Case Report

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Inflammatory Demyelinating Diseases of Childhood: Case Report and Literature Review

Çocukluk Çağında İnflamatuar Demiyelinizan Hastalıklar: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT

Multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) are demyelinating inflammatory diseases, considered to have a striking pathophysiological resemblance. However, due to the differences in both clinical course and clinical approaches, it is important to differentiate between the two conditions, to plan further investigations and therapy protocols. These diseases have similar but also distinct clinical, radiological and cerebrospinal fluid (CSF) findings. ADEM is typically a monophasic disease of children. MS occurs generally in adult age, but uncommonly may develop in childhood with variable features. Our case is a 14 year-old-girl, presented with a three-month history of left hemiparesis, followed by right hemiparesis, cerebellar signs, myelitis and cortical visual disturbances. Based on the clinical follow-up, MR and CSF findings, our patient was diagnosed with relapsing tumefactive multiple sclerosis. Steroid treatment was not significantly effective, however the patient has benefited from plasmapheresis clinically and radiologically. Our patient is still being followed under the disease modifying therapy without any relapse. *(Archives of Neuropsychiatry 2014; 51: 74-78)*

Key words: MS, ADEM, childhood, tumefactive MS

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ÖZET

Multipl skleroz (MS) ve akut dissemine ensefalomiyelitin (ADEM) benzer patofizyolojik özellikleri olduğu düşünülmesine karşın, klinik seyirlerindeki ve tedavi yaklaşımlarındaki farklılıklar nedeniyle, izleme programının ve tedavisinin planlanması açısından birbirinden ayırt edilmesi önem taşımaktadır. MS ve ADEM'de klinik bulgularda, radyolojik görüntüleme ve beyin omurilik sıvısı bulgularında ortak ve ayrılan özellikler görülür. ADEM sıklıkla çocukluk çağının monofazik bir enflamatuar demiyelinizan hastalığı olarak kabul edilmektedir. Erişkin dönemde daha sık görülen MS ise çocukluk çağında da gelişebilmektedir. Bu yazıda, 3 aylık bir süre içinde önce sol, sonrasında sağ hemiparezi, serebellar bulgular, medulla spinalis tutulumu bulguları ve ardından iki yanlı kortikal tutuluma bağlı görme kusuru gelişen 14 yaşında kız çocuğu sunulmakta ve ilgili literatür eşliğinde klinik, diğer laboratuar bulguları ve tedavi yaklaşımları tartışılmaktadır. Olgumuzun klinik ve seyir özellikleri, bu yaş grubunda gelişen MS ve ADEM'in kliniği, MR ve beyin omurilik sıvısı (BOS) bulguları göz önüne alınarak yineleyici tümefaktif MS tanısına varılmıştır. Steroid tedavisine belirgin yanıt alınmamasına karşın hasta, plazmaferezden belirgin olarak yarar görmüştür. Klinik düzelmiş, radyolojik bulgular gerilemiştir. Hasta, koruyucu tedavi altında belirli aralıklarla izleme alınmış, yeni tekrarlayan atağı olmamış, aktif yaşamını sürdürmektedir. *(Archives of Neuropsychiatry 2014; 51: 74-78)*

Anahtar kelimeler: MS, ADEM, çocukluk çağı, tümefaktif MS

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) are inflammatory demyelinizating diseases which have similar pathophysiological properties, but generally show different clinical, radiological and cerebrospinal fluid findings. Typical MS is a recurring disease characterized with attacks in young adults. However, ADEM is frequently known as a monophasic disease of the prepubertal childhood (1). Although treatment of both diseases in the acute phase is similar, the necessity of long-term administration of immunomodulator agents and planning a follow-up program in MS which is a chronic progressive process renders differentiation of MS from ADEM important. However, many investigators have reported that it is difficult to differentiate acute MS and ADEM and to predict transformation to MS in the first attack (1,2,3,4,5). In this article, the difficulties in diagnosis, differential diagnosis and treatment in acute inflammatory processes are rewieved in the light of the literature information by presenting a 14-year old girl.

