Pediatr Radiol (2011) 41:1229–1231
DOI 10.1007/s00247-011-2168-2

EDITORIAL

Comments on hippocampal sclerosis in children younger than 2 years

Gary L. Hedlund

Received: 1 June 2011 / Accepted: 8 June 2011 / Published online: 22 July 2011

I read with interest the original article by Kadom and colleagues [1] titled "Hippocampal Sclerosis in Children Younger than 2 years." I congratulate the authors for highlighting these cases of hippocampal sclerosis (HS), or mesial temporal sclerosis (MTS), in an unexpectedly young patient group.

While one cannot argue with the importance of MTS as a cause of refractory temporal lobe epilepsy in children and adults, I challenge the author's statement that "an infectious trigger was present in all five patients." In Table 1, the authors indicate that patient 1 had infection as the etiology of MTS and that patients 3–5 had complex febrile seizures. Unfortunately, there is no serological or CSF laboratory evidence or histopathological evidence to support the assertion that infection was the trigger leading to MTS.

While the authors have increased our awareness of MTS in a younger-than-expected age group, their study raises several broader questions.

An ongoing contention in epileptology is the proposed relationship between febrile seizures and the development of MTS. The prevalence of febrile seizures among developed countries is about 4% and it is thought to be even higher in poorer countries [2]. Some authors suggest that prolonged febrile seizures lead to direct injury of the hippocampus and adjacent structures, and ultimately to MTS [3]. There is strong retrospective evidence supporting this belief [4, 5]. There is increasing evidence from animal and human data that prolonged febrile seizures are associated with physiological and anatomical changes within the hippocampus that may lead to hippocampal injury, subsequent mesial temporal sclerosis and temporal lobe epilepsy in some cases [6]. More recent MR imaging studies suggest that up to 30–40% of children with prolonged febrile seizures will have acute changes within the hippocampus demonstrated on MRI [7, 8]. Additionally, the presence and the severity of temporal lobe MRI signal changes are predictive of mesial temporal sclerosis preceding the development of clinical seizures. Provenzale et al. [9] in their MRI study of 11 children (mean age of 25 months) who suffered from febrile status epilepticus reported a strong positive correlation between the conspicuity of hippocampal T2 hyperintensity and subsequent development of MTS. On the other side of the argument of MTS genesis are population-based prospective studies that have failed to find an association between febrile seizures and MTS [10–12].

In addition to the role that prolonged or complex febrile seizures may play in the genesis of hippocampal injury, clinical pathological studies have demonstrated other potential causes of mesial temporal sclerosis [7]. Dual pathology (gray matter heterotopia or focal cortical dysplasia + MTS) or "double hit" abnormality may be found in 15% of pediatric patients with mesial temporal sclerosis [7]. Genetics may play a role in hippocampal malformation and function, and ultimately in the development of clinical seizures of hippocampal origin. Familial cases of mesial temporal sclerosis have been reported [13]. Syndrome-specific genes for febrile seizures (channelopathies) have been identified, as have mutations in the SOX2 gene that have been linked to mesial temporal malformation and clinical temporal lobe seizures [13, 14]. Human herpes virus

G. L. Hedlund (✉)
Department of Radiology, Neuroradiology Division,
Primary Children's Medical Center,
100 N. Mario Capecchi Drive,
Salt Lake City, UT 84113, USA
e-mail: Gary.Hedlund@imail.org

