Case Report
Volume 10:5, 2020
DOI: 10.37421/jccr.2020.10.1346

Clinical Case Reports

ISSN: 2165-7920 **Open Access**

Identification of a New Mutation (C.562G>T P. Gly188) in a Young Man Affected by *NLRP12* Associated Periodic Syndrome (*NAPS12*): Efficacy of Anti-IL1-Beta Treatment

Delfino Lorenzo, Tinazzi Elisa, Olivieri Bianca, Todesco Mattia, Caminati Marco and Lunardi Claudio*

Department of Medicine, University of Verona, Verona, Italy

Abstract

NLRP12 associated periodic syndrome, also called Familial Cold Autoinflammatory Syndrome-2 (*FCAS2*), is a monogenic autoinflammatory disorder caused by mutations of the gene *NLRP12* and is characterized by recurrent episodes of fever, often after cold exposure or physical stress, in association with arthralgias/arthritis, myalgias, headaches, aphthous ulcers, lymphadenopathy, abdominal pain, sierositis, dermatitis and urticaria. The episodes can last several days and can be very disabling. In the latest years different mutations of *NLRP12* have been identified, explaining the clinical heterogeneity and the different response to treatments. Here we describe a case of a 24-years-old man affected by *FCAS2* with a new nonsense mutation of the gene *NLRP12* who initially had a good response to steroid therapy and subsequently to anti-IL-1 beta treatment.

Keywords: Autoinflammatory disease • *NLRP12* mutation (c.562G>T) • *NAPS12* • *FCAS2* • Anti-IL-1 beta monoclonal antibody

Introduction

Autoinflammatory diseases are a heterogeneous group of disorders characterized by abnormal activation of innate immune system with a wide range of clinical manifestations such as recurrent episodes of fever in association with malaise, fatigue, skin rash, serositis, arthralgia and myalgia [1,2]. The identification of specific mutations has allowed the identification and classification of these disorders. One first classification included, under the name of Monogenic Hereditary Periodic Fever Syndromes (HPFS), disorders such as Familiar Mediterranean Fever (FMF) and TNF Receptor-Associated Periodic Syndrome (TRAPS). Then other disorders have been identified [3,4] and, thanks to the genetic analysis, the list of new monogenic disorders is continuously increasing. However, many of them are considered polygenic disorders [5-8]. Consequently, in the latest ten years different classification have been proposed. Furthermore, researchers are working to propose new classification criteria and databases such as infevers and Eurofever that have been developed to collect clinical and genetic information, helping clinicians to perform a correct diagnosis [9-11]. *NLRP12* associated periodic syndrome, also called Familial Cold Autoinflammatory Syndrome-2 (*FCAS2*), was first described in 2007 by Jèru and colleagues in two families from Guadeloupe [12].

The syndrome is characterized by recurrent episodes of fever, often after cold exposure or physical stress, associated with arthralgias/arthritis, myalgias, headaches, aphthous ulcers, lymphoadenopaty, abdominal pain, dermatitis and urticaria. The episodes can last 5-10 days or more and can be very disabling [6]. The involved gene encodes for a protein belonging to the intracellular Nod-like receptor (NLR) family. This protein is an intracellular sensor of innate immune system and has been shown to be capable to inhibit the NF-kB non-canonical activation pathway and to modulate negatively the T-Cell responses, by modulating IL-4 production. These features have suggested a possible role of *NLRP12* in the pathogenesis of inflammatory bowel diseases and tumorigenesis [6,12-16]. Although his potential antinflammatory role, *NLRP12* is also capable to activate caspase 1 signaling, increasing IL-1beta secretion. Missense mutations have been associated with gain of function of caspase 1 processing, leading to an overproduction of IL-1beta [12-15]. Treatment consists in using NSAID or corticosteroids. Few cases treated with anti-IL-1beta have been reported and the efficacy of the treatment is still unproven [6-17]. Here we describe a case of a 24-years-old man affected by *FCAS2* with a new nonsense mutation of the gene *NLRP12* who obtained a good response to high dose steroid treatment at the beginning followed by remission of the disease with Anti-IL1-beta treatment for two years and suspension of steroids.

