Excessively elevated C-reactive protein after surgery for temporal lobe epilepsy

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Abstract: OBJECTIVE: We present a series of 87 patients who underwent anteromesial temporal lobe resections for therapy refractory temporal lobe epilepsy. In addition to seizure outcome, we observed excessively elevated CRP-levels in this patient population. METHODS: We followed 87 patients (m=39, f=48; mean age 33.73±12.92, range 5-67 years) who underwent surgery between July 2003 and November 2011. Seizure outcome was classified in all patients according to the ILAE-classification by Wieser et al. (mean follow-up: 38.72 months). CRP levels were measured in 59 patients of the epilepsy surgery group and in a control group of 44 consecutive patients with supratentorial tumors (22 glioblastomas, 22 meningiomas). RESULTS: Clinical benefit was seen in 96.6% of the patients (ILAE classes 1-4), 80.5% were completely seizure free (ILAE class 1). Post-OP CRP values were significantly higher in the epilepsy group (n=59; mean CRP peak value: 100.86mg/l, range: 16-258mg/l) compared to the control group (n=44; mean CRP peak value: 36.85mg/l, range: 0.4-233mg/l) ($p<0.001$), but the correlation of mean CRP value and mean temperature peak is weak (r=0.31). CONCLUSIONS: Seizure outcome after surgery for temporal lobe epilepsy was excellent, CRP levels were excessively elevated in these patients in the absence of clinical infection and significantly higher compared to resections of supratentorial lesions.

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Excessively elevated C-reactive protein after surgery for temporal lobe epilepsy

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Abstract

Objective:

We present a series of 87 patients who underwent anteromesial temporal lobe resections for therapy refractory temporal lobe epilepsy. In addition to seizure outcome, we observed excessively elevated CRP-levels in this patient population.

Methods:

We followed 87 patients (m=39, f=48; mean age 33.73 ± 12.92, range 5-67 years) who underwent surgery between July 2003 and November 2011. Seizure outcome was classified in all patients according to the ILAE-classification by Wieser et al. (mean follow-up: 38.72 months). CRP levels were measured in 59 patients of the epilepsy surgery group and in a control group of 44 consecutive patients with supratentorial tumors (22 glioblastomas, 22 meningiomas).

Results:

Clinical benefit was seen in 96.6% of the patients (ILAE classes 1 to 4), 80.5% were completely seizure free (ILAE class 1). Post-OP CRP values were significantly higher in the epilepsy group (n=59; mean CRP peak value: 100.86 mg/l, range: 16 – 258 mg/l) compared to the control group (n=44; mean CRP peak value: 36.85 mg/l, range: 0.4 – 233 mg/l) ($p<0.001$), but the correlation of mean CRP value and mean temperature peak is weak ($r=0.31$).

Conclusions:

Seizure outcome after surgery for temporal lobe epilepsy was excellent, CRP levels were excessively elevated in these patients in the absence of clinical infection and significantly higher compared to resections of supratentorial lesions.

Introduction

The effectiveness of neurosurgical procedures in the treatment of therapy refractory temporal lobe epilepsy (RTLE) is well established [1]. Surgical options include the standard anterior temporal lobe resection (TLR) as well as a more selective resection of the mesial temporal lobe structures, first introduced by Niemeyer in 1958 as selective amygdalohippocampectomy (SAH). After the establishment of microsurgery by Yasargil, multiple microsurgical approaches for SAH have been described with the proximal transsylvian selective transamygdalohippocampectomy [2], the transsylvian-transcisternal mesial en bloc resection [3], the subtemporal approach [4], and the trans-middle temporal gyrus approach [5] being the most frequently used ones.

C-reactive protein (CRP) is an acute-phase protein produced by hepatocytes in response to inflammation [6]. Although mainly used by clinicians to screen for infection, serum CRP physiologically rises following surgical procedures due to the inflammatory cascade triggered by surgical tissue damage, even in the absence of infection [7-9].

This retrospective study was undertaken to study the observed CRP elevation after resection of the mesial temporal lobe structures and describes seizure outcome of 87 patients following SAH for RTLE.

