LIVING WITH RECURRENT FEVERS

Hereditary recurrent fever syndromes are a group of rare genetic conditions, belonging to the family of auto-inflammatory diseases, which affect every part of patients' lives and that of their families.

Due to their hereditary nature, most of these disorders have an early onset and are lifelong diseases. They can affect every aspect of daily life, such as education, as well as social and emotional aspects and require changes of lifestyle for both children and their families.

Nowadays much more is understood about these diseases. Early diagnosis and current effective treatment approaches can change patients and their families lives.

Today there is more hope than ever before!

NOVARTIS

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WHAT ARE HEREDITARY RECURRENT FEVER SYNDROMES AND AUTO-INFLAMMATORY DISEASES?

Hereditary recurrent fever syndromes are caused by mutations in genes involved in the innate response of the immune system, i.e. in the inflammatory response. They are a sub-group of the big family of auto-inflammatory diseases. In all these conditions, the symptoms are due to an excessive activation of the inflammatory mechanisms. This is what the name means: auto = on its own, inflammatory = becomes inflamed. It means that inflammation is not initiated to an external cause (such as an infection), but it occurs 'on its own'.

IN AUTO-INFLAMMATORY DISEASES, THE INNATE IMMUNE SYSTEM WORKS TOO ACTIVE!

The 'innate immune system' is our body's first defence against infections. When viruses or bacteria get inside our body the innate immune system activates itself to block the replication of these germs. In order to defend ourselves, the cells of the innate immune response release molecules that cause inflammation. Inflammation is very important for killing the germs that make us ill; however, it is also responsible for unpleasant symptoms, such as fever. Usually when our immune system successfully fights off the infection, the inflammation reduces and the symptoms (such as fever) disappear. In hereditary recurrent fever syndromes, due to a genetic mutation, the innate immune system works too hard. Inflammation is activated without an infection, or is not capable of turning itself off when the infection has been defeated. It means that the defence system acts as if it were fighting germs, even when there is no infection, resulting in an unnecessary inflammatory response that affects the entire body.

WHAT ARE THEY?

In recurrent fever syndromes, inflammation most often presents as a sudden-onset fever and is associated with various other symptoms. Fever usually occurs and disappears 'on its own', even without treatment. After the fever has subsided, the body returns to its 'normal' state and there are no further symptoms.
These conditions have very long names related to the complex mechanisms involved. For this reason often simplified acronyms are used.

HEREDITARY RECURRENT FEVERS ARE RARE DISEASES.
However, there are many patients with these conditions all over the world.

YOU ARE NOT THE ONLY ONE!

Number of patients worldwide:
FMF~100,000
CAPS~1,000
TRAPS~1,000
HIDS/MKD~300

CAPS [Cryopyrin-Associated Periodic Syndromes]

The term CAPS includes three conditions of increasing severity related to a mutation of the gene called NLRP3, which encodes for cryopyrin, a protein that regulates the production of one of the most important molecules of inflammation (interleukin-1 beta). These diseases are:

1. FCAS [Familial Cold Auto-inflammatory Syndrome]
FCAS is characterised by very short episodes of fever, usually with urticaria and conjunctivitis, induced by exposure to cold.

2. MWS [Muckle-Wells Syndrome]
MWS is characterised by recurrent episodes of fever with urticaria, arthralgia and conjunctivitis. Hearing loss and amyloidosis, a chronic disease secondary to persistent inflammation, may develop as complications of this condition.

3. NOMID/CINCA Neonatal-Onset Multisystem Inflammatory Disorder, also known as CINCA Chronic Infantile Neurologic, Cutaneous, and Articular syndrome.
NOMID/CINCA is the most severe disease. In fact, together with fever and urticaria, patients with this disease may develop early-onset bone involvement, mental retardation and loss of hearing or vision; renal amyloidosis may occur as long-term complication.

