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Fevers and abnormal blood and cerebrospinal fluid studies after pediatric cerebral hemispherectomy: impact of etiology and age at surgery

Clinical article

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Object. The object of this study was to determine if etiology and age at surgery were linked with fevers and altered white blood cell and CSF laboratory values after cerebral hemispherectomy.

Methods. Seizure etiologies (n = 76) were classified into hemimegalencephaly (HME), cortical dysplasia (CD), infarcts (stroke), Rasmussen encephalitis (RE), history of infections, and Sturge-Weber syndrome (SWS) and were compared with clinical variables, maximum daily temperature (Tmax), and blood and CSF studies through Day 12 posthemispherectomy.

Results. The Tmax on Days 2–4 and 9–12 postsurgery were higher for HME and RE cases than for stroke cases. Patients with RE showed positive correlations, whereas those with SWS had negative correlations between Tmax and age at surgery. Blood WBC counts on postsurgery Days 3, 6, and 9–12 were higher in the HME and CD cases than in the stroke and RE cases. The percentage of blood polymorphonuclear cells (%bloodPMNs) was higher in the RE cases than in the HME, CD, and SWS cases. The RE, HME, and CD cases showed positive correlations between %bloodPMNs and age at surgery. The percentage of blood monocytes (%bloodMono) was higher in the patients with HME than in those with stroke or RE. The HME and CD cases showed negative correlations between %bloodMono and age at surgery. The CSF red blood cell counts were higher in the RE than in the CD and stroke cases. The percentage of CSF monocytes was higher in patients with CD than in those with stroke and RE. The percentage of CSF lymphocytes positively correlated with age at surgery.

Conclusions. Seizure etiology and age at surgery were associated with developing fevers and altered blood and CSF values after pediatric cerebral hemispherectomy. These findings indicate that besides infections, other clinical variables have an impact on developing fevers and abnormal laboratory values posthemispherectomy. Cultures appear to be the most reliable predictor of infections.

(<http://thejns.org/doi/abs/10.3171/2013.9.PEDS13264>)

KEY WORDS • seizure • epilepsy • hemimegalencephaly • cortical dysplasia • Rasmussen encephalitis • maximum daily temperature • craniotomy • infection

FEVERS and abnormal blood and CSF values after neurosurgical procedures raise concerns about possible infections and other intracranial problems. Beyond meningitis and encephalitis it is unclear what other

Abbreviations used in this paper: CD = cortical dysplasia; HME = hemimegalencephaly; PMN = polymorphonuclear cell; RBC = red blood cell; RE = Rasmussen encephalitis; SWS = Sturge-Weber syndrome; Tmax = maximum daily temperature; UCLA = University of California, Los Angeles; WBC = white blood cell; %bloodMonos = percentage of blood monocytes; %bloodPMNs = percentage of blood PMNs; %CSFLymphs = percentage of CSF lymphocytes; %CSFMonos = percentage of CSF monocytes.

clinical factors are associated with fevers and abnormal laboratory studies after craniotomy, especially after cerebral hemispherectomy, in which fevers are commonly observed postsurgery.^{9,17} Previous studies have shown an association between anatomical resections and Rasmussen encephalitis (RE), and posthemispherectomy fevers.^{3,4} However, other clinical epilepsy and laboratory variables have not been fully explored, especially in modern resection-disconnection procedures and in the era of antibiotic prophylaxis and perioperative clinical protocols designed to reduce the risk of infection.⁵

In a recent study, we found that the risk of CNS in-

fection was 4% in 100 consecutive pediatric epilepsy surgeries ranging from focal to cerebral hemispherectomy procedures. Furthermore, CNS infections were poorly predicted by postsurgery fevers and abnormal blood and CSF studies.¹² Given these findings, we designed our study to explore whether other clinical variables were associated with posthemispherectomy fevers and altered laboratory studies. To accomplish our goal, we focused on a resection-disconnection procedure performed via a standardized perioperative clinical protocol at a single referral center to minimize any variability that may have confounded data interpretation. We hypothesized that etiology and age at surgery would be associated with developing fevers and abnormal laboratory studies posthemispherectomy via our resection-disconnection procedure.

