

Familial glioblastoma clustering in adult patients: a case report of two non-twin siblings and review of the literature

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Purpose: Familial glioblastoma multiforme (gbm) has been described in children with hereditary tumor syndromes. The occurrence of gbm in adult members of the same family and in the absence of tumor syndromes is extremely rare. We describe the cases of a brother and a sister with multifocal gbm diagnosed at the age of 63 years. We discuss three further paired gbm in adult patients from the literature.

Patients and results: The sister was diagnosed with multifocal primary gbm in 2014 at the age of 63 years and 6 months. In 2018, her younger brother had to be operated on for a multifocal primary gbm at the age of 63 years and 9 months. Extended neuropathological examination revealed most markers to be similar, except for the percentage of O⁶-methylguanine-DNA methyltransferase promotor methylation, the presence of intratumoral immune cells and the immunohistochemical expression of C12ORF75. Comparison with further published cases of familial adult GBM reveals that most of these patients are male, about 65 years old and the tumor is localized predominantly in the left temporal lobe.

Conclusion: Paired adult familial gbm occurs mainly in the elderly male patient with an integrative diagnosis of primary gbm. Whereas a statistical coincidence seems to be most likely in these rare cases, supplementary and improved genetic studies may identify pathogenetic causes of gbm.

Keywords: multifocal glioblastoma, familial tumor clustering, IDH-1 wildtype, tumor syndrome

Introduction

Glioblastoma multiforme (gbm) is the most malignant tumor of the central nervous system with an extremely poor prognosis.¹ The average overall survival is 12–15 months after first diagnosis. Two molecular subtypes of gbm are described, divided into primary and secondary gbm. Primary gbm is characterized by de novo development and usually occurs in elderly patients over 50 years of age. Molecular analysis reveals an overexpression of EGFR, loss of heterozygosity of chromosome 10q and phosphatase and tensin homolog mutations. Secondary GBM occurs mainly in younger patients and its genetic profile is characterized by tumor protein p53 (TP53) mutations and isocitrate dehydrogenase 1 (IDH-1) mutations.²

There is faint evidence for the involvement of environmental factors in the genesis of glioblastoma, such as nonionizing electromagnetic fields and ionizing

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radiations.³ Furthermore, several hereditary tumor syndromes are associated with an increased occurrence of gbm in childhood and adolescence, for example, neurofibromatosis type-1, familial melanoma-astrocytoma syndrome, Li-Fraumeni syndrome, and Turcot syndrome.⁴⁻⁷

Familial gbm in the adult is extremely rare. A review of the literature revealed many well-documented descriptions of familial gbm in children, but there were only three case reports dealing with familial gbm in adult patients.⁸⁻¹⁰

This report describes familial gbm in two adult siblings. Interestingly, both patients suffered from multifocal gbm and were diagnosed at the same age of 63 years.

Case description

Case 1

Sibling 1 was the older sister, a 63-year-old female without malignant disease in her history (Table 1). She suffered from sudden paresthesia, ataxia, and vertigo. Brain magnetic resonance imaging (mri) disclosed mass lesions with gadolinium enhancement in the left parieto-temporal and the left frontal lobe infiltrating the splenium to the contralateral hemisphere with a total volume of 54.52 cm³ (Figure 1A-C). Craniotomy and partial resection of the tumor were performed 1 week after the first occurrence of clinical symptoms. Histopathologic examination of the tissue revealed a primary gbm, IDH-1 wild type (Table 2). The patient postoperatively developed focal epilepsy in the left upper limb, which was successfully treated with levetiracetam. She was discharged 14 days after surgery.

Concomitant radiation with temozolomide (tmz) was performed, followed by chemotherapy with tmz alone. The first recurrence occurred in the dorsal corpus callosum, left occipital lobe and left temporal lobe 1 year after the first diagnosis of gbm. A second palliative radiation of the recurrence was undertaken. The patient died 63 weeks after the first diagnosis of multifocal gbm.

Case 2

Sibling 2 was the younger brother of the patient described as case 1, a 63-year-old male without malignant diseases (Table 1). He presented to our institution with a 1-year history of progressive gait disturbance and motor aphasia. The mri scan revealed multifocal lesions in the left parieto-temporal and frontal lobe combined with ependymal spread and a total tumor volume of 8.97 cm³ (Figure 1D-F). Craniotomy and partial resection of the tumor in the left parietal lobe were performed. Histopathology disclosed primary gbm, IDH-1 wild type (Table 2). The patient was discharged 5 days after surgery with motor dysphasia, but the absence of further neurologic sequelae. Combined radiation and chemotherapy had been advised, but, in view of his sister's fate, the patient refused any further therapy or clinical follow-up examinations and died 3 months after the first diagnosis of gbm.

