

Paediatric gliomatosis cerebri presenting with deep gray matter lesions

¹Limin Li, ¹Choong Yi Fong, ¹Wei Kang Lim, ²Jen Chun Foo, ³Raja Rizal Azman, ⁴Nor Faizal Ahmad Bahuri, ⁵Kein Seong Mun

¹Division of Paediatric Neurology, ²Division of Paediatric Haematology & Oncology, Department of Paediatrics; ³Division of Biomedical Imaging, Department of Radiology; ⁴Division of Neurosurgery, Department of Surgery; ⁵Division of Histopathology, Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract

Gliomatosis cerebri (GC) is a rare extensively infiltrating growth pattern of diffuse glioma with wide clinical heterogeneity, often mimicking other disorders. GC usually affects the white matter and involvement predominantly of the deep gray matter at onset is uncommon. We describe a teenager who presented with bi-thalamic and left hippocampal-parahippocampal lesions at first presentation with a 1-month history of right-sided motor hemiparesis and hemiataxia. Over a 1-year period the lesion spread to the bi-temporal, right insular cortex, and bi-frontal cerebral hemisphere associated with multiple cranial palsies and progressive dementia. Histological examination revealed a high-grade anaplastic astrocytoma consistent with GC. Our case widens the phenotypic spectrum of GC. Clinicians need to consider GC in children with lesions in the deep gray matter in combination with pyramidal, cranial nerve palsies and extrapyramidal signs.

Keywords: Gliomatosis cerebri, gray matter, thalamus

INTRODUCTION

Gliomatosis cerebri (GC) was first described by Nevin in 1938 following description of three cases with widespread overgrowth of neuroglial cells in the cerebral hemispheres.¹ GC is an extremely rare form of neoplastic glial tumour with a grave prognosis. GC is distinctive amongst other primary central nervous system tumours due to its extensive, aggressively infiltrative growth and progression without the association of a tumour mass. GC usually affects three or more cerebral lobes and commonly extends into the deeper midline structures, infratentorial structures and less frequently into the spinal cord. GC was previously identified as a distinct pathological entity; however, under the recent 2016 World Health Organisation central nervous system tumour classification, it has been categorised under the various subtypes of diffuse gliomas with a widespread and very invasive pattern of growth.²

As there are no unique characteristic clinical features, GC notoriously mimics that of other medical conditions with similar clinical

and radiological criteria including acquired demyelinating diseases, various other encephalitis and even mitochondrial disorders.²⁻⁴ It is therefore not infrequent that patients are labelled with alternative diagnoses and have received other non-cancer treatment prior to arriving at this diagnosis. The long interval between symptom onset and pathological confirmation has been reported ranging from days to 23 years with the majority achieved in less than 24 months of symptom onset.⁵ Over the last 2 decades, paediatric patients are being diagnosed earlier, ranging between 3 weeks to 3 months.^{3,6,7} This significant improvement may reflect the advancement in neuroimaging techniques and also the greater awareness of this infiltrative entity.³

GC can invade both white and gray matter structures, with the former being more frequently seen and better described. To the best of our knowledge, there are only 2 paediatric GC reports describing exclusive gray matter involvement. Colosimo *et al.* described the neuroimaging findings of two paediatric patients with GC

Address correspondence to: Dr Choong Yi Fong, Division of Paediatric Neurology, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Tel: +603-79492065, e-mail: cyfong@ummc.edu.my

Date of Submission: 12 October 2021; Date of Acceptance: 22 February 2023

<https://doi.org/10.54029/2023hjd>

involving the thalamus⁸ and Chappe *et al.* published a series of 14 cases of paediatric GC affecting primarily the gray matter at initial disease presentation.⁹ We report another case of primary GC involving exclusively the deep gray matter at presentation.

CASE REPORT

A 15-year-old previously healthy boy presented with a 1-month history of progressive right-sided gait instability resulting in an inability to walk independently and a deterioration in his fine motor skills of his right hand causing increased difficulty with handwriting and using of cutlery. Neurological examination showed a combination of both pyramidal and extrapyramidal signs. His speech was soft, slow and staccato-like.

