Clinical Case Report

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Adult hippocampal ganglioneuroblastoma

Case report and literature review

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Abstract

Rationale: Intracranial ganglioneuroblastoma represents a rare subtype of primitive neuroectodermal tumor. Here, we report a hippocampal ganglioneuroblastoma and a literature review of cerebral anglioneuroblastoma is carried out.

Patient concerns: We report a 16-year-old male patient presenting with absence seizure and high-infiltration hippocampal ganglioneuroblastoma.

Interventions: Magnetic resonance imaging (MRI) indicates a space-occupying lesion with a well-defined margin in the right temporal lobe and hippocampus. However, hyper-signal on flair and diffusion-weighted imaging (DWI) with a low apparent diffusion coefficient (ADC) value is detected, which prompts high tumoral invasiveness.

Interventions: A total resection of tumor and subsequent chemotherapy combing with radiotherapy is performed.

Outcomes: For a follow-up period of 60 months, no evidence of recurrence and further seizures are detected.

Lessons: High-infiltration hippocampal ganglioneuroblastoma is a rare event. MRI examination often showed features of low-grade gliomas, while hyper-signal lesion on DWI with a low ADC value can be detected. Complete resection combined with fractionated radiotherapy and chemotherapy was the optimal treatment for cerebral ganglioneuroblastoma.

Abbreviations: ADC = apparent diffusion coefficient, Cho = choline, DWI = diffusion-weighted imaging, GFAP = glial fibrillary acidic protein, GNB = ganglioneuroblastoma, INPC = International Neuroblastoma Pathology Committee, MRI = magnetic resonance imaging, MRS = magnetic resonance spectrum, NAA = *N*-acetylaspartate, SOX 10 = Sry (sex determining region Y)-related high mobility group box protein 10, SYN = synaptophysin, T1WI = T1-weighted image, T2WI = T2-weighted image.

Keywords: ganglioneuroblastoma, hippocampal

1. Introduction

The occurrence of ganglioneuroblastoma (GNB) may be due to the developmental malformation or degeneration of the primary neural crest cells or neuroblasts. Degree of GNB differentiation is between high malignant neuroblastoma and benign ganglioneuroma.[1] GNB is composed of mature differentiated ganglion cells and undifferentiated neuroblasts,[2,3] and firstly reported by Wahl and Craig.[4] GNB is rarely seen in adults and commonly occur in infants and young children. GNB is usually located in the adrenal gland, posterior mediastinum, or retroperitoneum.[5] Intracranial GNB is rarely found. There are only 12 cases of intracranial GNB and here we report another adult patient with intracranial GNB in the mesial temporal lobe and hippocampus. Additionally, a literature review is carried out and we summarize clinical feature, diagnosis, and the treatment of intracranial GNB.

2. Case report

All procedures performed in this study were approved by the ethics committee of First Affiliated Hospital of Fujian Medical University. Informed consent was obtained from individual participant. A 16-year-old male patient presented with headache and pure absence seizure for more than 1 year. Absence seizure happened 3 to 5 times every day and lasted 30 to 40 seconds every time. Physical and neurological examination was normal. Magnetic resonance imaging (MRI) of the brain indicated a space-occupying lesion with a well-defined margin (3 cm in diameter) in the right temporal lobe and hippocampus (Fig. 1A–D). Slightly hypo-signal on T1WI (Fig. 1A), hyper-signal on T2WI (Fig. 1B), Flair (Fig. 1C), and diffusion-weighted imaging (DWI) were found. However, a low apparent diffusion coefficient (ADC) value was detected, which prompted high tumor

Editor: N/A.

P-SY, G-RC, and HCS-G equally contributed to this article.

