Novel NLRP12 variant in a patient with cold-induced autoinflammatory disease

Šimac, Daniel Victor; Štimac, Davor

Reumatizam 2023;70(1):10–14
https://doi.org/10.33004/reumatizam-70-1-2

CASE REPORT PRIKAZ BOLESNIKA

NOVEL *NLRP12* VARIANT IN A PATIENT WITH COLD-INDUCED AUTOINFLAMMATORY DISEASE

NOVA VARIJANTA *NLRP12* U BOLESNIKA S AUTOINFLAMATORNOM BOLEŠĆU IZAZVANOM HLADNOĆOM

Daniel Victor Šimac[1], Srđan Novak[1]

[1]Department of Rheumatology and Clinical Immunology, Clinical Hospital Centre Rijeka, Rijeka, Croatia / Odjel za reumatologiju i kliničku imunologiju, Klinički bolnički centar Rijeka, Rijeka, Hrvatska

Corresponding author /Adresa autora za dopisivanje:
Daniel V. Šimac,
Department of Rheumatology and Clinical Immunology
/ Odjel za reumatologiju i kliničku imunologiju
Clinical Hospital Center Rijeka / Klinički bolnički centar Rijeka
Tome Strižića 3, 51000 Rijeka
Croatia / Hrvatska
E-mail / e-pošta: danielsimac@hotmail.com

Received / Primljeno: 24th February 2023 / 24. 2. 2023.
Accepted / Prihvaćeno: 4th June 2023 / 4. 6. 2023.

Abstract

The pathogenesis and genetics of systemic autoinflammatory diseases (SAIDs) are becoming clearer and more descriptive with time. When it comes to these diseases, it must be noted that familial Mediterranean fever (FMF) is still known as one of the most common and well-known diseases of this group. Strides have been made in the family of cryopyrin-associated periodic syndromes (CAPS), among others, including familial cold-induced autoinflammatory syndrome (FCAS), in which the *NLRP3* gene variants have been shown to be causative by disrupting interleukin (IL)-1β secretion. In a subset of CAPS patients without causative *NLRP3* variants, the *NLRP12* gene, with its anti- and proinflammatory roles, has been shown to be causative in such patients. Common symptoms include fever, musculoskeletal and abdominal symptoms, and urticaria induced by the cold. Treatment includes non-steroidal anti-inflammatory drugs, antihistamines, and glucocorticoids. The case of a 40-year-old man with recurring fever and elevated C-reactive protein during winter months without any other clear cause after extensive work up is presented. Genetic testing was ordered under suspicion of SAID, and an *NLRP12* gene variant, c.850C>G, was found, which was not described in any databases or reports to date. *In silico* testing did not show changes to the protein, but functional studies are unavailable. Despite this, we diagnosed our patient with *NLRP12*-associated SAID or FCAS 2. Acquired SAID, given the age, was considered, but unlikely given the clinical presentation, and the *NLRP12* gene variant. Considering that the patient lives in a region that has mild winters, and the fact that the temperatures rarely go below 0 °C in this region, it is possible that this, in combination with an aging immune system, may explain why the patient did not manifest symptoms earlier. This case report presents a patient with a clinical presentation suggestive of CAPS or FCAS 2, with a novel *NLRP12* variant, c.850C>G, which is possibly causative. This case report also shows that novel variants are still being discovered, and that they should be researched if they are suspected in certain cases.

Keywords: systemic autoinflammatory disease, cryopyrin-associated periodic syndrome, familial cold-induced autoinflammatory syndrome, *NLRP12* gene