Case Presentation

A 24-year-old Sicilian man was admitted to our Autoimmune Diseases Unit for mild fever (37.5°C), arthralgias and arthritis, myalgias and severe abdominal pain in association with diarrhea. Since Winter-Spring 2017 these symptoms were reported as periodic and induced by physical stress or cold. His past medical history was unremarkable. A colonoscopy was normal, whereas an abdominal ultrasound showed the presence of abundant ascites. Biochemical tests showed increased ESR and CRP. On the admission blood tests were performed and Fibrinogen, CRP and electrophoretic profile were indicative of acute inflammation, while white blood cells count was normal. Microbiological and virological tests were also negative. Furthermore abdominal ultrasound Furthermore abdominal ultrasound and RMN confirmed the presence of ascites (Figure 1); a chest X-ray showed pleural effusion. We decided to perform a CT-PET that resulted substantially negative. The patient started treatment with NSAID with a mild benefit. In the hypothesis of an auto-inflammatory disease we performed a genetic analysis that documented the presence of heterozygous nonsense mutation of the gene *NLRP12* (c.562G>T p. Gly188).

We confirmed the diagnosis of Familial Cold Induced Autoinflammatory Syndrome-type 2 and administered high dose steroids (Prednisolone 50 mg/day: 1 mg/kg/day) with a good response and we started Anti-IL1-beta monoclonal antibody (Anakinra) 100 mg/day. A second abdominal US was performed a week after the beginning of the treatment; it showed an initial reduction of ascites and of pleural effusion. Moreover, we assisted to a reduction of inflammatory parameters at blood tests and to a significant reduction of the symptoms. After 2 weeks we started tapering of steroids till suspension after 2 months. One year later the patient started to complain abdominal pain and arthralgias and presented monolateral pleural effusion. We increased the

***Address for Correspondence:** Lunardi C, Department of Medicine, University of Verona, Verona, Italy, E-mail: Claudio.lunardi@univr.it*

Received 09 April 2020; **Accepted** 14 May 2020; **Published** 21 May 2020

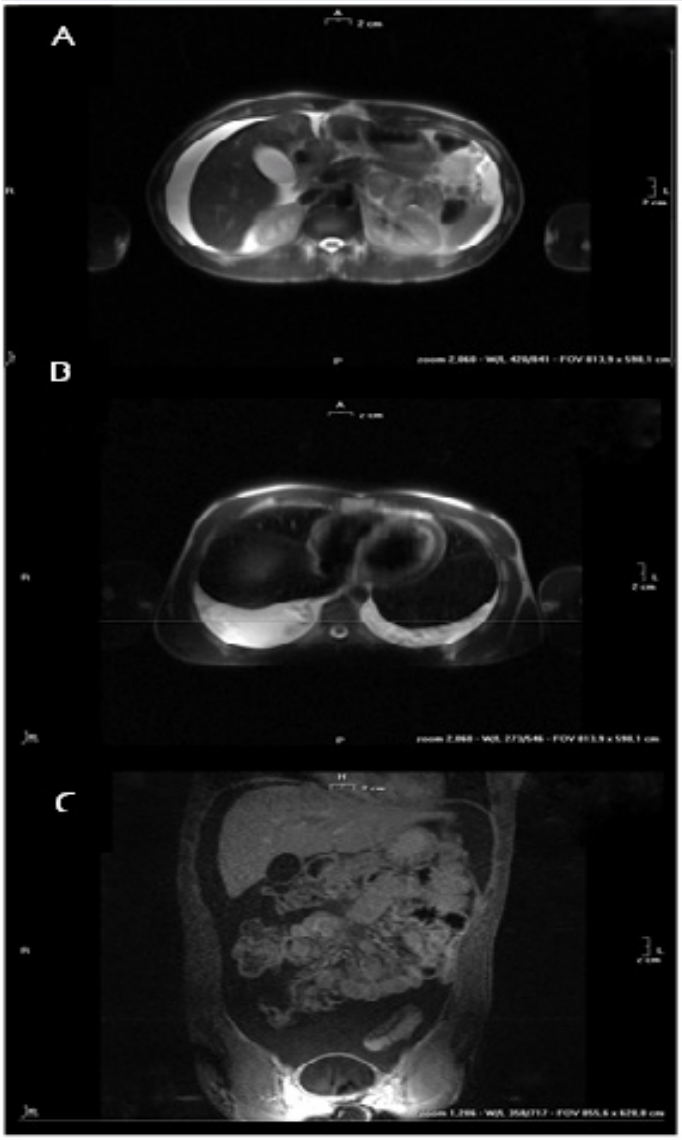

Figure 1. T2 weight RMN abdomen shows presence of conspicuous ascites and pleural effusion (A,B); Coronal section T1 weighted shows ascitic effusion among internal organs (C).

