The long pentraxin PTX-3 in prevalent hemodialysis patients: associations with comorbidities and mortality


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Summary

Background: Pentraxin (PTX)-3, a new candidate marker for inflammation is expressed in a variety of cell types. Recently, we have shown that increase in PTX-3 level is associated with clinical outcome in incident CKD stage 5 patients at start of renal replacement therapy. However, no data are available on PTX-3 and its relationship with clinical outcome in prevalent dialysis patients.

Methods: We analyzed plasma PTX-3 concentrations in relation to comorbidities (Davies score), protein-energy wasting (PEW) and inflammation markers in 200 prevalent hemodialysis (HD) patients, aged 64±14 years, who had been on HD treatment for a median period of 36 months. Survival (42 months) was analyzed in relation to PTX-3 levels (high PTX-3 tertile vs. low two tertiles).

Results: Plasma PTX-3 correlated positively with C-reactive protein and interleukin-6, and negatively with s-albumin and fetuin-A. Patients with cardiovascular disease (CVD) and PEW had higher levels of PTX-3 than their counterparts and PTX-3 was associated with comorbidity score. In multiple logistic regression analysis, the high comorbidity score and PEW were the significant predictive variables of high PTX-3. In unadjusted analysis high PTX-3 was significantly associated with all-cause mortality. After adjustment for sex, age, dialysis vintage, comorbidity score, PEW and CRP using the multivariate Cox regression analysis, death rate was still significantly higher in patients with high PTX-3 (HR 1.7; CI 1.1–2.7, P=0.03).

Conclusion: Markedly increased levels of PTX-3 were found in HD patients with signs of CVD and PEW. In addition, the concentration of PTX-3 was associated with inflammation markers and comorbidity score. Our data also shows that high PTX-3 level was independently associated with all-cause mortality.

Introduction

The lifespan of chronic kidney disease (CKD) patients is short, and cardiovascular disease (CVD) is recognized as a main life-limiting problem and accounts for premature death in >50% of dialysis patients.1 Traditional risk factors cannot alone explain the unacceptable high prevalence and incidence of CVD in this population.2 The search for nontraditional risk factors that may be involved in the pathogenesis of CVD in CKD patients has been an area of intense investigation. During the last decade chronic inflammation has become known as a culprit in a wide range of pathologic states, such as CVD, obesity, diabetes mellitus (DM), protein-energy wasting (PEW), and even aging.3,4 In this regard, it is becoming increasingly recognized that CKD is associated with a state of persistent
microinflammation\textsuperscript{5} that seems to be linked with oxidative stress, endothelial dysfunction, vascular calcification and PEW.\textsuperscript{2,3} Indeed, several inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin (IL)-6, are robust predictors of outcome in this patient population.\textsuperscript{4} In addition, the plasma levels of pentraxin (PTX)-3, a newly discovered acute phase protein, is associated with CVD and mortality in incident CKD 5 patients starting dialysis treatment with a prognostic power of similar magnitude as IL-6.\textsuperscript{6} Interestingly, we could recently demonstrate in two cohorts of albuminuric patients (incident dialysis patients and type-2 DM albuminuric patients but with normal renal function), that PTX3 was significantly and independently associated to the levels of albuminuria and flow mediated dilatation,\textsuperscript{7} highlighting the relevance of PTX-3 and supporting the growing body of evidence relating the appearance of albuminuric manifestations with increased CVD risk.\textsuperscript{8,9}

