Adult hippocampal ganglioneuroblastoma
Case report and literature review

Pei-Sen Yao, MD, PhD, Guo-Rong Chen, MD, Huang-Cheng Shang-Guan, MD, Qing-Song Lin, MD, Xing-Fu Wang, MD, Shu-Fa Zheng, PhD, De-Zhi Kang, MD, PhD

Abstract
Rationale: Intracranial ganglioneuroblastoma represents a rare subtype of primitive neuroectodermal tumor. Here, we report a hippocampal ganglioneuroblastoma and a literature review of cerebral angglioneuroblastoma.

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 T1-weighted diffusion-weighted imaging (DWI) with a low apparent diffusion coefficient (ADC) value is detected, which prompts high tumoral invasiveness.

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

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 ganglioneuroblastoma.[1,1] GNB is composed of mature differentiated ganglion cells and undifferentiated neuroblasts,[2,3] and firstly reported by Wahl and Craig.[1] 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.[3] 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 invasion.
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/m²/day for 42 days, subsequently followed by 6-monthly cycles, 150 mg/m²/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).
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                | Cerebellopontine | 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 | Yes | Unknown | Unknown | >39 |
| Passerotto 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 |

Figure 2. Immunohistochemical 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.
4. Discussion

GNB is defined by the International Neuroblastoma Pathology Committee (INPC 1999),[13] and classified as a subgroup of neuroblastoma.[6] GNB is a mixed tumor including mature ganglion cells and malignant neuroblastoma simultaneously.[12,13] 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, parieto-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.[6,13] 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 6-months follow-up without surgical intervention. Complete resection is the optimal treatment for intracranial 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 chromatim.[14] Ganglion-like large cells usually present with double nucleus.[13] Immunohistochemical staining for S100, neurofilaments, chromogranin,NSE, CD34, and synaptophysin were positive in ganglion cells and nerve sheath cells.[13,16] S100, synaptophysin, neurofilaments were positive in neuroblastoma cells.[12,13]

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.[15] The poorly differentiated type was composed of large round-to-oval spindle-shaped cells with pale staining nuclei.[15] 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.

