THE OPPORTUNITY OF THE ELECTROENCEPHALOGRAPHY IN THE DIAGNOSTIC APPROACH OF THE FEBRILE SEIZURES

RALUCA MARIA COSTEA[1], MIHAI LEONIDA NEAMȚU[2], BOGDAN NEAMȚU[3]

[1,3]Research and Telemedicine Centre of Neurological Diseases in Children, [1,2,3]Clinical Pediatric Hospital Sibiu, [2,3] "Lucian Blaga" University Sibiu

Keywords: *febrile seizure, febrile, electroencephalography, prognostic, recurrence*

Abstract: *The opportunity of electroencephalography (EEG) in the study of febrile seizures (FS) is controversial. Results of the studies are variable, even contradictory because of the study design: number of patients, criteria for inclusion and exclusion (type of seizures, neurological status of the patient, age), monitoring duration, time of recording/type of EEG (awake/natural sleep/pharmacologically induced sleep), anomalies in the recorded EEG noted as pathological. The EEG has a limited diagnostic value in very young patients due to a low rate of detecting the epileptic pattern. The predictive ability of the epileptiform discharges for epilepsy was noticed in a limited number of studies, especially being associated with focal, predominantly frontal, epileptiform abnormalities. EEG should not be performed in a child with normal neurological evaluation and with a first simple febrile seizure (SFS), but it may prove useful in patients with complex febrile seizures (CFS). The need for this investigation should be adapted and integrated into the patient's clinical context.*

INTRODUCTION

Febrile seizures (FS) represent the most frequent convulsive event under the age of 5 years.

The differentiation of FS from other paroxystic nonepileptic event may prove difficult in the absence of an illustrative case history, therefore it is necessary to identify new instruments (functional explorations, biomarkers) for the diagnosis. Recent data from the literature that show a high incidence of epilepsy in patients with frontal paroxysms or focal discharges would recommend conducting this investigation in patients with FS.(1,2) The usefulness of the interictal electroencephalography (EEG) in the optimal diagnostic approach of FS is limited by the available data in the literature, according to which the epileptiform trace does not necessarily determine the association of clinical manifestations. The EEG anomalies identified in the recordings are classified as epileptic (spikes, sharp waves, spike-wave complexes, polispike-wave complexes) or nonspecific (background asymmetry, changes in amplitude or frequency -slow background). The epileptiform discharges can be found in the general population: in healthy individuals or in the relatives of patients with epilepsy or FS.(3,4) The clinical diagnostic criteria/anamnesis are essential, given that patients with epilepsy or FS may associate febrile nonepileptic type events (syncope, sleep disorders) which enter in the differential diagnosis of FS.

MATERIALS AND METHODS

This review is an analysis of the literature to determine the opportunity of EEG exploration considering the followings: 1. diagnostic tool, 2. method of differentiating between types of FS, 3. method of prognosis regarding the recurrence (simple febrile seizures – SFS or complex febrile seizures - CFS) or epilepsy (identification of a specific EEG pattern in FS), 4. method for correlating the incidence of epilepsy with the type of CFS, 5. identifying the right moment and type of recording, 6. establishing the types of EEG abnormalities.We performed a meta-analysis on the dedicated databases (Cochrane Database) involving studies published until December 2015. Most of the studies identified are class III type but we also detected 15 Class II studies with implications in the use of EEG as functional exploration in: 1. diagnosis or prognosis regarding the type of FS (SFS/CFS), 2. the neurological status and patient age, 3. identifying the proper moment for EEG exploration to highlight the wave abnormalities.

The inclusion criteria for our analysis of these studies varies: 1. SFS or CFS patients, 2. healthy or with pre-existing neurological disorders, 3. patients with different lower age limits (1 months 3 months or 6 months) depending on the definitions applied (5,6,7), 4. patients having awake and/or sleep EEG at different times (postictal in the first 24 hours , between 72 hours and 7 days, after 7 days, after 21 days); only epileptiform or also nonspecific EEG abnormalities were recorded. We have not identified randomized, double-blind controlled class Ia studies in Cochrane Database; we have found partial results on patients with febrile status epilepticus in the prospective, blinded FEBSTAT study.

RESULTS AND DISCUSSIONS

The results of the studies are variable, even contradictory due to study design: the number of patients enrolled, inclusion and exclusion criteria (seizure type, monitoring period, the patient's neurological status, age range, time of EEG recording, EEG type-awake/natural sleep/pharmacologically induced sleep), and EEG changes recorded as pathological.