Case

A 14-year old girl presented with weakness in the right arm and leg, imbalanced gait and inability to urinate. There was no pathology in her personal history and familial history except for

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third-degree of consanguinity between parents. 4/5 level motor hemiparesia accompanied by sensory defect developed on the left side 1,5 months before the patient presented to our clinic. It was learned that she was diagnosed with ADEM based on brain and cervical spinal MR (Figure 1,2) imagings in the center where she was evaluated in that period, she received 1 g methyl prednisolone intravenously (IVMP) for 9 days and the findings improved completely. However, new complaints developed in the patient 15 days after this treatment was completed. The patient was evaluated in the center where she was initially followed up at this stage and found to have 3/5 level right motor hemiparesia, bilateral cerebellar findings and deep sensory defect. She was discharged with partial recovery after a second IVMP treatment given with the same dose for the same time period. Neurological examination of the patient who presented to our clinic in that period revealed bilateral paleness in the temporal regions on fundoscopic examination, right central facial paralysis, triparesia (right upper and bilateral lower extremities) (3-4/5 level), bilateral pyramidal findings, sensory defect at the T7 level, bilateral complete deep sensory loss, apendicular and truncal ataxia and sphincter control defect. The neurological findings observed in the patient were associated with medulla spinalis lesion and cranial lesions during that period were thought to be asymptomatic. On cranial MR examinations repeated to determine the general status of the patient, hypointense lesions creating edema effect with no contrast uptake were observed in T1-weighted sections in bilateral occipital regions extending to the parietal and temporal areas and occipital cortex. It was noted that the cervical lesions with contrast enhancement on previous MR imagings had no contrast enhncement. MR spectroscopy performed to elucidate the lesions was found to be compatible with active demyelinization. Examination of CSF revealed no cells, normal protein level, increased IgG index (0,78) and negative oligoclonal band (OCB). Since the cervical lesions exceeded the height of 3 vertebral corpi, NMO was tested to exclude neuromyelitis optica and found to be negative.

In the period when the patient was followed up without treatment, it was observed that motor hemiparesia regressed,

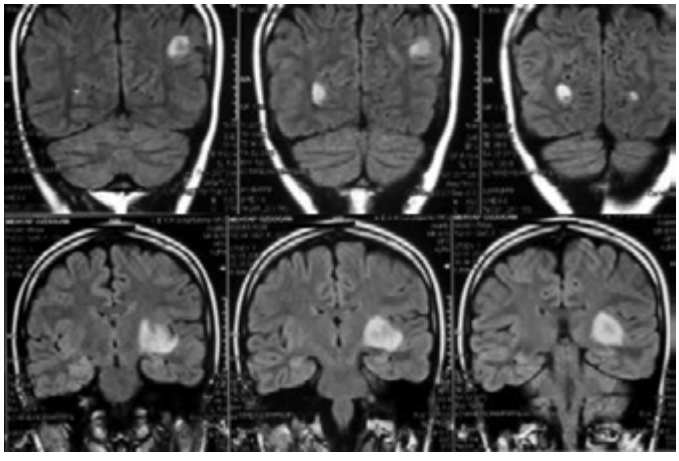

Figure 1. Cranial MR imaging, FLAIR, coronal: parietal subcortical white matter lesions in the capsula interna in the left hemisphere; subcortical, parietal hyperintense white matter lesions in deep white matter in the insula in the right hemisphere.

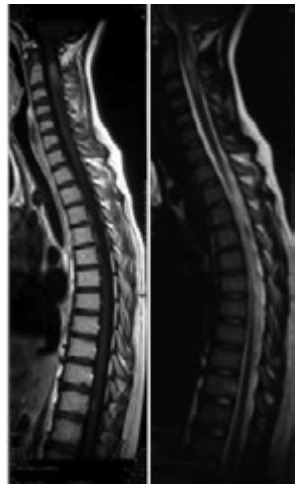

Figure 2. Cervical spinal MR examination, TIA-Gd-DTPA, T2A, sagittal: longitudinal contrast enhancement in the C1-3 and T11 level and peripheral-weighted contrast enhancement in the T1-weighted sections, hyperintense lesion areas in the T2-weighted sections showing perilesional edema.

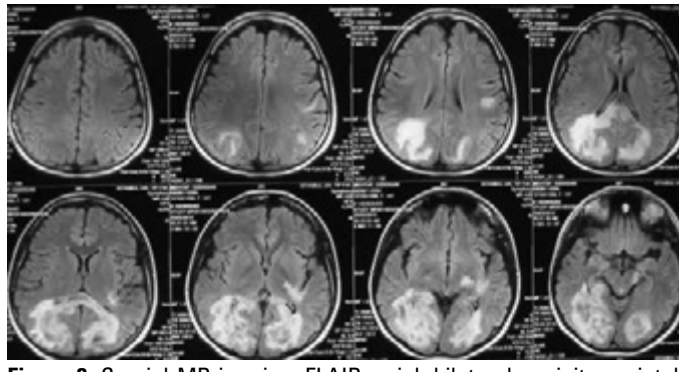

Figure 3. Cranial MR imaging, FLAIR, axial: bilateral occipito-parietal hyperintense lesions.