Pentraxin is a family of proteins considered to be markers of the acute phase of inflammation.\textsuperscript{10,11} PTX-3 is a long pentraxin structurally related to, although distinct from, classic short pentaxins, such as CRP and serum amyloid P. PTX-3 is the first cloned long pentraxin as an IL-1\textbeta-inducible gene in endothelial cells\textsuperscript{12} and a tumor necrosis factor (TNF)-\alpha stimulated gene (TSG14) in fibroblasts.\textsuperscript{13} After PTX-3 was cloned, other long pentraxins were identified.\textsuperscript{14} PTX-3 expression occurs in a variety of cell types, including endothelial cells, mononuclear phagocytes, dendritic cells, smooth muscle cells, fibroblasts, adipocytes and epithelial cells in response to inflammatory cytokines and Toll-like receptor engagement.\textsuperscript{15–17} Studies in transgenic mice suggest an important role for PTX-3 in the regulation of inflammatory reactions and innate immunity.\textsuperscript{18,19} This is supported by studies showing the ability of PTX-3 to bind to the C1q component of the complement cascade\textsuperscript{20} and to participate in the clearance of apoptotic cells.\textsuperscript{21} In addition, because PTX-3 is produced from vascular endothelial cells and macrophages, PTX-3 levels may directly reflect the inflammatory status.\textsuperscript{22} However, still much remains to be learned about its biological function. It has been reported that PTX-3 is elevated in critically ill patients, with a gradient from systemic inflammatory response syndrome to septic shock,\textsuperscript{23} and in several other diseases, such as CKD,\textsuperscript{6,24} myocardial infarction, atherosclerosis, vasculitis, lung disease, eclampsia, rheumatoid arthritis and psoriasis.\textsuperscript{15–17} Since a state of persistent low-grade inflammation is a common feature in prevalent hemodialysis (HD) patients,\textsuperscript{25} and has been suggested to enhance cardiovascular risk and mortality,\textsuperscript{3} we studied plasma PTX-3 in relation to comorbidities and mortality in this patient group.

Patients and methods

Patients

The study was performed at the Karolinska University Hospital in Stockholm (including four dialysis units) and at Uppsala Academic Hospital in Uppsala. This is a post hoc analysis from a cross-sectional study with a follow-up that originally aimed at investigating the variability of inflammatory markers in patients undergoing prevalent hemodialysis (n = 254) over time. Recruitment of the patients occurred from October 2003 through March 2004. All patients who were currently receiving regular therapy at any of the units were invited to participate; six patients declined and one patient with HIV infection was excluded. The 247 eligible patients were then followed for 12 weeks, during which time the concentration of CRP was measured weekly. Because the aim of the original study was to investigate the variability of inflammatory markers, patients were excluded from the study if available for fewer than six of these weekly CRP measurements. Eleven patients were excluded because insufficient baseline clinical information was available, seven were excluded because of insufficient CRP measurements and one patient died. The remaining 228 patients were further followed for assessment of overall and cardiovascular mortality in relation to biochemical markers. In the present study, 28 patients were further excluded because data on PTX-3 was not available, leaving 200 patients included in this analysis. The current study is limited only to baseline values.

Each patient’s medical chart was thoroughly reviewed by a nephrologist (S.S.-J.), who extracted data pertaining to underlying kidney disease, history of CVD, other comorbid conditions and survival data. Thus, the causes of renal failure were diabetic nephropathy (n = 33), chronic glomerulonephritis (n = 42), polycystic kidney disease (n = 27), hypertensive nephrosclerosis (n = 15), pyelonephritis (n = 15), interstitial nephritis (n = 7), amyloidosis (n = 3), other (n = 36) or unknown (n = 22).

Comorbidities score was assessed according to Davies comorbidity index.\textsuperscript{26} The index includes seven specified comorbidity domains for patients receiving renal replacement therapy: malignancy, ischemic heart disease, peripheral vascular disease (including cerebrovascular disease), left ventricular heart failure, DM, systemic collagen vascular disease and other significant pathology...
Each patient. Sweden, and informed consent was obtained from the Ethics Committee at Uppsala University Hospital, Uppsala, University Hospital, Stockholm and by the Ethics Committee of Karolinska Institutet at Huddinge University Hospital. Of patients, 67 (34%) were on lipid-lowering medication (statins). Of patients, 126 (63%) had clinical signs of ischemic cardiac disease, cerebrovascular disease, peripheral vascular disease and/or left ventricular dysfunction and were grouped as CVD. Of these 126 patients, 43 had one or more myocardial infarctions (defined by the presence of chest pain, confirmatory electrocardiograms and enzyme courses), 42 patients had experienced angina pectoris (stable or unstable), six patients had undergone percutaneous transluminal coronary angiography, 22 patients had undergone coronary artery by-pass graft and/or 43 had left ventricular dysfunction (based on ejection fraction, chest X-rays and/or typical clinical symptoms). Forty patients had suffered from cerebrovascular disease (stroke and/or history of transient ischemic attack). Thirty-four had clinical signs of peripheral atherothrombotic vascular disease and four patients had a history of an aortic aneurysm.

