When Baby's giggles are not funny: seven years overlooked diagnosis in a case of gelastic seizures

Saengpattrachai M, MD
email : montri_kid@hotmail.com

Montri Saengpattrachai, MD[1]

[1] Bangkok Child Health Center, Bangkok Hospital, Bangkok Hospital Group, Bangkok,Thailand.

Keywords:
Giggles, Pathologic laughter, Ictal laughing, Gelastic seizures, Hypothalamic hamartoma, Tuber cinereum

Laughter actually has positive emotional effect. However, it could be pathologic when laughter is not related to emotion and occurs independent of a stimulus in the environment. We reported a 7-year-6-month old Thai boy who presented with *'early giggles'* since the age of 2 months. Despite parental concerns, the symptoms were overlooked until seven years of age, when he developed complex partial seizures. An MRI study of the brain revealed a small ill defined lesion within the tuber cinereum that was compatible with hypothalamic hamartoma. We also reviewed and emphasized the characteristics of the pathologic laughing in infancy that should not have been ignored. Early diagnosis leads to appropriate counseling and proper seizure management. Common comorbidity such as precocious puberty and cognitive impairment or behavioral impediment should be followed up closely in long-term care.

A baby's giggling or laughing is always adorable and most parents do not have any cause to be concerned. However, pathologic laughter is different, particularly when it happens at an inappropriate age, or occurs without specific stimuli. It can cause hesitation in the observer, as to whether or not this is in line with the normal development of the child. Laughing seizures, known as gelastic seizures or ictal laughing, are epileptic events characterized by bouts of laughter as an isolated event, commonly lasting less than 30 seconds but frequently are accompanied by other seizure types.[1,2] According to the International League Against Epilepsy (ILAE) classification, gelastic seizures were classified into *"localization-related epilepsy"*. Criteria for diagnosis of gelastic seizures include stereotyped recurrent bouts of laughter, absence of external precipitants, concomitant additional paroxysmal events considered epileptic, presence of ictal or interictal epileptiform discharges on the electroencephalogram, and the absence of other conditions in which pathologic laughter may occur.[1] Gelastic seizures have been associated classically to hypothalamic hamartomas (HH) that are rare congenital lesions presenting with the classic triad of gelastic epilepsy, precocious puberty and developmental delay.[3,4] This report detailed an interesting case of gelastic seizures in infancy, caused by hypothalamic hamartoma, in a Thai boy in whom diagnosis had been overlooked for seven years. We also reviewed the clinical characteristics that should have caused earlier suspicion about pathologic laughing.

Case Report

A 7-year-6-month old, right handed Thai boy was brought to the emergency department due to brief but intense staring during his doing a jigsaw puzzle followed by a 10 minute generalized tonic-clonic seizure which precipitated a loss of consciousness. At the emergency room, he developed seizures twice and was treated as status epilepticus.

Two weeks prior to admission, according to his parents, he was noticed to have episodes of standing still, eyes turning upward and wetting himself without collapse or convulsive seizure. Past history revealed that he had had spontaneous bouts of giggles a couple times a week since 2 months of age. They were described as brief moments of the child giggling to himself, lasting for 30 to 60 seconds, without any precipitants and these symptoms frightened his mother. Because of maternal concern, he was evaluated by many pediatricians but due to his physical examination developmental milestones being unremarkable, the parents were advised to wait and see. Birth history revealed that he was a first baby, born full-term, to non-consanguineous Thai parents with a birth weight of 3,150 grams. Pre-, peri-, and post-natal period were uneventful. Developmental milestones were age appropriate although he showed exceptional academic performance. He did not have any underlying disease. Family history was unremarkable for neurologic disorders.

On physical examination, he was drowsy due to being post-ictal. BP 120/60 mmHg, HR 110 /min, T 37.2 ^{o}C, RR 22/min. Weight was 23 kg (50th centile). Height was 122 cm (50th centile). Heart, lungs and abdomen were normal. There were no dysmorphic features or neurocutaneous lesions. Neurological examination after he fully regained wakefulness, revealed a delightful boy with good orientation to time, place and person. Other neurological signs including cranial nerves, motor system, sensory system, gait and coordination were normal. Genitalia showed normal male phenotype without sign of precocious puberty.