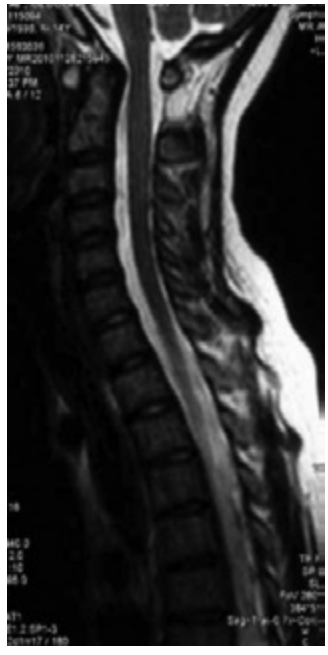

Figure 4. Cervical Spinal MR examination, T2A, sagittal: the lesion in Figure 2 is observed to be regressed in the T2-weighted sections.

deep sense normalized in the upper extremities and sensory impairment showing level and syphincter defect improved. However, an increase was observed in the patient's truncal ataxia. While the diagnosis was being reviewed, sudden visual defect developed 2,5 months after the initial complaints. On examination, the papilla borders were found to be mildly pale in the fundus, altitudinal visual field defect was present on the right side and concentric visual field defect was present on the left side, the right eye could count fingers at a distance of 1 m and the left eye could count fingers at a distance of 50 cm. Other neurological findings were not found to be diferent. On repeated cranial MR imaging, bilateral occipitoparietal lesions with no contrast enhancement and with increased dimensions when compared with the previous imaging were observed (Figure 3) and the cervical spinal lesions were found to be regressed (Figure 4). Visual evoked potential (VEP) examination revealed involvement which severly disrupted conduction in both visual pathways with predominance on the right side. The patient's visual defect was associated with the cortical lesions. Clinical improvement was not observed after IVMP treatment administered at a dose of 1 g/day for ten days. Afterwards, it was decided to administer 7 courses of plasmapheresis and IVMP at a dose of 1 g/day weekly in combination with oral steroid at a dose of 32-24 mg/day. Although there was no change in the neurological picture right after plasmapheresis treatment, clinical imporvement was observed after one week. The patients visual acquity increased to 1.6/10 bilaterally. The pyramidal and cerebellar findings improved almost completely and posterior cord findings improved partially. It was decided to administer 1 g IVMP monthly and interferon beta as prophylactic treatment in the follow-up period. It was planned to repeat the visual field, VEP, cranial and cervical spinal MRI examinations with regular intervals. Afterwards, attacks did not recur and it was observed that the visual field and VEP examination findings improved and the MR lesions regressed in the outpatient follow-up period (Figure 5,6). Recurrent tumefactive MS was considered to be the final diagnosis of our patient. 18 months after the last attack, our patient is currently a high-school student who continues her education with success, prefers to sit in the front row because of sequela visual problem and can participate in classess which require physical activity.

Discussion

When we reviewed the current approaches and controversial aspects of pediatric MS, it was noted that MS occured more rarely in the population below the age of 16 years (with a frequency of approximately 4-5%) (6,7). Incomplete maturation of the immune system, better repair capacity of the central nervous system (CNS) in children compared to adults and differences in tolerance to drugs affect the prognosis and treatment response (2). It has been reported that it is difficult to detect newly emerging visual defects and somatosensory defects in clinical practice in contrast to adult-onset MS and concentration difficulty and fatigue may be associated with attention deficit or non-organic causes in this age group. It has been proposed that myelitis, sphinter impairment, vestibular symptoms or pure motor hemiparesia are observed more rarely, but ataxia, encephalopathy and epileptic seizures which are the classical findings of ADEM develop more frequently in pediatric MS (2,6). However, most of these results have been obtained from retrospective studies.