Sažetak

Patogeneza i genetika sustavnih autoinflamatornih bolesti (SAIB) danas postaje sve jasnija i opsežnija. Obiteljska mediteranska groznica je među najčešćim i najpoznatijim SAIB-ovima. Otkrićem varijanti gena *NLRP3* koje dovode do poremećaja sekrecije interleukina (IL)-1β prati se napredak u razumijevanju obitelji periodičnih sindroma povezanih s kriopirinom (CAPS, prema engl. *Cryopyrin-associated periodic syndrome*), uključujući i obiteljski autoinflamatorni sindrom izazvan hladnoćom (FCAS, prema engl. *Familial cold-induced autoinflammatory syndrome*). U podskupini CAPS-a bez uzročnih varijanta *NLRP3*, pokazalo se da važnu ulogu ima gen *NLRP12*, koji ima protuupalnu i proupalnu ulogu. Uobičajeni simptomi uključuju vrućicu, mišićno-koštane i trbušne simptome te urtikariju izazvanu hladnoćom. Liječenje uključuje nesteroidne protuupalne lijekove, antihistaminike i glukokortikoide. Prikazan je slučaj muš-

karca u dobi od 40 godina s rekurentnim vrućicama i povišenim C-reaktivnim proteinom tijekom zimskih mjeseci bez drugoga jasnog uzroka nakon proširene obrade. Učinjeno je genetsko testiranje pod sumnjom na SAIB, koje je otkrilo novu varijantu u genu *NLRP12*, c.850C>G, koja do danas nije opisana ni u jednoj bazi podataka niti u literaturi. *In silico* ispitivanje nije dokazalo oštećenje proteina, te funkcijske studije nisu dostupne. Unatoč tomu postavili smo dijagnozu SAIB-a povezanu s *NLRP12* ili FCAS 2. Zbog dobi pacijenta razmatrala se i stečena SAIB, ali s obzirom na kliničku sliku i na varijantu gena *NLRP12*, smatramo da je ona manje vjerojatna. Moguće objašnjenje zašto pacijent nije ranije razvio simptome jest blaže vrijeme u regiji u kojoj pacijent živi, gdje temperatura rijetko pada ispod 0°C, u kombinaciji sa „starenjem" imunološkog sustava. Prikaz slučaja opisuje pacijenta s kliničkom slikom koja je karakteristična za CAPS ili FCAS 2, uz novu varijantu gena *NLRP12*, c.850C>G, koja je mogući uzročnik bolesti. Nove varijante stalno se otkrivaju te kod karakteristične kliničke slike treba na njih posumnjati i istražiti ih.

Ključne riječi: sustavna autoinflamatorna bolest, periodični sindrom povezan s kriopirinom, obiteljski autoinflamatorni sindrom izazvan hladnoćom, gen *NLRP12*

INTRODUCTION

The pathogenesis of hereditary systemic autoinflammatory diseases (SAIDs) along with their genetic basis are increasingly investigated which led to new entities being discovered and described. Familial Mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), and tumor necrosis factor type 1 A receptor-associated periodic syndrome (TRAPS) are among the most common and well-known diseases of this type, monogenic in nature, and they often occur in the Middle East. (1–3) The hallmark of these diseases is innate immune system dysfunction presenting with symptoms such as recurrent fever, arthritis, rash, and serositis, with amyloidosis as a possible complication. (1–3)

Familial cold-induced autoinflammatory syndrome (FCAS), chronic infantile neurologic, cutaneous, articular syndrome (CINCA), and Muckle-Wells syndrome (MWS) fall within the family of CAPS. (1–3) They are associated with *NLRP3* gene mutations, which lead to interleukin (IL)-1β secretion disruption. (1–3) In a subset of patients with CAPS without *NLRP3* gene mutations, it has been found that mutations in the *NLRP12* gene are responsible for these syndromes. (2,3) The NLRP12 protein is known to have both anti and proinflammatory roles, downregulating NF-κB and stimulating IL-1β and IL-18, respectively, thus in theory, variants could cause SAID. (2–4) Common symptoms of *NLRP12*-associated SAID, or FCAS 2, include fever in 93% of cases, followed by musculoskeletal symptoms in 61%, urticaria in 52%, abdominal symptoms in 38%, headache in 22%, and elevated acute phase reactants in 30% of cases, which is triggered by exposure to the cold in 36% of cases; and other than that symptoms such as fatigue, other types of rashes, and conjunctivitis have also been reported. (2,4) Antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids are used in treatment as needed. (2,4) There has been positive results with anakinra, and research suggests the possibility of using tumor necrosis factor (TNF) as well as IL-6 inhibitors, although the exact behaviour of cytokines in this disease is unclear. (2,4)

