HSPI The Open Access Publisher

IDA INSIGHTS ON THE DEPRESSION AND ANXIETY
ISSN 2640-2882

Research Article

Clinical and immunological characteristics of depressive patients with a clinical high risk of schizophrenia

Omelchenko MA, Zozulya SA, Kaleda VG and Klyushnik TP*

FSBSI "Mental Health Research Centre", Moscow, Russian Federation

Abstract

Objective: To study clinical and immunological characteristics of depressive patients with high clinical risk of schizophrenia.

Materials and methods: We examined 30 depressive patients with attenuated positive symptoms (APS), which indicates a clinically high risk of schizophrenia, 20 depressive patients without APS and 27 healthy volunteers with no mental disorders. APS identified according to the presence of three or more scores on at least one of the following items on the Scale of Prodromal Symptoms (SOPS) positive symptoms subscale: P1 (Unusual thought content/Delusional ideas), P2 (Suspiciousness/Persecutory ideas) and P4 (Perceptual abnormalities/Hallucinations). The psychometric assessment was carried out on the Hamilton Depression Rating Scale (HDRS), SOPS, and the Scale for Assessment of Negative Symptoms (SANS). The activity of leukocyte elastase (LE) and α1-proteinase inhibitor (α1-PI), the autoantibodies to neoantigens S100B and myelin basic protein, and the ratio of LE and α1-PI activity or Leukocyte Inhibitory Index (LII) were determined.

Results: The activity of inflammatory markers LE and α1-PI was increased in patients in both clinical groups compared with controls. In the total group of patients, the associations between LII and the score on the positive subscale SOPS, and between LII and the score on the negative subscale SOPS and SANS scale with the most pronounced association with the SANS subscales «Affective Flattening or Blunting» and «Alogia» were established.

Conclusion: The identified correlations between immune response features and positive and negative symptoms in depressive patients may have prognostic value for establishing a high risk of schizophrenia.

More Information

Submitted: February 20, 2023
Approved: March 02, 2023
Published: March 03, 2023

How to cite this article: Omelchenko MA, Zozulya SA, Kaleda VG, Klyushnik TP. Clinical and immunological characteristics of depressive patients with a clinical high risk of schizophrenia. Insights Depress Anxiety. 2023; 7: 001-003.

DOI: 10.29328/journal.ida.1001034

https://orcid.org/0000-0001-5148-3864

***Address for correspondence:** Klyushnik TP, FSBSI "Mental Health Research Centre", Moscow, Russian Federation, Email: klushnik2004@mail.ru

Keywords: First depressive episode; Clinical high risk of schizophrenia; Attenuated positive symptoms; Inflammatory markers; Leukocyte inhibitory index

Introduction

Currently, the focus of researchers is on finding diagnostic biomarkers that are able not only to confirm the presence of the mental disorder but also to identify its stages and have a predictive value for further courses and outcomes. First of all, this concerns such a highly disabling disorder as schizophrenia, whose prevention has long been a subject of interest. More recently, a focus group has been identified that can serve as a model for the early prodromal stage of schizophrenia: these are young patients seeking psychiatric help for the first depressive episode with attenuated positive symptoms (APS), allowing to establish a clinical high risk of schizophrenia [1]. The study of the biological characteristics of such patients opens up opportunities for understanding the pathogenetic mechanisms of schizophrenia and the development of methods for its primary prevention.

Objective

To study clinical and immunological characteristics of depressive patients with high clinical risk of schizophrenia.

Materials and methods

We examined 30 young patients (19.3 ± 2.2 years) hospitalized in the Mental Health Research Centre with the first depressive episode (diagnoses according to ICD-10: F32.1, F32.2, F32.28, F32.8) with APS identified according to the presence on the three or more scores on at least one of the following items on the SOPS positive symptoms subscale: P1 (Unusual thought content/Delusional ideas), P2 (Suspiciousness/Persecutory ideas) and P4 (Perceptual abnormalities/Hallucinations), which allowed to establish a clinical high risk of schizophrenia [2].

The comparison group consisted of 20 patients comparable in age and gender to patients hospitalized in the clinic with the first depressive episode (the same diagnoses according to ICD-10) without APS. The control group included 27 healthy volunteers without mental disorders. Non-inclusion criteria: comorbid mental pathology, clinically significant chronic somatic, neurological, and acute infectious diseases. The psychometric assessment was carried out as follows: the

severity of depressive symptoms was rated according to the Hamilton Depression Rating Scale (HDRS) and the severity of APS was assessed using the Scale of Prodromal Symptoms (SOPS). The negative symptoms were additionally determined on the Scale for Assessment of Negative Symptoms (SANS). For more accurate verification of negative symptoms, additional SANS subscales «Affective Flattening or Blunting», «Alogia», «Avolition – Apathy», «Anhedonia – Asociality» and «Attention» were used.

