Temporal lobe epilepsy due to type IIIa dysplasia. What do we know about this disease?

Epilepsia del lóbulo temporal por displasia tipo IIIa. ¿Qué sabemos de esta entidad?

Abstract

In this article we analyze whether there are clinical, radiological and histological findings of temporal lobe epilepsy caused by focal cortical dysplasia type IIIa and with these contribute to its clinical diagnosis. We performed a search in Pubmed and Medline with the following Mesh terms: dysplasia type IIIa, dysplasia type I, dysplasia type I and temporal lobe epilepsy, hippocampal sclerosis and dysplasia type I, reelin, filtered from 2010 to 2017. We considered letters to the editors, clinical observations, descriptive studies, cases and controls, prospective or retrospective studies, but in which the histological studies were published. We found that mesial temporal lobe epilepsy caused by focal cortical dysplasia type IIIa may be a specific disease with its own clinical, radiological findings and prognostic features. Perhaps it better individualization will depend on the contributions of molecular studies aiming to studying the impact of cell signaling pathway abnormalities, which would determine, both the death of hippocampal neurons and the dispersion of the dentate gyrus cells as well as the abnormal neuronal migration with the consequent cortical dislamination, abnormal neurons polarization and final position.

Keywords

Malformation of cortical development, cortical dysplasia, Epilepsy, Temporal Lobe, hippocampal Sclerosis, reelin protein.
Resumen

En este artículo se analiza si existen características clínicas, imagenológicas e histológicas de la epilepsia del lóbulo temporal causada por displasia tipo IIIa y con ello contribuir a incrementar su sospecha clínica. Realizamos una búsqueda en Pubmed y Medline con los siguientes descriptores, Mesh: displasia tipo IIIa, displasia tipo I, displasia tipo I y epilepsia del Lóbulo temporal, esclerosis del hipocampo y displasia tipo I, reelin desde el 2010 hasta el 2017. Se consideraron cartas al editor, comentarios clínicos, estudios descriptivos, casos y controles, prospectivos o retrospectivos, los estudios deberían contener un reporte patológico. Las crisis en pacientes con displasia tipo IIIa debutan en la segunda década de la vida, con frecuencia existen antecedentes de crisis febriles, los estudios de IRM muestran una pobre diferenciación de la interfase sustancia gris sustancia blanca, ausencia de banda de sustancia blanca que separa la amigdala de la corteza entorrinal y los estudios histológicos muestran pérdida de la normal laminación cortical de las capas II, III y IV, con agrupaciones de neuronas heterotópicas en sustancia blanca. Estos hallazgos permiten considerarla una entidad nosológica con identidad propia. Aunque su mejor caracterización dependerá de los aportes de los estudios moleculares encaminados a estudiar el impacto de las vías de señalización celular, que determinan por una parte, la muerte de neuronas hipocampales y la dispersión del giro dentado y por otra, las alteraciones en la migración neuronal y de la estructura de la neocorteza.

Palabras clave
Malformación del desarrollo cortical, displasia cortical, epilepsia, lóbulo temporal, esclerosis hipocampal, proteína reelin.

Corresponding author:
René Andrade-Machado.
Neurólogo-Epileptólogo, Neuroclínica SA.
Programa de doctorado en Ciencias de La Salud, área de Profundización Neuropatología, Universidad CES, Cl. 10 #22-04, Medellín, Antioquia, Colombia.
Phone: +57 4 4440555.
E-mail: reneandrade1970@yahoo.es
Introduction

Focal cortical dysplasia (FCD) is characterized by disorganization and structural alteration of the cerebral cortex due to alterations in cell proliferation, differentiation, and migration during cortical development. Its presence is associated with a high risk of drug-resistant epilepsy in children and adults and postsurgical relapses. FCD can appear at any location in the neocortex. It used to be classified as a dual pathology when located specifically in the temporal lobe, which occurred in about 50% of patients with hippocampal sclerosis (HS). The clinical importance of this association led to the introduction of the term FCD type IIIa in the International League Against Epilepsy’s (ILAE) latest revision of the FCD classification.

Dysplasia type IIIa is known as mesial temporal sclerosis, defined as neuronal loss and gliosis in the hippocampus associated with irregularities of the temporal cortical lamination and the presence of neurons with neurofilament protein accumulation in layers II, III, and IV, called hypertrophic neurons. However, the causal relationship between FCD and HS remains unknown, as well as the etiopathogenesis.

