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ASSESSMENT OF HIPPOCAMPAL VOLUMES IN INFANTS WITH A HISTORY OF BACTERIAL MENINGITIS

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ABSTRACT:

Purpose: To assess the hippocampal damage that occurs soon after a meningitic episode with a view to obtaining data that might contribute to an understanding of whether such changes were likely to be caused by the meningitis.

Materials and Methods: Children under the age of 2 years were enrolled in the study. Hippocampal volumes and T2 relaxation times were measured. The results were compared with those of 12 control subjects undergoing magnetic resonance imaging of the brain for reasons other than epilepsy.

Results: Ten of the 26 study infants had hippocampal reduction; six of them had bilateral and four had unilateral hippocampal reduction. Six of the study subjects that had experienced convulsions during the acute stage of meningitis had hippocampal reduction.

Conclusion: There is a high prevalence of hippocampal damage in infants with a recent history of bacterial meningitis and this has a strong correlation with convulsions during meningitic episodes. Assessment of hippocampal atrophy in patients with a history of meningitis should warrant a volumetric analysis of the hippocampi with volume correction to identify possible bilateral volume loss.

Keywords: Hippocampal Volume, Bacterial Meningitis, Infants

BAKTERİYELMENENJİTGEÇİRMİSSÜTÇOCUKLARINDA HİPOKAMPAL HACİMLERİN DEĞERLENDİRİLMESİ

ÖZ:

Amaç: Merkezi sinir sistemi enfeksiyonu hikayesi bulunan epilepsi gelismis hastalarda temporal bölge değerlendirilmesi ve hipokampuslarının hacimsel incelenmesi önerilmektedir. Bu çalısmada yakın dönemde menenjit tedavisi görmüs süt çocuklarının hipokampus hacimleri kantitatif olarak değerlendirildi.

Gereç ve Yöntem : Menenjit tanısı konulan 2 yas altı 26 olgu çalısmaya alındı. Aynı yas grubu 12 kontrol olgusu hipokampus hacimlerinin kıyaslanması açısından çalısmaya dahil edildi.

Bulgular: Yirmialtı olgunun onunda hipokampal küçülme saptandı. Bunlardan altısı çift taraflı, dördü tek taraflı idi. Enfeksiyon döneminde konvülziyon geçiren 12 olgunun altısında çift taraflı üçünde tek taraflı küçülme gözlendi.

Sonuç: Hipokampal etkilenme özellikle çocukluk döneminde menenjit geçirmis olgularda enfeksiyon döneminde gelisen komplike nörolojik sorunlarla ve de sıklıkla tedaviye dirençli konvülziyonlarla yakından iliskilidir. Bu hastaların hipokampal değerlendirmesi etkilenmenin sıklıkla her iki hipokampusuda içermesi ve de sıklıkla asimetrik olmayısı ile kantitatif yöntemlerle yapılmalıdır.

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INTRODUCTION

Patients with a history of an encephalitic or meningitic illness have a greater risk than the general population of developing temporal lobe epilepsy,[1] because their seizures are commonly intractable to medical therapy.[2]

In previous studies, when a patient had a history of febrile convulsions and a clear hippocampal asymmetry was observed visually, we suggest that an assessment of unilateral hippocampal volume loss is generally valid. However, a history of an encephalitic or meningitic illness with subsequent occurrence of complex partial seizures should warrant a volumetric assessment of the hippocampi with volume correction to identify possible bilateral volume loss.[3]

In all these studies, only those patients with a history of meningitis or encephalitis that preceded the onset of seizures were selected. However, the results of previous studies indicate that the greatest degree of volume reduction is seen in patients with a history of early onset seizures.[4, 5] Therefore, this condition cannot explain the exact relation between the hippocampal damage and meningitis or encephalitis.

In this study, hippocampal damage was evaluated via MR scanning in children younger than two years old who had had meningitis a short time before.

MATERIALS AND METHODS

Patients aged 1 month to 2 years with meningitis were enrolled in this prospective study in the Pediatric Clinics of Sisli Etfal Education and Research Hospital. Exclusion criteria comprised a history of previous epileptic seizures, prematurity, developmental problems, or pre-existing neurological abnormality, and contraindication to general anesthetic.

