THE ROLE OF TOLL-LIKE RECEPTOR 4 GENE POLYMORPHISM IN THE DEVELOPMENT OF ORGAN DYSFUNCTION IN PATIENTS WITH SEVERE PNEUMONIA ASSOCIATED WITH A/H1N1 INFLUENZA

Malyarchikov A.V., Shapovalov K.G.

Chita State Medical Academy (Gorkogo str. 39A, Chita 672090, Russian Federation)

Corresponding author:
Andrey V. Malyarchikov,
e-mail: malyarchikov@bk.ru

ABSTRACT

The aim. *To identify the frequency of occurrence of TLR4 Asp299Gly (rs4986790) gene polymorphism and to establish its contribution to the development of organ dysfunction in patients with severe pneumonia associated with A/H1N1 influenza.*
Materials and methods. *The study included 55 patients with severe pneumonia associated with A/H1N1 influenza. Inclusion criteria: severe pneumonia; consolidation/ground-glass syndrome according to chest X-ray/CT. Exclusion criteria: unstable hemodynamics; body mass index > 30; diabetes mellitus; HIV; tuberculosis, oncopathology. Verification of the pathogen in the respiratory swab was carried out using PCR method: A/H1N1 influenza virus RNA was identified. The age of the patients was 47 [38; 62] years. Among all the patients the proportion of men was 47.8 %, of women – 52.2 %. Patients were divided into 2 groups: group 1 included patients with SOFA scale (Sequential Organ Failure Assessment) score ≥ 2 points; group 2 – patients with SOFA scale score < 2 points. Gene SNPs were determined by PCR method using standard kits developed by Research and Production Company "Litekh" (Moscow). Amplification of the TLR4 gene fragments was carried out in a thermocycler Bis-M111 (Bis-N LLC, Novosibirsk). Genomic DNA isolated from whole blood leukocytes using the "DNA Express Blood" reagent was analyzed followed by an amplification reaction. The amplification product was detected in a 3% agarose gel.*
Results. *Multiple organ dysfunction (SOFA scale score ≥ 2 points) in patients with severe pneumonia associated with A/H1N1 influenza was registered in 24 (43.6 %) cases. When analyzing the frequency of occurrence of the minor Gly allele, according to genetic models, the differences were established between patients of the groups 1 and 2 in codominant (p = 0.023; odds ratio (OR) – 8.82 (0.95–81.89)) and dominant (p = 0.005; OR = 12.35 (1.40–109.07)) models.*
Conclusion. *Severe pneumonia associated with A/H1N1 influenza is accompanied by a high incidence of organ dysfunction. The risk of organ failure development is 2.1 times increased in patients with severe pneumonia with identified TLR4 Asp299Gly gene polymorphism, which probably requires further study.*

Key words: *TLR4, polymorphism, A/H1N1 influenza, pneumonia, organ dysfunction*

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РОЛЬ ПОЛИМОРФИЗМА ГЕНА TOLL-ПОДОБНОГО РЕЦЕПТОРА 4 В РАЗВИТИИ ОРГАНОЙ ДИСФУНКЦИИ У БОЛЬНЫХ ТЯЖЁЛОЙ ПНЕВМОНИЕЙ ПРИ ГРИППЕ A/H1N1

Малярчиков А.В.,
Шаповалов К.Г.

ФГБОУ ВО «Читинская государственная медицинская академия» Минздрава России (672000, г. Чита, ул. Горького, 39А, Россия)

Автор, ответственный за переписку:
Малярчиков Андрей Викторович,
e-mail: malyarchikov@bk.ru

РЕЗЮМЕ

Цель исследования. *Выявить частоту встречаемости полиморфизма гена TLR4 Asp299Gly (rs4986790) и установить его вклад в развитие органной дисфункции у больных тяжёлой пневмонией на фоне гриппа A/H1N1.*