Patients and Methods

Patients

We retrospectively analyzed the medical records of 87 consecutive patients (m=39, f=48; mean age 33.73 ± 12.92, range 5-67 years) who underwent surgery for RTLE between July 2003 and November 2011 at our institution. In 73 cases, SAH was performed, an anterior 2/3 resection of the temporal lobe in 14 cases. Mean follow-up was 38.72 months (SD 26.53 months; range 3 -106 months). Seizure outcome was classified according to the ILAE classification by Wieser et al. [10].

CRP measurement

CRP was measured routinely in the plasma of all patients undergoing surgery pre- and postoperatively. The preoperative blood samples were collected on the morning of surgery at the same time. In the CRP-group, we had to exclude 28 patients due to a lack of a suffient number of postoperative CRP levels (preoperative CRP level, CRP on post-OP day 1 and on 4 additional time points were regarded as suffient). In addition, we collected CRP values of a control group (n=44) consisting of 22 consecutive patients undergoing surgery for glioblastoma (GBM) in 2011 (m=9, f=13; mean age 58.83, range 38-84 years) and 22 consecutive patients undergoing surgery for meningioma in the same year (m=3, f=19; mean age 52.99, range 30-74 years). CRP concentrations (mg/l) were determined by latex-enhanced immunoturbidimetric assays (Roche Diagnostics, Mannheim, Germany on a Roche COBAS INTEGRA analyzer, Rotkreuz, Switzerland) with interassay coefficients of variation below 5%.

Statistical analysis

All statistics were performed using commercially available software SPSS (IBM SPSS Statistics 20). The hypothesis tests performed were two-sided, a p value less than 0.05 was considered statistically significant.

Results

Preoperative data

In the group of 87 consecutive patients undergoing surgery for RTLE (m=39, f=48; mean age 33.73, range 5 - 67 years) - mean age at onset was 9.05 years (0 - 37 years) and mean duration of epilepsy before surgical treatment was 23.83 years (2 - 53 years) – 27 of 87 patients had febrile seizures. Preoperative MRI diagnoses included 70 cases of hippocampal sclerosis, 1 cavernoma, 8 gangliogliomas, 7 cases of focal cortical dysplasia, and one case of a suspected astrocytoma (Table 1) – 42 lesions were located on the right side, 45 on the left. Preoperatively, 37 of 87 patients underwent intracarotid sodium amobarbital injection (Wada test) as presurgical physiological assessment for language and memory. In all cases numerous antiepileptic drugs (AEDs) (at least two) have been tested and failed to provide adequate seizure control. Before surgery, 32 patients were on a single AED, 48 patients were on a dual regimen, and 7 patients received 3 AEDs (Table 2). Mean preoperative CRP values were 4.98 mg/l (range: 0.3 - 53 mg/l) in the epilepsy surgery group as well as 3.63 mg/l (range: 0.3 - 31 mg/l) and 8.21 mg/l (range: 0.3 - 120mg/l) in the GBM and meningioma control group, respectively. Temperature profiles of 51 patients in the CRP group (n=59) and of the control group were available (Figure 4). Mean preoperative temperature was 36.85°C (SD 0.37°C, range: 36.0 – 38.0°C).

Postoperative CRP values

In the epilepsy surgery group (n=59, m=29, f=30; mean age=36.04 years) mean CRP peak value was 100.86 mg/l (range 16 – 258 mg/l). Two patients (3.4%) had a CRP peak above 200 mg/l, 12 patients (20.3%) had a peak higher than 150 mg/l. Median peak days was the 2nd postoperative day in the epilepsy surgery group (Figure 3).

In the control group (n=44, m=12, f=32; mean age=55.91 years, range 38-84 years) consisting of 22 consecutive patients undergoing surgery for meningioma and 22 patients undergoing surgery for glioblastoma, mean CRP

value was 36.85 mg/l (range 0.4 – 233 mg/l. The difference in CRP peak levels between the epilepsy surgery group and the control group is statistically highly significant ($p<0.001$). Mean post-operative peak temperature in the epilepsy surgery group was 37.65°C (SD 0.59°C, range: 36.6°C – 39.3°C). Within the epilepsy surgery group the correlation between post-operative CRP peak value and post-operative peak temperature was weak (pearson's correlation coefficient, $r=0.31$). When looking at post-operative CRP and seizure outcome, ILAE 1 patients in the CRP group (n=51) had a mean CRP peak value of 102.28 mg/l (range: 25 – 258 mg/l) – ILAE 2-5 patients (n=8) had a mean CRP peak value of 91.83 mg/l (range: 16 – 168 mg/l). Differences in mean CRP peak value between the ILAE 1 group and the ILAE 2-5 group were not statistically significant (t-test; $p=0.64$, observed power 0.077). Furthermore, there was no significant difference within the CRP group between the patients undergoing SAH (n=48, mean CRP peak value: 102.15 mg/l, range: 16 – 258 mg/l) and anterior 2/3 resections of the temporal lobe (n=11, mean CRP peak value: 95.27 mg/l, range: 35 – 173 mg/l) (t-test, $p=0.67$).

