Focal Cortical Dysplasia and Generalized Epileptiform Discharges: Case Report and Literature Review

Hanin Algethami1, Vahe Poghosyan2, Eman Baksh3, Majed Alhameed4

ABSTRACT

Background: Focal epilepsy can have a varied etiology, including malformations of cortical development (MCD), that can often be detected by Magnetic Resonance Imaging (MRI). Here we show a distinct characteristic of two forms of MCDs on MRI, with two tight dipole clusters in her MEG magnetoencephalography study, in a patient with electroencephalography (EEG) features of generalized epilepsy. Case report: This is a case presentation of a 20 years old female with epilepsy, found to have upon EMU admission two pathologies (FCD, heterotopia) over the right side near the collateral sulcus, and two tight clusters of dipoles over the right parietal and left temporo-parietal region, with generalized inter ictal discharges in her EEG. FCD is a common etiology of medically intractable seizures and usually in EEG it will show either: pseudo-periodic spikes or rhythmic spikes, poly-spike or repetitive electrographic seizures or a brief discharge of fast rhythmic activity, atypical presentation with generalized epileptiform discharges were rarely reported. Conclusion: The presence of MCD does not preclude a patient from having other types of epilepsy. Generalized epilepsy and focal related epilepsy have a distinct pathophysiology.

Keywords: Epilepsy, focal cortical dysplasia, MRI, EEG, MEG.

1. BACKGROUND

The formation and development of the human cerebral cortex is a very complex process (1), that involves three stages. Any disruption during these three phases can lead to malformations of cortical development (MCD). This concept was first introduced in 1996 (2) and last updated in 2012 (3-5). Focal cortical dysplasia (FCD) is a form of MCD that is considered the second/third-most common etiology of medically intractable seizures in adults and the most common cause of medically refractory epilepsy in the paediatric population (6). It was first described by Taylor et al. in 1971 (7) who found specific microscopic findings, like cortical disorganization, bizarre neurons, and balloon cells in ten drug-resistant epileptic patients.

The classification of such an abnormality was proposed by Palmini in 2004, who described cortical dyslamination as a common characteristic of FCD, regardless of the subtype (8). Furthermore, by 2011, Blumcke et al. recommended a new classification system for FCD (9). Clinically, FCD may involve any part of the brain, can vary in size and location, and is either focal or multifocal (10). So, the clinical presentation depends on these factors. However, the main symptom of dysplasia is epilepsy, usually drug-resistant epilepsy, which sometimes is associated with mental retardation and often involves the temporal lobe (8). FCD may be invisible on MRI, especially in case of type I (11).

The intrinsic epileptogenicity of FCD has characteristic EEG patterns in scalp and intracranial EEG recordings, including: (1) pseudo-periodic spikes or bursts of spikes interrupted by suppression of activity; (2) spikes, poly-spikes and waves with a rhythmic and sub-continuous occurrence and an absence of physiological background; (3) repetitive electrographic seizures with recruiting/de-recruiting of prolonged trains of rhythmic activity; and (4) brief discharges of low-voltage, fast rhythmic activity with regular morphology. These changes are mainly focal at the site of the lesion. In fact, these patterns are characteristic for FCD, but they were also described in Rasmussen encephalitis and dysembrioplastic neuroepithelial tumors (12-18). Magnetoencephalography (MEG) is a non-invasive functional neuroimaging...
technique that helps with surgical planning in patients with intractable epilepsy (19). It can identify irritative zones in MCD lesions, including FCD (20). Our case is unique, rare and different. Patient showed two brain lesions on MRI, and two tight dipole clusters in her MEG study, but with generalized interictal epileptiform discharges (IED) in the EEG. This demonstrates the importance of MRI and MEG in patients with epilepsy as part of their routinely investigations to provide the best management.

2. OBJECTIVE

The aim of this study was to show a distinct characteristic of two forms of MCDs on MRI, with two tight dipole clusters in her MEG magnetoencephalography study, in a patient with electroencephalography (EEG) features of generalized epilepsy.

3. CASE PRESENTATION

Our patient is a 20-year-old female, left-handed, with a known case of epilepsy that was diagnosed 11 years back. Her history started at the age of 9. After being seen in a local hospital and starting treatment, the patient showed improvements with seizure frequency decreasing. The patient was following in a local hospital where her brain MRI was reported as normal. She was admitted to the epilepsy monitoring unit (EMU) in our tertiary hospital few months ago. Her current seizures are focal blurred vision, then head turns to left side, rarely with secondary generalization, which lasts for a few seconds, two to three times per month. No risk factors of epilepsy were recognized and she had unremarkable neonatal, developmental, past medical, and surgical history. She had an unremarkable physical examination.