Methods

Standard Protocol Approval, Registration, and Patient Consent

This study was approved by the University of California, Los Angeles (UCLA) institutional review board, and since the enactment of the Health Insurance Portability and Accountability Act (HIPAA), patients and their families have signed the proper informed consents and authorizations. This study was not a clinical trial, and it is not registered in any public registry.

Study Population

This was a retrospective review of consecutive cerebral hemispherectomy cases at UCLA's Pediatric Epilepsy Program from 2004 to 2012 where clinical information including pediatric intensive care unit, nursing notes, and blood and CSF laboratory data were available through electronic medical records (n = 95 cases). Excluded from analysis were patients who had a prior hemispherectomy and were undergoing repeat procedures (n = 8 cases) as well as those whose first operations were lobar or multilobar resections and were converting to cerebral hemispherectomy (n = 6 cases), thus making a cohort of 81 patients having first-time operations.

All operations were performed by a single surgeon (G.W.M.) using a standardized cerebral hemispherectomy technique and perioperative protocol.^{3,8} Antibiotics (cefazolin or, for patients who were allergic to cefazolin, clindamycin or vancomycin) were administered intravenously prior to skin incision and continued postoperatively as long as the ventriculostomy catheter remained. Foley catheters and arterial and central lines (triple-lumen subclavian, jugular, or groin) were placed using a sterile technique in the operating room after inducing anesthesia. Postprocedure, blood samples were generally drawn from the central line daily and as necessary and sent for culture, routine counts, and chemistry studies. Ventriculostomy catheters were placed in the operating room before closure of the dura mater and were not changed postsurgery. Beginning on the 2nd postoperative day, CSF was sampled daily from the closed loop ventriculostomy system and sent for cell analysis, culture, and chemistry studies. Ventriculostomy catheters were removed if an overnight test clamp did not result in intracranial pressures greater

than 18 cm H₂O. If this test failed in a patient, a ventriculoperitoneal shunt was placed. Antibiotics were continued until 24 hours after external ventriculostomy drains were removed or a ventriculoperitoneal shunt was inserted. Foley catheters and most peripheral venous and arterial lines were discontinued within 48 hours of surgery. Central venous lines were removed at hospital discharge or changed to peripheral venous lines after 2 weeks. Blood, urine, and pulmonary samples were sent for bacterial culture if a patient had a fever of 38.5°C or higher. The day of surgery was defined as Day 0.

Clinical Data Collected

The presurgical clinical protocols and evaluation process along with methods describing the collection of clinical epilepsy variables, seizure outcome, and complications have been described in detail elsewhere.^{6,7} Additional information gathered for this study included maximum daily temperature (Tmax), blood white blood cell (WBC) count and differential, CSF laboratory studies, and incidence and location of positive bacterial cultures for the first 12 days postsurgery, as previously described.¹² Fever was defined as a temperature of 38.5°C or higher at least once on a given day. An elevated blood WBC count was defined as > 15,000 cells/μl.

Study Design

Patients were cataloged into groups based on etiology, that is, groups with at least 3 patients, as previously described.⁸ Etiology was based on MRI results and histopathology of the brain specimen and cataloged, as follows:

- 1) Hemimegalencephaly (HME; n = 15 cases; Fig. 1A) in which 3 of 4 lobes were larger than expected;¹³
- 2) Hemispheric or multilobar cortical dysplasia (CD; n = 24 cases; Fig. 1B);
- 3) Perinatal cerebral ischemia/infarction (stroke; n = 18 cases; Fig. 1C);
- 4) Rasmussen encephalitis (RE; n = 12 cases; Fig. 1D);
- 5) History of (mostly unilateral) CNS infection (infection; n = 4 cases [3 cases of herpes simplex virus and 1 case of bacterial encephalitis]; Fig. 1E);
- 6) Sturge-Weber syndrome (SWS; n = 3 cases; Fig. 1F).

Excluded from the etiology classification because of the small sample size were 2 cases of extensive tumors (1 dysembryoplastic neuroepithelial tumor and 1 ganglioglioma), 2 cases of cerebral trauma history, and 1 case of deep thalamic damage and seizures after a prior ventricular endoscopic procedure.

Statistical Analysis

Etiology groups were compared for differences in clinical epilepsy variables, Tmax, blood and CSF counts, and chemistry values by using a statistical program (StatView 5, SAS Institute Inc.).¹ Statistical tests included ANOVA, repeated measures ANCOVA, Student t-test, and chi-square test, as appropriate. All tests were 2-tailed, and because of the multiple comparisons and large cohort size, the threshold for significance was set a priori at p < 0.01.

