Adult-onset Tumour Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) presenting as transfusion dependent refractory haemophagocytosis.

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A 31-year old Caucasian male presented in 2006 with fatigue, night sweats, and fever. His symptoms displayed no diurnal variation but worsened with exercise and cold exposure. There was mild splenomegaly without other lymphadenopathy. A full blood count was abnormal: Hb 65g/L, MCV 91.5fL, WBC 3.2 x 10^9/L, platelets 289 x 10^9/L. Bone marrow biopsy demonstrated haemophagocytosis, hypercellularity and red cell activity with prominent macrophages. Cytogenetics were normal and there were no JAK2 and CALR mutations.

Following extensive negative investigations, including autoimmune and infectious serology, two FDG-CT-PET scans and a lymph node biopsy, he was prescribed prednisolone 60mg daily with excellent clinical response. However, reduction in steroid dose to below 20 mg daily precipitated return of symptoms, inflammation and anemia. After 5years he had developed arthritis of the knees, ankles and small joints of the hands and was transfusion-dependent, receiving more than 150 units of blood in total.

In 2015 a further hematological opinion was sought; repeat bone marrow biopsy showed persistent haemophagocytosis, Rheumatology review confirmed synovitis in both knees and oral methotrexate (15 mg weekly) was initiated. However, the CRP remained >200 mg/L and anaemia continued. The treatment refractory nature of the illness, fever and arthritis raised the possibility of an auto-inflammatory syndrome and lack of family history due to adoption prompted the patient to be referred to the periodic fever clinic at the UK National Amyloidosis Centre.

Genetic sequencing revealed the presence of a mutation in intron 4 of the Tumor Necrosis Factor Receptor Superfamily 1A (TNFRSF1A) gene, c.473-72 G>A, suggesting the diagnosis of Tumor Necrosis Factor-Associated Periodic Fever Syndrome (TRAPS). A trial of the interleukin-1

antagonist anakinra was instigated (100 mg daily) and within two days there was symptomatic improvement, CRP and serum amyloid A levels began to normalize and there was no further transfusion requirement (Figure 1). Ferritin was statically elevated secondary to presumed transfusional iron overload (1,567 mcg/L, from 1,632 mcg/L at anakinra initiation). A repeat bone marrow analysis after 6 months of treatment revealed a normocellular marrow, with normal granulopoiesis, megakaryocytes and lymphocytes and considerable reduction in macrophage activity. Continued daily use of anakinra over a 14-month period has led to a sustained complete response, allowing complete corticosteroid withdrawal.

This is the first reported case of adult-onset TRAPS presenting with HLH. The TRAPS phenotype is broad and diagnosis relies on clinical suspicion supported by evidence of biochemical inflammation and genetic testing. There are no validated diagnostic criteria (Kallinich*, et al* 2013). In the largest published series of 158 cases 33% were diagnosed in adulthood and 9.1% reported their first symptoms after the age of 30 (Lachmann*, et al* 2014). Although recurrent discrete inflammatory episodes are commonest, 5% of patients experienced continuous symptoms with exacerbations as in our case. The most common presenting symptom is fever with rigors at onset, with abdominal pain, myalgia, arthralgia, cervical lymphadenopathy, maculopapular rash and periorbital oedema in decreasing order.

TRAPS, like all systemic autoinflammatory diseases is associated with dysregulated innate immunity and cytokine production, and as such would be expected to carry a risk of secondary HLH. However, there are no reports of HLH in the largest series and it has never been reported elsewhere as a presenting feature in adult-onset TRAPS. There is a single published pediatric case;

an 11 year- old Turkish girl who presented with recurrent spontaneously remitting episodes of fever lasting 5-7 days, arthralgia, and hepatosplenomegaly (Horneff*, et al* 2013). Bone marrow biopsy revealed histiocytosis with hemophagocytosis. She was treated with dexamethasone, cyclosporin A and etoposide with recovery. However, over the subsequent 3 years intermittent remitting fevers continued and arthralgia progressed and she was referred for rheumatology opinion aged 14 years. Sequencing of the TNFRSF1A revealed a known pathogenic mutation in TNFRSF1A and anakinra started with sustained complete clinical and biochemical remission.

