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Case report

A case of megalencephalic leukoencephalopathy with subcortical cysts

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= Abstract =

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare white matter disorder, first described in the early 1990s. The brain in patients with MLC appears swollen on MRI, with diffuse white matter abnormalities; in addition, there is an invariable presence of subcortical cysts, primarily in the anterior temporal region sparing the deep white matter, basal ganglia, thalami, and cerebellum. Patients with MLC present with macrocephaly and neurological abnormalities such as motor deterioration, ataxia, spasticity, and cognitive deficits. We report a twenty-month-old boy who presented with seizures and macrocephaly, delay in development, and abnormal brain MRI findings compatible with the diagnosis of MLC. The brain MRI revealed bilateral hypersignal intense subcortical white matter regions in the frontal, temporal, and parietal lobes on T2-weighted images, which were not yet associated with cystic changes. During follow-up, the frequency of seizures decreased after anticonvulsant medication was started, but the head circumference remained above the 97th percentile, and the patient continued to have developmental delay. (Korean J Pediatr 2008;51:1342-1345)

Key Words : Megalencephalic leukoencephalopathy with subcortical cysts, Developmental disabilities

Introduction

The formation of myelin and its maintenance require a complex interaction between neurons and other soluble and cellular factors[1]. Leukoencephalopathy refers to disorders that result from a disturbance of any of these factors[1]. The well known leukoencephalopathy conditions include diseases such as Alexander, Canavan and glutaricaciduria type 1[1-5].

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare degenerative disorder characterized by megalencephaly, cerebral leukoencephalopathy and a delayed onset of a slowly progressive neurological deterioration[1-15]. It was first described by Indian neurologists, Singhal et al.[6] in 1991 and reported as a formal paper in succession, in 1996, which presented a group of patients with the same ethnic background, referred to as Agarwals that showed the characteristic features including: megalencephaly, mild to moderate cognitive defects and progressive spasticity[8]. Brain imaging studies of all patients showed leukodystrophy with cysts[6, 8]. Van der Knapp et al.[9] also reported similar findings on a heterogeneous group of patients in 1995. MLC is also referred to as Van der Knapp disease. Soon after, many reports followed by various authors; there are currently more than 100 cases of MLC reported in the medical literature[1-15]. Even with many cases reported from diverse ethnic group[2, 7, 9, 11, 13, 15, 16], the largest number of cases has been reported from a specific Indian community, the Agarwals of India[4, 6, 8, 12].

We describe a 20 month old boy presenting with megalencephaly, delayed development, seizures, and typical MRI findings showing bilateral hypersignal intense subcortical white matter lesions of the frontal, temporal and parietal lobes.

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Case Report

A twenty-month-old boy presented to our hospital with his first seizure. He was born at term without a significant antenatal or prenatal history. His parents were non-consanguineous and he had no specific family history. At presen-

tation his head circumference was 52.5 cm, which was above the 97th percentile and the height and weight were within the 50-75th percentile. There was mild global developmental delay but the muscle tone was normal as were the deep tendon reflexes on the neurological examination. The patient could not yet walk independently, and had only one word, "mama".

The routine laboratory findings including a complete blood cell count, blood glucose, creatine kinase, lactate, pyruvate, serum electrolytes, and liver and renal function tests were all normal. The brain MRI revealed bilateral hypersignal intense subcortical white matter lesions in the frontal, temporal and parietal lobes on T2-weighted images and fluid-attenuated inversion recovery; however, there was no diffusion restriction on the diffusion weighted images, and which was not yet associated with cystic changes (Fig. 1). The electroencephalography showed diffuse fast wave activity but no epileptiform discharges. Additional evaluations included plasma very long chain fatty acids, plasma amino acid analysis and urine organic acid chromatography; all of the results were within normal limits. The chromosome analysis showed a normal 46,XY karyotype.

At a follow-up visit, there was no visible improvement in the development. He still could not walk independently and could say only mama at 30 months of age. However, the seizures were relatively well-controlled with valproic acid.

