CLINICAL OBSERVATIONS

Low-penetrance R92Q (p.Arg121Gln) mutation in the *TNFRSF1A* gene: the significance and variants of phenotypes. Successful experience with the interleukin-1 inhibitor canakinumab in a female patient, who is a carrier of R92Q mutation with a severe TRAPS phenotype

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The paper is devoted to the assessment of the R92Q (p.Arg121Gln) mutation/polymorphism in the TNFRSF1A gene associated with the monogenic autoinflammatory disease – Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS). It gives data on the frequency of this gene in the general population, which is 1.3% and significantly exceeds the incidence of TRAPS. The authors describe the variants of phenotypes associated with its mutation from asymptomatic carriage to the development of a severe systemic autoinflammatory state with persistent febrile fever and a significant increase in the level of acute-phase inflammatory markers that do not respond to standard antirheumatic therapy. They present a clinical case of the high efficiency of the anti-interleukin 1? monoclonal antibody canakinumab in a female patient with a severe TRAPS phenotype, who had the R92Q mutation and hormonal dependence. Canakinumab therapy led to complete relief from all manifestations of the disease and to discontinuation of glucocorticoids. The authors conclude that the decision to prescribe therapy with biological agents should be made on the basis of the clinical severity of the disease rather than a variant of the mutation that caused it.

Keywords: *autoinflammatory diseases; Tumor Necrosis Factor Receptor-Associated Periodic Syndrome; low-penetrance R92Q mutation; canakinumab.*

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The end of the 20th century was marked by the emergence of a fundamentally new paradigm in medical science – the doctrine of autoinflammation and monogenic autoinflammatory diseases (AID), as a pathology of the natural immunity. This doctrine grew out of the problem of hereditary periodic fevers and arose due to advances in the development of molecular and medical genetics. Human AID (syndromes) are a heterogeneous group of rare genetically determined conditions characterized by unprovoked attacks of inflammation and manifested by fever and clinical symptoms that resemble rheumatic, but in the absence of autoimmune or infectious causes. [1–3] Interest in these rare (orphan) diseases is due not only to the severity of their manifestations and the risk of developing life-threatening complications such as AA-amyloidosis of the kidneys, but to a large extent to the fact, that they represent a natural biological model of a systemic inflammatory disease with a clearly established cause in the form of a mutation of a single gene, the product of which is involved in the functioning of the innate immune system. In the process of studying the problem, it became clear that many common multifactorial diseases with polygenic predisposition, such as juvenile arthritis with systemic onset, adult-onset Still's disease, gout, and even atherosclerosis, are autoinflammatory in their mechanisms [3–6]. One of the classic monogenic AID is TRAPS (TNF receptor-associated periodic syndrome) [1, 7] TRAPS is a hereditary monogenic autoinflammatory disease with an autosomal dominant type of inheritance, due to a mutation of the *TNFRSF1A* gene located on the short arm of the 12th pair of chromosomes (12p13) and encoding type I receptor for tumor necrosis factor-α [1]. The disease is characterized by repeated prolonged attacks of fever lasting 1–3 weeks; in some patients, the febrile period can be prolonged to 5–6 weeks or, less often, shortened to 2–3 days [3, 8, 9]. The intervals between attacks are different, usually 4–6 months. Temperature rises are accompanied by various systemic manifestations.

The type of mutation largely determines the severity and prognosis of the disease. [10] The most severe course with a

high risk of AA-amyloidosis is typical of patients with a mutation that leads to the replacement of a cysteine residue with another amino acid in the protein product of the gene. This phenomenon is described in genetics as penetrance, i.e. the frequency of a phenotype manifestation (a sign or disease) determined by the dominant allele, or the recessive allele in the homozygous state, and expressiveness, i.e. the degree of expression of the mutant gene in a particular individual. [11] in accordance with this, the following classification of allelic variants in patients with AID is proposed [12]:

1. A true pathogenic variant, which is clearly associated with a specific hereditary autoinflammatory phenotype. An example of such variants is p.M694V mutation in patients with familial Mediterranean fever, or *TNFRSF1A* gene mutations that lead to replacement of the cysteine residue in the protein product of the gene in patients with TRAPS;
2. Variants with undetermined significance. These include frequent variants whose association with the pro-inflammatory phenotype is contradictory, or very rare allelic variants. This group includes two subtypes:
   A) A variant initially described as pathogenic, for which conflicting information was subsequently obtained; its relatively high prevalence in the population clearly exceeds the prevalence of monogenic AID. Examples of such mutations for TRAPS syndrome are mutations R92Q – p.Arg121Gln (NM_000243.2:c.442G>C) and P46L – p.Pro75Leu (NM_001065.3:c. 224C>T).
   B) Newly identified variants or variants for which there is no reliable information.
3. Variants that definitely cannot cause the development of AID. An example is p.Arg202Gln mutation of the *MEFV* gene.

As can be seen from the presented classification, the R92Q (p.Arg121Gln) variant of the *TNFRSF1A* gene is relatively widespread in the population; its prevalence exceeds that of the disease itself – TRAPS. This mutation located in the 4th exon of the *TNFRSF1A* gene, according to the researchers who first described it, was found in the chromosomes of 1.04% of healthy individuals from the North American and Irish populations [13]. Similar indicators are provided by the «Infevers» database: for example; when evaluating the exome, this mutation is detected in 1.32% of the population as a whole, whereas in specific ethnic groups, its frequency varies from 0.32% for Africans and 0.83% for Latin Americans, to 1.68% for European residents and 2.07% for Ashkenazi Jews [14]. In a healthy population of Saudi Arabs, the frequency of simultaneous carriage of R92Q and P46L mutations was 1.6% [15]. In a study conducted in the Italian population, the frequency of carriage of the R92Q mutation was 2.25% [16]. In a molecular genetic study of 200 patients with periodic febrile syndrome of unspecified origin in the Italian population, the detection rate of the R92Q mutation was 2.45%, i.e. it did not differ from the frequency in the corresponding healthy population [16]. TRAPS syndrome is a rare, orphan disease, so the estimated frequency of its prevalence among children in Eastern and Central Europe is 1 case per 1,080,000 children aged 0–19 years [17]. It is obvious that the frequency of occurrence of this mutation in the population significantly exceeds the prevalence of TRAPS, i.e. most carriers of this mutation remain healthy. But, at the same time, according to the largest register of patients with TRAPS – Eurofever/EUROTRAPS, more than a third of patients (34%) were carriers of the R92Q mutation [9]. Even a higher proportion of patients with TRAPS – carriers of the R92Q mutation – is given by a German observational study: among German children with the TRAPS phenotype, 83% were carriers of this mutation. [18] According to E. I. Alekseeva et al., who screened 90 patients with the diagnosis of systemic juvenile arthritis (sJA), 10 patients with a pronounced autoinflammatory phenotype had a *TNFRSF1A* gene mutation; and 8 out of 10 had an R92Q mutation. In all these patients, the diagnosis was changed to TRAPS. It should be noted that 2 patients with this mutation had a severe course of the disease that was resistant to all therapies, including biologics [19]. In our own study, which included 184 patients with diagnoses of autoinflammatory syndrome and systemic juvenile arthritis who had molecular genetic testing of the *NLRP3*, *TNFRSF1A* and *MVK* genes (the gene for mevalonate kinase deficiency syndrome/periodic febrile syndrome with hyperimmunoglobulinemia D(MVK/HIDS)) mutations of the *TNFRSF1A* gene were detected in 10 patients, and 2 of them had the R92Q mutation (p.Arg121Gln) [20]. Thus, based on above data, the R92Q variant of the *TNFRSF1A* gene cannot be considered a harmless insignificant polymorphism.