UVOD

Patogeneza i genetika nasljednih sustavnih autoinflamatornih bolesti (SAIB) sve se više istražuju, što dovodi do novih otkrića i opisa novih entiteta. Obiteljska mediteranska groznica (engl. *Familial Mediterranean Fever*, FMF), s kriopirinom povezani periodični sindromi (engl. *cryopyrin-associated periodic syndromes*, CAPS) i periodični sindrom povezan s receptorima za faktor nekroze tumora tipa 1A (engl. *TNF Receptor–Associated Periodic Syndrome*, TRAPS) među najčešćim su i najpoznatijim monogenskim SAIB-ovima, a najčešće se javljaju na Bliskom istoku. (1–3) Obilježje ovih bolesti jest urođena disfunkcija imunološkog sustava koja se manifestira povratnom vrućicom, artritisom, osipom i serozitisom te amiloidozom kao mogućom komplikacijom. (1–3)

Obiteljski autoinflamatorni sindrom vezan uz hladnoću (engl. *Familial cold-induced autoinflammatory syndrome*, FCAS), kronični infantilni neurološki, kožni i zglobni sindrom (engl. *Chronic Infantile Neurological, Cutaneous, Articular Syndrome*, CINCA) i Muckle-Wellsov sindrom (MWS) spadaju u obitelj kriopirinom povezanih periodičnih sindroma (CAPS). (1–3) Povezani su s mutacijama gena NLRP3 koje dovode do poremećaja lučenja interleukina (IL)-1β. (1–3) U podskupini bolesnika s CAPS-om bez mutacija gena NLRP3 otkriveno je da su za nastanak tih sindroma odgovorne mutacije u genu NLRP12. (2,3) Poznato je da protein NLRP12 ima protuupalne i proupalne uloge, da smanjuje NF-κB i stimulira izlučivanje IL-1β, odnosno IL-18, stoga bi teoretski njegove varijante mogle uzrokovati SAIB. (2–4) Uobičajeni simptomi SAIB-a povezanog s NLRP12 ili FCAS 2, uključuju vrućicu u 93% slučajeva, nakon čega slijede mišićnokoštani simptomi u 61% slučajeva, urtikarija u 52% slučajeva, abdominalni simptomi u 38% slučajeva, glavobolja u 22% slučajeva i povišeni reaktanti akutne faze u 30% slučajeva koji se aktiviraju izlaganjem hladnoći u 36% slučajeva, a bolesnici osim toga navode i simptome kao što su umor, druge vrste osipa i konjunktivitis. (2,4) U liječenju se po potrebi upotrebljavaju antihistaminici, nesteroidni protuupalni lijekovi (NSAID) i glukokortikoidi. (2,4) Pozitivni rezultati po-

A number of variants of *NLRP12* have been reported to date, including c.1206C>G, most commonly, and R284X, D294E, R352C, c.2072+3insT, c.1352G>A, among others (2,4). Herein we present the case of a patient with symptoms suggestive of a hereditary SAID, in particular FCAS 2, with a variant in the *NLRP12* gene which has not been reported to date.

CASE REPORT

A 40-year-old male patient was referred to our rheumatology clinic in spring 2021 by an infectious disease specialist after extensive workup for recurrent febrile episodes. The patient had several febrile episodes the previous winter, generally with elevated C-reactive protein (CRP) and was treated repeatedly with antibiotics. Upon the use of antibiotics, the CRP level normalised. The bouts of fever were usually followed by unspecific chest pain and dry cough, and occasionally the patient experienced morning stiffness in his right hip. The patient also experienced bouts of fever two winters ago, but to a milder extent. Workup included infectious disease testing, anti-nuclear antibodies (ANA), computerised tomography (CT) of the thorax, echocardiography, and leukocyte scintigraphy, which were normal or insignificant. At this point, SAID was considered.

