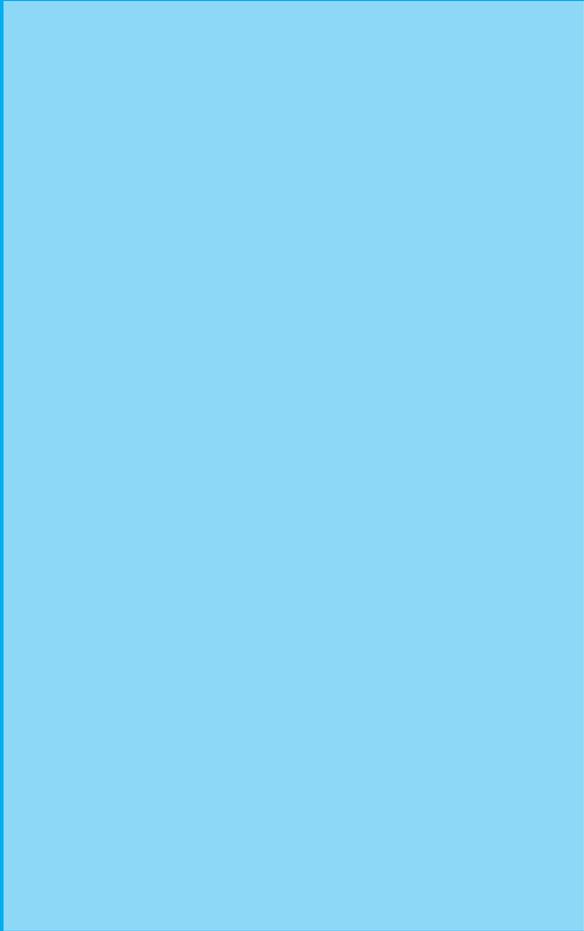


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# CAPS

## Cryopyrin-Associated Periodic Syndromes

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Familial Cold Autoinflammatory (or Urticaria) Syndrome (FCAS/FCU)  
Muckle-Wells Syndrome (MWS)  
Neonatal-Onset Multisystem Inflammatory Disorder (NOMID)—aka:  
Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)



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## Cryopyrin-Associated Periodic Syndromes are Autoinflammatory Diseases

Cryopyrin-Associated Periodic Syndromes (CAPS) are members of a growing family of autoinflammatory diseases, which were originally referred to as Hereditary Periodic Fever Syndromes. Autoinflammatory diseases are caused by genetic mutations in molecules that are involved in regulating the innate immune response—a “hard wired” defense system that evolved to quickly recognize and act against infectious agents and other danger signals produced by our bodies. It is important not to confuse autoinflammatory syndromes with autoimmune diseases, such as: Lupus, Rheumatoid Arthritis and others that are caused by the body’s adaptive immune system developing antibodies to antigens that then attack healthy body tissues.<sup>1</sup>

### THE THREE KNOWN FORMS OF CAPS DISEASES ARE:

- Familial Cold Autoinflammatory Syndrome (FCAS), also known as Familial Cold Urticaria (FCU), or Familal Cold Urticaria Syndrome (FCUS)
- Muckle-Wells Syndrome (MWS)
- Neonatal-Onset Multisystem Inflammatory Disorder (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)

### Mutations in the *NLRP3* (*CIAS1*) Gene Cause CAPS

CAPS diseases are associated with mutations or misspellings in the *Nucleotide binding domain, leucine rich family (NLR), pyrin containing 3 (NLRP3)* gene, also known as the *CIAS1* or *NALP3* gene. *NLRP3* encodes cryopyrin, which belongs to an emerging family of danger sensors, called NLRs (NOD-like receptors). When triggered by a danger signal, cryopyrin assembles with other molecules to coordinate an inflammatory response that leads to increased IL-1 $\beta$  production to help fight off infections.<sup>7</sup> This sensing and coordinating unit is called an “inflammasome.” A mutation of the *NLRP3* gene causes the cryopyrin inflammasome to constantly overproduce IL-1 $\beta$  instead of producing IL-1 $\beta$  only in response to infections. This overproduction of IL-1 $\beta$  causes many CAPS symptoms to be present at birth or in early infancy, and persist or increase throughout life. Rashes, fevers, joint pain, headaches, conjunctivitis and many other symptoms are noted in CAPS disorders.

