Change in hippocampal volume in children with febrile seizure at different periods

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Abstract

Background

This study aimed to investigate the change of hippocampal volume in children at different periods after febrile seizure.

Methods

MRI of the brain was performed in 60 children with febrile seizure (30 patients with simple febrile seizure and 30 patients with prolonged febrile seizure) and in 30 healthy children. The volume of the hippocampus was tested and compared at different periods after febrile seizure.

Results

The volumes of hippocampus in the two febrile seizure groups increased compared with that of the control group in acute period after seizure. There was no obvious difference in hippocampal volume between the simple febrile seizure group and the prolonged febrile seizure group in the acute or chronic period after seizure. The average annual growth of hippocampal volume in the simple febrile seizure group was greater than that in the prolonged febrile seizure group.

Conclusions

Febrile seizure can affect hippocampus volume in the acute stage of convulsion. Prolonged febrile seizure affects hippocampus development with aging.

What Is Already Known On This Topic

1. The HCV can increased with aging.
2. Epilepsy can influence the decrease in HCV of children.

What This Study Adds

- The volumes of hippocampus in the two febrile seizure groups increased compared with that of the control group. The average annual growth of hippocampal volume in the simple febrile seizure group was greater than that in the prolonged febrile seizure group.
- Simple and prolonged febrile seizures can both affect hippocampus volume in the acute stage of convulsion. Furthermore, prolonged febrile seizure affects hippocampus development more than

simple febrile seizure with time. It is important to control the duration of febrile seizure to reduce its impact on the hippocampus development.

Introduction

Febrile seizure (FS) is defined as a seizure accompanied by a fever of $\geq 38^{\circ}\text{C}$ (100.4°F), occurring in children aged 6 months to 5 years, exclusively caused by intracranial infection or metabolic abnormality, without incidence of previous neonatal seizures; FS may otherwise meet the criteria for other acute symptomatic seizures.¹ The peak incidence of FS is at 18 months of age. FS has been classified as simple or complex, depending on its duration, recurrence, and the presence of additional seizure features.² Simple febrile seizure (SFS) lasts for less than 15 minutes, is generalized, does not recur within 24 hours, and is comprised of generalized tonic and clonic activity without a focal component. Prolonged febrile seizures (PFS) is defined as the seizure lasts more than 15 minutes occurring in children aged 4 months to 5 years with febrile illness without infection of the central nervous system (CNS), electrolyte imbalance and previous history of FS.^{3–4}

The hippocampus is one of the important structures of the limbic system of the brain. Changes in hippocampus is considered an important influential factor of epilepsy.^{5,6} While multiple studies support that FS, especially the febrile status epilepticus, is one of the factors that impairs the hippocampus.⁷ Studies focused on differences in effects on hippocampal volume between SFS and PFS are limited. The purpose of this study was to analyze the dynamics of hippocampus volume (HCV) changes in children with different types of febrile seizure and to explore the relationship between the change in HCV and disease prognosis.

Methods

Study participants

We recruited 60 children with FS (30 patients with SFS and 30 patients with PFS) and 30 children without FS from Shengjing Hospital of China Medical University between January 2013 and September 2020. Forty patients with FS had their first MRI within 48–72 h after the seizure attack. All the children underwent complete MRI of the brain two times, within intervals of 12–20 months. Written informed consent was obtained for all patients from their parents or legal guardians. This study was approved by the human research ethics committees of Shengjing Hospital of China Medical University.

Specimen data collection

The head MRI scanning equipment used was 3.0T MR scanner (Philips Intera Achieva), TR / TE = 3000 / 80ms, matrix 256×256 , and contiguous 3-mm-thick sections were obtained. A profile of the hippocampus was manually delineated on successive coronal T2WI slices based on previously published methods.^{8–10}

The measurement of HCV

MRI analyses were performed by a Picture Archiving & Communication System (PACS) (Neusoft, China).

The volume of each slice= the hippocampus area of the plane × 3-mm-thickness.

The hippocampus area of the plane was collected in PACS (Fig 1).

The whole volume was calculated by accumulating the volume of each slice.

Standardized formula of HCV: $V_s = V_e \times M_m / M_e$.

V_e is actual HCV, M_m is the mean cranial cavity volume of the total MRI of all cases, M_e is the cranial cavity volume of the subject.

Cranial cavity volume= Anteroposterior diameter×Left and right diameter×upper and lower diameter.

