

Review

Genetic predictors of cytokine response in ENT-associated encephalitis

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Abstract: (1) Introduction: An imbalance of the genetically determined cytokine response plays a key role in the etiology of ENT-associated encephalitis. In recent years, an attempt has been made to evaluate the prognostic role of chronic pathology of the paranasal sinuses in the development of acute, subacute and chronic encephalitis and meningitis, which in clinical practice are manifested both as cerebral and focal neurological symptoms and as mental disorders: from borderline to psychotic ones. The problem requires a multidisciplinary approach on the part of the specialists in the following clinical disciplines: neurology (as well as neurobiology), psychiatry, immunology, experimental medicine, otorhinolaryngology, and pharmacogenetics. The solution of this problem is possible with the involvement of preventive and personalized medicine. (2) The purpose: Evaluation the prognostic role of genetic polymorphisms of pro- and anti-inflammatory cytokines in the development of ENT-associated encephalitis. (3) Materials and Methods: We conducted a keyword-based analysis of the English and Russian-language articles published within the past 30 years (from 1988 to 2018). The following databases were used in the study: PubMed, MedLine, Web of Science Core Collection (Clarivate Analytics), Web Science, Russian Science Citation Index, Scopus, Scientific Research, Google Scholar, Oxford Press, and eLibrary. (4) Results: In a number of the analyzed works, regardless of the causative agent and viral load, an increased level of pro-inflammatory cytokine production was noted in patients with more severe disease progression, neurological complications and unfavorable outcomes, both in viral encephalitis and in bacterial one. Based on this, 30 single nucleotide variants (SNV), their influence on the expression of pro- and anti-inflammatory cytokine genes, as well as their predictor role in the development of ENT-associated encephalitis were analyzed. Due to the nature of the systemic immune response, the analysis included both cerebral and extracerebral pathology-associated SNV. The inconsistency of the previously obtained results was noted, an attempt to explain this phenomenon was made. The analysis of the dynamics and geography of publications on the stated topic was made, the leading Russian scientific centers in the field were defined. The most promising SNV for further studies were identified. (5) Conclusion: The risk of developing ENT-associated encephalitis is associated with a genetically determined status of the cytokine response and its regulation. Studies of the association of various SNV of genes encoding pro- and anti-inflammatory cytokines in the Russian Federation need to be continued.

Keywords: interleukin, genetics, sinusitis, encephalitis, single nucleotide polymorphism, personalized medicine.

Introduction

The problem of encephalitis associated with acute and chronic pathology of ENT organs is far from having been solved and stays at the cutting edge on scientific discourse. Special attention in the research is given to pathology of the paranasal sinuses. The frequency of an acute sinusitis occurrence for adult patients varies from 15 to 40 cases per 1,000 of population a year [1] and that of chronic sinusitis accounts for from 19 to 150 [2]. The highest frequency of this pathology occurrence is registered in Europe and North America [1]. In the Russian Federation, the acute sinusitis frequency varies from 20 to 134 cases per 1,000 of population a year [3]. Data on large-scale population research of chronic sinusitis on the territory of the Russian Federation have not been found. In recent years, there has been made an attempt to estimate a prognostic role of the chronic pathology of the paranasal sinuses in the development of acute, sub-acute and chronic encephalitis and meningitis that manifest themselves in the general clinical practice as both cerebral symptoms and focal neurologic signs and mental disorders: from marginal to psychotic [3-7].

Within the aspect of the problem in question, that of chronic ENT-associated encephalitis, it is worth noting a role of cytokine response since a number of anti-inflammatory cytokines (IL-6, IL-1 β , TNF- α) is considered as a predictor of the chronicity of the inflammatory process in paranasal sinuses as well as a risk of the development of rhinogenous limbic encephalitis, mediobasal temporal lobar epilepsy, anxiety depressive disorder and schizophrenia [8,6]. The level of expression of pro- and anti-inflammatory cytokines and their balance ensuring an adequate response of the organism to the causative agent of a virus or bacterial nature is known to be genetically determined [9]. It is possible to solve this problem by means of preventive and personalized medicine, a branch that has been experiencing a booming development for the last decade. The amount of research dedicated to the problem in question and also to the possibility to detect patients with paranasal sinuses chronic pathology who have a high risk of the development of pathological processes in CNS structures is growing. But the results of Russian and foreign research differ, and there is no unequivocal solution to the problem in question up to the present moment.

Objective

Assessment of the prognostic role of genetic polymorphisms of pro- and anti-inflammatory cytokines in the development of ENT-associated encephalitis.