The *NLRP3* genetic mutation is autosomal dominant, so only one misspelled gene is needed in a person’s DNA to cause CAPS. Misspellings of the *NLRP3* gene can occur spontaneously at conception, as is often the case with NOMID, but in FCAS and MWS, the gene mutation is usually passed down by one affected parent for many generations.

## Help Increase CAPS Awareness

Please consider making a donation to The NOMID Alliance, a 501(c)(3) non-profit. Donations are tax-deductible to the fullest extent of the law. Feel free to request more copies of this brochure to distribute to patients, friends, or family. You can reach us by phone, e-mail, or by post. If you are requesting more than 50 copies of this brochure, please consider making a suggested donation to the NOMID Alliance of at least \$10 to cover our printing and mailing costs. Call us at 415-831-8782 to discuss your needs if you are requesting a large volume of brochures for distribution. Thanks!

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- I would like \_\_\_\_\_ copies of the CAPS brochure to share with:  
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I would like to make a donation to The NOMID Alliance to help promote awareness about autoinflammatory diseases so that more people afflicted with these disorders can receive the proper diagnosis, care and treatment.

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## The NOMID Alliance

The NOMID Alliance is a 501(c)(3) non-profit public charity dedicated to promoting awareness, proper diagnosis, treatment, and improved care for people with Cryopyrin-Associated Periodic Fever Syndromes (CAPS) and other autoinflammatory diseases.

### GOALS OF THE NOMID ALLIANCE:

Goal 1: To continue increasing awareness about Cryopyrin-Associated Periodic Syndromes (CAPS), and other autoinflammatory diseases.

Goal 2: Act as a united voice worldwide to promote improved collaboration amongst healthcare professionals dealing with autoinflammatory diseases, so that all people suffering from these rare syndromes can have an accurate diagnosis and improved access to the most beneficial care available.

Goal 3: To serve as a resource and advocate for individuals, families, and friends that are dealing with CAPS, and other autoinflammatory diseases.

Goal 4: Encourage medical and pharmaceutical groups to continue researching treatments for autoinflammatory diseases.

Goal 5: Increase collaboration on projects and awareness efforts with other organizations that deal with autoinflammatory diseases. We are also interested in working with organizations that are helping to improve research, care, awareness and quality of life for patients with rare diseases worldwide.

### More information is online at [www.nomidalliance.org](http://www.nomidalliance.org)

To learn more about autoinflammatory diseases, current findings, additional resources or more about The NOMID Alliance, please visit our website at [nomidalliance.org](http://nomidalliance.org). You can also follow us on Facebook to keep updated on the latest research findings, organizational activities and other efforts for autoinflammatory diseases.

We would appreciate your feedback about this brochure by phone, mail, or email. Your suggestions will help us improve our efforts in increasing awareness about autoinflammatory diseases. We value your input, and your feedback and identity will be kept confidential.

## Understanding the Range of Severity in CAPS

The disorders of FCAS, MWS and NOMID/CINCA are generally considered to represent the varying degrees of severity within the same autoinflammatory condition, now known as CAPS. Before the discovery of *NLRP3* gene mutations, these disorders were thought to be unique, independent syndromes. Increased research and awareness of the genetic causes for CAPS has led to better diagnosis, care and treatment for afflicted patients in the past ten years.