A number of studies have been undertaken worldwide to determine the clinical and pathogenetic significance of the R92Q genetic variant. A retrospective study by A D'Osualdo et al analyzed the clinical picture and course of the disease in 18 patients who were carriers of this variant, recruited over a 10-year period [21]. When using the preliminary European Classification criteria for TRAPS, 56% of this group met these criteria. In 61% of patients, the disease debuted in childhood, the mean age of onset (for children) was 7.6 years (range 1–15 years). In the majority of observations, the clinical picture included recurrent episodes of fever; other symptoms included arthralgia/arthritis, myalgia, asthenia/fatigue, abdominal pain, headache, pain when swallowing, skin rash, and chest pain. This combination of symptoms coincided with the results obtained in the previous studies that evaluated the clinical picture associated with the R92Q mutation: for example, in almost all studies, repeated episodes of fever were found in all or almost all patients, and only in the study by N. Ravet et al. this symptom was noted in less than half of the patients (48%). [22, 24] In the Russian cohort of patients with the R92Q mutation (N=8), all examined patients had fever, arthritis/arthralgia, rash, lymphadenopathy, hepato- and splenomegaly, headache (87.5%) and abdominal pain (75%) [19]. Table 2 shows that Russian patients were closest to the North American and British patients observed by K. M. Hull et al [23].

Interesting data were obtained by of a group of Italian researchers who evaluated clinical and laboratory manifestations in children with TRAPS carrying a "structural" mutation (with cysteine residue replacement or T50M), and also in patients with periodic attacks of systemic inflammation and the R92Q mutation of the *TNFRSF1A* gene in comparison with a group of children with PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis). When comparing the groups of patients with structural mutations and the R92Q variant, there was a significantly higher fre-

Clinical and laboratory patterns of children and adults with TRAPS syndrome-carriers of the R92Q allele variant according to various series of observations.

	Hull et al [23]	Ravet et al [22]	Gattorno et al [25]	Lachmann et al[9]	Fedirici et al [27]	Ruiz–Ortiz et al [24]	Е.И.Алексеева и соавт[19]
Number of pts	9	34	15	54	78	18	8
Demographic data							
Gender (F/M)	3/6	17/17	–	–	38/40	9/9	6/2
Age at onset(years)	22(<1–53)	19	58+64	6(0–53)	6(3–19)	12(1–43)	9,0 (8 months–10 yeaers)
Age of diagnosis (years)	–	–	–	–	–	16(5–48)	–
Interval between the onset of the disease and diagnosis(years)	–	–	–	–	6,4(3,4–25,9)	3(0,3–25)	–
The duration of follow-up (years)	–	–	–	–	13	5,5(1–10)	–
Burdened family history %	–	21	7	19	–	28	–
Clinical symptom%							
Fever >38,0°C	100	48	100	94	100	100	100
Asthenia/fatigue	–	–	–	–	72	44	–
Arthralgia/arthritis	89	48	17	66	65	61	100
Myalgias	89	48	53	66	28	39	–
Abdominal pain	56	39	60	66	59	39	75
Vomiting	–	–	40	26	26	6	–
Chest (pleuro-pericardial) pain	33	32	13	22	24	22	–
Skin rash	78	36	33	30	20	28	100
Headache	–	16	53	39	5	33	87,5
Conjunctivitis	100	6	13	17	20	17	–
Periorbital edema	78	12	7	17	19	11	–
Cervical adenitis	–	19	60	52	26	17	100
Pharyngitis/odynophagia	–	12	67	24	22	33	–
Oral aphthae	–	–	40	14	15	17	–
Attacks characteristics							
Duration (days)	16 (6–30)	7,4	4,7±3,7	–	–	11(2–160)	14(8,5–20,5)
Frequency (per year)	11 (9–>12)	–	–	–	–	6(0,3–50)	6(2,11)
Increased inflammatory markers during attacks (%)	100	100	–	–	–	80	100
Amyloidosis development (%)	0	6,2	–	0	–	0	–

quency of positive family history (81%) in the group of structural mutations with complete penetrance, whereas in the genetic study of the parents of 12 patients with R92Q mutation, one of the parents always carried the same genetic variant, but was completely asymptomatic.

