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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 1–4), 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.

1. 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.

2. Patients and methods

2.1. 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].

2.2. CRP measurement

CRP was measured routinely in the plasma of all patients undergoing surgery pre- and postoperatively. The preoperative blood

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Table 1
Pre-operative MRI diagnosis compared with the post-operative histological results.

	MRI diagnosis	Histological diagnosis
Hippocampal sclerosis	70	73
Cavernoma	1	0
Ganglioglioma	8	6
Focal cortical dysplasia	7	2
Astrocytoma	1	2
Gliosis	0	4

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 sufficient number of postoperative CRP levels (preoperative CRP level, CRP on post-OP day 1 and on 4 additional time points were regarded as sufficient). 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%.

2.3. 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.

3. Results

3.1. 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: 0.3–120 mg/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 (Fig. 4). Mean preoperative temperature was 36.85 °C (SD 0.37 °C, range: 36.0–38.0 °C).

3.2. 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 (Fig. 3).

Table 2
Pre- and postoperative antiepileptic drugs at last clinical follow-up.

AED	Pre-OP	Post-OP
0 AED	0	17 (19.5%)
1 AED	32 (36.8%)	48 (55.2%)
2 AEDs	48 (55.2%)	18 (20.7%)
3 AEDs	7 (8.0%)	2 (2.3%)
4 AEDs	0	2 (2.3%)
Lamotrigine	45	37
Valproic acid	6	1
Oxcarbamazepine	15	7
Levetiracetam	42	29
Topiramate	7	1
Carbamazepine	14	7
Phenytoin	5	5
Mephenytoin	1	0
Clobazam	8	5
Pregabalin	1	0
Sulthiame	1	0
Primidone	2	0
Zonisamide	1	2
Clonazepam	1	1
Lacosamide	0	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, $p = 0.67$).

3.3. 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).

Fig. 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