Patients were treated with HD three times a week (4–5 h per session) using bicarbonate dialysate and high-flux (26%) or low-flux (74%) dialysis membranes: 129 patients were dialysed with polyamide, 59 with polysulphone, 11 with cellulose membrane and one with a polyacrylonitrite membrane. The average Kt/V in these patients was 1.53 ± 0.33. Of patients, 117 (58%) had an arteriovenous fistula, 37 had a central dialysis catheter (19%) and 46 (23%) had a graft. Most patients were on antihypertensive medications (β-blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers), as well as other commonly used drugs in terminal CKD, such as phosphate and potassium binders, and vitamin B, C and D supplementation. Of patients, 67 (34%) were also on lipid-lowering medication (statins).

The study protocols were approved by the Ethics Committee of Karolinska Institutet at Huddinge University Hospital, Stockholm and by the Ethics Committee at Uppsala University Hospital, Uppsala, Sweden, and informed consent was obtained from each patient.

**Nutritional status assessment**

PEW was assessed by subjective global nutritional assessment (SGA) at the time of inclusion, concurrent with the drawing of blood samples by an investigator unaware of biochemical results. SGA includes six different components: three subjective assessments based on the patient’s history of weight loss, incidence of anorexia and incidence of vomiting, and three assessments that are performed by the evaluators and are based on the subjective grading of muscle wasting, the presence of edema and the loss of subcutaneous fat. Based on these assessments, each patient was given a score of 1–4, indicating normal, mild, moderate or severe PEW, respectively. PEW was defined as SGA score of 2–4, and patients meeting these criteria are grouped together as patients with PEW. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters.

**Laboratory analyses**

After collection of blood samples, plasma and serum were separated within 30 min and samples were kept frozen at −70°C pending analyses, if not analyzed immediately. Plasma PTX-3 concentration was measured by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Perseus Preteomics Inc., Japan). The serum levels of IL-6 and TNF-α were quantified on the Immulite* automatic analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum fetuin-A was measured by a sandwich immunoenzymometric assay using two polyclonal human fetuin-A antibodies (Epitope Diagnostics, Inc., San Diego, CA, USA). Serum cholesterol and triglyceride levels were analyzed by means of standard enzymatic procedures (Roche Diagnostics GmbH, Mannheim, Germany). High-density lipoprotein (HDL) cholesterol level was determined after precipitation of apolipoprotein (apo) B-containing lipoproteins by using phosphotungstic acid. Serum albumin (brom cresol purple method), high sensitive (hs)-CRP, creatinine, urea and hemoglobin were determined by routine procedures at the Department of Clinical Chemistry, Karolinska University Hospital Huddinge or Uppsala Academic Hospital.

**Statistical analyses**

All continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test before further statistical analysis. Normally distributed values presents as mean ± SD, whereas non-normally distributed values are presented as median (average). Categorical values are presented as number of patients and percent. Statistical significance was set at the level of *P* < 0.05. Comparisons between two groups were assessed for continuous variables with the Student’s unpaired *t*-test, Mann-Whitney test or χ²-test, as appropriate. Differences among three groups were analyzed by analysis of variance (ANOVA) using one-way ANOVA or Kruskal–Wallis test, as appropriate, followed by a
post hoc test if ANOVA was significant. Spearman’s rank correlation was used to determine correlations of PTX-3 concentration with other variables. Survival analyses used the Kaplan-Meier survival curve and the Cox proportional hazards model. The Cox proportional hazards model was used to examine survival differences after the analysis had been adjusted for potential confounding factors. A multiple logistic regression model was used to assess the odds ratios of the variables associated with high PTX-3 levels. All statistical analyses were performed with SAS statistical software (Version 9.1; SAS Institute, Inc., Cary, NC, USA).