The duration of febrile attacks was shorter in R92Q-positive patients: an average of 5.9 days compared to the carriers of structural mutations – 15.3 days, while the frequency of attacks per year was higher in R92Q carriers – an average of 10.3, compared to 4.6 in the patients with structural mutations. The age of the disease onset in patients with structural mutations and R92Q was almost the same – 3.1 and 3.6 years, respectively. In patients with R92Q, periorbital erythema was never observed, while in patients with structural mutations it was present in 36.3% of cases; in patients with R92Q, chest pain was significantly less frequent (5% and 27.2%, respectively), but in the carriers of this low-penetrance mutation aphthous stomatitis was significantly more common (36.5% vs. 9.1%). In general, when evaluating the clinical picture, children with structural mutations were more likely to have

abdominal pain, rash, and limb pain than R92Q carriers, and patients with the R92Q mutation were more likely to have pharyngitis. Over the 7-year follow-up period, spontaneous termination of febrile episodes occurred in 25% of patients with the R92Q mutation, and a decrease by more than 30% in the frequency of febrile attacks was observed in 56% of patients with R92Q, whereas among the carriers of structural mutations there were no patients with spontaneous termination or a decrease in the frequency of attacks. In 6% of patients with R92Q, the course of the disease did not change in dynamics, and in 13% there was a deterioration with the formation of the chronic course that required continuous drug therapy. [16] This team of researchers noted that carriers of the R92Q mutation had significantly milder symptoms and disease course [16, 21], which, however, does not exclude the possibility of developing severe variants of the phenotype. Analyzing the outcomes in patients with the R92Q mutation, most authors [9,19,23,25,27] note the absence of amyloidosis in these patients, but in the group of similar patients observed by N. Ravet et al., amyloidosis was detected in 2 (6%) patients with the R92Q mutation. [22] Thus, the risk of developing this life-threatening complication of TRAPS is not excluded in the presence of the mutation under discussion, although it occurs much less frequently than in carriers of structural mutations, whose frequency of amyloidosis is 24%. [7]

In the cohort of patients with periodic febrile attacks and the R92Q mutation observed by the Italian authors, 5 patients met the criteria for PFAPA syndrome (Marshall syndrome). [21] This fact fits well with the concept that PFAPA syndrome is a nonspecific autoinflammatory syndrome with periodic attacks of systemic inflammation and a favorable prognosis, which is due to the presence of low-penetrance pathogenic alleles in a variety of genes encoding various molecules of the innate immune system, which we discussed in our previous publications. [29]

Attempts were made to find out the details of the pathogenesis of TRAPS in carriers of the R92Q mutation, which demonstrated different pathogenesis in patients with TRAPS – carriers of mutations that lead to replacement of cysteine residues or T50M-mutation, and in carriers of the low-penetrance allelic variant R92Q, which, in the authors' opinion, works as a pro-inflammatory factor only in the appropriate genetic and environmental context. The dose-dependent effect of the R92Q mutation was shown. [21, 28, 30, 32]

For the treatment of TRAPS, especially of its severe variants with frequent relapses of systemic inflammation, a prolonged course of attacks and a high risk of AA-amyloidosis, it is proposed to use various biologics [33]. Initially, it was a recombinant TNF-α receptor – etanercept, which seemed promising, but turned out to give a large proportion of cases of secondary ineffectiveness. TNF-α inhibitors based on monoclonal antibodies to TNF-α were not effective, moreover, they worsened the course of the disease. Thus, IL-1 inhibitors came to the fore. A randomized controlled trial «CLUSTER» demonstrated the effectiveness and safety of human monoclonal IgG1/Kappa isotype antibodies to interleukin-1β, canakinumab, in patients with TRAPS; on the basis of this trial, the drug, canakinumab, was registered for this indication. [34]

Hereafter we present a case of severe TRAPS in a child with the R92Q mutation and discuss the choice of therapy in such cases.

