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The role of advanced magnetic resonance imaging techniques in a pediatric Progressive Multifocal Leukoencephalopathy patient associated with Bruton disease : The pediatric radiologist‘s approach within a case report

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Öz

Jc papovavirüs nörontropik virüs olup oligodendrositlerde demyelinizasyona neden olmaktadır. Difüzyon tensör incelemede beyaz cevher yolaklarında sağ frontal bölgede kesinti izlenmektedir. Multivoksel spektroskopi incelemede Cho/Cr ve mI/Cr oranlarında artış izlenirken NAA miktarlarında düşme izlenmektedir.

Bu bulgular demyelinizan hasarı gösterir-ken, mI hastalığın şiddetini göstermektedir. Bizim bu çalışmada amacımız ileri MRG tekniklerini kullanarak immün yetmezlik olan bir olguda gelişen PML hastalığının bulgularını tartışmaktır.

Anahtar Kelimeler: pediatrik radyoloji, JC virus, DTİ görüntüleme, multimodality görüntüleme

Abstract

JC papovavirus, which is a neurotropic virus, causes a demyelinating process in oligodendrocytes. Diffusion tensor imaging (DTI) showed white-matter tract interruptions in the right frontal hemispheric region. Multivoxel spectroscopy revealed an increase in the Cho/Cr and mI/Cr ratios, and a decreased in the N-acetylaspartate (NAA) values. These values show the demyelinating process and damage, whereas mI levels are known to be the predictor of the severity of the disease. In this case report, our goal is to discuss the supportive findings and benefits of using advanced MR techniques in an immunocompromised pediatric patient suffering from PML disease.

Keywords: Pediatric radiology, JC virus, DTI imaging, multimodality imaging

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Introduction

The JC papovavirus, which is a neurotropic virus, causes a progressive demyelinating process in an infection, resulting in myelin-producing oligodendrocytes.

Progressive multifocal leukoencephalopathy (PML) has an increased incidence in im-mune-compromised patients, including those with T- or B-cell dysfunction or congenital hu-man immunodeficiency virus. Bruton's disease is a type of immunodeficiency disorder that is associated with X-linked agammaglobulinemia [1–3].

The myelin breakdown in PML causes a progressive and serious destruction of white matter, resulting in neurologic deficits [4]. The symptoms are nonspecific in pediatric patients, which could be the reason for delays in the diagnosis of the disease. Additionally, the demye-linating process interferes with the evaluation of mass effect, which could be another reason for delays in the diagnosis, consequently causing an occurrence of the emerging symptoms. A definitive diagnosis of PML is made by determining the presence of JC papovavirus deoxyribonucleic acid (DNA) in the cerebrospinal fluid within the polymerase chain reaction (PCR) [3, 5–7].

Magnetic resonance imaging (MRI) is acknowledged to be the first-line diagnostic tool for use in following the course of PML. Relevant advanced MRI techniques, such as diffusion tensor imaging (DTI) or magnetic resonance spectroscopy (MRS), have enabled physicians to predict the prognosis of PML. The DWI signal from a clinical DWI sequence is representative of the average diffusion in all directions (a scalar measure) and is often calculated by averaging diffusion measurements from three gradient directions. DTI is, more accurately, a simplistic mathematical model of 3-D diffusion requiring measurement of diffusion along a minimum of 6 non-collinear directions to compute the 3x3 diffusion tensor (the tensor is symmetric so there are 6 unknowns which must be measured) DTI allows the quantification of white-matter injury and the differentiation of edemas into vasogenic or cytotoxic types. The use of multimodal MR techniques in PML has been described in the literature, but these reports include only those findings related to adult patients [3, 6–8].

The aim of this report is to describe multimodality MR imaging techniques, including DTI and MRS, in a pediatric patient with progressive multifocal leukoencephalopathy associat-ed with X-linked agammaglobulinemia.

