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CASO CLÍNICO

Double cortex syndrome: case report

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ABSTRACT

The disturbances of neural migration (cortical dysplasias) are a group of relatively rare diseases of the central nervous system. Among the diffuse or generalized forms, the Double Cortex Syndrome (DCS) is on the other side of severity. We report the case of a 14 year-old female patient, with a hard control epilepsy. In the Cranial Magnetic Resonance (CMR), a continuous lamina of neurons was noted in a subcortical situation. This lamina was separated from the suprajacent cortex by an organized white matter, which is compatible with a double cortex configuration. The migration disturbances are caused by interferences in the activity between neuroblast and glial fibra, or with neuroblastic movimentation through glial fibra during central nervous tissue's maturation. Symptoms vary from normal to a severe growth disturbance or mental retardation. Almost all patients course with epilepsy, which begins in childhood. The DCS diagnosis is made by characteristic pictures in Magnetic Resonance (MR). The EEG alterations are extremely variable. Functional Magnetic Resonance is useful in the investigation of the double cortex role in the normal cerebral functioning. Some patients give a good response with antiepileptic medication. Surgical treatment is controversial.

Key words: Cortical dysplasias, double cortex syndrome, epilepsy.

El síndrome de la doble corteza: reporte de un caso

RESUMEN

Los trastornos de la migración neural (displasias corticales) son un grupo de enfermedades relativamente raras del sistema nervioso central. Entre las formas difusas o generalizadas, el síndrome de la doble corteza (SDC) se halla en el lado extremo de la severidad. Reportamos el caso de una paciente de 14 años con epilepsia de difícil control. En la Resonancia Magnética de cráneo, se aprecia una lámina continua de neuronas en una situación subcortical. Esta lámina fue separada de la corteza suprayacente por una organizada materia blanca, que es compatible con una configuración de doble corteza. Los trastornos de la migración son causados por interferencias en la actividad entre el neuroblasto y la fibra glial, o con movimiento neuroblástico a través de la fibra glial durante la maduración del tejido nervioso central. Los síntomas varían desde normal hasta un trastorno severo del crecimiento o retardo mental. Casi todos los pacientes cursan con epilepsia, la cual empieza en la niñez. El diagnóstico del síndrome de la Doble Corteza se realiza mediante imágenes características de Resonancia Magnética (RM). Las alteraciones del electroencefalograma (EEG) son extremadamente variables. La Resonancia Magnética funcional es útil en la investigación del papel de la doble corteza en el funcionamiento cerebral normal. Algunos pacientes responden bien a la medicación con antiepilépticos. El tratamiento quirúrgico se presta a controversias.

Palabras clave: *Displasias corticales, síndrome de la doble corteza, epilepsia.*

INTRODUCTION

The neural migration (cortical dysplasias) disturbances can be defined as macroscopic or microscopic alterations of the cortical architecture, and/or of the relations between the cerebral cortex and the white subcortical matter.[1] They are a group of the central nervous system (CNS)'s relatively rare diseases, classified in lateralized and diffuse cortical dysplasias.[2,3] Among the diffuse or generalized forms, the Double Cortex Syndrome (or subcortical laminar heterotrophy) is placed in the opposing extreme of severity. This malformation is clearly rela-

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ted to, although more benign than, lissencefaly and the diffuse pachygyria.[3]

Many kinds of neuronal migration defects have been found in anatomopathologic examinations since the XIX century.[4] After the arrival of the Nuclear Magnetic Resonance (NMR) the DCS has been diagnosed in life. The NMR provides a good outline of the anatomic details and in the differentiation between the white and gray matters. It is, therefore, the ideal instrument to diagnose and distinguish the different cortical dysplasias.

In the present study, the case of a young female patient with DCS clinicoradiologic diagnosis is related.

CASE REPORT

A 14-year-old female patient, illiterate, born in Salvador-Bahia, Brazil. She was taken by her parents to the Neurology and Neurosurgery Foundation at Brain Institute, situated in Salvador, capital of the state of Bahia, Brazil, for a neurological evaluation due to a hard control epilepsy picture.

