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A family case of a rare autoinflammatory disease associated with mutations in the *NLRP3* and *TNFRSF1A* genes in the practice of a rheumatologist

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ABSTRACT

The article presents a clinical case of a rare autoinflammatory disease – a family case of Muckle – Wells syndrome. The diversity of clinical manifestations and the impossibility of confirming the diagnosis without a genetic study by DNA sequencing determine the complexity of and delay in the diagnosis. The development of severe complications and, as a consequence, a fatal outcome necessitates early diagnosis. The described clinical case demonstrates the importance of DNA sequencing for the timely diagnosis of the disease, the features of the disease course, and the familial nature of the disease. The diagnosis of Mackle – Wells syndrome in young family members before the development of severe complications will allow to start adequate and timely treatment and prevent the development of amyloidosis.

Keywords: autoinflammatory diseases, DNA sequencing, Muckle – Wells syndrome

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Семейный случай редкого аутовоспалительного заболевания, ассоциированного с мутациями в генах *NLRP3* и *TNFRSF1A*, в практике ревматолога

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РЕЗЮМЕ

Представлен случай из клинической практики редкого аутовоспалительного заболевания – семейного случая синдрома Макла – Уэллса. Разнообразность клинических проявлений и невозможность подтверждения диагноза без проведения генетического исследования методом секвенирования ДНК определяет сложность и несвоевременность диагностики. Развитие тяжелых осложнений и, как следствие, летального исхода обусловливает необходимость ранней постановки диагноза. Описанный клинический случай демонстрирует как важность проведения секвенирования ДНК для своевременной диагностики заболевания, так и особенности течения болезни и семейный характер заболевания. Постановка диагноза синдрома Макла – Уэллса у членов семьи молодого возраста до развития тяжелых осложнений позволят начать адекватное своевременное лечение и предотвратить развитие амилоидоза.

Ключевые слова: аутовоспалительные заболевания, секвенирование ДНК, синдром Макла – Уэллса

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INTRODUCTION

Autoinflammatory diseases (AID) refer to a group of rare monogenic and polygenic diseases characterized by innate immunity activation in response to endogenic and exogenic stimuli without the production of autoantibodies[1]. Nowadays almost 32 nosological forms of diseases are registered in the Eurofever registry with definite clinical presentatiton, the common feature of all these forms is recurrent episodes of periodic fever. The main variants of monogenic periodic fevers involve cryopyrin–associated periodic syndrome (CAPS), familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency, etc. CAPS includes a group of diseases caused by variants of cryopyrin-encoding *NLRP3* gene leading to inflammasome activation and interleukin (IL)-1 overproduction [2].

Diversity of clinical features (fever, hives, iridocyclitis, sensorineural hearing loss, elevated inflammation markers) and confirmation of the diagnosis exclusively by genetic testing (DNA sequencing) make the diagnosis challenging [3]resulting in excessive inflammasome activation with subsequent overproduction of interleukin (IL. To date, early diagnostic criteria have been developed to help suspect AID [4]. The need for timely diagnosis is due to the development of fatal complications, usually amyloidosis. Successful treatment for CAPS is directly associated with early administration of IL-1 inhibitors. Nowadays two monoclonal antibody drugs blocking IL-1 have been registered in the Russian Federation: canakinumab and anakinra. Also, there is some experience of using IL-6 and tumor necrosis factor (TNF)α inhibitors, but the greatest clinical effect is achieved using IL-1 inhibitors [5]efficacy and tolerability of biological disease-modifying antirheumatic drugs (bDMARDs. The main limitation associated with routine use of IL-1 inhibitors is high cost of the drug. We would like to present a clinical case of diagnosing familial CAPS in the practice of a rheumatologist.

CLINICAL CASE

The study was carried out in accordance with ethical standards developed in accordance with the Declaration of Helsinki of the World Medical Association “Ethical principles for medical research involving human subjects” as amended in 2000 and Rules of Clinical Practice in the Russian Federation approved by

the Order of the Ministry of Healthcare of the Russian Federation No. 266 of 19.06.2003.

Female patient X., proband (Fig. 1), aged 28 years, sought a consultation with a rheumatologist at the Research Institute of Clinical and Experimental Lymphology, branch of the Institute of Cytology and Genetics SB RAS, Novosibirsk, in October 2021. The patient complained of recurrent hives on the body and limbs, inflammatory pain in small wrist joints, and episodes of hyperthermia up to 37.5 °C.