The diagnosis of meningitis caused by a specific bacterial pathogen was based on clinical findings compatible with meningitis and at least one of the following: a positive cerebrospinal fluid culture or a negative cerebrospinal fluid culture with a finding of neutrophilic pleocytosis plus one of the following: a positive cerebrospinal fluid antigen test, a positive blood culture, identification of gram-negative diplococci on Gram staining of cerebrospinal fluid (CSF), or sputum or throat cultures positive for Neisseria meningitidis in patients with a petechial or purpuric rash and a fulminant course.[6,7] Tuberculous meningitis was diagnosed if: (1) mycobacterial culture/acid fast bacilli stain was positive in the CSF or (2) basal enhancement or tuberculoma was seen on computed tomography (CT) scans and a clinical response to antituberculous treatment.[8, 9] On the other hand, "culture-negative" bacterial meningitis (CNBM) was diagnosed on the basis of a compatible clinical picture and pleocy-

tosis of at least 100 neutrophils per cubic millimeter (0.1 x 109 per liter) despite negative blood and cerebrospinal fluid cultures and results of cerebrospinal fluid Gram staining that were negative, positive for organisms other than gram-negative diplococci , or not available.[6,7]

Subjects presenting with neurological changes were also studied. A complicated convulsion was defined as one fulfilling at least one of the following criteria: convulsions lasting more than 30 minutes, with focal features (hemiconvulsion, ictal head turning or eye deviation, postictal hemiparesis) or recurrent within 24 hours despite medical therapy.[10] MRI was performed 21 to 98 (mean, 45±19) days after the onset of the disease. The control subjects (n: 12) were randomly selected from among children (aged 1 month to 2 years) who had had MRI records for reasons other than convulsions (such as minor trauma).

MRI studies were performed on a 1.5 T Siemens Magnetom 63 SP. T1-weighted images were collected with a 3D (three-dimensional) MP-RAGE (magnetization prepared-rapid acquisition gradient echo) sequence. The images for a slice thickness of 1 mm were obtained from the coronal plane. Thirty-eight MR scans were analyzed by a blinded observer. The hippocampal volume was measured in a posterior to anterior direction. The hippocampal volume was measured in a posterior to anterior direction. The most posterior slice was identified as the transverse section through the fimbria (where the fornices could be seen projecting beneath the cingulate gyrus, and merging with the hippocampus). All of the gray matter comprising the hippocampus, dentate gyrus, and subiculum was measured, and particular attention was paid to exclude the characteristic dark appearing CSF often seen dorsal and lateral to the hippocampus. At the anterior hippocampal head the pes was separated from the amygdala by the often visibly lighter band of cells forming the alveus, or by the visual differences between the hippocampus and amygdale.[11] The hippocampal volumes were calculated by multiplying the slice thickness by the sum of the hippocampal cross-sectional areas (Cavalieri's principle).[12]

The volumes were normalized to the intracranial volume. In brief, intracranial volume is modeled as a sphere where the height of the intracranial vault is the diameter (D) of the sphere, whose volume is Sm=p D3/6. The MRI slice that contained the first bilateral frontal ventricular horns was the index section for all of the measurements. The corrected hippocampal volumes were computed as VD=Vm(S1/Sm), where S1 is the intracranial sphere volume at 1 year of age as computed from a linear regression of sphere volume with age.[13,14]

Mean hippocampal volumes of control subjects were computed. Standard deviation (SD) from the mean of the corrected hippocampal volumes was calculated. Hippocampal reduction was defined as 3 SD below the mean of the control group. Volume ratios of the control subjects were computed. Hippocampal asymmetry were defined as 3 SD below the mean of hippocampal ratios of the control group.[10]

RESULTS

Twenty-six subjects (11 girls and 15 boys) with a mean age of 9.3±3.8 months that had experienced meningitis and 12 control subjects (5 girls and 7 boys) with a mean age of 9.1±6.4 months were included in the study. The patient and control groups had a similar age and sex distribution (respectively, p=0.9, p>0.05).

The pathogens isolated from the CSF of the 20 children with meningitis were Streptococcus pneumoniae (n=7), Mycobacterium tuberculosis (n=6), Klebsiella pneumoniae (n = 3), Neisseria meningitidis (n = 2), and Haemophilus influenzae type b (n = 2). The specific microorganisms could not be identified in six of the 26 subjects.