During the EMU admission, the patient underwent basic laboratory work, including complete blood count, electrolytes, liver and renal function test, thyroid profile, and carbamazepine level, and all were within normal limits. Her long term video EEG showed normal background: 9 Hz bilaterally and symmetrically in the parieto-occipital regions with good reactivity to eye opening and closure. She had normal sleep EEG features in the form of vertex sharp waves, K complexes, and bilaterally symmetric synchronous sleep spindles; however, these were intermixed with frequent runs of moderate-to-high amplitude generalized synchronized spike-poly-spike and slow wave complexes, ranging from 1-4 Hz, lasting from 2 seconds up to 6 seconds, and not associated with a clinical event (Figure 1 and 2). The patient was seen and assessed by a neuropsychology team. Her assessment showed cognitive dysfunctions on tests that rely on the temporal lobe, including short-term memory, working memory, learning and verbal long-term memory tests; however, she scored within normal ranges on
Focal Cortical Dysplasia and Generalized Epileptiform Discharges

4. DISCUSSION

FCD and heterotropia are two pathologies that can occur together or separately and each has its own clinical presentation, neuroimaging findings and pathology. Epilepsy is a common presentation for both. Our patient had these two lesions, with interesting EEG findings in the form of generalized epileptiform discharges. For decades, the epileptogenicity of FCD lesions has always been a curiosity among electroencephalographers and many studies were conducted before, looking for a specific EEG finding in cases with FCD lesions. In 1996, Gambardella et al. compared two groups, group 1 had FCD and group 2 had non dysplastic structural lesions. His main objectives were to examine the frequency and the significance of rhythmic epileptiform discharges (REDs) on the scalp EEGs and to analyzed the relationship of this abnormality to the continuous epileptiform discharges (CEDs) on ECoG. He found that a RED was present in 44% of group 1 and none in group 2, and 80% of patients with RED had CED. Therefore, Gambardella et al. concluded that rhythmic epileptiform discharges and continuous epileptiform discharges are highly specific and sensitive indicators of FCDs, in fact the rhythmic epileptiform discharges were associated with more intermittent interictal spikes involving other regions, but had a greater significance for the localization of the epileptogenic area (14). By 2013, there was another retrospective, descriptive study of 31 patients with FCD type II, that aimed to analyze the patients’ electroclinical features and surgical outcomes. The authors found inter-ictal abnormalities characterized by rhythmic spikes and poly-spike discharges, which increased during sleep in 13 (41.9%) of the 31 patients (15).

Another interesting study that showed similar findings to our patient was done in 2016 in Korea, where they retrospectively reviewed epilepsy patients who presented at the Epilepsy Clinic in Konkuk University Hospital in Seoul, adequate evaluation with epilepsy protocol MRI and EEG were done. Overall, 1315 patients were classified as having partial seizures and 207 patients were classified as having generalized seizures. Five of 207 patients (2.4%) with generalized seizures had potentially epileptogenic lesions, such as FCD and...
Focal Cortical Dysplasia and Generalized Epileptiform Discharges

dysembryoplastic neuroepithelial tumors and their EEG showed generalized 3 to 4 Hz spike-wave complexes, while hyperventilation, photic stimulation, and sleep did not affect the generation of generalized spike-wave. They concluded that the presence of epileptogenic lesions in adult patients with generalized epileptiform discharges can be an incidental finding, and that’s can be explained by the limitations of EEG as it does not show the deeper electro-graphically sources (21).

Our patient experienced her first seizure by 9 years of age, which raised a question of what is the mean age of presentation of epilepsy in cases of FCD pathology or heterotropia? This question was answered by a nice retrospective study done in Germany, where 120 patients with FCD (adult and pediatric) were retrospectively analyzed to elucidate the initial clinical characteristics and clinical course of epilepsy. They found that the age at epilepsy onset without dual pathology ranged from <1 to 60 years (mean: 7.0 years, median: 3 years). Interestingly, they found that the initial manifestation of epilepsy through a generalized tonic-clonic seizure was observed in 15 out of 65 (23%) patients with temporal or temporoparietal FCD.

