

Case Report

Tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS): a rare cause of recurrent fever

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ABSTRACT

The one year old male child presented with fever on and off, associated with periorbital swelling and arthritis. Infectious, rheumatological and oncological diagnoses were ruled out. Further follow-up over 4-5 years revealed that, the child continued to have similar episodes every month and investigated for almost all possible causes but no conclusive diagnosis was made. Hence evaluation for rare causes of periodic fever was considered. Genetic testing revealed mutation in a novel variant of TNFRSF1A gene, thus confirming Tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant inherited condition of periodic fever and joint pain. Here we are presenting a case of this rare syndrome.

Keywords: Anakinra, Auto-inflammatory syndromes fever, Etanercept, TRAPS, Tumour necrosis factor receptor-associated periodic syndrome, TNF, TNFRSF1A, Periodic fever

INTRODUCTION

Tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS) is a autosomal dominantly inherited rare autoinflammatory, condition characterized by recurrent fever, rashes and musculoskeletal problems due to missense mutations of the 55 kDa tumour necrosis factor receptor superfamily 1A (TNF receptor 1).^{1,2} TRAPS seems to be the most common hereditary periodic fever (HPF) syndrome in some Western populations, and the second most prevalent HPF worldwide, behind familial Mediterranean fever (FMF).

The frequency and length of attacks are variable, but untreated attacks may last from days to weeks. Poorly controlled inflammation may predispose to amyloid formation with associated morbidity. Treatment is aimed at improving quality of life, preventing acute attacks of disease, which may require the concomitant use of

corticosteroids, and controlling inflammation to prevent amyloidosis.

CASE REPORT

A one-year male child presented with fever since 5 days which was high grade and continuous with rash, periorbital oedema, multiple joint pains. There was no h/o cough, fast breathing, ear discharge, sore throat, loose stools, vomiting, abdominal pain or seizure.

There was h/o many similar episodes of fever and previous hospitalizations from the age of 3 months and was investigated thoroughly but confirmation of diagnosis was never been obtained and child continued to have similar episodes of fever every month. He was immunized as per schedule and achieved all milestones according to age.

General and systemic examinations were otherwise normal. Investigations revealed: Hb-9.7 mg%, TLC-21300/cc, Platelets-71900/cc, RBC-4.7, ESR-105, CRP-130, PCV-30.1, PS-neutrophilic leucocytosis with thrombocytosis with normal LFT and KFT. Also, PS for MP, widal, sputum for AFB were negative. Fever episode subsided after 2 days of admission but taking past history into consideration, child was provisionally diagnosed to have Pyrexia of unknown origin (PUO) and investigated accordingly with blood c/s, urine c/s, chest x-ray, USG abdomen, ECHO, CSF culture, bone marrow biopsy, ANA, NBT stain and Interferon Gamma Release Assay all of which were non-yielding and child remain undiagnosed at end of these extensive investigations. He was discharged in stable condition after 2 weeks with follow up advice after next fever episode.

The child continued to have similar episodes of fever every month and was admitted in different hospitals and investigated thoroughly for infectious, autoimmune, malignant and other common causes for next 4-5 years. During this time, various antibiotics, steroids and even anti tubercular medications were tried empirically but still without any definitive diagnosis, periodic fever continued requiring further evaluation. Thus, child was considered to have the periodic fever which have following main differentials as:

- FMF-familial Mediterranean fever,
- PFAPA-Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis,
- TRAPS-Tumor necrosis factor associated periodic syndrome,
- HIDS-Hyperimmunoglobulinemia D syndrome.

With the history of duration, frequency and associated clinical features of fever, HIDS AND TRAPS were considered as initial diagnosis and investigation was sent for serum IgD levels which came back to be normal and excluded HIDS. So, test for TRAP syndrome was sent which identified novel variant of TNFRSF1A gene genetic blood testing confirming TRAP syndrome.

The counselling of parents of the child was done and Inj. Etanercept 10 mcg per week was advised, however parents chose to start alternative treatment with ayurvedic medications. At present, there is no substantial improvement in patient's condition and still follow up is going on.