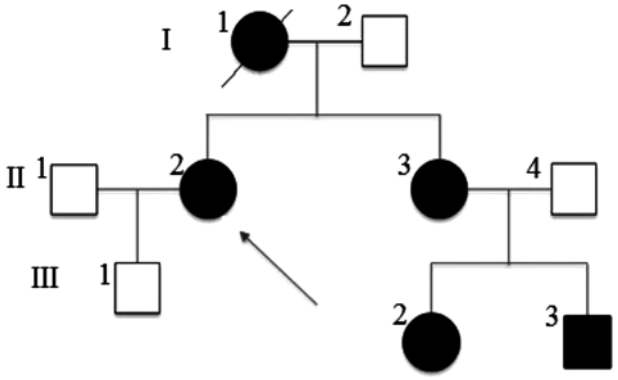

Fig. 1. Family tree

According to the medical history, since infancy, the proband has had relapses of hives on the body and limbs that do not respond to antihistamines and glucocorticoids. For that reason, the patient was repeatedly examined by an allergist and was followed-up with a diagnosis of chronic urticaria. In 2014, the proband turned to a rheumatologist for the first time with complaints of pain and swelling of wrist joints. Inflammation markers were elevated, rheumatoid factor (RF) and anti-cyclic citrullinated peptides (ACCP) were negative. The patient was diagnosed with rheumatoid arthritis and prescribed methotrexate 15 mg which showed a good clinical response, joint syndrome became minimal (DAS28 = 3.08).

In May 2020, the patient discontinued methotrexate due to pregnancy planning. No exacerbation of joint syndrome was recorded during pregnancy and after childbirth. When taking a family history, it was revealed that patient's mother (born in 1966) had the same recurrent hives, sensorineural hearing loss, arthritis, and chronic kidney disease which caused her death at the age of 55. Also, proband's sibling (born in 1989) has manifestations of hives, arthralgia in wrist joints, and episodes of hyperthermia up to 37.5 °C. Sibling's children (boy and girl) were observed by a rheumatologist with juvenile arthritis. After genetic testing, which revealed a pathogenic variant of the *NLRP3* gene, in 2018, their diagnosis was changed to cryopyrin-associated periodic syndrome, Muckle – Wells syndrome. Both children receive canakinumab with a good clinical response. The sibling also underwent a genetic testing in 2019 and the pathogenic variant *chr1:247587529C>T [hg19], NM_004895.4:c.784C>T, P_004886.3:p.(Arg262Ter) (R262X), dbSNP:rs121908150* in the *NLRP3* gene and the pathogenic variant *chr12:6442643C>T [hg19], NM_001065.3:c.362G>A, NP_001056.1:p.(Arg121Gln) (R121Q), HGMD:CM012483, dbSNP:rs4149584* in the *TNFRSF1A* gene were identified (Table 1, 2). According to clinical data and genetic testing results, the diagnosis of Muckle – Wells syndrome was established.

Table 1

Characteristics of the pathogenic variant of the *NLRP3* gene: Arg262Ter, found in the *NLRP3* gene

Parameter	Value
Genomic coordinates [hg19]	chr1:247587529C>T
dbSNP identifier	rs121908150
Transcript	NM_004895.4:c.784C>T
Protein	NP_004886.3:p.(Arg262Ter)
Gene	NP_004886.3:p.(Arg262Ter)
Exon	4/10
Pathogenicity	Pathogenic
Pathogenicity criteria	
PVS1	The nonsense variant of a gene, for which LoF variants are the known cause of pathology
PM2	The variant is absent in the control (or occurs with extremely low frequency). The highest known frequency in the population is 0.0004% (TOPMED).
PM1	The variant is located in an important functional protein domain that does not have known benign changes. According to InterPro Domain, protein NACHT domain is located here.
PP5	Reliable sources indicate the variant pathogenicity. According to CLINVAR, the variant is considered pathogenic (CV000004622.5, RCV000004623.6, RCV000221297.4, RCV001067187.1, RCV001285973.1)

Table 2

Characteristics of the pathogenic variant of the *TNFRSF1A* gene: Arg121Gln, found in the *TNFRSF1A* gene

Parameter	Value
Genomic coordinates [hg19]	chr12:6442643C>T
dbSNP identifier	rs4149584
Transcript	NM_001065.3:c.362G>A
Protein	NP_001056.1:p.(Arg121Gln)

Table 2 (continued)

