Blau syndrome (BS) and early-onset sarcoidosis (EOS) are granulomatous autoinflammatory diseases defined as familial and sporadic forms of the same clinical condition, respectively. These syndromes are caused by a mutation in the nucleotide oligomerization domain 2 (NOD2) gene localized in the 16q12 chromosome. Clinical symptoms are characterized by the clinical triad of granulomatous dermatitis, symmetric arthritis, and recurrent uveitis with onset before 4 years of age.\(^1\)\(^-\)\(^3\) Non-caseating granulomatous inflammation in affected organs is a hallmark of the disease.\(^4\) Other expanded manifestations of BS/EOS are fever, pneumonitis, bronchial granulomas, hepatosplenomegaly, hepatic granulomas, sialadenitis, erythema nodosum, leukocytoclastic vasculitis, transient neuropathies, arterial hypertension, pericarditis, pulmonary embolism, granulomatous glomerular and interstitial nephritis, and chronic renal failure.\(^5\) In this report, we present a patient who developed encephalitis while being followed with EOS diagnosis.

### Case Report

A 12-year-old girl was diagnosed with juvenile idiopathic arthritis at 3 years of age. During that time, she had arthritis on both knees and received methotrexate (MTX) therapy. Because MTX response was inadequate, etanercept (ETN) was added. While she was on MTX and ETN treatment, at 6 years of age, she was hospitalized because of fever, neutropenia, and liver and renal failure. Multiple organ failure...
secondary to sepsis was considered. MTX and ETN were discontinued. After an antibiotic and supportive therapy, she improved in three weeks. She was hospitalized again two months later, because of fatigue and weakness. Physical examination revealed hepatomegaly and splenomegaly. Her hemoglobin level was 6.2 g/dl. The blood smear was consistent with normochromic and normocytic features. She had no evidence of nutritional and hemolytic anemia. Bone marrow aspiration showed normocellular marrow findings. She had renal failure (blood urea nitrogen 40 mg/dl, creatinine 2.0 mg/dl) without oliguria and hypertension. Proteinuria was 23 mg/m²/hour. We performed liver and kidney biopsies; non-caseating granulomatous interstitial nephritis and non-caseating granulomatous inflammation of liver were detected. Urinary calcium/creatinine ratio and serum angiotensin-converting enzyme levels were normal. Tuberculin skin test was anergic, PCR for Mycobacteria of the liver tissue sample, and QuantiFERON test were negative. Since the patient was treated with ETN, we considered drug-induced sarcoidosis, and we discontinued ETN. Oral prednisolone was given and tapered. MTX was continued. Involvement of bilateral proximal interphalangeal joints and distal interphalangeal joints, boggy synovitis, and camptodactyly developed in the following year.

We reevaluated all clinical signs, and NOD2 gene analysis was performed. M513T heterozygous mutation was detected. There was consanguinity, but no family history. Thus, we diagnosed EOS and added infliximab (IFX) treatment. In the last three years, the disease activations occurred as arthritis, interstitial lung disease, interstitial nephritis, and bilateral panuveitis. Systemic steroids were added on attack periods, MTX, and IFX were continued. She was admitted to our clinic with a headache and vomiting in June 2018. These complaints were present for two weeks and were increasing, especially in the morning. She was still on MTX (15 mg/week), prednisolone (10 mg/day), and IFX (200 mg per month) treatment. High fever, high blood pressure, lethargy, diplopia, and bilateral papilledema were detected on physical examination. Laboratory examination revealed leukocytosis, increased erythrocyte sedimentation rate and C-reactive protein, and pyuria. *Escherichia coli* was isolated in the urine culture. Antibiotic treatment was started for urinary tract infection, and then fever resolved. Brain magnetic resonance imaging (MRI) and MRI angiography were normal. The patient underwent repeated lumbar punctures; opening pressures were 23 cm H2O and 38 cm H2O, respectively. Study of cerebrospinal fluid (CSF) revealed pleocytosis (120 leukocyte / mm³ with lymphocyte predominance), slightly elevated protein level (35 mg/dl), normal chloride, and glucose level. CSF cultures were negative. The serology for viruses and *Mycobacterium tuberculosis* were negative. Electroencephalography (EEG) showed delta brush waves compatible in the temporal-occipital and the parietal-occipital regions. The patient was diagnosed as autoimmune encephalitis. Cerebrospinal fluid limbic encephalitis antibody panel that included NMDA, AMPA1, AMPA2, CASPR2, LGI1, GABA B antibodies were negative. Anti-nuclear antibody (ANA), ANA subgroups, anti-phospholipid antibodies, anti-neutrophil cytoplasmic antibodies, and direct Coombs test were negative. Although intravenous immunoglobulin was given at a dose of 400 mg/kg/day for 5 days, lethargy, diplopia, and papilledema were not resolved. Following pulse methylprednisolone (1 g/day for 5 days) her neurological and ophthalmologic findings improved rapidly (Fig. 1). MTX, prednisolone (40 mg/day) were continued, but IFX was switched to adalimumab.

The written consent form for publishing was obtained from the patient’s parents.