We have not found any review that shows the clinical, imaging, and electrographic characteristics or a pathogenic approach of this disease. Are there clinical, electroencephalographic, or imaging elements that could make us suspect the presence of dysplasia type IIIa and determine what we know of its pathogenesis? Answering this question could have an impact on the decisions of the epilepsy surgery groups, on the recognition of the disease, and on the approach of molecular studies aimed at finding markers of the disease or new therapeutic targets.

Methodology

A PubMed and Medline search was performed with the following descriptors:

Mesh: dysplasia type IIIa, dysplasia type I, dysplasia type I and temporal lobe epilepsy, hippocampal sclerosis, dysplasia type I and reelin. Published in English or Spanish in the years from 2010 to 2017 due to the fact that the ILAE classification proposal was published in 2010. We did not limit the type of article, we considered letters to the editor, clinical comments, descriptive studies, cases and controls, prospective and retrospective, as long as the histological results were published. Duplicate cases were excluded.

The results of the search can be seen in Figure 1.

Temporal lobe epilepsy caused by dysplasia type IIIa

Frequency

FCD type IIIa is a disorder whose frequency is yet to be defined. The study by Jiang Wu et al. reported that FCD type IIIa was present in 60.8% of patients. Laura Tassi et al. found in 2010 that 69% of patients had this type of dysplasia. The frequency of dysplasia type IIIa does not seem to be as high as initially thought but is present around 16% of cases. This is because the histological criteria are not yet well defined. This wide range in frequency could also depend on the lack of clinical suspicion, the absence of reliable markers, and the inherent biases of retrospective studies.

Onset age

FCD type IIIa is expressed by epileptic seizures with a greater incidence in the second decade of life. Its mean evolution time is 19.2 years [median 17 years with a range between one year and 50 years of age]. This time is significantly longer than the time of evolution of isolated FCD crises but earlier than FCD type IIIc [median 31, range 4-46]. Figure 2 is constructed from the descriptions.
of several studies which compared the time of evolution of epilepsies associated with different types of dysplasia.\textsuperscript{3,6–9} We know that the time of evolution depends on the moment in which the patients were operated on. This could depend on whether they are pediatric series or adult patients. This differentiation was only possible after the implementation of the new classification of cortical dysplasias. So we could point out that studies published on mesial temporal lobe epilepsy (MTLE) evaluating the presence of associated cortical dysplasia prior to this classification would have the bias of evaluating the natural history of epilepsy caused by HS, including cases in which there might have also been patients who suffered dysplasia type IIIa.

### Onset of epilepsy

Epilepsy in patients with FCD type IIIa debuts at 7.8 years [median 6.5, range 1-24], which is significantly shorter than that of patients with isolated FCD. In the case of patients with dysplasia type IIIb, the debut is 3.5 years [median 2.0, range 1-10], which is even shorter than the epilepsy debut of FCD subtypes IIIa, IIIc, and IIId.\textsuperscript{3} This may be an index of suspicion of the syndrome, although more prospective studies are needed to consider this a key element in the diagnosis. We hope that, with the application of this classification, the next studies will provide data that will allow us to draw conclusions in this regard.

### Crisis frequency

The mean frequency of seizures before surgery is 17.7 per month [median 10.0, range 1-330], which is not significantly different from those occurring in isolated FCD or types III b, c, and d.\textsuperscript{3}

### History of febrile seizures

The history of febrile seizures is present in 19.5% of patients with FCD type IIIa. This is significantly more frequent than the other subtypes of FCD of the temporal lobe (IIib, IIic, and IIId). Data from Tassi L. et al. suggest that patients with FCD are more prone to febrile seizures than other patients and that the highest prevalence of febrile seizures is found in patients with FCD type I at 48%.\textsuperscript{4}

A recent study in patients with temporal lobe sclerosis shows that febrile seizures occur in 73%
of patients, compared to 36% of patients without sclerosis of the temporal lobe. The study by Faucer et al. also documented that the history of febrile seizures is more frequent in patients with FCD type IIIa than in other types of temporal lobe epilepsy. In the study by Jian Wu et al. the data showed that febrile seizures occurred in 36% of the cohort and that they were significantly more frequent in FCD type IIIa than in other subtypes, which supports the results of previous studies and suggests that there is a high susceptibility to the occurrence of febrile seizures in this type of epilepsy.

Thus, FCD type IIIa could occur during postnatal development and the maturation period. It is yet to be determined if FCD Type IIIa is a pathology acquired from a main lesion or a different pathological entity, however, clinical studies seem to delimit that it exists as an entity of its own. In addition, the association with febrile seizures could suggest the need for a second factor for its definitive development. However, this relationship will have to be defined in prospective studies and, at present, we do not have elements to support or refute this theory.