**Results**

This study included 200 prevalent HD patients [91 (45%) females] with an average age of 64 ± 14 years and who have been on HD a median of 29 months (range 1–378 months). The HD patients had significantly higher median PTX-3 concentrations [10.6 (2.4–75.1) ng/ml] compared with our previous report on age-matched control subjects [1.8 (0.1–9.2) ng/ml], CKD 3–4 patients [2.2 (0.4–16) ng/ml] and incident dialysis (CKD5) patients [5.7 (0.9–64.3) ng/ml], using the same method for PTX-3 analysis.

The PTX-3 concentrations did not differ between males and females or between diabetic and non-diabetic patients (data not shown). There was no significant difference in PTX-3 concentration between HD patients using low-flux membranes and those who used high-flux membranes. Of patients, 94 (48%) with signs of PEW (SGA > 1) had significantly higher PTX-3 concentrations than patients with normal nutritional status [12.9 (5.2–75.1) ng/ml vs. 9.4 (2.4–70.0) ng/ml; P < 0.01]. Moreover, patients with CVD (63%) had significantly higher median PTX-3 concentrations than patients without clinically manifest CVD [12.1 (3.0–75.1) ng/ml vs. 9.9 (2.4–70.0) ng/ml; P < 0.01].

The PTX-3 concentration was associated with Davies comorbidity score (Figure 1) and patients with ‘high risk’ of comorbidities [16.1 (3.9–49.5) ng/ml] had significantly higher levels of PTX-3 (P < 0.01) compared with patients having ‘medium risk’ of comorbidities [11.4 (3.0–75.1) ng/ml] or patients with ‘low risk’ of comorbidities [8.1 (2.4–70.0) ng/ml].

In univariate analysis, the concentrations of PTX-3 were positively correlated with hsCRP (rho = 0.26, P < 0.0001), IL-6 (rho = 0.30, P < 0.0001) and negatively with s-albumin (rho = −0.38, P < 0.0001), fetuin-A (rho = −0.28, P < 0.0001) and s-creatinine (rho = −0.19, P < 0.01). There were no significant correlations between PTX-3 concentrations and age, vintage, TNF-α, fibrinogen and urea. Moreover, no association with lipids, calcium or phosphate was noted.

The patients were divided into tertiles with respect to low (2.4–8.1 ng/ml), medium (8.1–14.2 ng/ml) and high (14.6–75.1 ng/ml) PTX-3 concentrations. Table 1 shows that the patient in the 3rd tertile, compared with others, more often had PEW, had higher prevalence of CVD and higher Davies comorbidity score. Moreover, they had higher levels of hsCRP, IL-6 and lower s-albumin compared with the other tertiles. The patients in the 2nd tertile did not show significant differences from the patients in the 1st tertile except for BMI and s-albumin, which were significantly lower in the former group.

To determine which variables were significantly associated with high PTX-3 level, we created a multiple logistic regression model (Table 2) including sex, age, SGA and Davies comorbidity index. This analysis showed that high PTX-3 was significantly associated with high odds ratios for high comorbidity (Davies score) and PEW (SGA), but not sex or high age.

Survival was determined after a median follow-up of 31 (range, 3–42) months. There was no loss to follow-up. Within the follow-up period 78 (39%) patients died. Plasma PTX-3 concentrations were significantly (P < 0.0001) higher in non-survivors [14.5 (3.9–49.5) ng/ml] than in survivors [9.7 (2.4–75.1) ng/ml]. Across tertile categories, the percentages of deaths that occurred during the follow up were 32, 27 and 57%, respectively.
The death rate was significantly higher in patients within the 3rd tertile as compared with the other tertiles; whereas there was no significant difference in percentage of mortality between the patients in the 1st and 2nd tertiles. For this reason, further survival analysis was performed comparing the group within the 3rd tertile vs. the other two tertiles combined (Table 3).

In univariate analysis, the cumulative proportion of surviving patients in the highest PTX-3 tertile was lower than in those within the two lower tertiles (Table 3, model 1 and Figure 2). This significant difference in survival persisted after progressive adjustments for Davies comorbidity score (Table 3, model 2), age, gender, dialytic vintage and SGA (Table 3, model 3 and Figure 2) and even after adjustment for hsCRP (Table 3, model 4).

