Acta Epileptologica

CASE REPORT

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Ganglioglioma surgery associated with postoperative status epilepticus: a case report

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Abstract

Background: Gangliogliomas are brain tumors associated with drug-resistant focal epilepsy. In most cases, seizures improve after surgical treatment. It is still not concluded to what extent the lesion itself or the perilesional area contributes to the epileptogenicity.

Case presentation: In the case presented in this report, the patient, a 24-year-old Caucasian male, developed a refractory status epilepticus after a surgical attempt to remove a cerebral ganglioglioma. The postoperative magnetic resonance imaging revealed that the lesion was intact, and that inadvertently only the perilesional area and adjacent cortex had been resected. The patient underwent a new surgical procedure where the ganglioglioma was removed, and the status epilepticus cessated.

Conclusions: This clinical case suggests that the lesion itself plays an important role in seizure generation and propagation, and notably, that the surrounding cortex by an inhibitory action can act as a gate to seizure spread.

Keywords: Postoperative complication, Epilepsy surgery, Seizures, Epileptogenicity, Seizure outcome

Background

Gangliogliomas are slow-growing brain tumors that, in general, have a benign course although malignant transformation may occur [1]. They are very frequently associated with drug-resistant focal epilepsy [2]. Gangliogliomas are usually treated by surgery and the rate of long-term seizure improvement following surgery is 80% [2]. A majority of patients do not have seizure or tumor recurrences, and long-term survival is good [1].

In order to achieve seizure freedom in epilepsy surgery it is necessary to completely resect or disconnect the epileptogenic zone [3]. However, in ganglioglioma, the extent of the epileptogenic zone is unclear and the pathophysiological mechanisms underlying epileptogenicity are not well characterized. It is still not concluded whether ganglioglioma seizure onset and propagation is due to the dysfunctional neurons within the tumor itself, or if the perilesional area participates in the seizure initiation and propagation [4–7].

Here we present a case of ganglioglioma surgery where, inadvertently, only cortex adjacent to the lesion and perilesional area were resected, with immediate postoperative worsening of seizures as a result. To our knowledge, this is the first reported case of postoperative status epilepticus after incomplete resection of ganglioglioma. The case proposes that the lesion itself is key in the seizure initiating zone, and importantly, the adjacent cortex, by an inhibitory action, can act to dampen seizure spread.

Case presentation

The patient, a Caucasian right-handed male, presented with a few nocturnal generalized tonic and clonic seizures at the age of 10 months. Computed tomography

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(CT) of the brain and electroencephalogram (EEG) initially produced normal findings. It became evident that the seizures were actually focal-onset motor seizures, starting with tonic seizures in the left hand. Seizures were scarce, one per year until the age of four, whereafter there was a temporary seizure remission. At the age of seven years seizures relapsed and the patient commenced antiepileptic medication. A new CT scan showed an area of low attenuation in the right parietal operculum (gyrus supramarginalis). Magnetic resonance imaging (MRI) of the brain confirmed a cortical and subcortical lesion in the same area, with high T2 signal, and no contrast enhancement (Fig. 1a). Neoplasm was suspected, however, follow-up MRI exams showed partial regression of the lesion, which contested the initial diagnosis and instead, focal cortical dysplasia was suspected. EEG revealed a few focal fronto-central spikes on the right side, but was otherwise normal. Consistently, semiology showed strictly nocturnal focal onset motor seizures with impaired awareness of 15–20 s duration, starting with a panting followed by focal tonic seizure in the left hand, with a subsequent generalization into bilateral tonic–clonic seizures. Some of the seizures were accompanied by an aura of tingling in the left hand. Between the age of 10 and 14 years, the patient was seizure free with antiepileptic drugs. At the age of 14 years seizures relapsed. Despite multiple antiepileptic drugs, the patient developed daily seizures, approximately 20 per week (Table 1). EEG demonstrated interictal spikes and seizure onset zone localized to the right frontal lobe. The patient was evaluated for epilepsy surgery and functional MRI implied motor and sensory activity of the tongue, in direct relation to the lesion. As the lesion was close to eloquent areas, and a focal cortical dysplasia was suspected, the patient underwent an invasive investigation with subdural grids and strips. Unfortunately, the patient suffered from a large postoperative subdural hematoma, which had to be surgically evacuated. Nevertheless, the lesion in the right supramarginal gyrus was found to be the seizure onset zone. Functional stimulation of the subdural electrodes showed sensory symptoms in the left hand and motor symptoms of the tongue near the lesion. The epilepsy surgery team at that time conferred with the family, and surgical treatment was deferred due to the risk of postoperative sequelae. During subsequent years semiology was constant. However, a decade later, at the age of 24 years, seizure frequency increased to more than 20 per week, with seizures occurring also at daytime. The previous aura of tingling in the left hand had disappeared, and instead the patient sometimes experienced a feeling of disappearing or being controlled at onset. Both types of seizures with non-impaired and impaired awareness occurred. The seizures started with a twitching in the left hand, spreading to face and thereafter leg, sometimes with generalization. No postictal paresis occurred. The patient suffered several traumatic injuries, including clavicle fracture and elbow fracture due to seizures. Radiology was unchanged and focal cortical dysplasia was still suspected. A re-evaluation was made by a new epilepsy surgery team, who assessed that the risks caused by a lesionectomy were low and were outweighed by the patient's dreadful seizure situation, and the patient accepted surgery (Table 2).