To reduce the error caused by subjective factors, all data were measured by one person, who used the average value of three repeated measurements. We proposed an average annual growth of total HCV(ΔV) to represent the changes of HCV.

$$\Delta V = [V_{s2} - V_{s1}] / T.$$

V_{s2} is the standardized HCV of the second time; V_{s1} is the standardized HCV of the first; T is the time interval between the two visits.

Statistical analysis

We used SPSS 20.0 software for statistical analysis. Comparison between the groups was performed by two-sample T test or paired T test. The measurement data meeting normal distribution is expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$). The Mann–Whitney U test was used for comparison between the two groups meeting abnormal distribution. The value ($p < 0.05$) was used for considering statistical significance.

Results

Sixty children with FS and 30 healthy children were retrospectively analyzed between January 2013 and September 2020. The age of the patients with the first episode of FS varied between 1 year and 6 years (mean 2.4 years). Thirty-eight patients (63.3%) were male, 22 (36.7%) were female, and the male-to-female ratio was 1.72:1. All patients were term infants, and there were no differences associated with vaginal versus cesarean delivery. None of the patients differed from healthy children with respect to growth, development, or intelligence before the attack of FS.

The measurement on HCV after FS at the first MRI scan

The volume of the right hippocampus was clearly larger than that of the left hippocampus in the control group ($p < 0.05$). There was no significant difference in the volume of the left and right hippocampus within the SFS group ($p > 0.05$) nor within the PFS group ($p > 0.05$)(Fig. 2).

The volume of the left and right hippocampus in the SFS as well as PFS group was significantly increased compared with that of the control group (both, $p < 0.05$). There was no significant difference in the left and right HCV between the SFS group and PFS group (both, $p > 0.05$)(Fig. 2).

Measurement of hippocampal volume after FS at the second MRI scan

The volume of the right hippocampus was larger than that of the left hippocampus but with no statistical significance in the SFS group ($p > 0.05$) or in the PFS group ($p > 0.05$). There was no significant difference in the volume of the left or right hippocampus between the SFS group and PFS group ($p > 0.05$).

The average annual growth of HCV(ΔV)

We proposed an average annual growth of total HCV(ΔV) to represent the changes of HCV. The ΔV of the left as well as right hippocampus in the SFS group was clearly greater than that in the PFS group (both, $p < 0.05$). The ΔV of the bilateral hippocampus in the SFS group was more than that in the PFS group ($p < 0.05$)(Table. 1).

Discussion

FS is the most frequently occurring seizure in children.^{1,12} The incidence of FS has been reported as 2–5% in the USA and Western Europe, 6–9% in Japan, and around 10% in India.¹³ The age for FS ranges from 1 month to 6 years. Most affected children have their first FS before 3 years of age, with the peak range from 18 to 24 months of age.^{14,15} In our study, the age of all the patients with the first episode of FS varied between 1 year and 6 years (mean 2.4 years). The age of onset is a critical standard in the diagnosis of FS in children. FS is more common in male children than in female children.¹⁶ In our study, the male/female ratio was 1.72:1. The reason for this difference between the genders is thought to be because male children are more susceptible to infections and because of the temporal differences in development of the nervous and endocrine systems.

The risk factors and causes of FS include viral infection, vaccinations, and genetic predisposition.^{17–19} Some cohort studies have found that the recurrence rate of FS is about 30% and with an increase in recurrence within one year of onset of FS.^{21–23} The risk factors for recurrence include the age at onset, temperature accompanying the seizure, duration of FS, and day nursery.^{20–25}

Studies reported that the incidence of FS developing to epilepsy is about 2–5%,²⁶ which is higher than the rate within the general population. The risk factors for FS developing to epilepsy include developmental delay, abnormal neurologic examination, early age of onset, the duration of FS, and a family history of epilepsy.^{26,27} FS can partly cause hippocampal injury as hippocampal sclerosis and hippocampal malformations, that could contribute to the development of epilepsy.^{28,29} Studies have reported that skeletal changes of the nerve cells in the hippocampus without cell death were observed in young mice by silver staining from hours to days after PFS.^{30,31}

