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OLGU SUNUMU CASE REPORT

Acute disseminated encephalomyelitis in a child with Griscelli syndrome

Griselli sendromlu bir olguda akut dissemine ensefalomiyelit

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ABSTRACT

Griscelli syndrome (GS) (MIM 214450) is a rare autosomal recessive genetic disorder characterized by partial albinism with silvery gray hair, recurrent infections, cellular immunodeficiency and neurological abnormalities. Acute disseminated encephalomyelitis (ADEM) is a monophasic, immune-mediated disorder that produces multifocal demyelinating lesions within the central nervous system. We report a three years and six months old girl patient with GS who presented ADEM. GS was diagnosed when she was six months old. She was admitted to hospital because of ataxia, gait disturbance and somnolence for four days. The physical examination revealed hyperreactive deep tendon reflexes, lower limb power was grade 3/5, bilaterally positive Achilles' clonus and Babinsky's sign. Laboratory investigations including complete blood cell count, serum biochemistry analysis, fibrinogen level and bone marrow examination were all within normal limits. The cerebrospinal fluid showed no pleocytosis with increased protein level. Brain and spinal magnetic resonance imaging (MRI) revealed multifocal abnormal high-signal intensity mainly in the white matter of the cerebellum, brainstem and spinal cord as well as in the cerebrum. The typical MRI

ÖZET

Griselli sendromu (GS) (MIM 214450) parsiyel albinizm, açık-gri renkli saçlar, tekrarlayan enfeksiyonlar ile karakterizie nadir görülen ve otozomal resesif geçiş gösteren bir hastalıktır. Bu hastalarda hücresel immune yetmezlik ile birlikte değişik oranda nörolojik semptomlar da görülebilir. Akut dissemine ensefalomiyelit (ADEM) ise immune sistem aracılıklı oluşan ve monofazik seyir gösteren bir hastalıktır. Görüntüleme çalışmaları yapıldığında, santral sinir sisteminde multifokal demiyelinize alanlara rastlanır. Burada Griselli sendromu tanısı ile izlenen ve takibinde ADEM gelişen 3.5 yaşında bir kız olgu sunulmuştur. Altı aylık iken Griselli sendromu tanısı alan hasta, 4 gün önce başlayan ataksi, yürüme bozukluğu ve uykuya eğilim şikayeti ile polikliniğimize başvurdu. Fizik muayenesinde derin tendon refleklekslerinin arttığı, alt ekstremitelerde kas gücü kaybı olduğu (3/5) ve iki taraflı Babinski işareti ve Aşil klonusunun pozitifleştiği tesbit edildi. Hastanın tam kan sayımı, biyokimyasal analizleri, serum fibrinojen düzeyi ve kemik iliği incelemesi normaldi. Beyin omirilik sıvısı (BOS) incelemesinde protein düzeyinde hafif artış dışında bir anormallik yoktu. Beyin ve omiriliğin manyetik resonans görüntülemesi (MRI) sonucunda beyin, beyin sapı, beyincik

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findings and an acute monophasic clinical course of this case led to a diagnosis of ADEM. Patient was treated with high dose corticosteroids, but she was died in seventh days of the therapy. ADEM and GS association has not been reported previously to the best of our knowledge. ADEM also should be mind when a child with GS was encountered neurological findings.

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Key words: Griscelli syndrome, acute disseminated encephalomyelitis, children

ve omirilikte özellikle ak maddeyi tutan multifokal hiperintens alanlar tespit edildi. Hastalığın monofazik seyri ve tipik MRI bulguları sonucunda hastaya ADEM tanısı konuldu. Yüksek doz steroid ve intravenöz immünglobulin tedavisine rağmen hasta tedavinin 7. gününde öldü. Literatürde ADEM ve Griselli sendromu birlikteliği ile ilgili herhangi bir bilgiye rastlanmamaktadır. Bu sebeple, Griselli sendromu tanısı alan olgularda, nörolojik semptomlar geliştiğinde ADEM'in de akılda bulundurulması gerektiğine inanıyoruz.

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Anahtar kelimeler: Griselli sendromu, akut dissemine ensefalomiyelit, çocuk.

