Still's Disease, TRAPS, and Other Episodic Febrile Syndromes

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First described by Bywaters in 1971 (1), Adult Onset Still's Disease (AOSD) has since been recognized as one of the leading causes for fevers of unknown origin among the connective tissue diseases. With the publication of several large series from multiple countries that have a broad range of ethnic distribution, awareness of the disease as a real entity has increased. Although several non-standardized diagnostic criteria have been proposed, diagnosis is usually a challenge and of exclusion as characteristic. Serological tests and proven etiological agents remain undiscovered.

Most patients present similar clinical syndromes including: sore throat, a transient, salmon-pink maculopapular rash often associated with recurrent high, spiking fevers, arthralgias or arthritis, and neutrophilic leukocytosis. Most of the patients are seronegative for the rheumatoid factor and antinuclear antibodies. Associated findings often include the presence of hepatosplenomegaly, lymphadenopathy, and myalgias. Less frequently, serositis, pneumonitis, disseminated intravascular coagulopathy, acute organ system failure, and even death, may occur (1). Diagnosis of AOSD requires exclusion of multiple infectious etiologies, malignancies, other collagen-vascular disorders, and an enlarging group of familial periodic febrile syndromes (1, 2) (Table 1).

Table 1.
Clinical manifestations in our 39 patients with AOSD and other three series.

	39 patients Our series %	65 cases in France (%)	90 cases in Japon (%)	62 cases in Canada (%)
Arthritis	39 (100%)	69%	72%	94%
Fever	39 (100%)	93%	100%	100%
Rash	37 (94.8%)	84%	87%	87%
Score Throat	35 (89.7%)	67%	70%	92%
Lymphadenopathy	14 (35.8%)	47%	69%	74%
Neumonitis	8 (20.5%)	9%	6%	27%
Pericarditis	8 (20.5%)	23%	10%	37%
Pleuritis	7 (17.9%)	15%	12%	53%
Hepatomegaly	9 (23.0%)	9%	48%	44%
Splenomegaly	8 (20.5%)	21%	65%	55%
Myocarditis	4 (10.2%)	4%		
Deaths	4 (10.2%)	7%	4%	6%
Erythema Nodosus	2 (5.1%)			
Polyneuropathy	2 (5.1%)	2%	6%	2%
Abdominal Pain	2 (5.1%)	6%		48%
Aseptic Meningitis	1 (2.5%)		4%	
Necrotizing Adenitis	1 (2.5%)		4%	
Dissemm. Intrav. Coagulat.		3%	3%	3%
Koebner Fenom.	1 (2.5%)			32%

Increased serum ferritin or more recently, glycosalated ferritin, can be used as (AOSD) markers, but serum ferritin can be elevated in infectious diseases, malignancy and primary liver diseases. Table 1 summarizes the clinical manifestations observed in our 39 patients included in the ARTHROS 6.0 data base system and compares with other national series from France, Japan and Canada (2).

Management of AOSD has included the same medications used to manage polyarticular forms of rheumatoid arthritis (1, 2). A more targeted therapy is available now with Etanercept, Ramicade and Anakindra, as elevated serum and synovial fluid levels of tumor necrosis factor and interleukin-1 are associated with active AOSD. Elevated levels of interleukin 18 also have been found recently in these patients, and these findings will probably offer new future therapeutic targets (2).

Clinical and molecular genetic studies have defined several heritable disorders that present with self-limited episodes of fever (Table 2), abdominal pain, myalgias, joint pain, polyserositis and skin manifestations (1). Two of these entities. Familial Mediterranean Fever (FMF, MIM249100) and the hyper-immunoglobulinemia D with periodic fever syndrome (HIDS, MIM260920) are inherited as autonomic recessive traits, and their genetic defects have been identified (3). Dominant inherited periodic fever syndromes are less well-characterized (3-9). The most recent best characterized entity which was first described as Familial Hibernian Fever (FHF, MIM 14268) (3) in a large Irish-Scottish family, is not being recognized in other ethnic groups as TNFR1 associated periodic syndromes or TRAPS (3-9). In families with Irish ancestry and others with Scottish, Scottish-Irish, Scottish-German, Finnish, Irish-North American, French, and Puerto Rican, Argentenian, Lebanese and Arab-Israeli ancestries, the syndrome has been linked to 20 different mutations of the TNFR1- 55kD tumor necrosis factor receptor and associated in most of them, with a half-normal level of soluble plasma TNFR1 (3).