Approximately a month later, during follow-up, the patient reported another bout of fever with an elevated CRP level of 25 mg/L and a leukocyte range of 20x10^9/L. As recommended, echocardiography was done during an attack, and its results were insignificant. Genetic testing was arranged at this time.

Through genetic testing, sequencing of clinical exome LG235, heterozygous variant in the *NLRP12* gene, NM_001277126.1, position 19:54314063, c.850C>G was detected, which causes the substitution of arginine for glycine in codon 284, p.Arg284Gly. This variant is absent from databases. Predictions from *in silico* analysis showed that the variant does not damage the structure or the function of the protein, although no functional studies are available to confirm this.

Illumina TruSight One reagent set was used to prepare libraries for DNA sequencing. NextSeq 550 analyser was used for sequencing, and Variant Interpreter for data analysis. Online Mendelian Inheritance in Man (OMIM), Clinical Variant (ClinVar) Database, Human Gene Mutation Database (HGMD), Single Nucleotide Polymorphism Database (dbSNP), Genome Aggregation Database (GnomAD), Clinical Genome (ClinGen) Resource, 1000 Genomes Project, Database of Genomic Variants (DGV) databases were searched. The analysis included 4800 genes known to cause disease, as annotated in OMIM, ClinVar and HGMD, for the following phenotypes: recurrent fever, fever of unknown origin, elevated CRP, leukocytosis.

Based on the clinical presentation and considering the genetic testing results, despite the lack of functionstignuti su primjenom anakinre, a istraživanja upućuju na mogućnost upotrebe faktora nekroze tumora (TNF) kao i inhibitora IL-6, iako je ponašanje citokina u sklopu ove bolesti još uvijek nejasno. (2,4)

Do danas je zabilježen niz varijanti proteina NLRP12, najčešće uključujući, među ostalima, c.1206C>G, R284X, D294E, R352C, c.2072+3insT, c.1352G>A (2,4). U ovom radu predstavljamo slučaj bolesnika sa simptomima koji upućuju na nasljednu sustavnu autoinflamatornu bolest (SAIB), preciznije rečeno FCAS 2, s varijantom gena NLRP12 koja do danas nije zabilježena.

PRIKAZ BOLESNIKA

Četrdesetogodišnjeg bolesnika infektolog je u proljeće 2021. uputio u našu Kliniku za reumatologiju nakon opsežne obrade zbog ponavljajućih febrilnih epizoda. Bolesnik je imao nekoliko febrilnih epizoda prethodne zime, općenito s povišenim C-reaktivnim proteinom (CRP), a više je puta liječen antibioticima, nakon čega se razina CRP-a normalizirala. Napadi vrućice obično su popraćeni nespecifičnom boli u prsima i suhim kašljem, a povremeno je bolesnik imao jutarnju ukočenost u desnom kuku. Pretprošle zime bolesnik je također imao napade vrućice, ali tada su oni bili blaži. Obrada je uključivala testiranja za infektivne bolesti, antinuklearna protutijela (ANA), računalnu tomografiju (CT) toraksa, ehokardiografiju i scintigrafiju leukocita, a nalazi su bili u normalnom rasponu ili bez značajnih odstupanja. U tom trenutku počela se razmatrati dijagnoza SAIB-a.

Pacijent je tijekom praćenja mjesec dana kasnije prijavio još jedan napad vrućice s povišenim CRP-om od 25 mg/L i leukocitima od 20 x 10^9/L. Kao što je preporučeno, ehokardiografija je učinjena tijekom napada, a rezultati su bili bez značajnih odstupanja. Tada je dogovoreno genetsko testiranje.

Genetskim testiranjem, sekvenciranjem kliničkog egzoma LG235 otkrivena je heterozigotna varijanta u genu NLRP12, NM_001277126.1, pozicija 19:54314 063, c.850C>G, koja uzrokuje izmjenu arginina u glicin u kodonu 284, p.Arg284Gly. Ova varijanta nije zabilježena u bazama podataka. Predviđanja iz *in silico* analize pokazala su da predmetna varijanta ne oštećuje strukturu ili funkciju proteina, iako nema dostupnih funkcionalnih studija koje bi to potvrdile.