References

[1] Jiang M, Stanke J, Lahti JM. The connections between neural crest development and neuroblastoma. Curr Top Dev Biol 2011;94:77–127.
[2] Shimada H, Ambros IM, Dehner LP, et al. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. Cancer 1999;86:349–63.
[3] Shimada H, Ambros IM, Dehner LP, et al. The international neuroblastoma pathology classification (the Shimada system). Cancer 1999;86:364–72.
[4] Wahl HR, Craig PE. Multiple tumors of the sympathetic nervous system: report of a case showing a distinct ganglioneuroblastoma, a neuroblastoma and a cystic calcifying ganglioneuroblastoma. Am J Pathol 1938;14:797–808.
[5] Lonergan GJ, Schwab CM, Suarez ES, et al. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. Radiographics 2002;22:91–34.
[6] Hsiao CC, Huang CC, Sheen JM, et al. Differential expression of delta-like gene and protein in neuroblastoma, ganglioneuroblastoma and ganglioneuroma. Mod Pathol 2005;18:656–62.
[7] Hoechner JC, Hedborg F, Eriksson I, et al. Developmental gene expression of sympathetic nervous system tumors reflects their histogenesis. Lab Invest 1998;78:289–45.
[8] Schipper MH, van Dunnen SG, Taphoorn MJ, et al. Cerebral ganglioneuroblastoma of adult onset: two patients and a review of the literature. Clin Neurol Neurosurg 2012;114:529–34.
[9] Akin M, Egen SA, Oktay B, et al. Ventricle ganglioneuroblastoma in an adult and successful treatment with radiotherapy. Balkan Med J 2014;31:173–6.
[10] Kramilmos GP, Crockard HA. Cavernous sinus neuroblastoma. Br J Neurosurg 1993;7:691–6.
[11] Gasperiello ET, Rosenberg S, Matsusita H, et al. Ganglioneuroblastoma of the cerebellum: neuroimaging and pathological features of a case. Arq Neuropsiquiatr 2007;65:338–40.
[12] Peuchmaur M, d’Amore ES, Jossi VV, et al. Revision of the International Neuroblastoma Pathology Classification: confirmation of favorable and unfavorable prognostic subsets in ganglioneuroblastoma, nodular. Cancer 2003;98:2274–81.
[13] Umehara S, Nakagawa A, Matthy KK, et al. Histopathology defines prognostic subsets of ganglioneuroblastoma, nodular. Cancer 2000;89:1150–61.
[14] Yokoyama M, Okada K, Tokue A, et al. Ultrastructural and biochemical study of neuroblastoma and ganglioneuroblastoma. Invest Urol 1971;9:156–64.
[15] Ryou KH, Woo SY, Lee MY, et al. Morphological and biochemical changes induced by arsenic trioxide in neuroblastoma cell lines. Pediatr Hematol Oncol 2005;22:609–21.
[16] Yasu Y, Ohta Y, Ueda Y, et al. Spontaneous ganglioneuroma possibly originating from the trigeminal ganglion in a B6C3F1 mouse. Toxicol Pathol 2009;37:343–7.
[17] Hachitanda Y, Tsuneyoshi M, Enjoji M. Expression of pan-neuroendocrine proteins in 33 neuroblastic tumors. An immunohistochemical study with neuron-specific enolase, chromogranin, and synaptophysin. Arch Pathol Lab Med 1989;113:381–4.
[18] Campos MS, Fontes A, Marrocos LS, et al. Clinico-pathologic and immunohistochemical features of oral neuroblastoma. Acta Odontol Scand 2012;70:577–82.
[19] Hirose T, Tani T, Shimada T, et al. Immunohistochemical demonstration of EMA/Glut1-positive perineurial cells and CD34-positive fibroblastic cells in peripheral nerve sheath tumors. Mod Pathol 2003;16:293–8.
[20] Schaberg KB, Chou AS, Wang KC, et al. A fibrous papule with abundant CD34-immunoreactive ganglion-like multinucleated giant cells: a case report and review of the literature. Dermatol Online J 2015;21:pii:1303/qt1bd989kn.
[21] Rusu MC, Cretoiu D, Vrapciu AD, et al. Telocytes of the human adult trigeminal ganglion. Cell Biol Toxicol 2016;32:199–207.
[22] Frankenmont DW, Mills SE, Lack EF. Immunohistochemical detection of neuroblastomatous foci in composite adrenal phaeochromocytoma-neuroblastoma. Am J Clin Pathol 1994;102:163–70.
[23] Crary GS, Singleton TP, Neglia JP, et al. Detection of metastatic neuroblastoma in bone marrow biopsy specimens with an antibody to neuron-specific enolase. Mod Pathol 1992;5:308–11.
[24] Taxy JB. Electron microscopy in the diagnosis of neuroblastoma. Arch Pathol Lab Med 1980;104:355–60.
[25] Fatimi SH, Bawany SA, Ashfaq A. Ganglioneuroblastoma of the posterior mediastinum: a case report. J Med Case Rep 2011;5:322.
[26] Mattix ME, Mattix RJ, Williams BH, et al. Olfactory ganglioneuroblastoma in a dog: a light, ultrastructural, and immunohistochemical study. Vet Pathol 1994;31:262–5.
[27] Klijanienko J, Couturier J, Brisse H, et al. Diagnostic and prognostic information obtained on fine-needle aspirates of primary neuroblastic tumors: proposal for a cytology prognostic score. Cancer Cytopathol 2011;119:411–23.
[28] Omi K, Kitano Y, Agawa H, et al. An immunohistochemical study of peripheral neuroblastoma, ganglioneuroblastoma, anaplastic ganglio-glioma, schwannoma and neurofibroma in cattle. J Comp Pathol 1994;111:1–4.
[29] Powers JM, Balentine JD, Wisniewski HM, et al. Retroperitoneal ganglioneuroblastoma: a kaleidoscope of neuronal degeneration. A light and electron microscopic study. J Neuropathol Exp Neurol 1976;35:14–25.