Материалы и методы. *В исследование включено 55 больных тяжёлой пневмонией на фоне гриппа A/H1N1. Критерии включения: пневмония тяжёлого течения; наличие консолидации/синдрома «матового стекла» по данным рентгенографии/компьютерной томографии органов грудной клетки. Критерии исключения: нестабильная гемодинамика; индекс массы тела > 30; сахарный диабет; ВИЧ; туберкулёз; онкопатология. Верификация возбудителя в респираторном мазке выполнялась при помощи метода полимеразной цепной реакции (ПЦР): идентифицирована РНК вируса гриппа A/H1N1. Возраст пациентов составил 47 [38; 62] лет. Мужчин было 47,8 %, женщин – 52,2 %. Пациенты были поделены на две группы: 1-я группа – с оценкой по шкале SOFA (Sequential Organ Failure Assessment) ≥ 2 баллов; 2-я группа – с оценкой по шкале SOFA < 2 баллов. Определение однонуклеотидных полиморфизмов (SNP, single nucleotide polymorphism) генов осуществлялось методом ПЦР с использованием стандартных наборов НПФ «Литех» (Москва). Амплификацию фрагментов гена TLR4 проводили в термоциклере «Бис-М111» (ООО «Бис-Н», Новосибирск). Анализу подвергалась геномная ДНК, выделенная из лейкоцитов цельной крови с помощью реагента «ДНК экспресс-кровь», затем проводилась реакция амплификации. Детекцию продукта амплификации проводили в 3%-м агарозном геле.*

Результаты. *У больных тяжёлой пневмонией на фоне гриппа A/H1N1 частота развития полиорганной дисфункции (SOFA ≥ 2 баллов) составила 24 (43,6 %) случая. При анализе частоты встречаемости минорного аллеля Gly, согласно генетическим моделям, установлены различия между пациентами 1-й и 2-й групп в кодоминантной (p = 0,023; отношение шансов (ОШ) – 8,82 (0,95–81,89)) и доминантной (p = 0,005; ОШ = 12,35 (1,40–109,07)) моделях.*

Заключение. *Тяжёлое течение пневмонии при гриппе A/H1N1 сопровождается высокой частотой развития органной дисфункции. Риск развития органной недостаточности увеличивался у больных тяжёлой пневмонией с выявленным полиморфизмом гена TLR4 Asp299Gly, что, вероятно, требует дальнейшего изучения.*

Ключевые слова: *TLR4, полиморфизм, грипп A/H1N1, пневмония, органная дисфункция*

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INTRODUCTION

The systemic inflammatory response, being the basis for the formation of critical conditions, regardless of the inducing factor, proceeds in two phases – from a hyperinflammatory reaction to a compensatory anti-inflammatory response [1, 2]. In the pro-inflammatory phase, damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) initiate signaling, activating innate and subsequently adaptive immune responses. To date, various physiological and pathophysiological mechanisms of innate and adaptive immune responses have been identified, implemented through the involvement of a large repertoire of immune receptors in the process, one of which is Toll-like receptors (TLR) [3]. Moreover, single-nucleotide polymorphisms of the Toll receptor genes have been identified, in some cases leading to a change in signal transmission realized through the receptor, which significantly affects the function of the receptor and contributes to the pathogenesis of inflammation and infectious diseases [3].

One of the most well-studied Toll receptors is TLR4. The main ligand of the receptor is a bacterial lipopolysaccharide, but TLR4 is also able to bind endogenous structures, such as heat shock proteins (HSP), including HSP70, Gp96, HSP22 and HSP7, proteins S100A8 and S100A9, as well as extracellular matrix molecules (ECM), such as biglican, tenascin-C, versican, and fragments of molecules ECM, including hyaluronic acid oligosaccharides and heparan sulfate [4]. The *TLR4* gene is located on 9q32-33 chromosome. The polymorphic locus rs4986790 is a single-nucleotide substitution of adenine (A) for guanine (G) at the +896 position of exon 3 (896A>G), leading to an amino acid substitution of aspartic acid for glycine at position 299 of the polypeptide chain of the Asp299Gly receptor [5]. The described *TLR4* gene mutation is associated with the lack of a proper immune response upon receptor activation. The *TLR4* Asp299Gly polymorphism has been shown to be associated with the development of a number of diseases [5–7]; it is of interest to study the role of the *TLR4* Asp299Gly gene polymorphism in critically ill patients with severe pneumonia associated with A/H1N1 influenza.

