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Neurogenic inflammation: biochemical markers, genetic control and diseases

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ABSTRACT

Neurogenic inflammation is a pathological process based on bidirectional interactions between cells of the nervous and immune systems as well as on a wide range of biologically active substances.

Aim. Basing on scientific publications and information provided in databases, to analyze markers of neurogenic inflammation (biochemical, genetic) and characterize their involvement in the pathogenesis of diseases of various organ systems.

Results. Neurogenic inflammation that occurs during the development of various diseases (asthma, urticaria, atopic dermatitis, psoriasis, rheumatoid arthritis, pain syndrome, interstitial cystitis, colitis, etc.) is characterized by common stages and pathophysiologically active substances. Mediators released by nerve cells (substance P, calcitonin gene-related peptide, vasoactive peptide), acting on specific receptors, contribute to mast cell degranulation with the release of a complex of biologically active substances (histamine, tryptase, nerve growth factor, etc.), which activate inflammatory processes. Biologically active substances and receptors significant for the development of neurogenic inflammation are under genetic control. At the same time, there are overlaps of the spectrum of diseases for which importance in the pathogenesis of neurogenic inflammation is proved and an association between variants of neurogenic inflammation genes. This makes it possible to conclude that the course of neurogenic inflammation will depend not only on the etiological factors, but also on the genetic features of key molecules involved in neurogenic inflammation processes. The similarity of the pathogenetic links of neurogenic inflammation (at the genetic and biochemical levels) in various pathologies may underlie the formation of comorbid conditions.

Conclusions. Understanding the biochemical and genetic components of the development of neurogenic inflammation is of interest for prevention and treatment of diseases (including comorbid ones) based on this pathological process.

Key words: neurogenic inflammation, genetics.

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Нейрогенное воспаление: биохимические маркеры, генетический контроль и болезни

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РЕЗЮМЕ

Актуальность. Нейрогенное воспаление представляет собой патологический процесс, в основе которого находятся двунаправленные взаимодействия между клетками нервной и иммунной систем, а также широкий спектр биологически активных веществ.

Цель. На основании научных публикаций и информации, представленной в базах данных, проанализировать маркеры нейрогенного воспаления (биохимические, генетические) и охарактеризовать их вовлеченность в патогенез болезней различных систем органов.

Результаты. Нейрогенное воспаление, протекающее при развитии различных заболеваний (астма, крапивница, атопический дерматит, псориаз, ревматоидный артрит, болевой синдром, интерстициальный цистит, колит и др.), характеризуется общностью этапов и патофизиологически активных веществ. Выделяемые нервными клетками медиаторы (субстанция Р, кокальцигенин, вазоактивный пептид), воздействуя на специфические рецепторы, способствуют дегрануляции тучных клеток с высвобождением комплекса биологически активных веществ (гистамин, триптаза, ростовой фактор нервов и др.), которые активируют воспалительный процесс. Биологически активные вещества и рецепторы, значимые для развития нейрогенного воспаления, находятся под генетическим контролем.

При этом наблюдается перекрывания спектра заболеваний, для которых доказана значимость в патогенезе нейрогенного воспаления, с одной стороны, и ассоциированность с вариантами генов нейрогенного воспаления – с другой. Это позволяет заключить, что характер течения нейрогенного воспаления будет зависеть не только от этиологических факторов, но и от генетических особенностей ключевых молекул, вовлеченных в процессы нейрогенного воспаления. Общность патогенетических звеньев нейрогенного воспаления (на генетическом и патогенетическом уровнях) при различных патологиях может лежать в основе формирования коморбидных состояний.

Заключение. Понимание биохимических и генетических компонент развития нейрогенного воспаления представляет интерес для профилактики и лечения заболеваний (в том числе и коморбидных), в основе которых лежит данный патологический процесс.

Ключевые слова: нейрогенное воспаление, генетика.

Ключевые слова: системы анализа, антибиотикорезистентность, антимикробные препараты, эпидемиологический надзор.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The relationship between the nervous and immune systems is actively studied in terms of their involvement in the pathogenesis of various diseases, and in this aspect, neurogenic inflammation is of particular interest [1, 2]. Neurogenic inflammation is understood as a cascade of pathogenetically significant events due to the local release of inflammatory mediators from nerve cells in response to non-infectious stimuli [3–5]. The effect of certain stimuli (allergens, chemicals, etc.) on the nerve endings triggers processes involving different types of immune cells, peripheral and central nervous system nerve fibers, and numerous physiologically active substances. In particular, it has

