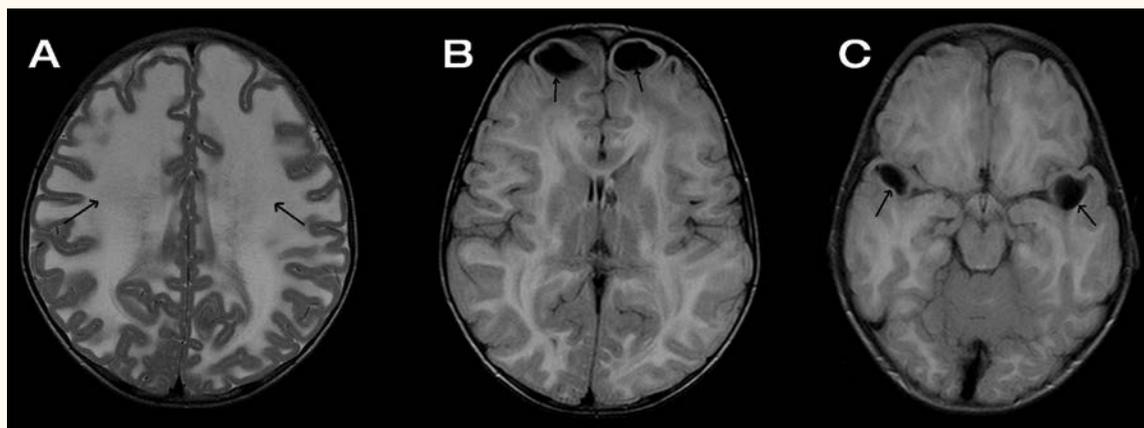


## Megalencephalic Leukoencephalopathy with Subcortical Cysts

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اعتلال وتضخم بويضات الدماغ مع تكيسات تحت قشرة المخ

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**Figure 1 A to C.** A: Axial magnetic resonance images (T2-weighted) of patient T, showing diffuse white matter swelling and hyperintensity (arrows). B: Axial fluid liquid attenuation inversion recovery (FLAIR) image showing subcortical cysts in the frontal region (arrows). C: Axial FLAIR image with subcortical cysts in the anterior temporal region (arrows).

**M**EGALENCEPHALIC LEUCOENCEPHALOPATHY with subcortical cysts (MLC) is a genetic degenerative disease of the white matter of the brain. The white matter degenerates and swells, resulting in patients with large head sizes. Cysts are also seen in white matter.<sup>1</sup> Children with MLC usually present in the first year of life, though some discrepancy has been reported in their clinical course.<sup>1</sup> MLC is a rare neurodegenerative disorder and is reported here for the first time in two siblings in Oman.

Two children of consanguineous parents presented in 2004, a girl (A), currently 19 years of age, and a boy (T), currently 11 years. Their main complaint was mild developmental delay and the large head size, the latter noted by the parents during the first year of life, compared to their siblings. The patients gained initial milestones normally but after the first year had difficulty walking. Over time there

was an increase in spasticity and weakness of the limbs. At the time of writing, neither child could walk or sit unsupported. The elder sibling (A) had eating difficulties and was fed through a nasogastric tube. She could understand simple commands but had difficulty in speaking. The younger sibling (T) was still able to eat with assistance and had preserved speech. However, he had recently developed gastro-oesophageal reflux. Neither sibling had a history of seizures. The other 6 children in the family (3 sons and 3 daughters) were normal; there was no family history of similar or other neurologic conditions in the past two to three generations.

In 2004, upon examination at presentation, there was macrocephaly in both patients. The head circumference of patient T was 58 cm at 4 years of age and 59 cm in patient A at 11 years; both measurements are well above the 97<sup>th</sup> percentile for their ages. The cranial nerves and language were

normal. Bipyramidal signs were noted in the upper and lower limbs. There was spasticity in lower limbs with upgoing plantar responses. Although the upper limb muscles were wasted, the power was normal (Medical Research Council grade 5), with brisk deep tendon reflexes. Routine blood and metabolic investigations were normal. Electroencephalography and visual evoked potentials were not performed, as there were no seizures or visual abnormalities. A magnetic resonance imaging (MRI) brain scan revealed bilateral white matter diffuse changes with subcortical cysts [Figure 1]. A diagnosis of MLC was made after consultation with an expert.<sup>1,2</sup> Although the diagnosis was clinically certain, there was no genetic confirmation. Recently, *MLC1* gene sequencing revealed a homozygous c.432+1G>A mutation. The mutation is predicted to cause aberrant splicing, and it was not found in more than 400 control chromosomes; features which suggest the likely pathogenicity of this mutation.<sup>1</sup> Both patients were severely handicapped and on symptomatic treatment only, not yet having developed seizures. Patient A was bedridden and on nasogastric feeding.

## Conclusion

MLC is a rare entity, inherited in an autosomal recessive manner. The classic phenotype presents in the first year of life with macrocephaly, often present at birth. The early development is normal or mildly delayed. Slow deterioration starts in early childhood, and spasticity, extrapyramidal signs and cerebellar signs develop with time. Seizures are often seen,<sup>1</sup> and mental decline usually occurs later in life. By their teens, patients are generally wheelchair-bound. Clinically, there could be other conditions with macrocephaly and bipyramidal signs in differential diagnoses, e.g. Alexander disease, metachromatic leukodystrophy, gangliosidosis or Canavan disease. However, the MRI images are helpful in the differential diagnosis; findings of diffuse white matter abnormalities with swelling and subcortical cysts in the frontal, anterior temporal and parietal regions are diagnostic of MLC. All these abnormalities were noted in the MRI scans of patients A and T, with both having cysts in the frontal and anterior temporal regions. Mutations in the *MLC1* gene have been identified as one of the causes for MLC.<sup>3</sup> Typically, MLC is due to

the biallelic mutation of the *MLC1* gene (75% of all cases). Atypically, MLC occurs due to the biallelic mutation of the *hepaCAM* gene (c. 20% of cases). The management of MLC is currently symptomatic care and physiotherapy, with no definite curative treatment being available. The condition has been reported worldwide; however, this is the first case of siblings from Oman with genetic confirmation of MLC.

## References

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