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INTRODUCTION

Griscelli syndrome (GS) (MIM 214450), a rare autosomal recessive disorder, is characterized by partial albinism, along with immunologic abnormalities and/or neurological impairment such as raised intracranial pressure, cerebellar signs, encephalopathy, hemiparesis, peripheral facial palsy, spasticity, hypotonia, seizures, psychomotor retardation and progressive neurologic deterioration especially in accelerated phase[1,3].

Two closely linked genes (RAB27A and MYO-5A) on chromosome 15q21 region have been found to be responsible for the GS. According to mutation analysis three subtypes have been described. GS type 1 represents hypomelanosis with a primary neurologic deficit and without immunologic impairment which is caused by mutations in the MYO5A gene. Patients exhibit severe developmental delay and mental retardation occurring early in life. GS type 2 is characterized by partial albinism, immunodeficiency and hemophagocytic syndrome (HS) which is caused by mutation in RAB27A gene. Primary neurological presentation without the accelerated phase is rare in type 2. GS type 3 is characterized by hypomelanosis without immunologic or neurologic manifestations which is due to mutation of melanophilin or MYO5A genes[9,10].

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system that occasionally presents in association with a preceding viral infection or vaccination[15]. This is an acute widespread demyelinating condition, which principally affects brain and spinal cord, and characterized by multifocal white matter lesions on neuroimaging. ADEM is usually a monophasic disease with peak disability occurring a few days or weeks after the onset of illness[4]. The development of ADEM in patients with immunosuppression is quite rare[15]. In the present study we report a 3-years and 6 months old girl with GS. We describe the clinical and paraclinical manifestations with emphasis on neurological and neuroimaging findings. This is unique case of GS associated with ADEM that has not been previously reported.

CASE REPORT

A 6 months old girl was admitted firstly to our pediatric immunology clinic for the complaints of recurrent respiratory tract infections after one month. She was the first child of the consanguineous parents. Her immunisations were done on time with no complications. She had a striking hypopigmentation (silvery-gray sheen) of her scalp hair, eyebrows and eyelas-

hes and partial albinism increased with time (Figure 1). Light microscopic examination of her hair showed irregular agglomeration of pigment, predominantly within the medullar zone. She was diagnosed as GS with this light microscopic examination of her hair. Her immunological investigations were all within normal limits (Table 1). She was neurologically normal during the period of follow-up in our out-patient clinic. When she was 3 years and 6 months old, she was admitted to the hospital with ataxia, gait disturbance and somnolence for 4 days. She had a mild gastroenteritis that resolved spontaneously three weeks ago. The physical examination revealed hyperreactive deep tendon reflexes, lower limb power was grade 3/5 compared to upper limbs (5/5). Achilles' clonus and Babinsky's sign was bilaterally positive. There were no hepatosplenomegaly, lymphadenopathy and fever. Complete blood cell count, serum chemistry analysis, fibrinogen level and bone marrow examination were all within normal limits. The cerebrospinal fluid showed no pleocytosis, but increased protein level (120 mg/dL), culture remained sterile and viral serology test results for Herpes simplex virus (HSV), hepatitis viruses, Epstein-Barr virus (EBV), Cytomegalovirus (CMV) and Human immunodeficiency virus (HIV) were negative. For this clinical and laboratory results, the accelerated phases of GS were excluded. Brain and spinal magnetic resonance imaging (MRI) revealed multifocal ab-

Figure 1. The typical silvery gray hair, scalp hair, eyebrows and eyelashes.