The study was supported by special fund for the Young and Middle-aged Backbone Key Research Project of National Health and Family Planning Commission of Fujian Province (No. 2017-ZQN-46 to Pei-Sen Yao), key clinical specialty discipline construction program of Fujian, P.R.C, major project of Fujian provincial department of science and technology (No. 2014YZ0003 and No. 2014YZ01 to De-Zhi Kang) and public health of Fujian province department of finance (No. BPB-LZY2013 to Zhang-Ya Lin).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:51(e8894)

Received: 3 September 2017 / Received in final form: 3 November 2017 / Accepted: 6 November 2017

http://dx.doi.org/10.1097/MD.0000000000008894

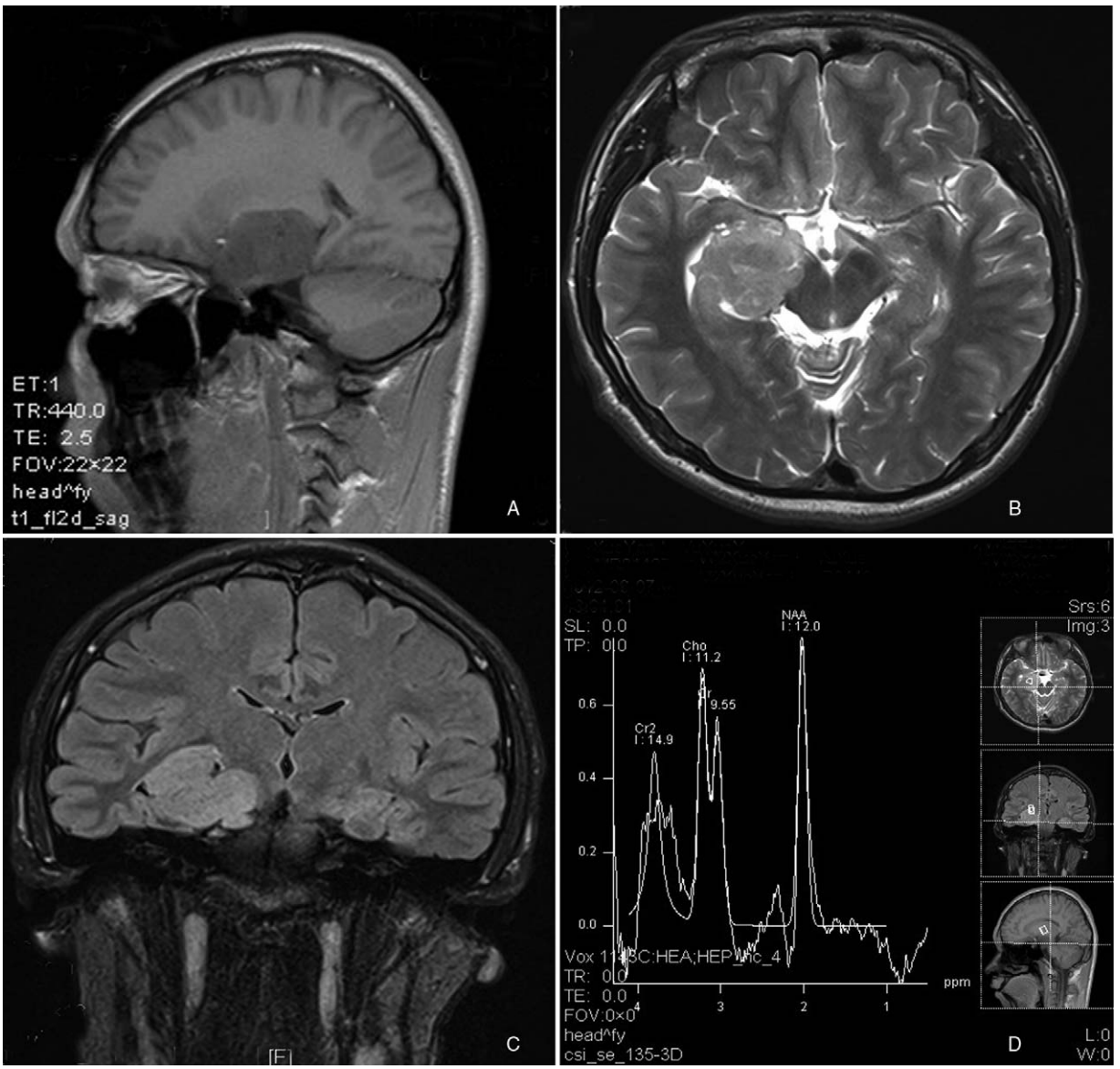

Figure 1. Magnetic resonance imaging (MRI) of the brain indicated a space-occupying lesion with a well-defined margin (3 cm in diameter) in the right temporal lobe and hippocampus, slightly hypo-signal on T1WI (A), slightly hyper-signal on T2WI (B), Flair (C). And MRS analysis demonstrated elevated Cho and slightly decreased NAA with a Cho/NAA ratio less than 1.00 (D). MRI magnetic resonance imaging, MRS = magnetic resonance spectrum, NAA=*N*-acetylaspartate, T1WI=T1-weighted image, T2WI=T2-weighted image.

invasiveness. Further work-up, including CT scan of thorax and abdomen, showed no other tumor elsewhere. The patient started with carbamazepine (200 mg bid) and had no further seizures. However, the patient developed absence seizure after medical treatment for half a year. MRI showed no increase in size of tumor. However, magnetic resonance spectrum (MRS) analysis demonstrated elevated Cho and slightly decreased *N*-acetylaspartate (NAA) with a Cho/NAA ratio less than 1.00 (Fig. 1D).