DISCUSSION

TRAPS is an auto-inflammatory multisystem disease characterized by active and remission phases alternatively, which may be complicated with organ injury, in particular amyloidosis. TRAPS is also known as Hybernian fever and was first described in 1982 and seems to be homogeneously distributed among different ethnic groups.³ International medical literature has more than 200 recorded TRAPS cases.⁴

During an acute episode of TRAPS, there is a significant rise in acute phase reactants, neutrophil count and various degrees of hypochromic anemia with low levels of soluble TNF receptor, both during attacks and during intercritical period.^{5,6} Molecular studies revealed about 80 variants of the TNFRSF1A gene and about 64 of these have been identified in patients with a typical phenotype of TRAPS with R92Q and P46L as common mutations showing low penetrance, as supported by their presence in asymptomatic relatives of patients.⁷ Further, genotype-phenotype studies, even in the paediatric population, showed that mutations with substitution of a cysteine residue are associated with a severe course of the disease and increased possibility to develop renal amyloidosis.⁸

The frequency and length of attacks are variable which lasts from days to weeks. Amyloid formation is predisposed by poorly controlled inflammation and is associated with increased morbidity. Aim of treatment is mainly towards improving quality of life, preventing acute attacks of disease by using corticosteroids and controlling inflammation to prevent amyloidosis. Conventional immuno-suppressants like cyclosporine, methotrexate, azathioprine, and cyclophosphamide, are less effective for this but initial studies with etanercept yielded promising results, but it has been observed that the effect of this treatment may decline over time.^{9,10} Infliximab and adalimumab induce attacks of inflammation paradoxically while anakinra may have clinical benefit in patients with TRAPS.¹¹⁻¹³

CONCLUSION

Thus, for conclusion, Tumour necrosis factor receptor associated periodic syndrome is a rare periodic fever due to genetic defect. It is a disabling condition for the patient and has a great impact on psychosocial aspects of whole family's life. At present, we don't have definitive treatment of disease and all treatments available are giving temporary relief of symptoms, but none is able to change natural history of disease and so the need for further research and clinical trials in that area is a must for better understanding and effective management of the disease.

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REFERENCES

1. McDermott MF, Aksentjevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family

- of dominantly inherited autoinflammatory syndromes. *Cell*. 1999 Apr 2;97(1):133-44.
2. McDermott EM, Smillie DM, Powell RJ. Clinical spectrum of familial Hibernian fever. *Mayo Clin Pro*. 1997;72:806-17.
3. Cassidy JT, Petty RE, Laxer RM, Lindsley CB. Periodic fever syndromes in children. *Textbook of Pediatric Rheumatology*. Elsevier Saunders. Philadelphia, 2005;5.
4. Bodar EJ, Drenth JPH, van der Meer JSM, Simon A. Dysregulation of innate immunity: hereditary periodic fever syndromes. *Br J Haematol*. 2009;144: 279-302.
5. Gattorno M, Federici S, Pelagatti MA, Caorsi R, Brisca G, Malattia C, et al. Diagnosis and management of autoinflammatory diseases in childhood. *J Clin Immunol*. 2008;28:73-83.
6. Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM, et al. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine*. 2002 Sep 1;81(5):349-68.
7. Aganna E, Hammond L, Hawkins PN, Aldea A, McKee SA, van Amstel HK, et al. Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. *Arthritis Rheumatology*. 2003 Sep 1;48(9):2632-44.
8. D'osualdo A, Ferlito F, Prigione I, Obici L, Meini A, Zulian F, et al. Neutrophils from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications. *Arthritis Rheumatol*. 2006 Mar 1;54(3):998-1008.
9. Drewe E, McDermott EM, Powell PT, Isaacs JD, Powell RJ. Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. *Rheumatology*. 2003 Feb 1;42(2):235-9.
10. Drewe E, Powell RJ, McDermott EM. Comment on: failure of anti-TNF therapy in TNF receptor 1-associated periodic syndrome (TRAPS). *Rheumatology (Oxford)*. 2007;46:1865-6.
11. Jacobelli S, Andre M, Alexandra JF, Dode C, Papo T. Failure of anti-TNF therapy in TNF receptor 1-associated periodic syndrome (TRAPS). *Rheumatology (Oxford)*. 2007;46:1211-2.
12. Simon A, Bodar EJ, van der Hilst JC, van der Meer JW, Fiselier TJ, Cuppen MP, et al. Beneficial response to interleukin 1 receptor antagonist in TRAPS. *Am J Med*. 2004;117:208-10.
13. Gattorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. *Arthritis Rheum*. 2008;58:1516-20.

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