Postoperative neurological outcome

In 73 cases, SAH was performed, an anterior 2/3 resection of the temporal lobe in 14 cases. Post-operative histological diagnoses included 73 cases with hippocampal sclerosis, 6 gangliogliomas, 2 focal cortical dysplasias, 2 cases of astrocytoma (both WHO grade II), and 4 cases with gliosis (Table 1).
Figure 1 shows seizure outcome according to the ILAE classification by Wieser et al.[10]. In 70 cases (80.5%) patients were postoperatively completely seizure free and no auras were observed (ILAE class 1), 3 patients (3.4%) had only auras, but no seizures (ILAE class 2), in 8 cases (9.2%) one to three seizure days per year were noted (ILAE class 3). Only 3 patients (3.4%) belonged to the ILAE class 4 (four seizures per year to 50% reduction of baseline seizures) and another 3 patients (3.4%) had less than a 50% reduction of baseline seizure days (ILAE class 5). At last follow-up (mean 38.72 months, range 3 - 106 months), 17 patients (19.5%) were completely off antiepileptic medications, in 24 cases (27.6%) the antiepileptic regimen was reduced, 42 (48.3%) patients stayed on the same medications, and 4 patients (4.6%) needed additional

medications (Figure 2) – 48 patients were on AED monotherapy (55.2%) and 22 patients were on a polytherapeutic regimen (25.3%). Perioperative complications included one case (1.1%) of a left-sided hemiparesis, one case (1.1%) of oculomotor nerve palsy, three cases (3.4%) of wound infections and one case (1.1%) of a deep vein thrombosis.

Discussion

Elevation of C-reactive protein levels

Although it is known that CRP rises as a response to surgical tissue damage even in the absence of clinical infection [7-9] our results show that this post-operative CRP-response is significantly stronger in patients undergoing surgery for RTLE compared to other intracranial neurosurgical procedures. Even patients undergoing extended resections and therefore suffering a greater amount of tissue damage, i.e. patients undergoing surgery for glioblastoma, have significantly lower post-operative CRP-levels.

Circumventricular organs

We hypothesize that this observation is due to an inflammatory response triggered by the circumventricular organs (CVOs). CVOs are vascularized structures surrounding the surface of the third and fourth ventricle; they are lacking a blood brain barrier and thereby providing an interface between the blood stream, the CSF, and the brain parenchyma [11]. Functions of the CVOs include participation in the homeostasis of energy metabolism, cardiovascular regulation, sodium and water balance, fever, vomiting, immunomodulation, and regulation of body temperature [11]. Unlike other sites of the CNS blood vessels in the CVO are fenestrated and do not express tight junction proteins such as cadherin-10 [12]. Thus cytokines may reach the circulation not via active transport mechanisms, but rather by movement through the endothelial cell layer. The topographical relation of the resection zone in epilepsy surgery and the location of the circumventricular organs is shown in Figure 5.

Inflammatory response

It was shown that the activation of Toll-like receptors (TLRs) on macrophage-like cells residing in the CVOs lead to the production of pro-inflammatory cytokines [13]. In accordance with the danger model introduced by Matzinger [14], we hypothesize that tissue damage by surgical manipulation of the mesial

