of PTX3 in scleroderma patients, since it is manly produced by fibroblasts at the place of fibrosis. It is of importance to mention that diagnosis was made clinically and the PTX3 did not correlate with disease activity, so it could be considered as epiphenomenon. Prospective observational studies should show if it is relevant biomarker of JScl.

In conclusion, circulating PTX3 level is significantly higher in both JSS and JLS than in patients with JDM and HC. In JSS patients, PTX3 is in positive correlation with mRSS. Prospective observational studies should show if the PTX3 could be a relevant biomarker of JScl.

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