A total resection of tumor was performed. Tumor had a well-defined margin (from ambient cistern to basal ganglion region) without abundant blood supply (Fig. 2G). The patient accepted subsequent postoperative chemotherapy (temozolomide, 75 mg/m^2/day for 42 days, subsequently followed by 6-monthly cycles, 150 mg/m^2/day for 5 days, every 4 weeks) and radiotherapy (60 Gy, 30 fraction). Histology revealed diffuse infiltration of both ganglion cells and neuroblasts (Fig. 2). Tumor tissue was infiltrated by highly cellular proliferation, and larger cells with double nucleus could be found (Fig. 2A).

Histopathology also showed the positive staining of CD34, calretinin, GFAP, Ki-67, Sry (sex determining region Y)-related high mobility group box protein 10 (SOX-10), and synaptophysin (SYN) in gangliocellular area (Fig. 2B–G), while negative staining of NeuN, Oligo-2, and TIF-1. Also in neuroblastic area, CD34, calretinin, GFAP, Ki-67, and SYN were positive (Fig. 2H–L), while NeuN, Oligo-2, SOX-10, and TIF-1 not. Furthermore, Ki-67 was positive in only 1% of neoplastic cells. For a follow-up period of 60 months, no evidence of recurrence and further seizures were detected with sodium valproate.

3. Review of patients with intracranial GNB

We reviewed all reports published in English language on cerebral GNB (Table 1).

