Social impact

TRAPS limits the daily activities of both children and adult patients in many areas including school and work, personal relationships, and social activities. Attendance and performance are both impacted due to the unpredictability of symptoms and long-lasting flares, which can add stress affecting the patient's physical and emotional well-being. Sleep quality is a common issue for TRAPS patients, and they should be evaluated for comorbid sleep apnea. Other issues may include anxiety, depression, and fatigue.

Photo by Carolina on Unsplash

Genetics and epidemiology

TRAPS is associated with variants in the TNFRSF1A gene. It is autosomal dominant, meaning an affected individual has a 50% chance of passing the disease on to each child. The disease is caused by germline heterozygous pathogenic variants in the TNF receptor superfamily member 1A.
TRAPS has an estimated prevalence of one per one million individuals worldwide. While most cases are reported in Caucasian and Asian populations, TRAPS has been reported in a variety of ethnic groups with all genders being equally affected.

Photo by Planet Volumes on Unsplash

Documenting symptoms

Patients should keep a symptom diary with detailed notes on all organs/body parts impacted before, during, and after flare. This type of documentation can be very helpful to track and present how the disease manifests in a particular case. Recording fevers, abdominal pain, mouth ulcers, muscle pain, fatigue status/activity, rashes, pain score, all per specific body part can help the clinician have a clear overview of the symptoms occurring during a flare.

Keeping this diary over time will also allow patients to spot trends and ask additional pointed questions. Another way to help develop a disease diary is by taking pictures of rashes, red eyes, and any other visible symptom.

Photo by Getty images on Unsplash

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The brochure has been reviewed and endorsed by
PD Dr. Juergen Rech, Senior Physician and Head of the
Autoinflammation Clinic, University of Erlangen, Germany.

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TNF Receptor-Associated Periodic Fever Syndrom (TRAPS)

Photo by Brooke Cagle on Unsplash

ENGLISH

Introduction

TRAPS is an autosomal dominant inherited autoinflammatory syndrome caused by mutations in the TNFRSF1A gene and characterized by prolonged and recurrent episodes of fever, abdominal pain, chest discomfort, arthralgia, myalgia, and erythematous rash. Since SAA amyloidosis is an important cause of morbidity and mortality in TRAPS, it is essential for patients to be treated with appropriate biological medications. The disease may affect all populations globally.

Age of onset

The average age of symptom onset is early childhood (average age 3 to 10 years old) with some patients presenting in the teenage years. Ten percent of cases may also occur in individuals over the age of 30. Some of these adult patients may present with somatic variants, thus late onset of symptoms.

Symptoms

Clinical symptoms may include recurrent fevers, headaches, chills, fatigue, insomnia, seizures, abdominal pain, diarrhea, constipation, vomiting, splenomegaly, hepatomegaly, aseptic peritonitis, GI bleeding, conjunctivitis, periorbital edema and pain, pharyngitis, mouth ulcers, joint pain (arthralgia and arthritis), muscle pain (myalgia/myositis), joint stiffness and swelling (oligoarthritis), fasciitis, monoarthritis (inflammation of one joint), polyarthritis (at least 5 joints affected), bone pain, maculopapular/migratory rash, urticarial rash, erysipelas-like erythema, chest pain, pericarditis, persistent cough, pneumonia, enlarged and painful cervical lymph nodes, generalized lymphadenopathy, amyloidosis, and gonadal pain.

Flares

Flares typically occur every four to six weeks and last between 5 and 25 days. The frequency of episodes and clinical symptoms range in severity and are unique to each patient.

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Amyloidosis risk

Amyloidosis has been reported in approximately 25% of cases with higher risk factors in patients who carry specific variants. AA amyloidosis is an important cause of morbidity and mortality in TRAPS that may be avoided with adequate and timely treatment. Proteinuria and kidney failure occur in 80%-90% of affected individuals with amyloidosis, while intestinal, thyroid, myocardium, liver, and spleen deposits are less common .

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Diagnostic criteria

According to the PFS Eurofever/PRINTO classification criteria. A confirmatory TNFRSF1A genotype and at least one among the following:

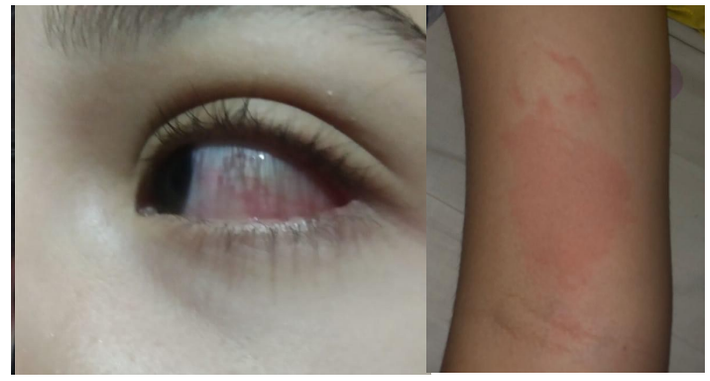
- Duration of episodes ≥7 days
- Myalgia
- Migratory rash
- Periorbital edema
- Relatives affected

or

Presence of a not confirmatory TNFRSF1A genotype and at least two among the following:

- Duration of episodes ≥7 days.
- Myalgia
- Migratory rash
- Periorbital oedema
- Relatives affected

Reference: Gattorno M, Hofer M, Federici S, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis. 2019;78(8):1025-1032. doi:10.1136/annrheumdis-2019-215048



Patient provided picture.

