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Serum levels of long pentraxin PTX3 in patients with polymyalgia rheumatica

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ABSTRACT

Objectives. *To evaluate PTX3 feasibility to provide a prognostic tool in PMR clinical practice.*

Methods. *Circulating PTX3 levels were measured in 93 PMR patients at disease onset and during corticosteroid therapy and in 46 normal controls (NC) by ELISA.*

Results. *No difference in PTX3 concentrations was observed between NC and PMR either at disease onset and during follow-up or between groups of patients defined according to the presence of recurrence/relapse.*

Conclusions. *PTX3 serum levels do not increase significantly in active PMR. Further studies on patients with giant-cell arteritis could evaluate whether large vessel involvement may be associated to increased PTX3 levels.*

Introduction

Polymyalgia rheumatica (PMR) is a common disorder in the population over 50 years; the pathogenesis of PMR is poorly understood but genetic and environmental factors might have a role. The symptoms seem to be related to synovitis of proximal joints and extra-articular synovial structure associated to an increase in both eryrtrocyte sedimentation rate (ESR) and levels of acute-phase proteins, such as C-reactive protein (CRP) (1).

One of the most prominent inducers of CRP is IL-6, cytokine with a pivotal role in PMR, demonstrated both by its elevated systemic levels (2, 3), and by evidence supporting the identification of sIL-6R as a potential prognostic marker of PMR outcome (4).

CRP belongs to the pentraxin family, a family of multimeric pattern recognition proteins phylogenetically highly conserved. CRP is classic short pentraxin, whereas the prototype of the long pentraxins is PTX3. PTX3 is released in response to primary proinflammatory signals (bacterial product, IL-1, TNF but not IL-6). Evidence suggests that PTX3 is a useful new serological marker, rapidly reflecting tissue inflammation and damage under diverse clinical conditions (5). In PMR, no evidence about the involvement and role of PTX3 is available. Therefore, we investigated this alternative pathway of innate immunity evaluating the modulation of systemic levels of PTX3 in untreated and treated PMR patients during a follow up period.

Materials and methods

Patients

Ninety-three consecutive untreated patients with PMR (24 men, 69 women; mean age: 74 years, range: 53-86 years) were prospectively assessed. All patients were diagnosed according the criteria of Healey (6). These patients had been evaluated in previous studies and their demographic and clinical features had already been reported elsewhere (4).

Written informed consent was obtained by all patients and the study was approved by the Ethics Committees of the hospitals involved.

Evaluation of PTX3 circulating levels

We analysed PTX3 serum levels in PMR patients at disease onset and at 1, 3, 6, 12, and 24 months of follow-up during corticosteroid therapy and in 46 age-matched normal controls (NC).

PTX3 was measured with a sandwich ELISA based on a monoclonal antibody (mAb) MNB4 (ascites diluted 1:5000 in coating buffer) and rabbit antiserum as previously described (7).

Statistical analysis

One-way ANOVA was applied under the hypothesis of normality and variance equality of data sets. If the assumptions were not fulfilled, non-parametric analysis was performed: Kruskal-Wallis test with Dunn's multiple comparison post-hoc test or Mann-Whitney U-test (two independent groups) to analyse unpaired data; multiple comparison of pared data were evaluated by Friedman test. When Friedman test was significant, the Wilcoxon test was applied.

Spearman's correlation analysis was used to assess relationships between variables. Statistical Analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 14.1 (SPSS Inc., Chicago, USA) and GraphPad Prism for Windows (CA, USA).