temporal lobe structures sets off damage associated molecular pattern molecules (DAMPs) which activate a non-infectious inflammatory response mainly by binding to TLRs of immunocompetent cells in the CVOs. For example TLR9 recognizes self-DNA and TLR3, TLR7 and TLR8 bind dsRNA or ssRNA, which are all released in conditions of tissue damage induced by surgery. As a consequence of TLR binding, cells are activated and produce pro-inflammatory cytokines such as IL-1, IL-6, or TNFα via MyD88 dependent mechansims. Those cytokines are released by the CVOs and trigger the overexpression of so called acute-phase proteins in the liver including an increase in the production of CRP [6]. We suspect that due to the anatomical proximity of the surgical resection side and the location of the circumventricular organs (Figure 5), the inflammatory response and the subsequent CRP production is more pronounced than in neurosurgical procedures. Another key factor leading to the observed inflammatory response in patients undergoing epilepsy surgery might be ventricular opening, which is part of the surgical strategy in epilepsy surgery (both TLR and SAH), but it rarely happens during tumor surgery. Opening the ventricles should lead to a direct release of DAMPs into the CSF and thereby increased concentrations of DAMPs reaching the CVOs. Binding of DAMPs to TLRs triggers an inflammatory response as described above, ultimately also leading to CRP production in the liver. In future studies it would be worthwhile to monitor the inflammatory response in other neurosurgical procedures with ventricular opening in a prospective fashion.

Seizure Outcome

Seizure outcome was excellent with 80.5% of the patients being completely seizure free with no auras (ILAE class 1) and clinical benefit was seen in 96.6% of the patients (ILAE classes 1 to 4) – mean follow-up was 38.72 months (SD 26.53 months; range 3 -106 months). Different classification systems are used in the medical literature, but just by looking at the seizure-free patient group, which is for multiple reasons the most important group, our results compare well to the literature. There is one randomized controlled trial that compared seizure outcome after surgery to outcome after medical treatment [1]. In the surgery group of this trial, 58% of the patients were free of disabling seizures at

the end of 1 year, 38% were free of all seizures including auras, 10%-15% had little or no improvement compared to 8% being free of disabling seizures in the medical group [1]. Clinical outcome after surgery for temporal lobe epilepsy has also been extensively reviewed by Engel et al. [15]. Seizure outcome after anteromesial temporal lobe resections (not differentiating between SAH and tailored anterior temporal lobe resections) of 21 retrospective analyses yielded 1769 patients of whom 1150 (65%) were free of disabling seizures, 372 (21%) were improved, and 347 (14%) were not improved. Only one of these centers reported on auras as well and consequently found 45.9% of the patients to be completely seizure free. In another meta-analysis by Téllez-Zenteno et al. the proportion of long-term seizure-free patients in 40 studies (n=3895) after temporal lobe surgery was 66% [16].

Our favorable outcome is not only due to some special surgical approach, but to a rather restrictive patient selection. The group of patients reported on in this study was evaluated in a center that initiated its presurgical epilepsy program with these patients starting in 2003. Therefore, only patients with concordant findings from neurophysiological, neuropsychological, imaging studies and invasive studies predicting post-surgical seizure control were admitted to epilepsy surgery.

Surgical complications in our series including neurological morbidity and perioperative surgical complications were comparable to the literature review by Engel et al. [15].

Postoperative pharmacotherapy after surgery for temporal lobe epilepsy in our group is similar to a report by Bien et al. were in a group of 148 patients with a mean follow-up of 4.8 years, 44.6% of the patientes were seizure-free and 8.8% were free of AEDs, 55.4% received monotherapy, and 35.8% were on more than one AED [17].

The mean duration of epilepsy before surgery of 23.83 years (2-53 years) in our series is well comparable to the medical literature. Lowe et al. showed that in a series of 76 patients the mean duration of epilepsy before surgery was 23.0 years (range 2.9 - 46.9 years) and that there was no difference in the mean duration of epilepsy between patients with good seizure outcome (mean duration 22.4 years) and patients with poor seizure outcome (mean duration 24.3 years) (p=0.49)[18]. Since there is increasing evidence in the medical

literature in the recent years suggesting that surgery for RTLE is not only effective, but also superior to medical treatment, Choi et al. investigated whether the mean duration of epilepsy before surgery is decreasing due to faster referral and earlier decisions to perform surgery. In a retrospective analysis 213 of a single institution, no difference in the mean duration of epilepsy in a group of 83 patients treated between 1996 and 1999 (mean duration: 22.6 years), a group of 65 patients operated between 2000 and 2003 (mean duration: 22.4 years), and a group of 65 patients between 2004 and 2007 (mean duration: 21.1 years)[19].

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Limitations

We are aware of some notable limitations of our study. For one, this is a single-center analysis in a retrospective fashion. Also, the levels of pro-inflammatory cytokines such as IL-1, IL-6, or TNFα were not measured in our patient population. Further studies should not only measure the levels of pro-inflammatory cytokines but also compare the inflammatory response after epilepsy surgery to other neurosurgical procedures in a prospective fashion.