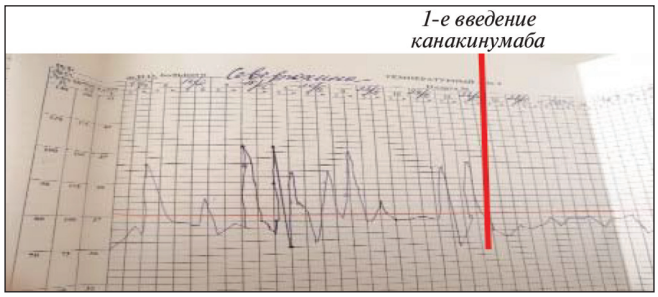

Fig. 1. *Dynamics of fever in Patient S. during canakinumab treatment*

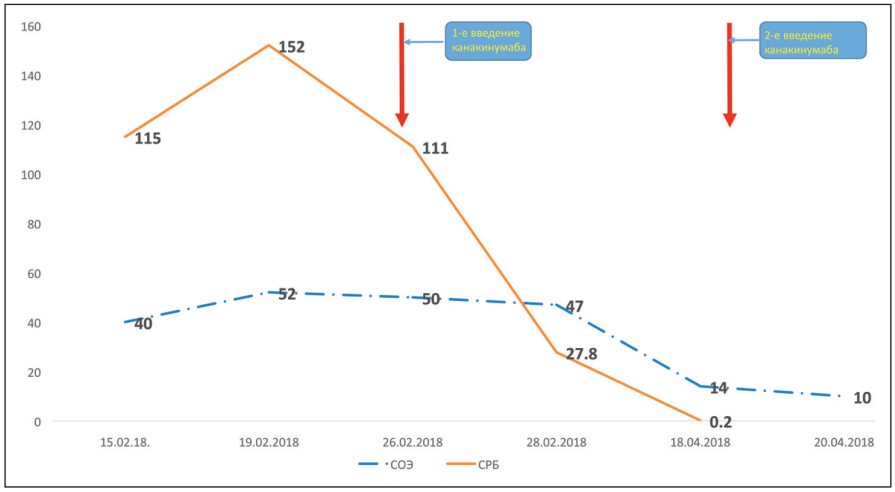

Fig. 2. *Changes in ESR and CRP level in Patient S. during canakinumab therapy*

***Patient 1**, female, Russian, born in 2008 (10 years old) from the 1st pregnancy; childbirth by caesarean section; congenital malformation of the urinary system – bladder exstrophy, complicated by secondary pyelonephritis. There is no family history of periodic fevers and rheumatic diseases.*

***Anamnesis morbi:** the patient has been ill since the age of 9 years. At the onset – daily fever up to 40.0°C. She was hospitalized at the place of residence. In the hospital, she had no clinical manifestations other than fever. There was an increase in the acute phase markers: erythrocyte sedimentation rate (ESR) in the range of 51–61 mm/h; leukocytosis with neutrophilia (90%), with a shift to band forms. The urinalysis did not reveal any pathology. The x-ray of the lungs showed changes that were regarded as a manifestation of pneumonia. Antibiotic therapy was performed (ceftriaxone, amoxivin, clarithromycin); against the background of the therapy the patient developed unstable macular rash on the face, thighs and buttocks which lasted less than a day and was regarded as an allergic reaction*