Our patient had FCD along the right collateral sulcus, and her initial seizure was generalized tonic-clonic (22). It is well known that heterotropia causes epilepsy, and there was an extensive study about the unique presentation of such pathology conducted in Italy. They observed 120 patients with epilepsy and malformations of cortical development, 16 of whom had periventricular nodular heterotopia (PNH). Of these, eight patients had periventricular nodules only (simple PNH) and eight (PNH plus) presented with other cortical or cerebral malformations (subcortical heterotopia; polymicrogyria; focal dysplasia; schizencephaly; cortical folding; agenesis of the corpus callosum; mega cisterna magna; and cerebellar atrophy). All of them underwent clinical, neurophysiological, and MRI investigation. Eventually the authors found two electroclinical patterns. The first pattern, are simple PNH, and the second pattern is the PNS plus patient. Patients with the first pattern had normal intelligence, and focal seizures started during the second decade of life, with focal abnormalities in the EEG. Patients with the second pattern had mental retardation and very frequent seizures that started earlier, majority during the first decade of life. Their EEG showed focal and bisynchronous abnormalities (23). Our patient did not show a focal EEG finding, but instead showed generalized IED, with neuropsychological assessments showing dysfunctional temporal lobe, including in short-term memory, working memory, learning and verbal long-term memory. No mental retardation was found.

According to the recent recommendations by American Academy of Neurology and the American Epilepsy Society for first unprovoked seizure in adults, EEG should be considered as a part of the routine neurodiagnostic evaluation (Level B). Brain imaging with CT or MRI should be considered as part of the routine neurodiagnostic evaluation (Level B). Laboratory tests: such as blood counts, blood glucose, and electrolyte panels (particularly sodium), lumbar puncture, and toxicology screening may be helpful based on the history, physical, and neurologic examination, but there are insufficient data to support or refute recommending any of these (Level U).

The MEG findings were clearly superior in this case to routine EEG and might be even superior to standard structural neuro-images. MEG showed two distinct sources which the EEG failed to show. The MRI on the other hand only showed likely source in the right side (Figure 2). This is in the same line to support routine MEG usage in evaluation of epileptic patients (24).

5. CONCLUSION

FCD and heterotropia are well known brain pathologies that can lead to epilepsy. The EEG changes that are commonly recognized in such cases are focal inter-ictal and ictal changes. However, the presence of generalized epileptiform activities does not exclude a focal brain lesion, and the EEG can show a generalized spikes phenomenon where in fact there is no generalized epilepsy. Therefore, MEG showed more evidence in term of the diagnosis of cortical malformations.

Acknowledgement: We would like to thank Mr. Palaniappan Arunachalam for his extreme help in organizing and picturing the EEG findings.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms.

Author's contribution: HJ, VP gave a substantial contribution to the conception and design of the work. EB, MA gave a substantial contribution of data. VP, EB, MA gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. HJ, VP, EB, MA had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the
Focal Cortical Dysplasia and Generalized Epileptiform Discharges

REFERENCES

1. Gleeson JG, Walsh CA. Neuronal migration disorders: from genetic diseases to developmental mechanisms. Trends Neurosci. 2000 Aug; 23(8): 352-359. doi: 10.1016/s0166-2236(00)01607-6.

2. Barkovich AJ, Kuzniecky RI, Dobyns WB, Jackson GD, Becker LE, Evrard P. A classification scheme for malformations of cortical development. Neuropediatrics. 1996 Apr; 27(2): 59-63. doi: 10.1055/s-2000-273750.

3. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development: update 2001. Neurology. 2001 Dec 26; 57(12): 2168-2178. doi: 10.1212/wnl.57.12.2168.

4. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27; 65(12): 1873-1887. doi: 10.1212/01.wnl.0000183747.05269.2d.

5. Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. Brain. 2012 May; 135(Pt 5): 1348-1369. doi: 10.1093/brain/aws019.

6. Kabat J, Król P. Focal cortical dysplasia - review. Pol J Radiol. 2012 Apr; 77(2): 35-43. doi: 10.12659/pjr.882968.

7. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry. 1971 Aug; 34(4): 369-387. doi: 10.1136/jnpn.34.4.369.

8. Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, et al. Terminology and classification of the cortical dysplasias. Neurology. 2004 Mar 23; 62(6 Suppl 3): S2-S8. doi: 10.1212/wnl.0100145070.30388.7e.

9. Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, et al, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commis- sion. Epilepsia. 2011 Jan; 52(1): 158-174. doi: 10.1111/j.1528-1167.2010.02777.x.

10. Fauser S, Sisodiya SM, Martinian L, Thom M, Gumbinger C, Huppertz HJ, et al. Multi-focal occurrence of cortical dysplasia in epilepsy patients. Brain. 2009 Aug; 132(6): 2079-2090. doi: 10.1093/brain/awp145.

11. Seo JH, Holland K, Rose D, Rozhkov L, Fujiwara H, Byars A, Arthur T, DeGraw T, Leach JL, Gelfand MJ, Miles L, Mangano FT, Horn P, Lee KH. Multimodality imaging in the surgical treatment of children with nonlesional epilepsy. Neurology. 2011 Jan 4;76(1):41-8. doi: 10.1212/2001n.12052014.380.