Materials and Methods

We analyzed both Russian and English-language scientific articles on a given topic. Inclusion criteria in the search: 1) full-text original articles cited in databases: PubMed, MedLine, Web of Science Core Collection (Clarivate Analytics), Web of Science, Russian Science Citation Index, Scopus, Scientific Research, Google Scholar, Oxford Press, and eLibrary; 2) articles in Russian and English; 3) search depth 1988-2018 years (30 years); 4) keyword matching: interleukin, genetics, sinusitis, encephalitis, single nucleotide variant (SNV), personalized medicine. Exclusion criteria: abstracts, monographs, manuals, guidelines. A total of 659 354 publications were found. However, only 645 works met the purpose of our research. In accordance with all the abovementioned search criteria, we analyzed 128 original full-text articles (table 1).

The review used the built-in Scopus analytical services. A reference was made to each graph.

Table 1. Keyword search results in a number of databases

Cytokine	Web of Science			Russian Science	
	Core Collection	Scopus	PubMed	Citation Index	Selected
IL-6	5435	6195	2438	33	23
TNF-a	4947	9195	4872	41	22
IL-1b	2690	2016	1284	9	16
INF-y	2319	4277	1606	5	11
IL-12	1648	2476	493	8	7
IL-18	1332	1657	485	13	14
IL-10	4165	6502	2097	34	12
IL-4	3824	5950	912	42	15
IL-2	5732	8059	558	65	6
TGF-b	1883	3271	1962	5	2

The work was carried out in 2 stages. At the first stage, according to the data of a 30-year search (1988-2018), we were able to assess the scientific interest in the problem above. At the second stage, according to a 20-year search (1998-2018), we were able to analyze articles indicating associative genetic studies of cytokines in otorhinolaryngology and allied sciences.

Results

The interest to SNV genes encoding interleukins arose for the first time in 1994 [10] and has reached its maximum growth for the last decade (Figure 1).

The dynamics of publications presenting the results of research in the role of different cytokinins in ENT-associated encephalitis development are basically similar, the peak of scientific activity being in 2014-2015 (Figures 2,3).

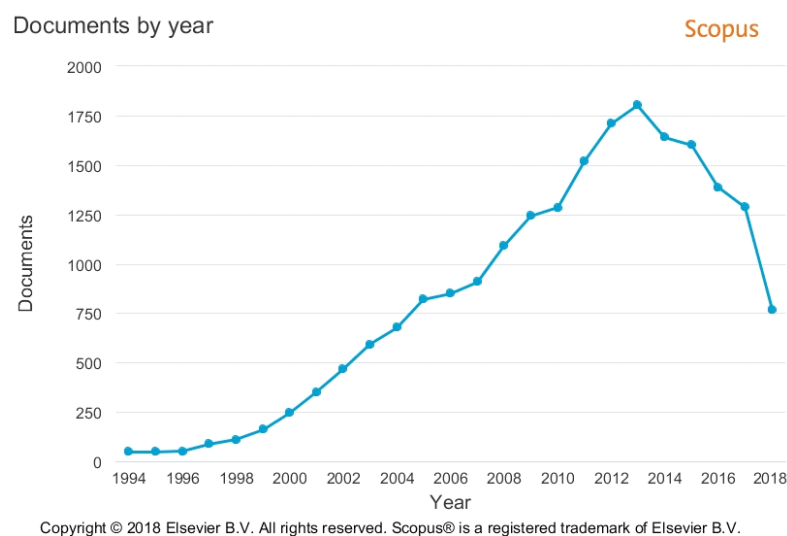


Figure 1. The dynamics of a number of publications presenting the results of research in SNV of genes encoding interleukins (according to the data provided by analytical service Scopus, 2018) [11].

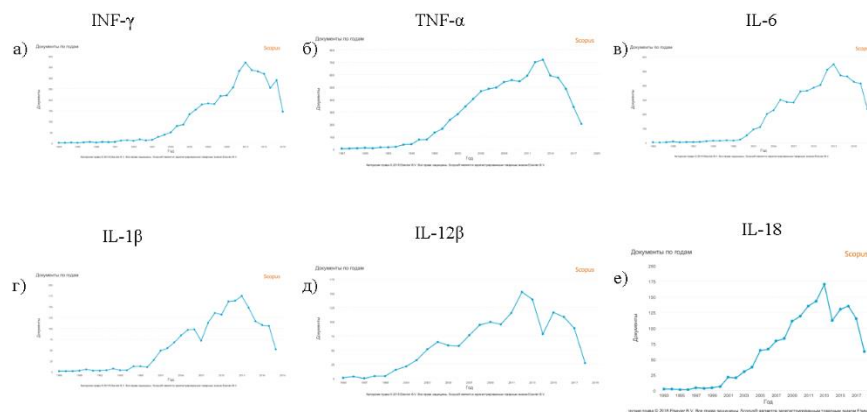


Figure 2 (2, a-e). The dynamics of publications presenting the results of research in the role of different SNV of genes encoding pro-inflammatory cytokines (according to the data provided by analytical service Scopus, 2018) [12-17].

