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**EDİTÖRE MEKTUP / LETTER TO THE EDITOR**

# Coexistence of two rare genetic disorders: cystic fibrosis and megalencephalic leukoencephalopathy with subcortical cysts in a child

## Nadir görülen iki genetik bozukluğun bir arada bulunması: bir çocukta kistik fibroz ve subkortikal kistleri olan megalensefalik lökoensefalopati

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To the Editor,

Cystic fibrosis (CF) is the most common autosomal recessive disease with fatal outcome in Caucasians with a frequency of 1 in 2500 live births. It is caused by mutations in a single gene on the long arm of chromosome 7 encoding a protein called the cystic fibrosis transmembrane regulator (CFTR)[1]. CF is a progressive disease that involves exocrine glands, lungs, gastrointestinal system, pancreas, liver, kidneys and reproductive system. Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an another rare autosomal recessive neurological disorder characterized by macrocephaly, motor and cognitive decline, ataxia, spasticity and occasional seizures. MLC gene locus has been mapped as *MLC 1* gene at chromosome 22q[2]. In literature, there are only a few reliable reports of concomitant diagnosis of CF and other diseases[3,4], whereas, not with MLC. Here we report the case of an Turkish 15-year-old boy with CF and MLC.

A 15-year-old boy presented to the hospital with progressive difficulty in walking since three years. His parents were first-degree relatives. His developmental milestones were mild delayed and a large head size was noted by the parents since childhood. Family history was negative for epilepsy and neurological diseases. He was hospitalized for an uncomplicated pulmonary exacerbation and poor feeding in his early life. Considering the possible diagnosis of CF, sweat chloride was measured by pilocarpin iontophoresis method and found to be 100 mEq/L. His CF diagnosis was confirmed CF genotype ΔF508. He was medically stable until age 12 years. On his examination, head circumference was 59.5 cm which was above the 95th percentile for age. Deep tendon reflexes were hyperactive and there was spasticity in his legs. Planter responses were bilateral extensor. The remainder of the neurological and physical examinations did not reveal abnormalities. Cranial magnetic resonance imaging (MRI) was shown diffuse increased T2 signal of white matter (Figure 1, 2, 3). Diffusion-weighted imaging showed increased diffusion of the affected white matter sparing the corpus callosum and internal capsule. Metabolic investigations including serum and cerebrospinal fluid lactate and pyruvate, serum ammonia, urine organic acids, and lysosomal enzyme analysis revealed no abnormalities. The clinical and radiological findings suggested MLC. To confirm the diagnosis MLC, we analyzed the *MLC1* gene sequencing in the patient, and revealed a novel homozygous p. V303Gfs*76 (c.908-918delinsGCA) mutation.

In literature, coexistence of CF with phenylketonuria, trisomy 21, celiac disease, and were reported3-5. But, coexistence of CF and MLC has not been described before. To our knowledge, this is the first report. MLC is a rare and genetically heterogeneous cerebral white matter disease. Distinctive clinical and imaging features are characterized by macrocephaly detected either at birth or developed within the first year of

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life, often in association with motor developmental delay, ataxia, spasticity, seizures, and extrapyramidal manifestations[2]. The disease is of variable severity in clinical symptoms and disease progression. Most children have delay in walking without support and unstable gait. Brain MRI of diffuse swollen white matter with subcortical cysts in temporal or frontoparietal lobes are the diagnostic hallmarks of the disease.

Mutations in *MLC1* (22q13.33) and GLIALCAM have been identified in patients with MLC[2]. Mutations in *MLC1* account for approximately 75% of the cases. In literature, Topcu et al.[6], Yis et al.[7], and Yüzbaşioğlu et al.[8] have reported mutation in *MLC1* gene from Turkish patients. We have found a novel homozygous p.V303Gfs*76 (c.908-918delinsGCA) mutation in the *MLC1* gene.

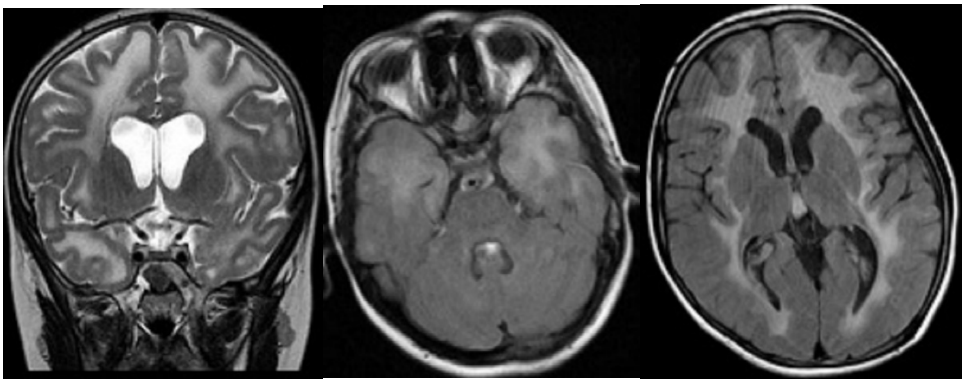

**Figure 1,2,3. Flair and T2-weighted images demonstrate high signal white matter and subcortical cysts in the temporal lobes.**

In conclusion, to date the coexistence of CF and MLC has not been reported, and our patient is the first example of CF and MLC coexistence in the literature. The fact that the chromosomal location of these two diseases are different is well known. In CF, the gene is located on chromosome 7, whereas the gene for MLC is located on the chromosome[22]. We have not observed genetic similarities between CF and MLC syndrome. These diseases have a high incidence in population in which consanguinity is common as in our country. As the two gene loci are not related, it is most likely that two independent mutation events have occurred.

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