Table 1 Antiepileptic drug medication

Age	Antiepileptic drug
0–6 years	0
7–13 years	CBZ
14–17 years	CBZ + LTG
	CBZ + VPA
	CBZ + VPA + LTG
	CBZ + LEV
	OXCA + LEV
	OXCA + GBP
	OXCA + VPA
	OXCA + VPA + CLOB
	OXCA + VPA + NIF
	OXCA + VPA + TOP
	OXCA + VPA
	First diagnostic surgery
	OXCA + VPA + CLOB
	OXCA + VPA + LTG
24 years	Surgery with lesionectomy
	OXCA + VPA + LTG
26 years	OXCA + LAC

Abbreviations CBZ Carbamazepine, *LTG* Lamotrigine, *VPA* Valproate, *LEV* Levetiracetam, *OXCA* Oxcarbazepine, *TOP* Topiramate, *NIF* Nifedipine, *GBP* Gabapentin, *CLOB* Clobazam, *LAC* Lacosamide

The surgical strategy was to perform a complete removal of the lesion and removal of adjacent cortex by endopial emptying of the supramarginal gyrus. The surgical procedure was uneventful. However, immediately after the operation, the patient had an increasing number of seizures, with focal left-sided motor and sensory symptoms and initially non-impaired awareness. Postoperative CT was unremarkable, but clinically the patient deteriorated to have focal motor seizures with impaired awareness and progressed into a status epilepticus requiring intubation and sedation. An extra-cranial EEG showed no epileptiform activity; however, it was performed when the patient was under sedation, with no clinical seizures. A postoperative brain MRI on the second postoperative day revealed resection in the area of the angular gyrus and perilesional area of the tumor. Thus, even though neuronavigation had been used during surgery, there was

Table 2 Epilepsy surgery evaluation before lesionectomy

Seizure type	Focal onset left motor seizures to bilateral tonic clonic. Impaired and non- impaired awareness
Seizure frequency	20 seizures per week
Symptomatogenic zone	Right frontal lobe
Radiology	Structural lesion in the right supramarginal gyrus
Irritative zone	Surface EEG: Initially normal. Development of interictal spikes in the right frontocentral lobe, and later bilateral spikes Dipole analysis: Right motor area
Ictal onset zone	Video surface EEG: Right frontal lobe Video EEG with subdural grid: Right supramarginal gyrus with spread to the frontal central areas
Functional deficit zone	Face memory test decrement > 2.5 standard deviations, otherwise normal or supranormal results in neuropsychology evaluation
Functional investigation	Functional MRI: Motor and sensory activity of the tongue, in direct relation to the lesion Functional-stimulation subdural grids: Sensory symptoms in the left hand and motor symptoms of the tongue near the lesion in the right supramarginal gyrus
Epileptogenic zone	Preoperatively presumed to be the lesion and adjacent perilesional area in the right supramarginal gyrus