Mycobacterium tuberculosis was isolated in the CSF cultures of four subjects. Two patients with tuberculous meningitis had negative culture results but these two subjects had positive acid fast bacilli stains along with positive tuberculin skin tests and a family history. The clinical and laboratory findings of all six patients were compatible with tuberculous meningitis.

The clinical condition of the 12 control subjects and their hippocampal measurements are shown in Table 1. Hippocampal volumes of the control subjects were normalized to 1 years of age. The means of the right and left corrected hippocampal volumes for the 12 control subjects were 2365 mm3 (SD 36) and 2365 mm3 (SD 36), respectively. The lower reference limit for normal hippocampal volumes was 2257 mm3 for the right hippocampus and 2150 mm3 for the left hippocampus, 3 SD below the control mean. The evaluation of hippocampal volumes of subjects according to their etiologies is given in Table 2. Three of the patients with a history of tuberculous meningitis had bilateral and one of them had unilateral hippocampal reduction. Three of the patients with a history of Streptococcus pneumoniae meningitis had bilateral and one of them had unilateral hippocampal reduction. One of the three subjects with a history of Klebsiella pneumoniae meningitis and one of the six subjects with CNBM had unilateral hippocampal reduction.

The evaluation of hippocampal volumes of subjects who had experienced convulsions during meningitic episodes is given in Table 3. Six of the twelve patients that had experienced convulsions during the acute stage of meningitis had bilateral and three had unilateral hippocampal reduction. All of the patients who had experienced complicated convulsions (n=5) had hippocampal reduction. Four of the 26 subjects had significant hippocampal volume asymmetry. Three of these had a history of tuberculous meningitis and one had a history of Streptococcus pneumoniae meningitis. All subjects with hippocampal volume asymmetry had experienced convulsions.

Table 1: Data on the control subjects.

No of subjects	Sex	Scan age (months)	Reason for MRI	Hippocampus volume ratio	Corrected right hippocampus volume	Corrected left hippocampus volume
1	F	14	Hypotonia	1.01	2312	2268
2	M	6	Hypotonia	1.03	2312	2234
3	M	7	Nystagmus	1.05	2402	2275
4	F	1	Ptosis	1.00	2412	2374
5	F	18	Spastic dysplegia	1.03	2352	2264
6	M	22	Spastic dysplegia	1.04	2342	2242
7	F	11	Hypotonia	1.02	2350	2294
8	M	13	Hypotonia	1.03	2366	2292
9	F	5	Hypotonia	1.05	2342	2227
10	M	3	Tremor	1.08	2420	2233
11	M	9	Hypotonia	1.03	2390	2304
12	M	2	Nystagmus	1.03	2390	2308

TABLE 2: Evaluation of hippocampal volumes of subjects according to their etiologies.

	N	N. of subjects experienced convulsion	Hippocampal volume loss bilateral	unilateral	Hippocampal asymmetry
Mycobacterium tuberculosis	6	6	3	1	3
Streptococcus pneumoniae	7	3	3	1	1
Neisseria meningitidis	2	1	--	--	--
Klebsiella pneumoniae	3	1	--	1	--
Haemophilus influenzae	2	--	--	--	--
CNBM	6	1	--	1	--
TOTAL	26	12	6	4	4

CNBM: culture-negative bacterial meningitis

Table 3: Evaluation of hippocampal volumes of subjects who had experienced convulsions during meningitic episodes.

	No. of subjects who had not experienced convulsions	No. of subjects who had experienced convulsions (n=12) Simple	Complicated[a]
Reduction (-)	12	3	--
Reduction (+)	2	4	5
Bilateral	1	1	2
Unilateral	1	1	1
Bilateral+asymmetry	--	1	2
Unilateral+asymmetry	--	1	--
TOTAL	14	7	5

a Lasting more than 30 minutes, with focal features (hemiconvulsion, ictal head turning or eye deviation, postictal hemiparesis) or recurrent within 24 hours despite medical therapy.