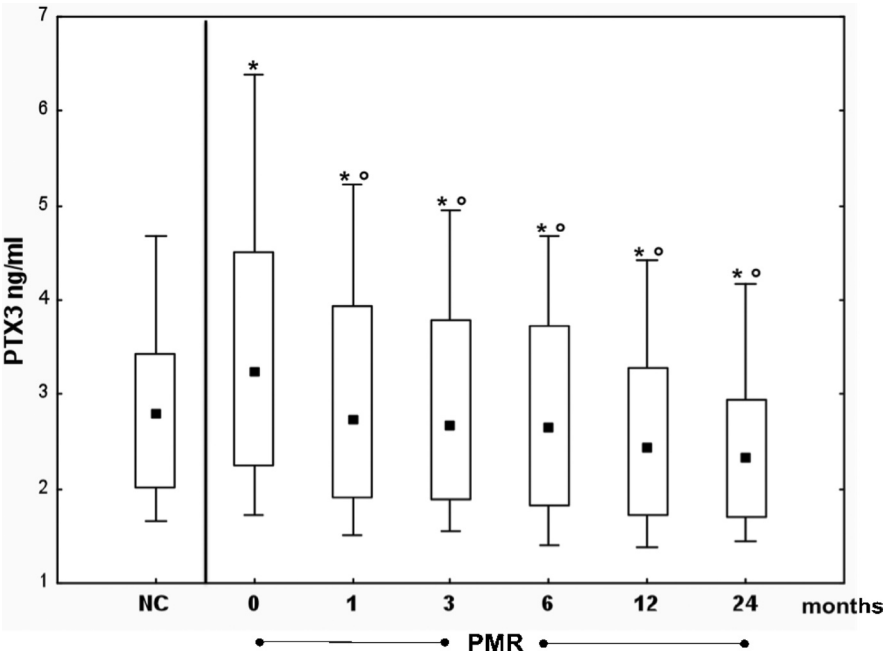

Fig.1. Serum concentrations of long pentraxin PTX-3 in the normal control group (NC) and in patients with polymyalgia rheumatica (PMR) at diagnosis and during corticosteroid treatment. Boxes show 25th and 75th percentiles. Squares within boxes show medians. Vertical lines below and above boxes show 10th and 90th percentiles.
*Not significant compared to normal controls (NC)
°p<0.05 compared to disease onset samples.

Results

No difference in PTX3 serum levels was observed between NC and PMR either at disease onset or during follow-up (Fig. 1). Conversely, a significant decrease of PTX3 levels compared to disease onset samples was obtained at all follow-up times (Fig. 1).

No significant correlation was found between the number of relapses and PTX3 concentrations at diagnosis and during follow-up period. In addition, dividing the patients according to the outcome (no relapse and at least one relapse), we did not observed significant differences in PTX3 levels among classes.

Finally, no significant differences were found at disease onset between PMR patients with or without the following clinical features: systemic symptoms (fever, anorexia, weight loss), hip involvement, neck involvement, pitting edema, peripheral synovitis. Furthermore, no significant correlation was obtained between duration of morning stiffness and serum levels of PTX3.

Discussion

Several proinflammatory cytokines have been investigated in PMR in order to identify key molecules in driving pathogenic mechanism features and which could also be useful in recognising subsets of patients with chronic, relapsing disease (3, 8, 9). The majority of these studies underline the pivotal role of IL-6 in PMR. IL-6 is the major inducer of the classic short pentraxin CRP, which indeed is commonly elevated in PMR patients. Conversely, in the present study, prototype of the long pentraxin family PTX3 was found not significantly different in PMR patients compared to normal subjects, either at disease onset or during corticosteroid treatment.

PTX3 systemic levels have been shown to be elevated in patients with various vascular and inflammatory disorders including acute myocardial infarction (10), vasculitis (11), systemic sclerosis (12) and psoriasis (13) and in these contexts, PTX3 serum levels correlate with the clinical outcome and disease activity.

In contrast, in other chronic rheumatic diseases such as rheumatoid arthritis (11) and systemic lupus erythematosus (11, 14, 15) no elevation of PTX3 serum levels has been reported.

In PMR, IL-1 and TNF, major inflammatory inducer of PTX3 are barely produced whereas IL-6, that is an inefficacious stimulus for PTX3 production, significantly increases in PMR patients with active diseases (2, 8). This cytokine pattern could hamper PTX3 production.

In RA, synoviocytes constitutively express high level of PTX3 and joint fluid from RA patients contained elevated levels of PTX3 (16), nonetheless serum concentrations remain in normal range in rheumatoid patients (11).

In PMR, histological, arthroscopic, radioisotopic, ultrasound and magnetic resonance imaging studies reported mild to moderate joint synovitis and/or bursitis (17) and although no knowledge on PTX3 joint expression is yet available, we may hypothesise that, similarly to RA, even if local overexpression occurs, no evidence is detectable at systemic level.

Population based studies have shown that 16–21% of patients with PMR have giant-cell arteritis (GCA), and prompt recognition of GCA is important because blindness may occur without premonitory symptoms (17).

GCA and PMR are often overlapping conditions and PMR may be the initial manifestation of a silent (subclinical) GCA (18). Indeed, a population-based study disclosed subtle clinical differences between isolated PMR and PMR in the setting of GCA. Lower ESR values and lower incidence of anemia and trombocytosis are found in patients with isolated PMR compared to those with PMR associated to biopsy-proven GCA (19). These observations suggested that severe abnormalities associated with the inflammatory response in PMR might have prognostic value for more severe disease, which may be linked to the presence of GCA (19). Therefore, a study trying to assess differences of serum levels of PTX3 between isolated PMR and PMR associated to GCA is warranted.