Parameter	Value
Gene	TNFRSF1A
Exon	4/10
Pathogenicity	Variant of uncertain clinical significance
Pathogenicity criteria	
BS1	The allele frequency is higher than expected for the disease. The highest frequency is 2.7% (population of Northern Sweden).
PM1	The variant is located in an important functional protein domain that does not have known benign changes. According to InterPro Domain, TNFR / NGFR cysteine-rich region is located here.
PP5	Reliable sources indicate the variant pathogenicity. According to HGMD, the variant is considered pathogenic (HGMD: CM012483)

The proband examination revealed the following: erythema on cheeks, hives on the body and limbs. There were vesicular breath sounds in the lungs. The heart sounds were clear and rhythmic. The patient did not feel pain in joints which were also not swollen. As for laboratory tests, ESR was elevated up to 45 ml / h, CRP 49 mg / l, creatinine 76 μmol / l, RF was negative (8 U / ml with the reference value 20 U / ml), ACCP was slightly positive (32 U / ml with the reference value 25 U / ml). Wrist and foot X-ray revealed no joint space narrowing, periarticular osteoporosis or erosive arthritis.

Taking into account that the proband and her relatives have the variant of the *NLRP3* gene with typical manifestations of Muckle – Wells syndrome, Sanger sequencing of all exons of the *TNFRSF1A* and *NLRP3* genes was performed in the proband in October 2021. As a result, pathogenic gene variants previously found in the patient's sibling were revealed in both genes: the pathogenic variant *chr1:247587529C>T [hg19]* in the *NLRP3* gene and the pathogenic variant *chr12:6442643C>T [hg19]* in the *TNFRSF1A* gene (Fig. 2).

Based on the clinical data and the results of molecular genetic testing, the diagnosis of cryopyrin-associated periodic syndrome: Muckle – Wells syndrome was verified. According to ACR / EULAR 2010 criteria, the proband did not match with the diagnosis of rheumatoid arthritis, and joint syndrome was most likely caused by CAPS. Special attention should be paid to the examination of ACCP which was slightly increased in the patient, as its significant increase allows to diagnose rheumatoid arthritis by the ACR / EULAR criteria (symmetric polyarthritis of small wrist joints accompanied by elevated CRP). The combination of AID and rheumatoid arthritis is a rare and difficult to differentiate case. The proband's sibling and mother were invited to the clinic of the Research Institute of Clinical and Experimental Lymphology, branch of the Institute of Cytology and Genetics SB RAS for further examination (Table 3).

Table 3

Clinical manifestations of the family case of Muckle–Wells syndrome

Parameter	Proband, 28 years old	Proband's mother, 54 years old	Sibling, 32 years old	Sibling's son, 11 years old	Sibling's daughter, 9 years old
Hives	+	+	+	–	–
Fever	+	+	+	–	–
Arthritis / arthralgia of small wrist joints	+	+	+	+	+
Conjunctivitis	–	–	+	–	–
Sensorineural hearing loss	–	+	–	–	–
Renal lesion (chronic kidney disease most likely due to amyloidosis)	–	+	–	–	–
Uveitis	–	–	–	+	+
Elevated acute phase reactants (ESR, CRP)	+	+	+	+	+

According to Table 3, all family members had typical clinical manifestations of Muckle – Wells syndrome including fever, recurrent hives, joint syndrome, and elevated inflammation markers. All family members, with the exception of the proband's mother, underwent a molecular genetic testing, which revealed the pathogenic variant of the *NLRP3* gene. A proband's child did not undergo genetic testing due to the absolute absence of any clinical manifestations of the disease. However, it is planned to conduct genetic testing later as the disease is likely to manifest itself not in early childhood.

The proband's mother had the most severe course of the disease with sensorineural hearing loss and chronic kidney disease that possibly caused her death in 2021. The presence of verified Muckle – Wells syn-

drome with clear clinical manifestations and elevated inflammation markers was an indication for the use of genetically engineered biologicals. Also, the presence of a pathogenic variant of the *TNFRFS1A* gene is associated with a high level of TNFα, which may also determine the choice of genetically engineered biologicals. Currently, the patient and her sibling are undergoing safety screening to assess the possibility of prescribing genetically engineered biologicals, including canakinumab.