to antibiotics. A month after the onset of the disease, she was transferred to the Cardiorheumatology Department of Central Regional Children's Hospital. The source of infection that could explain the persistent fever could not be identified. By this time, the values of acute phase inflammatory markers had increased: ESR up to 92 mm/h, leukocytosis up to 54×10⁹/l, CRP 12.6 mg/l(normal <5 mg/l), ferritin 975 μg/l (normal 20–150 μg/l /l). Bone marrow trepanobiopsy did not reveal any evidence of hemoblastosis. Triple blood culture for sterility was negative. The disease was diagnosed as juvenile arthritis with systemic onset (sJA). Pulse-therapy with methylprednisolone was performed intravenously at a dose of 750 mg for 3 days, followed by oral administration of prednisolone at a dose of 25 mg per day (body weight at that time was 34 kg), and intravenous immunoglobulin infusions were performed. On the background of glucocorticoid (GC) therapy, the temperature normalized, but increased acute phase markers persisted. With reduction of the dose, a relapse of fever occurred, which took a strictly ordered pattern with the development in the morning hours. No significant joint syndrome was observed throughout the disease. MRI of the brain was performed, the results of which were interpreted as cerebrovasculitis in the primary care setting. In February 2018, she was first admitted to the children's clinic of the Nasonova Research Institute of Rheumatology. The dose of GC on admission – 12.5 mg/ day (in prednisolone equivalent). Body weight 38 kg, height 145 cm. In the hospital the patient's daily temperature rose to 40.5°C in the time interval from 8 to 10 a.m., once the peak temperature coincided with the appearance of several elements of macular rash on the right hand, which disappeared within a few hours, and once more – with an episode of abdominal pain, accompanied by vomiting. ***Blood count:*** *hemoglobin in the range from 115 to 129 g/L; leukocytosis from 30.9 to 41.7×10⁹/L due to neutrophilia with a shift to band forms of up to 16%; platelets from 328 to 419×10⁹/L.* ***Biochemistry of blood:*** *an increase in cholesterol to 6.67–8.29 mmol/L (normal 3.9–6.2 mmol/L); gamma-GTP – 182 U/L(normal 5–50 U/L), a slight increase in ferritin 166–218 μg/L (normal 20–150 μ/L). Other parameters of the biochemical blood test were normal. Electrophoresis of serum proteins showed a slight increase in α_2-globulins – to 14.51%.* ***Blood coagulation assay:*** *hypercoagulation via the internal pathway of thrombi formation (APTT – 26 sec [normal 26.2–31.2 sec]), fibrinogen 5.46 g/L (normal 2–4 g/L); D-dimer normal (<0.1 mg/L). Immunological* ***analysis of blood:*** *CRP 115–152 mg/L (normal 0–5 mg/L); ANA, antibodies to dsDNA, antibodies to Sm-antigen, Ro-Ab and La–Ab, ANCA were negative, ASLO normal, C3-and C4-complement components, IgG, IgM and IgA were normal, procalcitonin test 0.329 ng/ml (normal up to 0.1 ng/ml).* ***Urine analysis:*** *absence of protein, leukocyturia 10–14 in field of view (FoV), a small number of bacteria. Cellular elements in the urine: leucocytes 2,900/ml (normal up to 2,000), red blood cells 200/ml.* ***ECG:*** *sinus bradycardia 65/min. Increased electrical activity of the left ventricle.* ***Echocardiography:*** *signs of pericarditis (a small amount of fluid in the pericardium).* ***Ultrasonography of internal organs:*** *without significant changes.* ***CT of the chest organs:*** *without pathology.* ***MRI scans of the brain*** *(reviewed by an expert): no evidence of systemic or any other brain pathology.* ***Ophthalmological examination:*** *angiopathy of the retina. A* ***molecular genetic assay*** *was performed on TNFRSF1A and NLRP3(CIAS1) genes. Exons 2,3,4 were studied in the TNFRSF1A gene. Exon 4 revealed a change in the nucleotide sequence NM_001065 c. G362A; p.R121Q (R92Q-mutation) in the heterozygous state. No pathogenic alleles of the NLRP3 gene were found. The patient was diagnosed with TRAPS and prescribed canakinumab. On the day after the first administration of canakinumab at a dose of 150 mg subcutaneously (February 26, 2018) the temperature normalized, and the other symptoms did not recur. The acute phase reactants significantly decreased. The decrease in ESR was more delayed. The dynamics of fever and CRP are shown in Figures 1 and 2.*