The current study found that the volume of the right hippocampus was larger than that of the left hippocampus in the control group, which was consistent with previous reports, and is possibly due to right-handedness.³² At the first MRI scan, the right side of the hippocampus was slightly larger than the left side, but there was no statistical difference in the SFS group or PFS group. The reason for this may be that the increased in the left HCV slightly more than the right side in the two FS groups, when compared with the control group. In our opinion, the nerve cells in the left hippocampus may be marginally fewer than those in the right side. Moreover, the function of the cells of the left hippocampus may be slightly reduced than that of the right. Therefore, the left hippocampal cells are more vulnerable to injury than those of the right, and the volume change is more obvious. The left HCV of the PFS group increased significantly compared with that of the control group ($p < 0.05$), as did that on the right side. Findings from some studies are consistent with this result.^{41,42} The left hippocampal volume in the SFS group also clearly increased compared with the control group ($p < 0.05$), but showed no clear difference compared with the PFS group ($p > 0.05$). This difference occurred simultaneously in the right HCV. This result may be explained by the first MRI scans performed within 48–72 hours after the acute FS, because the internal structure and function of nerve cells have transient disturbance as inflammation or intracellular edema. The course of febrile seizure is often accompanied by inflammation and the pathogenesis may be related to some inflammatory factors.^{35–38} These inflammatory factors have also existed in the development of epilepsy.^{39,40} The degree of injury involved in the hippocampus nerve cells varied according to the duration of the seizure. Complete recovery of the internal structure and function of the nerve cells is difficult and development to pathological changes occurs when the duration of the seizure reaches a threshold. However, the threshold is vague and not clearly defined. The nerve damage may result in spontaneous, progressive cell death in the months or years after seizure, culminating in the formation of the hippocampus atrophy and hardening.^{43,44}

PFS may cause the development of epilepsy, which is related to hippocampus atrophy and hardening.^{26–29} In this study, the second MRI scan of the head was completed after 12–20 months after the first scan. In the second MRI scan, the volume of the right hippocampus was larger than that of the left hippocampus but with no statistical significance in the SFS group ($p > 0.05$) or the PFS group ($p > 0.05$). There was no significant difference in the volume of unilateral hippocampus between the SFS group and the PFS group ($p > 0.05$). The HCV increased with aging, with no significant difference between the bilateral sides. The HCV of the children increased compared with that of their own in the first MRI scan, and no atrophy was shown in the numerical value. There is no evidence to prove that the growth curve of

hippocampus volume matched the curve of growth and development in children. The ΔV of the left or right hippocampus in the SFS group was clearly greater than that in the PFS group ($p < 0.05$). The growth of the hippocampus volume is slower in PFS group than in the SFS group. Therefore, PFS can injure the hippocampus development more severely than SFS. Hippocampus injury will affect the prognosis of PFS patients, inducing the development of epilepsy, and long-term neurocognitive disability.^{27–29, 33, 34}

In conclusion, SFS and PFS can affect HCV in the acute stage of convulsion. However, PFS affects hippocampus development more than PFS with aging. Therefore, it is important to control the duration of FS to reduce its impact on the hippocampus development.

Declarations

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Disclosure Statement: The authors declare that they have no competing interests.

Category of Study: clinical study

Consent Statement: All cases were reviewed in our hospital. Informed consent for participation in this study was obtained from the patients' guardians. All study methods were carried out in accordance with relevant guidelines and regulations, consistent with the Declaration of Helsinki.

Author Contributions: Hua Wang designed the research protocols; QingJun Cao executed the literature search and wrote the manuscript; JinYing Huang analyzed data; Hua Wang modified the article. All authors edited the manuscript's final draft.

Ethical Approval

This study was approved by the human research ethics committees of Shengjing Hospital of China Medical University (No:2020PS111K).

All the patient's guardians consent to participate the study.

Consent to Publish

All authors consent to publish the manuscript.

Availability of data and materials

All the data and materials are available in ShengJing Hospital of China Medical University.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to personal privacy for the children but are available from the corresponding authors.

