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Short communication

# Albumin storage in neoplastic astroglial elements of gangliogliomas

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ABSTRACT

*Purpose:* Low-grade neuroepithelial tumors are frequent neuropathological findings in patients with pharmacoresistant epilepsies. Little is known regarding epileptogenic mechanisms in this group of neoplasms with gangliogliomas (GG) as the most common entity. Presence of hemosiderin deposits in GG points to impairment of the blood-brain barrier (BBB). Therefore, we hypothesized a potential role of BBB dysfunction and astrocytic albumin uptake as potential epileptogenic factor in GG.
*Methods:* Prussian blue staining and fluorescent double-immunohistochemistry with antibodies against albumin, GFAP, CD34 and GLUT-1 were used to analyze hemosiderin deposits and astroglial albumin accumulation in tumor and adjacent pre-existing brain tissue of GG ($n = 10$) and several control groups, i.e. dysembryoplastic neuroepithelial tumors (DNT; $n = 5$), focal cortical dysplasia with balloon cells (FCD IIb; $n = 10$), astrocytomas WHO grade II ($n = 5$) and clear renal cell carcinoma brain metastases (RCCM, $n = 6$).
*Results:* Our results revealed strong hemosiderin deposits in GG. Intriguingly, we noted substantial albumin uptake exclusively in neoplastic glial cell components of GG and DNT, whereas no significant albumin was present in perilesional reactive astrocytes. Strikingly, we did not observe substantial albumin uptake in further controls.
*Conclusion:* Glial albumin uptake was restricted to long-term epilepsy associated, vasculature-containing tumors. Intratumoural BBB dysfunction in concert with subsequent accumulation of albumin by neoplastic glial cell elements represent a new putatively epileptogenic mechanism for long-term epilepsy-associated tumors.


## 1. Introduction

Gangliogliomas (GG) represent the most frequent tumor entity in young patients undergoing surgery for drug-refractory epilepsy.[1] GG commonly correspond to WHO grade I tumors and are histopathologically characterized by dysplastic neurons and neoplastic astroglial cells. Typically, contrast enhancement is present on magnetic resonance imaging (MRI) pointing to blood-brain barrier (BBB) dysfunction. Mechanisms underlying the high epileptogenicity of GG are still enigmatic.

Factors such as impaired neurochemical homeostasis, genetic and peritumoural changes have been suggested to underlie increased neuronal excitability.[2,3] Recent data emphasized a contribution of BBB leakage to the progression of epilepsy,[4–6] with astroglial albumin uptake as a key pathogenic factor.[4,7,8] Frequent deposits of hemosiderin indicate an impairment of the BBB in this tumor entity.

Accordingly, we analyzed hemosiderin deposits and astroglial albumin accumulation in tumor and adjacent brain tissue of GG and in several 'control' pathologies.

## 2. Materials and methods

### 2.1. Patients and surgical specimens

Biopsy specimens were obtained from patients who underwent neurosurgery at the University of Bonn using controls as follows. Dysembryoplastic neuroepithelial tumors (DNT; WHO grade I) represent a further highly epilepsy-associated glioneuronal tumor entity. Diffuse astrocytomas (DA; WHO grade II)

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**Table 1A**
Clinical and neuropathological parameters of patients.