THE AIM OF THE STUDY

To identify the incidence of the *TLR4* Asp299Gly gene polymorphism and determine its contribution to the development of organ dysfunction in patients with severe pneumonia associated with A/H1N1 influenza.

MATERIALS AND METHODS

The study included 55 patients with severe pneumonia associated with A/H1N1 influenza hospitalized in ICU/CCU of the Municipal Clinical Hospital No. 1 (Chita), the Regional Clinical Hospital (Chita), the Regional Clinical Infectious Diseases Hospital of the Trans-Baikal Territory during the morbidity peak in 2019. The study was conducted in compliance with the principles of the World Medical Association Declaration of Helsinki (1964, ed. 2013), and approved by the local Ethics Committee of the Chita State Medical Academy of the Ministry of Health of the Russian Federation (Protocol No. 84 dated March 01, 2017). Inclusion criteria: severe pneumonia; consolidation/ground-glass syndrome according to chest X-ray/CT. Verification of the pathogen in the respiratory swab was carried out using PCR method: A/H1N1 influenza virus RNA was identified. The age of the patients was 47 [38; 62] years. The proportion of male was 47.8 %, female – 52.2 %. Exclusion criteria: unstable hemodynamics; body mass index > 30; diabetes mellitus; HIV; tuberculosis, oncopathology. To diagnose and assess the severity of pneumonia, the CURB/CRB-65, SMART-COP scales, as well as the federal clinical guidelines of the Ministry of Health of the Russian Federation "Community-acquired pneumonia in adults" and the IDSA/ATS criteria (in the presence of one "large" or three "small" criteria, pneumonia was regarded as severe) were used. In order to assess the degree of organ dysfunction, the following were used: qSOFA scale (Sequential Organ Failure Assessment [Quick]) (respiratory rate ≥ 22/min; systolic blood pressure ≤ 100 mmHg; decrease in consciousness < 15 points as per the Glasgow scale) – 1 point for each block; SOFA scale, which included an assessment of consciousness as per the Glasgow Coma Scale in points, a modified respiratory coefficient as the ratio of oximetry as a percentage to the oxygen content in the inhaled air in units (SpO_2/FiO_2), the level of bilirubin and creatinine in blood serum, the number of blood platelets, the level of average blood pressure with the presence or absence of inotropic and (or) vasopressor support in points. The patients were divided into two groups: Group 1 – patients with SOFA score ≥ 2; group 2 – patients with SOFA score < 2. Gene SNPs were determined by PCR method using standard kits developed by Research and Production Company "Litekh" (Moscow). Amplification of *TLR4* gene fragments was carried out in a thermal cycler "Bis-M111" (Bis-N LLC, Novosibirsk). Genomic DNA isolated from whole blood leukocytes using the "DNA Express Blood" reagent was analyzed followed by an amplification reaction. The amplification product was detected in a 3% agarose gel. Statistical processing of the obtained data was carried out using Statistica 10 software package (StatSoft Inc., USA) and SNPStats online calculators (https://medstatistic.ru/calculators.html). The distribution of genotypes was evaluated for compliance with the Hardy – Weinberg equilibrium. The genotype frequencies in the groups were compared using the Yates' continuity-corrected χ^2 test using the contingency table; if the expected phenomena in one of the cells were less than 5, the Fisher's exact test was used. To assess the association of genotypes with disease severity, the odds ratio (OR) was calculated with 95% confidence intervals (95% CI) using five genetic models: codominant, dominant, recessive, superdominant and log-additive.