an intact remaining tumor in the supramarginal gyrus (Fig. 1b). The patient underwent a new attempt of surgical resection of the lesion. He was extubated three hours postoperatively and became awake, with a slight left-sided hemiparesis and left-sided hemisensory symptoms. He presented with a few novel focal onset motor seizures with non-impaired awareness; waving of the right arm followed by laughter. EEG was unremarkable. On the following days, the seizures completely resolved. After a period of neurorehabilitation, the patient improved neurologically. Follow-up brain MRI demonstrated that the lesion had been completely resected (Fig. 1c). At the two-year follow up, the remaining sequelae was a slight sensory deficit, especially for proprioception, in the left leg and foot. Currently, the patient reported nocturnal seizures two to three times a year, which occurred only when inadvertently skipping antiepileptic medication, as compared to two to three seizures a day before surgery. He was still on two antiepileptic drugs. However, the patient was pleased with the outcome. Pathology report from the first attempt of lesionectomy showed normal brain. Pathology report from the reoperation showed a ganglioglioma grade 1 (Fig. 2). The evaluation was made by multiple experienced neuropathologists, including a second opinion from an external epilepsy neuropathologist.

Discussion

Gangliogliomas are more common in children, constituting 10% of primary brain tumors as opposed to 1% in the adult population. The majority of gangliogliomas are considered to be low-grade tumors (WHO grade1). The tumor is composed of a mixture of glial and neuronal elements, including atypical neurons and neoplastic proliferative astrocytes [8, 9]. Low-grade gangliogliomas have dysplastic features, and share similarities with malformations of cortical development [10].

Gangliogliomas are surrounded by cortical disorganization [11]. They are difficult to diagnose, even with immunohistochemistry, as the histopathological variability is significant [9]. The inter-observer concordance for histopathological diagnosis is poor, around 50% [12].

The underlying physiological basis of the epileptogenicity of gangliogliomas is still not elucidated. Increased excitability due to abnormal glutamatergic transmission, as well as alterations in GABA-ergic networks, has been implicated in epileptogenesis [13]. There are reports of overexpression of glutamatergic neurotransmitter receptors in intralesional neurons of gangliogliomas, but also in reactive astrocytes in the perilesional cortex [5]. Further, data support dysfunction of the GABAA-ergic system in perilesional cortex in ganglioglioma [6]. However, there is also reduced GABAA expression in ganglioglioma neurons relative to adjacent cortical neurons [7]. Taken together, studies support roles for both tumor-intrinsic mechanisms in seizure generation as well as cortical perilesional secondary alterations of excitability.

Although the surgical aim is complete removal of ganglioglioma, divergent results on seizure outcome have been published in relation to the extent of resection. Gross total resection (GTR) is reported to be a strong significant predictor of excellent seizure control [14, 15]. However, patients with a partial resection of a ganglioglioma may be seizure free, and, conversely, patients with radiological GTR can continue to have seizures [16].

It seems that in either case, patients with ganglioglioma respond well to surgery in view of seizure outcome. However, in our case the actual lesion was not