Conclusions

Besides excellent seizure outcome our study shows that postoperative CRP levels in patients undergoing surgery for RTLE were significantly higher compared to the CRP levels following neurosurgical resections of supratentorial mass lesions. This observation may be related to the close anatomical proximity of the resection site to the circumventricular organs and the subsequent inflammatory response triggered by this tissue damage. Further studies should not only measure the levels of pro-inflammatory cytokines but also compare the inflammatory response after epilepsy surgery to other neurosurgical procedures in a prospective fashion.

Disclaimer

All authors report no conflicts of interest.

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Figures

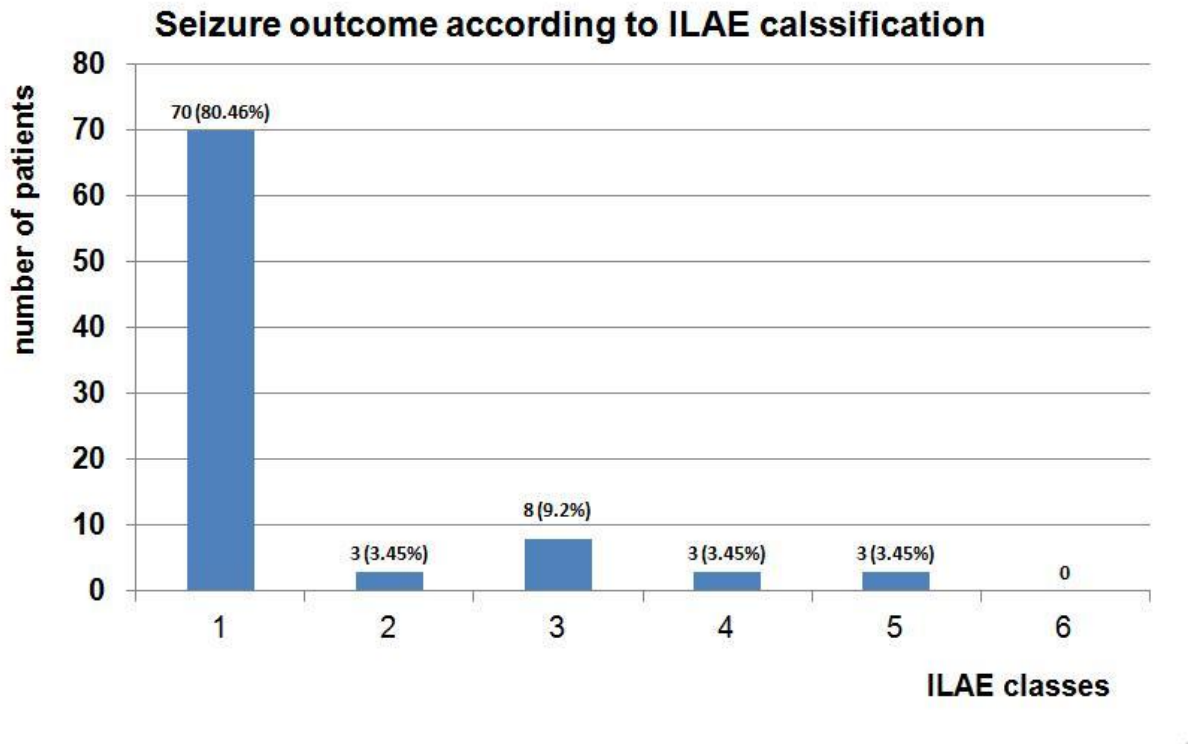

Figure 1: Seizure outcome according to the ILAE classification by Wieser et al. [10]