Hematologic and biochemical laboratory tests including CBC, electrolytes, calcium, magnesium, phosphate, liver function, BUN, creatinine, thyroid function were normal. The 30 minutes, video electroencephalogram (vEEG), during wakefulness and natural sleep, using standard 10-20 system displayed normal background activity for age and no evidence of epileptiform discharge.

MRI of the brain with gadolinium revealed a small ill defined lesion at left side of hypothalamus (tuber cinereum) about 1.23 x 1.21 x 0.87 cm, which has slightly decreased T1, slightly increased T2 signal intensity without definite enhancement (Figure 1). These findings were consistent with sessile type, hypothalamic hamartoma. The pituitary stalk and suprasellar sellar region were within normal range. The cerebral parenchyma, brain stem and cerebellum showed normal signal intensity and appearance without definite space taking lesion. No infarction or hemorrhage was seen. MRA study of the brain showed normal vascularity without stenosis (Figure 2).

Seizures were well controlled by using topiramate at dosage of 3 mg/kg/day. Clinical seizures, developmental milestones, and signs of precocious puberty have been followed up in long term care.

Discussion

Pathologic laughter is defined as inappropriate laughter. The criteria, first proposed by Poeck in 1969, included laughter as response to non specific stimuli, no corresponding change in affect, no voluntary control of expression and no relief after the laughter.[5] This condition frequently is part of an associated syndrome of disease particularly in Angelman's syndrome. However, it has copious etiologies such as acquired neurologic damage, metabolic defects, and epilepsy known as gelastic seizures.[6] Gelastic seizures or ictal laughing, classifiedinto *"localization-related epilepsy"* according to the ILAE classification, are epileptic events characterized by bouts of laughter that are commonly deemed a hallmark of the evolution of hypothalamic hamartomas (HH).[1, 7] However, several studies have also reported that other conditions could cause laughing seizures such as focal cortical dysplasia, pituitary tumors, astrocytomas of mamillarybodies, third ventricular papillomas, lesion of the temporal lobes, frontal lobes, etc.[8]

Early detection and prevention of HH are important. Gelastic seizures are rarely diagnosed at their onset and may be misinterpreted as normal laughter or misdiagnosed as *'parental overconcern'* or even as infantile colic.[9] The clinical course of patients with gelastic seizures associated with HH is progressive, beginning with gelastic seizures in infancy and progressing to other seizure patterns in childhood and adulthood. Delay in diagnosis worsens seizure response leading to increases in both severity and frequency of seizures that directly cause cognitive impairment and behavioral hindrance.[10-13]

Our case of HH was diagnosed at age of seven years old because of overt convulsive seizures. His history of uncommon giggles during infancy was retrospectively discovered after detection of HH from MRI study of the brain. It is difficult to know whether or not the small lesion (less than one centimeter) of tuber cinereum found at the age of diagnosis (seven years of age) could have been detected in infancy. The size of HH reportedly correlates to the severity of the cognitive dysfunction, particularly in patients with large HH.[14-16] The cognitive function of our reported case is as yet, intact, perhaps his pathologic lesion in MRI is rather small. The location and anatomical features of HH have shown correlation with the clinical presentation. HH is classified into 2 types: pedunculated or type I, and sessile or type II. Pedunculated HH, clinically associating with precocious puberty, divide into type Ia that attach to the tuber cinereum and type Ib that attach to the angle between the tuber cinereum. Sessile HH, correlating to gelastic seizures, have a broad attachment to the floor of the third ventricle and the mamillary bodies.[17, 18] For our case, HH was compatible with sessile type, his first clinical manifestation was gelastic seizures.