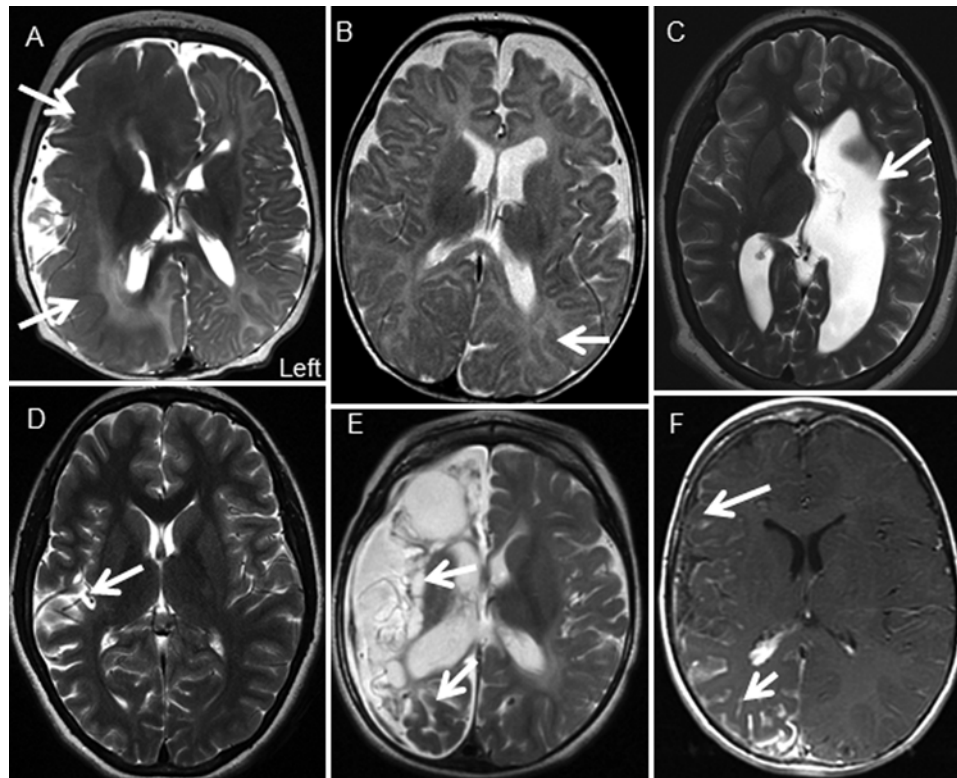


Fig. 1. Axial T2-weighted MR images (A–E) and T1-weighted MR image with contrast (F) representative of the major seizure etiology groups in a cohort who underwent cerebral hemispherectomy. Etiologies included HME (A), CD (B), stroke (C), RE (D), history of CNS infection (E; herpes simplex virus), and SWS (F). Areas of affected cortex are indicated by arrows.

Results

Cohort Description and Clinical Comparisons

Patients who underwent cerebral hemispherectomy (n = 76) were classified into 1 of 6 seizure etiology groups (Table 1). Clinical epilepsy characteristics were similar to those in previous reports from our center.^{3,6,7} The mean (± standard deviation) age at seizure onset was 1.9 ± 3.1 years (range birth–17 years); mean age at surgery, 4.9 ± 4.5 years (range 1 month–18 years); mean epilepsy duration, 3.0 ± 3.0 years (range 1 month–11.9 years); postsurgery ventriculostomy duration, 7.3 ± 3.2 days (range 4–21 days); mean hospital stay, 14.2 ± 6.2 days (range 7–38 days); and mean follow-up duration, 2.5 ± 1.6 years (range 1–5 years). Females were 46% of the cohort (n = 35), 50% of patients had left-sided operations (n = 38), and 83% of patients were seizure free at the last follow-up (n = 63). There was no operative mortality in this cohort. Nonlethal complications were identified in 22% of cases (n = 17), consisting of non-CNS infections (n = 11), CNS infections (n = 4), and transient third nerve palsy (n = 2). The types of complications, infections, and treatment have been described in detail elsewhere.¹²

As might be expected from previous reports,^{3,8} etiology groups in this cerebral hemispherectomy cohort showed differences in age variables but not in other epilepsy surgery characteristics (Table 1). Post hoc ANOVA revealed that for age at seizure onset and age at surgery, patients with HME and CD were younger than those with

stroke and RE (p < 0.01) and that for epilepsy duration, patients with stroke had longer intervals from seizure onset to surgery than patients with HME, CD, and SWS (p < 0.01). Other clinical variables, including percentage of complications, number of CNS and non-CNS infections, and percentage of seizure-free patients after surgery, were not different by etiology classification.

