Int. j. adv. multidisc. res. stud. 2026; 6(4):1646-1648

Received: 04-07-2026
Accepted: 14-08-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

A Familial TRAPS Phenotype Masquerading as Autoimmune Disease: The Pitfalls of Polyclonal Hypergammaglobulinemia and Low-Titer ANA in Diagnosis

[1] G Khellaf, [2] A Benziane

[1, 2] Faculty of Medicine, University of Health Sciences Dr. Youcef El Khatib, Algiers, Algeria
[1, 2] Department of Nephrology, Bab El Oued University Hospital, Algiers, Algeria

Corresponding Author: **G Khellaf**

Abstract

Autoimmune and autoinflammatory disorders can exhibit significant clinical and immunological overlap, often leading to diagnostic delays and therapeutic misdirection. Polyclonal hypergammaglobulinemia and antinuclear antibodies (ANA), although classically associated with autoimmune processes, have been occasionally reported in monogenic autoinflammatory syndromes such as tumor necrosis factor receptor-associated periodic syndrome (TRAPS). We describe a familial cohort of three siblings presenting with recurrent febrile episodes, serositis, arthralgia, and mucocutaneous involvement since childhood. Comprehensive laboratory, immunological, and genetic investigations were performed, including serum protein electrophoresis, IgG subclass quantification, ANA testing by immunofluorescence, autoantibody profiling by immunodot, and next-generation sequencing of autoinflammatory gene panels. All three siblings exhibited marked polyclonal hypergammaglobulinemia with predominant IgM/IgG3/IgG4 elevation, and low-titer ANA (1/160–1/320, speckled) in the absence of specific extractable nuclear antigen antibodies. Inflammatory markers were persistently elevated during flares. Genetic analysis revealed a pathogenic heterozygous variant in *TNFRSF1A* (p.Phe141Leu), confirming TRAPS. Therapeutically, colchicine was ineffective, whereas IL-1 blockade with anakinra induced rapid and sustained remission in the two treated siblings. This family illustrates that polyclonal hypergammaglobulinemia and nonspecific autoantibodies may accompany TRAPS and mimic autoimmune disease. Such findings should not preclude genetic testing for autoinflammatory syndromes in patients with recurrent systemic inflammation, especially in familial cases. Early IL-1 inhibition represents an effective targeted therapy and may also serve as a diagnostic tool in phenotypically ambiguous cases.

Keywords: TRAPS, Autoinflammatory Syndrome, Hypergammaglobulinemia, Autoantibodies, IL-1 Inhibition, Familial Autoinflammatory, Diagnostic Mimicry

1. Introduction

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant autoinflammatory disorder caused by heterozygous mutations in the *TNFRSF1A* gene encoding the 55-kDa TNF receptor [1]. TRAPS was originally described in a family of Irish and Scottish descent-hence the historical name "Familial Hibernian Fever"-[2] but has since been reported in many different ethnic groups. The disease is characterized by recurrent, prolonged episodes of fever, migratory myalgia, abdominal and chest pain, erythematous rashes, periorbital edema, and a significant risk of AA amyloidosis in approximately 10% to 15% of untreated patients [3].

The pathophysiology of TRAPS involves the accumulation of misfolded TNFR1 in the endoplasmic reticulum, which activates the unfolded protein response. This response generates reactive oxygen species that trigger chronic inflammation [2]. More than 70 mutations in the *TNFRSF1A* gene have been associated with TRAPS; approximately 50% of these are structural mutations involving cysteine residues and are associated with higher disease penetrance and a more severe phenotype [4].

The differential diagnosis of TRAPS includes other periodic fever syndromes such as familial Mediterranean fever (FMF), hyperimmunoglobulinemia D syndrome (HIDS), Muckle-Wells syndrome, and PFAPA syndrome, as well as autoimmune

diseases such as systemic lupus erythematosus and juvenile idiopathic arthritis. This diagnostic challenge is compounded by the presence of immunological findings that may mimic autoimmune conditions. Polyclonal hypergammaglobulinemia is a known nonspecific finding during TRAPS flares [3], and low-titer antinuclear antibodies can occasionally be detected [5]. These findings, when present in a patient with systemic inflammation, can lead clinicians down a diagnostic pathway focused on autoimmune diseases rather than autoinflammatory syndromes.

We describe a familial cohort of three siblings with genetically confirmed TRAPS who presented with marked polyclonal hypergammaglobulinemia and low-titer ANA, highlighting the diagnostic pitfalls and the importance of genetic testing in patients with recurrent systemic inflammation.

2. Case Series

2.1 Family History

A familial cohort of three siblings (two females and one male) from a non-consanguineous family presented with recurrent systemic inflammatory episodes since childhood. The mother was identified as an asymptomatic carrier of the *TNFRSF1A* mutation, and the youngest sibling developed symptomatic disease at age 7, confirming autosomal dominant inheritance with variable expressivity [4]. There was no family history of autoimmune or rheumatic diseases.