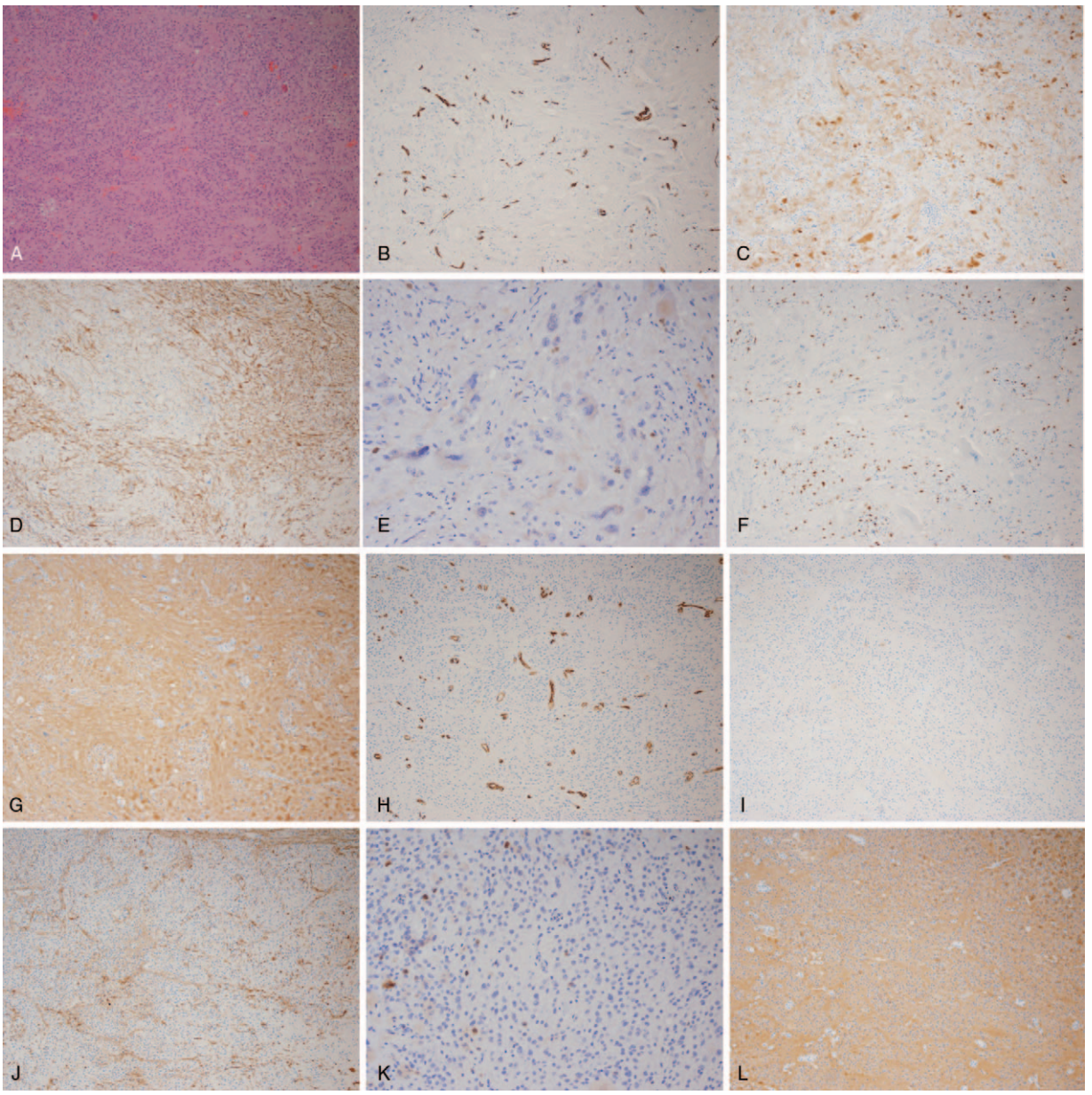

Figure 2. Immumohistochemical staining. The tumor tissue was infiltrated by highly cellular proliferation, and larger cells with double nucleus could be found (A). Histopathology also showed the positive staining of CD34 (B), calretinin (C), GFAP (D), Ki-67 (E), SOX-10 (F), and SYN (G) in gangliocellular area. And in neuroblastic area, CD34 (H), calretinin (I), GFAP (J), Ki-67 (K), and SYN (L) were positive. GFAP = glial fibrillary acidic protein. SOX-10 = Sry (sex determining region Y)-related high mobility group box protein 10, SYN = synaptophysin.

Table 1

Cases with cerebral ganglioneuroblastoma reported in present studies.

Author/year	Age (years)/ Gender	Location	Metastasis	Surgery	recurrence	Radiotherapy	Chemotherapy	Survival, months
Sabatino G	60/F	Left occipital lesion	No	Total	No	Yes	Yes	>18
Sohma T	11/M	Cerebeilopontine	No	Partial	No	Yes	No	>5
Schipper MH/2012	28/M	Frontal lobe	No	Total	No	Yes	Yes	>14
Schipper MH/ 2012	42/F	Frontal lobe	No	Partial	No	Yes	Yes	>12
Nishihara H	32/F	Parietal lobe	No	Total	No	Yes	No	>14
Takahashi M	14/M	Frontal lobe	No	Total	No	Yes	No	>13
Hosaka T	36/F	Unknown	No	Total	No	Yes	Unknown	>39
Gasparetto EL/2007	One year and eight-month/F	Cerebellum	No	Total	–	Yes	Yes	>36
Akin and Ergen/2014	34/M	Ventricular	No	Partial	3 months	Yes	No	>12
Nakazato Y	32/M	Left temporal lobe	No	Total	Unknown	Unknown	Unknown	Unknown
Steenberge SP	4/F	Parietal-occipital lobe	Ependymal spread	Subtotal	9 days	Yes	Yes	60
Tanaka M	57/M	Pineal region	No	Total	No	Yes	No	>15

