SERUM uPAR CONCENTRATION IN PATIENTS WITH A DEPRESSIVE DISORDERS - A PRELIMINARY STUDY

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Dear editor,

Depressive disorder is a complex mood disorder, associated with an inflammatory response. Cytokines, including tumour necrosis factor (TNF)-α and interferon (IFN)-ɣ, are implicated in depressive symptom development (Petralia et al. 2020). Inflammatory processes are accompanied by extravascular deposition and breakdown of fibrin. The possible contribution of the fibrinolytic system to the development of depression and the link between fibrinogen system molecules and inflammation-related cytokines are described in a review by Idell et al. (2017)

The urokinase plasminogen activator receptor (uPAR) level is associated with the activation of an immune-inflammatory reaction and this has been observed in inflammatory-related disease (Portelli et al. 2017). Below, a new report on uPAR in recurrent depressive disorder (rDD) is provided.

Forty-one patients with rDD and 36 healthy subjects were studied. The number of depressive episodes, duration of the disease and number of hospitalizations were recorded for each patient. Patients and control subjects with other psychiatric Axis I and II diagnoses as well as those diagnosed with an (auto)immune, chronic and acute inflammatory disease were excluded from the study. Participation in the study was voluntary. The study conduct was reviewed and approved by the local bioethics committee. Written informed consent was obtained from all the participants of the study.

Peripheral blood samples were drawn from the analysed subjects between 7:00 and 9:00 AM in the morning, after an all-night fast. Human enzyme-linked immunosorbent (ELISA) assays were used to detect protein levels in the serum samples; uPAR, TNF-α, IFN-ɣ ELISA Kit (R&D Systems, INC. MIN USA, respectively: cat. No. DUP00, DTA00C, DIF50). Serum uPAR TNF-α, IFN-ɣ protein values were presented as pg/ml.

Statistical analysis was carried out using Statistica 13.0. We used the nonparametric Mann-Whitney U test to compare data between the subjects with rDD and controls. Correlations between quantitative variables were analysed with Spearman's rank correlation. Statistical significance was defined as $p<0.05$ for all the analyses.

The age presented as median with lower/upper quartile was not significantly different between the patient group [42(30/48)] and the control group [29.5(26/43)]; p=0.053; No significant differences were observed with respect to gender distribution (p=0.94, χ^2=0.01).

There were differences for uPAR between rDD patients 450.26 (425.71/498.06) and control 376.62 (331.49/404.40); p<0.0001. A statistically significant difference was also found with respect to the levels of TNF-α between patients with rDD 11.25 (10.22/11.51 and controls 4.77 (4.10/5.42); p<0.0001. These results are applicable to both sexes: for uPAR [rDD women - 474.15 (437.34/544.20) vs. control women - 376.62 (330/396), rDD male 443.80 (423.13/460/60) vs. control male 390.83 (361.11/419.25); p<0.0001), for TNF-α [rDD women - 10.25 (10.09/11.42) vs. control men 4.57 (4.09/5.11); p<0.0001). There were no differences between rDD female and rDD male, both for uPAR and TNF-α, p>0.05. No significant difference between patients and controls was observed with respect to the level of IFN-ɣ. A correlation between uPAR levels and the number of hospitalizations and a correlation between uPAR and TNFα levels were observed in women with depression. A detailed analysis of all correlations is presented in Table 1.

Table 1. Correlations between age, uPAR concentrations and selected clinical feature and parameters (Spearman correlation p<0.05)

Clinical feature and parameters	rDD patients
Age & HDRS final	r=0.49; p=0.001
Age & duration of the disease	r=0.38; p=0.02
	rDD women n= 22
Age & HDRS baseline	r=0.47; p=0.03
Age & HDRS final	r=0.53; p=0.01
Age & duration of the disease	r=0,54; p=0.01
Age & number of depressive episodes	r=0.58; p=0.005
uPAR & number of hospitalization	r=-0.44; p=0.04
uPAR & TNF-α	r=0.62; p=0.002
	rDD men n=19
Age & DRS final	r=0.52; p=0.02

rDD – recurrent depressive disorders; HDRS – Hamilton depression rating scale: uPAR – urokinase plasminogen activated receptor; TNF-α - tumor necrosis factor; α, r – correlation coefficient; p – level of statistical significance

Data from studies of depressive disorders found increased uPAR and/or suPAR concentrations in patients with a depressive disorder compared to healthy subjects. A possible explanation for the increase in uPAR/suPAR levels is inflammation. While uPAR is a nonspecific factor involved in inflammation and increased concentrations are seen in a variety of diseases, it may nevertheless be useful as a screening tool in patients with psychiatric diseases. Baseline expression of uPAR is generally low in humans, but increased concentration of uPAR assists with inflammation provoked by fibrin deposition (Leth et al. 2021). Increase in uPAR is biologically significant, as uPAR participates in stimulation of cytokine (interleukin) Il-1β, IL-6, and TNF-α (Rasmussen et al. 2021).

The mechanism that can explain the increase and correlation between uPAR and TNF-α levels in depressive

patients may be related to uPAR signalling. Various immune cell types (monocytes/macrophages, neutrophils) express high amounts of uPAR, which has the potential to activate transcription factors such as nuclear factor kappa B (NFκB) and promote the secretion of cytokines, including TNF-α (Dinesh & Rasool 2018). On the other hand, cytokines affect different genes, for example, TNF-α-driven uPAR mRNA expression is observed.

In conclusion, a higher level of serum uPAR observed in patients when compared to controls suggests the role of uPAR in depressive disorder and related processes. A correlation between uPAR and TNFα serum levels in female with depressive disorder may confirm a link between inflammation and the activation of the fibrinolytic system and is further suggestive of a pleiotropic role of these molecules in depressive disorder. Additional studies, including those enrolling a larger sample size of patients, are needed to confirm these findings and to investigate the potential impact of confounding factors on serum uPAR levels.

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