RESULTS

In patients with severe pneumonia associated with A/H1N1 influenza, the incidence of multiple organ dysfunction (≥ 2 points on the SOFA scale) was 24 (43.6 %) cases, men prevailed among them – 17 (70.8 %) patients. In the structure of concomitant pathology among pneumonia patients with organ dysfunction, the most common were: chronic obstructive pulmonary disease – 7 (29.1 %) cases; type 2 diabetes mellitus – 6 (25.0 %) cases; alcoholism – 4 (16.6 %) cases. Furthermore, 16 (66.6 %) alimentary-constitutional obesity was revealed in patients as a background pathology. In the second patient group, ischemic heart disease was more common – in 9 (29.0 %) cases. Systemic inflammatory response syndrome (SIRS) was detected in 55 (100 %) cases. When analyzing the structure of organ dysfunction according to the SOFA scale, the highest incidence of organ failure development was found in the blocks of oxygenation, coagulation, central nervous system (CNS) function and hemodynamics parameters (Fig. 1). Besides, the frequent combination of organ disorders among patients with severe pneumonia associated with A/H1N1 influenza draws attention: for example, a combination of hemostasis and oxygenation disorders was noted in 10 (41.6 %) cases, and a combination of disorders of oxygenation, hemostasis, hemodynamics and CNS function – in 6 (25 %) cases.

The *TLR4* Asp299Gly gene polymorphism was studied in the test groups (Table 1). The value of $\chi^2 = 7.493$ for two degrees of freedom, with a statistical significance level of $p = 0.024$, which indicates statistically significant differences between comparable groups. When studying the *TLR4 Asp299Gly* gene polymorphism, a statistically significant difference in the groups was found for the Asp/Asp genotype ($p = 0.021$; OR = 0.081; 95% CI: 0.009–0.715). At the same time, there was no statistically significant difference in the incidence of the Asp/Gly variant and the homozygous Gly/Gly variant, which is probably due to the small sample size and low frequency of occurrence of the Gly allele (Table 1).

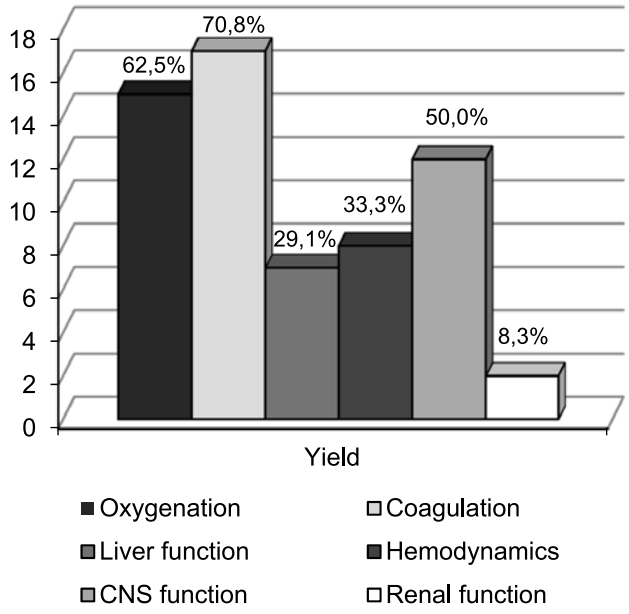

FIG. 1.
The structure of organ dysfunction by the SOFA scale blocks in patients with severe pneumonia associated with A/H1N1 influenza

When analyzing the frequency of occurrence of the minor Gly allele, according to genetic models, the most significant result was established for the dominant model ($p = 0.0052$; OR = 12.35 (95% CI: 1.40–109.07)), according to which the genotype carrying at least one Gly allele has an increased risk (Table 2). The results obtained in the superdominant and log-additive models are considered as uninformative at the obtained genotype distribution frequencies.

DISCUSSION

One of the leading pathophysiological components of a critical condition and organ dysfunction development is systemic inflammation. In the pro-inflammatory phase,

TABLE 1

DISTRIBUTION OF *TLR4* GENE GENOTYPES IN PATIENTS WITH SEVERE PNEUMONIA ASSOCIATED WITH A/H1N1 INFLUENZA

Genotypes	Frequency of genotypes		Fisher's exact test, *p*	*p* Bonferroni adjusted	OR	95% CI
	1st group (*n* = 24)	2nd group (*n* = 31)				
Asp/Asp	17 (70.8 %)	30 (96.8 %)	0.0159	0.0477	0.081	0.009–0.715
Asp/Gly	5 (20.8 %)	1 (3.2 %)	0.0755	0.226	7.895	0.855–72.882
Gly/Gly	2 (8.3 %)	0	0.186	0.558	–	–