been proven that, with the development of allergic inflammation, neurons actively interact and regulate the functioning of mast cells, dendritic cells, eosinophils, Th2 cells, etc., and complex and often bidirectional relationships are formed between different types of cells [6, 7]. The pathogenesis of a large number of diseases and/or symptoms of diseases (including asthma, urticaria, contact dermatitis, atopic dermatitis, psoriasis, rheumatoid arthritis, pain syndrome, autism, cystitis, etc.) is associated with neurogenic inflammation, and their spectrum is constantly increasing [1, 2, 8–18]. The bronchopulmonary system, gastrointestinal tract, urogenital system and skin are the most well-studied systems in terms of processes occurring in the development of neurogenic inflammation, as they are primarily exposed to various damaging exogenous agents. Clinical and experimental data accumulated so far show similarities between the stages of neurogenic inflammation in different organ systems [6, 11, 19, 20].

BIOCHEMICAL MARKERS OF NEUROGENIC INFLAMMATION

In a generalized (and simplified) form, the development of the neurogenic inflammatory process can be presented in the following way (Fig. 1). In response to irritation, the sensory neurons located in the epithelial layer of the skin, respiratory tract, gastrointestinal tract, and urinary system secrete neuropeptides (substance P – SP, vasoactive intestinal peptide – VIP, calcitonin gene-related peptide – CGRP), which activate mast cells by acting on appropriate receptors (NK1, MRGPRX2, VIPR1, CGRP-R).