### SEVERITY OF CAPS INFLAMMATION

mild	moderate	severe
FCAS	MWS	NOMID

Overlap of CAPS symptoms can exist between each syndrome classification

If you can visualize the CAPS diseases on a spectrum of varying intensity, FCAS is considered to be the least severe, since the inflammation usually does not cause permanent damage to any of the body systems. MWS lies in the middle of the spectrum, since it shares some traits with FCAS, but can have more intense and enduring flares of inflammation. MWS can cause permanent damage to some areas of the body, including progressive hearing loss, and amyloidosis caused by a buildup of amyloid protein in the kidneys that can lead to kidney failure. MWS patients are generally spared from damage to the brain, and do not have chronic aseptic meningitis, as seen in NOMID. At the most severe end of the CAPS spectrum lies NOMID/CINCA. The persistent inflammation from NOMID causes profound damage throughout most areas of the body. The majority of patients with NOMID have significant inflammatory damage to their joints, brain, eyes, hearing and other organs, and can also develop amyloidosis. The most severe patients do not live into adulthood, and many also have some degree of mental and/or cognitive disability.<sup>1</sup>

## Diagnosis of CAPS

There can be a great deal of overlap in symptoms between FCAS, MWS and NOMID, so understanding the range of CAPS conditions can help aid in diagnosing and treating patients. Please look at the chart in the center of this booklet to compare symptoms within the CAPS disease spectrum, and also to see how CAPS symptoms compare to other autoinflammatory diseases.

Most FCAS or MWS patients have *NLRP3* gene mutations. *NLRP3* gene mutations have been discovered in the majority of patients with NOMID, thanks to new genetic testing methods, including some cases involving somatic mosaicism.<sup>8</sup> Genetic tests are helpful, but a clinical diagnosis based on symptoms is essential. The diagnosis of CAPS should include genetic testing for *NLRP3* and other autoinflammatory diseases, along with a full evaluation of symptoms, lab tests, a skin biopsy, and a complete medical history from birth onwards.

## COMMON SYMPTOMS PRESENT IN ALL FORMS OF CAPS:

- Rash
- Headaches
- Periodic Fevers
- General Malaise
- Joint Pain
- Conjunctivitis

### A Rash is Often the First Notable Symptom of CAPS



Fig. 1. Characteristic rash & facial features on a newborn with NOMID – a form of CAPS.

Most CAPS patients develop the rash at or shortly after birth. In a few cases of MWS and FCAS the rash starts later in life. The maculopapular, urticaria-like rash covers the entire body, generally resembles hives, and intensifies during periods of increased flare-ups of inflammation. In most cases, the rash is not itchy, but a few patients do complain of an itchy, or even burning sensation.<sup>3</sup> Skin biopsy findings of the rash often include the presence of increased numbers of neutrophils at the eccrine coils.<sup>4</sup> Some patients, usually with FCAS, have the rash only during flares of inflammation, but for most, the rash is present almost every day, and can become very pronounced during flares.<sup>3</sup>

### Familial Cold Autoinflammatory Syndrome (FCAS/FCU)

- Symptoms are triggered by cold or cooling temperatures
- Large Family groups with FCAS for many generations
- NOT Acquired Cold Urticaria, (ACU) – aka “allergy to cold”

Patients with FCAS can suffer greatly on a regular basis from flares of symptoms listed above, starting 1-2 hours after exposure to even mildly cold or cooling temperatures. Symptoms of varying intensity can last at least 12-24 hours. The rash and symptoms are not immediate, as seen in Acquired Cold Urticaria (ACU). Patients with FCAS usually do not suffer from the more permanent or debilitating complications seen in MWS or NOMID, but a few have developed amyloidosis. Many do have significant suffering with disease flares. People with FCAS also have a great deal of daily challenges in trying to avoid cold triggers in their environment. Cold foods, air conditioning, weather changes or swimming can set off fevers, rashes, aches and conjunctivitis.<sup>1,2,3</sup>

### CAPS is a Rare Condition That May Be Underdiagnosed

CAPS mutations are believed to occur in 1 out of 1 million people worldwide, however, this is only a statistical estimate.<sup>5</sup> Some believe that these diseases may be more prevalent, but may be misdiagnosed. A few patients possess characteristic symptoms of more than one CAPS subtype, which can complicate or delay the proper diagnosis of FCAS, MWS or NOMID. Increased understanding and awareness of these rare and complex syndromes is essential.