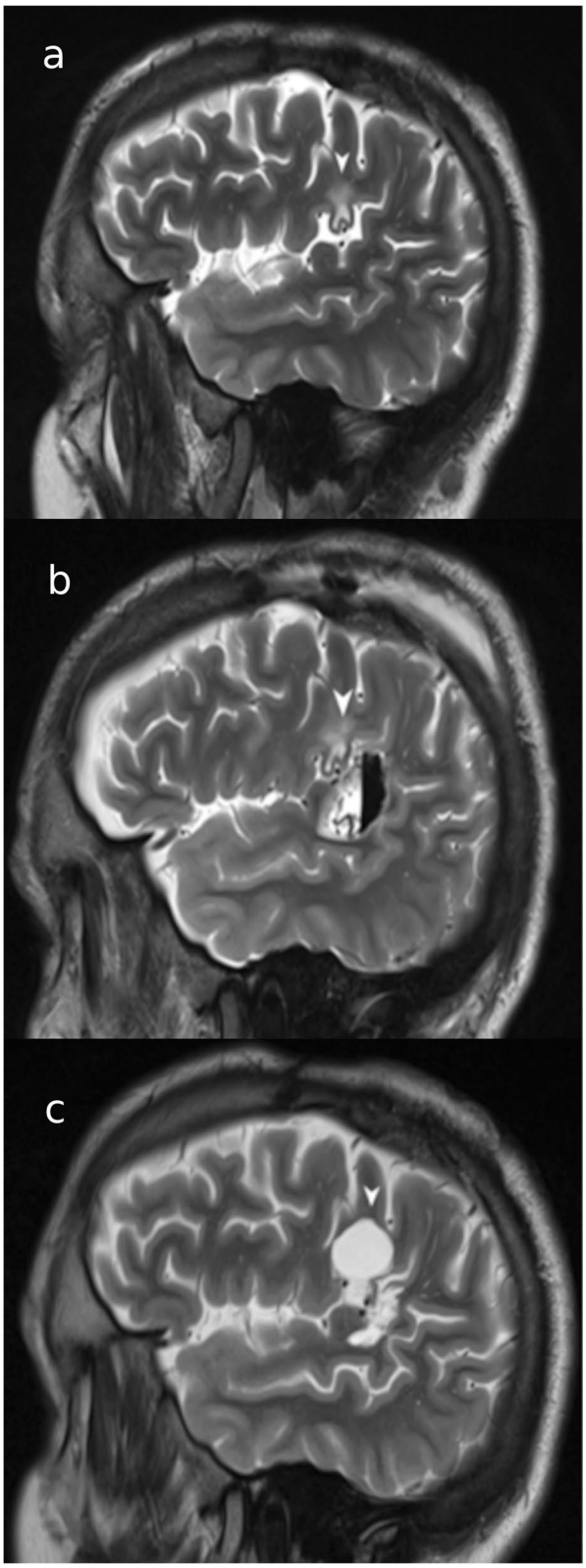

Fig. 1 **a** Brain magnetic resonance imaging (MRI) sagittal sequence T2-weighted images demonstrating the lesion (ganglioglioma) in the supramarginal gyrus (as indicated by the white arrowhead). **b** Demonstration of an intact lesion (ganglioglioma) in the supramarginal gyrus (as indicated by the white arrowhead) after the first surgical resection. **c** Demonstration of complete resection of the ganglioglioma (indicated by the white arrowhead) after the second surgery

resected at all, and only the adjacent gyrus and some perilesional cortex were resected. A possible explanation for the resection of the wrong area could be the inaccuracy of neuronavigation, perhaps due to brain shift. Intraoperative electrocorticography (ECoG) was not used during the surgery. Reports on the usefulness of ECoG in resection of gangliogliomas are divergent. Studies of gangliogliomas are difficult to interpret and compare, as different definitions and terminology were used for the ECoG patterns. In a descriptive study, Ferrier [17] reported that continuous spiking was seen significantly more often during ECoG in focal cortical dysplasia (FCD) versus gangliogliomas, and when present in gangliogliomas, indicated the coexistence of FCD. However, Rosenow [18], who found no correlation between ECoG and seizure outcome, reported that ECoG spiking was more extensive in patients with gangliogliomas as compared to FCD. The same study revealed high-amplitude slow activity within intratumoral cortex of gangliogliomas, whereas the epileptogenic activity was mainly recorded from the surroundings of the tumor or even in remote areas. After the second surgery, complete lesionectomy resulted in seizure outcome ILAE III at the two year follow up. The persistence of seizures at this point indicates that, probably, the epileptogenic zone still extends beyond the tumor area. It is less likely that there are seizure generating areas independent of the lesion. The many years of seizure duration might have established widespread ictogenic networks contributing to the persistence of seizures. About 30% of gangliogliomas are associated with FCD, which are often connected to the tumor or directly adjacent to it [19]. The invasive preoperative investigation, which was limited to the area of the subdural grid and strips, did not indicate other nearby seizure-generating areas, and the pathology report did not indicate other lesions.

Rasmussen [20] reported that 30%–50% of the epilepsy surgery patients with long-term seizure freedom have some attacks in the first postoperative months or years, before eventually becoming seizure free. Wingkun [21] found that recurrent seizures after extratemporal resections were more likely to persist in the subsequent years and more likely to become intractable

