Malignant transformation in a case of megalencephalic leukoencephalopathy with subcortical cysts: An extreme rarity in a rare disorder

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Abstract

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an autosomal recessive inherited disorder characterized by macrocephaly, progressive motor disability, seizures, mild cognitive decline, slow progression, and typical magnetic resonance imaging (MRI) findings. Age of onset of symptoms is described from birth to 25 years. Late onset presentation is very rare, only few cases have been reported worldwide. Most important clue for diagnosis is the characteristic MRI changes that include diffuse involvement of subcortical white matter mainly in frontoparietal region with relative sparing of central white matter along with subcortical cysts mostly in anterior temporal region. Cysts are usually benign and slowly progressive. Malignant transformation of cysts has not been reported as yet. We herein report a very unusual and probably the first case of MLC who presented to us in a unique manner with late onset and malignant transformation of cyst in left temporal region leading to rapid neurological decline. This case report highlights a possible life-threatening complication of a previously known slowly progressive disease warranting urgent neurosurgical intervention.

Key Words

Malignant transformation, megalencephalic leukoencephalopathy, subcortical cysts, van der knaap disease

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Introduction

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a disorder of white matter, characterized by macrocephaly in infancy, progressive difficulty in walking due to spasticity and ataxia, delayed motor development, and seizures.[1,2] Typical magnetic resonance imaging (MRI) changes include involvement of subcortical white matter mainly in frontoparietal region with relative sparing of central white matter along with subcortical cysts mostly in anterior temporal region. Cysts may slowly increase in size and number.[3,4] Beside the subcortical cysts, no other space-occupying lesion has been described in MLC. Age of onset of symptoms is described from birth to 25 years and disease is usually slowly progressive.[1] Late onset and rapid deterioration has not been reported till now. We herein report a very unusual and probably the first case of MLC who not only presented with delayed onset but also developed malignant transformation of cyst in left temporal region leading to rapid neurological decline.

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Case Report

A 52-year-old female, belonging to the Agrawal community of north Indian state of Haryana, presented with 6 years history of seizures which were well controlled on antiepileptics. There was no history of difficulty in walking, cognitive decline, head injury, and similar illness in the family. She was diagnosed as a case of MLC on the basis of characteristic findings in MRI brain, which revealed diffuse symmetrical cerebral white matter hyperintensities on T2-weighted (T2W) images with corresponding hypointensities on T1-weighted (T1W) images along with cystic lesions in bilateral anterior temporal (right 12 × 20 mm, left 28 × 25 mm) and frontal regions [Figure 1a-f]. Now, for the last 5 days she developed acute deterioration in consciousness in the form of confusion, irrelevant talking which further progressed to decreased speech output, and difficulty in walking. On general examination; pulse rate was 70/min, blood pressure 130/90 mmHg, and respiratory rate 18/min. The head circumference was 57.5 cm. Neurological examination

revealed disorientation and expressive aphasia. Cranial nerves including pupils and fundus examination were normal. Motor examination showed hypertonia and paucity of movement on right side. Deep tendon reflexes were brisk on right side with positive Babinski's sign. Cerebellar signs and signs of meningeal irritation were absent. Examination of other systems was unremarkable. Routine investigations including hematology, biochemistry, electrocardiogram, and X-ray chest were normal. Computed tomography (CT) head showed 55 × 30 × 50 mm, ill-defined, heterogeneous space-occupying lesion in left temporal region with surrounding edema and heterogeneous contrast enhancement in medial part of lesion. Mass effect was observed in the form of gyral swelling, sulcul effacement, effaced left lateral ventricle with dilated right lateral ventricle, midline shift to right, subfalcine herniation of left lateral ventricle, and left uncal herniation. Small cystic areas were seen in bilateral frontal and right temporal region. Hypodensity was present in bilateral periventricular and subcortical white matter. MRI brain confirmed the CT scan findings and revealed solid cystic mass in left temporal lobe. Cystic component was isointense to cerebrospinal fluid (CSF) on T2W and short tau inversion recovery (STIR) images, while slightly hyperintense on T1W images. Solid component appeared heterogeneously hyperintense on T1W and T2W images with small necrotic area and showed heterogeneous post-contrast enhancement. Ring enhancement was seen in cystic component on post-contrast images. Diffuse symmetric hyperintense signals were observed in subcortical and periventricular white matter extending into subcortical "U" fibers on T2W and fluid attenuated inversion recovery (FLAIR) images [Figure 2a-f]. MR spectroscopy of brain demonstrated increased choline peak in solid component. Choline/creatine and choline/N-acetyl aspartate (NAA) peak ratio were increased. NAA peak was decreased. MR spectroscopy (MRS) findings were suggestive of tumoral pathology. On comparison with previous MRI (at the onset of disease) of September 2009, there was significant increase in size of left temporal lobe lesion with development of mass effect in the form of subfalcine and uncal herniation with midline shift to right [Figure 2a-f]. The patient was transferred under the care of neurosurgery team and underwent subtotal excision of left temporal mass. Histopathological examination revealed increased cellularity and pleomorphism without any evidence of mitosis and vascular proliferation suggestive of astrocytoma grade II [Figure 3a-b]. Patient came for follow-up after 1 month of surgery and has recovered completely. She has been advised radiotherapy by neurosurgeon. We had planned and discussed for genetic testing, but patient's relatives were not willing for the same.