Discussion

Macrocephaly might be the first manifestation of MLC that draws attention to a patient[1, 12]. It may be present from birth and is usually detected during the first year of life[1, 2, 10]. Our patient presented with an increased head circumference, above the 97th percentile for age, compared to the general Korean population[17]. The neurological signs and symptoms associated with MLC usually develop after 2 years of age when developmental delay becomes apparent[9]. Motor deterioration tends to be very slowly progressive in most patients[1, 9]. A delay in walking might be the first symptom of motor abnormalities[1]. Slow but progressive spasticity and cerebellar ataxia follow[1, 2, 11, 12]. Extrapyramidal symptoms such as dystonia and athetosis, and neuropsychological symptoms such as depression, aggression and dementia generally develop at advanced ages[11]. However, the cognitive

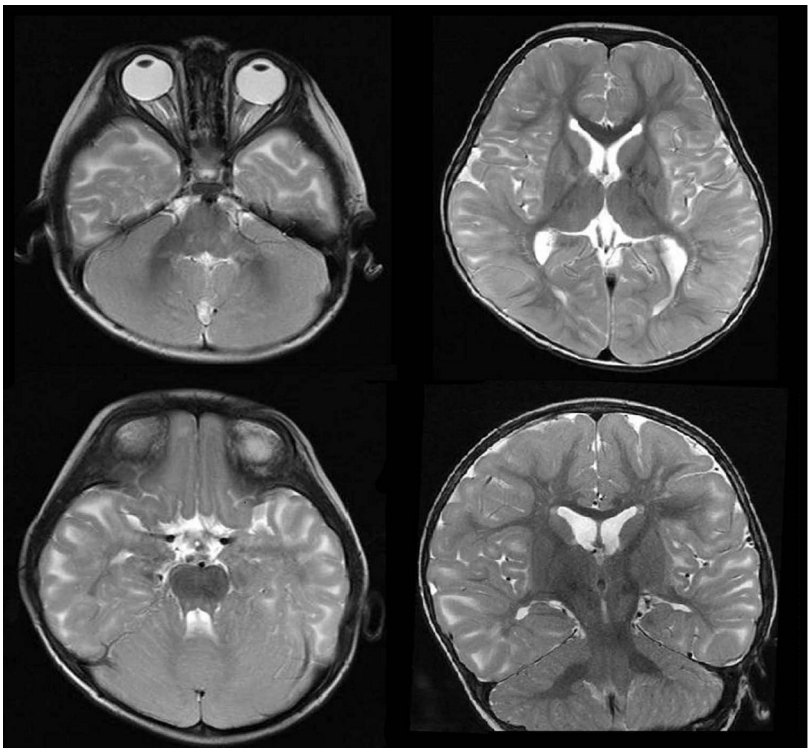

Fig. 1. Brain MRI shows bilateral hypersignal intense subcortical white matter regions in the frontal, temporal, and parietal lobes on T2-weighted images, which were not yet associated with cystic changes.

impairment is usually mild[1, 2, 6, 13]. Recurrent epileptic seizures might be present from the early stages of the disease; but they are usually easily controlled by antiepileptic drugs[1, 12]. Seizure episodes may be precipitated by minor trauma[1, 4], and are characterized by tonic-clonic, focal or secondarily generalized seizures[4].

Typical MRI findings, together with the clinical manifestations, are sufficient for the diagnosis of this disorder[10, 12]. No specific biochemical or metabolic abnormalities associated with MLC have been identified[1, 5, 7]. Diffusely involved swollen subcortical white matter with relative sparing of central structures such as the corpus callosum, internal capsule and brain stem are characteristic findings of megalencephaly[1-15, 18]. Cerebellar involvement is variable and usually mild[4]. Bilateral cystic changes, mainly in the temporal lobes and occasionally in the fronto-parietal lobes, are usually present[3, 10, 18]. Over time, the size and number of the cysts increase so that they eventually occupy a large portion of the frontoparietal cortex, which leads to volume loss[1, 10, 18]. In our patient, the subcortical cysts were not yet apparent; this was likely due to the very young age at presentation.

Histopathology reveals cavitating spongiform white matter changes caused by numerous vacuoles observed only in the outer lamella of the subcortical white matter[1, 2, 9, 10, 13, 14]. This finding suggested either incomplete compaction or splitting of the lamellae along the intraperiod line[1, 2, 9, 10, 13, 14].