From the age of seven years old on, complex generalized and partial tonic-clonic convulsive crises began to occur during sleep. At the same time, the girl gradually presented intellectual deterioration, stopping studying before becoming literate. The convulsive crises changed their character little by little during the years. At the moment, the atonic crisis predominates. During this period, she made use of many anticonvulsivants like fenobarbital, valproic acid and gabapendine associated to fenitoine, in spite of the fact that any of them could control the crisis. At this time, she is making use of carbamazepine and clobazam, presenting satisfactory control of the crisis.

The parents reported that there were not any problems during the girl's labour and that she had a normal pattern of neuropsicomotor development. In relation to the previous pathologies, the occurrence of childhood viruses (measles, varicella and parotiditis) was notified. Any other morbid process and previous surgeries were denied. Besides, there is familiar history of epilepsy.

At the segmentary examination, she didn't show any alterations. At the neurologic one, the girl obtained only seven points at the mental state miniexam. The other parameters were normal.

The first eletroencephalogram (EEG), taken in 2/12/96, revealed paroxystic activity with slow waves of 4 to 6 Hz as the basis rhythm. The second EEG, obtained in 26/05/97 after the use of carbamazepine and partial control of the crisis, showed irregular slow waves' activity with low amplitude of 4 to 5 Hz.

The radiographies of the cranium didn't identify abnormalities. In the NMR of the cranium, a continuous lamina of neurons localized in subcortical situation was noted, apart from the suprajacent cortex by a well organized white matter, compatible with a configuration in double cortex *(Figures 1, 2, 3).*

DISCUSSION

The formation of the cerebral cortex is initiated with the proliferation of glial and neuroblast elements in the preventricular germinative matrix. This process of cellular proliferation begins between the fourth and sixth week of embrionary life, and continues during the migratory phase, which starts two weeks after that.[5-7] This last stage stands until the twentieth and twenty-fourth weeks of gestation, or, according to some authors, the migratory process may even occur until the first months of post-birth life.[3] The neuroblasts migrate centrifugally-joined to the glial processes of the germinative matrix as far as the subpial region.[5-7] The migrational disorders are provoked by interferences with the glial neuroblast-fibra affinity, or with the neuroblastic movimentation along the glial fibras. These interferences commonly lead to neurons persistence in heterotopic position, varying from subcortical nodular heterotopias until more diffuse heterotopias, including the double cortex.[8]

In reference to etiology, experimental studies have evidenced that physical (radiations) and chemical (drugs and alcohol) interferences in the initial embrionary period may lead to disorders in the formation of the cerebral cortex.[5,8-13] In a study realized by Palmini et al., gestational histories pre and post-birth of patients with hard control epilepsy associated to cortical dysplasia were compared to those of patients with hard control epilepsy due to other etiologies. It was observed that the pre-birth events potentially prejudicial to the embrionary development in the first tri-

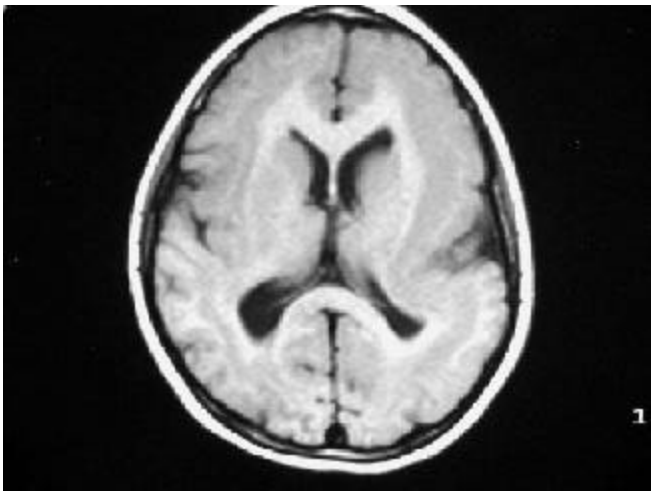

Figure 1.