Case Report

A 15-year-old boy with known X-linked agammaglobulinemia (Bruton's disease) was referred to our hospital for further evaluation of rapidly progressive headache and neurologic distortion. The physical examination in our hospital showed left-sided symptoms, including hemiparesis, limb weakness, and aphasia. The patient had been on steroid therapy for several years. His blood pressure was normal. An investigation of his neurologic symptoms was completed via MR scanning with a 1.5-tesla scanner (Philips, 1.5T Achieva, USA). After a neurologic consultation, he was examined for PML, and an analysis of the cerebrospinal fluid revealed that it was JCV DNA positive.

A conventional T2-weighted fast spin-echo, FLAIR, was performed, and pre- and post-contrast T1-weighted spin-echo images were obtained. Following the conventional sequences, the patient underwent DTI and multivoxel MRS. He could not tolerate the MR perfusion study because of his neurologic condition and distortness. A Philips workshop machine dedicated to the evaluation of fractional anisotropy maps and tracts visualization was used. Fractional ani-sotropy values were obtained from both the normal and abnormal white-matter tracts from multiple anatomic locations, including the posterior limb of the internal capsule. Multivoxel TE :144 MRS was then performed.

The conventional MRI sequences on the T2 weighted sequences revealed right frontal hemispheric hyperintensities. The T1 weighted sequences demonstrated hypointensity on the lesion and did not show contrast enhancement after gadolinium administration. The right frontal lobe lesion extended to the right gyrus cingulate posteriorly. On diffusion–weighted images, the lesion showed increased diffusion (diffusion-weighted: hypointense, ADC: hyperintense) which is indicative of vasogenic edema. Moreover, although a large area was indicated, there was no mass effect to the left side.

The colored DTI map shows that the corticospinal tracts were interrupted in the right frontal white matter (Figure 1-a–c). An analysis of the FA values demonstrated that the values calculated from the right frontal area were significantly lower than those of the left symmetric frontal hemisphere. Fractional anisotropy was also decreased within the right posterior limb of the internal capsule (Figure 1-b).

MRS imaging (TE 144 via the multivoxel technique) revealed elevated choline-containing compounds (Cho) at 3.2 ppm and a low N-acetylaspartate (NAA) peak at 2.0 ppm. These findings suggest active demyelination and dysfunction of neurons and axons. There were no inverted lactate (LAC) signals at around 1.3 ppm, which excludes the possibility of necrosis in the white-matter region, whereas vasogenic edema in this area is suggested. At 3.4 ppm, there was a slight increase in the mI peak, and the mI/Cr peak was measured at 0.67 (Figure1-d).

After the initial and supportive findings of PML, the patient was treated with steroid, agammaglobulinemia, and antiviral therapies. Although this extensive treatment was adminis-tered to the patient, his neurologic distortion and condition became progressively worse. He was therefore referred to another center. The patient died after two months during the initial follow-up.

A 15-year-old boy with known Bruton's disease was admitted to our hospital for further evaluation of neurologic distortion. The patient underwent conventional MRI and advanced techniques, including DTI and TE 144 multivoxel spectroscopy.

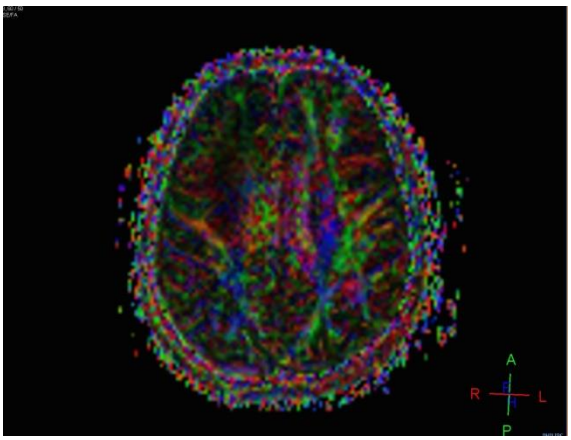

Figure 1-a presents a colored-coded map of the DTI imaging. There is an area in the right frontal area that is

moderately hyperintense when compared with the left hemispheric region.

