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■ Case report ■

A case of encephalitis in a juvenile rheumatoid arthritis patient treated with etanercept

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= Abstract =

Tumor necrosis factor-α (TNF-α) is a major proinflammatory cytokine involved in the pathophysiology of juvenile rheumatoid arthritis. Etanercept is an effective inhibitor of TNF-α and has shown a beneficial effect in patients with JRA. However, the most important cause of concern related to etanercept administration is infection. We report a case of encephalitis in a JRA patient receiving long-term treatment with etanercept. The patient was a 4-year-old boy with refractory JRA, and he received etanercept subcutaneously at a dose of 0.4 mg kg^{-1} day^{-1} twice a week for 14 months, along with non-steroidal anti-inflammatory drugs, methotrexate, oral steroids, and sulfasalazine. The patient presented with sudden fever, headache, vomiting, a generalized tonic seizure, and changes in mental status. We suspected a central nervous system infection, and simultaneously administered antibiotics, an antiviral agent, and steroids. After 2 days of hospitalization, his mental function returned to normal, and he showed no further seizure-like movements. Brain magnetic resonance imaging scan of the patient showed a multifocal cortical lesion on both sides of the temporoparietooccipital lobe, which indicated encephalitis. Although we were unable to identify the causative organism of encephalitis, we think that the encephalitis may be attributed to infection, and the use of etanercept may have increased the risk of severe infection. Therefore, etanercept was discontinued and the patient recovered shortly after. To the best of our knowledge, this is the first case of encephalitis in a juvenile rheumatoid arthritis patient treated with etanercept. (Korean J Pediatr 2010;53:262-266)

Key Words : Etanercept, Juvenile rheumatoid arthritis, Encephalitis

Introduction

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic and chronic disease of children, and it represents a major cause of disability. It is defined as developing in children before 16 years of age and shows persistent arthritis in 1 or more joints for at least 6 weeks[1]. Various pharmacological agents are used for the treatment of juvenile rheumatic disease, with a range of mechanisms of action, but all of them have the same aim of suppressing inflammation[1]. The traditional medications for JRA are non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), such as methotrexate[2]. Recently, biologic DMARDs were developed, like inhibitors of tumor necrosis factor-alpha (TNF-α), inhibitors of interleukin-1 or interleukin-6, as their pathogenesis.

TNF-α is a proinflammatory cytokine that has been proven to have a key regulatory role in the pathophysiology of JRA[3]. Etanercept, a dimeric fusion protein, consisting of the extracellular portion of the human p75 TNF receptor linked to the Fc fragment of IgG1, effectively binds the cytokines TNF and lymphotoxin-α and inhibits their interactions with cell-surface TNF receptors[4]. Etanercept is usually used to reduce the signs and symptoms of moderate to severe active polyarticular-course JRA that is refractory to 1 or more DMARDs[1]. However, if the symptoms of arthritis persist in spite of NSAIDs, corticosteroid and methotrexate, etanercept is used for systemic JRA. It has shown benefits soon after initiation in patients with systemic JRA, but disease flare-up and decreased effectiveness were observed with continued treatment in most patients with systemic JRA[5]. The most common adverse events were injection site reactions, headaches, fever, rash

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and upper respiratory infections of mild to moderate severity[1, 6]. Even though infection occurred at the same rate and frequency as in the placebo population, caution should be taken due to the risk of serious infection[7]. Delayed spinal infection after laminectomy in a patient who was interruptedly exposed to etanercept was reported in 2008 [8], and another study showed that etanercept increases the risk of tuberculosis[9]. We report a patient with JRA who was suspected of having encephalitis whilst receiving etanercept.

