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# Malformation of cortical development in adult patients

Paolo Tinuper, Giuseppe d'Orsi, Francesca Bisulli, Anna Zaniboni, Antonella Piraccini, Bruno Bernardi, Agostino Baruzzi

Department of Neurological Sciences, University of Bologna, Italy
Radiology Department, Hospital of Faenza, Italy
Neuroradiology Department, Bellaria Hospital, Bologna, Italy

**ABSTRACT –** Few studies have focused on the clinical, neurophysiological and prognostic features of adult epileptic patients with malformation of cortical development. We reviewed the clinical data of a series of sixty adult epileptic patients with different types of malformation of cortical development, who had been followed at the Epilepsy Centre of the Department of Neurological Sciences of the University of Bologna, with particular attention to age at seizure onset, mental retardation, response to therapy, and EEG features. The heterogeneity of our population, especially when divided into the different groups of malformation of cortical development, precluded any general conclusions, but we stress the following aspects: 1) epilepsy due to malformation of cortical development may begin in adolescents and young adults; 2) epileptic seizures with clinical and polygraphic features of infantile spasms may persist into adulthood; 3) complex cortical malformation is not necessarily associated with severe epileptic encephalopathy. In periventricular nodular heterotopias, the largest in our series (nine patients), age at onset of seizures, response to therapy and mental deterioration differed according to the presence of nodules confined to the ventricular wall ('pure' form) or periventricular nodules associated with other cerebral cortical malformations ('plus' form).

***KEY WORDS:*** malformation of cortical development, adult epilepsy, adult onset, periventricular nodular heterotopia, prognosis

## Introduction

Malformation of cortical development (MCD) is a common cause of epilepsy [1]. Until the introduction of new imaging techniques, in particular magnetic resonance imaging (MRI), MCD was revealed in pathology specimens from cortical resection in patients undergoing surgery. MRI has brought tremendous insights to our knowledge of abnormal cortical lesions and has facilitated the diagnosis of MCD in the usual diagnostic work-up of epileptic patients.

However, as the onset of most of the epilepsies due to MCD occurs in the first years of life or in childhood, few studies have focused on adult series [2, 3].

This paper reviews our series of adult MCD patients, and comments on a few aspects of epilepsy due to MCD.

## Patients and methods

We reviewed a series of 60 patients with MCD, who had been followed in recent years at the Epilepsy Centre of

**Correspondence:**
Paolo Tinuper,
Dipartimento di Scienze Neurologiche,
Università di Bologna,
Via Ugo Foscolo 7,
40123 Bologna, Italy.
Phone: + 39 051 585158
Fax: + 39 051 6442165
E-mail: tinuper@neuro.unibo.it

the Department of Neurological Sciences of the University of Bologna. The MR images were obtained with a 0.5 or 1.5 Tesla system, with axial, coronal and sagittal T1 and T2 weighted images, completed with inversion recovery, proton density and flair sequences.

The patients were classified according to Barkovich *et al.* [4] *(figure 1)*. We found 21 patients with a cellular proliferation disorder (eight tuberous sclerosis, nine focal dysplasia, three dysembryoplastic neuroepithelial tumor, one ganglioglioma). Seventeen patients had a neuronal migration disorder (nine periventricular nodular heterotopias, three subcortical heterotopias, five lissencephaly-pachygyria) and five had a disorder of cortical organisation (four polymicrogyrias, one schizenchephaly).

Five patients presented with a complex malformation suggesting disorders in different stages of cortical development. Twelve patients could not be classified because of incomplete clinical or radiological data.

We reviewed the clinical data, in particular age at seizure onset and mental retardation. Depending on response to therapy, we divided patients into drug-resistant (DR), i.e. patients with uncontrolled seizures despite all clinical trials, and non-drug-resistant, i.e. patients with complete or at least satisfactory seizure control *(table 1)*.