He walked with a broad-based unsteady gait. Cranial nerve examination revealed a right upper motor neuron facial nerve palsy, bilateral internuclear ophthalmoplegia and presence of horizontal nystagmus. He displayed right-sided hypertonia and weakness with proximal and distal muscles graded 3/5 on the Medical Research Council (MRC) scale. Additionally, bradykinesia, dysdiadochokinesia, dysmetria and intentional tremor were elicited over the right side. In contrast, his left upper and lower limbs were normal.

His first brain MRI showed enlarged thalami with hyperintensities at the left hippocampus and parahippocampal gyrus on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (Figure 1). Extensive investigations including blood and cerebrospinal fluid analysis to exclude

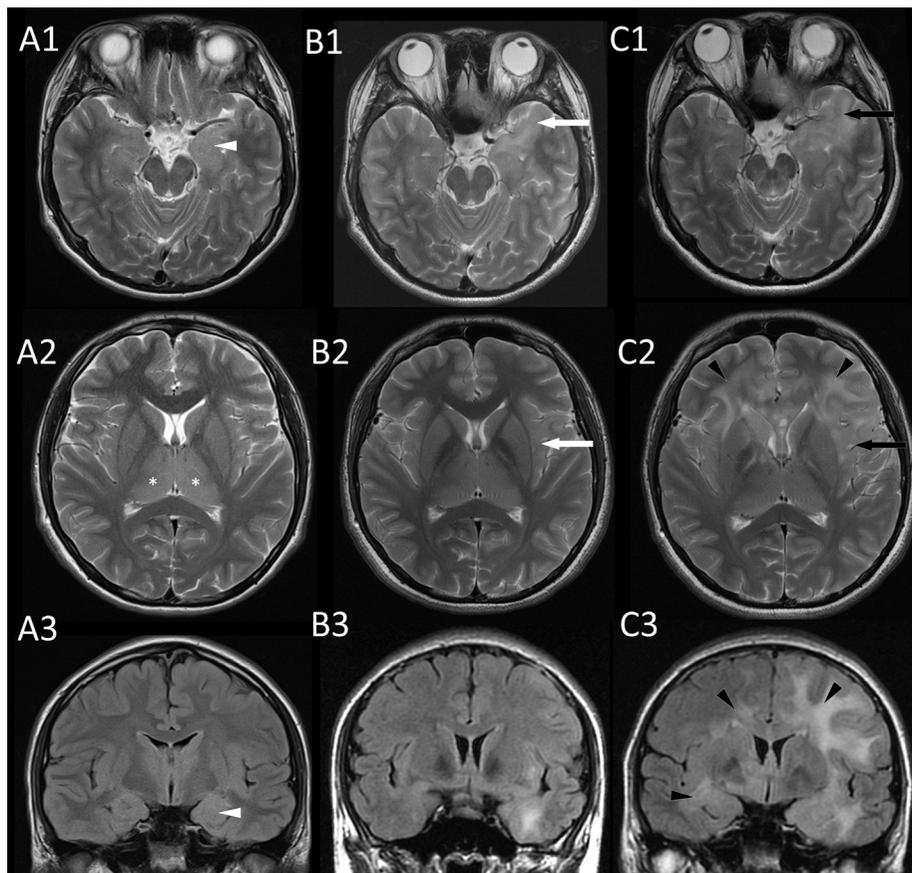


Figure 1. Serial axial T2-weighted and coronal fluid-attenuated inversion recovery (FLAIR) brain MRI images of the patient at presentation (A1-A3), three months (B1-B3) and one year later (C1-C3). At disease onset, the thalami were enlarged and diffusely hyperintense (white asterisks), with increased signal of the left hippocampus and parahippocampal gyrus (white arrow heads). Three months later, there was increasing involvement of the left anterior temporal lobe and left insula cortex (white arrows). One year after the initial MRI, there were increasing changes of the left temporal lobe and the left insula cortex (black arrows); and new changes of both frontal lobes, both centrum semiovale and the right temporal lobe (black arrow heads).

infectious, autoimmune and neurometabolic disorders were performed, all of which were normal. DNA for whole exome sequencing was sent to diagnose possible rare neurogenetic or neurometabolic disorders was also normal. Blood for tumour markers yielded negative results. He was given a course of pulsed intravenous methylprednisolone for three days, intravenous immunoglobulin and a trial of Levodopa for 3 months. He showed no improvement, and continued to deteriorate.