G. L. Hedlund
Department of Radiology, University of Utah,
Salt Lake City, UT, USA

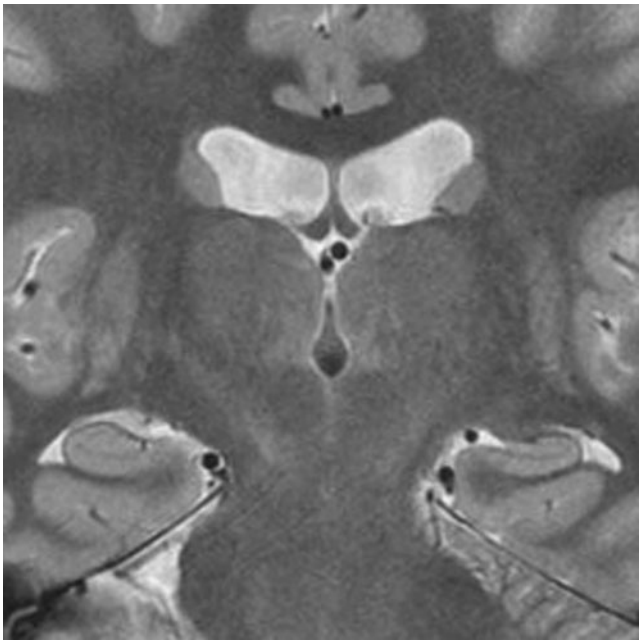

Fig. 1 Left mesial temporal sclerosis. Coronal inversion recovery T2-weighted image at 3.0 tesla through the body of the hippocampi shows a smaller left hippocampus with preserved architecture. Note the symmetrical hippocampal T2 signal. Histopathological evaluation after anterior left temporal lobectomy showed hippocampal sclerosis (5 mm, gap 1 mm, TE 42 msec, TR 5,300 msec, TI 140 msec, ET 8, BW 31.25, 512×416 matrix + parallel imaging)

6 (HHV6), the ubiquitous virus causing the common childhood illness roseola infantum, has been implicated in cases of limbic encephalitis and subsequent mesial temporal sclerosis and partial complex seizures [15]. Mesial temporal sclerosis has developed following methotrexate-induced leukoencephalopathy in the treatment of childhood leukemia [16].

Patients with medically refractory epilepsy due to mesial temporal sclerosis have one reliable method for cure and that is surgical resection of the hippocampus and anterior temporal lobe. Thus, accurate and timely imaging diagnosis of MTS reduces morbidity by accelerating focused treatment [17].

MRI is the imaging examination of choice for the early accurate diagnosis of MTS [7, 8, 18]. Although a wide range of MRI techniques is available for diagnosing MTS such as hippocampal MR volumetrics, MR T2 relaxometry and MR spectroscopy, simple visual inspection is the cornerstone of making this diagnosis in active clinical settings [19, 20]. When attention is given to obtaining coronal inversion recovery or fast spin-echo (FSE) T2 or FLAIR imaging perpendicular to the long axis of the hippocampal body, there is optimal opportunity to inspect the hippocampus [21]. The MR imaging hallmark of MTS is the atrophic hippocampus. The presence of T2 hyperintensity is less predictable and not necessary for the diagnosis. Another primary finding of MTS is obscuration of internal hippocampal architecture. Awareness of secondary features of MTS improves the sensitivity and positive predictive value of MRI. These secondary features include temporal lobe volume loss including loss of collateral white matter, ipsilateral mamillary body and fornix atrophy, and widening of the choroidal fissure and temporal horn. Loss of the amygdala pes digitations and increased signal within the anterior temporal white matter may be additional findings [22].

Nuclear medicine techniques valuable in the investigation of MTS include single photon emission tomography (SPECT), ictal SPECT and positron emission tomography (PET) [23].

More recently, many centers active in epilepsy diagnosis and treatment have integrated magnetoencephalography (MEG) and functional MRI (fMRI) into the preoperative evaluation of patients with refractory temporal lobe epilepsy [24–26] (Fig. 1).