Most pathogenic sequence variants of the TNFRSF1A gene are found within exons 2 to 4 and are missense substitutions disrupting cysteine–cysteine disulfide bonds in the extracellular domain (McDermott*, et al* 1999). Intronic mutations within the TNFRSF1A gene causing TRAPS account for 3% of pathogenic mutations in the EUROTRAPS registry (Lachmann*, et al* 2014). The c.473-72 G>A mutation has been previously reported in association with TRAPS in a mother and son (Lachmann*, et al* 2014). The mutation is at a splice site leading to a 45 nucleotide insertion into mRNA, resulting in a conformational change in the TNFR1 protein demonstrated by *in silico* modelling. In vivo functional consequences were shown by reduced serum and cell surface TNFR1 levels, increased pro-inflammatory cytokine production, and elevated basal NF-κB activation in peripheral blood mononuclear cells.

The mechanisms by which mutations in the TNFRSF1A gene result in inflammation remain poorly understood. Pathogenic mutations appear to lead to misfolding of the TNFR1 protein, which accumulates in the endoplasmic reticulum, leading to defective autophagy, which in turn induces

excessive IL-1β secretion via activation of the NLRP3 inflammasome (Bachetti*, et al* 2013, Simon*, et al* 2010).

The rapid onset and sustained benefit of IL-1 inhibition confirms its efficacy in treating secondary HLH and this case suggests that genetic testing for TRAPS should be considered in unexplained refractory cases even in cases with an adult onset.

References:

Bachetti, T., Chiesa, S., Castagnola, P., Bani, D., Di Zanni, E., Omenetti, A., D'Osualdo, A., Fraldi, A., Ballabio, A., Ravazzolo, R., Martini, A., Gattorno, M. & Ceccherini, I. (2013) Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS). *Ann Rheum Dis,* **72,** 1044-1052.

Horneff, G., Rhouma, A., Weber, C. & Lohse, P. (2013) Macrophage activation syndrome as the initial manifestation of tumour necrosis factor receptor 1-associated periodic syndrome (TRAPS). *Clin Exp Rheumatol,* **31,** 99-102.

Kallinich, T., Gattorno, M., Grattan, C.E., de Koning, H.D., Traidl-Hoffmann, C., Feist, E., Krause, K., Lipsker, D., Navarini, A.A., Maurer, M., Lachmann, H.J. & Simon, A. (2013) Unexplained recurrent fever: when is autoinflammation the explanation? *Allergy,* **68,** 285-296.

Lachmann, H.J., Papa, R., Gerhold, K., Obici, L., Touitou, I., Cantarini, L., Frenkel, J., Anton, J., Kone-Paut, I., Cattalini, M., Bader-Meunier, B., Insalaco, A., Hentgen, V., Merino, R., Modesto, C., Toplak, N., Berendes, R., Ozen, S., Cimaz, R., Jansson, A., Brogan, P.A., Hawkins, P.N., Ruperto, N., Martini, A., Woo, P., Gattorno, M., Paediatric Rheumatology International Trials Organisation, t.E. & the Eurofever, P. (2014) The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. *Ann Rheum Dis,* **73,** 2160-2167.

McDermott, M.F., Aksentijevich, I., Galon, J., McDermott, E.M., Ogunkolade, B.W., Centola, M., Mansfield, E., Gadina, M., Karenko, L., Pettersson, T., McCarthy, J., Frucht, D.M., Aringer, M., Torosyan, Y., Teppo, A.M., Wilson, M., Karaarslan, H.M., Wan, Y., Todd, I., Wood, G., Schlimgen, R., Kumarajeewa, T.R., Cooper, S.M., Vella, J.P., Amos, C.I., Mulley, J., Quane, K.A., Molloy, M.G., Ranki, A., Powell, R.J., Hitman, G.A., O'Shea, J.J. & Kastner, D.L. (1999) Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell,* **97,** 133-144.

Simon, A., Park, H., Maddipati, R., Lobito, A.A., Bulua, A.C., Jackson, A.J., Chae, J.J., Ettinger, R., de Koning, H.D., Cruz, A.C., Kastner, D.L., Komarow, H. & Siegel, R.M. (2010) Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. *Proc Natl Acad Sci U S A,* **107,** 9801-9806.

Declarations:

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- Availability of data and material: All data related to this case report is held on the National Amyloidosis Centre, London's own database and are available from the corresponding author on request.
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Figures:

Figure 1 Changes in C-reactive protein (CRP), serum amyloid A protein (SAA) and hemoglobin (Hb) before and after initiation of anakinra.