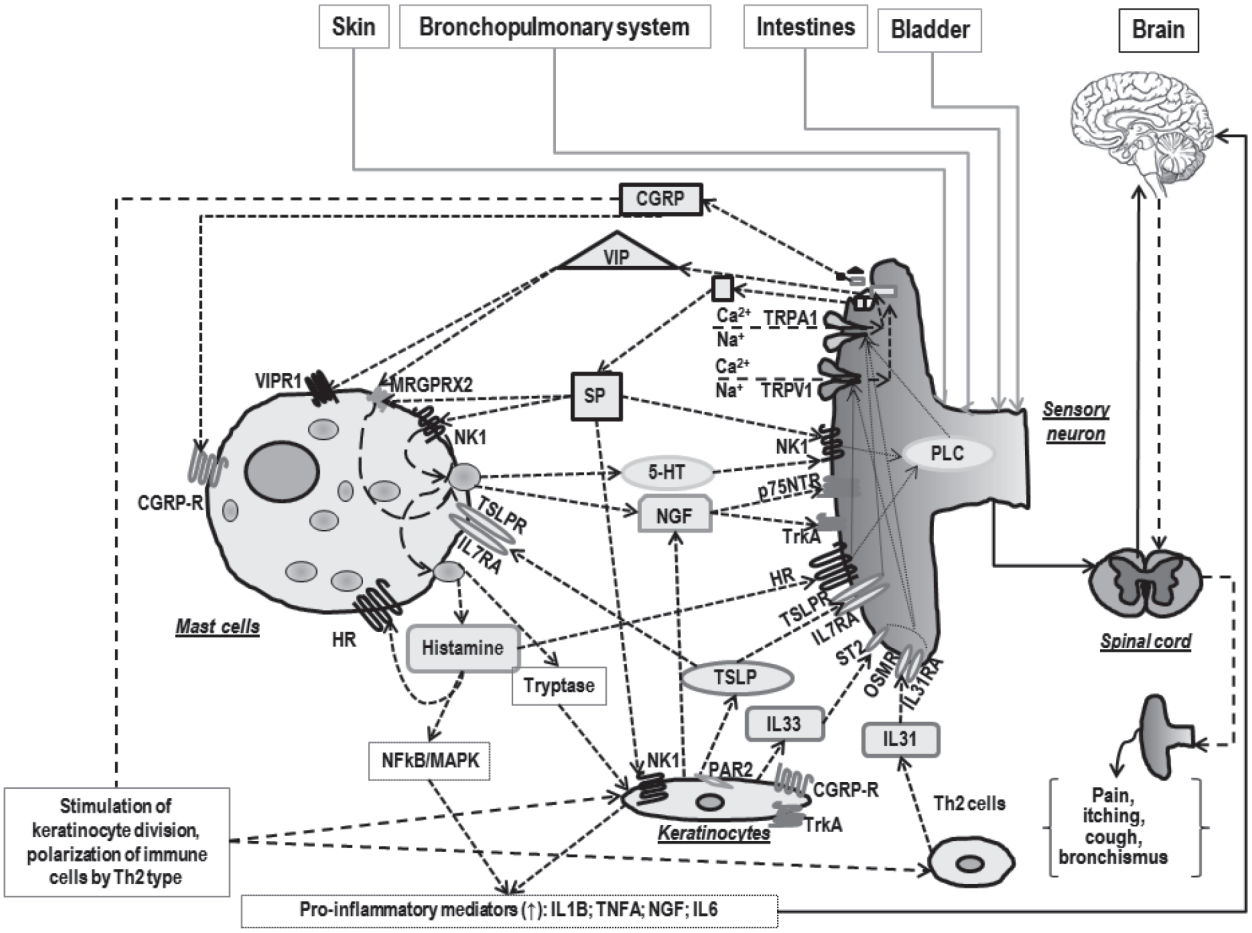

Figure 1. Schematic representation of the development of neurogenic inflammation (compiled from [6, 21, 22]). SP is substance P, NK1 is substance P receptor; VIP – vasoactive intestinal peptide, VIPR1 and MRGPRX – vasoactive intestinal polypeptide receptors; CGRP – calcitonin gene-related peptide, CGRP-R – receptor for calcitonin gene-related peptide; 5-HT – serotonin, NGF – nerve growth factor, p75NTR and TrkA – NGF receptors; TRPV1 and TRPA1 – calcium channels; IL1B, IL6, IL31, IL33 – interleukin-1B, -6, -31, -33, respectively, TNFα – tumor necrosis factor alpha, TSLP – thymic stromal lymphopoietin; OSMR and IL17RA form the receptor for TSLP and IL31; ST2 – receptor for IL33; HR – histamine receptors (four types of histamine receptors are known – H1R, H2R, H3R, and H4R), PLC – phospholipase C; MAPK – mitogen-activated protein kinase, NFkB – nuclear factor kappa-b. Details – see text

Following the activation, various physiologically active substances are released from mast cells – histamine, tryptase, serotonin (5-HT), nerve growth factor (NGF), and others. Histamine, by activating the NFkB/MAPK metabolic pathway, promotes the production of pro-inflammatory cytokines (IL1B, TNFA, NGF, IL6), resulting in the development of the inflammatory process. Influencing the receptors localized on nervous fibers, histamine, IL31 produced by Th2 cells, IL33, NGF, and TSLP (thymic stromal lymphopoietin) produced by tryptase-activated keratinocytes (in the case of a pathological process affecting the skin, as in allergies, for example) are capable of activating TRPV1 and TRPA1 calcium channels. The activation of calcium channels increases the entry of calcium ions into cells, which, in turn, promotes the release of neuropeptides, thereby increasing the immuno-inflammatory response. As a result, pathological reactions, such as itching, pain, bronchospasm, cough, sneezing, bowel spasm, abdominal pain, etc., are observed, i.e. there is a wide range of pathological reactions, depending on which organ develops neuroinflammation. In addition, CGRP released by skin sensory neurons in response to irritation not only induces polarization of immune cells along the Th2 pathway, but also stimulates keratinocyte division [6].

It is worth noting that the same biologically active substances (histamine, NGF, TSLP) are able to activate different types of cells and are involved in various pathophysiological processes, and some of them (histamine and substance P) have both paracrine and autocrine mechanisms of regulation, which complicates the development of the pathological process. In general, mediators involved in neuroinflammation, such as substance P, histamine, and 5-HT form a self-regulating cycle around the calcium channels, and regardless of the stage at which it started, even minor activation of more than one stage results in synergistic activation of the entire cycle [21]. This indicates that potentially neurogenic inflammation can act as a significant component of the pathogenesis for a wide range of diseases, regardless of the etiological factor, if there is an imbalance in the synthesis/degradation of neuroinflammatory mediators. For example, pathological processes by the type of neurogenic inflammation are recorded both in case of allergic asthma [1] and in case of exposure to tobacco smoke (in tissues of lungs, nasal mucosa, larynx, and brain) [4, 23].

Similar (or very close) mechanisms of inflammatory process development are observed in other pathologies. The development of neurodegenerative processes (Alzheimer's disease, Parkinson's disease, multiple sclerosis) involves inflammatory and neurotoxic mediators, such as IL1B, IL33, TNFα, substance P, and others [20], which are released by mast cells, neurons, and other cell types. This results in the increased concentration of Ca ions within cells and activation of mitogen activated kinase-like protein (MAPK) and nuclear factor NF-kappa-B (NFkB). In addition, when the blood-brain barrier is damaged (due to the progression of neurodegenerative diseases or for some other reason), immune cells and inflammation mediators may enter the brain from the periphery, which enhances neuroinflammation and neurodegenerative processes in these diseases.