1. Referring to the diagnosis of seizure, although Fetveit in 2008 discusses the possibility of using postictal EEG, the investigation has a limited diagnostic value given the lack of specificity of the anomalies in relation to the type of FS. The

[3]Corresponding author: Mihai Bogdan Neamțu, Str. Pompeliu Onofrei, Nr. 2-4, Sibiu, România, E-mail: bogdanneamtu76@gmail.com, Phone: +40773 994375

Article received on 08.09.2016 and accepted for publication on 21.09.2016
ACTA MEDICA TRANSILVANICA September 2016;21(3):50-53

diagnosis of seizure/FS is established using clinical/anamnestic criteria.(8,9)

2. Concerning the differentiation between SFS and CFS the intercritical EEG is not useful.(10,11,12,13) Although some authors conclude that the EEG is more likely to be abnormal in the CFS compared to SFS, this hypothesis is disputed by other studies according to which changes in EEG are rare in CFS (14) or early postictal EEG changes are reduced, or on the contrary the rate of paroxysmal discharges is high, but similar in the two types of FS.(14-28) EEG abnormalities are unable to differentiate between the two types of seizures.(12,13)

3. From the perspective of defining the prognosis in CFS since the EEG does not bring any benefit in the diagnosis and in the absence of evidence to certify that the intervention based on the EEG would change the outcome, the EEG should not be performed in the evaluation of the normal neurological child with CFS (significant recommendations, studies observations class II).(21,29,30,31) Wairuru and Mittal invoke the absence of any indications of early EEG in both febrile seizures if they are not associated with an unexplained acute encephalopathy.(9,18,32,33)

Regarding the prognosis of CFS although we have not identified class I studies to certify or deny the opportunity of the EEG anomalies for the recurrence or for future unprovoked seizures or to specify the optimum time for the exploration, the arguments that might recommend the EEG as a possible predictor factor for epilepsy ca not be ignored. In a study involving only patients with CFS Hunmin Kim and the collaborators identify epileptiform abnormalities (focal) that are more common in those who will present later afebrile seizures.(2) The result is consistent with that of the studies by Hwang, Wo Kimura and the Kanemura and collaborators according to which EEG abnormalities do correlate with the risk of epilepsy but not with the recurrence(1,13,18,34), and partly with that of Pavlidou and collaborators, Kuturec and collaborators who do not establish specific correlations between EEG abnormalities and recurrence or epilepsy.(27,35) EEG should be considered especially in the presence of clinical arguments associated with an increased risk of epilepsy, because documenting the first EEG abnormalities helps building the diagnostic and therapeutic approach in a patient with epilepsy.

Concerning the epilepsy risk this increases with each of the following clinical features associated: length, focal character or recurrence of seizures, persistent neurological abnormalities, so that the presence of risk factors could motivate the need for performing EEG. CFS are associated with a more than 5 times higher risk of epilepsy compared to the general population, the presence of a family history of epilepsy and neurological abnormalities causing a 10% risk of epilepsy.(36) The detection rate of the epileptic pattern is augmented by : the absence of a family history suggestive of FS, presence of the neurological abnormalities, age older than 3 years, the early postictal EEG recording (within 7 days).(22,24)

4. The studies undergone to correlate the incidence of epileptiform discharges with the type of FS led to inconclusive results. The following clinical aspects are described by some authors as being predictive of EEG abnormalities: 1) focal and prolonged seizures (2), 2) multiple seizures (repeated within 24 h) (12), 3) focal seizures with duration of more than 15 minutes (2), 4) older age and the history of increased number of seizures.(13,15,18)

Some authors have established correlations between the changes in EEG and other clinical factors: older age (13,21), abnormal psychomotor development (17), EEG within 72 hours, but it seems that these factors might not be predictive for epilepsy.(14,15,16,17) Opinions on this issue are divided: 1. Hoffman and Patel recommended to perform the EEG in patients with abnormal psychomotor development, family history of epilepsy and the association of CFS with more than one diagnostic criteria (37), 2. Stores considers the EEG in patients with developmental delay, neurologic abnormalities, younger than 1 year (20), 3. Pedespan takes in consideration especially patients with focal seizures (38) 4. Walt recommends it only for seizures facilitated by low fever, atypical seizures and for the extreme ages (16) 5. Capovilla recommends to perform the EEG as early as possible in CFS (39) 6. Crustas and the collaborators suggest the EEG recording only for CFS associated with abnormal neurological exam or psychomotor delay.(19)