References

1. Freeman JM. Febrile seizures: a consensus of their significance, evaluation, and treatment. *Pediatrics* 1980;66(6):1009.
2. Shinnar S. Febrile seizures and mesial temporal sclerosis. *Epilepsy Curr* 2003;3:115-8.
3. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia* 1993;34(4): 592-596.
4. Patterson KP, Baram TZ, Shinnar S. Origins of temporal lobe epilepsy: febrile seizures and febrile status epilepticus. *Neurotherapeutics*. 2014 Apr;11(2):242-50.
5. Squire LR, van der Horst AS, Mc Duff SG, et al. Role of the hippocampus in remembering the past and imagining the future. *Proc Natl Acad Sci U S A* 2010;107(44) : 19044-19048
6. Nee DE, Jonides J. Dissociable contributions of prefrontal cortex and the hippocampus to short-term memory: evidence for a 3-state model of memory. *Neuro Image*. 2011;54(2):1540-1548
7. Berg AT, Shinnar S. Complex febrile seizures. *Epilepsia* 1996;37:126-33.
8. Rod C Scott, Martin D King, David G Gadian, Brian G R Neville, Alan Connelly. Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. *Brain*, 2003, 126(Pt 11): 2551-2557.
9. Zhang YZ, Li WH, Gao Y, et al. Hippocampal volume in children with temporal lobe epilepsy compared to healthy children: a magnetic resonance imaging study. *Neurol India*, 2012, 60(1): 29-35.
10. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia*, 2017, 58(4): 512-521.
11. Knudsen FU. Febrile seizures—treatment and outcome. *Brain Dev* 1996;18:438-49.
12. Patel N, Ram D, Swiderska N, Mewasingh LD, Newton RW, Offringa M. Febrile seizures. *BMJ*. 2015 Aug 18;351:h4240.
13. Verity CM, Golding J. Risk of epilepsy after febrile convulsions: a national cohort study. *BMJ*, 1991;303:1373-6.
14. Offringa M, Hazebroek-Kampschreur AAJM, Derksen-Lubsen G. Prevalence of febrile seizures in Dutch school children. *Paediatr Perinat Epidemiol* 1991;5:181-8.
15. Hauser WA. The prevalence and incidence of convulsive disorders in children. *Epilepsia*, 1994;35:1-6.

16. Dreier JW, Li J, Sun YL, et al. Evaluation of long-term risk of epilepsy, psychiatric disorders, and mortality among children with recurrent febrile seizures: a national cohort study in Denmark. *JAMA Pediatr*; 2019, 173(12): 1164-1170.
17. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: a matched case-control study. *Epilepsia*. 1995;36(4):334-341.
18. Li X, Lin Y, Yao G, Wang Y. The Influence of Vaccine on Febrile Seizure. *Curr Neuroparmacol*. 2018;16(1):59-65.
19. Smith DK, Sadler KP, Benedum M. Febrile Seizures: Risks, Evaluation, and Prognosis. *Am Fam Physician*. 2019;99(7):445-450.
20. 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;124:574-84.
21. Berg AT, Shinnar S, Daresky AS, et al. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med* 1997;151:371-8.
22. Waruiru C, Appleton R. Febrile seizures: an update. *Arch Dis Child* 2004;89:751-6.
23. Rowhani-Rahbar A, Fireman B, Lewis E, et al. Effect of age on the risk of fever and seizures following immunization with measles-containing vaccines in children. *JAMA Pediatr*. 2013;167(12):1111-1117.
24. Hashimoto R, Suto M, Tsuji M, Sasaki H, Takehara K, Ishiguro A, Kubota M. Use of antipyretics for preventing febrile seizure recurrence in children: a systematic review and meta-analysis. *Eur J Pediatr*. 2021 Apr;180(4):987-997.
25. Sartori S, Nosadini M, Tessarin G, Boniver C, Frigo AC, Toldo I, Bressan S, Da Dalt L. First-ever convulsive seizures in children presenting to the emergency department: risk factors for seizure recurrence and diagnosis of epilepsy. *Dev Med Child Neurol*. 2019 Jan;61(1):82-90.
26. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med* 1987;316(9):493-498.
27. Hesdorffer DC, Benn EK, Bagiella E, et al. Distribution of febrile seizure duration and associations with development. *Ann Neurol*. 2011;70(1):93-100.
28. Chatzikonstantinou A. Epilepsy and the hippocampus. *Front Neurol Neurosci*. 2014;34:121-42.
29. Isnard J, Bourdillon P. Morphological imaging of the hippocampus in epilepsy. *Rev Neurol (Paris)*. 2015 Mar;171(3):298-306.
30. Chang YC, Huang CC, Huang SC. Long-term neuroplasticity effects of febrile seizures in the developing brain. *Chang Gung Med J*. 2008 Mar-Apr;31(2):125-35.
31. Dubé C, Yu H, Nalcioğlu O, Baram TZ. Serial MRI after experimental febrile seizures: altered T2 signal without neuronal death. *Ann Neurol*. 2004;56(5):709-14.
32. Szabo CA, Xiong J, Lancaster JL, Rainey L, Fox P. Amygdalar and hippocampal volumetry in control participants: differences regarding handedness. *AJNR Am J Neuroradiol*. 2001 Aug;22(7):1342-5.
33. Sierra A, Gröhn O, Pitkänen A. Imaging microstructural damage and plasticity in the hippocampus during epileptogenesis. *Neuroscience*. 2015 Nov 19;309:162-72.