FMF [Familial Mediterranean Fever]

FMF is caused by mutations in a gene (called MEFV) coding for the protein pyrin. Pyrin is another protein able to control the release of interleukin-1 beta, a very significant inflammation molecule. Familial Mediterranean Fever is the most frequent monogenic auto-inflammatory disease and it is most common in Mediterranean populations.

FMF is characterised by episodes of fever, lasting from few hours up to a couple of days, associated with signs and symptoms due to inflammation of the serosa (pleuritis, peritonitis, pericarditis): severe thoracic and/or abdominal pain.

Arthritis and skin rashes can also occur. Attacks subside spontaneously and their recurrences have no regular pattern.

Amyloidosis-related nephropathy is the most common long-term complication. In the past it was very common but nowadays, thanks to advances in the diagnosis and treatment of this disease, the occurrence of amyloidosis has become very rare.

TRAPS [Tumour necrosis factor Receptor Associated Periodic Syndrome]

TRAPS is caused by mutations in the p55 TNF Receptor (or TNFR1A), encoded by the TNF Super Family Receptor 1A gene (TNFRSF1A). The deficiency of the expression of this receptor is associated with uncontrolled inflammation.

TRAPS attacks are usually long-lasting (up to three weeks), with a variable frequency. Symptoms associated to fever attacks can be: abdominal or chest pain; nausea, vomiting, diarrhoea or constipation; painful red rash on the upper body and/or arms/legs; swollen eyes (periorbital oedema) and conjunctivitis; joint and muscle pain. Renal amyloidosis is the long-term complication of the disease.

HIDS/MKD [Hyperimmunoglobulinemia D Syndrome/Mevalonate Kinase Deficiency]

Recurrent fever associated with Mevalonate Kinase Deficiency (MKD), also known as Hyper IgD Syndrome (HIDS), is caused by a mutation in the Mevalonate Kinase (MVK) gene.

MVK is an essential enzyme in the biosynthesis of cholesterol. Its link with auto-inflammation has only been recently discovered: the lack of activity of MVK is associated with the lack of molecules, named isoprenoids, which are important for the inhibition of the inflammatory response. In patients with MKD, MVK enzyme works less, isoprenoids are lacking and therefore inflammation is over-active.

This disease usually starts in early childhood and is characterised by episodes of fever, with a quick onset, lasting 4-6 days. Gastrointestinal symptoms (severe abdominal pain, vomiting and diarrhoea) and cervical lymphadenopathy are the most frequent manifestations associated with fever attacks. Mucocutaneus symptoms, splenomegaly and arthralgia/arthritis can also be associated with episodes of fever. The symptoms of the disease tend to become less severe over time. However, in many patients the disease persists up to adulthood. Amyloidosis is a rare but possible complication.

DIAGNOSIS

Since many treatments available nowadays for recurrent fever syndromes are able to prevent both the recurrence of fever episodes and the occurrence of long-term complications, an early recognition of these diseases is crucial for the long-term outcome.

Difficulty in obtaining the correct diagnosis is the first significant hurdle for rare disease patients and their families. As these diseases are rare, the **diagnosis is often delayed**.

The signs and symptoms are not specific and vary greatly between patients. Some doctors may not be familiar with these diseases, and few centres are specialised in the molecular diagnosis of these diseases and the daily care of such patients.

Luckily, nowadays there is much greater awareness surrounding the recognition of these disorders. In fact, **diagnostic delay** has significantly decreased in the past few decades. However, the median time between onset of symptoms and **diagnosis is still 1-2 years**.

Many patients still receive more than one misdiagnosis before the disease is correctly identified. Excessive delays in diagnosis, and subsequent inappropriate interventions, can cause distress and discouragement in rare disease patients. This is a very difficult time for young patients and their families, who may have felt misunderstood.

Early and correct diagnosis and treatment can greatly impact the patient's quality of life and reduce the suffering that patients endure.

Moreover, early diagnosis and treatment significantly reduce the risk of complications.

WHAT SHOULD MY FAMILY DOCTOR KNOW ABOUT MY DISEASE?