dosage of Anakinra to 100 mg and 200 mg on alternative days with remission of symptoms and of pleural effusion. After two years of follow-up, no other episodes have been reported, and annual abdominal ultrasound, chest X-ray, full blood count and ESR and CRP were normal.

Discussion

In the latest years the list of autoinflammatory diseases has continuously grown, making a classification of these disorders a challenge for clinicians [1-10]. Recently a new monogenic syndrome has been identified related to mutations of the *NLRP12* gene. As far as the pathogenetic mechanisms concerns, very little is known. The clinical presentation of the syndrome is very heterogeneous and possibly the type of genetic mutation may contribute to the phenotypic heterogeneity [18-22]. The young patient described here, presented a clinical picture suggestive of an autoinflammatory disorder. Indeed, after excluding infectious or oncohematologic causes, we hypothesized a Familial Mediterranean Fever, considering also the patient's origin. However, genetic analysis revealed the presence of a new nonsense heterozygous mutation in the *NLRP12* gene that has not yet been included in the INFEVER or Eurofever databases. To date, novel variants of *NLRP12* have been identified which are associated with different clinical presentations [20-23]. The c.562G>T p. Gly188 variant described here, has never been described.

Conclusion

We suggested to the patient's family to perform the genetic analysis, since his sister and his sister's daughter have dermatitis and arthralgia. However, the analysis has not yet been carried out. It is difficult to explain the long term good response to Anti-IL1-beta monoclonal antibody treatment in this patient. Very few cases have been described in literature and in these cases the response to the treatment was not persistent. Therefore, a biomolecular mechanism that confers resistance to therapy has been hypothesized ref. 23. Anyway we cannot rule out that the type of mutation may predict the response to treatment with Anakinra. Further studies are needed to better understand the signaling pathways involved in the pathogenesis of this disorder.

References

1. Havnaer Annika and Han George. "Autoinflammatory Disorders: A Review and Update on Pathogenesis and Treatment." Am J Clin Dermatol 20 (2019): 539-564.
2. Ciccarelli Fedra, Massimo De Martinis and Ginaldi Lia. "An Update on Autoinflammatory Diseases." Curr Med Chem 21 (2014): 261-269.
3. Yu Justin R. Yu and Kieron S. Leslie. "Cryopyrin-Associated Periodic Syndrome: An Update on Diagnosis and Treatment Response." Curr Allergy Asthma Rep 11 (2011): 12-20.
4. Dickie Laura J, Sinisa Savic, Azad Aziz and Michael Sprakes, et al. "Periodic Fever Syndrome and Autoinflammatory Diseases." Med Rep 18 (2010): 3.
5. Somez Hafize Emine and Seza Özen. "A Clinical Update on Inflammasomopathies." Int Immunol 29 (2017): 393-400.
6. Touitou Isabelle, Galeotti Caroline, Rossi-Semerano Linda and Véronique Hentgen, et al. "The Expanding Spectrum of Rare Monogenic Autoinflammatory Diseases." Orphanet J Rare Dis 16 (2013): 162.
7. Sangiorgi Eugenio, Azzarà Alessia, Molinario Clelia and Pietrobono Roberta, et al. "Rare Missense Variants in the ALPK1 Gene May Predispose to Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) Syndrome." Eur J Hum Gene 27 (2019): 1361-1368.
8. Seza Ozen, Batu Ezgi Deniz, Ekim Z. Taşkıran and Özkara Hatice Asuman, et al. "A Monogenic Disease with a Variety of Phenotypes: Deficiency of Adenosine Deaminase 2 Subtitle: Deficiency of Adenosine Deaminase 2." J Rheumatol 47 (2019): 117-125.
9. Masters Seth L, Simon Anna, Aksentijevich Ivona and Daniel L. Kastner. "Horror Autoinflammaticus: The Molecular Pathophysiology of Autoinflammatory Disease." Annu Rev Immunol 27 (2009): 621-628.
10. Gattorno Marco, Hofer Michael, Federici Silvia and Vanoni Federica, et al. "Classification Criteria for Autoinflammatory Recurrent Fevers." Ann Rheum Dis 78 (2019): 1025-1032.
11. Marcuzzi Annalisa, Piscianz Elisa, Kleiner Giulio and Tommasini Alberto, et al. "Clinical Genetic Testing of Periodic Fever Syndromes." Biomed Res Int 2013 (2013): 1-8.
12. Jéru Isabelle, Sandrine Marlin, Gaëlle Le Borgne and Cochet Emmanuelle, et al. "Mutations in NALP12 Cause Hereditary Periodic Fever Syndromes." Proc Natl Acad Sci 105 (2008): 1614-1619.
13. Jéru Isabelle, Le Borgne Gaëlle, Cochet Emmanuelle and Hayrapetyan Hasmik, et al. "Identification and Functional Consequences of a Recurrent *NLRP12* Missense Mutation in Periodic Fever Syndromes." Arthritis Rheum 63 (2011): 1459-1464.
14. Lukens John R, Prajwal Gurung, Patrick J. Shaw and Maggie J. Barr, et al. "The *NLRP12* Sensor Negatively Regulates Autoinflammatory Disease