DISCUSSION

Modern seizure protocol MRI examinations are highly sensitive and specific for the detection of hippocampal damage, and have been shown to be predictive of outcome with respect to seizures.[15, 16, 17] A remote history of meningitis or encephalitis may be present in patients with medically refractory partial epilepsy of temporal lobe origin.[18] Additionally, the latent period between the occurrence of the meningitis or encephalitis and the onset of the epilepsy was significantly longer in patients in whom meningitis or encephalitis occurred before the age of 4 years. A latent period is considered a typical feature of medial temporal lobe epilepsy (MTLE).[19] However, it has not yet been demonstrated whether the age of occurrence of meningitis or encephalitis or the type of infection is of prognostic significance independent of the finding of hippocampal damage. Free et al.[20] reported bilateral hippocampal volume loss in 9 of 12 subjects with a history of encephalitis or meningitis. In that study, the mean time between meningitic or encephalitic episode and seizure onset was six years and the mean duration of seizures was 17 years. Those authors concluded that a history of an encephalitic or meningitic illness with a subsequent occurrence of complex partial seizures should warrant a volumetric assessment of the hippocampi with volume correction to identify possible bilateral volume loss. In another study, the clinical seizure characteristics, seizure localization, and postoperative pathology from 38 patients with medically refractory partial epilepsy who had a remote history of meningitis or encephalitis were investigated.2 In that study the authors found that a history of meningitis was usually associated with the syndrome of MTLE, with the characteristic MRI and pathologic findings of mesial temporal sclerosis (MTS). In contrast, a history of encephalitis was associated with neocortical seizure foci. The age at occurrence of meningitis or encephalitis was also found to be of importance, with encephalitis before the age of 4 years being associated with MTLE, and almost all the meningitis cases occurring before the age of 4 years. From these findings, the authors hypothesized that the mesial temporal region was particularly vulnerable to experiencing epileptogenic damage with a relatively minor insult early in life, whereas at an older age a more severe CNS infection was required to cause epilepsy, which consequently resulted in more widespread neocortical injury. In support of this, a more recent study of 18 patients with intractable partial epilepsy associated with previous CNS infections also found that the age at occurrence of CNS infection was significantly younger in the patients with MTLE as compared with those with neocortical epilepsy.[21] In that study, the investigators noted no evidence of bilateral hippocampal volume loss; but their imaging assessment was only visual, and these results showed that bilateral volume loss is difficult for radiologists to detect.

The data indicate that visual inspection of volumetric images only, even by an experienced neuroradiologist, does not adequately detect symmetric bilateral hippocampal volume loss and rarely detects asymmetric bilateral volume loss. In our study, we studied quantitative assessments to identify possible bilateral volume loss, which is generally valid in patients with a history of an encephalitic or meningitic illness. Different from other studies, all subjects underwent MRI before presenting with epilepsy in our study. In our study, only four of the 11 subjects with detected hippocampal reduction were observed to have unilateral volume loss and three of these four subjects also had bilateral volume loss. Only one patient was identified as having unilateral volume loss by a second blinded observer.

Case histories were reviewed for predisposing etiologies before the onset of chronic temporal lobe seizures, and events that involved loss of consciousness for greater than 30 minutes or alternations of cognitions for more than 4 hours were termed an initial precipitating injury.[22, 23]

A single order regression line is plotted for the best fit for intracranial volume by determining the diameter of the intracranial vault from the MRI data as mentioned in previous studies.13, 14, 24, 25 It is readily apparent that the most accurate and reliable method is estimation of intracranial volume.

All previous studies about hippocampal volume assessments were designed to determine the possible etiology of the existing epilepsy or to identify the relation between temporal region injury and developing epilepsy in patients with a history of

meningitis. However, all subjects in these studies had recurrent seizures, which promote the risk of hippocampal damage. If the relation between the experienced convulsion and hippocampal damages is considered, none of these studies can explain the relation between hippocampal damage and history of meningitis.

In our study, the mean time between meningitic or encephalitic episode and MR assessment was 45 days. Previous studies have shown a strong correlation between degree of atrophy and severity and frequency of epilepsy. This study is important to show the factors precipitating hippocampal injury before epilepsy develops.

In conclusion, assessment of hippocampal atrophy in patients with a history of meningitis should warrant a volumetric analysis of the hippocampi with volume correction to identify possible bilateral volume loss. Hippocampal injury generally occurs after meningitis and this has a strong relation with complicated convulsions during the acute phase of the infection. If neurological deficits of hippocampal origin are taken into consideration, complicated convulsions require more intensive and aggressive treatment during the acute stage of meningitis.

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REFERENCES

1.Annegers JF, Hauser WA, Beghi E, et al. The risk of unprovoked seizures after encephalitis and meningitis. Neurology 1998; 38:1407-1410.