According to I.V. Stagineva and A.G. Volkov [24], the division of facial pain symptoms in diseases of perinasal sinuses into somatic and neurogenic ones is justified only in terms of etiological factors, while in clinical manifestation of diseases, the pathogenetic mechanisms are inseparable. Involvement of substance P, histamine, and other substances significant for development of neurogenic inflammation in pathophysiological processes in rheumatoid arthritis [11], psychogenic urticaria [8], rhinosinusitis [13], facial pain in rhinosinusitis [24], cerebral dysfunction in chronic tobacco smoking [23], psoriasis [10], and cystitis [18] was established. Interestingly, histamine, being one of the key molecules of neurogenic inflammation, can not only provoke the development of well-known allergic pathological reactions of the skin (itching, urticaria) and bronchopulmonary system (nasal congestion, rhinorrhea, bronchospasm, etc.), but also lead to disruption of the cardiovascular and nervous systems (arrhythmias, anaphylaxis, hypotension/hypertension, dizziness, headache, migraine, vomiting, excitement, body temperature regulation, etc.), gastrointestinal tract (flatulence, abdominal pain), genitourinary system (dysmenorrhea, interstitial cystitis) , etc. [3, 25, 26]. Considering the importance of this amine for the development of neurogenic inflammation, it can be assumed that the neurogenic component may be significant to a certain extent for all these pathologies.

Neurogenic inflammation is a protective reaction of the body in response to certain exogenous stimuli. However, under certain conditions (long-term stimulus exposure, imbalance in the regulation of substances stimulating and inhibiting neurogenic inflammation, etc.), this pathophysiological process may become chronic.

ASSOCIATIONS BETWEEN GENES WHICH PRODUCTS ARE INVOLVED IN NEUROGENIC INFLAMMATION AND DISEASES

The development of neurogenic inflammation involves numerous molecules of different functional classes, the structural and functional properties of which depend on the genes encoding them or the genes which products are involved in the synthesis and degradation of such biologically active substances (in particular, histamine, serotonin synthesis). Neurogenic inflammation genes have been studied to varying degrees in terms of association with diseases and/or pathological phenotypes (table 1). Tumor necrosis factor alpha gene (*TNF*) and interleukin 1β (*IL1B*) gene were most frequently used for analysis, single reports are available for the tryptase beta 2 gene (*TPSB2*) and one MAS related GPR family member X2 (*MRGPRX2*). However, already at this stage of research, based on the accumulated data, it can be concluded that the overwhelming number of neurogenic inflammation genes can be characterized as highly pleiotropic (wherein the pleiotropy index is higher the more the gene studied). Yet, a high pleiotropy index of genes is combined with a low specificity index, i.e. gene variants more often show associations not with the disease, but with phenotypes (signs) and disease groups. It can be assumed that in this case the genes of neurogenic inflammation are more likely to act as genetic background determining the response to a particular exogenous stimulus (etiological factor) than as main causal factors of disease development.

Table 1

Functional "loading" of genes which products are involved in the processes of neurogenic inflammation*

Genes**	Total associated diseases/phenotypes	*DPI* – Disease Pleiotropy Index	*DSI* – Disease Specificity Index	The number of associated SNPs
TNF#	1640	0.966	0.263	21
IL1B	1035	0.931	0.312	15
PTGS2	832	0.897	0.338	24
POMC	557	0.862	0.382	20
NGF#	323	0.862	0.426	5
NTRK1	306	0.759	0.443	36
TRPV4#	289	0.759	0.519	51
CALCA#	274	0.828	0.456	1
TAC1#	252	0.793	0.473	–
TRPV1#	173	0.724	0.532	5
F2RL1	165	0.724	0.514	1
IL33	164	0.793	0.503	18
NGFR	160	0.724	0.508	2
VIP	152	0.759	0.526	2
DDC	131	0.621	0.554	50
IL7R	121	0.724	0.538	19
TSLP	107	0.690	0.547	9
TACR1#	105	0.724	0.559	6
MCAM	85	0.621	0.572	1
TRPA1	74	0.621	0.639	4
APP	71	0.862	0.430	63
PLCG1	62	0.517	0.611	4
VIPR1	56	0.483	0.624	2
IL1RL1	54	0.586	0.616	38
PNOC	52	0.414	0.672	–
HRH1	45	0.414	0.685	2
CRLF2	43	0.483	0.639	2
IL31RA	42	0.517	0.645	4
HDC	39	0.517	0.639	6
OSMR	38	0.448	0.648	8
HRH3	37	0.345	0.648	2

Table 1 (continued)