Discussion

In this study, we describe a sister and her younger brother who both suffered from gbm at an identical age with

Table 1 Clinical data and oncologic history of both cases

	Case 1	Case 2
Gender	Female	Male
Age at diagnosis, y	63+6 months	63+9 months
Diagnosis	Primary gbm; WHO IV, IDH-1 (R132H) negative	Primary gbm, WHO IV, IDH-1 (R132H) negative
Localization	Left parieto-temporal lobe over splenium to contralateral side, multifocal appearance	Left parieto-temporal lobe with ependymal spread, multifocal appearance
Medical history	Hypertension Hypothyreosis	Paroxysmal atrial fibrillation Allergic asthma
First symptoms	Paraesthesia in the right arm for 2 days, gait disturbance for 6 weeks, vertigo	Gait disturbance for 1 year, motor aphasia
Adjuvant treatment	Stereotactic radiation of parieto-temporal lobe with total dose of 59.4 Gray, simultaneous chemotherapy with tmz, followed by eight cycles of tmz	The patient declined adjuvant treatment
Recurrence	12 months after first diagnosis in corpus callosum, left occipital lobe and temporal lobe; adjuvant radiation with 35 Gray	n.a.
Death	15 months after first diagnosis	3 months after first diagnosis

Abbreviations: gbm, glioblastoma multiforme; IDH-1, isocitrate dehydrogenase 1; tmz, temozolomide.