**Discussion**

To the best of our knowledge, this is the first study investigating PTX-3 in relation to comorbidities and mortality in a large group of prevalent HD patients. The study shows that HD patients had markedly higher concentrations of plasma PTX-3 compared with our previous report on incident CKD 5 patients starting RRT. Increase in PTX-3 level was associated with CVD, PEW, inflammation markers and other comorbidities in HD patients. Moreover, PTX-3 was identified as an independent mortality risk factor in these patients. Because of the study design only correlative associations have been presented and thus, this study cannot provide mechanistic explanations.
Our study showed that HD patients had markedly higher PTX-3 concentrations than normal individuals, in agreement with the findings by Boehme et al.24 We could recently observe that both HD and peritoneal dialysis (PD) patients have higher PTX-3 levels than non-dialyzed CKD 5 patients.28 In contrast, Boehme et al.24 showed that the concentrations of PTX-3 in PD and pre-dialysis patients were not different from the healthy subjects. Clearly, this observation may need confirmation in larger cohorts. The increase in PTX-3 concentration in HD could be due to an increase induced by the HD procedure. It has been shown that a single HD session increased PTX-3, and that this raise was not associated with the changes in CRP or IL-6 concentrations.24,28 However, in this study we could not find an association between PTX-3 levels and the total time on dialysis therapy (vintage). Moreover, PTX-3 levels did not differ between HD patients using low-flux or high-flux membranes.

PTX-3 is a recently described inflammatory molecule that belongs to the same family as CRP. In agreement with, and confirming, our previous findings in incident dialysis patients,6 the current study reports strong association between PTX-3 and CRP in prevalent HD patients. In contrast, Peri et al.29 did not find any association between PTX-3 and CRP in a group of non-renal patients with acute myocardial infarction. They proposed that PTX-3 may represent a rapid marker for primary local activation of innate immunity and inflammation and the increase in PTX-3 is due to production of this molecule by cardiac myocytes after myocardial

Table 3  Univariate and multivariate Cox regression analysis for all-cause mortality in 200 prevalent hemodialysis patients according to baseline PTX-3 values

<table>
<thead>
<tr>
<th>PTX-3, high tertile vs. others</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1. Unadjusted</td>
<td>2.38</td>
<td>1.52</td>
<td>3.72</td>
</tr>
<tr>
<td>Model 2. Adjusted for comorbidities (Davies score)</td>
<td>1.87</td>
<td>1.18</td>
<td>2.96</td>
</tr>
<tr>
<td>Model 3. Adjusted for comorbidities (Davies score), age (median), gender, dialytic vintage (&gt;2 years) and wasting (SGA &gt; 1)</td>
<td>1.65</td>
<td>1.03</td>
<td>2.63</td>
</tr>
<tr>
<td>Model 4. Adjusted for comorbidities (Davies score), age (median), gender, dialytic vintage (&gt;2 years), wasting (SGA &gt; 1) and inflammation (hsCRP &gt; 10 mg/l)</td>
<td>1.67</td>
<td>1.04</td>
<td>2.68</td>
</tr>
</tbody>
</table>

The models report hazard ratio (HR) and 95% CI.

Figure 2. Probability of survival rate of 200 prevalent hemodialysis patients during 42 months of follow-up with regard to all-cause mortality in relation to plasma pentraxin (PTX)-3. In an unadjusted analysis, patients with high PTX-3 (highest tertile) concentrations had a worse survival than the patients with low PTX-3 (the lower two tertiles combined) concentrations. After adjustment for age, gender, dialysis vintage, PEW and comorbid score (Davies score) the survival rate for patients with high PTX-3 still was worse.

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injury. However, the same group showed an association between PTX-3 and CRP in critically ill patients with systemic inflammation. In accordance, the association between PTX-3 and CRP in our study could be explained by the fact that CKD patients are characterized by state of systemic low-grade inflammation and increase of PTX-3 in such patients could be a result of exposure of diversity of tissues to inflammatory stimuli induced by the unphysiologic uremic milieu.