Genes**	Total associated diseases/phenotypes	*DPI* – Disease Pleiotropy Index	*DSI* – Disease Specificity Index	The number of associated SNPs
AMN	36	0.517	0.701	19
HRH2	32	0.310	0.663	–
HRH4	32	0.379	0.676	8
VIPR2	31	0.483	0.667	2
CIRBP	30	0.448	0.663	–
TPH2	28	0.552	0.562	28
IL31	23	0.276	0.727	1
CALCRL	21	0.517	0.707	2
MRGPRX1	21	0.483	0.752	–
TPSAB1	15	0.345	0.762	–
TPSD1	11	0.276	0.799	–
TPSG1	11	0.276	0.773	–
TPSB2	2	0.103	1.0	–
MRGPRX2	1	0.069	1.0	–

Note. * The information is taken from the DisGeNET database [27, 28]. ** Included genes are categorized as "neurogenic inflammation" according to DisGeNET (in bold) and according to scientific publications (neurogenic inflammation proteins shown in the diagram, Fig. 1). Gene *TNF* encodes TNFA protein, *NTRK1* gene – TrkA; *CALCA* gene – CGRP, *TAC1* gene – substance P (SP), *F2RL1* gene – PAR2, *NGFR* gene – p75NTR, *DDC* and *TPH2* gene products are involved in serotonin synthesis (5-HT), *IL7R* gene encodes IL7RA, gene *TACR1* – NK1 receptor, *PLCG1* gene – PLC protein, *IL1RL1* gene – ST2 receptor, *HRH1*, *HRH2*, *HRH3,* and *HRH4* genes – 4 types of histamine receptors (HR), respectively, *CRLF2* gene – TSLPR, *HDC* gene – an enzyme involved in the synthesis endogenous histamine; *CALCRL* gene – CGRP-R, genes *TPSAB1*, *TPSD1*, *TPSG,* and *TPSB2* genes encode tryptase; names of other genes correspond to the name of the proteins they encode. # Genes that are related to neurogenic inflammation according to various sources used for analysis were noted. *DPI* – Disease Specificity Index: the higher the index, the greater the number of different classes of diseases (MeSH) associated with the gene; Disease Specificity Index – *DSI* –varies from 0.25 to 1; the larger the index, the smaller the number of diseases associated with the gene.

For example, variants of the *TAC1* gene (encoding substance P) are associated with a wide range of diseases and phenotypes (depressive disorder, mental depression, gastroesophageal reflux disease, hyperreactivity of the bronchi, hyperemia, cirrhosis, colitis, pain, itching, tactile allodynia, inflammation, hyperalgesia (secondary), neuralgia, fibrosis, hypotension, bradycardia, allergic reactions, edema, etc.). Some of these diseases are also associated with variants of the *TACR1* gene encoding the substance P receptor (including hyperalgesia, mental depression, bradycardia, tactile allodynia, colitis, etc.) [27, 28]. This is consistent with the pathogenetic significance of proteins encoded by these genes in the universal neurogenic component of the pathogenesis of a wide range of diseases of various organs and systems.

As indirectly evidenced by associative studies, the spectrum of diseases for which neurogenic inflammation may be pathogenically significant is wider than that currently recognized. Neurogenic inflammation genes are overrepresented among genes associated with diseases of various organ systems (that is, they are recorded more frequently than if associations of the corresponding diseases with these genes were randomly detected) (table 2). Given the functional significance of neurogenic inflammation genes, it is expected that they are overrepresented among genes associated with such diseases/signs as hyperalgesia, swelling, inflammation and pain, itching, asthma, atopic dermatitis, and psycho–neurological disorders. In addition, genes of this pathological process are overrepresented among genes associated with diseases of the cardiovascular system (hypotension, hypertension, atherosclerosis, bradycardia, etc.), gastrointestinal tract (colitis), urogenital system (glomerulonephritis, albuminuria, cystitis), etc. For example, according to the DisGeNET database [27, 28], associations between the variants *DDC*, *HRH1*, *IL1B*, *PNOC*, *POMC*, *TAC1*, *TNF*, and *VIP* and hypotension were established (for 8 out of 82 genes associated with this pathology, the achieved level of the false discovery rate was FDR = $1.27 \cdot 10^{-6}$, see tab. 2); *CALCA*, *HRH3*, *IL1B*, *POMC*, *PTGS2*, *NACR1*, *TNF* were associated with hypertension (for 7 out of 302, FDR = 0.029), *HRH1*, *PTGS2*, *TNF*, *TRPV1*– with atherosclerosis (for 4 out of 59, FDR = 0.0164), *IL1B*, *NGF*, *POMC*, *TNF* – with glomerulonefrity (for 4 out of 40, FDR = 0.004), *IL1B*, *PTGS2*, *TNF* – with colitis (for 3 out of 40, FDR = 0.031), etc. In general, these associations are easily explained in view of the importance of