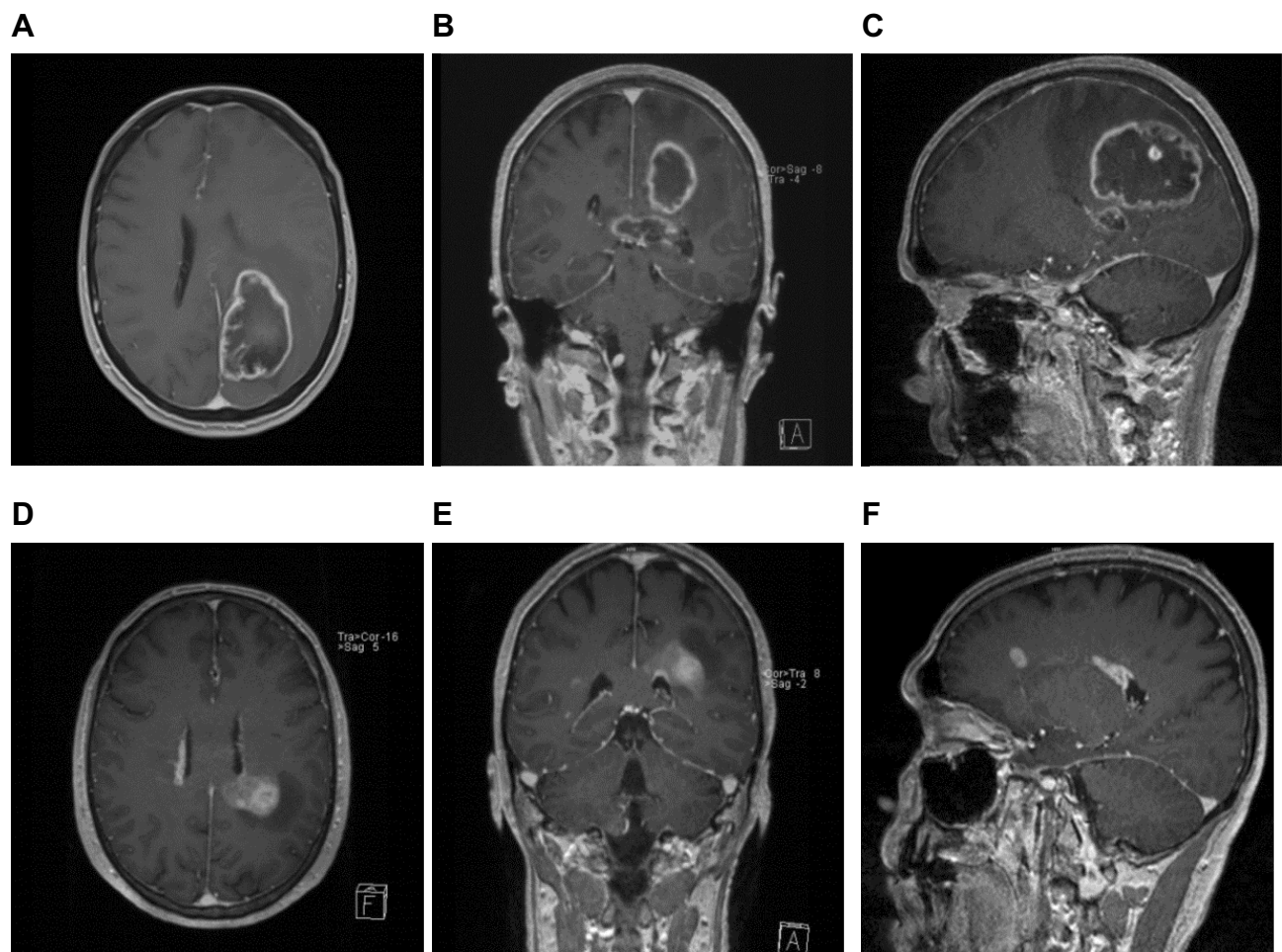


Figure 1 Magnetic resonance imaging (mri) scan of the neurocranium, gadolinium-enhanced T1-weighted sequences. **(A-C) Sibling 1.** mri axial **(A)**, coronal **(B)** and sagittal view **(C)** large mass located in the parieto-temporal lobe, multifocal localization, extension into the corpus callosum and infiltration to the right hemisphere. **(D-F) Sibling 2.** mri axial **(D)**, coronal **(E)** and sagittal view **(F)**. Tumor mass located in the parieto-temporal lobe with periventricular, ependymal spread. Multifocal localization, up to the right frontal and temporal regions.

nearly the same tumor localization and multifocal appearance. Furthermore, the histological, immunohistochemical, and molecular findings can be considered to be nearly identical.

Familial gbm has been associated in pediatric patients with specific tumor syndromes (Table 3).

In contrast to this, the familial occurrence of gbm in adult patients is an extremely rare event, with only a few case reports found in the recent literature (Table 4).

Heuch et al described two brothers aged 65 and 68, one case only diagnosed at autopsy.⁹ The second report of adult familial gbm was illustrated by Hardman: one pair of identical twins suffered from gbm, the first at the age of 61 and the second at 63. Normal karyotypes of blood leukocytes and similar environmental exposure are described.¹⁰ Thirdly, Ugonabo published a report of two brothers with the diagnosis of gbm at the age of 63 and 81

years.⁸ There was no clinical information given about any environmental risk factors or genetic alterations to depict pathophysiologic mechanisms.

In summary, all four case reports of adult familial gbm describe elderly patients with an average age of 65.9 years at first diagnosis and seven of eight patients are male. Frequent tumor localizations are the temporal lobe (54%, 6 of 11 tumors), the parietal lobe (36%, 4 of 11), occipital lobe (27%, 3 of 11), and the frontal lobe (18%, 2 of 11). A multifocal localization was detected in half of the patients. The left hemisphere was more often implicated than the right hemisphere (63% left vs 36% right). The average overall survival was 6 months. These findings are in good accordance with the natural epidemiology of primary gbm, pointing to a statistical coincidence as an explanation for the familial occurrence, rather than to a causal connection.¹¹