Set reagensa *Ilumina TruSight One* upotrijebljen je za pripremu biblioteka uzoraka DNK za sekvenciranje. Za sekvenciranje je upotrijebljen uređaj za analizu *NextSeq 550*, a za analizu podataka upotrijebljen je uređaj *Variant Interpreter*. Pretražene su baze podataka u nastavku: *Online Mendelian Inheritance in Man* (OMIM), *Clinical Variant* (ClinVar) *Database*, *Human Gene Mutation Database* (HGMD), *Single Nucleotide Polymorphism Database* (dbSNP), *Genome Aggregation Database* (GnomAD), *Clinical Genome* (ClinGen) *Resource*, *1000 Genomes Project*, *Database of Genomic*

al studies, the patient was diagnosed with NLRP12-associated hereditary SAID or FCAS 2. Colchicine was recommended as a treatment method. At follow-up, a significant reduction in the number of febrile attacks with colchicine was noted, which may additionally confirm the diagnosis.

DISCUSSION

Our patient presented with a clinical presentation highly suggestive of SAID, more specifically CAPS, considering the recurrent fever and elevated CRP primarily during winter, and with the *NLRP12* gene variant, we narrowed this down to the possibility of FCAS 2 or *NLRP12*-associated SAID. The patient presented with cough and chest pain, which may be indicative of serositis, although this was not objectively shown. Although the pathogenesis of *NLRP12*-associated SAIDs and effect of *NLRP12* variants is unclear, such variants have been associated with FCAS 2, and shown to be causative. (2–4) The c.850C>G gene variant in our patient was shown to be benign with *in silico* analysis, but in the absence of another clear cause of the patient's clinical presentation, it is possible that this variant is the one that caused the disease. Therefore, the patient was diagnosed with FCAS 2 or *NLRP12*-associated SAID, despite the lack of functional studies.

The method for whole exome sequencing (WES) in recent years has become readily available, reliable, and cost effective, (5) and it has even been implemented and routinely performed in a national centre in Zagreb. WES can confirm diagnosis, especially in the case in which a pathogenic disease variant is detected in a patient with a matching clinical phenotype for the assumed disease. (5) However, in other detected variants, also known as variants of unknown clinical significance, as in our case, a definite diagnosis cannot be made. (5) Chances increase based on the location and type of mutation, and computational studies, or *in silico* analysis. (5) However, these tools are not designed for clinical practice, and results should be interpreted with caution. (5) At this time, functional studies remain as the only option for validating such variants, but current methods such as mRNA or protein expression, rescue experiments, and animal or cell culture model systems, are not easily or readily attainable. (5) In our case, the mutation location and *in silico* analysis currently do not suggest a pathogenic variant, but a functional study would be needed for confirmation. Unfortunately, such a study is not available at our centre due to personnel, equipment, and funding limitations.

Although results using colchicine for treatment of *NLRP12*-associated SAIDs are weak, considering the relatively mild clinical presentation of the patient, it was decided to try the treatment method with colchicine first before opting for other, more uncomfortable

Variants (DGV). Analiza je uključivala 4800 gena za koje je poznato da uzrokuju bolest, kao što je navedeno u bazama podataka OMIM, ClinVar i HGMD, za sljedeće fenotipove: povratna vrućica, vrućica nepoznatog uzroka, povišeni CRP, leukocitoza.

Na temelju kliničke slike i s obzirom na rezultate genetskog testiranja, unatoč nedostatku funkcionalnih studija, bolesniku je dijagnosticirana nasljedna sustavna autoinflamatorna bolest (SAIB) ili FCAS 2 povezana s proteinom NLRP12. Za liječenje je preporučena primjena kolhicina. Tijekom praćenja primijećeno je značajno smanjenje broja napada vrućice uz primjenu kolhicina, što dodatno potvrđuje dijagnozu.