Any patient presenting with CAPS symptoms should be evaluated for these rare diseases, especially if they have rashes from early infancy that are frequent or persistent, and accompanied by: Fevers, joint pain and inflammation, eye redness and/or pain, or headaches. If flares develop after an exposure to cold, FCAS should be considered. Although these conditions are rare, early diagnosis and proper treatment can help CAPS patients to live healthier lives.

### THANK YOU FOR YOUR INTEREST IN CAPS

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### References

1. Kastner, DL. Hereditary Periodic Fever Syndromes. Hematology 2005—American Society of Hematology Education. Program\_2005: 74-81.
2. Hoffman HM, Mueller JL, et al. Mutation of a New Gene Encoding a Putative Pyrin-like Protein causes FCAS and MWS. Nat. Genet. 2001; 29: 301-305.
3. Rosengren S, et al. Monocytes from FCAS Patients Are Activated by Mild Hypothermia. J. Allergy Clin. Immunol. Allergy. 2007; 119 (4): 991-996.
4. Huttenlocher, A, Frieden, IJ, Emery, H. Neonatal Onset Multisystem Inflammatory Disease. J. Rheumatol. 1995; 22 (6):1171-3.
5. Cuisset, L, et al. Genetic Linkage of the Muckle-Wells Syndrome to Chromosome 1q44. Am. J. Hum. Genet. 1999; 65 (5): 1054-59.
6. Goldbach-Mansky, R, Dailey, NJ, et al. Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1 Beta Inhibition. N.Engl. J. Med. 2006 Aug. 10; 355 (6): 581-92.
7. Drenth, JPH, van der Meer, JWM. The inflammasome—A Linebacker of Innate Defense. N.Engl. J. Med. 2006;355(7):730-732.
8. Kazushi, I, et al. Detection of Base Substitution-Type Somatic Mosaicism of the *NLRP3* Gene with >99.9% Statistical Confidence by Massively Parallel Sequencing. DNA Res. 1st pub. online Jan. 24, 2012 doi:10.1093/dnares/dsr047.
9. Hoffman, H & Simon, A. Recurrent Febrile Syndromes—What a Rheumatologist Needs to Know. Nature Reviews Rheumatology. 2009 (5): 249-256.

## Other Characteristics of NOMID/CINCA

Some NOMID patients can have unique facial characteristics, such as saddle back noses (fig.1) or frontal bossing, but these are also not essential criteria for diagnosis. Amyloidosis can develop in some patients after years of chronic inflammation with elevated serum amyloid. Some also have enlarged livers and spleens. The eyes are usually affected with bouts of conjunctivitis, uveitis, iritis, persistent papilledema, and even progressive vision loss as the optic nerve gets damaged from persistent high brain pressure caused by inflammation. Early diagnosis and treatment can prevent or reduce some symptoms.<sup>6</sup>

### CURRENT TREATMENTS FOR CAPS

- New drugs can prevent the cellular signalling of IL-1 $\beta$  in CAPS patients

Luckily, now that the genetic mutation and cause for CAPS has been found, better treatments have been discovered, or are being developed and produced that target the main source of inflammation—the overproduction and oversecretion of Interleukin-1 $\beta$  by altered cryopyrin inflammasomes. Many patients with FCAS, MWS and NOMID have responded very well in recent research studies, and in clinical use with various drugs that block Interleukin-1 $\beta$ . Many CAPS patients have shown dramatic improvement in their health with a great reduction of overall inflammation throughout their bodies after starting these medications, but more research is needed.<sup>6</sup> Please visit our website at [www.nomidalliance.org](http://www.nomidalliance.org) to learn more about current CAPS treatments.

## More Awareness and Education about CAPS is Necessary

Early and correct diagnosis and treatment can greatly impact the patient's quality of life, and reduce the suffering that CAPS patients must endure. This is especially important since long-term inflammation can cause permanent damage over time, especially in most NOMID patients, and also in many with MWS. Most CAPS sufferers struggle with their symptoms for years before they are correctly diagnosed and treated, which can have devastating effects. CAPS disorders are very rare, so many doctors are still unfamiliar with these syndromes. Even if a doctor has heard of these rare syndromes, many have never seen a CAPS patient in their practice, and need more guidance on how to properly care for these patients. Our hope is that if more CAPS patients can get proper care and treatment early in their life, that many serious complications from these syndromes may be prevented.