There were significant differences between patients with APS and without APS on the SOPS and SANS scales and almost all their subscales (except general symptoms which indicate only the severity of mental disorder) in the absence of differences on the HDRS scale. This indicates that clinical differentiation between depressive patients with a clinically high risk of schizophrenia and without it is possible (Table 1).

The markers of systemic inflammation the activity of leukocyte elastase (LE) and α1-proteinase inhibitor (α1-PI), and also the autoantibodies (aAbs) to neuroantigens S100B and myelin basic protein (MBP) were detected in blood plasma using certified standard kits produced by the Biopharmtest Co, LLC, Russia (http://www.biopharmtest.ru). The enzymatic activity of the LE was determined by the spectrophotometric method using a specific substrate N-tert-butoxy-carbonyl-alanine-β-nitrophenyl ether (BOC-Ala-ONp) (Sigma). The functional activity of the LE inhibitor, α1-proteinase inhibitor, and α1-PI was assessed using a unified enzymatic method based on the interaction of the inhibitor with trypsin. N-α-benzoyl-L-arginine ethyl ether hydrochloride (BAEE) (ICN Biomedical Inc) was used as a substrate. The quantitative determination of antibodies to the S100B protein and MBP (Sigma) was carried out by the method of standard enzyme-linked immunosorbent assay [3].

LE can exhibit significant destructive potential against the vascular endothelium. In the case of brain damage, it can disrupt the permeability of the blood-brain barrier vessels, contributing to secondary metabolic brain damage [4]. α1-PI creates conditions for limiting the focus of inflammation and/or destruction [5]. The ratio of LE and α1-PI activity or leukocyte inhibitory index (LII) [6] was also calculated. We detected aAbs to S100B protein, which is a Ca2+-binding protein of nervous tissue and a trophic factor for serotonergic neurons that enhances the migratory activity of neuroblasts, and the aAbs to MBP, a structural protein involved in the organization of myelin assembly of nerve fibers [7].

Our previous studies have shown that the first episode of schizophrenia is accompanied by a marked increase in the activity of both inflammatory and immune markers (the level of aAbs to the neuroantigen S100B) and the correlation with the severity of psychopathological symptoms on the PANSS scale, which confirms the involvement of inflammatory mechanisms in the pathogenesis of schizophrenia [8].

Results

The following results in inflammatory and autoimmune plasma markers were obtained (Table 2).

A significant increase in LE and α1-PI activity ($p < 0.01$, $p < 0.001$) in patients with APS and in the comparison group compared with the control was detected. The leukocyte inhibitory index in both groups of patients was lower ($p < 0.01$) than in the control (6.45 [5.85;6.70]). There were no inter-group differences in the level of aAbs to neuroantigens.

In the total group of patients, a direct correlation between the average total score on the HDRS scale with LII ($r = 0.502$; $p = 0.0002$) was established, which confirms the association between the activity of the immune response and the severity of depression.

A comparative analysis of immunological indicators with the results of psychometric scales showed a significant increase in LII due to an increase in both LE and α1-PI in depressive patients with high values on the positive SOPS subscale ($p < 0.05$). At the same time, a decrease in LII due to an insufficient increase in the activity of LE against the background of an increase in the functional activity of its inhibitor α1-PI ($p < 0.05$) in patients with high values on the

Table 1: HDRS, SOPS, and SANS scores in depressive patients with and without APS.

Indicators	Depression with APS ($n = 30$)	Depression without APS ($n = 20$)	p - value
Age (years) (mean value ± standard deviation)	19,5 ± 2,3	19,8 ± 2,7	0,690
HDRS, Me [IQR]	22 [19;27]	25 [19;28]	0,227
SOPS sum, Me [IQR]	44 [37;51]	35 [27,25;41,75]	0,000
SOPS subscale «Positive symptoms», Me [IQR]	9 [6;12]	4,5 [3;8,75]	0,000
SOPS subscale «Negative symptoms», Me [IQR]	17 [14,5:20]	14,5 [11;17]	0,000
SOPS subscale «Disorganization symptoms», Me [IQR]	8 [6;10]	5,5 [3,25;7]	0,000
SOPS subscale «General symptoms», Me [IQR]	10 [7;11]	10 [8;12]	0,526
SANS sum, Me [IQR]	45,5 [36,75;53]	24 [13;42]	0,000
SANS subscale «Affective Flattening or Blunting», Me [IQR]	14 [12;18]	5 [3;14]	0,003
SANS subscale «Alogia», Me [IQR]	7 [4,75;8]	3 [1;6]	0,005
SANS subscale «Avolition – Apathy», Me [IQR]	8 [7;9]	5 [5;8]	0,000
SANS subscale «Anhedonia – Asociality», Me [IQR]	12 [10;14,25]	8 [2;11]	0,025
SANS subscale «Attention», Me [IQR]	5 [3,75;6]	3 [2;4]	0,000

Note. $p < 0.05$ – statistically significant differences

Table 2: Inflammatory and autoimmune plasma markers in patients of identified clinical groups, Me [IQR].

