Epilepsy Research 157 (2019) 106189

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Type IIB focal cortical dysplasia with balloon cells in medial temporal lobe epilepsy: Clinical, neuroimaging, and histopathological findings

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ARTICLE INFO

Keywords:
Focal cortical dysplasia
Balloon cells
Hippocampus
Medial temporal lobe
MTLE-FCDIIB

ABSTRACT

Purpose: Type IIB focal cortical dysplasia (FCD) is an important cause of drug-resistant epilepsy. However, balloon cells located in the medial temporal lobe have been seldom reported. We aimed to discuss the clinical and pathological features of Type IIB FCD with balloon cells in the medial temporal lobe (MTLE-FCDIIB) and the differential diagnosis with other types of mesial temporal lobe epilepsy.

Methods: Three MTLE-FCDIIB cases were enrolled from Peking Union Medical College Hospital. Clinical and neuroimaging data were analyzed and histology features observed on hematoxylin-eosin (H&E) staining and immunochemical staining, including vimentin, nestin, S-100, CD34, neuronal nuclei antigen (Neun), glial fibrillary acidic protein (GFAP), neurofilament heavy chain (SMI32), were discussed.

Results: All cases involved drug-resistant epilepsy patients with childhood onset. The semiology of the epileptic seizure was a highly frequent partial seizure with or without generalized tonic-clonic seizures. Magnetic resonance imaging showed hyper-intensity in the medial temporal lobe without atrophy, different from mesial temporal sclerosis. Histological examination indicated the presence of balloon cells in the white matter of the para-hippocampal gyrus, subiculum, and cornu ammonis with cortical disorganization, and SMI32 positive dysmorphic neurons in the gray matter. Balloon cells were immunohistochemically stained with vimentin and nestin. Granular cell dispersion and pyramidal cell loss were not found.

Conclusions: The presence of balloon cells in the medial temporal lobe is observed in a rare subgroup of FCD, named MTLE-FCDIIB. It has distinct clinical manifestations, neuroimaging features, pathological changes, and prognosis, which should be differentiated from mesial temporal lobe sclerosis and mesial temporal lobe tumors. Our findings enable more accurate diagnosis of mesial temporal lobe epilepsy.

1. Introduction

Diagnosis and treatment of drug-resistant epilepsy is still a challenge for neurologists. Evaluation of surgical pathology is important for determining prognosis in surgeries associated with epilepsy. Ingmar et al. examined the brain bank and found that focal cortical dysplasia was the most common diagnosis among children (39.3%) and hippocampal sclerosis was the most common histopathological diagnosis among adults (44.5%) (Blümcke et al., 2017).

Focal cortical dysplasia (FCD) is congenital architectural and cytoarchitectural abnormalities of the six layers of the cerebral cortex. Type II FCD is the most common subtype of this malformation (45.3%) (Blümcke et al., 2017). As defined by Taylor and colleagues in 1971 (Taylor et al., 1971) and by Ingmar et al. (Blümcke et al., 2011) in 2011, type II FCD is characterized by the presence of dysmorphic neurons and balloon cells (BC), the latter being hallmarks of type IIB FCD. Most BC are extratemporally located, 50% of in the frontal lobe (Blümcke et al., 2017; Spreafico and Blümcke, 2010). The onset of the seizures in type II FCD typically occurs during childhood. The majority of epilepsy caused by type II FCD is drug-resistant. The prognosis after the operation is favorable, with satisfactory control of the disease, and in some cases, complete healing may be observed.

Hippocampal sclerosis is the most common cause of medial temporal lobe epilepsy (MTLE), accounting for 36.4% in all surgical

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https://doi.org/10.1016/j.eplepsyres.2019.106189
Received 2 June 2019; Received in revised form 2 August 2019; Accepted 12 August 2019
Available online 13 August 2019
0920-1211/

specimens (Blümcke et al., 2017). Medial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is a syndromic diagnostic entity with both clinical and pathological features. Surgery is helpful for better seizure control, but the postoperative outcome is associated with the severity and type of HS, and is not as good as MTLE with foreign tissue lesions (Wieser, 2004). Early and proper diagnosis through clinical examination and imaging helps in the selection of the most appropriate timing for the operation.