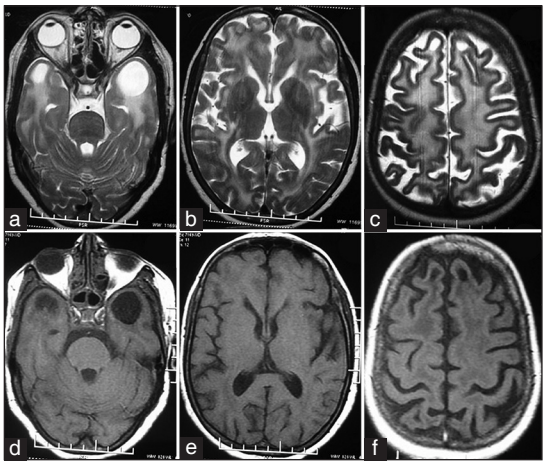

Figure 1: T2W (a-c) axial MR images of brain showing diffuse, symmetrical hyperintense signals in white matter with corresponding hypointense signals on T1W images (d-f) and cystic lesions in bilateral temporal (a and d) and frontal regions (c and f). T2W = T2-weighted, T1W = T1-weighted, MR = magnetic resonance

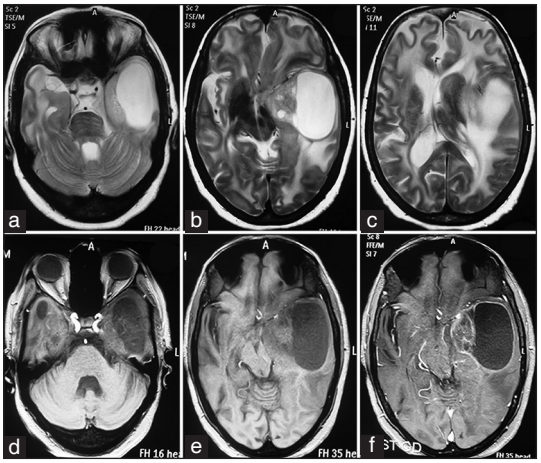

Figure 2: T2W (a-c) and T1W (d and e) MR images of brain showing large solid cystic space-occupying lesion in left temporal lobe, associated with perilesional edema and mass effect, along with a small cystic lesion in right temporal lobe. Post-contrast image (f) showing heterogeneous and ring enhancement in left temporal lesion. Diffuse symmetric white matter hyperintensities on T2W images is also evident. On comparison with previous MRI at disease onset [Figure 1], the size of left temporal lesion has markedly increased, with appearance of solid component in medial aspect

Discussion

MLC was first described by Singhal *et al*., (1991) in 18 patients at a meeting in Japan.[5] Later in 1995, Van der Knaap *et al*., formally published an article. He described the clinical and MRI features of disease in a series of eight patients.[3] Another series of 12 patients was published from Turkey in 1998 by Topcu *et al*.[6] He proposed that disease is autosomal recessive, inherited with a locus at chromosome 22q.[4,7] Singhal *et al*., reported the disease in specific community named "Agrawals" from Northern India.[1] On detailed genetic analysis, Gorospe *et al*., found the common locus at MLC 1 gene in all 31 patients described in the Agrawal community.[4,8] Two phenotypes of MLC have been mentioned.