Recurring fevers represent a group of pathologies belonging to the broader category of auto-inflammatory diseases.

These conditions, secondary to the mutation of genes involved in the inflammatory response, are characterised by recurrent episodes of systemic inflammation that generally manifest themselves with fever and various accompanying associated symptoms, which most frequently involve skin, osteoarticular and gastrointestinal systems – although they can potentially affect all organs and systems.

These episodes are in no way influenced by antimicrobial treatments, as they are not supported by an infectious etiology.

The referral centre that treats the patient will give you suggestions on the management of typical episodes and on the checks required for patient follow-up. Some patients will be prescribed a treatment to prevent febrile episodes. These medications can belong to the category of immunosuppressants or biological medications and can therefore affect the body's ability to respond to infectious episodes. In the case of an infection, a specific treatment should be started immediately. It is also useful to contact the referral centre to assess the need of a temporary stop of the current anti-inflammatory medication.

It should also be remembered that immunosuppressant and biological medications contraindicate live attenuated vaccinations, inactivated vaccines are recommended.

I HAVE A FRIEND AFFECTED BY A RECURRENT FEVER SYNDROME

I met Claire at a birthday party and we immediately got on because we had so many things in common. Unfortunately, after a few months the friendship became rather complicated and **it became impossible to get in touch or meet up with her**.

I asked mutual friends if they had heard from her, but her behaviour was a mystery for everyone... so nice and friendly one moment and then she would just disappear for a whole week. When she finally resumed contact, she seemed more detached, almost annoyed.

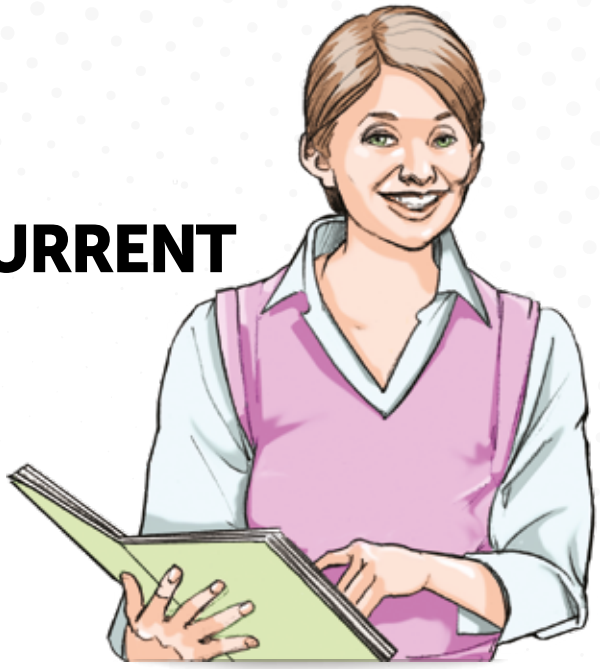
One day I asked her for an explanation, and **she confided to me that she was ill**. It was for this reason that **she had become afraid of cultivating friendships**.

I made some enquiries and discovered that Claire is not a danger to anyone; her symptoms, such as fever and rashes, are not contagious. She can happily come into contact with people, even when she is not well.

I decided to call her, and we started seeing each other just like any other couple, because that is the way it should be. We have become close and we do a lot of things together – it is just a question of choosing the right moment. **When she doesn't feel well, we talk, we play games online, we watch films together**.

Now we have a very strong friendship and Claire is a great companion for me.

I HAVE A STUDENT AFFECTED BY A RECURRENT FEVER SYNDROME



This year the parents of one of my students informed me that, after years of uncertainty, the doctors were finally able to understand what condition their son was suffering from. They clarified what it entails and finally the whole ordeal of last year began to make sense.

Contrary to what we as teachers had thought, it turns out that Mat is not just listless, volatile, unable to concentrate and maintain any interest for more than a few months. Mat has a condition that causes recurrent episodes of fever, and for which he needs to stay at home...

He would very much like to be with his classmates all the time and be more active at school!!!