Family history

Only one study has been published of siblings from a family with epilepsy who developed a similar clinical, electroencephalographic, and histological picture and had FCD type IIIa. The authors described two siblings with MTLE caused by FCD type IIIa. There was a family history of epilepsy (in cousins and the maternal grandmother), and their mother had suffered from febrile seizures in childhood. These patients also had febrile seizures. They developed epilepsy in the second decade of life characterized by having crisis with initial awareness with autonomic, sensory (olfactory or gustatory), and emotional phenomena, followed...
by automatisms, asymmetric tonic postures, and focal clonias affecting the muscles of the face and hand. In both, the epilepsy was drug-resistant, had HS, and effaced the delineation of the gray-white substance interface in the temporal lobe according to the results of the MRI. PET scan showed temporary hypometabolism. Both patients underwent anterior temporal lobectomy and the biopsy showed FCD type Ib associated with HS [dysplasia type IIIa]. This description suggests that there may be a family component in cases of FCD type IIIa.11

Pathogeny
In a study conducted by Gianluca Marucci et al. of 30 patients with drug-resistant MTLE [11 men, 19 women] who underwent antero-mesial lobectomy at the Bellaria Hospital in Bologna, it was shown that in all cases, alterations of the organization and cytoarchitecture of the cortical layers associated with HS were present. Of the 30 patients studied, 8 had FCD type IIIa without granule cell dispersion in the dentate gyrus (GCD), 7 had HS and GCD type 1, and 15 had FCD type IIIa and GCD type 2. In the first group, FCD type IIIa without GCD, 53.3% of the neurons of the temporal cortex showed reelin mRNA and in the hippocampus 86.6%. In contrast, in the second group, HS and GCD, only 20% of the cortical cells were positive for reelin mRNA and only 13.4% in the hippocampus.12

The study by Gianluca Marucci et al. showed that a global decrease in reelin mRNA is associated with the dispersion of the granular cells of the dentate gyrus in patients with MTLE caused by FCD IIIa.12 This is due to finding an inverse correlation between the number of cells expressing reelin mRNA in the dentate gyrus and the degree of its dispersion of cells. This study suggests that reelin deficiency in adulthood could lead to cortical structural reorganization. This reorganization could include an increase in the migratory activity of the neurons and of the aberrant plasticity of their dendritic processes, thus the reelin appears to be involved in the maintenance of the architecture in the mature brain.12 Therefore, reelin could play an important role in the remodeling of the hippocampus during hippocampal sclerosis [HS] and in the stability of the cortical architecture, which may be related to the presence of FCD type IIIa.12

Another important finding from the histological point of view in patients with FCD type IIIa is the presence of lentiform heterotopias. The possible implication of reelin in this finding comes from the demonstration that reelin is a glycoprotein acting as a stop signal for neuronal migration during brain ontogenesis.2

It has been reported that, in adults, reelin is expressed mainly by GABAergic interneurons and regulates the functioning and composition of the glutamate receptor, which could be associated with alterations in memory present in patients with MTLE by affecting the mechanisms of long-term potentiation mediated by this neurotransmitter.13–15

However, the molecular mechanisms involved in the signaling pathway of reelin, and its relationship to the proteolytic fragments and the clinical, electrophysiological, and histological findings found in patients with MTLE and reelin are still unknown.

Magnetic resonance imaging (mri) studies
In general, it is known that FCD type I is not detected by MRI. However, in a 2012 study with 55 patients with MTLE, Robert Kuba et al. found that patients with FCD type IIIa may have certain subtle alterations in MRI. These alterations can be summarized as the existence of an inadequate delimitation of the gray and white substance, temporal lobe FLAIR hyperintensity, and atrophy of the temporal lobe. These findings showed high inter-observer concordance [Fleiss’ kappa 0.732, p <0.0001] and were seen in 52.4% of patients with FCD type IIIa [ILAE classification].2 These alterations occurred mainly in the temporal pole (Figure 3 shows one of our patients).16

Inadequate delimitation between the amygdala and the adjacent cortex with effacement of the white matter surrounding it have also been described as indirect signs of FCD type IIIa (see arrows in Figure 3, D, E).16
With the advent of new brain imaging techniques, probably with the use of ligands, signaling pathways that have not yet been demonstrated, we may, in the future, perhaps elucidate with greater sensitivity and specificity the presence of dysplasia type IIIa before subjecting the patient to surgical treatment.

**Histological findings**

Architectural abnormalities (histologically equivalent to FCD type I) in the temporal lobe associated with HS are classified as FCD type IIIa, but not as “dual pathology,” according to the current ILA classification of FCD.

Let’s start with the findings in the hippocampi of patients with FCD type IIIa, since those of FCD type Ia, Ib, and Ic will be explained later.