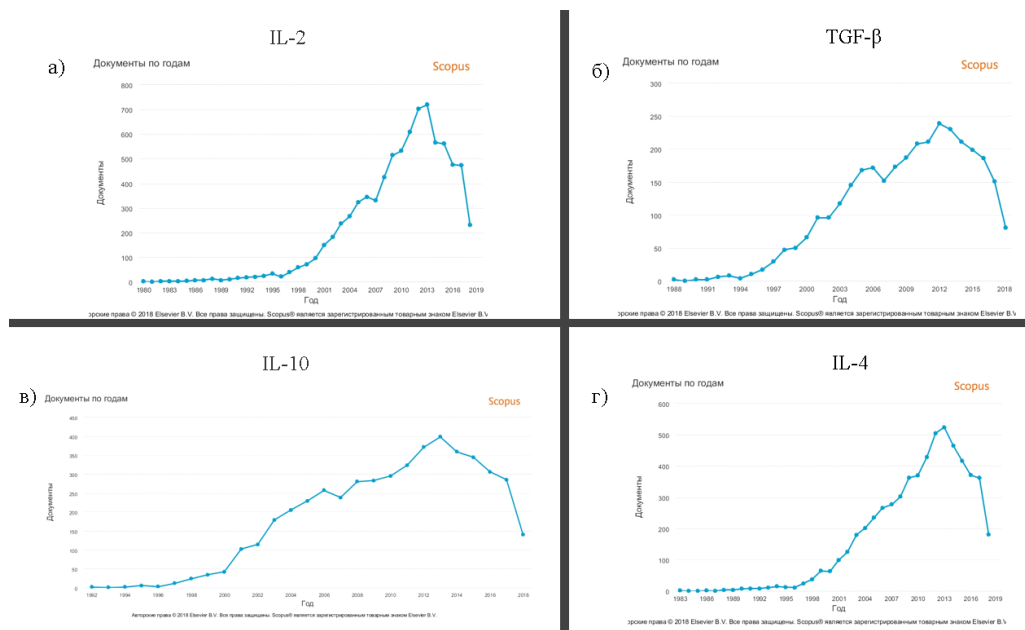


Figure 3 (3, a-d). The dynamics of a number of publications presenting the results of research in the role of certain SNV of genes encoding anti-inflammatory cytokines (according to the data provided by analytical service Scopus, 2018) [18-21].

The problem in question provoked the strongest interest of specialists of the following clinical disciplines: neurology (and also neurobiology), psychiatry, immunology, oncology, experimental medicine, rheumatology, otorhinolaryngology (Figure 4).

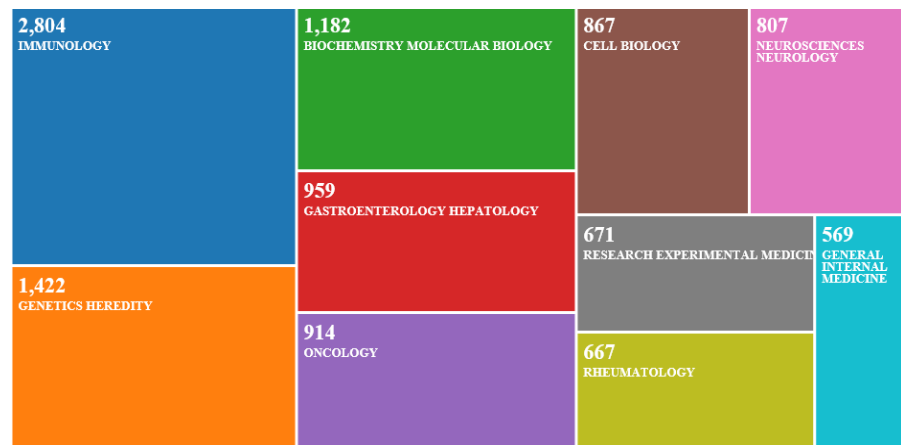


Figure 4. Flowchart showing a number of publications on a role of pro- and anti-inflammatory cytokines in clinical disciplines (according to the data provided by analytical service Web of Science, 2018) [22].