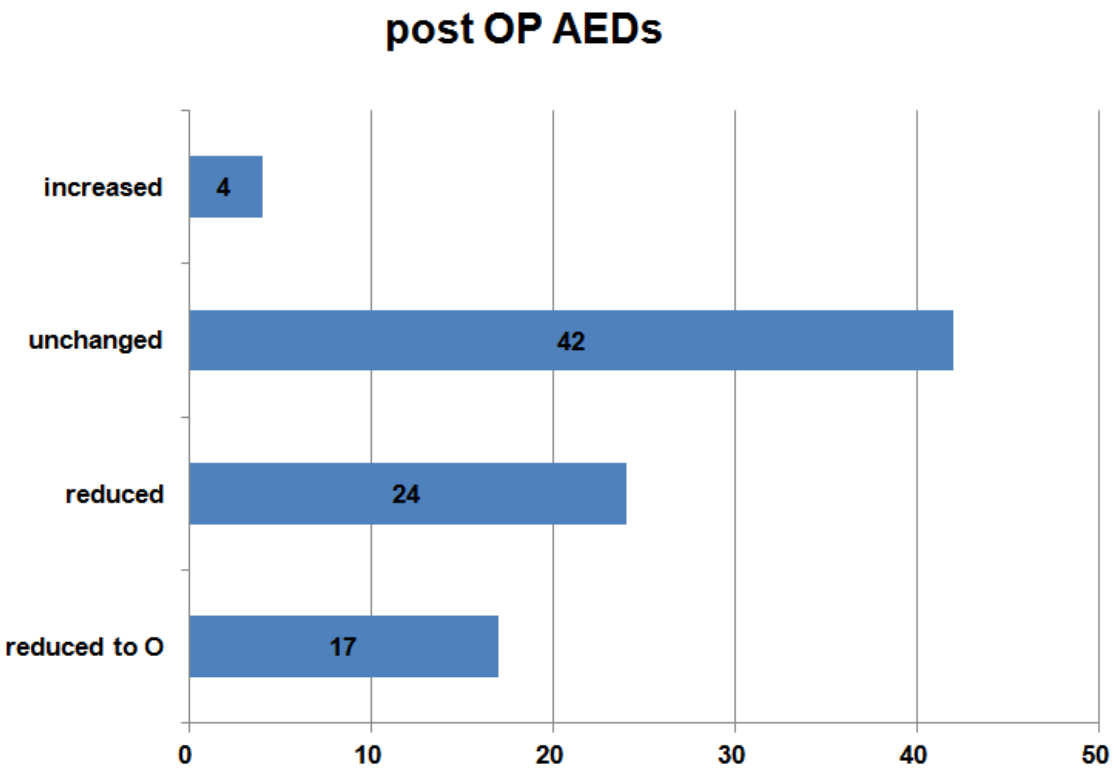

Figure 2: Postoperative changes in antiepileptic medications at last clinical follow-up