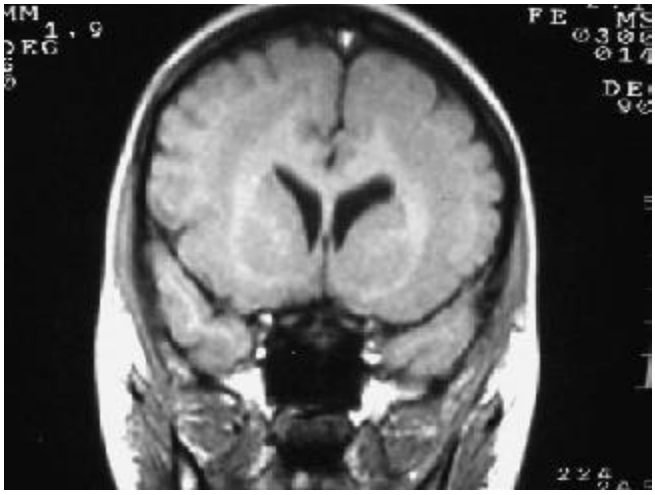

Figure 2.

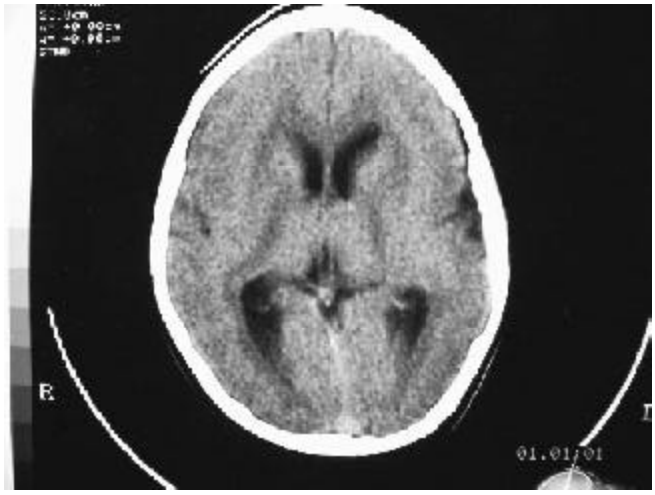

Figure 3.

mester, such as physical trauma, medication ingestion, exposition to X-rays, infections, metabolic alterations or anomalies in the uterine anatomy, were present in the gestational history of 58% of the patients with cortical dysplasia against only 15% of those without dysplasia ($p = 0.0002$).[14] The failure in neural migration that causes the DCS can occur between the 13th and 16th week of gestation. In the present report, there wasn't any significant event observed during this period.

Some patients with DCS have mutation of the 17p13.3 (*LIS1*) or Xq22.3-q23 (*DCX or XLIS*) chromosome.[15] In patients with mutation of the *LIS1*, the parietal and occipital cortex are more severely affected, whereas in patients with mutation in the *XLIS*, the frontal cortex is more endangered.[16] The evidence suggests that the doublecortin, protein produced by the gene *XLIS*, works as a critical intracellular signalizing molecule for the migration of the developing neurons.[17] In general, the DCS is found exclusively in women, for the *XLIS* gene is located in the X chromosome. Men with mutation in the gene related to the disease frequently die in the uterus or show much more severe cerebral abnormality.[15] Male patients in whom all the neuroblasts have abnormal X chromosomes tend to manifest complete lissencefaly. There are few reports of men with DCS; in these patients the genetic mutation allows some residual protean function, existing normal migration of some neuroblasts.[18] Pinard, et al.[19] reported two families and studied a third one in which the mother had DCS and the daughters showed similar heterotopias, while the sons showed lissencefaly. This suggests a straight relation between these two forms of defeat in the neural migration. In the present report, there wasn't familiar history of cortical dysplasias.