Other conditions with megalencephaly, cognitive impairment and motor delay, should be considered in the differential diagnosis in addition to MLC[1, 2, 4, 5]. Alexander disease, an autosomal dominant disorder results from mutations in the GFAP gene, has a rather rapidly progressive course with an average survival of 2 to 10 years after onset[1, 3, 4, 5]. Extensive white matter changes are noted on neuroimaging studies with a frontal predominance and a periventricular rim; in addition, there is usually basal ganglia involvement[1, 4, 5]. Canavan disease is another condition that presents in infancy with megalencephaly, hypotonia and later spasticity and cortical blindness[4]; imaging studies show extensive white matter changes without enhancement or subcortical cysts, in addition to involvement of the thalamus and globus pallidus[3-5]. Increased N-acetylaspartic acid in the urine and a rapidly progressive clinical course distinguishes it from MLC[4]. For glutaricaciduria type 1, involvement of the dentate nuclei and severe atrophy of the cerebellar vermis are additional features; there are less prominent white matter changes on neuroimaging[4, 5]. The clinical course can be static, progressive or relapsing[3, 4]. Lysosomal storage disorders such as the mucopolysaccharidoses and GM2 gangliosidosis can also present with megalencephaly, however they have a less prominent leukoencephalopathy[4].

MLC has an autosomal recessive mode of inheritance[7]; mutations of the *MLC 1* gene have been identified in about 80% patients among the reported cases[1, 10]. The *MLC1* gene encodes a putative membrane protein, *MLC 1*, that is located on chromosome 22qtel[1, 3, 4, 7, 10-13, 15]. Since this mutation was first reported[15], about 50 different mutations have been identified in this gene[10]. Compound heterozygous cases have been reported in almost all racial groups[1, 10]. Common mutations have been reported in different populations: insertional mutations (135insC) among the Agarwals of India, G59E in Libyan Jewish families and a Jewish Turkish family and the S93L mutation in Japanese patients[1, 10]. These findings strongly suggest mutations with a founder effect[1, 10, 16]. In about 20% of the patients with the typical clinical and MRI findings, no mutations in the MLC 1 gene are found[5, 10], which suggest that there are other genes involved in MLC[5, 7, 10]. In our patient, the parents declined genetic studies. The clinical manifestations of MLC vary even with uniform MRI findings and identifiable molecular etiology; the clinical features can vary even in the same family[1, 7, 10]. In addition, the severity of the MRI findings is not always reflected by the clinical symptoms[1, 9, 11] that frequently are inconsistent with the severity of the MRI findings[1, 9]. The clinical course varies as well. Some patients are not able to walk at an early age while others are ambulatory up until the 4th decade[5, 7]. Some affected individuals function below the average cognitive level, while others finish higher education and have a job[1, 5, 13]. Others die during the teenage years, while some live into their 40s[1, 4].

This case illustrates a rare childhood case of megalencephalic leukoencephalopathy with subcortical cysts in a 20 month old boy presenting with megalencephaly, delay in development and typical MRI findings compatible with the diagnosis of MLC.

한 글 요 약

피질하 낭종을 동반한 거대뇌성 백질뇌병증 1예

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박은영 · 김영옥 · 김지윤 · 여채영
백희조 · 김찬종 · 김은영* · 우영종

피질하 낭종을 동반한 거대뇌성 백질뇌병증은 뇌백질의 희귀성 질환으로 1990년대에 처음 보고되었다. 이는 자기공명 영상(MRI)에서 미만성의 백질 이상 및 다양한 정도로 발견되는 피질하 낭종과 함께 뇌의 종창을 보이는 것이 전형적이며, 이 병변은 특징적으로 대뇌 측두엽의 전반부를 침범하고, 심부의 뇌백질, 대뇌 기저핵, 시상과 소뇌는 상대적으로 보존되는 경향을 보인다. 피질하 낭종을 동반한 거대뇌성 백질뇌병증이 있는 환아는 큰 머리와 함께 운동 장애, 실조증, 강직과 인지 기능 장애 등의 신경학적 결함을 보인다. 저자들은 큰 머리와 함께 경련, 발달 지연, 뇌 MRI 의 T2 강조영상에서 양측성으로 전두, 측두, 두정엽에서 고신호강도의 백질 병변을 보이는 피질하 낭종을 동반한 거대뇌성 백질뇌병증에 합당한 소견을 보이는 20개월의 남자 환아를 경험하였기에 보고하는 바이다.

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