2.2 Clinical Presentation

All three siblings experienced recurrent febrile episodes beginning in early childhood. The attacks were characterized by high fever lasting 7 to 21 days, migratory myalgia with tender overlying erythema, abdominal pain, arthralgia, and periorbital edema. Skin manifestations included migratory erythematous plaques. The episodes occurred spontaneously or following minor triggers such as stress, infection, or minor trauma. Between flares, patients were asymptomatic, but acute-phase reactants remained persistently elevated in some cases [3].

2.3 Laboratory Findings

Comprehensive laboratory investigations during flares revealed:

- **Marked polyclonal hypergammaglobulinemia**: Gamma fraction 22.8% (total protein 19.2 g/L).
- **Elevated total IgG**: 23 g/L with predominant IgM, IgG3, and IgG4 elevation.
- **Low-titer ANA**: 1/160 to 1/320 (speckled pattern).
- **Negative extractable nuclear antigen antibodies**: Anti-dsDNA, anti-Sm, anti-RNP, anti-SSA/Ro, and anti-SSB/La were all negative.
- **Elevated inflammatory markers**: Erythrocyte sedimentation rate and C-reactive protein were markedly elevated during flares.
- **Neutrophilic leukocytosis**: Present during acute episodes.

2.4 Genetic Analysis

Next-generation sequencing of autoinflammatory gene panels revealed a pathogenic heterozygous variant in *TNFRSF1A* (p.Phe141Leu), confirming the diagnosis of TRAPS. The unaffected mother was identified as an asymptomatic carrier, and the youngest sibling developed symptomatic disease at age 7, consistent with autosomal dominant inheritance with variable expressivity [4].

2.5 Therapeutic Response

Colchicine therapy was initiated but proved ineffective, as is typical for TRAPS [4]. Treatment with the interleukin-1 receptor antagonist anakinra (1.5 mg/kg/day) was then introduced in the two treated siblings. A prompt and sustained response was observed, with disappearance of symptoms and normalization of acute-phase reactant levels. No major adverse reactions or severe infections were observed during follow-up. This response is consistent with published data demonstrating that IL-1 blockade is highly effective in TRAPS [6].

3. Discussion

3.1 Diagnostic Challenges in TRAPS

The diagnosis of TRAPS is frequently delayed due to its rarity and the overlap of its clinical features with other inflammatory conditions [2]. The median age of symptom onset is 4.3 years, but diagnosis may be delayed by several years, particularly in patients without a clear family history [4]. The presence of polyclonal hypergammaglobulinemia and low-titer ANA in our patients could have easily led to a misdiagnosis of an autoimmune disease, such as systemic lupus erythematosus or mixed connective tissue disease.

Polyclonal hypergammaglobulinemia is a well-recognized but nonspecific finding during TRAPS flares [3]. Elevated IgG, IgA, and IgM levels have been reported in affected individuals [4]. The presence of these immunological abnormalities in the context of recurrent fever, serositis, and arthralgia may mimic the laboratory profile of autoimmune diseases, particularly systemic lupus erythematosus.

Low-titer antinuclear antibodies have been documented in patients with TRAPS [5]. In a Japanese patient with TRAPS associated with systemic lupus erythematosus, a novel *TNFRSF1A* mutation (T61I) was identified, illustrating the potential overlap between autoinflammatory and autoimmune phenotypes [5]. This case and others highlight that autoinflammatory and autoimmune diseases are not mutually exclusive, and the presence of autoantibodies does not exclude an autoinflammatory diagnosis. However, it should be noted that autoantibodies are mostly negative in TRAPS, which remains a key distinguishing feature.

3.2 Pathophysiology of TRAPS

TRAPS is caused by heterozygous mutations in the *TNFRSF1A* gene, which encodes the 55-kDa TNF receptor [1]. The mutation leads to aberrant inflammation due to the accumulation of misfolded TNFR1 in the endoplasmic reticulum, which activates the unfolded protein response. This response generates reactive oxygen species that trigger inflammation [2]. Unlike familial Mediterranean fever, where colchicine is highly effective, TRAPS responds poorly to colchicine but shows excellent response to tumor necrosis factor inhibitors and interleukin-1 inhibitors [4].

Structural mutations involving cysteine residues (approximately 50% of described mutations) are associated with higher disease penetrance and a more severe phenotype, including a higher risk of AA amyloidosis [4].

The p.Phe141Leu mutation identified in our family is a cysteine mutation, consistent with the severe phenotype observed.