Herein, we have summarized the clinical, neuroimaging, and neuropathological features of MTLE-FCDIIB, which will aid differential diagnosis for other causes of MTLE.

2. Methods

Three MTLE-FCDIIB cases from the epilepsy tissue bank of the Neuropathology Laboratory in the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, were evaluated. Written informed consent was obtained from the parents of the participants and from the patients themselves. The study was approved by the ethics committee of the Chinese Academy of Medical Sciences (proposal number 2017006, year 2017).

Clinical information, including demographic data, seizure semiology, and neuroimaging, was collected. Brain MRI scanning was performed on a magnet operating at 3.0 T (Discovery MR750w, GE Healthcare, Buckinghamshire, England). The parameters of the MRI scan were T1-weighted (T1) sequence (320 * 160 matrix, TE = 21.94, TR = 1607.47, flip angle = 90, inversion time = 740, slice thickness = 4 mm, slice gap = 0, 36 slices, field of view 240 mm) and T2-weighted fluid-attenuated inversion recovery (T2FLAIR) sequence (352 * 224 matrix, TE = 119.4, TR = 12000, flip angle = 90, inversion time = 2200, slice thickness = 4 mm, slice gap = 0, 36 slices, field of view 240 mm). With regard to the histology, resected tissues were fixed in 10% buffered formalin and then embedded in paraffin, and 10-μm-thick sections were stained with H&E. The immunohistochemistry staining was performed in a Ventana automated stainer, using an avidin-biotin complex, peroxidase-based method with the following polyclonal antibodies (Ab): anti-NeuN (1/3000, Abcam, UK), anti-GFAP (1/500, Abcam, UK), anti-nestin (1/100, ZSGB-Bio, China), anti-SMI32 (1/1000, Abcam, UK), anti-vimentin (1/400, Leica, Germany), anti-CD34 (1/100, Leica, Germany), and anti-S-100 (1/200, Leica, Germany). Photomicrographs were taken with the LEICA DM2500 microscope and the digital camera (Leica, Germany).

3. Results

3.1. Clinical results

Table 1 summarizes the clinical data of the patients. All of the patients had drug-resistant epilepsy with childhood onset and long duration before operation (8, 19, and 21 years, respectively). The semiology was a focal seizure with or without secondary generalized tonic-clonic seizures (GTCS). The frequency of the seizures varied from 2 to 3 per day to more than 10 per day. No auras were reported. Case 1 manifested as loss of consciousness, upper gazing of the eyes with murmuring, swallowing, groping, clenching, or hugging for several seconds. Secondary GTCS was reported several times every year. Case 2 manifested as a numbness of the limbs and gastric discomfort for around 1 min without loss of consciousness. The patient occasionally developed GTCS during her sleep. Case 3 manifested as a loss of consciousness for several seconds to 30 s with groping and wandering, some of which occurred with secondary GTCS and urinary incontinence. None of the patients had a history of febrile convulsions during infancy. The patients' family history and growth milestones were all unremarkable. None of them had mental retardation. On physical examination, no significant neurological signs were found. The patients were given several anti-epilepsy drugs including carbamazepine, valproate, gabapentin, phenytoin, phenobarbital, and topiramate without seizure control.

Video electroencephalography (VEEG) revealed temporal lobe origin discharging (Fig. 1A). Computed tomography of the head was normal. In Case 1, MRI showed a region of hyper-intensity in the left hippocampal formation. In Case 2, structural MRI indicated hyper-intensity in the right medial temporal lobe with volume enlargement (Fig. 1B, C) while magnetic resonance spectroscopy (MRS) revealed an obvious decrease in N-acetyl-aspartate (NAA). In Case 3, MRI showed hyper-intensity in the right hippocampal formation (Fig. 1D). An ^{18}F-FDG PET in Case 2 showed hypo-metabolism in the right medial temporal lobe (Fig. 1E), which was not present in the other two patients.