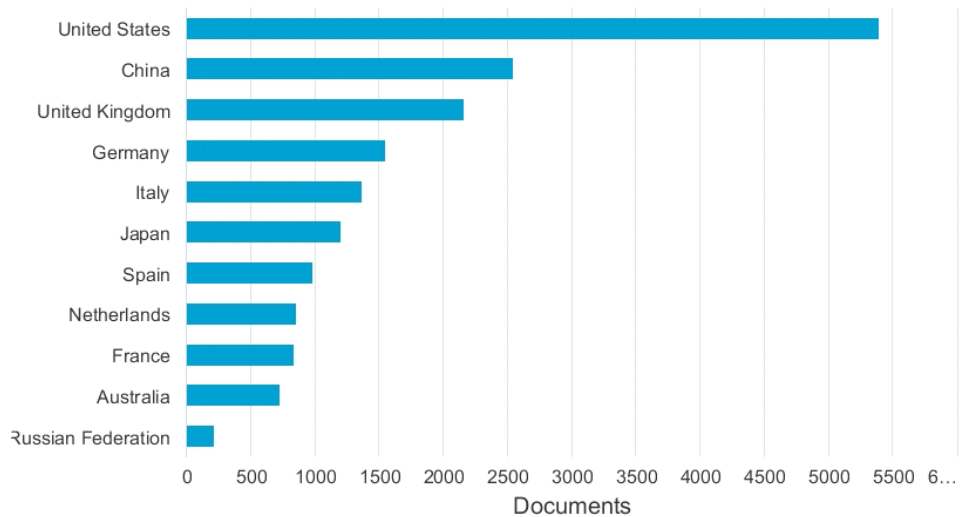
The most studied, judging by the general number of analyzed publications, are polymorphisms of gene TNF- α , IL-10, IL-2.

The majority of works on this theme was published in the USA, China and Great Britain (Figure 5).

Documents by country or territory

Compare the document counts for up to 15 countries/territories

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Figure 5. The number of publications presenting the results of research in the role of polymorphisms of pro- and anti-inflammatory cytokines in the Russian Federation and abroad (according to the data provided by analytical service Scopus, 2018) [23].

Table 2. The number of publications in Russian institutions

Title of the institution	Number of publications
Siberian State Medical University	9
N.F.Katanov Khakass State University	4
Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences	3
Kemerovo State University	3
M.V. Lomonosov Moscow State University	3
Research Institute of Medical Genetics, Omsk Scientific Center of the Siberian Branch of the Russian Academy of Medical Sciences	3
Federal State Budget-funded Scientific Institution “ V.A. Nasonova Research Institute of Rheumatology”	3
Omsk State Medical Academy	3
Federal State Budget-funded Institution “ Federal Research and Clinical Center for Specialized Types of Medical Care and Medical Technology”, Federal Biomedical Agency of Russia	3
Federal Budget-funded Research Institution “Federal Scientific Center for Medical and Preventive Health Risk Management Technologies”	3

The number of Russian publications indexed in the data-bases Scopus and Web of Science (Clarivate Analytics) accounted for 208. The leading scientific groups, according to the fulfilled search, are scientific-research centers and universities of Moscow and Siberia (table 2).

The following SNV of the genes are of the greatest researchers' interest: 308 A>G rs1800629 of gene *TNFA*, -1082 A>G rs 1800896 of gene *IL10* and -174 G>C rs1800795 of gene *IL6* (table 3).

Interleukin-6 (IL-6)

Interleukin 6 acts as a pro- and anti-inflammatory cytokine; it is synthesized by activated macrophages, T-cells and glial cells; stimulates the immune response. The production of IL-6 is activated by pathogen-bound molecules, the response is mediated via TOLL-like receptors, besides, IL-1 and TNF- α stimulate IL-6 expression. This interleukin is encoded by the *IL6* gene located on chromosome 7p15.3. Currently, the role of the following SNV is known: -572 C>G (rs1800796), -174 G>C (rs1800795), -6331 T>C (rs10499563), -634 C>G (rs1800796) (Table. 3). However, the prognostic role and effect of specific alleles remain ambiguous. Thus, the association of allele G (-572 C>G) with IL-6 hyperexpression and, as a consequence, the risk of ENT-associated encephalitis is shown in the following studies [24-28]. However, we found a study that revealed the opposite effect on expression and showed the protective role of the G allele in the pathogenesis of Alzheimer's disease [29]. The role of allele C -174 G>C is still ambiguous: a number of studies [30-36] showed a positive association of the C allele and the IL-6 cytokine expression (hyperexpression) whereas some other studies demonstrated the opposite result (hypoexpression) [37, 38].

