

## Case Report

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# Megalencephalic leucoencephalopathy with subcortical cysts: A cause of early seizures after trivial head trauma

Elena Pasini\*; Patrizia Riguzzi; Roberto Michelucci

Unit of Neurology, IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy.

### \*Corresponding Author: Elena Pasini

Unit of Neurology, IRCCS Istituto delle Scienze Neurologiche Via Altura, 3 Bologna, Italy.

Tel: 0039-051-6225368; Email: elena.pasini@isnb.it

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### Abstract

Megalencephalic Leucoencephalopathy with subcortical Cysts (MLC) is a rare autosomal recessive disease with onset in infancy. Typically, the first symptom is macrocephaly which becomes evident in the first year of life [1-3]. After several years, usually within the first decade of life, slowly progressive ataxia, pyramidal signs, mild cognitive impairment and sporadic seizures complete the phenotype. Diagnosis is suggested by the peculiar aspect of brain MRI showing extensive alterations in white matter along with subcortical cysts in temporo-parietal regions [1,3,4] and is confirmed by genetic tests on MLC1 gene [5,6].

The overall prognosis of this condition is dismal, with most patients becoming wheel-chair dependent as teenagers. Due to this invalidating course, most studies of MLC are confined to infancy/childhood but adult cases, although rarely, have been reported [7-12].

At variance with other leucoencephalopathies, epileptic seizures are common in MLC, accounting for about 60% of the patients, but systematic studies of long-term follow-up are lacking [13].

Here we describe two adult sisters with MLC, aged respectively 46 and 43 years, showing recurrent seizures evoked by cranial trauma.

### Case reports

The first-born sister showed macrocephaly since her birth. At the age of 4 years, she had her first tonic clonic seizure after a minor head injury; at the age of 6 years, she had a convulsive status epilepticus preceded by an accidental fall with minor head trauma. Since then she underwent a rapidly progressive psychomotor regression which forced her to wheel-chair at the age of 7. When she was 14, another minor head injury was immediately followed by tonic-clonic seizures and subsequently by progressive pseudobulbar syndrome and tetraplegia. Since the age of 25 years the patient was bedridden. When admitted in our Neurology Unit at the age of 46, neurological examination showed severe cognitive impairment, mutism, spastic

laughing and crying, slow saccades, horizontal nystagmus and spastic tetraplegia. She died at the age of 47 years due to bronchopneumonia.

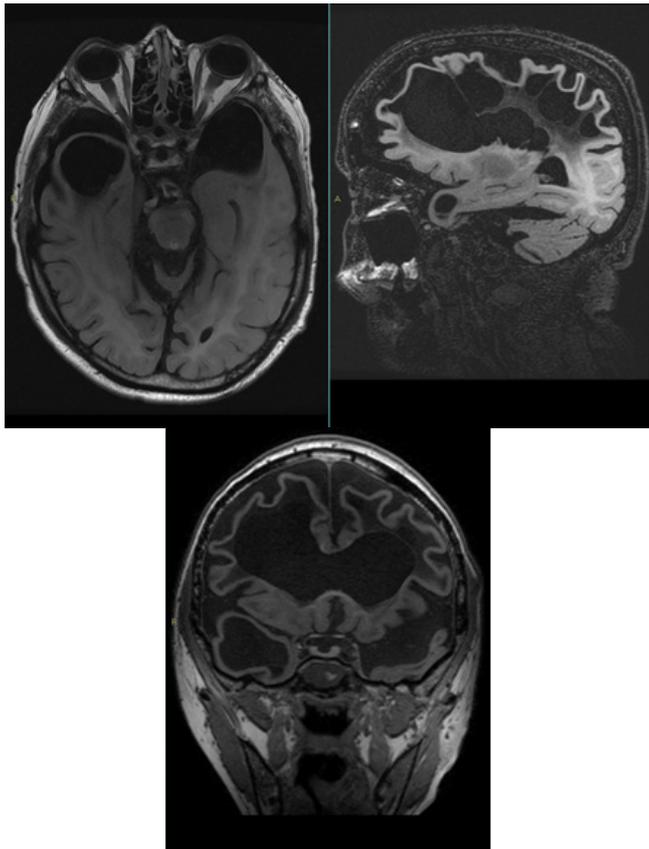
The younger sister manifested macrocephaly since the age of four months and ataxic gait since the age of 2 years. One year later, a minor head trauma was followed by a tonic-clonic seizure. Progressive psychomotor impairment developed over the years causing inability to walk and wheel-chair use since the age of 7 years. A more severe cognitive and neurological decline with emotional lability, mutism, dysphagia and tetraplegia occurred in her forties. When admitted at our Neurology Unit at the age of 43, neurological examination was strictly similar to that of her sister, showing marked cognitive impairment, inability