A repeat brain MRI three months later showed interval disease progression. The ill-defined thalami bulkiness remained, but new lesions were seen at the left hippocampus, parahippocampal gyrus, medial temporal lobe and left insular cortex (Figure 1). There were no restricted diffusion or blooming artefact. Magnetic resonance spectroscopy (MRS) and angiography of the cerebral vessels were normal. Within four months from presentation, he developed left cerebellar signs and gradual neurocognitive decline. Unfortunately, due to the Covid-19

outbreak, he could not be followed-up earlier due to a movement control order in Malaysia. He re-presented to us 1 year after his initial presentation in a dementia-like state. He was encephalopathic and aphasic and required nasogastric tube feeds. There were no reported seizures. Urgent brain MRI showed extensive spread to both gray and white matter of the cerebral cortex, involving the left corona radiata and centrum semiovale of the left frontal lobe and corpus callosum. Similar lesions of lesser degree were also seen on the right, extending into the dorsal midbrain and pons, and surrounding the fourth ventricles. There was no hydrocephalus. MRS remained non-contributory.

He then underwent an urgent left frontal lobe biopsy. Gross brain tissue was noted to be firm in consistency, with gray and white matter clearly discernible, although the demarcation was slightly blurred. Histopathological analysis confirmed anaplastic astrocytoma, WHO grade III of gliomatosis cerebri pattern (Figure 2). Additionally, tumour cells were glial fibrillary acidic protein (GFAP) antibody-positive with

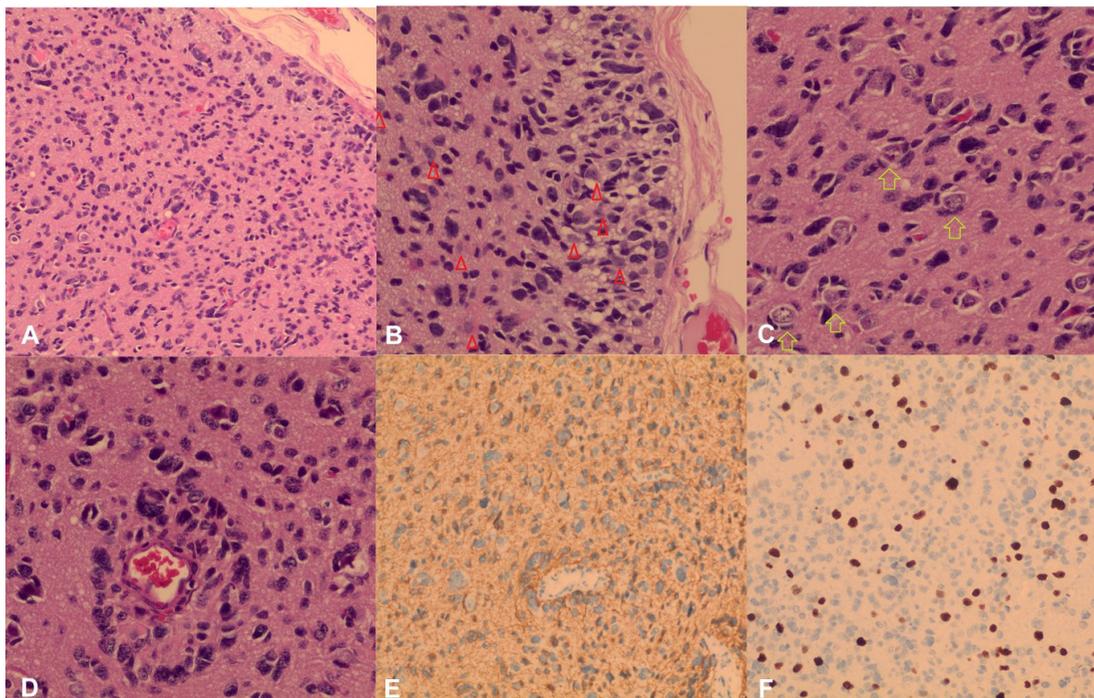


Figure 2. Histopathology slides of the brain tissue sampled from the patient's frontal lobe. A: Photomicrograph showing brain matter with infiltrating astrocytoma cells causing increased cellularity. (H&E stain, OM x10 objective); B: The dense subpial region consists of pleomorphic tumour cells dispersed diffusely against a background of non-neoplastic cells [red arrowheads] (H&E stain, OM x20 objective); C and D: Tumour cells showing perineuronal wrapping or satellitosis [green arrows] and perivascular resetting (H&E stain, OM x20 objective); E and F: Tumour cells are GFAP antibody-positive with high Ki67 proliferation index (H&E stain, OM x10 objective).