All of the three patients underwent medial temporal lobe resection and Engle I outcomes were achieved.

3.2. Neuropathological results

Macroscopic examination indicated no obvious lesions or atrophy in all of the samples. However, firmness on touching was noted.

The microscopic features of the patients are summarized in Table 2 and shown in Fig. 2. Most of the lesions were located in the para-hippocampal gyrus, with involvement of the subiculum in Case 1 and the cornu ammonis in Case 3. The normal cortical structure and the neuropil were generally disturbed, and the gray and white matter junction was distinguishable. Dysmorphic neurons were found patchily distributed in the neuropil of the para-hippocampal gyrus with enlarged and bizarre nucleoli and aggregated Nissl bodies. Balloon cells were found in the white matter of the para-hippocampal gyrus. However, both the subiculum in Case 1 and the cornu ammonis in Case 3 were affected. Typical neurons with malformations manifested as enlarged cells with homogenous eosinophilic cytoplasm and eccentric nucleoli were present. Gliosis was seen around the area of the lesions. In the dentate gyrus, granular cell dispersion, pyramidal cell loss, and gliosis were not seen as in hippocampal sclerosis. There was no calcification, vascular malformation, or proliferation and inflammatory cell infiltration.

The dysmorphic neurons were immunohistochemically stained positive with SMI32, and negative with NeuN and GFAP (-). The balloon cells in the three patients had the same immunohistochemical staining pattern. They were positive with vimentin and nestin and negative with NeuN, GFAP, S-100, and CD34. These immunohistochemical results suggested that the cells were poorly differentiated, because these cells lacked the markers for mature neurons and astrocytes. Additionally, S-100 and CD34 stain, which were positive in malformation-related tumors such as ganglia glioma, were negative in these cells, so they were not tumors.

Table 1
Clinical data of the patients.

No.	Duration (years)	Onset Age(years old)	Seizure manifestation	Seizure frequency	Automatism	History of febrile convulsion
1	8	5	Focal impaired awareness ± GTCS	several/day	Limb& Oropharynx	None
2	19	10	Focal aware ± GTCS	several/day	None	None
3	21	6	Focal impaired awareness ± GTCS	several/day	Limb	None

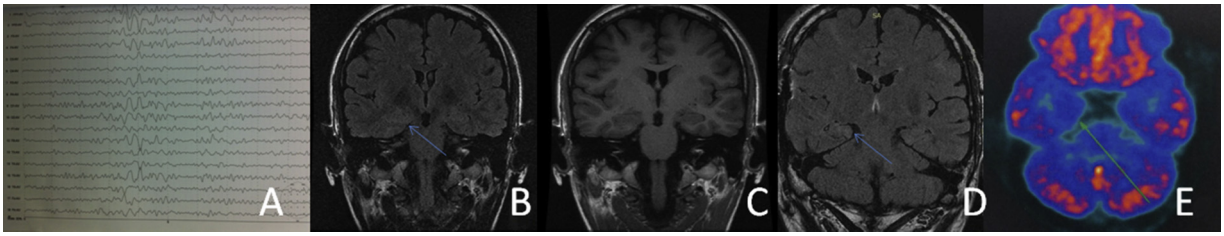

Fig. 1. A: sharp waves in right anterior temporal leads. B: Hyper-intensity of the right medial temporal lobe (arrow, T2 Flair, Case 2); C: No atrophy and slight enlargement of the right medial temporal lobe (T1, Case 2); D: Hyper-intensity of the right medial temporal lobe (arrow, T2 Flair, Case 3); E: Hypo-metabolism in the right medial temporal lobe (arrow, ^{18}F-FDG PET, Case2).