If you are an autoinflammatory diseases specialist, or have a helpful resource please contact us at [www.nomidalliance.org](http://www.nomidalliance.org). If you would like to have more copies of this booklet to share with patients, or help with our awareness efforts for all autoinflammatory diseases, we would love to hear from you too.

## Muckle-Wells Syndrome (MWS)

- Symptoms triggered by cold, stress or unknown factors
- Progressive, significant hearing loss starting in adolescence
- Many develop Amyloidosis from elevated serum amyloid

Muckle-Wells Syndrome is characterized by flares of the rash, fevers, joint aches, nausea, abdominal pain, headaches, malaise, and conjunctivitis that can last from 1-3 days. The flares can be triggered by cold, possibly stress or exercise, or random unknown factors. MWS patients often develop progressive, even profound sensorineural deafness starting in early adolescence. Later in life, 25% of MWS patients develop amyloidosis due to buildups of amyloid deposits from chronic inflammation that can be life-threatening if the amyloid builds up in the kidneys or liver, and can cause these organs to fail. MWS patients do not have chronic aseptic meningitis, as often seen in NOMID.<sup>1,2</sup>

## Neonatal Onset Multisystem Inflammatory Disease (NOMID/CINCA)

- Chronic aseptic meningitis—from inflamed tissues surrounding the brain
- Papilledema—from increased intracranial pressure on the optic nerves
- Joint problems – many with bony overgrowth & enlarged kneecaps
- Constant flares with chronic high inflammatory lab values
- Mental and physical delays are common, but not all have delays
- Progressive hearing loss, starting in early childhood

People with NOMID are the most severely affected of all the CAPS syndromes, since they have continuous inflammation in multiple organs starting in early infancy. These patients have persistent rashes, often increasing in intensity with frequent flares of fevers, accompanied by a multitude of inflammatory symptoms. Most NOMID patients suffer from chronic inflammation of the central nervous system (CNS), such as: Chronic aseptic meningitis, severe headaches, elevated brain pressure, papilledema, progressive sensorineural hearing loss (from early childhood), along with cognitive and mental deficits. Not all NOMID patients have mental deficits even if they have CNS symptoms, but it is common.<sup>1,6</sup> Joint pain is frequent and persistent, often with varying degrees of physical disability.

Up to half of NOMID patients also have bony changes and enlarged knee caps from changes to their growth cartilage. However, it is not an absolute criteria to present with these bony changes to have a diagnosis of NOMID. Many have weaker muscle tone all over the body, knee valgus or varus deformities, clubbing, contractures or arthralgias.<sup>6</sup>

