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

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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, lymphadenopathy, 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-κB 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 antiinflammatory 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 electrocardiographic profile were indicative of acute inflammation, while white blood cells count was normal. Microbiological and virological tests were also negative. Furthermore abdominal ultrasound showed increased ESR and CRP. On the admission blood tests were performed and Fibrinogen, CRP and electrocardiographic profile were indicative of acute inflammation, while white blood cells count was normal. Microbiological and virological tests were also negative. Furthermore abdominal ultrasound was negative. 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 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...
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