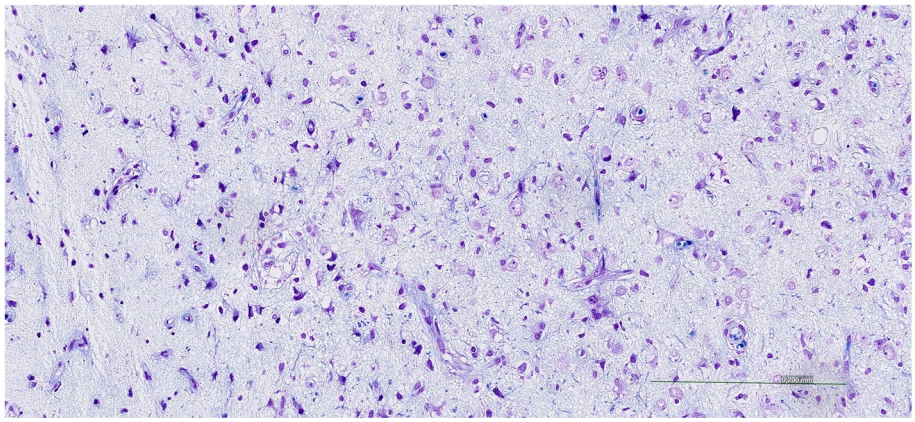

Fig. 2 Histopathology of ganglioglioma. Luxol fast blue and cresyl violet staining

than recurrent seizures after temporal lobe resections. Sarkis [22] reported that after epilepsy surgery (cases predominantly temporal), long-term follow-up indicated new-onset status epilepticus in 2.2%. However, it is difficult to interpret if it was caused by the surgery itself, as it is known that 10%–15% of epilepsy patients develop status epilepticus at some point in their life. Nonetheless, the same author found that of those with new-onset status epilepticus after epilepsy surgery, a third developed the condition within 24 h from surgery. There are reports on seizure worsening and even status epilepticus in the postoperative setting after resection of focal cortical dysplasia. Sarkis found that three out of eight patients developed focal status epilepticus after resection of FCD type IIb in the rolandic area [23]. Seizures were terminated after reoperation with resection of the perilesional area. Interestingly, in those cases they interpreted the epileptogenic drive to emanate from the perilesional cortex. They speculated that perhaps removal of balloon cells that could have an inhibitory role, would lead to a release of excitatory environment in the surrounding cortex.

In our case report, there were no postoperative hemorrhagic, ischemic, infectious, metabolic, or pharmacological explanations to the patient's seizure deterioration after the first surgical attempt to remove the ganglioglioma. Neither the presurgical evaluation nor the postoperative MRI re-evaluation indicated any coexisting dysplasia or epileptogenic scarring from the primary surgery performed years before. The mild and transient acute postoperative seizures after the final surgery might possibly represent a running-down phenomenon.

Seizure generation is a result of imbalance between excitation and inhibition. Trauma *per se* can induce factors that may increase excitability [24]. Experimental models have demonstrated that undercutting the cortex causes an increase in both intrinsic and synaptic excitability of neurons in adjacent intact cortex, sufficient for the generation of electrographic paroxysmal activity [25]. Surgical trauma damages axons and creates a partial deafferentation [26]. Alterations in network activities can change the intrinsic properties of neurons, including the firing pattern [27]. In this case, surgical removal of perilesional cortex and severing of axons could possibly have silenced the short cortico-cortical associative fibers destined for the adjacent gyrus containing the ganglioglioma, and through deafferentation have shifted the balance towards excitation.

Conclusions

Removal of the MRI-negative cortex adjacent to the ganglioglioma might have directly or indirectly eliminated inhibitory signals exerted by this area onto the seizure-prone tumor tissue, releasing the brake which resulted in a refractory status epilepticus. This case might argue in favor of the presence of an inhibitory network in regions immediately adjacent to a ganglioglioma.

Abbreviations

CT: Computed tomography; ECoG: Electrocorticography; EEG: Electroencephalogram; FCD: Focal cortical dysplasia; GTR: Gross total resection; ILAE: International League Against Epilepsy; MRI: Magnetic resonance imaging.

Acknowledgements

Not applicable.

Authors' contribution

This study was conceptualized by JB, as the principal investigator, with contributions from MCS. The data were collected and analyzed by IG, who also drafted the article. Critical revision of the article and final approval was done by all authors.

Funding
This work was supported by grants from Region Skane and from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (PI J Bengzon).

Availability of data and materials
Not applicable.

Declarations

Ethical approval and consent to participate
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study was approved by the Swedish ethical review board (2019–05400). Authors have followed the CARE guidelines (http://www.care-statement.org/resources/checklist). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests
The authors have no conflicts of interest to disclose.

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Received: 16 January 2022 Accepted: 19 April 2022
Published online: 01 October 2022

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