Table 2

Results of enrichment analysis for genes which products are involved in neurogenic inflammation

Disease/symptom	Calculated parameters*				
	N	*E*	*R*	*p*	*FDR*
Hyperalgesia	80	0.349	34.36	$4.44 \cdot 10^{-16}$	$1.14 \cdot 10^{-12}$
Edema	69	0.301	26.56	$4.25 \cdot 10^{-10}$	$7.25 \cdot 10^{-7}$
Bronchial hyperreactivity	12	0.052	95.44	$9.42 \cdot 10^{-10}$	$1.02 \cdot 10^{-6}$
Inflammation	114	0.498	18.08	$1.00 \cdot 10^{-9}$	$1.02 \cdot 10^{-6}$
Pain	79	0.344	23.20	$1.28 \cdot 10^{-9}$	$1.01 \cdot 10^{-6}$
Hypotension	82	0.358	22.35	$1.74 \cdot 10^{-9}$	$1.27 \cdot 10^{-6}$
Pruritus	59	0.258	27.18	$4.96 \cdot 10^{-9}$	$3.17 \cdot 10^{-6}$
Amnesia	17	0.074	67.378	$7.24 \cdot 10^{-9}$	$4.12 \cdot 10^{-6}$
Mental depression	260	1.135	9.69	$8.37 \cdot 10^{-8}$	$4.28 \cdot 10^{-6}$
Experimental arthritis	40	0.175	34.36	$1.60 \cdot 10^{-8}$	$7.42 \cdot 10^{-6}$
Bipolar disorder	516	2.253	5.77	$1.39 \cdot 10^{-7}$	$5.93 \cdot 10^{-5}$
Depressive disorder	413	1.803	6.100	$9.37 \cdot 10^{-7}$	$3.69 \cdot 10^{-4}$
Substance withdrawal syndrome	53	0.231	21.61	$3.00 \cdot 10^{-6}$	0.0011
Asthma	99	0.432	13.88	$3.86 \cdot 10^{-6}$	0.0013
Glomerulonephritis	34	0.149	26.95	$1.31 \cdot 10^{-5}$	0.0041
Mood disorders	187	0.816	8.57	$1.14 \cdot 10^{-5}$	0.0041
Fever	127	0.554	10.82	$1.63 \cdot 10^{-5}$	0.0044
Trigeminal neuralgia	12	0.052	57.26	$1.65 \cdot 10^{-5}$	0.0044
Atopic dermatitis	37	0.161	24.76	$1.85 \cdot 10^{-5}$	0.0047
Hyperemia	13	0.057	52.86	$2.14 \cdot 10^{-5}$	0.0052
Memory disorders	40	0.175	22.91	$2.53 \cdot 10^{-5}$	0.0059
Neuralgia	14	0.061	49.08	$2.71 \cdot 10^{-5}$	0.0060
Multiple sclerosis	42	0.183	21.81	$3.08 \cdot 10^{-5}$	0.0066
Gastric ulcer	18	0.0795	38.18	$6.00 \cdot 10^{-5}$	0.0123
Schizophrenia	1,041	4.54	3.08	$7.06 \cdot 10^{-5}$	0.0139
Necrosis	53	0.231	17.88	$7.79 \cdot 10^{-5}$	0.0148
Lung injury	20	0.087	34.36	$8.33 \cdot 10^{-5}$	0.015
Cerebrovascular accident	57	0.276	14.49	$1.53 \cdot 10^{-4}$	$9.46 \cdot 10^{-3}$
Overactive Bladder/Cystitis/Hereditary sensory and autonomic neuropathies/Acral ulceration and osteomyelitis leading to autoamputation/Anthracosis/HIV wasting syndrome**	4	0.017	114.53	$1.11 \cdot 10^{-4}$	0.016
Major depressive disorder	262	1.144	6.12	$1.19 \cdot 10^{-4}$	0.016
Atherosclerosis	59	0.258	15.53	$1.19 \cdot 10^{-4}$	0.016
Nerve degeneration	120	0.524	9.54	$1.61 \cdot 10^{-4}$	0.022
Albuminuria	25	0.109	27.49	$1.66 \cdot 10^{-4}$	0.022
Hereditary sensory autonomic neuropathy, type 5/Absence of pain sensation/Polymyositis**	5	0.022	91.62	$1.84 \cdot 10^{-4}$	0.022
Learning disorders	29	0.127	23.70	$2.60 \cdot 10^{-4}$	0.029
Congenital pain insensitivity/Sleep–wake disorders/Infection/ Postmenopausal osteoporosis /Dermatomyositis/Extravasation of diagnostic and therapeutic materials**	6	0.026	76.35	$2.76 \cdot 10^{-4}$	0.029
Hypertensive disease	302	1.319	5.31	$2.85 \cdot 10^{-4}$	0.029
Cognitive disorders	30	0.131	22.91	$2.88 \cdot 10^{-4}$	0.029
Colitis	31	0.135	22.17	$3.18 \cdot 10^{-4}$	0.031
Transitional cell carcinoma	33	0.144	20.82	$3.83 \cdot 10^{-4}$	0.037
Occupational asthma	7	0.031	65.44	$3.85 \cdot 10^{-4}$	0.037
Bradycardia	36	0.157	19.09	$4.97 \cdot 10^{-4}$	0.045
Common migraine/Pleurisy/Cutaneous leishmaniasis**	8	0.035	57.26	$5.12 \cdot 10^{-4}$	0.045
Thyroid neoplasm	37	0.162	18.57	$5.40 \cdot 10^{-4}$	0.047
Pneumonia	89	0.389	10.29	$5.80 \cdot 10^{-4}$	0.0495