**Discussion**

We reported an EOS patient with joint involvement, granulomatous inflammation, uveitis, who developed encephalopathy in the
follow-up. Our patient was diagnosed as JIA and received JIA treatment at first because her initial finding was only arthritis. While the patient was receiving ETN and MTX, liver and kidney involvement with granulomatous inflammation in the biopsy was identified. After tuberculosis was excluded, we diagnosed drug-induced sarcoidosis as the development of sarcoidosis in patients treated with ETN has been demonstrated in previous studies.6 However, later, the diagnosis was reconsidered, because the patient’s joint involvements in follow-up were boggy synovitis and camptodactyly. It is known that common joint involvements of BS/EOS are camptodactyly and tenosynovitis.7,8 Thus, we requested a genetic analysis. M513T heterozygous mutation was detected in the NOD2 gene. NOD2 gene localized in 16q12 chromosome encodes NOD2 protein. NOD2 protein, one of the pattern recognition receptors, is activated by muramyl dipeptide.9,10 It is involved in response to bacterial infections. NOD2 protein comprises of caspase activation and recruitment domain, NOD, leucine-rich repeat domains (LRRs). While mutations in LRRs lead to Crohn’s disease, BS/EOS has associated with mutations in NOD.11-14 More than 80% of patients with BS/EOS had R334Q/W mutation. M513T is a rare NOD mutation and seen only in EOS.4,15 Mutations in the domain of M513T inhibit folding, so the protein constantly remains in an active state. Active NOD2 protein has initiated pathways of NF-κB and stress kinase and has played a role in inflammation.16 In the functional analysis in EOS patients with M513T mutation, NF-κB activation increased compared to wild type.17,18 NF-κB activation is hypothesized to be responsible for granulomatous inflammation, also, which was detected in our patient’s biopsy. But we did not perform functional analysis. The clinical findings of our patient were consistent with BS/EOS, and sporadic NOD2 mutation strongly supported the diagnosis of EOS.
The classical triad of BS/EOS is rash, uveitis, and arthritis.\textsuperscript{1,2,20} When our patient was diagnosed with BS/EOS, there was only arthritis from the classic triad and granulomatous inflammation in the biopsy. Uveitis, another component of the triad, developed in our patient under treatment. Similar EOS cases with uveitis developing under treatment were reported.\textsuperscript{21}

Encephalopathy was a remarkable event because neurologic involvement was infrequent in BS/EOS. Neurologic involvement of EOS, central nervous system infections, and posterior reversible encephalopathy syndrome (PRES) were considered in the differential diagnosis. Hypertension is a common cause of PRES.\textsuperscript{22} But, in our patient, high blood pressure was seen in first examination and did not persist. Also, brain MRI was not compatible with PRES. Fever and elevated acute phase reactants were suggestive for infections and EOS activation; we considered urinary tract infection as the cause of fever as it resolved following treatment for urinary tract infection. In addition, CSF examination had no significant findings for central nervous system infection. EOS reports were not informative about CSF findings in neurologic involvement. But, in neurosarcoidosis, raised protein and lymphocytosis were detected.\textsuperscript{23} Therefore, we thought that CSF findings in our patient could be due to EOS. Reported neurological involvements of EOS were cranial neuropathy, papilledema, and steroid-sensitive sensorineural hearing loss.\textsuperscript{15,24-26} Emaminia et al.\textsuperscript{27} presented a BS patient who had seizures, with normal neurologic examination, cranial MRI, and EEG. They could not verify that seizures were associated with BS. In another case, seizure was detected with NOD2 mutation. This case had left middle cerebral artery and bilateral renal artery stenosis was regarded as Takayasu arteritis.\textsuperscript{28} EOS patients with M513T mutation reported in the literature had a fever, rash, arthritis, and uveitis. Also, renal calcification and erythema nodosum were seen except for the classical triad. However, there were no neurologic abnormalities in these patients with M513T mutation.\textsuperscript{17,18}

We detected delta brush waves in EEG. There are case reports and case series with a delta brush pattern in patients with autoimmune encephalitis.\textsuperscript{24,25} However, Baykan et al.\textsuperscript{29} showed that this pattern was seen for various reasons in patients followed in intensive care unit. The detection of specific autoantibodies helps in the definitive diagnosis of autoimmune encephalitis and the differential diagnosis of atypical cases. The absence of autoantibodies does not exclude autoimmune encephalitis, and the positive titer does not always imply an accurate diagnosis.\textsuperscript{30}

In a study, NOD2-deficient mice and wild type mice were immunized with muramyl-dipeptide and human serum albumin. Then the researchers assessed the antigen-specific serum immunoglobulins. Human serum albumin specific antigens were detected in wild-type mice but not in NOD2 +/- type mice. These results suggested that NOD2 activates the adaptive immune system by acting as an adjuvant receptor for antibody production directly or by increasing the production of immune-stimulatory molecules.\textsuperscript{31} Shaw et al.\textsuperscript{32} showed that resistant autoimmune encephalitis dependent on peptidoglycan in NOD1 +/-, NOD2 +/-, RIPK2 +/- mice. The authors also reported that the RIP2 signaling pathway taken part in the self-activation of the central nervous system infiltrated dendritic cells, not in the migration of T cells and dendritic cells. Our patient did not reveal any autoantibodies. Although our patient’s clinical and EEG findings were compatible with autoimmune encephalitis, we could not be sure whether the autoimmune mechanism works in our patient or disease affect itself.

In conclusion, central nervous system involvement can be seen as encephalitis apart from classical findings of BS/EOS. We think that with the clarification of immune mechanisms in the pathogenesis of the disease, we can understand the cause of autoimmune encephalitis in our patient.
REFERENCES