H&E: Haematoxylin & Eosin; *OM*: original magnification; *GFAP*: Glial Fibrillary Acidic Protein

a high Ki67 proliferation index. Molecular profiling to determine prognostic molecular alterations including isocitrate dehydrogenase (*IDH*) mutation was not performed. The patient passed away two months later.

DISCUSSION

GC spans across all age groups with an adult predominance. There are paediatric publications describing the occurrences and characteristics in the paediatric population.^{3,5-7,9} In paediatric GC, median age of diagnosis ranged between 10.2 to 12 years.^{3,6,7} GC's variable evolution and heterogenous clinical presentation often make establishing this diagnosis a challenge. The presenting symptoms at disease onset are dependent upon the neurologic structures involved. Seizures have been reported to be the commonest clinical presentation (38-66% of patients), usually refractory to drug therapy with disease progression.^{3,5-7,9-10} Other presenting features include raised intracranial pressure, focal motor deficits, headache and ataxia.^{2,4,6,9-10} Gradual neurocognitive decline culminating in dementia has been described in patients at advanced stages of the disease, like in our patient.^{2,4,9} Contrary to many paediatric case reports, seizure and symptoms of raised intracranial pressure were not observed in our patient despite serial neuroimaging showing significant tumour expansion to the frontal and temporal lobes.

Brain imaging, in combination with biopsy and histopathologic analysis are the gold standard to achieve diagnosis. The challenge for clinicians is to decide when a brain biopsy is indicated if the initial clinical and radiologic features are not typical of an infiltrative glioma, and biopsy is associated with a high risk of morbidity due to the location of the lesion in the deep gray matter like in our case. It becomes imperative that clinicians recognise the characteristic neuroimaging features that favour GC. Typical lesions are abnormally hyperintense on MRI T2-weighted or FLAIR sequences, whereas hypo- or iso-intense on T1-weighted sequence. As demonstrated in our patient, the absence of contrast enhancement in these lesions is not uncommon. In a recently published meta-analysis of 182 paediatric GC patients¹⁰, the most commonly affected CNS regions were the temporal (75%), frontal (69%), and parietal lobes (55%), closely followed by the diencephalon and basal ganglia (49%). Up to 60% of patients had bilateral disease, while 39% had tumour expansion to the infratentorial

CNS. Desclee *et al.*¹¹ reported that the corpus callosum and/or the anterior white commissure were always affected in patients with bilateral disease but was not seen in our case. Despite the extent of tumour invasion causing diffuse enlargement of cerebral structures, mass effect is reportedly absent or minimal and hydrocephalus rare¹¹, as was similarly observed in our patient.

MRS may be diagnostically helpful in some cases. An increased choline (Cho)/ creatine (Cr) ratio and reduced N-acetylaspartate/ Cr ratio are observed in areas of abnormal T2-hyperintensities, similar to other malignant brain tumours. However, diagnostic MRS was exhibited in only 3 of the 14 cases of primary GC involving gray matter in Chappe *et al.*'s⁹ cohort. MRS was not helpful in our case either.

MRI findings in our patient were similar to that illustrated by Chappe's cohort of 14 paediatric primary GC involving gray matter. Similarly, our patient's MRI showed specific topography towards both thalami, simultaneously affecting the temporal cortex, insular cortex and basal ganglia, all representing a strong distinctive radiographic characteristic of GC of the gray matter.⁹ Our patient's disease began predominantly at the thalami. Other case series have also reported symmetrical bi-thalamic involvement (as high as 28%) in their respective cohort as a prominent feature of GC.⁷ This unique anatomic preference of GC further reinforces that this diagnosis must be considered in the differential diagnoses of disorders preponderantly affecting the thalami.