Mat's parents decided to share with us the regular appointments with doctors, the times when he would be absent for exams and other such things; and on this basis we started organising Mat's school year, knowing that, he could have made absences. So, then I was able to prepare myself by creating:

- An **alternative curriculum** not particularly simplified, but providing for the teaching of **primary objectives** and the **achievement of the essential requirements**.
- **Interesting topics** that could be **approached with books, videos, CDs and games**, to fill the moments of necessary absence from school.
- For days of physical recovery before returning to school, **I provided his parents with enough information for Mat to know what we would be doing when he returned**, so that he would not feel like a fish out of water.
- In agreement with his parents and with Mat, **we explained to his classmates why he is sometimes absent** and how his symptoms can influence his daily life, emphasising that **Mat is not infectious and does not represent any danger to others**.

Nowadays I am very happy because Mat is much more integrated in the class and is far more productive!

I HAVE A PATIENT AFFECTED BY A RECURRENT FEVER SYNDROME

I am a family paediatrician and I am treating a child with Mevalonate Kinase Deficiency Syndrome.

The first years of his life were complicated for my patient, but also for me. His parents often brought him to me because he had a fever, enlarged lymph nodes in the neck and frequent vomiting. At first, I thought he was just a more delicate child, who often fell ill with various inter-related infections. I advised the family not to send him to nursery school, in the hope that things would improve, but that did not happen. Bryan continued to become ill very often. I prescribed several antibiotic, probiotic and immunostimulant treatments, but they had no effect. On a couple of occasions, I sent the child to the hospital. The exams were not normal, but a specific germ was never identified that could be responsible for the clinical picture.

Then, later on I happened to read an article in a scientific journal on recurrent monogenic fevers and I realised that this could be applicable in Bryan's case. So, I **prescribed a medical evaluation in a specialised medical centre for these conditions**. After a series of tests, my colleagues requested the genetic test that finally confirmed the diagnosis.

Understanding which disease was affecting Bryan came as a great relief, not only for the family but also for me. Now I know that when the child is unwell it is likely due to his disease, although I always examine him anyway in order to rule out an infection. I have to admit that I am very much helped in this by his family.

The parents are very good at understanding when it is 'his fever' or when we have to consider something different. I contacted the colleagues in the referral centre, who provided useful advice for managing Bryan's daily problems.

Recurring fevers often represent a source of frustration, not only for those affected and their families, but also for professionals who are involved in the management of such diseases without having much experience of them, such as family doctors.

Knowing and recognising a recurrent fever syndrome can indeed be complicated for those who are not experts in the diagnosis and management of these conditions.

I HAVE A CHILD IN MY TEAM AFFECTED BY A RECURRENT FEVER SYNDROME

TRAINER | **Team sports**

Amongst my team I have had for some months now a boy suffering from a rare auto-inflammatory disease. At first, I was somewhat afraid, thinking that I would not be able to handle this situation, but in reality it has turned out to be a rewarding experience for me.

The dialogue with the parents was crucially important: after a long and in-depth meeting with them I understand what symptoms he has and how he deals with them... and I started to find a way to manage the most difficult moments:

- In agreement with the family, first of all **I carefully managed his introduction into the team, making him feel an integral part of it**, while informing the other athletes that our new team member is more than just a player he is also our support on the bench.
- **His symptoms are not indicative of an infectious disease and he is not endangering anyone's health**.
- **I prepared a gradual training plan** to help him feel active even in periods where the symptoms are present and do not allow him to train normally.
- **When he returns to training after a period of absence, he initially supports me as an assistant coach**, and I discuss with him the more technical aspects. I have discovered a great confidant who 'knows his teammates better than me'.
- **During his absences**, his **teammates** and **I update him with messages or phone calls** to allow him to follow what is going on, even from a distance.

I am proud of how this experience is enriching all of us and is not precluding him from healthy activities!!!

TRAINER | **Individual sports and activities**

I was asked if I could train a young girl with FMF, and after asking and understanding what the condition entailed, I said 'why not!!!'