**Table 1. Clinical features in 60 patients with CMD.**

| | Proliferations abnormalities | Migration abnormalities | Organization abnormalities |
|---|---|---|---|
| | 21 pts | 17 pts | 5 pts |
| Age | 34 yrs (14-60 yrs) | 34 yrs (13-60 yrs) | 39 yrs (27-53 yrs) |
| Age at epilepsy onset | 7,5 yrs (1 m-42 yrs) | 12 yrs (9 m-33 yrs) | 10 yrs (1-17 yrs) |
| • DR | 10 | 7 | 3 |
| Age at epilepsy onset | 8 yrs (1 m-42 yrs) | 8 yrs (9 m-24 yrs) | 8 yrs (1-9 yrs) |
| • NDR | 11 | 10 | 2 |
| Age at epilepsy onset | 8,5 yrs (6 m-26 yrs) | 14,5 yrs (8 m-33 yrs) | 16,5 yrs (16-17 yrs) |
| • Mental Deficit | 7 (6 DR) | 6 (4 DR) | 2 (1 DR) |
| Age at epilepsy onset | 2 yrs (1 m-7 yrs) | 4 yrs (9 m-14yrs) | 9 yrs (1-17 yrs) |

**Yrs:** years; **m:** months;
**DR:** drug resistant; **NDR:** non-drug resistant.

EEG tracings were reviewed with particular attention to localised fast activity [5-9], response to intermittent photic

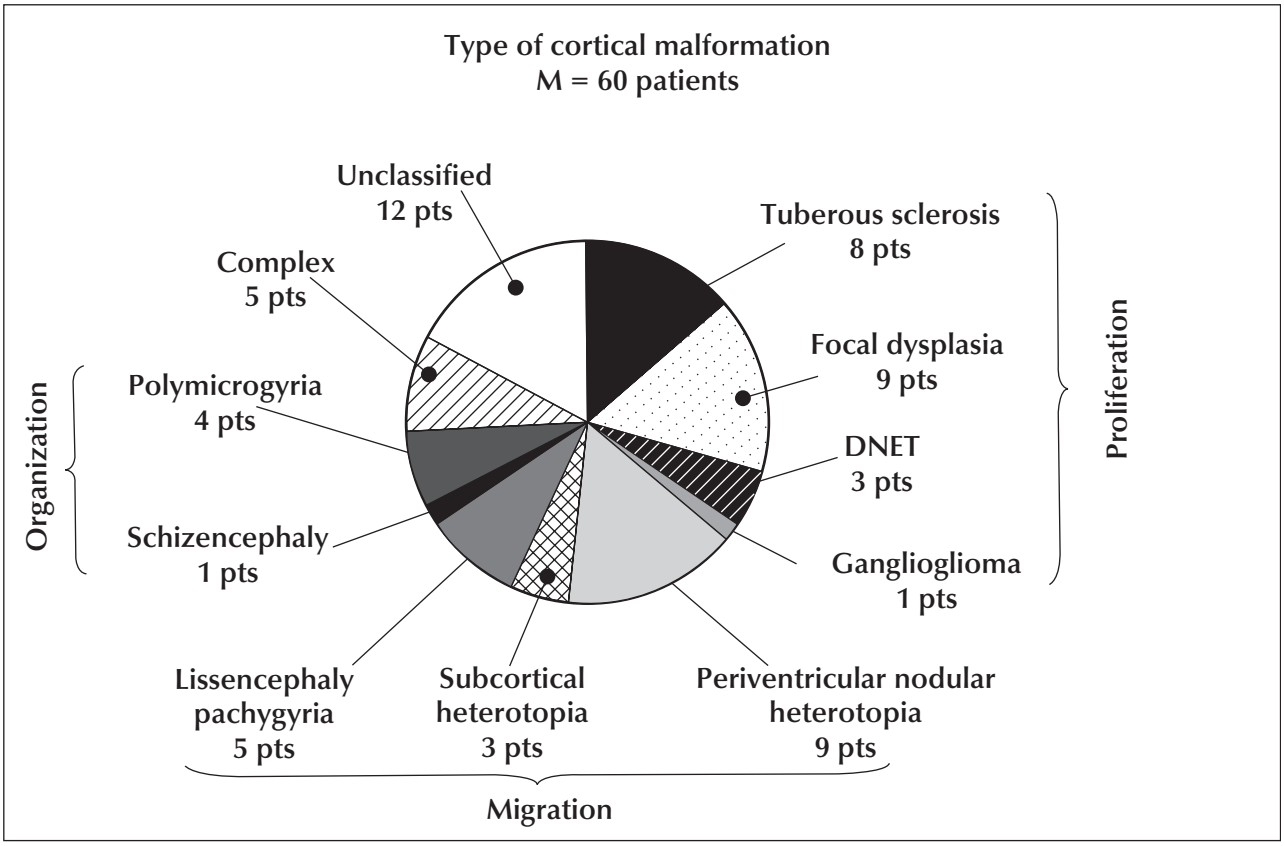


**Figure 1.** *Type of cortical malformation.* Based on Barkovich *et al., Neurology* 2001, with permission.

stimulation [10], paroxysmal abnormalities and any seizures recorded.