4. Discussion

MTLE-HS is one of the most common causes of drug-resistant epilepsies. Initial precipitating incidents, including febrile convulsions, traumas, hypoxia, and infections, may occur before the age of 5. The typical features of the seizure comprise a characteristic aura, loss of consciousness, and automatism. Secondary GTCS is rare. Seizures begin typically in childhood, and a latent period between the initial precipitating incidents and habitual seizures always exists (Wieser, 2004). The course is progressive. Seizures are initially easily controllable before they become medically refractory, a phase known as the silent period. Neuroimaging is helpful in the diagnosis of HS. Typical changes associated with HS include unilateral atrophy of the hippocampus formation with abnormal signals. FLAIR and T2 hyper-signal changes are more obvious than are hypo-signal changes in T1. The structure of the hippocampus is usually disturbed. Furthermore, the ipsilateral amygdala, thalamus, and cerebral white matter also show a significant volume loss (Alhusaini et al., 2012). Sometimes, volume loss of the contralateral hippocampus and the bilateral cerebrum are found, a phenomenon that is correlated with generalized damage caused by the seizures. On the 7 T MRI, sub-regional analysis for selective cornu ammonis atrophy, diffuse cornu ammonis atrophy, and dentate gyrus atrophy is performed, and further helps in early diagnosis of hippocampal sclerosis (Henry et al., 2011). The histopathological features include neuronal loss in the CA region, dentate dispersion, and gliosis. Different clinical and pathological subgroups were defined by Blümcke I et al. (Blümcke et al., 2007). However, the extra-hippocampal pathology also affects the amygdala and other limbic structures resulting in neuronal loss and gliosis. It is still controversial whether the pathophysiology of MTLE-HS is restricted to the hippocampus. Although surgical removal of the hippocampus and the amygdala helps reduce the seizures, the outcome varies depending on the duration, initial precipitating incidents, surgical areas, and the different pathological subgroups (Wieser, 2004).

FCD is a developmental malformation of cortical organization which causes drug-resistant epilepsies. FCD IIB is defined by the presence of balloon cells with a large cytoplasm, displaced nucleus, lack of dendrites, and astrocyte-like cells. These cells usually cluster in the subcortical white matter and may extend into the cortical ribbon (Sisodiya et al., 2009). The sulcus is more easily affected compared with the gyral crowns. The cells may also localize extra-temporally. Seizure onset is usually in early childhood and many patients suffer from mental retardation. The characteristic MRI features include focal cortical thickening, blurring of the gray-white matter interface, and a series of increased signals from the cortex to the underlying ventricle on T2-weighted imaging. This signal is called the trans-mantle sign (Sisodiya et al., 2009). Early detection of the lesions typically results in rapid surgical removal to prevent the short-term and long-term consequences associated with long-term seizures (Sisodiya et al., 2009; Pascual-Castroviejo et al., 2012). The early onset of severe partial epilepsy with high seizure frequency, stereotyped seizures, extra-temporal location especially in the frontal lobe, and involvement of the eloquent cortex suggests type II FCD. However, further testing is needed to determine the entity of the lesion (Chassoux et al., 2012). Besides the regular battery of diagnostic tests performed in this condition, 3D coronal MRI imaging including T1-weighted, T2-weighted, and FLAIR are helpful for the detection of the lesions (Mellerio et al., 2012). Morphometric MRI analysis is also helpful in the detection of FCD in MRI-negative patients (Wagner et al., 2011a). Comprehensive analysis of seizure history, neurologic examination, cognitive and psychiatric impairments, interictal-ictal electroencephalography and stereo-EEG data, MRI and fluorodeoxyglucose PET are crucial for precise localization and resection of FCD as well as for prognosis. Magnetoencephalography is also a new tool used to define the resection area during surgery (Widjaja et al., 2008). Complete surgical resection has been shown to lead to seizure freedom in 92% of patients in the study by Wagner J. et al. (Wagner et al., 2011b).