I prepared a gradual training plan that included rest periods due to the symptoms, during which I tried to give her a better knowledge of the discipline. This also included talking about her own experiences, her sporting heroes and finding simple books or manuals that could fuel her passion for this discipline.

We have made a diary of her progress, setting ourselves gradual practical and theoretical objectives, so that there are no periods in which she is distanced from the discipline.

I am satisfied because we have established a good relationship that is constructive for both of us.

We have created her own space for her, where she can feel independent.

Thanks to the advice of her parents and her doctor, she is the real driving force behind our meetings... **I see that this is giving her a lot of strength and increasing her self-esteem,** which is threatened everyday by her disease.

FOR MORE INFORMATION

YOU CAN FIND GROUPS OR SUPPORT ORGANIZATIONS:

http://www.periodicfevers.com

FRANCE
KOURIR https://www.kourir.org/

ISRAEL
Inbar https://www.inbar.org.il
Mifrakim Tze'irim http://www.mifrakim.org.il/

ITALY
AIFP https://www.febbriperiodiche.it/
AMRI Onlus http://www.amri.it/

NETHERLANDS
KAISZ http://www.kaisz.nl/

RUSSIA
Sunflower Foundation
http://www.fondpodsolnuh.com/

SPAIN
ASPANIJER http://aspanijer.org/
FMF Spain http://www.fmfspain.com/
STOP FMF https://fmf.org.es/

UK
Versus Arthritis https://www.versusarthritis.org/

INTERNATIONAL ASSOCIATIONS

- Autoinflammatory Alliance www.autoinflammatory.org
- ENCA www.enca.org
- FMF&AID International www.fmfandaid.org

PLEASE REACH OUT TO YOUR PATIENT ORGANISATION FOR EXPERT CENTRE INFORMATION

WHAT SHOULD I DO IN CASE OF AN EMERGENCY, WHEN I HAVE TO BE EXAMINED BY A DOCTOR THAT DOES NOT KNOW MY HISTORY AND MY DISEASE?

Show this brief letter to the examining doctors.

Dear colleague,

the patient you are examining is affected by a recurrent fever syndrome. These pathologies, which belong to the group of auto-inflammatory diseases, are caused by mutations in genes involved in the regulation of the inflammatory response. These conditions are characterised by an inflammatory state, which can be chronic or recurrent, generally presenting with fever associated with variable clinical manifestations and an increase in acute phase reactants.

Most patients are asymptomatic in the attack-free intervals, even if, in some cases, chronic symptoms of disease are present. The spectrum of severity of these diseases is very broad.

These conditions are characterised by the presence of a multi-systemic involvement during the episodes; therefore, fever is often accompanied by malaise and different symptoms according to the organ involved. The organs most commonly involved are the skin (some patients have urticarial, erysipeloid-like or erythematous rash), the mucous membranes (oral ulcers, conjunctivitis, tonsillar exudate), the gastrointestinal system (vomiting, diarrhea), the serosa (patients may present with intense thoracic or abdominal pain, sometimes so severe as to suggest acute abdomen), the reticuloendothelial system (adenopathy, hepatosplenomegaly) and the osteoarticular system (fasciitis, myositis, arthritis or arthralgia).

Some patients have chronic complications of these diseases such as renal amyloidosis, neurosensorial hearing loss, visual deficiencies or chronic arthropathy.

Blood tests taken during an episode will generally show a neutrophilic leukocytosis, sometimes associated with mild anaemia, and an increase in the main acute phase reactants. They are therefore difficult to distinguish from that usually observed in case of infections.

Generally, the patients and their families know how to distinguish the fever episodes typical of their disease from episodes of a different nature. If, however, there are doubts in this regard, it is useful, where possible, to perform coltural tests (such as a pharyngeal swab, blood culture and/or urine cultures) and/or serological tests and, if necessary, to undertake a specific treatment.

Patients are usually well-informed on how to treat acute episodes. In some cases, symptomatic medications are enough. However, in many cases, depending on the patient's condition, steroids are needed.