Many authors conclude that there is no correspondence between the age, family history, duration or recurrence of seizures and the EEG changes, inclusively for recurrent CFSs. For example, Maytal and the collaborators describe similar EEG changes in the 2 types of seizures without assessing any benefit for the routine early EEG in the first CFS in patients with a normal neurological examination.(14) After analyzing the data present in the literature, Wairuru believes that the EEG is not justified either in FS patients with recurrent seizures with normal neurological examination, regardless of the type of seizures.(16) Although some clinical trials identified frequently epileptiform abnormalities in recurrent CFS, this are considered to be statistically insignificant. Olaffson and Thorn could not demonstrate an increased rate of epileptic discharges in patients with early or late first extended CF.(16,29)

5. The timing and the type of registration (early/late, sleep/wake) as guidelines for the introduction of the EEG recording in the diagnostic and monitoring protocol of CFS is a difficult task. The detection rate of the EEG changes varies between 2 and 86% due to the variations of the timing of the EEG recording, age, selection criteria and types of the trace changes (excluding epileptiform discharges and/or nonspecific abnormalities).

Unspecific abnormalities as background slowing are more common in the early postictal EEG, predominantly in the early days especially for febrile status epilepticus. The FEBSTAT study is a prospective, cohort, blinded, multicentral trial involving patients with febrile status epilepticus (with a mean duration of 70 minutes) without pre-existing severe neurological abnormalities. In this study, the EEG recording highlights changes in 42.7% of the enrolled patients within 72 hours after the postictal event most of them of nonepileptic type (42.7% versus 6.5%), predominantly focal slowing in temporal derivations and focal attenuation irrespective of the area, rare focal spikes (45% with temporal location) correlated with imaging markers of acute injury.(40,41)

Kajitani and the collaborators, Lennox-Buchthal and the collaborators advocate for the opportunity of the EEG recording after the first week regarding epileptiform discharges concluding in their studies the rarity of this postictal changes in the first week. Yucel and the collaborators describe a high rate of postictal EEG abnormalities in patients with CFS after the 7-10 days.(16,21,43) Hamal recommends performing the EEG after the 7th day to reduce the risk of false positive results. The conclusions of these studies are in antithesis with the results of other authors for example: 1. Joshi and the collaborators, Kanemura and collaborators, who identified in their research on patients with CFS, a 3.5 times higher rate of EEG changes (epileptic and nonepileptic) or exclusive paroxysmal discharges in the first week, 2. Karimzadeh et al who found no statistically significant difference between the distribution of EEG abnormalities in the early or late recordings.(1,15,17)

6. Referring to the types of EEG abnormalities, the

findings vary depending on the study protocol. Joshi et al enrolled in their study patients with CFS including those with pre-existing neurological conditions, describing in 40.58% of the cases epileptic abnormalities and in 44.93% background abnormalities (both expressed predominantly in the early EEG, recorded in the first week).(17) Jeong et al enrolled patients with both types of seizures but they did not report statistically significant differences between the EEG in the *2* types of seizures, describing an abnormal EEG pattern in 31% cases (predominantly nonspecific abnormalities like slowing, pathological theta rhythm in the first week, and epileptic paroxysms after day 7).(12) Maytal and the collaborators describe a low rate of EEG abnormalities in the early postictal EEG in children with CFS with normal neurological exam, similar to that of SFC (all patients having normal sleep EEG), possibly due to difficulties in identifying nonspecific anomalies like (slowing) on the sleep trace.(14)

The distribution of the pathological graphic elements is variable: Wo et al notes paroxysmal type discharges like spikes predominantly with central (55.6%), and temporal localization (16.7%) and the absence of generalized or occipital spikes, Kanemura and the collaborators describe generalized or focal downloads (frontal 75%, rolandic 28.5%), Frantzen and Lennox-Buchtal predominantly occipital asymmetric slowing.(1,18,21) An increased risk of epilepsy is particularly associated with frontal paroxysms (1) or focal epileptiform abnormalities.(2) The use of EEG is limited also by the reduced sensitivity of the examination in the unprovoked seizures at 3 years of age (12,15) and by the rare epileptic pattern detection at a young age.(12,15) The epileptic pattern detection rate increases linearly with age.(12,15,42) Although the importance of the EEG changes in CFS was of interest to the scientific community, the predictive ability of the epileptiform discharges for epilepsy objective was however sustained by a limited number of studies. It remains in question the possibility of using EEG in excluding central nervous system infections, hence the need to integrate this exploration in the clinical context. This investigation has limited value in identifying associated structural abnormalities.(33)

CONCLUSIONS

Most studies do not acknowledge the predictive value of the EEG for recurrence or epilepsy, but the importance of this investigation should not be ruled out especially based on recent studies that support the increased incidence of epilepsy in patients with frontal paroxysms or focal discharges.