Note. * The enrichment analysis was conducted by WebGestalt [30, 31] using the ORA (Overrepresentation Enrichment Analysis) method, for the "Diseases" category – according to DisGeNET [27, 28]; *N* – the total number of known genes associated with the disease/trait; *E* – the expected number of associated genes for a given disease/trait from those tested; *R* – excessive representation of genes in the test panel compared with the expected number (enrichment); *p* – the achieved level of significance in assessing the enrichment, *FDR* – the level of significance with the Benjamin–Hochberg adjustment. ** Diseases with the same calculated parameters are given, but which may be associated with different genes.

inflammation in the development of the above-mentioned diseases. Support for neurogenic inflammation as one of the pathogenetically significant processes in these pathologies is provided by clinical and experimental studies [2, 29, etc.].

The data given in the DisGeNET database [27, 28] on the association of genes with diseases have different evidence base, but for 18 of them highly significant connections were established (table 3). Variants of neurogenic inflammation genes not only predisposed to the development of diseases of the multi-factorial nature, but also acted as a cause of monogenic diseases. Among the diseases with the proven involvement of neurogenic inflammation genes in the pathogenesis, there is a wide range of mental and neurological disorders (vascular dementia, familial autonomic dysfunction, mental incapacity, etc.), asthma, migraine, endocrine disorders (obesity), pain sensitivity disorder, immune disorders, etc. Certainly, not all of the diseases listed in tables 2 and 3 have neurogenic inflammation as the only mechanism in the pathogenesis, but this component can be expected to be at least a modifying factor in the development and clinical picture of the disease.

Table 3

Diseases for which the pathogenetic significance of genes involved in neurogenic inflammation has been proven

Genes	Diseases
TNF	Susceptibility to asthma {600807/AD}, malaria, cerebral, {611162}, migraine without aura {157300/AD}, vascular dementia[$], septic shock[$]
IL1B	Familial Ménière disease (L); gastric cancer risk after *H. pylori* infection {137215/AD}
PTGS2	Familial Ménière disease (L)
POMC	Obesity, adrenal insufficiency, and red hair due to POMC deficiency {609734/AR}; susceptibility to obesity, early onset {601665/Mu, AR, AD}
NGF	Intellectual disability* (S); pain disorder (S); Charcot–Marie–Tooth disease (S); familial dysautonomia (S); sensory and autonomic hereditary neuropathy, type V {608654/AR}
NTRK1	Intellectual disability* (S); pain disorder (S); Charcot–Marie–Tooth disease (S); familial dysautonomia) (S); congenital insensitivity to pain with anhidrosis {256800/AR}; familial medullary thyroid carcinoma {155240/AD}
TRPV4	Charcot–Marie–Tooth disease (S); arthrogryposis (S); intellectual disability* (M); Klein–Levin syndrome (L)
DDC	Intellectual disability* (S); aromatic L-amino acid decarboxylase deficiency {608643/AR}
IL7R	Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type {608971/AR}
TRPA1	Pain disorder (S); familial episodic pain syndrome {615040/AD}
APP	Periodic fever syndrome (L); familial Alzheimer's disease, 1{104300/AD}; cerebral amyloid angiopathy, Dutch, Italian, Iowa, Flemish, Arctic variants {605714/AD}
CRLF2	Intellectual disability* (L)
IL31RA	Periodic fever syndrome (L); primary localized cutaneous amyloidosis, 2 {613955/AD}
HDC	susceptibility to the Tourette syndrome {37580/AD}
OSMR	Periodic fever syndrome (S); primary localized cutaneous amyloidosis, 1 {105250/AD}
AMN	Congenital anemia (S), cytopenia** (S); megaloblastic anemia – 1, Norwegian type {261100/AR}
TPH2	Intellectual disability* (S); susceptibility to attention deficit hyperactivity disorder, 7 {613003}; susceptibility to unipolar depression {608516}
TPSAB1	Ehlers–Dunlos syndrome (L)