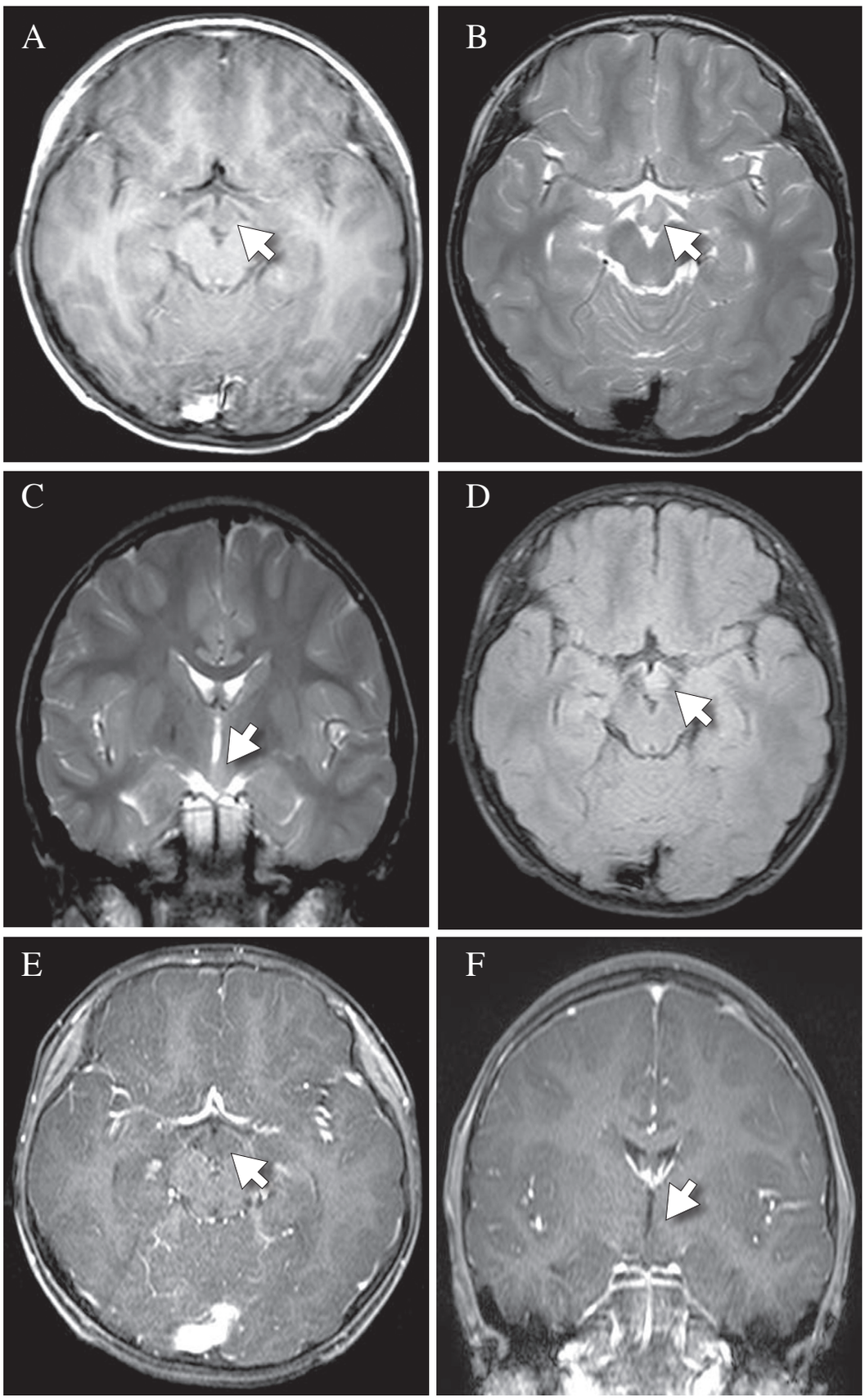

Figure 1: *MRI scan of the brain demonstrated small ill defined lesion at left side of hypothalamus (tuber cinereum) about 1.23 x 1.21 x 0.87 cm (white arrow), which had slightly decreased signal intensity in T1W (A, axial view), and slightly increased signal intensity in T2W (B, axial; C, coronal view) and FLAIR (D) without definite enhancement (E, axial; F, coronal view).*