4. Discussion

GNB is defined by the International Neuroblastoma Pathology Committee (INPC 1999),[3] and classified as a subgroup of neuroblastoma.[6] GNB is a mixed tumor including mature ganglion cells and malignant neuroblastoma simultaneously.[2,3] Degree of GNB differentiation is between high malignant neuroblastoma and benign ganglioneuroma.[1] However, it is difficult to draw a clear demarcation line based on morphology or gene expression differences.[7]

There are only 12 cases (6 males and 6 females) of intracranial GNB and here we report another adult patient with intracranial GNB in the mesial temporal lobe and hippocampus. The location of intracranial GNB, including frontal, temporal, parietal, occipital, parietal-occipital, pineal, cerebellar, cerebellopontine region and ventricle, determine its clinical symptoms, such as seizures, visual impairment, hemianesthesia, unilateral sensory disturbance, headache, and transient global amnesia.

MRI often showed features of low-grade gliomas, including a space-occupying lesion with a well-defined margin.[8,9] However, hyper-signal on DWI with a low ADC value were detected, which prompted high tumor malignancy. Furthermore, MRS analysis showed an increase of Cho/NAA. In addition, we suggest that MRS, ADC, and DWI are essential for diagnosis.

Although high invasiveness is the typical characteristic of GNB, the multiplication capacity is relatively slow as well as low-grade glioma. In addition, metastasis is rarely detected in patients with GNB. In this case, no increase of tumor size was detected after a 6-months follow-up without surgical intervention. Complete resection is the optimal treatment for intrarcranial GNB. Partial resection or subtotal resection should be performed if the tumor extends into the cavernous sinus.[10] Moreover favorable outcome will be obtained after fractionated radiotherapy and chemotherapy. It was reported that the longest asymptomatic period of the patients with intracranial GNB is 60 months following the above treatment.[11]

GNB is composed of neuroblastoma cells, ganglion cells with different degrees of differentiation, nerve sheath, and glial fibers.[12,13] The common characteristic of pathological findings is the highly infiltrated and proliferated cells with dense chromatin.[14] Ganglion-like large cells usually present with double nucleus.[15] Immunohistochemical staining for S100, neurofilaments, chromogranin, NSE, CD34, and synaptophysin was positive in ganglion cells and nerve sheath cells.[16–21] S100, synaptophysin, neurofilaments were positive in neuroblastoma cells.[22,23] In the study, histopathology showed the positive staining of CD34, calretinin, GFAP, Ki-67, SOX-10, and SYN in gangliocellular area (Fig. 2B–G), while negative staining of NeuN, Oligo-2, and TIF-1. Also in neuroblastic area, CD34, calretinin, GFAP, Ki-67, and SYN were positive (Fig. 2H–L), while NeuN, Oligo-2, SOX-10, and TIF-1 not. Furthermore, Ki-67 was positive in only 1% of neoplastic cells.

GNB is further divided into 2 subtypes (undifferentiated and poorly differentiated types)[24] under electron microscope. The undifferentiated type was consisting of small round-to-oval cells with hyperchromatic nuclei.[25] The poorly differentiated type was composed of large round-to-oval spindle-shaped cells with pale staining nuclei.[25] The tumor cells forming chrysanthemums were arranged radially, which was one of the pathological features of GNB.[26,27] Nuclei of the GNB cells were usually round or oval, and a large number of rough endoplasmic reticulum and poly-ribosomes in cytoplasm could be found.[28,29]

Lastly, the diagnosis and treatment of intracranial GNB were summarized: (1) MRI examination often showed features of low-grade gliomas, while hyper-signal lesion on DWI with a low ADC value could be detected; (2) Complete resection combined with fractionated radiotherapy and chemotherapy was the optimal treatment.

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