Groups	LE activity, nmol/min×ml	α1-PI activity, IU/ml	LII	aAbs to S100B, opt. dens.	aAbs to MBP, opt. dens.
Healthy volunteers *n* = 27	198.6 [173.4;219.8]	38.4 [31.4;38.4]	6.45 [5.85;6.70]	0.72 [0,66-0,82]	0.70 [0,65-0.77]
Depression with APS *n* = 30	239.8* [213.8;261.4]	43.6** [36.9;51.7]	5.55* [4.4;6.7]	0.75 [0.62-086]	0.76 [0.67-0.84]
Depression without APS *n* = 20	235.4* [224.6;263.5]	46.1** [35.5;50.1]	5.74* [4.79;7.0]	0.73 [0.63;0.90]	0.73 [0.64;0.81]

Note: ** - $p < 0,05$, **$p < 0,01$ - statistically significant differences

negative subscale of SOPS, the SANS scale, as well as on its subscales «Affective Flattening or Blunting» and «Alogia».

Conclusion

The association between the level of activation of the immune system and the severity of depression in the total group of patients was revealed. The established immunological heterogeneity of patients with APS is determined by the degree of severity of positive and negative symptoms and allows us to discuss the possibility of using immunological markers as additional diagnostic and prognostic criteria for the risk of schizophrenia.

References

1. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkötter J, McGuire P, Yung A. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry. 2013 Jan;70(1):107-20. doi: 10.1001/jamapsychiatry.2013.269. PMID: 23165428; PMCID: PMC4356506.
2. Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. Schizophr Res. 2004 May 1;68(1):37-48. doi: 10.1016/S0920-9964(03)00214-7. PMID: 15037338.
3. Kliushnik TP, Zozulia SA, Androsova LV, Sarmanova ZV, Otman IN, Dupin AM, Panteleeva GP, Oleĭchik IV, Abramova LI, Stoliarov SA, Shipilova ES, Borisova OA. [Immunological monitoring of endogenous attack-like psychoses]. Zh Nevrol Psikhiatr Im S S Korsakova. 2014;114(2):37-41. Russian. PMID: 24662343.
4. Ma X, Niu X, Zhao J, Deng Z, Li J, Wu X, Wang B, Zhang M, Zhao Y, Guo X, Sun P, Huang T, Wang J, Song J. Downregulation of Sepina3n Aggravated Blood-Brain Barrier Disruption after Traumatic Brain Injury by Activating Neutrophil Elastase in Mice. Neuroscience. 2022 Nov 1;503:45-57. doi: 10.1016/j.neuroscience.2022.08.023. Epub 2022 Sep 8. PMID: 36089165.
5. Guttman O, Baranovski BM, Schuster R, Kaner Z, Freixo-Lima GS, Bahar N, Kalay N, Mizrahi MI, Brami I, Ochayon DE, Lewis EC. Acute-phase protein α1-anti-trypsin: diverting injurious innate and adaptive immune responses from non-authentic threats. Clin Exp Immunol. 2015 Feb;179(2):161-72. doi: 10.1111/cei.12476. PMID: 25351931; PMCID: PMC4298394.
6. Paramonova NS, Gurina LN, Volkova OA, Karchevsky AA, Sinitsa LN. Sostojanie jelastaza-ingibitornoj sistemy u detej v norme i pri otdel'nyh patologicheskih sostojanijah. Pod red. Paramonovoj N.S.: Grodno: Izdatel'stvo GrGMU; 2017. (In Russ.).
7. Pollak TA, Rogers JP, Nagele RG, Peakman M, Stone JM, David AS, McGuire P. Antibodies in the Diagnosis, Prognosis, and Prediction of Psychotic Disorders. Schizophr Bull. 2019 Jan 1;45(1):233-246. doi: 10.1093/schbul/sby021. PMID: 29474698; PMCID: PMC6293207.
8. Zozulya SA, Tikhonov DV, Kaleda VG, Klyushnik TP. Immunovospalitel'nye markery stanovleniya remissii posle pervogo psikhoticheskogo pristupa v yunosheskom vozraste [Immune-inflammatory markers in remission after a first-episode psychosis in young patients]. Zh Nevrol Psikhiatr Im S S Korsakova. 2021;121(6):59-66. Russian. doi: 10.17116/jnevro202112106159. PMID: 34283531.