It is possible that the patient you are examining is receiving a long-term treatment, which can be an immunosuppressant, a biological medication or a regulator of neutrophilic activity. If the patient has symptoms related to the underlying disease, it is advisable to maintain this treatment. A possible temporary discontinuation should be considered in the case of severe infections, major surgical procedures, or if it is necessary to treat the patients with medications that are not compatible with his long-term treatment.

In fact, since they interfere with the inflammatory and immune response, these medications can sometimes alter the body's normal response to an infectious agent. Therefore, in case of infections, an adequate antimicrobial treatment is advisable.

In any case it is advisable to contact the centre in charge of the patient to discuss decisions regarding treatment.

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GLOSSARY

Amyloidosis	Deposit of abnormal protein called amyloid in organs and tissues throughout the body. The build-up of amyloid proteins (deposits) can make it difficult for the organs and tissues to work properly.
Antigen	Any substance eliciting an immunological response, such as the production of antibody specific for that substance.
Arthralgia	Pain affecting a joint.
Arthritis	Inflammation of a joint.
Bacteria	(sing. Bacterium) Microscopic organism visible under the electron microscope. Bacteria display a wide diversity of shapes and sizes. Most bacterial species are either spherical, called cocci (sing. Coccus) or rod-shaped, called bacilli (sing. Bacillus). They are widely prevalent in nature and in relation to plants and animals and may be pathogenic, i.e. capable of producing disease.
Biosynthesis	The synthesis of a substance in living matter.
Cell	The structural and functional unit of the living organism that can grow, reproduce and respond to stimuli.
Cervical	Pertaining to the neck or the neck region of the body.
Cholesterol	A constituent of all animal's fats and oils, of bile, gallstones, nerve tissue, egg yolk, and blood. It is a white, crystalline substance insoluble in water. It has an important role in metabolism.
Conjunctivitis	Inflammation of the conjunctiva (the membrane covering the anterior portion of the eyeball).
Cryopyrin	Protein, it is a member of a family of proteins which are found in the fluid inside cells (cytoplasm). Cryopyrin is found mainly in white blood cells and in cartilage-forming cells. It is involved in the process of inflammation.
Diagnosis	Determining the nature of a patient's disease. A conclusion reached in the identification of a patient's disease.
DNA	Molecule composed by two chains that coil around each other to form a double helix carrying the genetic instructions used in the growth, development, functioning and reproduction of all known organisms.
Enzyme	A substance, protein, formed by living cells and having a specific action in promoting a chemical change.
Erythematous	Pertaining to or characterised by erythema (redness of the skin occurring in patches of variable size and shape).
Etiology	The cause of a disease or abnormal condition.
Gene	The unit of transmission of hereditary characteristics. Genes in general are constituted of DNA. When a disease is transmitted through the genes, this means that it is possible that this disease has been transmitted by your parents.