TABLE 2

GENETIC MODELS OF THE ASSOCIATION OF *TLR4* GENE GENOTYPES WITH THE RISK OF ORGAN DYSFUNCTION DEVELOPMENT IN PATIENTS WITH SEVERE PNEUMONIA ASSOCIATED WITH A/H1N1 INFLUENZA

Genotypes	1st group (*n* = 24)	2nd group (*n* = 31)	OR (95% CI)	*p*
		Codominant model		
Asp/Asp	17 (70.8 %)	30 (96.8 %)	1.00	
Asp/Gly	5 (20.8 %)	1 (3.2 %)	8.82 (0.95–81.89)	0.02369
Gly/Gly	2 (8.3 %)	0 (0.0 %)	–	
		Dominant model		
Asp/Asp	17 (70.8 %)	30 (96.8 %)	1.00	0.005191
Asp/Gly-Gly/Gly	7 (29.2 %)	1 (3.2 %)	12.35 (1.40–109.07)	
		Recessive model		
Asp/Asp-Asp/Gly	22 (91.7 %)	31 (100 %)	1.00	0.1859
Gly/Gly	2 (8.3 %)	0 (0 %)	2.7 (0.32–153)*	

Note. * – adjusted value for a small sample.

damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) initiate signaling, activating innate and subsequently adaptive immune responses [2, 8]. Detection of conservative molecular patterns associated with pathogens (for example, lipopolysaccharide) through leucine-rich repeats (LRR) leads to dimerization of TLR, bringing together the TIR (Toll-interleukin receptor) signaling domains, forming intracellular docking platforms that allow recruiting adapter proteins and kinases into the signal transmission process, inducing nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and immune response [9, 10]. The single-nucleotide polymorphism of the *TLR4* 896A>G gene is associated with a decrease in the intensity of the immune response to TLR4 stimulation by lipopolysaccharide of gram-negative bacteria [11]. At the same time, as a pattern recognition receptor, TLR4 interacts not only with PAMPs, but also with a number of endogenous structures involved in the systemic inflammatory response cascade, such as heat shock proteins (HSP), including HSP70, Gp96, HSP22 and HSP7, proteins S100A8, and S100A9 [4]. In addition, the intensity of the emerging immune response depends on the ligand interacting with TLR4 [12]. The relationship of the *TLR4* Asp299Gly polymorphism with the course of the infectious process and inflammation in various diseases has been described [6, 7, 13]; a relationship with the severity of the critical condition in sepsis has been also shown [14]. This study demonstrated the prevalence of the Asp299Gly *TLR4* mutant allele and the combination of Arg753Gln *TLR2,* Leu412Phe TLR3 polymorphisms among influenza and influenza pneumonia patients [15]. We obtained comparable results: the presence of the *TLR4* gene polymorphic variant in patients with severe pneumonia associated with A/H1N1 influenza is connected with an increase in the severity of the disease and is accompanied by an increase in the frequency of organ dysfunction in this category of patients.

CONCLUSION

The severe course of pneumonia associated with A/H1N1 influenza is accompanied by a high incidence of organ dysfunction. The revealed presence of the *TLR4* Asp299Gly gene polymorphism was accompanied by an increased risk of organ failure, which probably requires further study.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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Information about the authors

Andrey V. Malyarchikov – Cand. Sc. (Med.), Head of The Department of Simulation Training Education, Chita State Medical Academy, e-mail: malyarchikov@bk.ru, https://orcid.org/0000-0003-0559-797X

Konstantin G. Shapovalov – Dr. Sc. (Med.), Professor, Head of the Department of Anesthesiology, Resuscitation and Intensive Care, Chita State Medical Academy, e-mail: shkg26@mail.ru, https://orcid.org/0000-0002-3485-5176

Authors' contribution:

Malyarchikov A.V. – study concept and design; material collection and processing; statistical data processing; copywriting.

Shapovalov K.G. – study concept and design; copywriting.