After discharge from the hospital, the dose of GC was reduced. On March 30, 2018, the temperature rose to 38.5°C, accompanied by an increase in ESR to 34 mm/h, CRP to 79.72 mg/L, and leukocyturia 14 in FoV. The primary care physician regarded the symptoms as an exacerbation of a urinary tract infection, which was stopped within 2 days with antibiotics administration. There were no further episodes of fever. ESR (April 18, 2018) 14 mm/h, CRP 0.2 mg /L, ferritin 20 μg/L. The blood coagulation parameters normalized. There was an increase in cholesterol up to 7.23 mmol/L (normal 3.9–6.2). The manifestations of pericarditis disappeared according to the echocardiography data. The treatment with canakinumab was continued with an interval of 8 weeks between the injections. In May 2018, the GC therapy was completely discontinued. There were no relapses of fever and increase in acute phase reactants. Periodically, there were episodes of leukocyturia up to 28,000/ml in the urine analysis. In these cases, antibiotics and uroseptics were prescribed.

A similar mutation of the *TNFRSF1A* gene was detected in the patient's mother, who had no systemic inflammatory symptoms.

Thus, the presented case demonstrates manifestations of a rather severe phenotype in a patient with the R92Q mutation with debilitating fever, requiring long-term hospitalization and high doses of GCs, which did not control the clinical symptoms, but caused side effects, which would increase further in the course of continuing treatment. At the same time, the use of IL-1-inhibitor quickly and completely stopped all manifestations of the disease and made it possible to completely discontinue GC therapy.

However, we would like to give another example of a patient with TRAPS who had an R92Q mutation with a completely different course of the disease, in order to show the heterogeneity of phenotypes and therapeutic tactics in such patients.

Patient 2*, female, born in 2008 (9 years old) from the 1st pregnancy, childbirth eutocia. Before the onset of the present disease the child was practically healthy, with a history of only infrequent acute respiratory infections. The family history of periodic fevers and rheumatic diseases is negative.*

Anamnesis morbi: *The patient has been ill since the age of 7. In June 2016, she developed fever up to 40.0°C and erythematous ring-shaped rash with irregular contour and mild itching (Fig. 3, a, b). She was admitted to an infectious disease hospital, where a significant increase in acute phase reactants was detected (ESR 52 mm/h, CRP 62 mg/L, leucocytes. 22.3×10⁹/L). Treatment with antibiotics (ceftriaxone, azithromycin) and antihistamines was ineffective. The improvement was observed after the administration of GCs. On July 29, 2016, a bone marrow trepanobiopsy was performed, which made it possible to exclude*