Table 2 Neuropathologic results of tumor samples

Method	Case 1	Case 2
IDH-1(Codon 132) and IDH-2 (Codon 172) sequencing	No mutations of IDH-1 or IDH-2	No mutations of IDH-1 or IDH-2
MGMT promotor methylation (CpG-Loci 74–78)	Average methylation of 8.75%	Average methylation of 14.6%
Histology	High cellular density, moderate pleomorphic tumor with increased mitotic activity and vascular endothelial proliferation, no sarcomatotic components	High cellular density, confluent necrosis, Moderate pleomorphic tumor with increased mitotic activity and vascular endothelial proliferation, astroglially differentiated tumor with gemistocytic aspect
Immunohisto- chemistry		
Mib-1	30% of tumor cells positive	Focally up to 15% of cells positive
GFAP	Prominent positivity in tumor components	Diffusely positive
ATRX	Mainly positive nuclear expression	Positive nuclear expression
Olig2	Tumor cells predominantly positive with nuclear staining	Nuclear positivity
MAP2	Single cells, axon-related	Focally weak positivity, axon-related
IDH-1 (R132)	Negative	Negative
P53	2% dominant, 10% with weak to moderate nuclear accumulation	10% of tumor cells weak nuclear positivity
CD68	Negative	Signs of microglial activation within tumor components
pHH3	3 cells in metaphasis/10 HPF	Up to 55 cells in metaphasis/10 HPF
LCAx	Accentuated positivity in mesenchymal stroma components	Diffuse infiltration of leukocytes
CD3	Positive, focally perivascular in tumor stroma	Single cells positive
ApoC1	Weakly positive	Moderately positive
LuzP6	Negative	Negative
Myotrophin	Moderately positive	Strongly positive
C12ORF75	Negative	Moderately positive

Abbreviations: IDH-1, isocitrate dehydrogenase 1; IDH-2, isocitrate dehydrogenase 2; Mib-1, molecular immunology Borstel; GFAP, glial fibrillary acidic protein; ATRX, X-linked alpha-thalassemia mental retardation; Olig2, oligodendrocyte transcription factor; MAP2, microtubule associated protein 2; CD68, cluster of differentiation 68; pHH3, phosphohistone H3; LCA, leukocyte common antigen; CD3, cluster of differentiation 3; ApoC1, apolipoprotein C1; LuzP6, leucine zipper protein 6; C12ORF75, Chromosome 12 open reading frame 75.

Integrated diagnosis was only available in the two current cases due to the retrospective nature of case reports. In the present cases, the integrated diagnosis and the detailed immunohistochemical markers can be considered to be almost identical, revealing the diagnosis of primary gbm, IDH-1 wild type.

However, we detected discrete differences concerning MGMT promoter methylation and the number of immune cells within the tumor stained by cluster of differentiation 68. In case 1 MGMT promoter methylation was classified as absent, whereas in case 2 the MGMT promoter was strongly methylated. These findings would have suggested a better overall survival and chemotherapeutical response for case 2 compared to case 1, as has been detailed by the MGMT promoter methylation score,¹² but unfortunately patient 2 declined further therapy.

Differing results were also shown for the immunohistochemical staining of C12orf75, whereas the staining for ApoC1, leucine zipper protein 6 (LuzP6), and myotrophin were rather similar, all of them proteins that have been associated with cystic appearance of gbm (Figure 1, Table 2).¹³

The intriguing finding of tumor occurrence at nearly the same age with a large amount of corresponding radiological and neuropathological results inspires the search for a potential common pathogenetic mechanism. Further detailed genetic analysis would help to describe the precise driver genes to distinguish between familial hereditary occurrence and mere coincidence.

Ugonabo et al performed cytogenetic analysis in one sibling and illustrated multiple chromosomal abnormalities, such as triploidies 4, 8, 12 and 22, and loss of

Table 3 Pediatric tumor syndromes with reported familial clustering of glioblastoma multiforme

Tumor syndrome	Gene mutation (gene localization)	Malignancies
Constitutional mismatch repair deficiency syndrome	MLH1 (3p21.3) PMS2 (7p22) MSH2 (2p22-p21) MSH6 (2p16)	- hematological malignancy - malignant brain tumors (medulloblastoma and glioblastoma) - Lynch syndrome-associated carcinomas (colorectal cancer, urinary tract cancer, bladder cancer, ovarian cancer, endometrium cancer, small bowel cancer, pancreaticobiliary cancer)
Familial melanoma-astrocytoma syndrome	CDKN2A (9p21.3)	- melanoma - diffuse astrocytoma - peripheral nerve sheath tumor - meningioma - pleomorphic xanthoastrocytoma
L-2-hydroxyglutaric aciduria Li-Fraumeni syndrome	L2HGDH (14q21.3) TP 53 (17p13.1)	- medulloblastoma and glioblastoma - sarcoma - adrenocortical carcinoma - breast cancer - leukemia - brain tumors (glioma, choroid plexus carcinoma)
Muir-Torre syndrome	MSH6 (2p22-p21)	- sebaceous neoplasms (adenoma, epithelioma, adenocarcinoma, keratoacanthoma, squamous cell carcinoma) - gastrointestinal cancer, urological cancer - brain tumor (glioblastoma)
Neurofibromatosis type I	NF1 (17q11.2)	- brain tumors (optic pathway glioma, glioblastoma) - peripheral nerve tumors (neurofibroma, malignant peripheral nerve sheath tumor)
Ollier/Maffucci syndrome	PTHRI (3p21-22)	- central cartilaginous tumor - enchondroma - lymphangioma - soft tissue hemangioma - chondroma - glioma - acute myeloid leukemia
Tuberous sclerosis	TSC1 (9q34) TSC2 (16p13.3)	- renal angiomyolipoma - rhabdomyoma - facial adenoma sebaceum - brain tumors (hemangioma, subependymal giant cell astrocytoma, meningioma, neurinoma, ependymoma, glioblastoma)
Ullrich-Turner syndrome	Complete or partial X-chromosome monosomy	- gastrointestinal cancer - hematologic cancer - bladder cancer - melanoma - uterine corpus cancer - brain tumor (glioblastoma, meningioma)
Von Hippel-Lindau disease	VHL (3p25.3)	- hemangioblastoma - renal cell carcinoma - pheochromocytoma and paraganglioma - pancreatic tumors (cystadenoma, neuroendocrine tumor) - brain tumors (hemangioblastoma, glioblastoma)