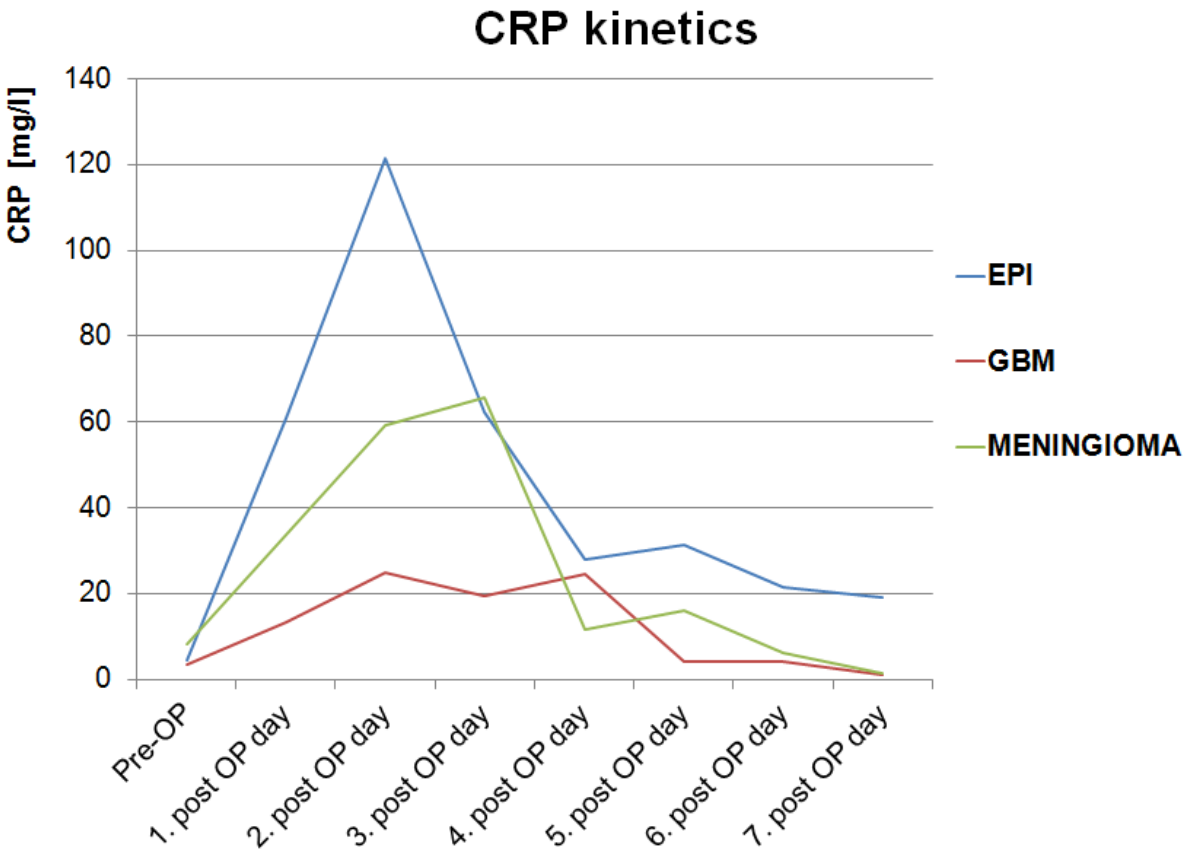

Figure 3: Kinetics of C-reactive protein (CRP) [mg/l]