## Results and discussion

The relatively small number of patients, particularly when divided into the different classification groups, precluded any general conclusions. However, the following aspects of MCD in adult patients emerged:

1) epilepsy due to MCD may begin in adolescents and young adults;

2) epileptic seizures with the clinical and polygraphic features of infantile spasms may persist into adulthood;

3) complex cortical malformation is not necessarily associated with severe epileptic encephalopathy.

### Epilepsy due to MDC may begin in adolescence or early adulthood.

In our series, seizures started at any age *(table 1)*, independent the stage of cortical development affected. Among our patients with proliferation disorder epilepsy, which usually begins early in life, seizures began at 42 years of age in a woman with a dysembryoplastic neuroepithelial tumour.

In the largest group in our series, i.e. the periventricular nodular heterotopias (9 patients), we studied age at epilepsy onset, response to therapy and presence of mental deterioration according to the MRI findings of nodules confined to the ventricular wall (four patients with a 'pure' form) or periventricular nodules associated with other cerebral cortical malformations (five patients with a 'plus' form). This group of malformations, excluding periventricular nodules, included other concomitant abnormalities (one patient with subcortical heterotopia; two with polymicrogyria; one with focal dysplasia; one with schizencephaly and agenesis of the corpus callosum).

Age at onset differed considerably between the two groups. All the patients with a 'pure' form started having seizures after the age of 15 years, whereas epilepsy began earlier in all the patients with associated malformations ('plus group') *(figure 2)*.

In 'pure' cases, epilepsy was less severe, usually with partial and secondarily generalised seizures, responsive to therapy and with a clinical course characterised by prolonged periods of remission. Mental deterioration was absent and patients could maintain a satisfactory family and professional life.

Evolution was worse in 'plus' patients, with very frequent seizures from the beginning of the disease, failure to control seizures and, in most cases, attacks characterised by sudden falls, which is an ominous prognostic sign [11]. Mental deterioration was always present in these patients.

In 'pure' cases, EEG tracings were characterised by focal interictal discharges, mostly on the temporal areas and on the site of the periventricular nodules. In some cases, EEG was normal.

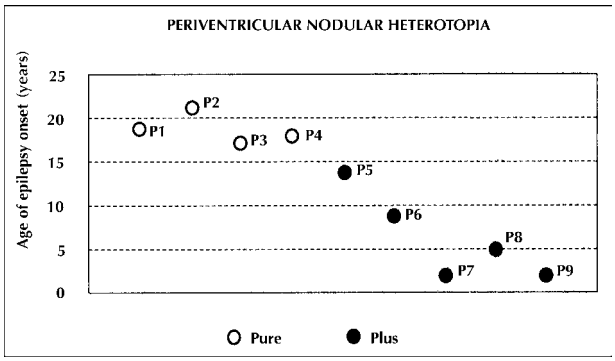


**Figure 2.** *Age at epilepsy onset in nine patients with periventricular nodular heterotopia.*
Pure: pure forms;
Plus: forms associated with other malformations.

In 'plus' cases, the EEG was always pathological, with focal or diffuse paroxysmal abnormalities, slowing of background activity and a strong tendency towards a process of secondary bilateral bisynchrony. In our series, we did not find a paroxysmal response to intermittent photic stimulation, as described by other authors [10].

### Persistence of epileptic spasms in adulthood

Epileptic spasms (ES) are a well described seizure pattern occurring in severe epileptic encephalopathies of childhood, such as West Syndrome [12-16]. They have also been described in neonates and children with MCD [17-23]. We report on three patients with malformation of cortical development in which the epileptic spasms, showing the typical EEG and polygraphic pattern described in children [12-14], persisted into adulthood [24]. Since then we have seen another 28 year-old patient with a complex cortical malformation (polymicrogyria associated with corpus callosum agenesis), who had unmodified spasms until the age of 16 years.