2.Marks DA, Kim J, Spencer DD, et al. Characteristics of intractable seizures following meningitis and encephalitis. Neurology 1992; 42: 1513-1518.

3.Free SL, Bergin PS, Fish DR, et al. Methods for normalization of hippocampal volumes measured with MR. Am J Neuroradiol 1995; 16: 637-643.

4.Trenerry MR, Jack CR, Sharbrough FW, et al. Quantitative MRI hippocampal volumes: association with onset and duration of epilepsy, and febrile convulsions in temporal lobectomy patients. Epilepsy Res 1993; 15: 247-252.

5.Kuks JBM, Cook MJ, Fish DR, et al. Hippocampal sclerosis in epilepsy and childhood febrile seizures. Lancet 1993; 342: 1391-1394.

6.Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993; 328: 21-28.

7.Dunbar SA, Eason RA, Musher DM, et al. Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis. J Clin Microbiol 1998; 36: 1617-1620.

8.Kumar R, Singh SN, Kohli N. A diagnostic rule for tuberculous meningitis. Arch Dis Child 1999; 81: 221-224.

9.Shankar P, Manjunath N, Mohan KK, et al. Rapid diagnosis of tuberculous meningitis by polymerase chain reaction. Lancet 1991; 337: 5-7.

10.Grunewald RA, Farrow T, Vaughan P, et al. A magnetic resonance study of complicated early childhood convulsion. J Neurol Neurosurg Psychiatry 2001; 71: 638-642.

11.Obenaus A, Yong-Hing CJ, Tong KA, et al. A reliable method for measurement and normalization of pediatric hippocampal volumes. Pediatr Res 2001; 50: 124-132.

12.Cavalieri B. Geometrica indivisibilibus continurium (typis clementis ferronij, bononiae), 1635. Reprinted as: Geometrica degli indivisibili. Torino: Unione Tipografico-Editrice Torinese, 1966.

13.Marsh L, Morrell MJ, Shear PK, et al. Cortical and hippocampal volume deficits in temporal lobe epilepsy. Epilepsia 1997; 38: 576-587.

14.Mathalon DH, Sullivan EV, Rawles JM, et al. Correction for head size in brain-imaging measurements. Psychiatry Res 1993; 50: 121-139.

15.Kuzniecky R, Burgard S, Faught E, et al. Predictive value of magnetic resonance imaging in temporal lobe epilepsy surgery. Arch Neurol 1993; 50: 63-69.

16.Berkovic SF, McIntosh AM, Kalnins RM, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. Neurology 1995; 45: 1358-1363.

17.Garcia PA, Laxer KD, Barbaro NM, et al. Prognostic value of qualitative magnetic resonance imaging hippocampal abnormalities in patients undergoing temporal lobectomies for medically refractory seizures. Epilepsia 1994; 35: 520-524.

18.Falconer MA, Taylor DC. Surgical treatment of drug-resistant epilepsy due to mesial temporal sclerosis. Etiology and significance. Arch Neurol 1968; 19: 353-361.

19.French JA, Williamson PD, Thadani VM, et al. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Ann Neurol 1993; 34: 774-780.

20.Free SL, Li LM, Fish DR, et al. Bilateral hippocampal volume loss in patients with a history of encephalitis or meningitis. Epilepsia 1996; 37: 400-405.

21.Lee JH, Lee BI, Park SC, et al. Experience of epilepsy surgery in intractable seizures with past history of CNS infection. Yonsei Med J 1997; 38: 73-78.

22.Mathern GW, Babb TL, Vickrey BG, et al. The clinical-pathogenic mechanisms of hippocampal neuron loss and surgical outcomes in temporal lobe epilepsy. Brain 1995; 118: 105-118.

23.Mathern GW, Pretorius JK, Babb TL. Influence of the type of initial precipitating injury and at what age it occurs on course and outcome in patients with temporal lobe seizures. J Neurosurg 1995; 82: 220-7.

24.Briellmann RS, Jackson GD, Kalnins R, et al. Hemicranial volume deficits in patients with temporal lobe epilepsy with and without hippocampal sclerosis. Epilepsia 1998; 39: 1174-1181.

25.Sullivan EV, Marsh L, Mathalon DH, et al. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. Neurobiol Aging 1995; 16: 591-606.