It seems that the EEG assessment should not be carried in a child with normal neurological exam and seizures in SFS. Although still uncertain, the predictive value for recurrence or epilepsy EEG abnormalities cannot be ignored because of the recent studies findings that correlate epileptiform discharges (focal discharges, frontal paroxysms) with an increased risk of epilepsy.

EEG can prove its usefulness in patients with CFS, but requires integration into clinical context.

Acknowledgment:

This work has been conducted in the Pediatric Clinic Hospital Sibiu, within Research and Telemedicine Center in Neurological Diseases in Children - CEFORATEN project (ID 928 SMIS-CSNR 13605) financed by ANCSI with the grant number 432/21.12.2012 through the Sectoral Operational Programme "Increase of Economic Competitiveness".

REFERENCES

1. Kanemura H, Mizoroqi S, Aoyaqi K, Suqita K, Aihara M. EEG characteristics predict subsequent epilepsy in children with febrile seizure. Brain Dev. 2012;34:302-307.
2. Hunmin K. Clinical and EEG risk factors for subsequent epilepsy in patients with complex febrile seizures July 2013;105(1-2):158-163.
3. Cavazzuti GB, Cappella L, Nalin A. Longitudinal Study of Epileptiform EEG Patterns in Normal Children; 1980.
4. Okubo Y, Matsuura M, Asai T, et al. Epileptiform EEG discharges in Healthy Children: prevalence, Emotional and Behavioral Correlates, and Genetic Influences; 1994.
5. Commission on Epidemiology and Prognosis, International League against Epilepsy: Guidelines for epidemiologic studies on epilepsy. Epilepsia. 1993;34:592-596.
6. National Institutes of Health: Febrile Seizures: Consensus Development Conference Summary, vol 3, no 2. Bethesda, MD, National Institutes of Health; 1980.
7. American Academy of Pediatrics: Provisional Committee on Quality Improvement: Practice parameter: The neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 1996;97:769-775.
8. Fetvei A Assessment of febrile seizures in children Eur J Pediatr. 2008 Jan;167(1):17-27. Epub 2007 Sep 2.
9. Wairuru C. Febrile seizures: an update. Archives of disease in childhood. 2004:89:751-756.
10. Felipe L, Siqueira M. febrile seizures: update on diagnosis and management. Siqueira LFM. 2010;56(4):489-92. (PubMed)
11. Elkis LC. Crises sintomáticas agudas. In: Manreza MLG, Grossmann RM, Valério RMF, Guilhoto LMFF. Epilepsia (infância e adolescência). São Paulo: Lemos Editorial; 2003. p. 207-28.
12. Jeong KA, Han MH, Lee EH, Chung S. Early postictal electroencephalography and correlation with clinical findings in children with febrile seizures. Korean Journal of Pediatrics. 2013;56(12):534-539. doi:10.3345/kjp.2013.56.12.534.
13. Hwang G, Kang HS, Park SY, et al Predictors of unprovoked seizure after febrile seizure: short-term outcomes. Brain Dev. 2015 Mar;37(3):315-21. doi: 10.1016/j.braindev. 2014.06.003. Epub 2014 Jun 28.
14. Maytal J, et al. The value of early postictal EEG in children with complex febrile seizures Epilepsia. 2000 Feb;41(2):219-21.
15. Karimzadeh P, Rezayi A, Togha M, et al. The best time for eeg recording in febrile seizure. Iranian journal of child neurology. 2014;8(1):20-25.
16. Yücel O, Aka S, Yazicioglu L, Ceran O. Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. Pediatr Int. 2004 Aug;46(4):463-7.
17. Joshi C, Wawrykow T, et al. Do clinical variables predict an abnormal EEG in patients with complex febrile seizures? Seizure. 2005;14(6):429-434.
18. Wo SB, et al. Risk for developing epilepsy and epileptiform discharges on EEG in patients with febrile seizures Brain and Development. 2013;35(4):307-311.
19. Cuestas E. Is routine EEG helpful in the management of complex febrile seizures? Arch Dis Child. 2004 Mar;89(3):290.
20. Stores G. When does EEG contribute to the management of febrile seizures Arch Dis Child. 1991;66:554-557.
21. Frantzen E, Lennox-Buchthal M, Nygaard A. Longitudinal EEG and clinical study of children with febrile convulsions. Electroencephalogr Clin Neurophysiol. 1968;24:197-212.
22. Annegers JF, Hauser WA, Shirts SB, et al: Factors prognostic of unprovoked seizures after febrile convulsions