Table 1. Immunological investigations of the patient

	Result	Normal values	Result	Normal values
Total lymphocyte count: 7.6 x 10^9/L				
	Six months old		**3.5 years old**	
	%	%	%	%
CD45	99.8		99.4	
CD14	0.8		0.00	
CD3+	67.9	**51-79**	62.9	**55-79**
CD4+	38.2	**33-55**	34	**28-51**
CD8+	19.3	**11-33**	28.4	**16-42**
CD16+56+	12.1	**5-23**	8.01	**5-28**
CD19+	20.0	**14-44**	24.6	**11-31**
HLADR+	24.3	**15-48**	25.0	**18-38**
Lymphoproliferative response to PHA	75%			**65.8 ± 9.2**
PPD response at 72th hour	8 mm			**(5-10)**
IgG (mg/dL)	799	**304-1231**	1200	**640-2010**
IgA (mg/dL)	42	**7-123**	82	**44-244**
IgM (mg/dL)	123	**32-203**	94	**52-297**
IgE (IU/mL)	17.5	**16.26**	17.6	**16.8**

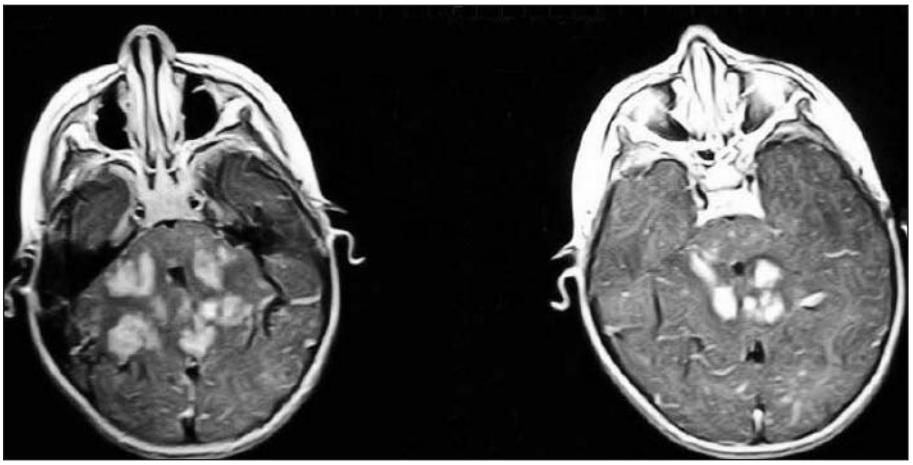

Figure 2. Axial MRI scans showing multifocal abnormal high-signal intensity in the white matter of the cerebellum and brainstem.

normal high-signal intensity mainly in the white matter of the cerebellum, brainstem and spinal cord as well as in the cerebrum (Figure 2,3). The typical MRI findings and an acute monophasic clinical course of this case led to a diagnosis of ADEM. The patient was treated with high dose methyl prednisolone (30 mg/kg body weight/day) and intravenous immunoglobulin (0.4 g/kg body weight). There was a fast progression of the neurological deterioration, which was characterized by flaccid quadriparesis that progressed quickly to a state of coma. Despite intensive supportive care, the patient's clinical condition worsened and cardiopulmonary arrest happened and the patient died in seventh days of the therapy. We thought that the cause of the death was the involvement of the central nervous system due to ADEM in the patient. His family refused autopsy.

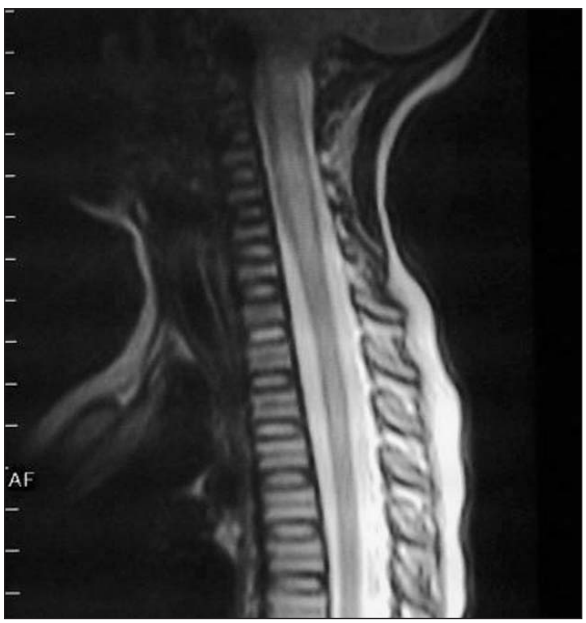

Figure 3. The sagital T2-weighted of spinal cord MRI image showing a hyperintense signal with cervical expansion.