12. Chassoux F, Devaux B, Landré E, Turak B, Nataf F, Varlet P, Chodkiewicz JP, Daumas-Dupont C. Stereoelectroencephalo- graphy in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain. 2000 Aug;123( Pt 8):1733-51. doi: 10.1093/brain/123.8.1733.

13. Francione S, Nobili L, Cardinale F, Citterio A, Galli C, Tassi L. Intra-lesional stereo-EEG activity in Taylor’s focal cortical dysplasia. Epileptic Disord. 2003 Sep;5 Suppl 2: S105-14.

14. Gambardella A, Palmini A, Andermann F, Dubeau F, Da Costa JC, Quesney LF, Andermann E, Olivier A. Usefulness of focal rhythmic discharges on scalp EEG of patients with focal cortical dysplasia and intractable epilepsy. Electroencephalogr Clin Neurophysiol. 1996 Apr;98(4):243-9. doi: 10.1016/0164-4694(95)00266-9.

15. Noli D, Bartuluchi M, Gonzalez FS, Kaltenmeier MC, Cer- sosimo R, Rugilo C, Prinich JP, Lubieniecki F, Pomata H, Caraballo R. Type II focal cortical dysplasia: electroclinical study and surgical outcome in 31 pediatric patients. Childs Nerv Syst. 2013 Nov;29(11):2079-87. doi: 10.1007/s00381-013-2165-x.

16. Palmini A, Gambardella A, Andermann F, Dubeau F, da Costa JC, Olivier A, Tampieri D, Gloo P, Quesney F, Andermann E, et al. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. Ann Neurol. 1995 Apr;37(4):476-87. doi: 10.1002/ana.436701.

17. Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, Cardinale F, Cossu M, Ferrario A, Galli C, Bramero M, Citterio A, Spreafico F. Focal cortical dysplasia: neuropathologi- cal subtypes, EEG, neuroimaging and surgical outcome. Brain. 2002 Aug;125( Pt 8):1719-32. doi: 10.1093/brain/awf175.

18. Tassi L, Garbelli R, Colombo N, Bramero M, Russo GL, Mai R, Deleo F, Francione S, Nobili L, Spreafico F. Electroclinical, MRI and surgical outcomes in 100 epileptic patients with type II FCD. Epileptic Disord. 2012 Sep;14(3):257-66. doi: 10.1684/epd.2012.0525.

19. Carlson, N. R., & Birkett, M. A. (2017). Physiology of behavior / Neil R. Carlson, Melissa A. Birkett (Twelfth edition. Global edition.). Pearson.

20. Bast J, Oezkan O, Rona S, Stippich C, Seitz A, Rupp A, Fauser S, Zentner J, Rating D, Scherg M, EEG and MEG source analysis of single and averaged interictal spikes reveals intrinsic epileptogenicity in focal cortical dysplasia. Epilepsia. 2004 Jun;45(6):621-31. doi: 10.1111/j.1528-1167.2004.02777.x.

21. Kim DW, Lee SY, Lee SK. Focal Epileptogenic Lesions in Adult Patients with Epilepsy and Generalized Epileptiform Discharges. J Epilepsy Res. 2016 Dec 31;6(2):75-78. doi: 10.14581/ je.red.16014.

22. Fauser S, Huppertz HJ, Bast T, Strobl K, Pantazis G, Alten- mueller DM, Feil B, Rona S, Kurth C, Rating D, Kornthengen R, Steinhoff BJ, Volk B, Schulze-Bonhage A. Clinical characteris- tics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. Brain. 2006 Jul;129(Pt 7):1907-16. doi: 10.1093/brain/awl133.

23. d’Orsi G, Tinuper P, Bisulli F, Zaniboni A, Bernardi B, Rub- boli G, Riva R, Michelucci R, Volpi L, Tassinari CA, Bar- ruzzi A. Clinical features and long-term outcome of epi- lepsy in periventricular nodular heterotopia. Simple com- pared with plus forms. J Neurol Neurosurg Psychiatry. 2004 Jun;75(6):873-8. doi: 10.1136/jnnp.2003.023415.

24. Krumbholz A, Wiebe S, Gronseth G, Shinnar S, Levisohn P, Ting T, Hopp J, Shafer P, Morris H, Seiden L, Barkley G, French J; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society. Practice Parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review); report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2007 Nov 20;69(21):1996-2007. doi: 10.1212/01.wnl.0000285084.93652.43.