| Patient no. | Sex | Therapy-refractory epilepsy | Epilepsy duration (yrs) | Age at surgery (yrs) | Site of specimen collection | Astrocytic albumin uptake[a] | | Hemosiderin deposits | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Lesion | Perilesion | Lesion | Perilesion |
| Ganglioglioma (GG, WHO grade I) | | | | | | | | | |
| 1 | f | Yes | 26 | 30 | Temporal left | ++ | 0 | ++ | 0 |
| 2 | f | Yes | 15 | 31 | Temporal left | ++ | 0 | ++ | 0 |
| 3 | f | Yes | 15 | 39 | Frontal right | + | 0 | + | 0 |
| 4 | m | Yes | 3 | 6 | Frontal left | ++ | 0 | ++ | 0 |
| 5 | m | Yes | 38 | 51 | Temporal left | ++ | 0 | ++ | + |
| 6 | m | Yes | 2 | 17 | Temporal right | ++ | 0 | + | 0 |
| 7 | m | Yes | 2 | 12 | Temporal left | ++ | 0 | + | 0 |
| 8 | f | Yes | 13 | 36 | Temporal right | +++ | 0 | 0 | 0 |
| 9 | m | Yes | 3 | 39 | Temporal left | ++ | + | + | 0 |
| 10 | m | Yes | 1 | 20 | Temporal right | + | 0 | 0 | 0 |
| Dysembryoplastic neuroepethelial tumor (DNT, WHO grade I) | | | | | | | | | |
| 11 | f | Yes | 5 | 20 | Frontal left | + | 0 | 0 | 0 |
| 12 | m | Yes | 7 | 54 | Temporal left | + | 0 | + | 0 |
| 13 | m | Yes | 50 | 59 | Frontal left | ++ | 0 | ++ | + |
| 14 | m | Yes | 10 | 35 | Temporal right | + | 0 | + | 0 |
| 15 | f | Yes | 1 | 28 | Frontal left | + | 0 | 0 | 0 |
| Focal cortical dysplasia type IIb (FCD IIb) | | | | | | | | | |
| 16 | f | Yes | 8 | 9 | Parietal left | 0 | 0 | 0 | 0 |
| 17 | f | Yes | 2 | 9 | Temporal left | 0 | 0 | 0 | 0 |
| 18 | m | Yes | 10 | 10 | Insula left | 0 | 0 | 0 | 0 |
| 19 | m | Yes | 11 | 13 | Parietal left | + | 0 | 0 | 0 |
| 20 | f | Yes | 13 | 32 | Temporal right | + | 0 | 0 | + |
| 21 | m | Yes | 2 | 2 | Temporal left | 0 | 0 | 0 | 0 |
| 22 | m | Yes | 6 | 7 | Parietal left | 0 | 0 | + | 0 |
| 23 | f | Yes | 15 | 17 | Frontal left | 0 | 0 | 0 | 0 |
| 24 | f | Yes | 9 | 23 | Frontal right | 0 | 0 | 0 | 0 |
| 25 | m | Yes | 14 | 22 | Parietal left | + | 0 | 0 | 0 |
| Astrocytoma (WHO grade II) | | | | | | | | | |
| 26 | f | No | | 45 | Temporal left | 0 | 0 | 0 | 0 |
| 27 | f | No | | 20 | Temporal right | 0 | 0 | 0 | 0 |
| 28 | m | No | | 36 | Insula right | 0 | 0 | 0 | 0 |
| 29 | m | No | | 33 | Temporal left | 0 | 0 | 0 | 0 |
| 30 | f | No | | 50 | Frontal left | 0 | 0 | 0 | 0 |
| Renal cell carcinoma metastasis (RCCM) | | | | | | | | | |
| 31 | f | No | | 61 | Frontal left | / | + | + | 0 |
| 32 | m | No | | 65 | Temporal left | / | 0 | ++ | + |
| 33 | m | No | | 57 | Frontal left | / | 0 | +++ | +++ |
| 34 | f | No | | 69 | Temporal left | / | + | ++ | 0 |
| 35 | f | No | | 43 | Frontal left | / | 0 | + | + |
| 36 | m | No | | 44 | Temporal left | / | 0 | + | 0 |

[a] Astrocytic albumin storage as observed in lesional and perilesional areas of gangliogliomas, DNT, FCD IIb and astrocytomas. Due to mainly absent astrocytes in lesional regions of carcinoma metastasis, only the perilesional brain tissue was considered for examination.

largely share morphological features of the astroglial component in GG but lack contrast enhancement and the strong association with drug-refractory epilepsy. Focal cortical dysplasias with balloon cells (FCD IIb) represent non-neoplastic epilepsy-associated lesions without a vascular component.[9] Finally, clear renal cell carcinoma brain metastases (RCCM) often encounter neuropathological hemosiderin deposits and contrast enhancement on MRI. Here, seizures are rather acute than chronic (GG: $n = 10$; DNT: $n = 5$; FCD IIb: $n = 10$; DA: $n = 5$; RCCM: $n = 6$). All procedures were carried out in accordance with the declaration of Helsinki. The clinical parameters of the patients are summarized in Table 1A.

### 2.2. Tissue processing, immunohistochemistry, double-immunofluorescence and image analysis

These procedures were performed as described before,[10] see Appendix A for more details. Prussian blue staining and GFAP/albumin double-immunofluorescence labeling was used in all cases to analyze semiquantitatively (none, few, intermediate, abundant) hemosiderin deposits and astrocytic albumin uptake in lesional and perilesional regions (Tables 1A and 1B). Representative neuropathological findings for the different groups are shown in Figs. A1–A3.

**Table 1B**
Summarized lesional characteristics.

| | GG[a]/DNT[b] | FCD IIb[c] | Astrocytoma[d] | RCCM[e] |
|---|---|---|---|---|
| Impaired BBB[f] | Yes | No | No | Yes |
| Glial tumor cell component | Yes | No | Yes | No |
| Chronic epilepsy | Yes | Yes | No | No |
| Astroglial albumin uptake | Yes | No | No | No |

[a] Ganglioglioma WHO grade I.
[b] Dysembryoplastic neuroepethelial tumor complex variant.
[c] Focal cortical dysplasia type IIb.
[d] Astrocytoma WHO grade II.
[e] Cerebral metastases of clear renal cell cancer.
[f] As indicated by hemosiderin deposits and contrast enhancement.