Patients with small-vessel vasculitis have significantly higher concentrations of PTX3 compared to healthy controls (11) and if this condition could be confirmed also in GCA patients, PTX3 could represent a diagnostic

marker that allows to differentiate PMR patients with GCA from patients with 'pure' PMR.

In conclusion, our study shows that IL-6 independent acute phase protein PTX3 does not increase significantly in active PMR. Further studies on patients with GCA could evaluate whether large vessel involvement may be associated to high circulating PTX3.

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References

1. SALVARANI C, CANTINI F, HUNDER GG: Polymyalgia rheumatica and giant-cell arteritis. *Lancet* 2008; 372: 234-45.
2. SALVARANI C, CANTINI F, NICCOLI L *et al*.: Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: a prospective followup study. *Arthritis Rheum* 2005; 53: 33-8.
3. MARTINEZ-TABOADA VM, ALVAREZ L, RUIZSOTO M, MARIN-VIDALLED MJ, LOPEZ-HOYOS M: Giant cell arteritis and polymyalgia rheumatica: role of cytokines in the pathogenesis and implications for treatment. *Cytokine* 2008; 44: 207-20.
4. PULSATELLI L, BOIARDI L, PIGNOTTI E *et al*.: Serum interleukin-6 receptor in polymyalgia rheumatica: a potential marker of relapse/recurrence risk. *Arthritis Rheum* 2008; 59: 1147-54.
5. BOTTAZZI B, DONI A, GARLANDA C, MANTOVANI A: An integrated view of humoral innate immunity: Pentraxins as a Paradigm. *Annu Rev Immunol* 2010; 28: 157-83.
6. HEALEY LA: Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. *Semin Arthritis Rheum* 1984; 13: 322-8.
7. MULLER B, PERI G, DONI A *et al*.: Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. *Crit Care Med* 2001; 29: 1404-7.
8. ALVAREZ-RODRIGUEZ L, LOPEZ-HOYOS M, MATA C *et al*.: Circulating cytokines in active polymyalgia rheumatica. *Ann Rheum Dis* 2010; 69: 263-9.
9. DOCKEN P: Polymyalgia rheumatica can recur years after discontinuation of corticosteroid therapy. *Clin Exp Rheumatol* 2009; 27 (Suppl. 52): S25-7.
10. PERI G, INTRONA M, CORRADI D *et al*.: PTX3, a prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. *Circulation* 2000; 102: 636-41.
11. FAZZINI F, PERI G, DONI A *et al*.: PTX3 in small-vessel vasculitides: an independent indicator of disease activity produced at sites of inflammation. *Arthritis Rheum* 2001; 44: 2841-50.
12. IWATA Y, YOSHIZAKI A, OGAWA F *et al*.: Increased serum pentraxin 3 in patients with systemic sclerosis. *J Rheumatol* 2009; 36: 976-83.
13. BEVELACQUA V, LIBRA M, MAZZARINO MC *et al*.: Long pentraxin 3: a marker of inflammation in untreated psoriatic patients. *Int J Mol Med* 2006; 18: 415-23.
14. MANTOVANI A, GARLANDA C, BOTTAZZI B *et al*.: The long pentraxin PTX3 in vascular pathology. *Vascul Pharmacol* 2006; 45: 326-30.
15. KIM J, KOH JK, LEE EY, PARK JA *et al*.: Serum levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and pentraxin 3 (PTX3) as markes of infection in febrile patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2009; 27: 773-8.
16. LUCHETTI MM, PICCININI G, MANTOVANI A *et al*.: Expression and production of the long pentraxin PTX3 in rheumatoid arthritis (RA). *Clin Exp Immunol* 2000; 119: 196-202.
17. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Polymyalgia rheumatica. *Best Pract Res Clin Rheumatol* 2004; 18: 705-22.
18. GONZÁLEZ-GAY MA: Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. *Semin Arthritis Rheum* 2004; 33: 289-93.
19. GONZÁLEZ-GAY MA, GARCÍA-PORRÚA C, VÁZQUEZ-CARUNCHO M: Polymyalgia rheumatica in biopsy proven giant cell arteritis does not constitute a different subset but differs from isolated polymyalgia rheumatica. *J Rheumatol* 1998; 25: 1750-5.