by Modulating Interleukin-4 Production in T Cells." Immun 42 (2015): 654-664.

15. Allen Irving C, Justin E. Wilson, Monika Schneider and John D. Lich, et al. "*NLRP12* Suppresses Colon Inflammation and Tumorigenesis through the Negative Regulation of Noncanonical NF-κB Signaling." Immun 36 (2012): 742-754.
16. Udden Nashir, Youn-Tae Kwak, Victoria Godfrey and Abdul Wadud Khan, et al. "*NLRP12* Suppresses Hepatocellular Carcinoma via Downregulation of cJun N-terminal Kinase Activation in the Hepatocyte." Elife 16 (2019): 8.
17. Cavalli Giulio and Charles A. Dinarello. "Anakinra Therapy for Non-cancer Inflammatory Diseases." Front Pharmacol 9 (2018): 1157.
18. Shen Min, Lin Tang, Xiaochun Shi and Xiaofeng Zeng. "*NLRP12* Autoinflammatory Disease: A Chinese Case Series and Literature Review." Clin Rheumatol 36 (2017): 1661-1667.
19. Kostik Mikhail M, Evgeny N. Suspitsin, Marina N. Guseva and Anastasia S. Levina, et al. "Multigene Sequencing Reveals Heterogeneity of *NLRP12*-related Autoinflammatory Disorders." Rheumatol Int 38 (2018): 887-893.
20. Wang Wei, Yu Zhou, Lin-Qing Zhong and Zhuo Li, et al. "The Clinical Phenotype and Genotype of *NLRP12*-Autoinflammatory Disease: A Chinese Case Series with Literature Review." World J Pediatr 36 (2019): 1661-1667.
21. Gupta Latika, Sakir Ahmed, Bharati Singh and Satya Prakash, et al. "Novel *NLRP12* Variant Presenting with Familial Cold Autoimmunity Syndrome Phenotype." Ann Rheum Dis 24 (2019): 1-2.
22. Wang Jiajia, Qian Zhang, Lingxiao Xu and Chengyin Lv, et al. "A Case of Episodic and Refractory Arthritis due to a Novel Variant of *NLRP12*." Ann Rheum Dis 20 (2020): 1.
23. Jéru Isabelle, Hentgen Véronique, Normand Sylvain and Duquesnoy Philippe, et al. "Role of Interleukin-1β in *NLRP12*-Associated Autoinflammatory Disorders and Resistance to Anti-interleukin-1 Therapy." Arthritis Rheum 63 (2011): 2142-2148.

How to cite this article: Delfino Lorenzo, Tinazzi Elisa, Olivieri Bianca, Todesco Mattia, et al. "Identification of a New Mutation (C.562G>T P. Gly188) in a Young Man Affected by *NLRP12* Associated Periodic Syndrome (*NAPS12*): Efficacy of anti-IL-1 beta Treatment." Clin Case Rep 10 (2020): 1346