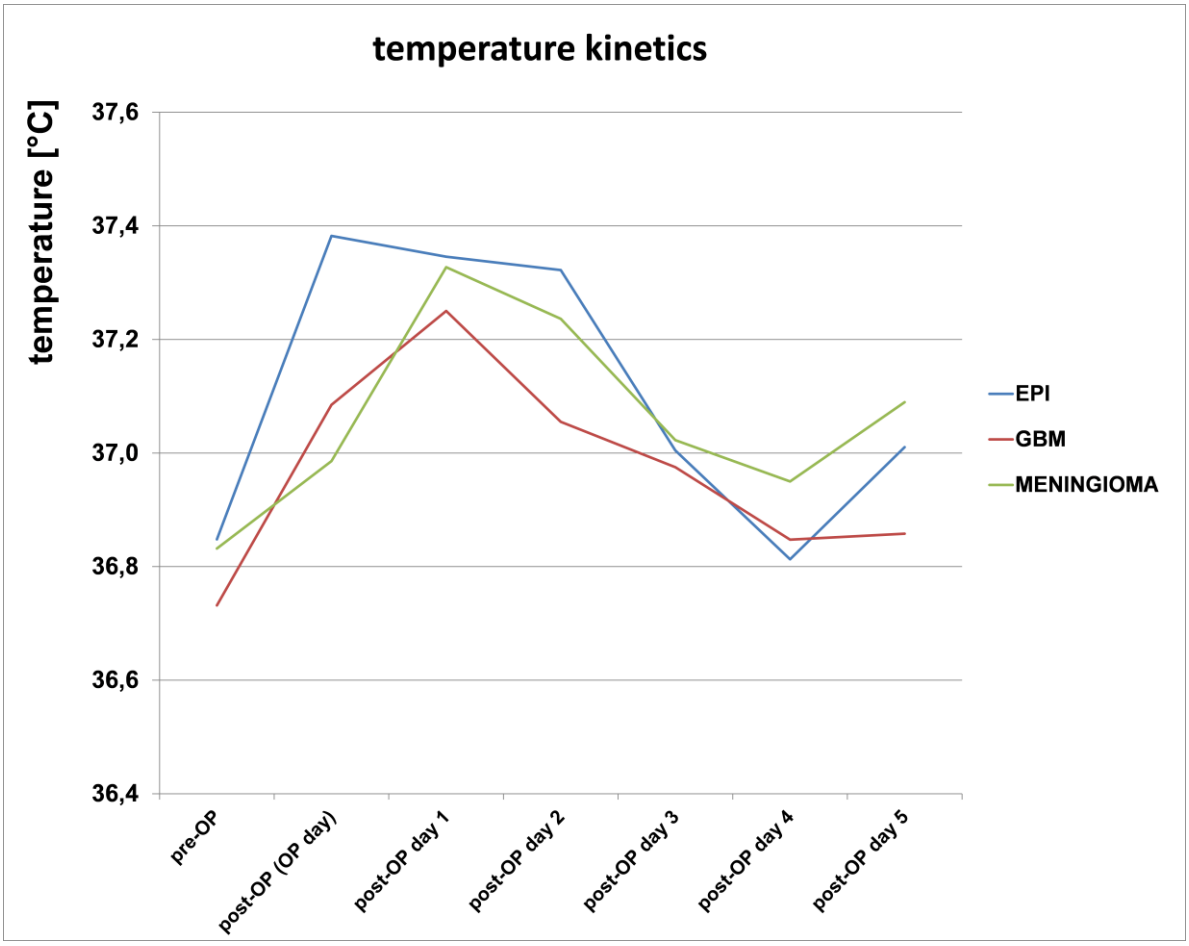

Figure 4: Temperature [°C] profile of 51 patients undergoing surgery for temporal lobe epilepsy compared to the two control groups. EPI = epilepsy surgery group; GBM = glioblastoma

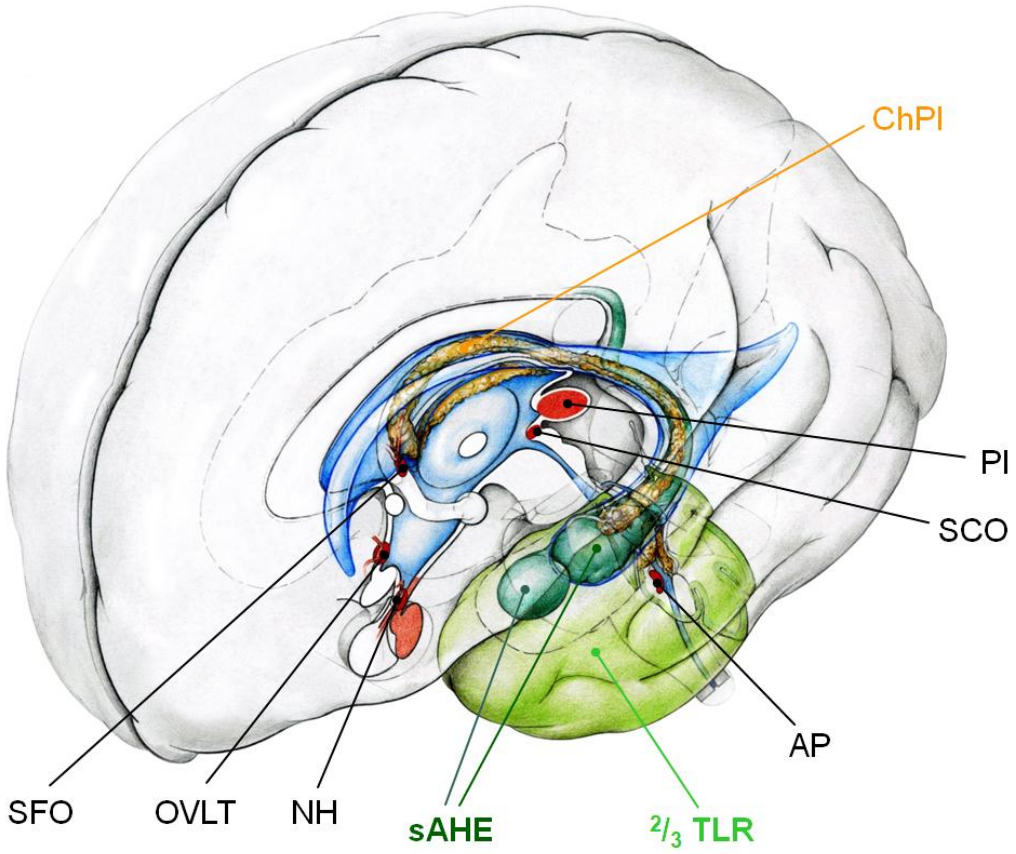

Figure 5: Illustration of the topographical relation of the resection zone to the circumventricular organs. SFO = subfornical organ; OVLT = organum vasculosum laminae terminalis; NH = neurohypophysis; AP = area postrema; SCO = subcommissural organ; Pl = pineal gland; sAHE = selective amygdalohippocampectomy; 2/3 TLR = anterior 2/3-resection of the temporal lobe; ChPl= choroid plexus