The representative findings can be better observed with NeuN immunohistochemistry in fragments of brain tissue obtained after surgical resection of the hippocampus.

Four types of HS have been defined. HS type 1 shows neuronal loss, almost complete in CA1, moderate to marked in CA4, mild in CA3, sparing the CA2 and subiculum region. The granule cell layer of the dentate gyrus shows both neuronal loss and scattering.

In type 2, what happens is a neuronal loss in CA1 with no loss of the other sectors.

In type 3, neuronal loss is marked in the CA4 sector and other sectors are spared.

A type 4 is accepted in which there is no HS. This subtype does not belong to the histological findings of FCD type IIIa since it shows well-preserved hippocampal neurons.

The temporal cortex in patients with HS can show histological alterations, such as irregular cortical lamination and the presence of hypertrophic neurons outside the V layer of the cerebral cortex. Cortical structural anomalies can be summarized in the following findings: focal blurring of the cortical-white matter junction, unequal cortical thickness, zones of atrophy, and/or thinning of the cortex. A set of subcortical neuronal heterotopias is usually observed. NeuN immunohistochemistry reveals several patterns of abnormal neuronal disposition and stratification in the cerebral cortex, including layers of reduced thickness, predominant vertical columnar structure, and disorganization of the cortical structure. This is evident when comparing the relatively normal hexalaminar structure and normal thickness.

The irregularities of cortical lamination can be radial (which would classify as dysplasia type Ia), tangential (which would classify as dysplasia type Ib), or combined (which would classify as dysplasia type Ic). These alterations are associated with hypertrophic neurons dispersed outside the V layer, but never with dysmorphic neurons or globoid cells.

The following five patterns can be recognized as FCD type IIIa variants. See Figure 4 which represents a diagram of the different types of FCD type IIIa associated with sclerosis of the temporal lobe.

1. HS with architectural abnormalities in the temporal lobe, Figure 4 A
2. HS with TLE and heterotopic neurons in the subcortical white matter, Figure 4 B
3. HS with small “lentiform” heterotopias in the subcortical white matter, Figure 4 C
4. HS with TLE and small “lentiform” heterotopias in the subcortical white matter, Figure 4 D
5. HS with TLE, Figure 4 F

Sclerosis of the temporal lobe expresses severe neuronal loss and laminar gliosis in cortical layers II and III of the cerebral cortex (see Figure 4, the loss of layer II neurons in all cases of temporal lobe sclerosis, compare with normal cortex, figure 4C), with cortical reorganization, as suggested by observing horizontal lines of aberrant myelinated fibers in this area. In fact, TLE can be observed in about 10% of surgical cases of MTLE as an abnormal band of small “granular” neurons grouped outside the cortical layer II.
Figure 3. NMR images showing findings associated with dysplasia type IIIa. Magnetic Resonance 1.5 T of a 38-year-old female patient. A: Coronal section with T2 technique, there is evidence of erasure of the white-gray matter delimitation in the pole of the right temporal lobe. Compare with the contralateral one (see yellow arrow). B: MRI of the same patient. Observe the hyperintensity of the right temporal pole, the white-gray matter interface is not well defined (white arrow). C: Brain PET of the same patient. Observe the marked hypometabolism of the cortex of the right temporal pole. D: FLAIR coronal section showing the typical hyperintensity observed in the hippocampus of patients with hippocampal sclerosis (arrow). E: Shows the subtle loss of a band of white matter that separates the amygdala from the adjacent supra cortex.

Individual heterotopic neurons in subcortical white matter should be considered pathological and significant for heterotopias when their number in the deep white matter is greater than 30/mm. Although its epileptogenic meaning remains to be determined. For practical purposes, immunostaining with NeuN can be useful for estimating the number of heterotopic neurons in the deep white matter. However, reference photographs must be prepared by each laboratory since the actual enlargement of the photographs differs depending on the microscope and the connected digital camera, as well as the distance between the optical lens and the digital camera.

The “lentiform” heterotopias are usually undetectable in MRI and are composed
histologically of projection neurons, and are different from nodular heterotopias which are usually detected by MRI and consist of projection neurons and neurons that form local circuits. Due to the similarity between them and to normal structures such as the claustrum, special care must be taken not to confuse them during the histological examination.\(^2\)

For better interpretation of the histological findings we recommend reviewing the comments and the figures of the articles by Blümcke I et al. and Miyata H et al.\(^2,20\)

**Dysplasia type IIIa and post-surgical prognosis**

Much has been discussed regarding whether the presence of FCD type IIIa is a factor that affects the postoperative outcome. In recent publications, it has been found that patients with MTLE caused by FCD type IIIa may have a poor postoperative prognosis compared with patients with epilepsy and isolated HS.\(^4,21,22\)

There are few studies that have specifically evaluated post-surgical prognosis in relation to crisis-free patients operated with refractory epilepsy caused by dysplasia type IIIa. We did not find studies that investigated the prognosis in relation to the cognitive evolution, memory, and psychiatric complications of these patients.