In our patient, predominance of involvement of the medulla spinalis and lack of encephalopathy findings were primarily compatible with MS. No consensus related with the time between the attacks have been made in pediatric MS. Generally, the interval between the initial two attacks has been reported to be long in cases where the disease onset occurs below the age of 10 years and 1-2 years in cases where the disease onset occurs above the age of ten years similar to adults (8). Some authors reported that this period was shorter compared to adults and some others reported that it was longer (9,10). It was observed that the second attack developed 2,5 months after the initial complaints in our patient. It has been reported that im-

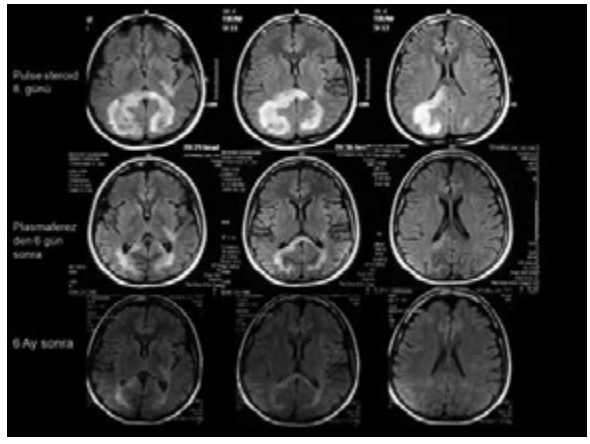

Figure 5. Cranial MRI, FLAIR, axial: Reduction in the dimensions of the lesion is observed on cranial MR examinations repeted 1 month and 6 months after visual defect which developed 2.5 months after the initial complaints of the patient.

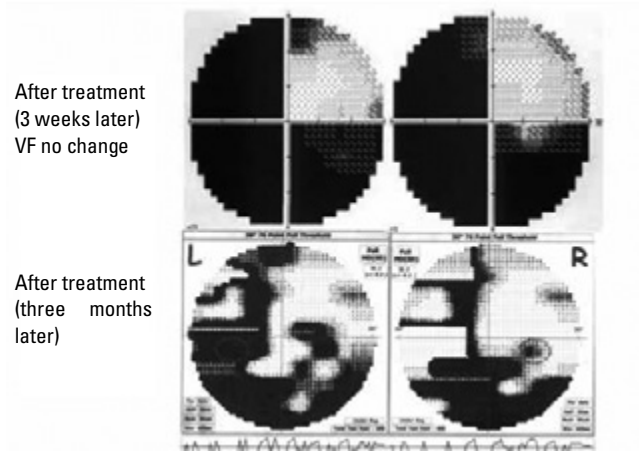

Figure 6. Improvement is observed in the evaluation of the visual field repeated 3 weeks and 3 months after treatment.

provement in MS attack occurs in a shorter time (in 3-4 weeks after the clinical picture gets severe) (9,10), less disability developed in this age group (10) and progressive phase occurs more rarely in children. Marked clinical improvement was observed one week after appropriate treatment. Our patient who had a very severe clinical picture during the 18-month follow-up period had a good prognosis and developed no cognitive dysfunction. On the other hand, there are also observations that disability related with cognitive functions which may be observed in MS may be more severe in this age group compared to adult patients (11,12). Applicability of the imaging criteria used for the diagnosis of MS developing in the adulthood in childhood-onset MS is controversial. In a study published recently in which the diagnostic criteria were reviewed, the issue was attempted to be elucidated and it was reported that Mc Donald criteria would be an appropriate approach for the diagnosis of MS in children (13). The clinical picture of our patient showed extension in time and in CNS according to Mc Donald criteria (14) and no better cause could be found to explain this picture. In a study conducted by Huhn et al., Mc Donald criteria were used in terms of areal extension in the first and second attack and only 53-67% of the patients were diagnosed with MS (15). This is explained with a high number of silent lesions in the pediatric age group. Nevertheless, Mc Donald criteria are considered the most appropriate approach for the diagnosis of MS in children (2) and the difficulty of differentiating acute MS attack from ADEM renders repetition of imaging with regular intervals in the follow-up necessary. In the same study of Hahn et al, it was proposed that tumefactive lesions were observed more frequently in the peidatirc group (15). On the other hand, it has been reported that this picture is mostly maintained monophasic compared to the other demyelinating pathologies (16,17) and has a recurring course in some cases (18,19,20,21). The laboratory findings in pediatric MS are similar to adult-onset patients. The CSF protein level is withing the normal limits and pleocytosis has been reported rarely (6). OCB has been found in 90% of the cases (22). In tumefactive MS patients, the positivity is found with a rate of 33% and intrathecal IgG synthesis has been reported with a rate of 35% (18%). OCB was negative and the IgG index was found to be high indicating increased IgG synthesis in CNS in our patient.

Treatment of attack and prophylactic treatment in MS in this age group is planned similar to adult patients considering the age and body weights of children. The aggressive clinical picture of our patient did not benefit from classical steroid treatment and gave good response to plasmapheresis and interferon beta treatment.