References

1. Kadom N, Tsuchida T, Gaillard WD (2011) Hippocampal sclerosis in children younger than 2 years. Pediatr Radiol 41: doi:10.1007/s00247-011-2166-4
2. Nelson KB, Ellenburg JH (1978) Prognosis in children with febrile seizures. Pediatrics 61:720–727
3. Cendes F, Andermann F, Dubeau F et al (1991) Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures and temporal lobe epilepsy: an MRI volumetric study. Neurology 43:1081–1087
4. VanLandingham KE, Heinz ER, Cavazos JE et al (1998) Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. Ann Neurol 43:413–426
5. Tarkka R, Paakko E, Phytinen J et al (2003) Febrile seizures and mesial temporal sclerosis: no association in a long-term follow-up study. Neurology 60:215–218
6. Cendes F (2004) Febrile seizures and mesial temporal sclerosis. Curr Opin Neurol 17:161–164
7. Bote RP, Blázquez-Llorca L, Fernández-Gil MA et al (2008) Hippocampal sclerosis: histopathology substrate and magnetic resonance imaging. Semin Ultrasound CT MR 29:2–14
8. Ng YT, McGregor AL, Wheless JW (2004) Magnetic resonance imaging detection of mesial temporal sclerosis in children. Pediatr Neurol 30:8–85
9. Provenzale JM, Barboriak DP, VanLandingham K et al (2008) Hippocampal MRI signal hyperintensity after febrile status epilepticus is predictive of subsequent mesial temporal sclerosis. AJR 190:976–983
10. Berg AT, Shinnar S (1996) Unprovoked seizures in children with febrile seizures: short-term outcome. Neurology 47:562–568
11. Nelson KB, Ellenberg JH (1976) Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 295:1029–1033
12. Nelson KB, Ellenberg JH (1978) Prognosis in children with febrile seizures. Pediatrics 61:720
13. Sisodiya SM, Ragge NK, Cavalleri GL et al (2006) Role of SOX2 mutation in human hippocampal malformations and epilepsy. Epilepsia 47:534–542
14. Kroll-Seger J, Bien CG, Huppertz HJ (2009) Non-paraneoplastic limbic encephalitis associated with antibodies to potassium

channels leading to bilateral hippocampal sclerosis in a pre-pubertal girl. Epileptic Disord 11:54–59
15. Theodore WH, Epstein L, Gaillard WD et al (2008) Human herpes virus 6B: a possible role in epilepsy? Epilepsia 49:1828–1837
16. Hamamoto K, Oriuchi N, Kanazawa T et al (2009) Mesial temporal sclerosis associated with methotrexate-induced leukoencephalopathy. Pediatr Neurol 40:306–309
17. Ray A, Kotagal P (2005) Temporal lobe epilepsy in children: overview of clinical semiology. Epileptic Disord 7:299–307
18. Bronen RA, Cheung G, Charles JT et al (1991) Imaging findings in hippocampal sclerosis: correlation with pathology. AJNR 12:933–940
19. Van Paesschen W (2004) Qualitative and quantitative imaging of the hippocampus in mesial temporal lobe epilepsy with hippocampal sclerosis. Neuroimaging Clin N Am 14:373–400
20. Jack CJ Jr, Sharbrough FW, Cascino DG et al (1992) Magnetic resonance image-based hippocampal volumetry: correlation with outcome after temporal lobectomy. Ann Neurol 31:138–146
21. Bronen RA (1992) Epilepsy: the role of MR imaging. AJR 159:1165–1174
22. Mamourian AC, Cho Ch, Saylin A (1998) Lateral ventricular size and fornix asymmetry: more than coincidence in patients with temporal epilepsy? AJNR 19:9–13
23. Carne RP, O'Brien TJ, Kilpatrick CJ et al (2007) 'MRI-negative PET-positive' temporal lobe epilepsy (TLE) and mesial TLD differ with quantitative MRI and PET: a case control study. BMC Neurol 7:16
24. Wennberg R, Valiante T, Cheyne D (2011) EEG and MEG in mesial temporal lobe epilepsy: where do the spikes really come from? Clin Neurophysiol 122:1295–1313
25. Zhang X, Tokoglu F, Negishi M et al (2011) Social network theory applied to resting-state fMRI connectivity data in the identification of epilepsy networks with iterative feature selection. J Neurosci Methods 199:129–139
26. Bonelli SB, Powell R, Thompson PJ et al (2011) Hippocampal activation correlates with visual confrontation naming: fMRI findings in controls and patients with temporal lobe epilepsy. Epilepsy. doi:10.1016/j.eplepsyres.2011.04.007