As for the clinical manifestations, the symptoms vary from normal to a severe disturbance of development or mental retardation.[14,15] The severity of the clinical involvement is directly related to the thickness of the heterotopic band. Practically all patients course with epilepsy, which begins in childhood. The most common crises are partial complex and atypical absence crises. Some patients that suffer in a more severe way can present crises of sudden falls to the ground (drop attacks).[15] It seems that the gravity of the clinical involvement can vary with the patient's epileptic syndrome. Therefore, the patients with Lennox-Gastaut syndrome have the worst prognosis of low intelligence.[20] The patient of this report showed a clinical picture of mental retardation and generalized and partial complex tonic-clonic convulsive crisis during sleep.

The improvement of the investigation techniques by image, obtained through NMR from its start 15 years ago, allowed more frequent diagnoses of heterotopias.[2,15] Since then, reports of many types of heterotopias and their clinical manifestations have been appearing in the literature.[21-28] The DCS's diagnosis is made by characteristic findings in NMR. A layer of peripheric plain gray matter is seen in a parallel situation with the ventricle, separated from the cortex and the ventricle by white matter.[21] The upper cortex vary from an almost normal shape (with normal thick-ness and quite superficial sulci) to a complete or almost complete agyria. Because of the importance of the NMR in this pathology, the DCS can be considered as a clinicoradiological entity. The case reported showed an NMR of the cranium with a continuous lamina of neurons placed in a subcortical situation, separated from the suprajacent cortex by well organized white matter, which is compatible with a double cortex configuration.

Histologic studies show that the heterotopic band doesn't constitute a second cortex, since the physio-

logic standard of horizontal layers hasn't been found.[15] The EEG alterations are extremely variable: from normal basis rhythm, associated to focal or multifocal epileptogenic discharges, up to diffuse lentification and slow point-wave complexes, generalized and synchronic. Morel et al.[29] showed that there is an electrophysiologic activity in the subcortical heterotopic band. This activity was registered by deep electrodes during epilepsy's surgery. The electrogenic patterns showed were similar to the upper cortical surface. Beyond this, the heterotopic neurons generated *spikes* and slow waves, independent from the epileptic activity of the adjacent normal cortex. This suggests that the heterotopic band has an independent functional activity.[29] The Positron Emission Tomography (PET) at Double Cortex presents similar or more elevated levels of glucose as compared to the normal cortex.

The Functional Magnetic Resonance (FMR) is useful in the investigation of patterns of motor activity at the double cortex. It can show the activation of the subcortical heterotopic tissue and the adjacent normal cortex. This way, the double cortex' dysgenic tissue can play a part in the normal cerebral functioning, in spite of its epileptogenic activity.[30] The cerebral regions recruited during the motor stimulus include dysgenetic or heterotopic zones and a suprajacent motor cortical area similar to that stimulated in normal patients.[31] Another observation with front-parietal heterotopia and upper cortical dysplasia also suggests a compensatory cortical reorganization. A wide zone of cortical dysgenesis and heterotopia presents normal sensorial or motor function in spite of the alteration in the cortical metabolism and in the cytoarchitectonic organization.[32] These results suggest that the involvement of the heterotopic tissue during the motor function's test can be analogous to the normal cortex. In experimental models of DC in rats, the heterotopic neurons of the somatosensorial region have afferent or efferent conexions with the ventral-basal thalamic complex, beyond projections to the *corpus callosum* of the contralateral homotopic cortex and efference with the contralateral corticospinal tract, similar to the normal neocortex.[33] These conexions can allow a "physiologic" activity of the heterotopic band.[30]

As far as the treatment is concerned, some patients give a good response with antiepileptic medication. The focal or lateralized cortical dysplasias deserve attention as to the option of doing surgical treatment. A degree of predominance of epileptic abnormalities in a hemisphere or in another area was found in some individuals. However, this is not enough to suggest a surgical resection.[4] The patient of this report has been doing well with the therapheutic prescribed: carbamazepine and clobazan.

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