Table 2. Febrile Periodic Syndromes

Clinical Feature	FMF	Hyper IgD	TRAPS	AOSD	Muckle W.
Age of onset	< 10 years	< 10 years	Children new born	16-35 years	Adolescence
Ethnic background	Jewish, Armenian, Arab, Turkish	French, Dutch, European	Irish and others.	No association	No association.
Cutaneous Manifestations	Occasional erysipeloid erythema, H-Schonlein.	Common erythematous maculas and papulas, urticaria.	Erysipeloid, migratory rash. Eyes involvement.	Maculopapular rash, evanescent, pink.	Urticaria Rash.
Lymphadenopathy	Uncommon	Very common with attacks	Sometimes	Frequent	Uncommon
Amyloidosis	Common	None observed	Sometimes present	Sometimes present	Present
Genetics	Autosomal recessive. Py retin o Mavelonatokinasa	Autosomal recessive	Automosal dominant TNFR1 55kd	None association	Autosomal dominant.
Prognosis	Depends of Amyloidosis	No apparent effect on longevity	Depends of Amyloidosis	Depends of complication	Depends Amyloidosis/Renal failure.
Treatment	Colchicine, steroids. inferferon	NSAIDs, steroids	Steroids, etanercept.	NSAIDs, steroids, immunosuppress. gammaglobulin	

* Familial Mediterranean Fever.
* Hyper IgG: Hyper immunoglobulinemia G
* TRAPS: tumor necrosis factor associated periodic febrile syndrome
* AOSD: Adulto onset Still's Disease.
* Muckle W.: Muckle Wells Syndrome.

TRAPS syndrome is one of the auto-inflammatory syndromes characterized by systemic fever, skin rash, myalgias, and arthritis induced by apparently unprovoked inflammation in the absence of high-liter auto-antibody antigen-specific T- lymphocytes. TRAPS presents with prolonged attacks of fever and has localized inflammation. TRAPS is caused by dominantly inherited mutations TNFRSFIa (formerly termed TNFR1), the gene encoding the 55 kDa TNF receptor. All known mutations affect the first two cysteine-rich extracellular subdomains of the receptor, and several mutations are substitutions directly disrupting conserved disulfide bonds. One likely mechanism of inflammation TRAPS is the impaired cleavage of TNFRSFIA ectodomain upon cellular activation, with diminished shedding of the potentially antagonistic soluble receptor. Preliminary experience with recombinant p75 TNFR-Fc fusion protein for the treatment of TRAPS has been favorable in controlling the episodes and decreasing the frequency of attacks.

Clinical manifestations of TRAPS include the presence of high fever, chills, leucocytosis, polyarthralgias-itis, myalgias, myositis, and a wide spectrum of dermatological manifestations including migratory patches, edematous plaques, periorbital edema, and or conjunctivitis. Skin biopsy usually shows perivascular infiltrates of lymphocytes and monocytes. Table 3 summarizes a modification of McDermott criteria. Systemic amyloidosis is the most serious manifestation of TRAPS and sometimes leads to hepatic and/or renal failure and death. About 14 percent of patients present with this complication, and in 99 percent of these patients, amyloid occurs among with cysteine mutations.

TABLE 3. DIAGNOSTIC CRITERIA FOR HIBERNIAN FEVER OR TRAPS (Modified from EM McDermott, et.al.)

Major Criteria:	
Recurrent Fever	95%
Recurrent Abdominal Pain	95%
Severe Myalgia/Myositis	94%
Minor Criteria:	
Erysipelas-like Rash - Upper Extremity	Common
Conjunctival Injection	Common
Periorbital Edema	Common
Positive Family History - Response to Prednisone	Autosomic Dominant
Within 72 Hours	Common
Amyloidosis	Cysteine Mutations
TNFR Mutation	Approx. 20 and increasing.
Response to Etanercept	Successful

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