Abbreviations: MLH1, mutL homolog 1; PMS2, postmeiotic segregation increased 2; MSH2, mutS homolog 2; MSH6, mutS homolog 6; CDKN2A, cyclin dependent kinase inhibitor 2A; L2HGDH, L-2-hydroxyglutarate dehydrogenase; PT53, tumor protein p53; NF1, neurofibromatosis type I; PTHRI, parathyroid hormone I receptor; TSC1, tuberous sclerosis 1 protein; TSC2, tuberous sclerosis 2 protein; VHL, Von Hippel-Lindau tumor suppressor gene.

Table 4 Reports on familial gbm in the adult

Author	Patients (age at diagnosis in y)	Multifocal localization	Cytogenetic or immunohistological information	Overall survival (months after first diagnosis)
Heuch et al (1986) ⁹	1) Male (65)	Yes	n. a.	3
	2) Male (68)	No		3
Hardman et al (1989) ¹⁰	1) Male (61)	No	n. a.	8
	2) Male (63)	No	Normal karyotype of peripheral blood lymphocytes	n. a.
Ugonabo et al (2011) ⁸	1) Male (63)	Yes	n. a.	4
	2) Male (81)	No	Triploidies of 4, 8, 12 and 22 and LOH of 1p, 9p and 10	n. a.
Present report	1) Female (63)	Yes	IDH-1 wild type	15
	2) Male (63)	Yes	IDH-2 wild type	3

Abbreviations: gbm, glioblastoma multiforme; LOH, loss of heterozygosity; IDH-1, isocitrate dehydrogenase 1; IDH-2, isocitrate dehydrogenase 2.

heterozygosity of 1 p, 9 p and 10.⁸ All of these chromosomal aberrations have already been well described in gbm.^{14–19} However, the frequent hallmarks of gbm, gain at chromosome 7 and loss of chromosome 10, were absent, thus, the genetic imbalances illustrated did not allow to define a “familial clustering subtype”.

Conclusion

In addition to the two gbm siblings presented in this report, a review of the literature revealed only a very limited number of reports on familial gbm clustering in adults. Different from the pediatric population and although supplementary and improved genetic studies may disclose further common aberrations in the future, our results support the hypothesis of statistical coincidence without an underlying genetic cause.

Informed Consent

Both patients gave their written informed consent to the operation and the use of their data in pseudonymized form for research purposes and publication of the case details prior to the neurosurgical intervention.

Ethics approval

Ethics approval had been obtained from the ethics committee of the University of Leipzig (277/15-ff). The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in Tokyo 2004).

Abbreviation list

ApoC1, apolipoprotein C1; C12ORF75, chromosome 12 open reading frame 75; CD68, cluster of differentiation 68; gbm, glioblastoma multiforme; IDH-1, isocitrate

dehydrogenase 1; IDH-2, isocitrate dehydrogenase 2; LOH, loss of heterozygosity; LuzP6, leucine zipper protein 6; MGMT, O⁶-methylguanine-DNA methyltransferase; mri, magnetic resonance imaging; PTEN, phosphatase and tensin homologue; tmz, temozolomide; TP53, tumor protein p53.

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Disclosure

The authors report no conflicts of interest in this work.

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