	Cryopyrin-Associated Periodic Syndromes (CAPS)			Other Known Autoinflammatory Periodic Fever Syndromes		
	NOMID/CINCA	MWS	FCAS/FCU	FMF (Familial Mediterr. Fever)	TRAPS (TNF Receptor APF)	HIDS (Hyper Ig D)
GENES & INHERITANCE	<i>NLRP3/CIAS1/NALP3</i> Autosomal Dominant Spontaneous mutations, few familial inherited. <sup>1</sup>	<i>NLRP3/CIAS1/NALP3</i> Autosomal Dominant Spontaneous mutations, some familial groups. <sup>1</sup>	<i>NLRP3/CIAS1/NALP3</i> Autosomal Dominant Large familial groups, some spontaneous mutations. <sup>1</sup>	<i>MEFV</i> Autosomal Recessive Most common inherited periodic fever syndrome. <sup>1</sup>	<i>TNFRSF1A</i> Autosomal Dominant Spontaneous mutations, some familial groups. <sup>1</sup>	<i>MVK</i> Autosomal recessive
ETHNICITY	Any—present in all races. <sup>1</sup>	Affects all races, but many of European decent. <sup>1</sup>	Affects all races, but most are of European decent. <sup>1</sup>	Turk, Armenian, Arab, Jew, Sephardic Jew, or Italian. <sup>1</sup>	Any—present in many diverse races. <sup>1</sup>	Mostly of Dutch descent, or Northern European. <sup>1</sup>
FREQUENCY OF THE MUTATION IN THE WORLD	Statistical estimate 0.001=1:1 million=possibly 6,500+ w/ CAPS mutation in world. <sup>5</sup>	(see NOMID) 1:1 million, maybe more due to some family groups. <sup>5</sup>	1:1 million, or more. In USA 300+ diagnosed—most in large family groups. <sup>2,5</sup>	1:5-1:7 people carry recessive <i>MEFV</i> gene in affected ethnic groups (above). <sup>1</sup>	Unknown—over 1000 pts. diagnosed so far in the world.	Unknown >200 known patients so far on HIDS registry (www.hids.net).
DURATION OF SYMPTOMS OR ATTACKS (FLARES)	Continuous w/ increased symptoms during flares, fever, or inflammation. <sup>1</sup>	Often lasts 2-3 days, random onset—some pts. flares triggered by cold temperature. <sup>1</sup>	12-24 hours—Onset 1-3 hr. after exp. to cold or cooling temperatures. <sup>1</sup>	12-72 hours <sup>1,9</sup>	Days—up to weeks. Average flare is 3 weeks. <sup>1,9</sup>	3-7 days, recurrent bouts every 2-12 weeks. <sup>1,9</sup> Some flares occur after vaccines. <sup>9</sup>
AGE OF ONSET	Neonatal/early infancy. Rash, symptoms, abnormal labs often at birth. <sup>1,6</sup>	Infancy, but a few present w/ symptoms later in childhood or adolescence. <sup>1</sup>	Infancy—after exposure to cold or cool temperatures. <sup>1</sup>	Infancy, to under 20 years of age for the first symptoms. <sup>9</sup>	Most first attacks by 3 yrs, almost all begin by 20 yrs of age, a few start later in life. <sup>9</sup>	>90% present with symptoms in infancy. <sup>9</sup>
<b>SYSTEMIC FINDINGS</b>						
SKIN/CUTANEOUS	Ever present <sup>1</sup> Urticaria-like rash w/increased neutrophils at the eccrine coils. Rash increases w/ flares. <sup>4</sup>	Urticaria-like rash w/ increased neutrophils at the eccrine coils. <sup>4</sup> Almost daily rash—increases w/ flares. <sup>1</sup>	Cold induced Urticaria-like rash w/ increased neutrophils at the eccrine coils. <sup>4</sup> Some w/ daily rash. <sup>1</sup>	Erysipeloid erythema on the ankle—foot—below knee region, lasts 2-3 days during flares of symptoms. <sup>1</sup>	Migrating rash w/ deep pain under rash areas. Severe pain follows the rash path from the trunk out to limbs. <sup>9</sup>	Diffuse maculopapular rash and urticaria. Some w/ petechiae or purpura present. A few w/aphthous ulcers. <sup>1,9</sup>
NEUROLOGIC	Headaches, fever, chronic aseptic meningitis, high CNS pressure. Many w/ mental &/or cognitive impairments, papilledema common.	Some have headaches with fever & flares. Uncommon to have many other CNS symptoms.	Some have headaches with fever after cold exposure. Unknown if there are notable CNS affects at this time.	Fevers. Acute aseptic meningitis is rare and can occur during flares, but is never chronic.	Fevers lasting >3 days at over 38° C w/ flares. Some have headaches w/ flares of symptoms. <sup>1,9</sup>	Headaches & fevers w/ flares of symptoms are common. <sup>1,9</sup> More severe neurological symptoms are rarely present in HIDS. <sup>9</sup>