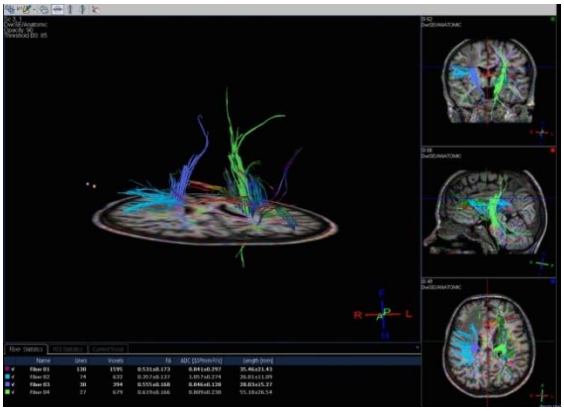

Figure 1-b shows the fiber-tracking map of the white-matter tracts. On the right frontal lobe, as shown with the purple-colored tract, there is interruption of the tracts in this area. The FA values in the right frontal area are lower than those of the left hemispheric region. The ADC values are inversely correlated with the FA values.

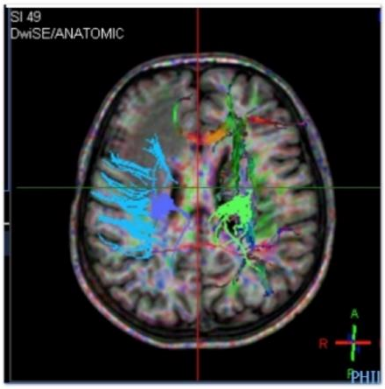

Figure 1-c shows the orientation of the white-matter tracts as captured by the DTI technique. The tracts in the right frontal area are suddenly interrupted. Additionally, the integration of the other white-matter tract is already well done.

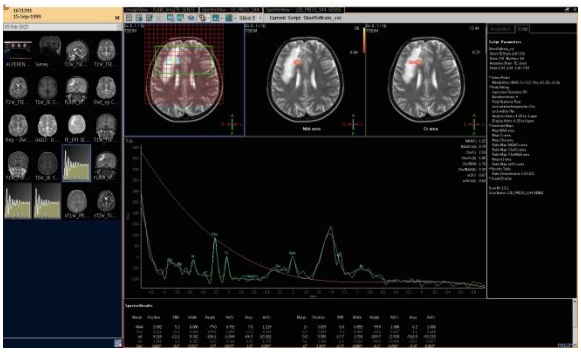

Figure 1-d shows the TE 144 multivoxel spectroscopy metabolite imaging ratio map. As shown in the map, at 3.2 ppm, there is a choline peak, whereas the NAA values were decreased at 2.0 ppm. The mI, at 3.6 ppm, was slightly increased in this spectrogram.

Discussion

PML is a type of subacute progressive demyelinating disease of the brain caused by a papovavirus infection of oligodendrocytes. Histologically, oligodendrocytes produce and maintain the myelin sheaths in the white matter. Therefore, damage to the oligodendrocytes by a neurotropic virus could affect both the cell membrane and the myelin sheath [1, 3]. Radiologically, via the use of advanced MR techniques, we were able to measure the myelin sheath and the membrane turnover destruction products extracellular region. In addition, we used DTI to identify the white-matter tract evaluation and integration.

Conventional MR sequences show no predictive signs of a PML prognosis. Alternatively, the absence of a mass effect is accepted as a diagnosis of PML [8,9]. Additionally, the mass effect is so infrequent and minimal that it is not a useful prognostic sign. The need for additional, more predictive diagnostic tests is clearly indicated. However, while this finding is accepted in adults, no findings exist that indicate either adverse or acceptable outcomes in terms of pediatric or adolescent age groups [1, 3].

Diffusion–weighted imaging provides information about the Brownian motion of water. Apparent diffusion coherent is an alternative technique for quantifying isotropic water diffu-sion, which is an estimative and discriminative way of differentiating between cytotoxic and vasogenic edemas [3, 7]. The diffusion imaging technique measures the motion of water in one vectorial way, whereas DTI provides information quantitatively via a minimum of six vec-torial

images. The degree of anisotropic diffusion is recognized as being correlative to the myelination of white matter [1–3]. Additionally, microstructural knowledge of the tract evaluation could be best estimated via the use of DTI, which is a good predictor of the disease prognosis [3, 8].