3.3 The Role of Interleukin-1 Inhibition in TRAPS

Interleukin-1 blockade has emerged as a highly effective therapy for TRAPS. Gattorno and colleagues demonstrated that continuous treatment with anakinra effectively controlled both clinical and laboratory manifestations in patients with TRAPS and prevented disease relapses [6]. In their study of five patients, all had a prompt response to anakinra, with disappearance of symptoms and normalization of acute-phase reactant levels, including serum amyloid A. When anakinra was withdrawn, disease relapse occurred within a few days, dramatically responding to reintroduction of the drug [6].

Gentileschi and colleagues reported the efficacy and safety of anakinra in a patient with TRAPS complicated by amyloidosis-related renal failure, showing that even at higher than conventional dosages, the treatment was well-tolerated and led to the disappearance of all TRAPS-related manifestations and a prompt decrease of proteinuria [7]. These findings support the use of IL-1 inhibition as a targeted therapy in TRAPS, particularly in patients with severe disease or complications such as amyloidosis.

3.4 Implications for Clinical Practice

This family illustrates several important points for clinical practice:

1. **Polyclonal hypergammaglobulinemia and nonspecific autoantibodies may accompany TRAPS:** These findings should not preclude genetic testing for autoinflammatory syndromes in patients with recurrent systemic inflammation, especially in familial cases [3].
2. **TRAPS should be suspected in patients with recurrent, prolonged febrile episodes:** The characteristic features of TRAPS include fever episodes lasting 7 to 21 days, migratory myalgia, periorbital edema, and migratory erythematous rash [4].
3. **Colchicine is ineffective in TRAPS:** While colchicine is the mainstay of treatment for familial Mediterranean fever, it is not effective in TRAPS [4]. The failure of colchicine therapy should raise suspicion for an alternative diagnosis.
4. **IL-1 inhibition is highly effective:** Early IL-1 inhibition with anakinra represents an effective targeted therapy and may also serve as a diagnostic tool in phenotypically ambiguous cases [6].
5. **AA amyloidosis is a serious complication:** Patients with TRAPS should be screened regularly for proteinuria to detect the development of AA amyloidosis, which occurs in approximately 10% of untreated patients [3].

4. Conclusion

We describe a familial cohort of three siblings with TRAPS who presented with marked polyclonal hypergammaglobulinemia and low-titer ANA, highlighting the diagnostic pitfalls of this condition. The presence of these immunological abnormalities in the context of recurrent systemic inflammation can mimic autoimmune disease and delay the correct diagnosis. This family illustrates that polyclonal hypergammaglobulinemia and nonspecific autoantibodies may accompany TRAPS and should not preclude genetic testing for autoinflammatory syndromes. Early IL-1 inhibition with anakinra represents an effective targeted therapy and may also serve as a diagnostic tool in phenotypically ambiguous cases.

5. References

1. McDermott MF, *et al*. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. (in eng), Cell, Apr 2, 1999; 97(1):133-144. Doi: 10.1016/s0092-8674(00)80721-7
2. Amarilyo AMG. TNF Receptor-Associated Periodic Syndrome (TRAPS). Merck Manual Professional Edition. Reviewed/Revised November 2025. [Online]. Available: https://www.merckmanuals.com/professional/pediatrics/hereditary-periodic-fever-syndromes/tnf-receptor-associated-periodic-syndrome-traps.
3. Hull KM, *et al*. The TNF receptor-associated periodic syndrome (TRAPS): Emerging concepts of an autoinflammatory disorder. (in eng), Medicine (Baltimore), Sep 2002; 81(5):349-368. Doi: 10.1097/00005792-200209000-00002
4. Deuitch N, Cudrici C, Ombrello A, Aksentijevich I. TNF Receptor-Associated Periodic Fever Syndrome. In GeneReviews(®), M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, and A. Amemiya Eds. Seattle (WA): University of Washington, Seattle Copyright © 1993-2026, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved. Test, 1993.
5. Ida H, *et al*. A novel mutation (T61I) in the gene encoding tumour necrosis factor receptor superfamily 1A (TNFRSF1A) in a Japanese patient with tumour necrosis factor receptor-associated periodic syndrome (TRAPS) associated with systemic lupus erythematosus. (in eng), Rheumatology (Oxford), Oct 2004; 43(10):1292-1299. Doi: 10.1093/rheumatology/keh320
6. Gattorno M, *et al*. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. (in eng), Arthritis Rheum, May 2008; 58(5):1516-1520. Doi: 10.1002/art.23475
7. Gentileschi S, *et al*. Efficacy and safety of anakinra in tumor necrosis factor receptor-associated periodic syndrome (TRAPS) complicated by severe renal failure: A report after long-term follow-up and review of the literature. (in eng), Clin Rheumatol, Jul 2017; 36(7):1687-1690. Doi: 10.1007/s10067-017-3688-4