Genetic	Pertaining to or having reference to genetics.
Germ	Any microorganism.
Hereditary	Pertaining to hereditary.
Immune system	Processes of the body that provide resistance to infection. It consists of a very large number of small living things, called cells. Cells travel in the blood and can get to all parts of the body to 'police' for invaders.
Infection	The invasion of a host by organisms such as bacteria, fungi, viruses, protozoa, helminths, or insects which caused a pathologic status in the host.
Inflammation	The reaction of the tissues to injury, characterised clinically by heat, swelling, redness, pain and loss of function; the body's natural defence to protect itself from infections and injuries.
Inflammatory	Adjective of inflammation.
Innate response	Involving innate immunity. Innate immunity refers to nonspecific defence mechanisms that come into play immediately or within hours of an antigen's appearance in the body.
Interleukin-1 beta	A protein that in humans is encoded by the IL1β gene. It has a role in the inflammatory response.
Isoprenoid	A large and diverse class of naturally occurring organic chemicals. Isoprenoids play widely varying roles in the physiological processes of plants and animals.
Live attenuated vaccination	Inoculation of live attenuated vaccine in order to induce immunity in the recipient. Live attenuated vaccine is a vaccine created by reducing the virulence of a pathogen but keeping it viable (or "live"). Attenuation takes an infectious agent and alters it so that it becomes harmless or less virulent.
Lymphadenopathy	Lymph node enlargement in response to any disease.
Molecule	A group of atoms bonded together, representing the smallest fundamental unit of a chemical compound that can take part in a chemical reaction.
Monogenic	Involving or controlled by a single gene.
Morbidity	The ratio of the number of sick individuals to the total population of a community.
Mucocutaneous	Pertaining to a mucous membrane and the skin, and to the line where these joins.
Mutation	A change of the structure of a gene, resulting in a variant form that may be transmitted to subsequent generations, caused by the alteration in DNA.
Nephropathy	Any disease of the kidney.
Oedema	Excessive accumulation of fluid in the tissues, due to increased transudation of the fluid from capillaries.
Orbital	Pertaining to an orbit (the bony cavity containing the eye).
Pericarditis	Inflammation of the pericardium (membranous sac enveloping the heart).

Peritonitis	Inflammation of the peritoneum (membrane lining the interior of the abdominal cavity and surrounding the viscera).
Plaque	A patch, or an abnormal flat area on any internal or external body surface.
Pleuritis	Inflammation of the pleura (membrane enveloping the lung and lining the internal surface of the thoracic cavity).
Protein	Any of a class of nitrogenous organic compounds which have large molecules composed of one or more long chains of amino acids and are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, and as enzymes and antibodies.
Pyrin	A protein produced in certain white blood cells that play a role in inflammation and in fighting infection.
Rash	A lay term used for nearly any skin eruption.
Receptor	A molecule at the cell surface or within the cell which can combine with other molecules (such as toxins, hormones, antigens) resulting in a given alteration of cell function.
Replication	Any behaviour of a microorganism that yields construction of an identical copy of itself.
Serosa	A serous membrane lining the pericardial, pleural, and peritoneal cavities.
Serositis	Inflammation of a serous membrane.
Splenomegaly	Enlargement of the spleen.
Urticaria	A skin condition characterised by the appearance of intensely itching wheals, usually white, in the center and surrounding area of an erythema.
Virus	Vast group of minute structures composed of a sheath of protein encasing a core of nucleic acids (i.e. DNA or RNA), capable of infecting almost all members of the animal and plant kingdoms.

References •CAPS Fact Sheet from website Rheumatology. Available from https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Cryopyrin-Associated-Autoinflammatory-Syndrome-CAPS-Juvenile. Accessed October 2018. •Cattalini M, et al. Intern Emerg Med 2016; 11(6):781-791. •Ciccarelli F, et al. Curr Med Chem 2014; 21(3):261-269. •Favier LA and SchulertGS. Appl Clin Genet 2016; 9:101-110. •Karen L.W. Durrant RN, et al. CAPS. Cryopyrin-Associated Periodic Syndromes. ©2012 The NOMID Alliance www.nomidalliance.org. •National Amyloidosis Centre. Available from http://www.amyloidosis.org.uk/fever-syndromes/inherited-fever-syndromes/. Accessed October 2018. •Rheumatology. Available from https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Cryopyrin-Associated-Autoinflammatory-Syndrome-CAPS-Juvenile. Accessed October 2018. •Stych B and Dobrovolny D. Curr Med Res Opin 2008; 24(6):1577-1582. •Ter Haar NM, et al. Ann Rheum Dis 2015; 74(9):1636-1644. •The Voice of 12,000 Patients. Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe. EurordisCare 2009. Available from https://www.eurordis.org/publication/voice-12000-patients. Accessed October 2018. •US National Library of Medicine. Available from https://ghr.nlm.nih.gov/condition/tumor-necrosis-factor-receptor-associated-periodic syndrome#statistics. Accessed October 2018. •Wurster VM, et al. Pediatr Ann 2011; 40(1):48-54.

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