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CASE REPORT

Early Onset of Periodic Fever Syndrome in a Patient Carrying Both Tumor Necrosis Factor Receptor Superfamily 1A and Mediterranean Fever Mutations

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ABSTRACT

In this article, we report a nine-month-old male patient with a history of three unexplained, prolonged attacks of high fever, including one in the neonatal period, accompanied by an erythematosus, migratory rash. There was no family history that might have suggested a hereditary periodic fever syndrome, but the overall clinical picture was in accordance with tumor necrosis factor receptor-associated disease. Genetic analysis revealed two heterozygous mutations: C30Y in the tumor necrosis factor receptor superfamily 1A gene and K695R in the Mediterranean fever gene. This case shows that diagnosis of an autoinflammatory syndrome should be considered even in the youngest infants with incomplete presentation and no family history of recurrent fever.

Keywords: Autoinflammatory disorder; genes; tumor necrosis factor receptor-associated periodic syndrome.

Hereditary periodic fever syndromes are characterized by recurrent spontaneous attacks of multi-systemic inflammation.[1] Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is caused by mutations in the gene encoding tumor necrosis factor receptor superfamily 1A (TNFRSF1A) and characterized by prolonged febrile episodes (>7 days) associated with abdominal pain, localized myalgia, migratory rash, periorbital edema, and conjunctivitis.[1] The flares are unresponsive to colchicine but usually respond to steroids.[2] The median age at disease onset is 4.3 years and cases of presentation in the neonatal period are scarce.[3] In this article, we report a case of periodic fever syndrome clinically compatible with TRAPS presenting in a young infant with combination of C30Y mutation in the TNFRSF1A gene and a heterozygous, milder familial Mediterranean fever associated variant in the Mediterranean fever (MEFV) gene (K695R).

CASE REPORT

A nine-month-old male patient was transferred to our clinic from another pediatric unit with a history of three unexplained, prolonged attacks of high fever accompanied by an erythematosus, migratory rash. At the time, the patient had been febrile for 10 days and treated with empirical broad-spectrum antibiotics for the last five days with no improvement. His blood, urine, cerebrospinal fluid, and throat cultures had shown no bacterial growth; thus viral infectious agents such as cytomegalovirus, Epstein-Barr virus, adenovirus, and human respiratory syncytial virus were excluded. Chest radiograph, echocardiogram,

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and abdominal ultrasound were unremarkable. At the admission, the infant was in good general condition and except for a serpiginous erythematosus rash, physical examination revealed no pertinent findings. Laboratory results showed raised levels of inflammatory markers: white cell count of 26.8, C-reactive protein level of 219 mg/L (normal range 0-5), erythrocyte sedimentation rate of 140 mm/hour (normal range 11-22), and serum amyloid A protein of 624 mg/L (normal range 0-6.8). The symptoms resolved spontaneously within three days. The patient had been hospitalized twice before while 3.5 and 6 months old with similar episodes of non-infectious fever lasting 12 to 14 days, associated with rash and profoundly elevated inflammatory markers. Furthermore, while three days old, the infant experienced an afebrile inflammatory attack characterized by jaundice, poor feeding, lethargy, urticarial rash, increased markers of inflammation (C-reactive protein of 47 mg/L, procalcitonin of 0.5 ng/mL, erythrocyte sedimentation rate of 35 mm/hour), and negative cultures. There was no family history of recurrent fever and both parents were Polish. The patient fulfilled the Eurofever clinical diagnostic/classification criteria for TRAPS.[4] Genetic testing revealed that the child carried heterozygous mutations in two autoinflammatory genes: C30Y in the TNFRSF1A gene and K695R in the MEFV gene. For a few years, febrile attacks accrued every eight to 10 weeks and were well-controlled with short, intermittent courses of oral steroids. Treatment with colchicine brought only temporary improvement including an asymptomatic period of 13 weeks. Additional symptoms such as abdominal pain, arthralgia, and conjunctivitis developed in time. So far, we have not observed clinical signs of amyloidosis. Currently, our patient is five years old and has been experiencing more frequent febrile attacks, hence immune modulating therapy is being considered. A written informed consent was obtained from the patient.

DISCUSSION

Tumor necrosis factor receptor-associated periodic syndrome usually manifests in young children around four to five years of age.[3] While onsets during early infancy are not unheard of, presentation in the first days of life is a sporadic phenomenon. In this article, we reported a male infant who experienced his first attack at the age of 3.5 months, or quite possibly while three days old. Despite the paucity of symptoms, we cannot rule out that the symptoms observed during early neonatal period derived from the autoinflammatory process. We excluded bacterial etiology, while, except for the rash, which could have been TRAPS-related, there were no clinical findings associated with viral infection. Apparently, not all features are universally present in all patients or during all episodes,[3] particularly when it comes to neonates and young infants, as previously observed by Savage et al.[5] The authors reported the youngest age of TRAPS onset in a four-day-old Irish boy with an incomplete presentation including fever, lethargy, and vomiting and a strong family history of the disease.[5] Family history of recurrent fever was also the main clue for the diagnosis of TRAPS in a two-year-old Japanese girl reported by Yasumura et al.[6] Similar to our patient, the girl experienced recurrent episodes of fever since six months of age. Apart from the irregular attacks of intermittent fever, no clinical signs that could evoke the diagnosis of TRAPS were observed in the two previously reported patients with early manifestation of the disease.[5,6] They both shared the same heterozygous mutation ($T_{50}M$) in the TNFRSF1A gene. Our patient had presented with typical migratory rash since the second episode of fever, but had no family history of recurrent fever. He also had a different, less common mutation in the TNFRSF1A gene -C30Y- which is a missense substitution (G to A transition in exon 2) in the first extracellular cysteine-rich domain of the TNFRSF1A.[7] Cysteine mutations participate in the assembly of disulfide bonds important for TNFR1 folding and are associated with a more severe phenotype and a higher risk of amyloidosis.[2,3] The mutation was first described by Palladini et al. and later reported in two siblings with TRAPS.[8,9] One of them was a boy in whom repetitive attacks of fever started at six months of age. As compared to our patient, the boy had more severe presentation of the disease, including prolonged episodes of fever, rash, arthritis, and pericarditis. The symptoms were misdiagnosed as systemic juvenile idiopathic arthritis and the diagnosis of TRAPS was not addressed until the sister and the mother of the patient also developed recurrent fever. The sister had presented with milder symptoms at three years of age. Though genetic testing toward

other hereditary periodic fever syndromes was not performed, the authors suggested that phenotypic differences between the siblings might be due to a coexisting mutation in another autoinflammatory gene.[9] In the current case, genetic testing revealed coexisting familial Mediterranean fever-associated mutation of reduced penetrance -K695R- a missense substitution in exon 10 encoding the PRYSPRY-domain of the MEFV gene.[7] K695R mutation meets the formal definition of polymorphism and has been detected in 60% of the asymptomatic MEFV mutations carriers from Central Europe.[7,10] We cannot exclude that the reduced-penetrance MEFV variant somehow contributed to the clinical phenotype of TRAPS in our patient. However, considering that the clinical picture in our patient was in accordance with TRAPS and there were no features that could evoke the diagnosis of familial Mediterranean fever, it is most likely that the presence of K695R mutation was purely coincidental.

In summary, we reported a young male patient with no family history of recurrent fever and presenting with symptoms of TRAPS since early infancy. Careful observation of clinical signs and symptoms and a thorough work-up led us to the diagnosis of TRAPS. This case shows that the diagnosis of an autoinflammatory syndrome should be considered even in the youngest infants with incomplete presentation and no family history of recurrent fever.

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