Case report

A 4-year-old boy presented at our hospital with fever for two days, headache, vomiting and a half hour-long seizure followed by change in his mental status. At age 13 months, he had intermittent fever of unknown origin for 3 months. When he was 16 months old, he complained Rt. Knee joint pain and swelling with fever, he received MRI study on Rt. Knee. The MRI findings were thick prominent enhancement along the synovial lining of the knee joint, compatible with JRA, he had been diagnosed with systemic JRA. Even though he had received NSAIDs, methotrexate, sulfasalazine and methylprednisolone pulse therapy, his symptoms flared up and intermittent fevers were noted. Furthermore, methylprednisolone pulse therapy resulted in cardiac arrhythmias. Therefore, he began to receive etanercept at a dose of 0.4 mg/kg/day twice a week subcutaneously at 3 years of age, in addition to the NSAIDs, methotrexate, sulfasalazine and oral steroids. After receiving etanercept for 14 months, he presented with fever, headache, irritability, and vomiting. He also had generalized tonic seizures and mental changes. A previous seizure history was not noted. On physical and neurological examination, the patient's body temperature was 38.6℃ and blood pressure was 105/60 mmHg. He showed a drowsy mental state and pupil reflexes were intact. No definite neck stiffness was noted and he had a slightly increased deep tender reflex on both knees. His breathing sounds were clear and heart sounds were regular without murmur. Initial laboratory findings showed leukocytosis, and elevated C-reactive protein and erythrocyte sedimentation rate (WBC, 43,220/μL; CRP, 6.94 mg/dL, normal range: 0.0-0.8 mg/dL; ESR, 81 mm/hr, normal range: 0.0-15.0 mm/hr). Cerebrospinal fluid (CSF) examination, brain MRI, and electroencephalogram were also performed. On CSF analysis, red blood cells and white blood cells were not seen, and the protein and glucose values were within the normal ranges. We were unable to identify the bacterium or any viruses in the CSF, and the serologic tests of IgM for herpes simplex virus, cytomegalovirus and Epstein-Barr virus were all negative. However, brain MRI showed multifocal cortical lesions in the bilateral temporoparietooccipital lobes (Fig. 1A) and electroencephalogram showed continuous rhythmic sharp wave discharges from the left occipital regions (Fig. 2A), these indicated encephalitis. After considering all possible diagnoses, we suspected encephalitis of unknown origin. The boy was treated with antibiotics, an antiviral agent and steroids simultaneously. His seizures were controlled with phenobarbital and phenytoin. After two days of hospitalization, his mental status was fully recovered and he showed no more signs of seizures. Although we didn't measure of his immune function, we suspected that etanercept had compromised his general immunity, left the patient vulnerable to infection and provoked encephalitis. Therefore, we decided to discontinue the etanercept and control the patient's JRA with intravenous corticosteroids during his hospitalization. On the 7th day in hospital, he no longer showed arthralgia or fever. We followed up the brain MRI, which no longer showed the previously seen lesions at the temporoparietooccipital lobes (Fig. 1B). However, the follow-up electroencephalogram still showed the presence of frequent sharp wave discharges from the left occipitofrontal regions (Fig. 2B). Therefore, the patient received carbamazepine and phenytoin, as well as JRA medication including NSAIDs, methotrexate, sulfasalazine, and prednisolone. He was discharged on the 23rd day in hospital without neurologic sequela and is being followed up in the outpatient clinic.

Discussion

The remission rate of JRA has frequently been cited to be about 80% until the child with JRA reaches adulthood[10], however a cohort study commenced in 1970 reported that only 32.8% of JRA patients achieved disease remission[11]. Another study showed that between 25% and 70% of children with JRA continue to have active arthritis 10 years after onset, and more than 40% will still have active disease when they enter adulthood[12].

The remission rate and course of the disease are highly variable according to subtype and prognostic factors. Poor prognostic factors are as follows: active systemic disease