The classicially described picture of ADEM is a monophasic disease of the childhood. Multifocal neurological findings accompanied by encephalopathy are observed. However, recurrence characterized with clinical findings compatible with the same localization which mostly develop in 1-2 months after an attack has been reported with a frequency of 10-30%. This has been associated with steroid withrawal or regarded as continuance of the first attack (23,24). Recently, the concepts of biphasic, recurrent or multiphasic ADEM have been proposed (25,26). The frequencies of these pictures has been reported to be 5-8%. In recurrent and multiphasic ADEM, a new attack should develop at least 3 months after the onset of an attack or at least one month after the end of steroid treatment to make the diagnosis (27). Biphasic ADEM is defined with presence of 2 attacks, recurrent ADEM is defined with presence of sterotypical attacks and multiphasic ADEM is defined with presence of multiple attacks characerized with new findings and lesions. Because of the difficulty of diferentiation o recurrent ADEM concept and MS, some authors state that the differential diagnosis can only be made retrospectively (28). It has been proposed that MS, vasculitis or granulomatous diseases should be considered in cases where more than 3 attacks develop similar to our case (1).

In our patient, attacks which suggested different clinical localizations (firstly left hemiparesia, then right hemiparesia), cerebellar findings, superficial and deep sensory loss, sphincter defect and visual defect related with bilateral occipital cortex involvement devepoled in a period of 3 months. Absence of a history of infection and vaccination, findings related with brain involvement, marked awakeness defect and epileptic seizures and presence of examination findings suggesting partial involvement of the medulla spinalis primarily suggested acute MS attack. However, cases of ADEM which are characterized only with hemiparesia have also been reported in the literature (17). These attacks compatible with different clinical localizations which could not be explained by a single anatomic localization not accompanied by awakeness defect and seizures characterized with new clinical finidngs primarily suggested the diagnosis of recurrent MS rather than ADEM.

When the radiological findings were evaluated, it was observed that the asymmetrical, annular contrast enhancement lesions found on the initial cranial imaging suggested ADEM and the patient was followed up with a diagnosis of ADEM in the center where she was evaluated during that period. Presence of the lesions involving cortical grey matter, brainstem and thalamus and exceeding the length of 3,5 vertabral corpi in the medulla spinalis on MR imaging repeated during the follow-up supported this diagnosis. On the other hand, these cranial lesions are compatible with tumefactive MS in contrast to classical MS defined. Brain MR spectroscopy performed because of this confirmed that the lesions had inflammatory, demyelinating character and thus other causes were excluded (central nervous system lymphoma etc.). In addition, accompaniment of cervical lesions to the picture radiologically and their appearance supported the diagnosis of demyelinating disease. It was observed that the lesions had no contrast enhancement, but increased in size on examinations repeated in the acute worsening period during which complaints of visual defect developed. This shows that radiological findings may not necessarily be compatible with clinical attacks. In addition, visual defect related with occipital involvement is not a common finding in classical recurrent MS; however, it was thought that the clinical and VEP findings of the patient could be explained with tumefactive lesions in the occipital regions (5).

When the CSF findings were examined, OCB positivity was found with a rate of 0-58% (29), but OCB was found to have be-

come negative in the period of remission. However, studies have reported that OCB is negative in the initial CSF examination, but becomes positive in the following period in cases which are characterized with relapses (30). In these patients, intrathecal IgG synthesis has been found in 3-30% of the cases (24,31,32) and pleocytosis in CSF has been found in 55% of the cases (30). The CSF findings of our patient (presence of IgG synthesis and absence of pleocytosis and increased protein) supported the diagnosis of MS rather than ADEM.

Inflammatory demyelinating disease was considered and the other possibilities were excluded in our patient. This patient is a good example which shows that necessity of treatment is determined by the clinical picture, though radiological findings compatible with objective clinical findings or contrast enhancement in the lesions are absent.

In conclusion, it was thought that all these clinical and laboratory findings could be compatible with recurrent tumefactive MS. Prophylactic treatment was initiated in the patient considering presence of frequent and severe attacks, requirement for frequent use of high dose steroid treatment, the negative effects of this treatment on growth and development and the controversial effects of plasmapheresis and intravenous immunglobulin. Repeated imaging was planned for the follow-up period.

This study demonstrates that a meticulous assessment and follow-up process is required to reach a definite diagnosis in pediatric demyelinating diseases as stated in the current diagnostic criteria and marked clinical improvement can be provided by an appropriate treatment approach which will be specified as a result of this process.

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