Recently [25], other authors have emphasised the possibility of ES persisting beyond the first years of life. We argue that, in children, evidence of epileptic seizures with the typical features of spasms is relatively easy to find, due to the high frequency of seizures and the possibility of observing the spells directly and, in most cases, recording them with video-polygraphic techniques. Conversely, in adults, anamnestic data on the clinical features of seizures occurring during the first years of life are often difficult to collect, and neurophysiological data are often not available or are incomplete. Moreover, ES in adults tend to be more sporadic, losing the feature of occurrence in periodic sequences or clusters. This makes direct observation and ictal EEG recording more difficult. Therefore, the occurrence of ES in adults may be underestimated.

**Complex cortical malformation is not necessarily associated with severe epileptic encephalopathy**

MCD is usually characterised by early onset of epilepsy, seizures that are frequent and difficult to treat, and mental disability [26-29]. However, some cases have delayed onset and minimal clinical manifestations [2, 3]. In our series of 60 patients, only 15 had a mental deficit (7/21 in MCD due to disturbance in proliferation, 6/17 with migration disorders and 2/5 with organisation abnormalities *(table 1)*. Most of these patients were drug resistant and had early onset epilepsy. On the other hand, we saw patients with good outcome and without mental deficit, despite diffuse and complex malformations.

*Case report*

We report the case of a 43-year-old woman, with normal physical and intellectual milestones who began having seizures at the age of 24 years. Seizures were characterised by a strange feeling of instability, unpleasant smell, without loss of contact. Since, episodes were very frequent (many per day). At the age of 29 years, seizure semeiology changed to a shivering sensation to the right side of her face and arm, followed by a rising gastric sensation and hypoesthesia of the left arm, without loss of contact. Seizures were frequent, despite several drug trials. Neurological examination disclosed slight facial asymmetry, with the left side smaller than the right and slight hyposomia of the left arm. Alopecia was present with an area of a few centimetres, on the right frontal cutis of the head. Intelligence was normal; she worcked as a manager of a restaurant and played piano. Magnetic resonance imaging revealed a complex malformation including partial agenesis of the corpus callosum that communicated with an interhemispheric CSF cyst (colpocephaly aspect), right temporal-parietal-occipital subcortical heterotopia, right fronto-temporal infolding, and hypo-development of the right hippocampus *(figure 3)*. The EEG showed an interictal right temporal focus, without background abnormalities *(figure 4)*. We recorded two seizures characterised by a sudden feeling of shivering in her right face and accompanied by a low amplitude fast discharge on the right temporal leads.