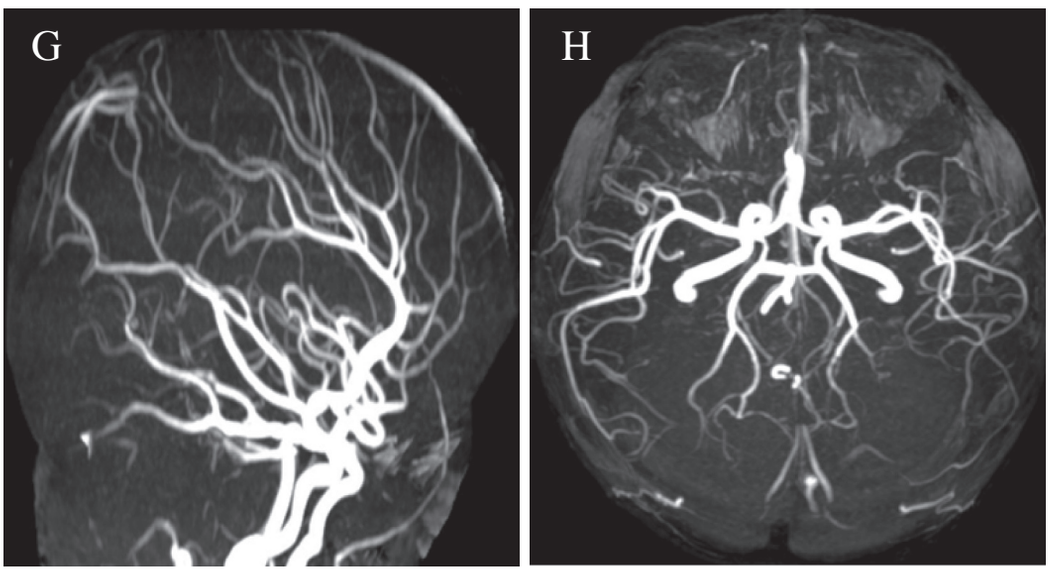

Figure 2: *MRA study of the brain demonstrated normal study without sign of vascular stenosis. The vascularity was normal (G, lateral view; H, top view).*

Precocious puberty, defined as the occurrence of puberty in girls aged less than 8 years and in boys aged less than 9.5 years, is a clinical finding that has been reported commonly in patients with gelastic seizures associated with HH which cause of 75% of precocious children aged between 1 and 3 years old.[19, 20] Even though this symptom has not shown up in our case, clinical observation of this aspect should not be forgotten in long term care.

Treatments of HH include both medical management for epilepsy and precocious puberty, and surgical interventions for those with medical failure or having intracranial hypertension caused by HH. A review of the literature illustrates that gelastic seizures are typically refractory to antiepileptic agents and these progressive symptoms will eventually deteriorate intellection and behavioral function.[21-24] Currently the best treatment for those with intractable seizures is the ablation of the HH that can be done with different procedures including surgery and nonsurgical treatments e.g. radiosurgery.[25] The nonconventional surgeries e.g. radiofrequency coagulation, stereotactic implantation of 125I radioactive seeds, and gamma-knife radiosurgery in particular seem to be safe and effective treatments even in children.[26] Stereotactic radiosurgery is generally used for emergency and suits for small intrahypothalamic hamartomas or the postoperative residue lesion.[27]

In Thailand, Bunyaratavej et al. applied transcallosal subchoroidal approach for resection of HH to a patient with intractable gelastic seizures and had a successful outcome without interfering with patient's memory function.[28]

For our case, gelastic seizures and complex partial seizures were well controlled by using topiramate (5 mg/kg/day). After 12 months follow up, developmental milestones were uneventful and there were no clinical signs of precocious puberty.

Conclusion

Pediatricians should remain aware of and pay attention to patients where there is parental concern about abnormal laughter. Pathologic laughter is not related to emotion but independent of a stimulus in the environment. An interview about seizure history, the child's developmental history and a complete physical examination are very important and absolutely necessary. MRI is the best investigation for confirmation the diagnosis of HH. The best treatment for patients with failed medical control is the ablation of the HH. This can be done with different procedures including surgery and nonsurgical treatments. The patients should have long term follow up to evaluate about seizure control, cognitive ability, development and precocious puberty.