Regarding the seizure-free postsurgical period, it has been reported that the shorter the time of evolution, the time of follow-up of epilepsy, and
the age at which the patients operate, the better prognosis regarding freedom from seizures.\textsuperscript{23,25} The controversy is mainly because, although histology is taken into account to determine the etiology of epilepsy, the authors rarely take into consideration the histological alterations that underlie the etiology to determine the postoperative prognosis in epilepsy. Therefore, the main author of the ILAE's most recent classification of focal cortical dysplasias has pointed out the urgent need to evaluate the histological subtypes of dysplasias and the cytoarchitectonic alterations of the specimens obtained in epilepsy surgery as possible predictors of postsurgical prognosis in patients undergoing surgery for epilepsy.\textsuperscript{18}

Giulioni opines that other factors he calls “crucial” should be considered to explain the worst postoperative outcome in the group of patients with FCD IIIa, suggesting that the HS subtype and the pathology of the dentate gyrus may play a preponderant role.\textsuperscript{24}

In a study published by Blümcke \textit{et al.}, the HS subtype did not show an influence on postoperative results. Patients with atypical patterns of HS (according to ILAE type 3) and those where mesial structures were not present in the sample did not have a worse postoperative outcome.\textsuperscript{25}

This was corroborated in a recent publication by Giulioni \textit{et al.} where they clearly defined that the isolated HS subtype, compared to the presence of FCD IIIa, did not influence the postoperative outcome. The only patient with FCD IIIa and atypical HS (TLE type 2) was crisis-free after surgery (Engel Ia).\textsuperscript{26}

However, Giulioni \textit{et al.} did find a difference in post-surgical outcome when they considered the presence of granular cell pathology of the dentate gyrus in patients with isolated HS. In this study, the authors did not present data regarding the presence of FCD type IIIa.

It is important to note that in these studies the examination of the hippocampus and presumably the dentate gyrus only took place in the middle region of the hippocampal body.\textsuperscript{24} This may have led to errors in the interpretation since the recent classification of HS proposed by the ILAE points out there can be difficulties classifying the dispersion of the granular cells of the dentate gyrus considering the dispersion can be focal.\textsuperscript{25}

It is also important to note that, when we talk about postoperative prognosis in epilepsy, we should not confine it to the prognosis for the recurrence of epileptic seizures, but we should consider its relationship with cognitive, neuropsychiatric, and behavioral prognosis. In this sense, there are no studies that relate these elements to histology. Neither have the different combinations of FCD, kind of HS (type 1,2,3), and pathology of the dentate gyrus (with double layer, with neuronal migration, or with thinning) been analyzed. Different associations may occur which can relate to different forecasts; this is yet to be determined. The authors of the classification of dysplasias of the ILAE expressed that the dispersion of the granular cells has no clear association with the clinical result.\textsuperscript{2}

The comments of Giulioni \textit{et al.} and Blümcke \textit{et al.} enhance the practical use and the importance of the pathological classification as well as the need for a greater correlation of results in this important area.

In general, it would be worthwhile not only to evaluate the relationship between the histological findings and the likelihood of relapse of the seizures but also to determine the relationship between histological findings and the presence of cognitive deficits and psychiatric complications, even if the neural networks involved in the processing of memory and language of these patients vary when compared with other pathologies of the temporal lobe.
Conclusions

Seizures in patients with dysplasia type IIIa debut in the second decade of life. There is often a history of febrile seizures, MRI studies show a poor differentiation of the gray-white matter interface, absence of white substance band that separates the amygdala from the entorhinal cortex associated with histological studies showing irregularities of cortical lamination of layers II, III, and IV, with groupings of heterotopic neurons in white matter. These findings allow us to consider it a nosological entity with its own identity. Although a better characterization will be favored by the contributions of molecular studies aimed at studying the impact of cell signaling pathways which determine, on the one hand, the death of hippocampal neurons and the dispersion of the dentate gyrus, and on the other hand, alterations in neuronal migration and the structure of the neocortex.

Conflicts of interest
Los autores declaramos que no tenemos conflicto de interés.

Funding sources
Los autores declaramos que no recibimos financiamiento para la realización del artículo.
Temporal lobe epilepsy due to type IIIa dysplasia

References