Table 3. Effect of the studied SNV of genes encoding pro-inflammatory cytokines on their expression in vivo

Cytokine / Gene	SNV	Effect (on gene expression)	Author
IL-6 / <i>IL6</i>	rs1800796 (-572 C>G)	Allele G – increases	[24-28]
		Allele G – decreases	[29]
	rs1800795 (-174 G>C)	Allele C – increases	[26,30-36]
		Allele C – decreases	[37-38]
	rs10499563 (-6331 T>C)	Allele T – increases	[39]
rs1800796 (-634 C>G)	Allele G – increases ¹	[40-41]	
IL-1 β / <i>IL1B</i>	rs1143634 (+3954 C>T)	Allele T – increases	[43-45]
		Allele T – decreases	[46]
		Allele C – increases	[4]
	rs1143627 (-31 C>T)	Allele C – increases	[47-48]
	rs16944 (-511 C>T)	Allele T – increases	[50-54]
TNF-a / <i>TNFA</i>	rs1800629 (-308 A>G)	Allele A – increases	[59-68]
		Allele G – increases	[70]
		Allele A – no association found	[68,69]
	rs361525 (-238 A>G)	Allele A – increases	[60,72]
	rs1799724 (-857 C>T)	Haplotype CC – decreases	[71]
rs1800630 (-863 A>C)	Haplotype AA – decreases	[71,73]	
Hsp70 ³ / <i>HSP70-2</i>	rs2227956 (+1267 A>G)	Allele G – increases ²	[58]
INF- γ / <i>INFG</i>	rs2069709 (-179 T>G)	Allele T – increases	[75,78]
	rs2430561 (+874 A>T)	Allele A – increases	[76-80]
IL-12b / <i>IL12B</i>	rs3212227 (+1188 A>C)	Haplotype CC – increases	[83-85]
		no association found	[86]
IL-18 / <i>IL18</i>	rs549908 (-105 A>C)	Allele A – increases	[88]
		Allele A – no association found	[89]
	rs187238 (-137 G>C)	Allele G – increases *	[88,90-93]
		Allele C – decreases	[94]
	rs1946518 (-607 A>C)	Allele A – increases	[94,95]
		no association found	[96]
	-920T>C, -133C>G, -132A>G.	Haplotype	[97]
	C/C/G – increases *		

1 – proven association in patients-smokers only; 2 – not applicable to pro-inflammatory cytokines, however, the corresponding gene's SNV is able to affect the level of TNF-a expression.

Table 4 – Effect of the studied SNV of genes encoding anti-inflammatory cytokines on their expression in vivo.

Interleukin / Gene	SNV	Effect (on gene expression)	Author
IL-10 / <i>IL10</i>	rs1800896 (-1082 A>G)	Allele G – increases	[99,102-106]
	rs1800871 (-819 C>T)	Allele T – increases	[107,108]
	rs1800872 (-592 A>C)	Allele A – increases	[107]
		Haplotype AA – decreases	[109]
	rs6703630 (-2849 A>G)	Allele G – increases	[110]
IL-4 / <i>IL4</i>	rs2243250 (-590 C>T)	Allele T – increases	[112-115]
		Haplotype CC – decreases **	[6]
		no association found	[116]
	rs2227284 (+33 C>T)	Allele T – increases *	[117,118]
	rs2243250(-589 C>T)	Allele T – increases	[118-120]
	rs2227284 (+3017 G>T)	Allele T – increases *	[121]
	IL-2 / <i>IL2</i>	rs2069762 (-330 T>G)	Haplotype GG – decreases
Haplotype GG – increases symptomatic epilepsy risk			[122]
rs2069763 (+166 T>G)		Allele T – increases autoimmune diseases risk	[123]
TGF-β / <i>TGFB1</i>	rs1800469 (-509 C>T)	Allele C – increases	[127]
	rs1800470 (29 C>T)	Allele T – decreases	

*- proven association of SNV with an increased level of IgE in blood serum; **- increases schizophrenia risk.

Interleukin-1 beta (IL-1β)

IL-1β is a pro-inflammatory cytokine synthesized by activated macrophages. It is known that induction of cyclooxygenase-2 (PTGS2/COX2) by this cytokine in the central nervous system (CNS) promote hypersensitivity to inflammatory pain [42]. According to several studies, some polymorphisms of the IL-1β gene could be associated with genetic predisposition to schizophrenia [8]. IL-1β is encoded by the *IL1B* gene located on chromosome 2q14. Among the analyzed studies, special attention is drawn to the following SNV: + 3954 C>T (rs1143634), -31 C>T (rs1143627), -511 C>T (rs16944) (table 3), alleles +3954 C>T having the most ambiguous effect. The results of the studies vary among different populations. In the Siberian Federal District of the Russian Federation there is a positive association of the C allele carrier status with the IL-1β expression [4]. The Asia-Pacific region shows studies with opposite results - a positive association of the T allele with the IL-1β expression [43-45]. In North America and Western Europe, the results of the studies are very contradictory, and therefore it is not possible to distinguish the prevailing effect of this SNV alleles C and T on the level of the IL-1β expression [46].