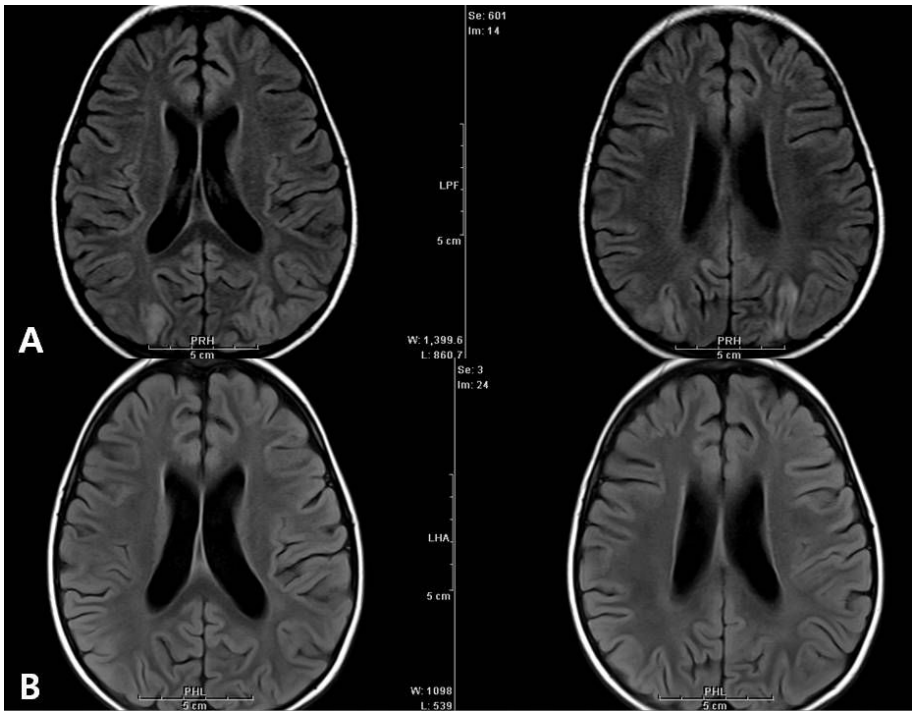

Fig. 1. Initial magnetic resonance imaging (MRI) scans (A) and follow-up MRI scans (B). The initial MRI scan shows multifocal cortical lesions on both sides of the temporoparietooccipital lobe. The follow-up MRI scan did not show the cortical lesions that were previously observed on the temporoparietooccipital lobe.

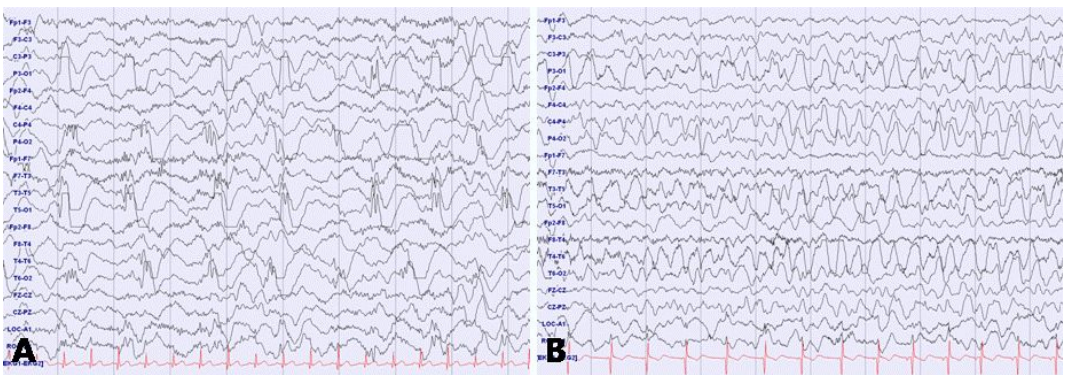

Fig. 2. Initial electroencephalogram (EEG) (A) and follow up EEG (B). The initial EEG shows continuous rhythmic sharp wave discharges from the left occipital regions. (B) The follow -up EEG continues tostill shows the presence of frequent sharp wave discharges from the left occipito-frontal regions.

at 6 months, polyarticular onset or disease course, female gender, rheumatoid factors, persistent morning stiffness, tenosynovitis, subcutaneous nodules, antinuclear antibodies, early involvement of small joints of hands and feet, rapid appearance of erosions, and extended pauciarticular disease course[1]. In this case, the patient has several poor prognostic factors such as active systemic disease within 6 months of onset, rheumatoid factor, persistent morning stiffness, and rapid appearance of erosion. His condition was refractory to usual treatment and did not respond properly even to methylprednisolone pulse therapy. Therefore, we prescribed etanercept to control the JRA.