Note. The level of evidence of the association between the gene and pathologies according to ClinGen and Genomics England (taken from DisGeNET [27, 28]) is given in parentheses: S is a strong link; M is a moderate bond, L is a weak bond; in curly brackets, catalog OMIM number and type of inheritance are given (AD is autosomal dominant; AR is autosomal recessive, Mu is mutational nature) [32]. The following notation is used: * groups of pathologies, ** phenotypes; [$] phenotype number in OMIM is not specified.

In addition to structural variants of genes, the course of neurogenic inflammation may be influenced by epigenetic mechanisms, which, in turn, may depend on environmental factors. Thus, between pregnant women with preeclampsia and women with normal pregnancy there are differences in the level of methylation of neurogenic inflammation genes (*POMC*, *CALCA*) in blood leukocytes [33], which can also determine differences in the level of expression of these genes. According to the information provided in DisGeNET

[27, 28], variants of these two genes are also associated with hypertension, as shown in the vast majority of associated studies performed.

COMORBIDITY OF DISEASES WITH A SIGNIFICANT COMPONENT OF NEUROGENIC INFLAMMATION IN THE PATHOGENESIS

The similarity of the genetic and biochemical components of neurogenic inflammation in various pathologies suggests the possibility of forming a comorbidity (polymorbidity). The largest number of clinical studies were carried out to investigate comorbidity between allergic and neuropsychiatric diseases (see review [34]). The obtained data strongly show that not only allergic diseases increase the probability of comorbidity with neuropsychiatric diseases, but patients with neuropsychiatric disorders have a higher risk of developing allergic pathologies. Other examples of comorbidity are also known. Thus, it has been shown that in bronchial asthma exacerbation of diseases of the gastrointestinal tract is often observed (in gastric mucosa, an increase in the number of cells activated by histamine is registered during exacerbation of bronchial asthma) [35]. In depression, dysregulation of the enzymatic production and degradation of catecholamines, neurotransmitters (including histamine), hormones, and immunological proteins is detected. Cyclic interactions are recorded between these molecules, when an increase or a decrease in one parameter can lead to stimulating or inhibitory action for others [22], which is well consistent with the model of neurogenic inflammation in which histamine is involved (Fig. 1). It has also been found that an increase in the level of inflammatory markers in brain tissues can lead to a change in the systemic immune response at the periphery [36]. In animal studies, chronic stress has been shown to increase the expression of *IL1B* and *TAC1* genes in white blood cells, as well as to disrupt the functioning of the pulmonary system [37]. In case of comorbidity of various diseases (for example, allergic and neuropsychiatric disorders), the commonality of the pathophysiological mechanisms is maintained not only by similar neurogenic inflammation mechanisms, but also by the results of genetic studies performed using both the candidate gene approach [38] and Genome Wide Association Studies (GWAS) [39].

CONCLUSION

Thus, the commonality of the pathophysiological processes in the development of neurogenic inflammation and the genetic features of individuals according to polymorphic variants of neurogenic inflammation genes may underlie the formation of comorbid conditions, such as allergic diseases, manifested at the level of various organ systems (bronchopulmonary system, gastrointestinal tract, etc.), and neuropsychiatric disorders. It can be assumed that the development of chronic neurogenic inflammation in one organ can increase the risk of comorbid inflammatory diseases in other organ systems. This can be facilitated by the transfer of histamine, substance P, and other key mediators of neurogenic inflammation (including penetration through the damaged blood-brain barrier), as well as some environmental factors with a unidirectional adverse effect (for example, excessive intake of histamine with food), especially if the genetic features of individuals are favorable for development of neurogenic inflammation.

Therefore, it is important to identify the diseases in the pathogenesis of which neurogenic inflammation plays a significant role. Establishing the commonality and specificity of the pathophysiological processes of neurogenic inflammation at biochemical and genetic levels in the development of pathological conditions of different organ systems is essential for understanding the patterns of disease formation, which may help prevent the disorders and determine the treatment strategy for patients, including the ones with comorbidities.

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