Triggers

Factors known to trigger flares are positive & negative stress, accidents/trauma, illness/infection, strenuous exercise, hormonal changes, fatigue, vaccinations. Other triggering factors remain unknown.

Diagnosing TRAPS

A diagnosis of TRAPS should be based on clinical symptoms, when meeting the diagnostic criteria, and confirmed through molecular genetic testing.

Labor findings

During a flare, acute-phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA) are typically elevated. Increased neutrophil count often presents (neutrophilia). Increased polyclonal immunoglobulin levels, especially IgA. Generally, acute-phase reactants stabilize between flares but may remain mildly elevated even in the absence of clinical symptoms.

Treatment

In particular, interleukin-1 (IL-1) inhibitors have been shown to be very effective in controlling the disease activity and preventing SAA amyloidosis. Other therapeutic options commonly used in conjunction with biologics include colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are often used to provide symptom relief during flares. The main goal of treatment consists of controlling symptoms, decreasing systemic inflammation, and preventing long-term complications.

The first line of biologics recommended for TRAPS patients are interleukin-1 inhibitors (IL-1): Ilaris (canakinumab) and Kineret (anakinra). Patients not responding to Kineret (IL-1α) should be offered Ilaris (IL-1β), and vice versa, as each medication works differently. Treatment with TNF-α inhibitors (e.g. Enbrel/Etanercept) have shown variable efficacy, while IL-6 blocker (Tocilizumab/Actemra/RoActemra) efficacy is more promising. All patients on biologics must be monitored and treated for infections, skin reactions, and lung problems. Corticosteroids may be effective controlling the inflammation, but they cannot be a substitute for a biological treatment in TRAPS.

Alle Patienten, die Biologika einnehmen, müssen überwacht und auf Infektionen, Hautreaktionen und Lungenprobleme behandelt werden. Kortikosteroide können die Entzündung wirksam kontrollieren, sie können jedoch keinen Ersatz für eine biologische Behandlung bei TRAPS darstellen.

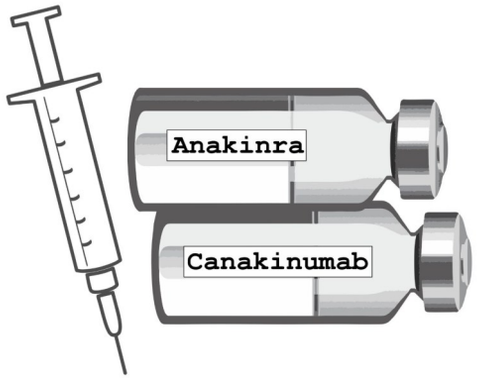
Dosing of Ilaris:
Children weighing less than 40kg are dosed by body weight with a recommended dose of 2mg/kg every 4 weeks by subcutaneous injection. Dosing can be increased to 4mg/kg every 4 weeks in patients not having an adequate response. Children and adults weighing 40kg or more should be given 150mg every 4 weeks by subcutaneous injection. Dosing can be increased to 300mg every 4 weeks in patients not having an adequate response.
Source:
https://www.ilarishcp.com/assets/pdfs/ilaris_dosing_guide.pdf

Post-treatment monitoring

It is recommended for patients to have a follow up every 6 months to evaluate treatment efficacy, flare breakthroughs, and to monitor acute-phase reactants (APR). Laboratory tests are recommended to monitor liver enzymes, complete blood count, kidney function, creatinine phosphokinase (CPK) and to identify proteinuria. The preferred APR are CRP, ESR and SAA.

Rare side effects of biologics

Adverse reactions experienced by TRAPS patients are injection site reactions and nasopharyngitis. Apart from these side effects, patients using these medications may also experience weight gain (despite no dietary changes), and infections.



FMF & AID picture

Emergency kit

TRAPS patients, in particular those on biologics, are more susceptible to getting infections, fungal issues, breakthrough flares and other immunological problems due to high levels of innate inflammation. It is therefore recommended that patients be provided with emergency medications prior to going on any biologic medication to be proactively prepared. The emergency kit should contain steroids, antibiotics, antihistamines, and pain medications. Patients should be instructed how to use all medications to control any unforeseen complications. Patients should always follow up with their treating physician, when requiring use of these medications.

Photo by Valeria Nikitida on Unsplash

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TRAPS Red Flags

- ✓ Flares last between 5 and 25 days
- ✓ Recurring fevers & chills
- ✓ Abdominal pain
- ✓ Headaches
- ✓ Diarrhea, constipation, vomiting
- ✓ Maculopapular/migratory rash
- ✓ Muscle pain (myalgia)
- ✓ Periorbital oedema & conjunctivitis
- ✓ Mouth ulcers
- ✓ Swollen lymph nodes
- ✓ Joint pain (arthralgia & arthritis)
- ✓ Sore throat (pharyngitis)
- ✓ Pericarditis
- ✓ Fatigue