AUDITORY	Many have increased sensorineural hearing loss, from infancy/childhood.	Many have increased sensorineural hearing loss, starting in adolescence. <sup>1</sup>	Some pts have mild hearing loss—not currently known if it's from CAPS inflammation.	Uncommon—not believed to be caused by FMF disorder. <sup>1</sup>	Uncommon—not believed to be caused by TRAPS. <sup>1</sup>	Uncommon—not believed to be caused by HIDS. <sup>1,9</sup>
OPHTHALMIC	Papilledema, uveitis, iritis, conjunctivitis Some w/ corneal haze or vision loss. <sup>6</sup>	Conjunctivitis (non-infectious) episcleritis during flares, or corneal haze. <sup>1</sup>	Conjunctivitis (non-infectious) during flares triggered by cold exposure. <sup>1</sup>	Very rare to uncommon <sup>1</sup> .	Conjunctivitis, & periorbital edema during flares. <sup>1,9</sup>	Very rare to uncommon. <sup>9</sup>
PLEURAL	Some cases of pericardial effusions, or pericarditis.	Rare	Not noted	45% have pleuritis, painful respiration, w/ flares. Some w/ pericarditis. <sup>1</sup>	Common, including pleurisy <sup>1</sup>	Rare <sup>1</sup>
ABDOMINAL	Nausea & vomiting, pain w/ flares, or high CNS pressure. <sup>6</sup>	Some have abdominal pain w/ flares or other GI issues. <sup>1</sup>	Uncommon <sup>1</sup>	Sterile peritonitis, pain, &/or constipation w/flares.	Peritonitis, diarrhea, & constipation w/ flares.	Extreme pain, vomiting & diarrhea w/ flares.
LYMPHATIC	Some pts. w/enlarged liver and/or spleens, many have large lymph nodes. <sup>1</sup>	Rarely noted. <sup>1</sup>	Not noted. <sup>1</sup>	Enlarged spleens common, some have enlarged lymph nodes. <sup>1</sup>	Enlarged spleens common, some have enlarged lymph nodes. <sup>1</sup>	Enlarged cervical lymph nodes common in children. <sup>1</sup>
JOINTS/BONES MUSCLES & CARTILAGE	Joint pain, knee valgus or varus. Some w/ frontal bossing, saddleback nose. contractures clubbing <sup>1</sup> <50% of pts. knees have bony overgrowth.	Pain and arthralgias often noted with flares. <sup>1</sup>	Arthralgias & stiffness with flares. <sup>1</sup>	Mono/Polyarthritis, oligoarthritis & clubbing common. Ankle arthralgias common. Severe arthritis of the hip or ankle is rare. <sup>1</sup>	Intermittent or chronic arthritis in large joints, w/ muscle pain & swelling. <sup>1</sup>	Arthralgias common, symmetric polyarthritis frequently noted. <sup>1</sup>
VASCULITIS	Vasculitis rarely develops. <sup>1</sup>	Not noted. <sup>1</sup>	Not noted. <sup>1</sup>	HSP, polyarteritis nodosa. <sup>1</sup>	HSP, lymphocytic vasculitis. <sup>1</sup>	Cutaneous vasculitis common, HSP is rare. <sup>1</sup>
AMYLOIDOSIS	Elevated SAA leads to amyloidosis in <2% pts. <sup>1,6</sup>	Elevated SAA in >25% of pts; >25 % w/amyloidosis. <sup>1,9</sup>	Elevated SAA, leads to amyloidosis in <10% pts. <sup>9</sup>	Common >50% in untreated pts., depends on genotype. <sup>9</sup>	10-20% occurrence—higher risk w/ cysteine mutation. <sup>9</sup>	<10%, not common. <sup>9</sup>
ABNORMAL LABS	Chronically high: ESR, CRP, SAA, anemia, granulocyte hyperleukocytosis. <sup>1,6</sup>	High: ESR, CRP, SAA. Leukocytosis, hypergammaglobulinemia w/flares. <sup>1</sup>	High: ESR, CRP, SAA. Leukocytosis w/ flares. <sup>1</sup>	High: ESR, CRP, SAA w/ flares. Fibrinogen, Leukocytosis present w/ flares. <sup>1</sup>	High: ESR, CRP, SAA. Elevated PMNs, polyclonal gammopathy, leukocytosis. <sup>1</sup>	High: ESR, CRP w/ flares. High IgD w/ IgA in 80% pts. Mevalonate aciduria noted. <sup>1</sup>