FCD IIB combined with HS is very rare, as are FCD IIB lesions located in the MTL. Thom M. et al. reported two cases with balloon cells in the dentate gyrus and hippocampal sclerosis manifested as mesial temporal sclerosis type 1 and type 3, respectively (Thom et al., 2008). Granular cell dispersion was severe in both cases. Kim S.H. et al. reported a 39-year-old woman with balloon cells in the layer of granular neurons accompanied by hippocampal sclerosis, which caused enlargement and signal change of the right hippocampus formation on an MRI (Kim et al., 2008). Mirsattari S.M. et al. also reported a case with dysmorphic neurons in the CA4 sector with hippocampal sclerosis. This dual pathology caused an enlargement and an increased signal intensity of the hippocampus on an MRI (Mirsattari et al., 2009). Rogerio F. et al. reported a 12-year-old boy with scattered balloon cells in CA4 as well as hippocampal sclerosis. A distinctive MRI feature of this patient was a hippocampal enlargement and a heterogeneous hypo-intense T1 and hyper-intense T2 signal with preservation of the external borders (Rogerio et al., 2014). The balloon cells co-expressed neuronal and glial markers as well as progenitor cell markers such as CD34 and nestin, thus indicating that the condition was caused by a malformation. The hippocampus sclerosis was determined to be an acquired pathology. These findings highlight the difficulty in determining the pathogenesis and classification of this condition. Miyahara H. reported a case with MTLE and a precipitating history of non-herpetic acute limbic encephalitis (Miyahara et al., 2011). In this case, hippocampal sclerosis was an apparently acquired alteration, rather than the result of maldevelopment. However, balloon cells in the molecular layer and in the granular cell layer labeled with vimentin, GFAP, GFAP-delta, CD34, and nestin suggested aberrant neuronal differentiation.

The origin of balloon cells remains controversial. However, it is primarily recognized as the product of an abnormal differentiation process. As in our patients, most of the balloon cells were labeled with nestin and vimentin. Nestin is expressed transiently in multipotent neuroepithelial stem cells in the developing central nervous system and may act as a neural stem cell marker. Vimentin is expressed during embryonic development and in the early developmental stage of the central nervous system. Thus, the expression of neural stem cell markers by balloon cells suggests their origin in the early neurogenic stage of cortical development (Oh et al., 2008). Additionally, CD34 is expressed in the nervous system during the early developmental period,

Table 2
Microscopic features of the patients.

No.	Lesion location	Cortical disorganization	Distinguishable grey white matter junction	Calcification	Dysmorphic SMI32(+) neurons	BC location	Hippocampus sclerosis	Immunohistochemistry of BC			
								Neun	GFAP	Nestin	Vimentin
1	Left subiculum & parahippocampal gyrus	+	+	-	Massive in parahippocampal gyrus	White matter	No	-	-	+	+
2	Right parahippocampal gyrus	+	+	-	Massive in parahippocampal gyrus	White matter	No	-	-	+	+
3	Right parahippocampal gyrus & cornu Ammonis	+	+	-	Massive in parahippocampal gyrus	White matter & cornu Ammonis	No	-	-	+	+

and the partially positive of balloon cells implies the same origin (Oh et al., 2008). Besides, CD133 as a marker of hematopoietic and neuropoietic cells was also found to be expressed in some balloon cells, suggesting they are heterogeneous cell populations expressing cell-surface markers for pluripotent stem cells and proteins for multipotent progenitors or immature neurons/glia (Ying et al., 2005). However, markers of mature neurons and glial cells, such as NeuN and GFAP, are relatively less expressed by balloon cells, as confirmed in our patients. However, the balloon cells present in FCD IIB are morphologically indistinguishable from the giant cells seen in the cortical tubers in tuberous sclerosis, which is a proven congenital developmental disease with a known pathogenesis. Isolation and culture of these cells by Yasin S.A. et al. further suggested their progenitor/stem cell nature (Yasin et al., 2010).