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ity to speak and understand verbal messages, horizontal nystagmus, spastic crying and laughing, tetraplegia.

Both patients were on chronic treatment with valproate. No abnormalities were found in interictal awake and sleep EEGs aside from diffuse slowing. Cerebral MRI respectively at 46 and 43 years old, showed extensive alterations in white matter and subcortical cysts in fronto-temporo-parietal regions (Figures 1 and 2).

MLC1 gene mutation screening confirmed an homozygous mutation (c.423+1g>a) in both sisters.



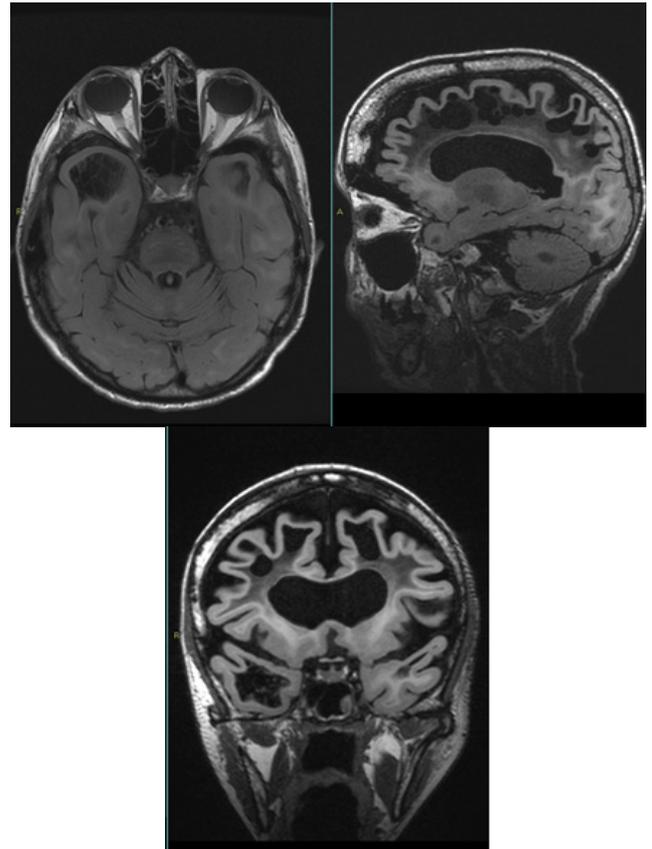
**Figure 1:** Axial T2 FLAIR-Sagittal FLAIR CUBE- Coronal CORE 3D BRAVO.

Cerebral MRI images of the older sister show severe leukoencephalopathy with supratentorial white matter spongiform degeneration. Multiple cystic formations are visible in the frontal, parietal and temporo-polar areas. The U-shaped fibers are involved, and a thin brain cortical mantle remains with swelling of the convolutions. Moderate cerebellar atrophy, marked dilatation of the lateral ventricles, enlargement of subarachnoid spaces of the convexity and cisterns are also observed.

### Discussion

In this paper we describe two adult sisters suffering from MLC and showing the typical phenotype of macrocephaly in the first months of life followed by progressive neurological dysfunction leading to severe psychomotor handicap (with wheelchair dependency since the age of 7 years).