To our surprise, whereas no correlation between circulating PTX-3 and TNF-α was observed, there was a rather strong correlation between IL-6 and PTX-3. Unlike CRP (produced in the liver and induced primarily by IL-6), PTX-3 gene and protein expression is induced by TNF-α or IL-1 in multiple human tissue cells. In contrast, IL-6 is generally considered a poor inducer for PTX-3 production. Therefore, an association between PTX-3 and TNF-α rather than an association between PTX-3 and IL-6 is expected. Nonetheless, it was reported that PTX-3 expression in Castleman’s disease is up regulated by IL-6 and viral IL-6 induces expression of PTX-3 in Kaposi’s sarcoma cells. These findings may suggest that IL-6 has a role in PTX-3 expression as well. On the other hand, PTX-3 may share the characteristic of being produced and released in response to systemic inflammatory response and all acute-phase reactants and inflammatory mediators are interrelated. Indeed, PTX-3 was also associated with s-albumin and fetuin-A (both are negative acute-phase reactants). The present data also demonstrate a high PTX-3 level in HD patients with PEW, a finding not surprising in view of the documented strong associations between inflammation and PEW in CKD.

A major aim of the present study was to evaluate the relationship between circulating PTX-3 levels and clinically manifest CVD in HD patients. Expression of PTX-3 pattern is tissue specific, as in cells of atherosclerotic lesions, like endothelial cells, smooth muscle cells, macrophages and neutrophils. Of note, whereas Rolph et al. showed strong PTX-3 expression in macrophages and endothelial cells in advanced atherosclerotic lesions, no PTX-3 expression was observed in arteries without atherosclerotic lesions. In addition, PTX-3 binds to the angiogenic growth factor (fibroblast growth factor-2) and modulates its action. Also, it has been shown that PTX-3 plasma levels are increased in vascular disorders including unstable angina pectoris, myocardial infarction and small vessel vasculitis and correlate with disease activity. In accordance, our results show a significantly higher median PTX-3 level in HD patients with clinical evidence of CVD, which confirms recent findings in chronic HD patients and CKD 5 patients close to start dialysis.

The current study also shows that PTX-3 concentration is associated with comorbidities (Davies score). The etiology of inflammation in CKD patients is multifactorial. Increased inflammatory markers reflect tissue damage, and, therefore, they may also represent the degree of severity of pre-existing cellular or organ damage of diverse nature. Thus, the association between PTX-3 and comorbidities is not surprising because inflammatory markers may definitely reflect the presence of comorbidity(ies) in these patients. One of the main domains in the evaluation of comorbidity score is diabetes. However, in this study, we found that in diabetic patients undergoing regular HD the median PTX-3 did not differ from non-diabetic HD patients, a finding confirming recent data in CKD 5 patients.

In this study, we found that patients in the 3rd PTX-3 tertile had a 1.7-fold increased risk for mortality independent of potential confounders, including age, sex, dialysis vintage, PEW and comorbidities. In a study of 748 non-renal patients, PTX-3, measured in parallel to established markers including CRP, emerged as an independent predictor of mortality and the risk of dying after myocardial infarction increased by 2.3% with every 1 ng/ml increase in PTX-3. In accordance, we have recently reported that PTX-3 was independently associated with all-cause mortality in incident dialysis patients. It remains to be elucidated whether this association with outcome actually reflects a role in the pathogenesis of vascular damage or if elevated PTX-3 mainly reflects a poor immune response unable to mitigate the sources of inflammation. In this study, cardiovascular mortality was not evaluated because the mortality classification was based on death certificates, which often are inappropriate for evaluation of cardiovascular death.

Several limitations should be addressed when evaluating the relevance of our findings. First, although a large cohort, we are still limited by the sample size of our material. Second, a single plasma sample at a certain time point may fail to reflect the natural course of the process studied. Third, the presence of a wide range of comorbid conditions in a population on multiple drugs represents a further limitation on the interpretation of the data. Fourth, although Davies score is intimately linked to mortality, it is still not a perfect way of adjusting for baseline disease, allowing a potential reverse causality in this setting. Finally, this study comprises a cohort of prevalent patients, including to some extent a group of survivors from CKD.
In summary, this study shows that high levels of PTX-3 were found in prevalent HD patients with CVD and PEW. Furthermore, this study also showed associations of PTX-3 with comorbidities. As PTX-3 predicts mortality independent of age and comorbidities in prevalent HD patients, further designed studies addressing the clinical implication and pathogenic mechanisms of this long pentraxin are warranted.

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Conflict of interest: None declared.

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