According to the literature, the severity of Muckle – Wells syndrome can be divided into mild, moderate, and severe[6]. As can be seen in the clinical case described, there are both severe manifestations of the disease among family members (in the proband's mother) and a moderate phenotype. It remains unclear whether the presence of a pathogenic variant of the *TNFRFS1A* gene affects the severity of Muckle – Wells syndrome phenotype. More and more studies are aimed at studying the effect of digenic mutations on the severity of the disease [7]. So, A. Blaschek et al. described the combination of genetic variants of *MEFV* and *TNFRSF1A* genes that led to the onset of multiple sclerosis in childhood [8]. Other authors discussed the digenic inheritance of *MEFV* and *NLRP3* genes or *MEFV* and *TNFRSF1A* genes [9]. We could not find any data in the literature on the combination of genetic variants of *TNFRSF1A* and *NLRP3* genes, but it may determine a more severe course of Muckle – Wells syndrome.

CONCLUSION

This clinical case demonstrates the complexity of differential diagnosis between autoimmune and autoinflammatory diseases. As can be seen, even if a case formally meets the criteria of rheumatoid arthritis and there are clinical manifestations that do not correspond to definite nosological forms, physicians should consider other causes of joint syndrome, hives, fever, etc. So, it is necessary for rheumatologists, clinical geneticists, and molecular diagnosis specialists to cooperate in such cases.

This clinical case represents an example of a rare monogenic disease, the diagnosis of which is highly difficult and impossible without DNA sequencing. The disease severity and the development of severe complications, which are the main cause of patient mortality, require early diagnosis and treatment. Patients should be timely referred to a clinical geneticist in order to identify indications for molecular genetic testing, so that the diagnosis of an autoinflammatory disease is confirmed and proper disease-modifying drug therapy is initiated. Also, testing of a larger number of genes may determine the treatment strategy and the choice of the drug.

REFERENCES

1. Masters S.L., Simon A., Aksentijevich I., Kastner D.L. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu. Rev. Immunol.* 2009;27:621–668. DOI: 10.1146/annurev.immunol.25.022106.141627.
2. Kelley N., Jeltema D., Duan Y., He Y. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. *Int. J. Mol. Sci*. 2019;20(13):3328. DOI: 10.3390/ijms20133328.
3. Welzel T., Kuemmerle-Deschner J.B. Diagnosis and management of the cryopyrin-associated periodic syndromes (CAPS): What do we know today? *J. Clin. Med.* 2021;10(1):128. DOI: 10.3390/jcm10010128.
4. Gattorno M., Hofer M., Federici S., Vanoni F., Bovis F., Aksentijevich I. et al. Classification criteria for autoinflammatory recurrent fevers. *Ann. Rheum. Dis.* 2019;78(8):1025–1032. DOI: 10.1136/annrheumdis-2019-215048/
5. Salugina S.O., Fedorov E.S. Biologic disease-modifying antirheumatic drugs in the treatment of major monogenic autoinflammatory diseases: literature review and clinical observation. *Modern Rheumatology Journal*. 2021;15(6):95–100 (in Russ.). DOI: 10.14412/1996-7012-2021-6-95-100.
6. Ben-Chetrit E., Gattorno M., Gul A., Kastner D.L., Lachmann H.J., Touitou I. et al. Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. *Ann. Rheum. Dis*. 2018;77(11):1558–1565. DOI: 10.1136/annrheumdis-2017-212515.
7. Ozyilmaz B., Kirbiyik O., Koc A., Ozdemir T.R., Kaya Ozer O., Kutbay Y.B. et al. Molecular genetic evaluation of NLRP 3, MVK and TNFRSF 1A associated periodic fever syndromes. *Int. J. Immunogenet.* 2019;46(4):232–240. DOI: 10.1111/iji.12431.
8. Blaschek A., Kries R., Lohse P., Huss K., Vill K., Belohradsky B.H. et al. TNFRSF1A and MEFV mutations in childhood onset multiple sclerosis. *Eur. J. Paediatr. Neurol.* 2018;22(1):72–81. DOI: 10.1016/j.ejpn.2017.08.007.
9. Neocleous V., Byrou S., Toumba M., Costi C., Shammas C., Kyriakou C. et al. Evidence of digenic inheritance in autoinflammation-associated genes. *J. Genet.* 2016;95(4):761–6. DOI: 10.1007/s12041-016-0691-5.

Authors' contribution

Kurochkina Yu.D., Korolev M.A., Letyagina E.A. – drafting of the manuscript. Korolev M.A. – final approval of the manuscript for publication. Fishman V.S., Gridina M.M., Valeeva E.S. – carrying out of the genetic study.

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