RASPRAVA

Naš bolesnik imao je kliničku sliku koja je iznimno upućivala na SAIB, točnije rečeno CAPS, uzimajući u obzir povratnu vrućicu i povišen CRP prvenstveno tijekom zimskog razdoblja, a s pomoću varijante gena NLRP12 dijagnozu smo suzili na FCAS 2 ili SAIB povezan s proteinom NLRP12. Bolesnik je imao simptome kašlja i bolova u prsima, što može upućivati na serozitis, iako se pokazalo da to nije objektivna dijagnoza. Iako su patogeneza SAIB-ova povezanih s proteinom NLRP12 i učinak varijanti proteina NLRP12 nejasni, te su varijante povezane s FCAS 2 i pokazalo se da su upravo one uzročnici bolesti. (2–4) *In silico* analiza pokazala je da je varijanta gena c.850C>G kod našeg bolesnika benigna, ali u nedostatku drugoga jasnog uzroka kliničke slike bolesnika moguće je da je upravo ta varijanta bila uzročnik bolesti. Stoga je pacijentu dijagnosticiran obiteljski autoinflamatorni sindrom izazvan hladnoćom (FCAS 2) ili SAIB povezan s proteinom NLRP12, unatoč nedostatku funkcionalnih studija.

Metoda sekvenciranja cijelog egzoma (WES) posljednjih je godina postala lako dostupna, pouzdana i isplativa (5), a čak se provodi i rutinski primjenjuje u jednom nacionalnom centru u Zagrebu. Metodom sekvenciranja cijelog egzoma (WES) može se potvrditi određena dijagnoza, posebice u slučaju kada se kod bolesnika otkrije patogena varijanta bolesti s odgovarajućim kliničkim fenotipom za pretpostavljenu bolest. (5) Međutim, kod drugih otkrivenih varijanti, poznatih i kao varijante nepoznate kliničke značajnosti, kao u našem slučaju, ne može se postaviti konačna dijagnoza. (5) Šanse se povećavaju na temelju mjesta i vrste mutacije, računalnih studija ili *in silico* analize. (5) Međutim, ti alati nisu osmišljeni za upotrebu u kliničkoj praksi te je potrebna određena doza opreza pri tumačenju rezultata. (5) U ovom trenutku funkcionalne studije ostaju jedina mogućnost za potvrdu takvih varijanti, ali trenutne metode kao što su ekspresija mRNA ili proteina, eksperimenti spašavanja i modelni sustavi životinjskih stanica ili staničnih kultura nisu lako dostupne. (5) U našem slučaju, mjesto mutacije i *in silico* analiza trenutačno ne upućuju na patogenu varijantu, ali bi bilo potrebno provesti

(subcutaneous) or costly (novel biologics) treatment method which has been suggested in literature. (2,4) With significant reduction in the number of attacks during follow-up, colchicine proved to be a successful treatment in the case of our patient.

Late disease onset is questionable in this case, but given the clinical presentation and associated genetic variant, an acquired SAID, such as adult-onset Still's disease or Schnitzler's syndrome, is less likely to occur. Considering that the region that the patient resides in has mild winters, and the fact that temperatures in that region rarely go below 0 °C, it is possible that this, in combination with an aging immune system which may have lost the ability to compensate for disbalances, may explain why the symptoms did not manifest earlier in this patient.

In conclusion, although there is a lack of functional studies in this case, given the clinical presentation indicative of CAPS, with the exclusion of other causes, and a favourable response to colchicine as a treatment method, we consider that the diagnosis of CAPS is the final one in the case of our patient (more specifically FCAS 2 or *NLRP12*-associated SAID). Furthermore, the discovered novel c.850C>G *NLRP12* gene variant could possibly be the one that causes this disease. With whole exome sequencing becoming a routine method, it is likely that an increasing number of novel gene variants of unknown clinical significance will be discovered. This will lead to an increase in the need for validating these variants through functional studies, which will pose an issue until such studies become more readily available and cost effective.