Etanercept has a beneficial effect in patients with JRA who have not responded to traditional medications, such as NSAIDs, corticosteroids or DMARDs[6, 13]. Etanercept received approval from the United State's Federal Drug Administration for the indication of polyarticular-course JRA in May 1999[14], and it has demonstrated sustained improve-

ments in the symptoms of polyarticular-course JRA with an acceptable safety profile in an open-label extension of a randomized controlled trial at 8 years. Lovell et al. reported that the overall rate of serious adverse events and medically important infections did not increase with long-term exposure to etanercept[14]. However, the most concerning adverse event of etanercept therapy is undoubtedly infection. This drug has a general immunosuppressive effect; therefore, it may be associated with increased susceptibility to infection. The most commonly reported infections were upper respiratory tract infection, pharyngitis, skin infections, flu syndrome, otitis and conjunctivitis[6]. In the adult, Shunsuke et al reported a case of delayed spinal infection after laminectomy in a patient with rheumatoid arthritis exposed to etanercept[8]. Another study showed that anti-TNF-α treatment increases the risk of TB by about 40 times[9]. Phillips et al reported that serious infections include a psoas abscess secondary to mycobacterium avium-intracellulare, septic wrist, bacteremia, and septic total hip replacement after use of etanercept[15]. In our patient, encephalitis occurred during the course of etanercept.

Encephalitis is the existence of an inflammatory process in the brain parenchyma with clinical evidence of brain dysfunction. It can be due to a non-infective condition or to an infective process, which is diffuse and usually viral. The diagnosis of viral encephalitis is suspected in this context of a febrile disease accompanied by headache, altered level of consciousness, and cerebral dysfunction signs, such as cognitive dysfunction, behavioral changes, focal neurological abnormality, and seizure[16]. After the encephalitis is suspected, we should approach to obtain the relevant evidence of encephalitis from diagnostic investigations. These may consist of peripheral blood count, erythrocyte sedimentation, blood cultures, electroencephalogram and MRI. The gold standard of diagnosis in encephalitis is virus isolation in CSF or brain cell culture[17], even though viral cultures from CSF are positive in young children with enteroviral infection but only seldom, in <5%, in other cases[18]. In this case, the patient presented with the meningeal irritation signs of headache, irritability, and vomiting as well as fever. The C-reactive protein and erythrocyte sedimentation rates were elevated, and leukocytosis existed. These findings reflect infectious disease. He also presented cerebral dysfunction such as generalized tonic seizures and mental changes, even though a previous history of seizures was not noted. Moreover, brain MRI and electroencephalogram were compatible with encephalitis. Therefore, we suspected encephalitis in spite of the CSF findings, which did not identify the cause of his condition.

The central nervous system involvement is an unusual manifestation of human viral infection, and the spectrum of brain involvement and the prognosis are dependent on the specific pathogen and the immunological state of the host [16]. Concerns have been raised about an increased risk of serious infections with immunomodulatory agents such as etanercept. Although we were not able to detect his immune function and the contribution of etanercept therapy to the encephalitis, it was strongly suspected that etanercept would increase the susceptibility of serious infection, which may induce encephalitis, because he was in the middle of treatment of etanercept and he had no seizure or serious infection history, especially encephalitis, before use of etanercept. Long-term use of steroids is needed in patients with JRA, especially of the systemic type. They can also compromise general immunity, which increases the risk of infection. Because TNF-α is not only a main mediator of inflammation, but also an essential component of immune responses against infection, the use of etanercept can further increase the risk of infection in JRA patients treated with steroids. Since there have been no case reports of encephalitis due to increased susceptibility to infection in JRA patient treated with etanercept, we hereby present our experience. We could not identify the cause of our patient's encephalitis, and because of the use of steroids and methotrexate, we were also unable to establish that etanercept was the cause of his increased susceptibility to infection. However, we stress that patients receiving etanercept should be followed up for signs and symptoms of infection, especially encephalitis, with a high index of suspicion. Even though etanercept has shown significant clinical benefit and generally good tolerability, it needs to be used with care.

한 글 요 약

소아기 류마티스모양 관절염 환자에서 etanercept 사용 후 발생한 뇌염 1예

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TNF-α 는 소아기 류마티스모양 관절염의 병태생리학에 관여하는 주요 cytokine 이다. Etanercept 는 TNF-α 억제제 중 하나로 소아기 류마티스모양 관절염에 효과적인 약물로 각광받고

있다. Etanercept의 주요 부작용은 면역력 저하에 의한 감염으로, 대게 중등도의 상기도 감염이 대부분으로 알려져 있으나, 최근 중증의 감염도 보고되고 있다. 저자들은 소아기 류마티스모양 관절염 환자가 etanercept를 14개월간 투약 후 발생한 뇌염 1예를 경험하였기에 보고하는 바이다.

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