34. Huberfeld G, Blauwblomme T, Miles R. Hippocampus and epilepsy: Findings from human tissues. *Rev Neurol (Paris)*. 2015 Mar;171(3):236-51.
35. Joshua R Francis, Peter Richmond, Christine Robins, Katie Lindsay, Avram Levy, Paul V Effler, Meredith Borland, Christopher C Blyth. An observational study of febrile seizures: the importance of viral infection and immunization. *BMC Pediatr*. 2016 Dec 3;16(1):202.
36. Talebian A, Hassani F, Nikoueinejad H, Akbari H. Investigating the Relationship between Serum Levels of Interleukin-22 and Interleukin-1 Beta with Febrile Seizure. *Iran J Allergy Asthma Immunol*. 2020 Aug 25;19(4):409-415.
37. Al Morshedy S, Elsaadany HF, Ibrahim HE, et al. Interleukin-1 β and interleukin-1receptor antagonist polymorphisms in Egyptian children with febrile seizures: A case-control study. *Medicine (Baltimore)*. 2017 Mar;96(11):e6370.
38. Choi J, Choi SA, Kim SY, Kim H, Lim BC, Hwang H, Chae JH, Kim KJ, Oh S, Kim EY, Shin JS. Association Analysis of Interleukin-1beta, Interleukin-6, and HMGB1 Variants with Postictal Serum Cytokine Levels in Children with Febrile Seizure and Generalized Epilepsy with Febrile Seizure Plus.
39. Rana A, Musto AE. The role of inflammation in the development of epilepsy. *J Neuroinflammation*. 2018 May 15;15(1):144.
40. Dupuis N, Auvin S. Inflammation and epilepsy in the developing brain: clinical and experimental evidence. *CNS Neurosci Ther*. 2015 Feb;21(2):141-151.
41. Huang CC, Chang YC. The long-term effects of febrile seizures on the hippocampal neuronal plasticity - clinical and experimental evidence. *Brain Dev*. 2009 May;31(5):383-7.
42. Mewasingh LD, Chin RFM, Scott RC. Current understanding of febrile seizures and their long-term outcomes. *Dev Med Child Neurol*. 2020 Nov;62(11):1245-1249.
43. Scantlebury MH, Heida JG. Febrile seizures and temporal lobe epileptogenesis. *Epilepsy Res*. 2010 Mar;89(1):27-33.
44. Pujar SS, Seunarine KK, Martinos MM, Neville BGR, Scott RC, Chin RFM, Clark CA. Long-term white matter tract reorganization following prolonged febrile seizures. *Epilepsia*. 2017 May;58(5):772-780.

Table

Table 1. The average annual growth of HCV(ΔV) in SFS and PFS

ΔV cm ³ /y	PFS group N=30	SFS group N=30	<i>p</i> value
Left ΔV	0.317 $\pm$ 0.112,0.416	0.482 $\pm$ 0.318,0.798	0.022
Right ΔV	0.358 $\pm$ 0.229,0.418	0.532 $\pm$ 0.314,1.028	0.021
Total ΔV	0.675 $\pm$ 0.404,0.768	1.014 $\pm$ 0.647,1.856	0.022

ΔV : average annual growth of HCV; PFS: prolonged febrile seizure; SFS: simple febrile seizure; All values in median (IQR), M(P25-P75), cm^3 / year.

Figures

Figure 1

The measurement of hippocampal volume on MRI

The PACS system software delineates the hippocampal contour and automatically obtains the delineated area.

Figure 2

Comparison of left and right hippocampal volume in control group, SFS group and PFS group at the first time of MRI scanning

The volume of the right hippocampus was obviously larger than that of the left hippocampus in the control group ($*p<0.05$). The volume of the left and right hippocampus in the SFS group, respectively, was significantly increased compared with those of the control group ($p<0.05$). The volume of the left and

right hippocampus in the PFS group, respectively, was significantly increased compared with those of the control group ($p<0.05$).

Abbreviations: PFS: prolonged febrile seizure; SFS: simple febrile seizure