23. Berg AT, Shinnar S, Darefsky AS, et al. Predictors of recurrent febrile seizures. Arch Pediatr Adolesc Med. 1997;151:371-378.ions. N Engl J Med. 1987;316:493-498.
24. Offringa M, Bossuyt PMM, Lubsen J, et al. Risk factors for seizure recurrence in children with febrile seizures: A pooled analysis of individual patient data from five studies. J Pediatr. 1994;124:574-584.
25. Sofianov N, Sadikario A, Dukovski M, Kuturec M. Febrile convulsions and later development of epilepsy. Am J Dis Child. 1983;137:123-126.
26. Sofianov N, Emoto S, Kuturec M, et al. Febrile seizures: Clinical characteristics and initial EEG. Epilepsia. 1992;33:52-57.
27. Kuturec M, Emoto SE, Sofianov N, et al. Febrile seizures: Is the EEG a useful predictor of recurrences? Clin Pediatr. 1997;36:31-36.
28. Tsuboi T. Correlation between EEG abnormality and age in childhood Neuropadiatrie. 1978;9:229-238.
29. Thorn I. The significance of electroencephalography in febrile convulsions. In: Akimoto H, Kazamatsuri H, Seino M, Ward A eds. Advances in Epileptology: XIIIth International Epilepsy Symposium. New York, NY: Raven Press; 1982. p. 93-95.
30. Gerber MA, Berliner BC. The child with a “simple” febrile seizure: appropriate diagnostic evaluation. Am J Dis Child. 1981; 135(5):431–443
31. Dunlop S, Taitz J. Retrospective review of the management of simple febrile convulsions at a tertiary paediatric institution. J Paediatr Child Health. 2005 Dec;41(12):647-51.
32. Mittal R. Recent Advances in Febrile Seizures The Indian Journal of Pediatrics September. 2014;81(9):909-916.
33. Berzosa LR, Ramos FR, Martínez A. Complex febrile seizures: Study of the associated pathology and practical use of complementary tests. Anales de Pediatria. 2014;80(6):365–369. doi: 10.1016/j.anpedi.2013.06.038.
34. Kimura S. Follow-up study on children with febrile convulsions having epileptiform EEG. Brain and Development. 1995;17(5):388.
35. Pavlidou E, Tzitiridou M, et al. Which factors determine febrile seizure recurrence? A prospective study Brain Dev. 2008 Jan;30(1):7-13. Epub 2007 Jun 21.
36. Chung S. Febrile seizures. Korean Journal of Pediatrics. 2014;57(9):384-395. doi:10.3345/kjp.2014.57.9.384.
37. Patel AD, Vidaurre J. Complex Febrile Seizures A Practical Guide to Evaluation and Treatment J Child Neurol. 2013 Jun;28(6):762-7. doi: 10.1177/0883073813483569. Epub 2013 Apr 10.
38. Pedespan L Febrile seizures Arch Pediatr. 2007 Apr;14(4):394-8. Epub 2007 Mar 13.
39. Capovilla G, Mastrangelo M, Romeo A, Vigevano F. Recommendations for the management of “febrile seizures” ad hoc Task Force of LICE Guidelines Commission. Epilepsia. 2009;50:2-6.
40. Frank LM, Shinnar RC, Sun S. FEBSTAT Study Team. Acute EEG findings in children with febrile status epilepticus. Results of the FEBSTAT study. Neurology. 2012;79:2180-2186.
41. Harden C. Findings from the FEBSTAT Study: Can Observations After a Provoked Seizure Occurrence Have Broad Implications for Epileptogenesis? Epilepsy Currents. 2013;13(3):143-145. doi:10.5698/1535-7511-13.3.143.
42. Kajitani T, Ueoka K, Nakamura M, Kumanomidou Y. Febrile convulsions and rolandic discharges. Brain Dev. 1981;3:351-9.
43. Shinnar S, Glauser TA. Febrile Seizures J Child Neurol. 2002 Jan;17 Suppl 1:S44-52.