Acknowledgments: Josipa Mateševac, Fran Borovečki

Conflict of interest statement: The authors declare no conflict of interest.

funkcionalnu studiju za konačnu potvrdu. Nažalost, takvu studiju nije moguće provoditi u našem centru zbog nedostatka osoblja, opreme i financijskih sredstava.

Iako su rezultati primjene kolhicina za liječenje SAIB-a povezanog s NLRP12 slabi, s obzirom na relativno blagu kliničku sliku bolesnika, odluka je bila prvo pokušati s kolhicinom prije uvođenja druge neugodnije (supkutane) ili skuplje (novi biološki lijekovi) metode liječenja koja je predložena u literaturi. (2,4) Uz značajno smanjenje broja napadaja tijekom razdoblja praćenja, kolhicin se pokazao kao uspješna metoda liječenja u slučaju našeg bolesnika.

Kasni početak bolesti upitan je u ovom slučaju, ali s obzirom na kliničku sliku i povezanu genetsku varijantu, nasljednu SAIB, kao što su Stillova bolest odrasle dobi ili Schnitzlerov sindrom, manja je vjerojatnost da će do njega doći. Uzimajući u obzir blaže zime u regiji u kojoj bolesnik živi, s temperaturama koje rijetko padaju ispod 0°C, moguće je da ta činjenica u kombinaciji sa starenjem imunološkog sustava koji je možda izgubio sposobnost regulacije neravnoteže može objasniti zašto se u bolesnika ti simptomi nisu javili ranije.

Zaključno, iako je očit nedostatak funkcionalnih studija, s obzirom na kliničku sliku koja ukazuje na CAPS, uz isključenje drugih uzroka i povoljan odgovor na liječenje kolhicinom, razmatramo dijagnozu CAPS-a u našeg bolesnika, točnije FCAS 2, ili SAIB-a povezanog s proteinom NLRP12. Nadalje, novootkrivena varijanta gena c.850C>G NLRP12 mogla bi biti uzročnik bolesti. Budući da sekvenciranje cijelog egzoma postaje rutinska metoda, vjerojatno će se otkrivati sve više i više novih genskih varijanti nepoznate kliničke značajnosti. To će dovesti do povećanja potrebe za potvrđivanjem ovih varijanti kroz funkcionalne studije, što će i dalje predstavljati problem sve dok takve studije ne postanu dostupnije i financijski isplativije.

Zahvala: Josipa Mateševac, Fran Borovečki

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Pathak S, McDermott MF, Savic S. Autoinflammatory diseases: update on classification diagnosis and management. Review J Clin Pathol [Internet]. 2017;70(1):1–8. Dostupno na: https://doi.org/10.1136/jclinpath-2016-203810. [Pristupljeno: 12. siječnja 2023.]
2. Ayla AY, Eren H, Zare J, Calhan SS, Karacan I, Seven M i sur. A rare case of an NLRP12-associated autoinflammatory disease. Eur J Med Genet [Internet]. 2021;64(4):104168. Dostupno na: https://doi.org/10.1016/j.ejmg.2021.104168. [Pristupljeno: 10. siječnja 2023.]
3. Borghini S, Tassi S, Chiesa S, Caroli F, Carta S, Caorsi R i sur. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheum [Internet]. 2011;63(3):830–9. Dostupno na: https://doi.org/10.1002%2Fart.30170. [Pristupljeno: 11. siječnja 2023.]
4. Vitale A, Rigante D, Maggio MC, Emmi G, Romano M, Silvestri E i sur. Rare NLRP12 variants associated with the NLRP12-autoinflammatory disorder phenotype: an Italian case series. Clin Exp Rheumatol [Internet]. 2013;31(3 Supl 77):155–6. Dostupno na: https://www.clinexprheumatol.org/abstract.asp?a=7272. [Pristupljeno: 13. siječnja 2023.]
5. Rodenburg RJ. The functional genomics laboratory: functional validation of genetic variants. J Inherit Metab Dis [Internet]. 2018;41(3):297–307. Dostupno na: https://doi.org/10.1007/s10545-018-0146-7. [Pristupljeno: 9. siječnja 2023.]