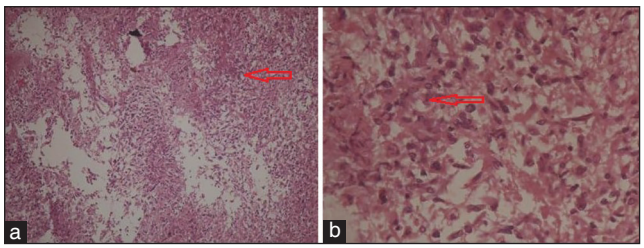

Figure 3: Histopathological examination of left temporal lobe lesion on (a) low power (H and E, ×100) and (b) high power (H and E, ×400) showing increased cellularity (a and b) and pleomorphism (b) without any evidence of mitosis and vascular proliferation is suggestive of astrocytoma grade II. H and E = Hematoxylin and eosin

One is the classic phenotype and another improving phenotype. In classic phenotypes, 75% cases are associated with mutation in *MLC1* gene, known as MLC1 and 20% cases are associated with mutation in *HEPACAM or GlialCAM* gene, known as MLC2A. Improving phenotype is associated with heterozygous mutation of *HEPACAM or GlialCAM* gene, known as MLC2B. Classic phenotypes (MLC1 and MLC2A) have autosomal recessive inheritance while improving phenotype (MLC2B) has autosomal dominant inheritance.[9,10] It has been suggested that MLC1 mutations alter the astrocyte's function in regulating extracellular ion homeostasis, leading to myelin degeneration.[11] Histological study of brain biopsies from MLC patients depicted spongy degeneration of myelin with intramyelinic vacuolation, alterations of blood brain barrier structure, and activation of astrocytes.[12] Pathogenesis of malignant transformation of cyst in our case is not very clear. It may be hypothesized that activated astrocytes may respond to various pathological insults, by secreting some mitogenic cytokines and growth factors, undergo morphological changes, collectively called "reactive astrogliosis", and subsequently lead to cell proliferation and scar formation.[12,13] Clinical picture of MLC has distinct heterogeneity. The age at onset of symptoms ranges from birth to 25 years, with a median of 6 months.[1,4] The maximum age of presentation is reported by Kocaman *et al*., in a 38-year-old patient.[14] The patient presented to us was exceptionally preserved till the age of 46 years. Macrocephaly is the most common and constant manifestation, which has been seen in all genetically proven cases. It is more noticeable in infancy and follows the normal growth pattern afterward. Head circumference remains several centimeters greater than the standard throughout the life. Other common features include ataxia (58%), spasticity (57%), recurrent seizures (49%), and mild cognitive decline.[1,4] Seizures are usually well controlled with antiepileptics and may be precipitated by minor head trauma.[1,4] MRI brain is the most important investigation for diagnosis. Characteristic MRI findings observed are diffuse hyperintense signals and swelling in supratentorial hemispheric white matter with subcortical cysts. Swelling is more prominent in young patients. Most common site of subcortical cysts is anterior temporal region. Cysts have also been observed in frontoparietal subcortical region. Central white matter structures, including corpus callosum, anterior limb of the internal capsule, a periventricular rim of occipital white matter, and (partially) the posterior limb of the internal capsule are typically spared.[3] Subcortical cysts may increase in size and number, but progression of disease is very slow.[3,4] Rapid neurological deterioration has not been reported due to enlargement of cysts as yet. Beside the subcortical cysts, no other space-occupying lesion in the brain has been reported in association with MLC.

Our case presented in a unique manner with late onset and developed malignant transformation of cyst in left temporal region, leading to rapid neurological deterioration, which was not evident in first MRI done at the onset of illness 6 years back. To the best of our knowledge this is the first case of MLC, who not only presented with delayed onset but also developed malignant transformation of subcortical cyst. Clinicians should be aware of this complication and follow-up imaging at a regular interval is warranted, as it may require lifesaving urgent neurosurgical intervention.

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