Another pathological entity that should be differentiated from MTLE-FCDIIB is a Low-Grade Epilepsy Associated Tumors located in the medial temporal lobe (MTLE-LEAT). No atrophy of the hippocampus is usually found in either of them. Several clinical and radiological characteristics helpful for differentiation are summarized in Table 3. MTLE-HS usually has an initial precipitating incident (such as febrile convulsion, trauma, infection, etc.) and a silent period. However, MTLE-FCDIIB usually causes severe and refractory seizures from onset, and is characterized by a higher frequency of seizure attacks. MTLE-HS causes cognition decline after refractory seizures. In contrast, MTLE-FCDIIB is a developmental disorder with abnormalities in cellular structure and function, which usually cause early cognition impairment. Clinically, MTLE-LEAT is similar to MTLE-FCDIIB. Apart from the clinical manifestations, an MRI is also helpful for diagnosis. Hippocampal atrophy is the typical MRI change associated with MTLE-HS. Signal change depends on the severity of gliosis and the duration of the seizure. The pathological basis of MTLE-FCDIIB involves cellular disorganization and changes in morphology with gliosis. Therefore, enlargement of hippocampus is more frequent than atrophy, and the signal changes on T1 and T2 are more obvious. MTLE-LEAT usually shows tissue enlargement without an effect on mass. The signal varies depending on the tumor subtype, including extensive hyper-intensity on T2/FLAIR, mixed signals, cyst formation and calcification. 7 T MRI shows the dentate gyrus and the cornu ammonis more clearly, which is helpful for differential diagnosis (Garbelli et al., 2011). However, none of these characteristics are arbitrary. Comprehensive analysis is always required. In our case series, all the patients experienced severe and frequent seizures from childhood, and no initial precipitating incidents were reported. MRI showed hyper-intensity on T2 and FLAIR with no atrophy of hippocampus. These features suggested the diagnosis was not MTLE-HS.

5. Conclusion

MTLE-FCDIIB is a rare subgroup of FCD. This disease may show similar clinical and neuroimaging features to MTLE-HS and MTLE-LEAT. Our findings outlined the typical clinical and neuropathological features of the disease, suggested several key points for differential diagnosis, and would help in more accurate diagnosis of mesial temporal lobe epilepsy. However, our study has several limitations. First, the sample size was small; we need to enroll more cases to verify the representation of our conclusions. Multicenter observation would be helpful in future. Second, our results were descriptive. More basic research, including animal model construction, would be helpful to study the origination and distribution of balloon cells and understand the pathogenesis of MTLE-FCDIIB.

Author contributions

C Mao: manuscript preparation, study design and pathological diagnosis; L Jin, Q Lu: pre-operation evaluation of the patients; W Dou: operation of the patients; L Zhou, H Ren, Y Zhao: tissue preparation,