Both sisters had sporadic epileptic seizures, invariably precipitated by minor head trauma. The seizures were apparently generalized tonic-clonic seizures and occurred usually as isolated, sporadic events or in the form of convulsive status epilepticus in one occasion. Interestingly the seizures (especially the



**Figure 2:** Axial T2 FLAIR-Sagittal FLAIR CUBE-Coronal MPR 3D BRAVO.

Cerebral MRI images of the younger sister show a severe, albeit less prominent than the sister, leukoencephalopathy with multiple cystic formations and dilatation of the lateral ventricles. The subarachnoid spaces of the convexity and cisternal spaces are enlarged.

status) heralded an acute or progressive sustained neurological deterioration and seemed to be associated with a more rapid worsening of the condition. At the time of our observation the routine and sleep EEGs were unrevealing.

The analysis of the MLC cases reported in the literature shows that "epilepsy" is a common feature of MLC, occurring in about 60% of cases [13]. The age of onset of epilepsy ranges between 1,5 and 14 years and seizures are mostly generalized tonic-clonic (sometimes with a clear focal onset). Myoclonic, atonic and complex partial seizures have been reported in a few patients [5,14-16]. The seizures are usually sporadic and easily controlled with antiepileptic therapy but cases with refractory seizures and status epilepticus have been described. Interestingly trauma has been recognized as a trigger in 10-50% of the previously reported cases. Most patients show EEG abnormalities, usually in the form of spike or polyspike foci in the parietal, temporal and frontal areas with migratory changes in wakefulness and sleep [13]. Abnormal photo-paroxysmal responses are present in some patients.

Among leucodystrophies and other leucoencephalopathies, the high incidence of epilepsy seems to be a particular feature of MLC [17] and the reason may be related to new insights into the pathogenesis of this condition. Around 75% of patients with MLC are associated with mutations of the gene encoding MLC1, a membrane protein mainly expressed in astrocytes of the CNS

regulating the ion flux and fluid and ion homeostasis [18,19]. The astrocyte dysfunction in turns has been quoted to play a role in epileptogenesis through disrupted astrocyte-neurons relationships, uptake and redistribution of ions and water, and glucose metabolism [20]. Therefore it is possible that astrocyte dysfunction may explain this relatively high incidence of epilepsy in this condition [21].

In addition in our patients seizures were precipitated by minor head trauma. In MLC minor head trauma can induce temporary deterioration, most often with seizure or status epilepticus, prolonged unconsciousness lasting days to months or acute motor deterioration [22-24].

Interestingly a syndrome of early seizures after trivial head trauma has been described in infants, usually in combination with sometimes very severe cerebral oedema ("early seizures and cerebral oedema after trivial head trauma" -ESCEATH) [25]. ESCEATH has been observed in association with CACNA1 S218L mutation, which may also cause, sometimes in the same patients, hemiplegic migraine attacks and comatose episodes after minor head injury [26]. This mutation causes rather dramatic changes in  $Ca_v2.1$   $Ca^{2+}$  channel function by increasing the cellular influx of  $Ca^{2+}$  and leading to enhanced release of neurotransmitters such as glutamate. As a result of this mutation, even weak and otherwise harmless stimuli (such as minor trauma) may readily depolarize  $Ca_v2.1$   $Ca^{2+}$  channels and trigger severe and protracted cytotoxic cerebral oedema and cell loss [27].

Chronic white matter oedema is the essential feature of MLC, caused by a genetic defect in brain ion and water homeostasis and volume regulation by astrocytes. It may be hypothesized that, in this pathological context of astrocyte dysfunction and impaired water homeostasis, even a minor trauma, by impairing the Brain Blood Barrier function, can easily trigger the cascade of events, involving astrocyte signaling, leading to a seizure.

We suggest that early post-traumatic seizures after trivial trauma are a distinctive clinical condition, suggesting the existence of a genetic cause. In detail this entity cannot be regarded as "epilepsy" (defined as recurrence of unprovoked seizures) but rather characterized by situation-related (provoked) seizures, most frequently caused by MLC1 mutations.

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