Tumor necrosis factor alpha (TNF-α)

TNF-α is an extracellular protein representing a multifunctional cytokine synthesized (mainly) by monocytes, macrophages, eosinophils and neurons. TNF-α stimulates production of IL-1, IL-6, IL-8, interferon-gamma, activates white blood cells. Excessive expression of TNF-α is associated with a disorder of cerebral hemodynamics and

cytotoxic effect on cells of various tissues of the human body. Dysregulation of TNF- α expression is involved into the pathogenesis of many mental disorders and organic CNS diseases, such as Alzheimer's disease [55], major depressive disorder [56]. Recent studies have shown that TNF- α can have a protective effect and prevent neuronal death and apoptosis by a mechanism involving the activation of transcription factor NF-kappaB, inducing expression of both Mn-SOD and Bcl-2 proteins [57]. TNF- α is encoded by the *TNFA* gene located on the chromosome 6p21.33. The most studied is the role of the following SNV: -308 A>G (rs1800629), -238 A>G (rs361525), -857 C>T (rs1799724), -863 A>C (rs1800630) (table 3). The association of SNV HSP70-2 +1267 A>G (rs2227956), in particular, the carriage of allele G with the expression of the cytokine by effector cells [58], is also reported. Due to the different designs of the analyzed works and the pathogenesis of the studied diseases, the results of associative studies of the role of polymorphism -308 A>G with the level of TNF- α in blood serum differ. Thus, many authors show the positive association of the A allele carrier status with an increased production of TNF- α [59-68]. However, according to the meta-analysis in the European population, allele A has statistically significant effect neither on the level of serum cytokine concentration, in general, nor on the pathogenesis of rheumatoid diseases, in particular [68, 69]. In the population of the South-Eastern region of Iran, on the contrary, the association of the G allele carrier status with hyperexpression of TNF- α [70] was revealed.

Interferon gamma (IFN- γ)

IFN- γ is a soluble cytokine that has both pro- and anti-inflammatory effects. It is the only member of type II interferon class. IFN- γ is secreted by T-helpers (Th1), cytotoxic T-cells, macrophages, mucosal epithelial cells, as well as by NK-cells (natural killers). IFN- γ has antiviral, immunoregulatory and antitumor properties, and in the central nervous system as well [74]. The protective role of cytokine in allergic encephalomyelitis has been shown [81]. IFN- γ is encoded by the *IFNG* gene located on chromosome 12q15. In the analyzed studies the association of the following SNVs with hyperexpression of the *IFNG* gene is shown: -179 T>G (rs2069709) allele T [75, 78] and +874 A>T (rs2430561) allele G [76-80] (table 3).

Interleukin-12B (IL-12 β)

IL-12 β is a pro-inflammatory interleukin produced by dendritic cells, macrophages, neutrophils, and B-lymphoblasts in response to antigenic stimulation. IL-12 β activates the production of INF- γ and TNF- α from T-cells and NK-cells, reduces the indirect IL-4 suppression of IFN- γ expression. The role of IL-12 β in the pathogenesis of encephalitis, including autoimmune encephalitis, is described [82]. IL-12 β is encoded by the *IL12B* gene located on the chromosome 3p12-q13.2. Association of SNV +1188 A>C (rs3212227) with the *IL12B* gene expression level is shown (table 3). The CC genotype carrier status is reported to significantly increase the production of IL-12 β cytokine [83-85].

Interleukin-18 (IL-18)

IL-18 (also known as interferon-gamma-inducing factor) is a pro-inflammatory cytokine produced by macrophages and other lymphoid cells. With the increasing production of IL-18 the overproduction of beta-amyloid in human brain neurons associated with Alzheimer's disease was found [87]. IL-18 is encoded by the *IL18* gene located on chromosome 11q23.1. Currently, the most studied is the role of the following SNV: -105 A>C (rs549908), -137 G>C (rs187238), -607 A>C (rs1946518) (table 3). One of the studies [84] revealed 3 non equilibrium coupled polymorphisms -920T>C, -133C>G, -132A>G; in the case of the carriage of C/C/G - haplotype increased expression of IL-18 was shown.

Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine produced by monocytes and, to a lesser extent, lymphocytes, especially T-helpers type 2 - (Th2), mast cells, (CD4+ CD25+ Foxp3+) regulatory T-cells, as well as some activated T - and B-cells. Association of IL-10 hypoproduction with the development of autoimmune encephalitis is shown [98]. IL10 is encoded by the *IL10* gene located in the chromosome 1q32.1. The association of the following SNV carrier status with *IL10* gene expression was studied: -1082 A>G (rs1800896), -819 C>T (rs1800871), -592 A>C (rs1800872), -2849 A>G (rs6703630) (table 4). In addition to the studies on the associations of individual polymorphism, there is an increasing number of studies evaluating the overall (additive) effect and the interaction of alleles of several specific SNV. In this case, the haplotype assessment becomes more informative but the contribution and the ratio of allele effects remain unclear. Thus, in carriers of haplotype -1082A/-819T/-592A elevated levels of IL10 gene expression and increased serum levels of IL-10 cytokine were revealed [99,101]. Nonequilibrium linkage and a priority influence of other SNV can cause the differences in the results of single factor analysis [100].

Interleukin-4 (IL-4)

IL-4 is an anti-inflammatory cytokine that induces differentiation of naive T-helpers (Th0 cells) into Th2-cells. Probably basophiles could be the effector cells for IL-4, and Th2, forming a feedback loop. It was found that IL-4 mediates the interaction between the stem neuron cells and neurons that undergo neurodegeneration. IL-4 initiates a cascade of neuronal regeneration via phosphorylation of the intracellular effector STAT6 (experimental model of Alzheimer's disease - zebrafish) [111]. IL-4 is encoded by the *IL4* gene located on chromosome 5q31.1. In this study of SNV of *IL4* gene, the most known and interesting in the aspect of ENT-associated encephalitis of SNV of *IL4* gene were revealed: -590 C>T (rs2243250), +33 C>T (rs2227284), -589 C>T (rs2243250), +3017 G>T (rs2227284) (table 4). In the case of allele T SNV +33 C>T and +3017 G>T carriage, the association with elevated serum IgE level was shown, which, consequently, increases the risk of autoimmune reactions, hypersensitivity of 1 type [117, 118, 121]. In one study [6], the CC genotype was associated with the risk of schizophrenia, the supposed mechanism of which was the immune imbalance in the central nervous system as a trigger for subsequent neurodegenerative changes.

Interleukin-2 (IL-2)

IL-2 is an inflammation and immunity mediator, produced by T-cells in response to antigenic and mitogenic stimulation. The role of IL-2 in the pathogenesis of viral encephalomyelitis is described [122]. IL-2 is encoded by the *IL2* gene located on the chromosome 4q27. The association of carriage of the following SNV with *IL2* gene expression: -330 T>G (rs2069762), +166 T>G (rs2069763) (tab. 4) is shown. It should be noted that the carriage of the GG genotype of SNV -330 T>G is associated with the increasing risk of symptomatic epilepsy and autoimmune genesis and neurotoxicity [122]. The T allele carrier status of SNV +166 T>G is associated with cytokine imbalance and risk of autoimmune diseases [123].

Transforming growth factor beta (TGF-β)

TGF-β controls proliferation, cell differentiation and other functions in most cells. TGF-β is produced by all cells of the white blood cell line and initiates apoptosis in many cell types. Via Foxp3 protein it affects regulatory T-cells and T-helper 17 type (Th17). Decrease in the TGF-β level leads to an increase of Th17-cells and a subsequent

increase in the TNF- α level, which leads to demyelination of neuronal axons [125]. It is also shown that TGF- β induces the growth of oligodendrocytes (cells producing myelin sheath) [125]. Consequently, the decrease of TGF β gene expression level can downregulate remyelination of neuronal axons [125]. Higher concentrations of TGF- β were found in blood and cerebrospinal fluid in patients with Alzheimer's disease compared to the control group [126], indicating a possible role of TGF- β in the neurodegenerative cascade leading to the neurodegenerative diseases. TGF- β is encoded by the *TGF β* gene located on chromosome 19q13.2. The studies about the association of the following SNV with *TGF β* gene expression were found: -509 C>T (rs1800469), +29 C>T (rs1800470) (tab. 4). In one research [127], the haplotype carrier status was analyzed together with two polymorphisms not included in table 4: -800 G>A (rs1800468) and +74 G>C (rs1800471). We present the results of associative studies only for G/T/C/G and G/C/T/G haplotypes, respectively.

Discussion

Imbalance of cytokine response has an important role in the etiology of secondary encephalitis in general, and ENT-associated in particular. In a number of analyzed studies, regardless of the pathogen, there was an increased level of pro-inflammatory cytokine production in patients with a more severe course of the disease, neurological complications and adverse outcome, both in viral [4, 128, 129] and bacterial [130, 131] encephalitis. It should be noted that viral or bacterial load in the examined patients remained the same and did not correlate with the level of cytokines in blood serum [129]. In this case, the leading role of the genetically determined immune response becomes evident.