Proton MRS enables us to obtain information about the chemical milieu of the neuronal microenvironment by shimming the homogeneity. In a routine MRS spectrum, there are nota-ble peaks at fixed ppms. The N-acetylaspartate (NAA) peak at 2.0 ppm shows neuron and axon viability, whereas the choline peak at 3.2 ppm is a marker for cell membrane constituency, and a creatinine (Cr) peak is known to have an active role in maintaining energy-dependent systems in white matter and in the myelin sheath membrane cells [7]. In addition, a Lac peak at 1.4 ppm or a double inversion shows inflammation or neuronal mitochondrial dysfunction or related due to an increased pathway of the active anaerobic glycolytic metabolism [7, 8]. In spectral imagining, the Cr peak is accepted as the constant metabolite; it is therefore used in the proportion of the other metabolites to understand metabolic conditions. However, this consideration is true for adult patients but not for children, since they are growing organisms; rather, additional and supplemental Cr cycles in overgrowth patterns are considered, since they enable Cr products and ingredients to be more easily measured in the blood. In other words, the Cr metabolite cannot be accepted as a fair stable metabolite in pediatric and adolescent patients [10].

PML features a progressive demyelinating process as well as destruction to the membrane cells. It is therefore expected that based on absolute quantification, there will be a substantial decrease in the NAA peak at 2.0 ppm or in the NAA/Cr ratio in the affected area. A choline peak at 3.2 ppm or an increase in the Cho/Cr ratio, reflecting myelin destruction, comprises the most common spectral findings in PML disease. In this case, the Cho/Cr ratio was measured at 2.14, which is moderately higher than that indicating membrane destruction. The literature does not contain definite findings regarding the relationship of high ratios and PML disease stages. However, Cho/Cr ratios over 2, such as is seen in lymphomas or high-grade neoplasms, are accepted as a high turnover in metabolism [4, 7]. An mI peak at 3.4 ppm may be normal or slightly elevated compared with contralateral, normal-appearing white matter. The level of the increase depends upon the stage of the disease [7]. In the early and active stage, there is an increased level of myoinositol, which gradually decreases to a normal level in the late quiescent stage. To describe a more definitive criterion, the myoinositol/Cr levels are used instead. In our case, this ratio was found to be 0.67, which is slightly higher and shows the acute phase of the PML disease progression. When estimating the disease progress, therefore, a longitudinal evaluation of the spectroscopic metabolites and the fractional anisotropy values should be determined clearly. [7]

In adult diffusion tensor studies, the fractional anisotropy values reflect the organized architecture of the white matter and neuronal tracts as well as the spread of the lesions from the parietal white matter to the frontal white matter [3]. In our case, however, the lesion is contained

only in the frontal white matter. In contrast to the adult patient group, the spread of the lesion is not from the posterior to the anterior region.

It is interesting to note that in adult case studies, conventional MR imaging sequences have not shown any correlating pathology with the posterior limb of the internal capsule. The finding in our case report is consistent with that finding. Therefore, both diffusion-weighted and DTI studies should be used to evaluate the posterior limb of the internal capsule. In terms of the relationship of the pathologic correspondence, in evaluations using the DTI technique, the destruction of the myelin sheath of the neurons and fiber tracts could be measured by the fractional anisotropy decrease, whereas the next step in the disease progress (i.e. diffuse cell loss) is represented by the ADC increase [1, 3, 7]. However, in this range of the spectrum, the metabolites obtained from the MRS, Cho/Cr, NAA/Cr, and mI/Cr could be used to estimate the stage of the PML disease as well as its progress.

In conclusion, DTI and MRS enable us to obtain information about the microstructural integrity of white-matter tracts and about the biomarker for the degree of tissue injury. The role of advanced MRI techniques at the neurologic findings of immunological diseases should be evaluated with the large cohort studies.

Conflict of interest

The authors in this case report no conflicts of interest.

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