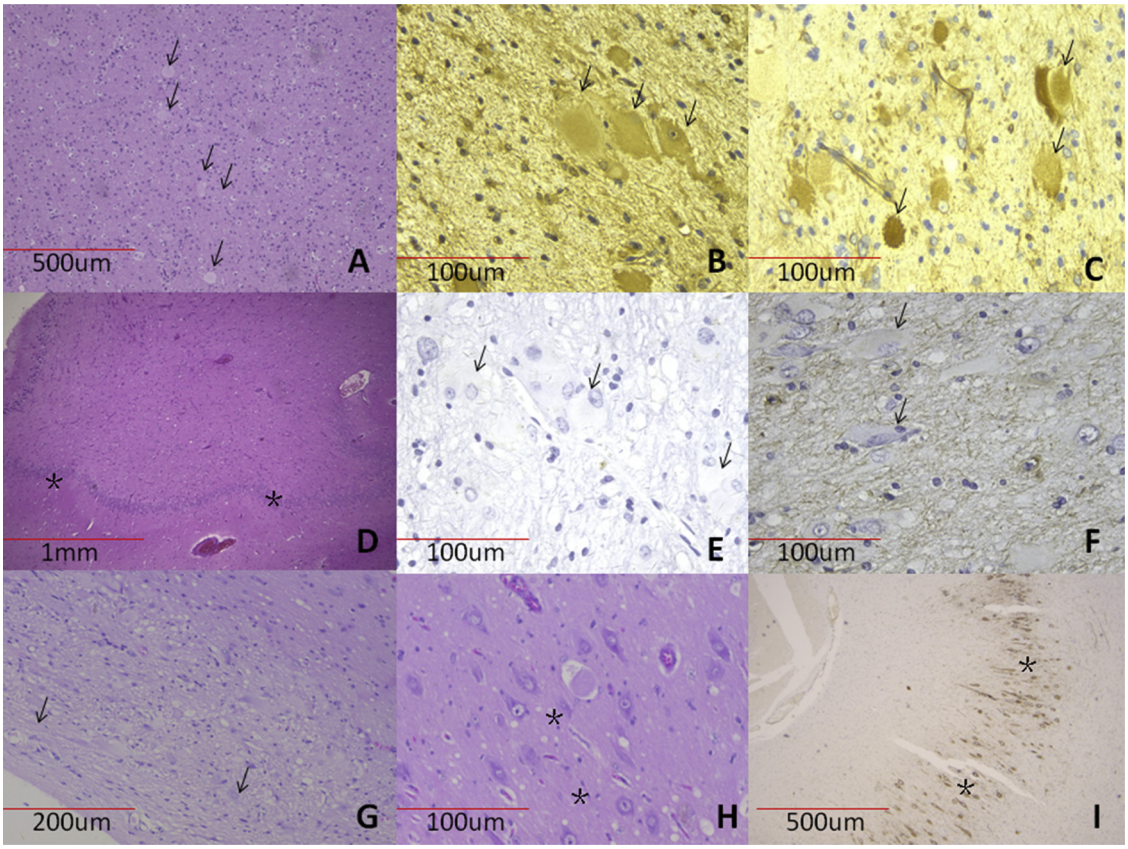

Fig. 2. A–C Case 1: A BC in the white matter (arrow, H&E x100); B Positive BC (arrow, vimentin x400); C Positive BC (arrow, nestin x400). **D–F Case 2**: D Normal dentate gyrus (asterisk, H&E x40); E Negative BC (arrow, NeuN x400); F Negative BC (arrow, GFAPx400). **G–I Case 3**: G BC in cornu ammonis (arrow,H&Ex200); H Areas of dysmorphic neurons in the para-hippocampal gyrus (asterisk,H&Ex400); I Areas of positive dysmorphic neurons (asterisk,SMI32×100).

Table 3
Characteristics for differential diagnosis.

	MTLE-FCDIIB	MTLE-HS	MTLE-LEAT
Silent period	No	Yes	No
Progressive course	No	Yes	No
Initial precipitating incidents	No	Yes	No
Frequency of seizure	Higher	Lower	Higher
Early cognition decline	Yes	No	No
Morphology of medial temporal lobe	Normal or enlargement	Atrophy	Enlargement with/o mass effect
Extrahippocampal atrophy	No	Yes	No
Signal of medial temporal lobe	Hypointense T1 and hyperintense T2 &FLAIR	Hyperintense T2 &FLAIR or normal	Hypointense T1 and hyperintense T2 &FLAIR, with/o mixed signals, with/o cyst formation, with/o calcification

staining and immunohistochemical staining; Feng Feng: neuroimaging interpretation; Y Guo, J Gao: study design and pathological diagnosis.

Funding

The study was supported by grants from the CAMS Innovation Fund for Medical Sciences (2016-I2M-1-004) and the National Natural Science Foundation of China (81271544, 81550021)

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

We are thankful to Ruixue Cui in the Department of Nuclear Medicine for her assistance in the PET/CT measurements, and to Heyang Sun in the EEG lab for her work related to the EEG analysis of the patients. We thank the patients and their families for participating in this study.

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