Conventionally, central nervous system (CNS) tumour classification was based on histological characteristics of the tumour. The many developments in the field of molecular diagnostics have led to revised publications of the 2016¹², and more recently in the 2021 WHO classifications, which placed emphasis on molecular parameters for tumour diagnosis, classification and grading.¹³ The inclusion of molecular markers is important, not only in accordance with our understanding that paediatric GC harbours mutations and oncogene amplifications, but also because these molecular aberrations, when present, can have prognostic and possible therapeutic implications. Despite the life-limiting nature of the disease, *IDH1* mutations were related to prolonged overall survival and favourable clinical outcomes among children and adolescents with GC.¹⁰ In future, such molecular features may also potentially have a therapeutic role. We acknowledge that molecular characterisation was not explored in our patient, which is recommended in the latest guidelines.¹³

In conclusion, our case widens the phenotypic spectrum of GC and reiterates the importance of clinicians to be vigilant in maintaining GC as a possible differential diagnosis in children who show multiple focal pyramidal, extrapyramidal neurological signs and cranial nerve palsies in combination with MRI features of deep gray matter involvement of the thalami, hippocampal and parahippocampal region.

DISCLOSURE

Financial support: None

Conflict of interests: None

REFERENCES

1. Nevin S. Gliomatosis cerebri. *Brain* 1938;61:170-91. doi.org: 10.1093/brain/61.2.170.
2. Greenfield JP, Castañeda Heredia A, George E, Kieran MW, Morales La Madrid A. Gliomatosis cerebri: A consensus summary report from the First International Gliomatosis Cerebri Group Meeting, March 26-27, 2015, Paris, France. *Pediatr Blood Cancer* 2016; 63(12):2072-7. doi: 10.1002/pbc.26169.
3. George E, Settler A, Connors S, Greenfield JP. Pediatric gliomatosis cerebri: A Review of 15 Years. *J Child Neurol* 2016;31(3):378-87. doi: 10.1177/0883073815596612.
4. Ranjan S, Warren KE. Gliomatosis cerebri: Current understanding and controversies. *Front Oncol* 2017; 7. doi:10.3389/fonc.2017.00165.
5. Jennings MT, Frenchman M, Shehab T, et al. Gliomatosis cerebri presenting as intractable epilepsy during early childhood. *J Child Neurol* 1995; 10:37-45. doi: 10.1177/088307389501000111.
6. Armstrong GT, Phillips PC, Rorke-Adams LB, Judkins AR, Localio AR, Fisher MJ. Gliomatosis cerebri: 20 years of experience at the Children's Hospital of Philadelphia. *Cancer* 2006; 107(7):1597-606. doi: 10.1002/encr.22210.
7. Broniscer A, Chamdine O, Hwang S, et al. Gliomatosis cerebri in children shares molecular characteristics with other pediatric gliomas. *Acta Neuropathologica* 2016; 131(2):299-307. doi: 10.1007/s00401-015-1532-y.
8. Colosimo C, di Lella G, Tartaglione T, Riccardi R. Neuroimaging of thalamic tumors in children. *Child's Nervous System* 2002; 18(8): 426-39. doi: 10.1007/s00381-002-0607-y.
9. Chappé C, Riffaud L, Tréguier C, et al. Primary gliomatosis cerebri involving gray matter in pediatrics: a distinct entity? A multicenter study of 14 cases. *Childs Nerv Syst* 2013; 29(4): 565-71. doi: 10.1007/s00381-012-2016-1.
10. Georgakis MK, Tsivgoulis G, Pourtsidis A, Petridou ET. Gliomatosis cerebri among children and adolescents: An individual-patient data meta-analysis of 182 patients. *J Child Neurol* 2019; 34(7): 394-401. doi: 10.1177/0883073819836551.
11. Desclée P, Rommel D, Hernalsteen D, Godfraind C, de Coene B, Cosnard G. Gliomatosis cerebri, imaging findings of 12 cases. *J Neuroradiol* 2010; 37(3): 148-58. doi: 10.1016/j.neurad.2009.12.001.
12. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 2016; 131(6): 803-20. doi: 10.1007/s00401-016-1545-1.
13. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro-oncology* 2021; 23(8): 1231-51. doi: 10.1093/neuonc/noab106.