References

1. Gascon GG, Lombroso CT. Epileptic (gelastic) laughter. *Epilepsia* 1971;12:63-76.
2. Arroyo S, Lesser RP, Gordon B, et al. Mirth, laughter and gelastic seizures. *Brain* 1993;116:757-80.
3. Harvey AS, Freeman JL. Epilepsy in hypothalamic hamartoma: clinical and EEG features. *Semin Pediatr Neurol* 2007;14:60-4.
4. Striano S, Striano P, Sarappa C, et al. The clinical spectrum and natural history of gelastic epilepsy-hypothalamic hamartoma syndrome. *Seizure* 2005;14:232-9.
5. Udaka F, Yamao S, Negata H, et al. Pathologic laughing and crying treated with levodopa. *Arch Neurol* 1984; 41:1095-6.
6. Nirenberg SA. Normal and pathologic laughter in children. *Clin Pediatr (Phila)* 1991;30:630-2.
7. Kerrigan JF, Nq YT, Chung S, et al. The hypothalamic hamartoma: a model of subcortical epileptogenesis and encephalopathy. *Semin Pediatr Neurol* 2005;12:119-31.
8. Cheung CS, Parrent AG, Burneo JG. Gelastic seizures: not always hypothalamic hamartoma. *Epileptic Disord* 2007;9:453-8.
9. Penfold JL, Manson JI, Caldicott WM. Laughing seizures and precocious puberty (case report and review of the literature). *Aust Paediatr J* 1978;14:185-90.
10. Frattali CM, Liow K, Craig GH, et al. Cognitive deficits in children with gelastic seizures and hypothalamic hamartoma. *Neurology* 2001;57:43-6.
11. Deonna T, Ziegler AL. Hypothalamic hamartoma, precocious puberty and gelastic seizures: a special model of "epileptic" developmental disorder. *Epileptic Disord* 2000;2:33-7.
12. Prigatano GP, Wethe JV, Gray JA, et al. Intellectual functioning in presurgical patients with hypothalamic hamartoma and refractory Epilepsy. *Epilepsy Behav* 2008; 3:149-55.
13. Nguyen D, Singh S, Zaatreh M, et al. Hypothalamic hamartomas: seven cases and review of the literature. *Epilepsy Behav* 2003;4:246-58.
14. Berkovic S, Anderman F, Melanson D, et al. Hypothalamic hemartoma and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. *Ann Neurol* 1988;23:429-39.
15. Quiske A, Frings L, Wagner K, et al. Cognitive functions in juvenile and adult patients with gelastic epilepsy due to hypothalamic hamartoma. *Epilepsia* 2006;47:153-8.
16. Striano S, Striano P, Cirillo S, et al. Small hypothalamic hamartomas and gelastic seizures. *Epileptic Disord* 2002;4:129-33.
17. Valdueza JM, Cristante L, Dammann O, et al. Hypothalamic hamartomas: with special reference to gelastic epilepsy and surgery. *Neurosurgery* 1994;34:949-58.
18. Téllez-Zenteno JF, Serrano-Almeida C, Moien-Afshari F. Gelastic seizures associated with hypothalamic hamartomas. An update in the clinical presentation, diagnosis and treatment. *Neuropsychiatr Dis Treat* 2008;4:1021-31.
19. Albright AL, Lee PA. Neurosurgical treatment of hypothalamic hamartomas causing precocious puberty. *J Neurosurg* 1993;78:77-82.
20. Starceski PJ, Lee PA, Albright AL, et al. Hypothalamic hamartomas and sexual precocity. Evaluation of treatment options. *Am J Dis Child* 1990;144:225-8.
21. Palmini A, Chandler C, Andermann F, et al. Resection of the lesion in patients with hypothalamic hamartomas and catastrophic epilepsy. *Neurology* 2002;58:1338-47.
22. Mullatti N, Selway R, Nashef L, et al. The clinical spectrum of epilepsy in children and adults with hypothalamic hamartoma. *Epilepsia* 2003;44:1313-19.
23. Striano S, Meo R, Bilo L, et al. Gelastic epilepsy: symptomatic and cryptogenic cases. *Epilepsia* 1999;40:294-302.
24. Brandberg G, Raininko R, Eeg-Olofsson O. Hypothalamic hamartoma with gelastic seizures in Swedish children and adolescents. *Eur J Paediatr Neurol* 2004; 8:35-44.
25. Cascino GD, Andermann F, Berkovic SF, et al. Gelastic seizures and hypothalamic hamartomas: evaluation of patients undergoing chronic intracranial EEG monitoring and outcome of surgical treatment. *Neurology* 1993; 43:747-50.
26. Romanelli P, Muacevic A, Striano S. Radiosurgery for hypothalamic hamartoma. *Neurosurg Focus* 2008;24:E9
27. Sturm JW, Andermann F, Berkovic SF. "Pressure to laugh": an unusual epileptic symptom associated with small hypothalamic hamartomas. *Neurology* 2000;54: 971-3.
28. Bunyaratavej K, Locharernkul C, Tepmongkol S, et al. Successful resection of Hypothalamic harmatoma with intractable gelastic seizures- by transcallosal subchoroidal approach. *J Med Assoc Thai* 2006;89:1269-76.