It is important that in most patients with secondary encephalitis caused by RNA/DNA viruses and bacteria, the genetic material of the pathogen was not determined neither in the cerebrospinal fluid (liquor) nor in the brain parenchyma during autopsy [129] but there was an inflammatory infiltrate and, as a consequence, neurodegenerative changes in the brain. It is important to note that the immune damage of CNS structures involves both the local immune system [137] and activated lymphocytes (including perivascular lymphocytes) on the periphery [135, 136]. It becomes clear that in the full analysis it is necessary to pay attention not only to the SNV associated with cerebral pathology but also to the SNV associated with extracerebral pathology. In other words, it is necessary to evaluate the immune response and its regulation in general, that is, the system "cytokine-receptor-antagonist" for pro- and anti-inflammatory cytokines. Such studies have not been found at the moment.

We should also focus on the features of the immune response in the central nervous system. A benign outcome and elimination of the pathogen in this case should occur without damaging the non-renewable neuronal population. Consequently, any imbalance, in the excessive or insufficient production can lead to fatal consequences. The mechanism of pathological infiltration of the brain parenchyma is also associated with hyperexpression of genes encoding pro-inflammatory cytokines. Thus, blood vessels of the blood-brain barrier (BBB) are normally intact and impervious to lymphocytes. When inflammatory reactions occur, TNF- α , IL-1 β and CXCL-10 produced by microglia and astrocytes induce the presentation of cell adhesion proteins, in particular ICAM1 and VCAM1 into the vessel lumen, which triggers active migration of B-, T-lymphocytes and macrophages into the central nervous system [137]. The absence or weakening of the feedback loop, in particular, with insufficient production of anti-inflammatory cytokines (IL-10, 4, 2) can lead to excessive infiltration or the chronic pathological process even in the case of pathogen elimination. Also, increased production of pro-inflammatory cytokines, especially IL-6, increases the permeability of the blood-brain barrier and enhances

immune neurotoxicity [132, 133]. In transgenic mice having elevated levels of IL-6 a greater number of neurological complications of the infection was observed [134].

At the same time, we revealed the contradictory results of the studies of the same SNV. This fact can be of great clinical importance. Firstly, the frequency of allele carriage and, possibly, their effect on the risk of ENT-associated encephalitis, vary among representatives of a particular ethnic group. The problem (in particular, [68, 69]) which is relevant in China, has no value in Europe. In Russia, taking into account the population and ethnic heterogeneity of the country, this aspect in the planning and analysis of the results of associative genetic research is crucial. Secondly, despite the expression of genes encoding the cytokine receptor of the same name and its antagonist, it is extremely difficult to assess the additive effect of hyper- or hypoproduction of cytokines and cytokine response in a specific clinical case, in general. This fact explains the need for further complex data analysis, as well as conducting multivariate studies in the Russian Federation. Thirdly, the subsequent formation of risk groups, methods and strategies for the treatment of ENT-associated encephalitis with immunocorrection drugs should, first of all, rely on the individual characteristics of the patient's immune response, which corresponds to the strategy of rapidly developing personalized medicine.

The role of ENT diseases, in particular, chronic and acute purulent-inflammatory sinusitis and otitis media, inflammatory infectious diseases of the upper respiratory tract, was identified in the pathogenesis of such disorders as epilepsy [138], meningoencephalitis [140], depression and anxiety-depressive disorders (as ENT-associated complications) [141]. These pathologies usually remain resistant to standard therapy in Otolaryngology and Psychoneurology because they require personalized disease-modifying treatment. Based on this, complex therapy and interdisciplinary cooperation with the participation of different specialists such as otolaryngologists, immunologists, neurologists, and psychiatrists are needed. For example, due to anatomical features, the purulent-inflammatory process in the sphenoid sinus, maxillary sinuses or middle ear can spread to the subdural and arachnoid space by infectious destruction of the bone tissue of the ENT organs, migration in the perivascular and perineural spaces. Also, the migration in the opposite direction, contributing to the formation of recurrent pathology is possible. The most difficult are smoldering processes in patients with a weak immune response and an imbalance of the cytokine response.

Conclusions

The risk of developing ENT-associated encephalitis is associated with a genetically determined status of the cytokine response and its regulation, while the most studied cytokines to date are IL-6, IL-1 β , TNF- α . Studies of the association of various SNV of genes encoding pro- and anti-inflammatory cytokines need to be continued.

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