Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by mutations in the *Tumor necrosis factor receptor superfamily, member 1A* (*TNFRSF1A*) gene encoding type 1 receptor of tumor necrosis factor (TNFR1) (1). TRAPS is characterized by recurrent episodes of inflammation accompanied by fever, rashes, myalgia, arthralgia, abdominal pain, chest pain, conjunctivitis and periorbital edema (2). TRAPS is a very rare disease, affecting one per million in Caucasians (3). Case reports are more frequent in Caucasians, although the condition is also seen in other ethnic groups, including Japanese.

TRAPS is a prototype of autoinflammatory diseases caused by abnormal activation of the innate immune system (1). Since the discovery of the responsible gene, *TNFRSF1A*, in 1999, the pathophysiology of TRAPS has been investigated extensively; however, it has not yet been completely clarified. Reduced TNFR1 shedding and impaired downregulation of TNFR1 was initially considered to cause inflammation (1). Subsequently, a defect in apoptosis or autophagy, increased nuclear factor-κB (NF-κB) transcription factor activation and/or retention of mutant TNFR1 in the endoplasmic reticulum (ER) were suggested to be responsible for TRAPS (4). These proposed mechanisms are variable and mutation-dependent, which reflects the multifaceted pathogenesis of TRAPS. Over 100 different mutations of *TNFRSF1A* have been reported in patients with TRAPS (Infevers database: http://fmf.igh.cnrs.fr/ISSAID/infevers/). One half of these defects are known as “structural mutations,” which disrupt TNFR1 structures by affecting cysteine residues or other critical residues of the N-terminal cysteine-rich domains CRD1 and CRD2. “Structural mutations” are usually associated with typical TRAPS symptoms as well as high disease penetration (4).

In accordance with the variety of the pathogenesis, the clinical features of TRAPS patients are also diverse. The clinical features of 158 patients with *TNFRSF1A* variants were recently reported from the Eurofever/EUROTRAPS international registry (5). According to these data, attacks are recurrent in 88% of cases and continuous with/without flares in the remaining cases. There is also considerable variation in the duration of attacks, and the most common features associated with pathogenic variants are fever (88%), limb pain (85%), abdominal pain (74%), rashes (63%) and eye manifestations (45%), followed by many other symptoms with lower frequencies. The acute-phase response and leukocytosis are almost always associated with TRAPS flares. The variety of symptoms and lack of specific biomarkers for TRAPS make it difficult to diagnose the disease based only on clinical features. The response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids is mostly favorable; however, in some refractory cases, the TNF antagonist etanercept and the interleukin (IL)-1 antagonist anakinra are used. The IL-6 antagonist tocilizumab was reported to be effective in one TRAPS patient resistant to etanercept and anakinra (6).

In order to clarify the features of TRAPS in Japan, the Ministry of Health, Labour and Welfare (MHLW) of Japan organized a study group chaired by Professor Horiuchi of Kyushu University. A nationwide survey revealed that there are at least 33 families with TRAPS associated with *TNFRSF1A* variants in Japan. In addition, we found that Japanese patients with TRAPS are less likely to suffer from abdominal pain, chest pain and eye manifestations than Caucasian TRAPS patients (7). Even in the same disease entity of TRAPS, critical features differ between different ethnic groups.

In this issue of *Internal Medicine*, Hosoya et al. reports a case of “TRAPS-like” illness without defects in *TNFRSF1A* or other known autoinflammatory disease-related genes (8). The authors raised an important issue concerning TRAPS: how to make the diagnosis? Currently, no validated diagnos-

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tical criteria are available for TRAPS; however, at present, two steps are taken before diagnosing the disease, initial screening according to the patient’s symptoms followed by the identification of TNFRSF1A mutations. If TNFRSF1A mutation(s) are not found in suspected cases, the patient is categorized as having “TRAPS-like” illness, but not “mutation-negative” TRAPS. The term “mutation-negative” TRAPS is misleading, as the definition of “mutation-negative” is unclear. Most genetic testing procedures utilize polymerase chain reaction (PCR)-based amplification and subsequent sequencing, which is limited to exons and their short flanking regions. It is of note that a number of variants affecting the expression and/or splicing are located in the introns of the TNFRSF1A gene or promoters away from exons (9, 10). Moreover, large insertions/deletions or somatic mosaicism cannot be detected using the usual PCR-based methods. Recently, mutations in the receptor activator of nuclear factor-κB (RANK) gene, TNFRSF11A, were shown to cause the typical clinical features of TRAPS (11). It is also possible that there exist more genes responsible for “TRAPS-like” illnesses. Notably, Hosoya et al. demonstrated the effectiveness of tocilizumab for “TRAPS-like” conditions (9). The application of molecular targeting agents, such as biologics, is expected to aid the proper stratification of the pathogenesis of “TRAPS-like” diseases.

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References