DISCUSSION

GS is a rare autosomal recessive disorder[1,3]. Clinical manifestations of GS vary from patients who are free of any symptoms to others with severe recurrent infections or neurological involvement[7,8,14]. The accelerated phase in GS is characterized by prolonged high fever, pancytopenia, lymphohistiocytic infiltration of spleen, liver, lymph nodes, and brain due to an uncontrolled process of lymphocyte and macrophage activation and proliferation, hemophagocytosis, hypertriglyceridemia and hypofibrinogenemia[14]. Neurological manifestations may be the first sign of an accelerated phase[13]. In neurological involvement due to active inflammation and/or cerebral lymphohistiocytic infiltration can also be a prominent feature with a wide spectrum ranging from mild cogni-

tive impairment to convulsions, cerebellar disturbance, hemiparesis, symptoms of intracranial hypertension and fatal degeneration[2]. Our patient had no neurological abnormalities and mental retardation initially and during the clinical follow-up from 6 months to the last admission. We thought neurological involvement of accelerated phase, but there was no clinical and laboratory findings of accelerated phase at admission and during one week period of hospitalization.

ADEM is an inflammatory demyelinating disorder related to autoimmunity. A non-specific term, ADEM refers to an acute disease that is post-infectious, para-infectious, post-vaccinal, or of an unknown precipitating factor[6]. A number of infectious agents, such as Influenza, Measles, Mumps, Rubella, Varicella, HSV, hepatitis viruses, EBV, Coxsackieviruses, Rotaviruses, *Mycoplasma, Campylobacter, Streptococcus, Legionella*, and *Rickettsia* have been implicated in ADEM. Occasionally, it can occur without any clearly defined preceding trigger factors[4]. ADEM usually begins 1-3 weeks after a systemic infection. It is characterized clinically by the acute onset of neurological abnormalities, including varying degrees of mental state changes ranging from drowsiness to coma[11]. Diagnosis of ADEM was generally made by clinical, neuro-radiological, and cerebrospinal fluid examinations[15]. The viral serology test results for HSV, hepatitis viruses (A, B, C), EBV, CMV and HIV were negative in our patient. There was no vaccination history in last two years before the clinical symptom of ADEM. The diagnosis of ADEM was done with neurological findings which had begun three weeks after attack of acute gastroenteritis and neurological deterioration existenced acute and rapidly.

MRI is helpful in making the diagnosis because it often reveals diffuse, symmetric white matter demyelinating lesions that homogeneously enhance with contrast administration[12]. Typical target areas of demyelination include: the corona radiata, centrum semiovale, periventricular white matter, cerebellar peduncles, and brainstem. Involvement of deep gray matter nuclei (thalamus, caudate, and putamen) is also frequent[5]. Her MRI revealed multifocal abnormal high-signal intensity mainly in the white matter of the cerebrum as well as in the cerebellum, brainstem and spinal cord. In our patient, the typical MRI findings, an acute monophasic clinical course and the cerebrospinal fluid findings of the patient led to a diagnosis of ADEM.

The most widely used treatment for ADEM is corticosteroid administration; clinical improvement is achieved in up to 60% of patients with ADEM[11]. However, the mortality rate of ADEM is up to 30%. Features that suggest a worse prognosis are hyperacute onset, coma, and complicating seizures[12]. Intravenous immunoglobulin administration is another effective therapy for ADEM, especially in recurrent cases. However, some patients do not respond to either steroid or intravenous immunoglobulin treatment. Plasmapheresis has been successfully used to treat ADEM, especially in patients with severe forms or in those who fail to improve with steroids (so-called steroid-failure cases)[11]. Our patient did not respond to high-dose steroid and intravenous immunoglobulin therapy, but plasmapheresis could not be performed and patient died in seventh day of therapy.

In conclusion, the development of ADEM in patients with immunodeficiency is quite rare[15]. There was no report about GS associated with ADEM in literature. ADEM should be kept in mind in the patients with GS admitted with the neurological findings without accelerated phase. This case report also suggested that the patients of GS with ADEM should be treated with aggressive approach such as plasmapheresis when the patients did not respond to high dose corticosteroid and IVIG treatments.

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