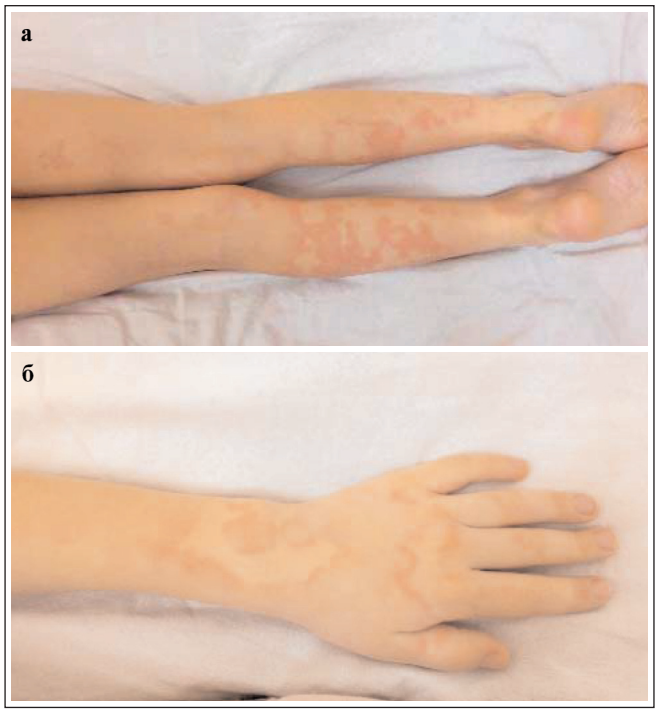

Fig. 3. *Rash in Patient E. (a, b)*

oncohematological pathology. The period from 05/08/16 to 11/08/16 was uneventful. On 12/08/16 a relapse occurred with subfebrile fever and rash. The patient was hospitalized to a local infectious disease children's hospital. Various infectious and parasitic diseases were excluded. Treatment with NSAIDs was prescribed. By the end of August 2016, the symptoms disappeared. Since September 2016, the symptoms were absent with normalization of laboratory parameters. In November 2016, a relapse with fever and chills occurred accompanied by erythematous rash at the fever height and pain in the knee and elbow joints without swelling. From 19/12/16 to 07/01/17, the patient was in a local hospital, where there was an increase in ESR to 40 mm/h, CRP to 14.2 mg/l. The diagnosis was made: sJA. Monogenic autoinflammatory syndrome was suggested. The treatment included pulse therapy with methylprednisolone 500 mg intravenously 22–24/12/16, then oral methylprednisolone at a starting dose of 10 mg/day, intravenous immunoglobulin at a total dose of 12.5 g. From the 2nd week of January 2017, complete disappearance of symptoms was noted.

In March–April 2017, for the first time, she was admitted to the children's clinic of the Nassonova Research Institute of Rheumatology. The dose of GCs on admission was methylprednisolone 5 mg/day; there were no complaints. The temperature was normal and stable; the skin without rash. There was a moderate enlargement of the tonsillar and posterior-cervical lymph nodes. No visible pathology of the internal organs and joints was found. Acute phase reactants were normal (ESR 4 mm/h, CRP 0.7 mg/L, leucocytes 8.7×10⁹/L). Ophthalmological examination did not reveal any pathology.

A molecular genetic assay of the TNFRSF1A and NLRP3(CIAS1) genes was performed. The TNFRSF1A-gene was found to have an R92Q mutation in the heterozygous state. No pathogenic alleles of the NLRP3 gene were detected. The patient was diagnosed with TRAPS. Taking into account the absence of clinical and laboratory activity of the inflammatory process, the benign course and the presence of a low-grade mutation, it was decided to continue gradually reducing the GC dose until complete withdrawal without prescribing a biologic. The GC therapy was gradually abolished. There were no relapses of the disease within 3 years.

Discussion and conclusions: Thus, the presented observations demonstrate a range of phenotypes in carriers of the R92Q mutation of the *TNFRSF1A* gene: from severe systemic inflammation with a prolonged high fever, significantly disrupting the quality of life, making impossible normal daily functioning and resistant to GC therapy; and a relatively favorable course in patient 2, to complete absence of symptoms in the mother of the first patient. We note certain difficulties in making a diagnosis: the clinical picture of patient 1 was absolutely dominated by daily recurrent fever and a significant increase in acute phase inflammatory markers with a minimum of other systemic manifestations. In the 2nd patient, the clinical course was characterized by fever, erythematous urticaria-like rash, lymphadenopathy, and increased level of acute phase markers. Almost all manifestations of the disease were stopped with systemic GC therapy, with subsequent withdrawal of GCs, without relapse for 3 years. The last observation corresponds to the variant described by the group of Italian authors [21] with complete relief of febrile manifestations and drug-free remission, which was observed in a quarter of these patients.

These observations of patients with TRAPS – carriers of the R92Q mutation, in conjunction with the data from the world scientific literature, allow us to draw the following **conclusions**:

1. Patients carrying the R92Q allele variant may develop a phenotype with severe systemic inflammation that is resistant to GC therapy and makes normal daily functioning impossible.
2. The decision on the administration of biologic therapy should be made based primarily on the severity of the disease and degree of the phenotype expression, and not on the type of mutation,
3. The IL-1 inhibitor canakinumab is as effective in treating patients with TRAPS carrying the R92Q allele variant as in patients with high-penetrance mutations.

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