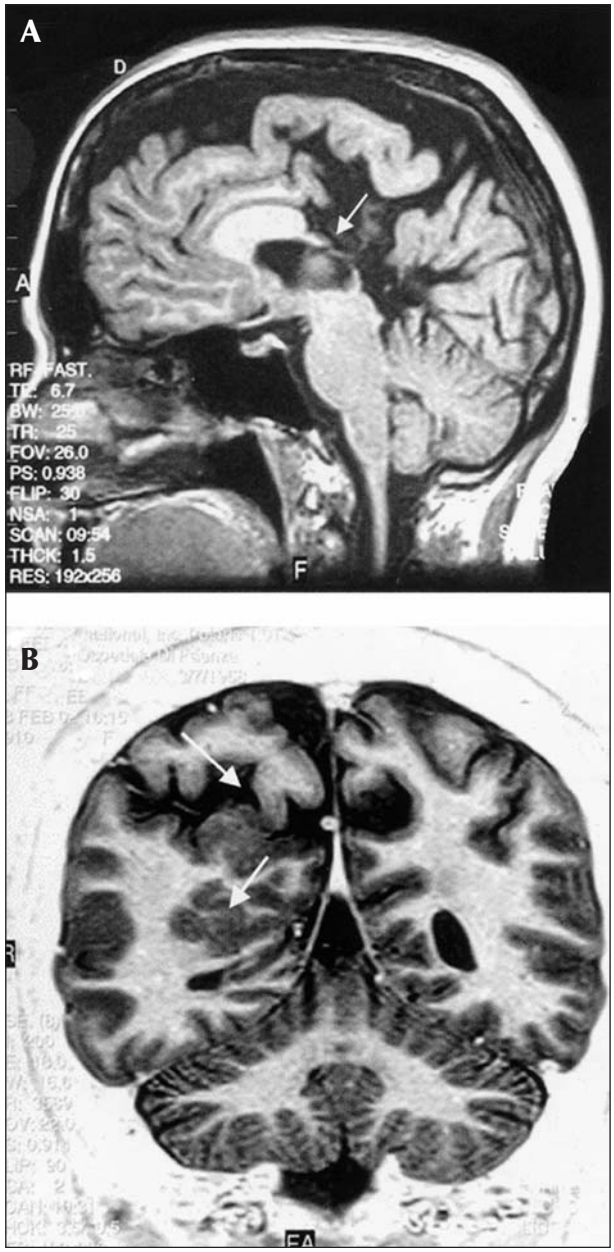


**Figure 3.** *MR imaging in a patient with a complex cortical malformation. a) sagittal plane: partial agenesis of the corpus callosum that communicates with an interhemispheric CSF cyst (colpocephaly aspect); b) coronal plane: right temporal-parietal-occipital subcortical heterotopia with right fronto-temporal infolding.*

## Comments

Before the introduction of MRI techniques, MCD was underestimated and visible only in a neurosurgical setting. Magnetic resonance imaging greatly increased the evidence of MCD *in vivo*. However, in the clinical setting many patients undergo repeated MRI studies without the correct anatomo-clinical hypothesis, and the scans are often performed routinely, i.e. without using the technical sequences appropriate to the search for MCD. For this reason, we believe that MCD in epileptic patients remains underdiagnosed.

On the other hand, when collecting cases with different malformations, or with the same malformation localised in different brain regions, clinical and neurophysiological results may be confusing. Moreover, long term prognostic studies on selected populations are rare, especially in adults.

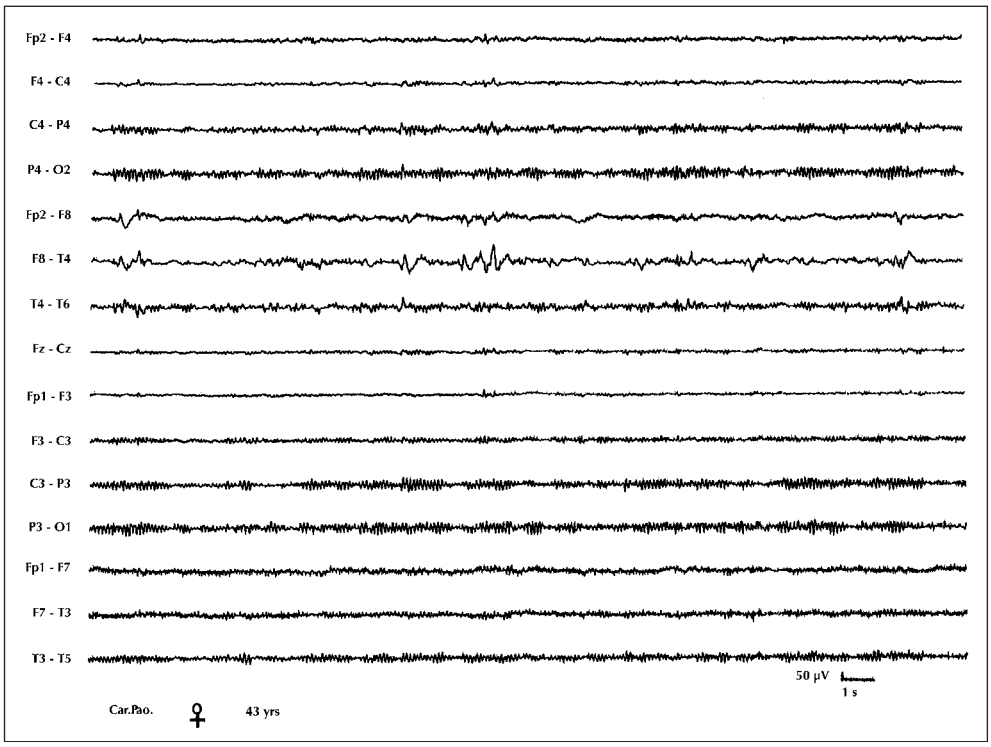


**Figure 4.** *Interictal EEG recording shows irregular background activity and epileptic abnormalities on the right temporal regions.*

An effort must be made to collect homogeneous patient cohorts (presenting with the same type of MCD) to better characterise the clinical profile. □

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