Maximum Daily Temperature and Blood and CSF Values According to Etiology

To determine if there were differences in Tmax and blood and CSF values, we performed an ANCOVA with etiology and age at surgery as the independent variables (Table 2). This analysis included repeated measures for the first 12 days posthemispherectomy for temperature, blood, and CSF data. The results revealed differences by etiology for Tmax, blood WBC count, percentage of blood polymorphonuclear cells (%bloodPMNs) and monocyte counts (%bloodMonos), CSF red blood cell (RBC) count, and percentage of CSF monocytes (%CSFMonos); correlations with age at surgery for Tmax and percentage of CSF lymphocytes (%CSFLymphs); and interactions between etiology and age at surgery for Tmax, %bloodPMNs, and %bloodMonos.

These differences according to etiology, age at surgery, and interactions between etiology and age at surgery are illustrated in Figs. 2–4. The Tmax was higher for HME and RE cases than for stroke cases (Fig. 2A), and this was most pronounced on postsurgery Days 2–4

TABLE 1: Clinical variables by hemispherectomy etiologies*

Clinical Variable	HME	CD	Stroke	RE	Infection	SWS	p Value
no. of cases	15	24	18	12	4	3	
mean age at seizure onset (yrs)	0.2 ± 0.7	0.3 ± 0.33	3.0 ± 2.9	6.2 ± 4.3	0.1 ± 0.1	0.5 ± 0.2	<0.0001
mean age at surgery (yrs)	1.7 ± 2.5	2.4 ± 2.1	8.8 ± 4.1	8.9 ± 4.2	4.0 ± 4.2	2.4 ± 0.3	<0.0001
mean epilepsy duration (yrs)	1.5 ± 2.4	2.1 ± 2.0	5.8 ± 3.4	2.7 ± 2.2	3.9 ± 4.3	1.9 ± 0.5	0.0001
sex (% female)	33%	37%	50%	58%	75%	67%	0.495
side of op (% lt)	60%	42%	78%	17%	75%	0%	0.051
% repeat surgeries	13%	8%	0%	0%	0%	0%	0.039
total % complications	20%	33%	17%	25%	0%	0%	0.484
% w/ any infection	20%	25%	17%	17%	25%	0%	0.533
% CNS infections	7%	8%	6%	0%	0%	0%	0.924
mean duration of ventriculostomy (days)	7.3 ± 2.6	7.4 ± 3.4	7.3 ± 4.0	7.7 ± 2.7	5.2 ± 1.0	7.3 ± 2.3	0.910
mean hospital stay (days)	14 ± 7.8	15 ± 6.3	13 ± 6.3	14 ± 3.8	15 ± 6.2	14 ± 6.5	0.873
% seizure-free patients at last FU	80%	79%	89%	92%	50%	100%	0.987
mean FU duration (yrs)	3.1 ± 1.8	2.6 ± 1.6	1.7 ± 1.0	2.2 ± 1.4	4.0 ± 1.2	3.5 ± 2.1	0.435

* Tests were ANOVA and chi-square; mean values are expressed with SD. Significant differences (p < 0.01) are indicated in bold type. FU = follow-up.

and 9–12 (Fig. 3 upper). Furthermore, RE cases showed a positive correlation while SWS cases showed a negative correlation between Tmax and age at surgery (Fig. 4A). Blood WBC counts were higher in HME and CD cases than in stroke and RE cases (Fig. 2B), and this was most pronounced on postsurgery Days 3, 6, and 9–12 (Fig. 3 lower). The %bloodPMNs was higher in RE cases than in HME, CD, and SWS cases (Fig. 2C). Furthermore, RE, HME, and CD cases showed positive correlations between %bloodPMNs and age at surgery (Fig. 4B). The %bloodMonos was higher in HME cases than in stroke and RE cases (Fig. 2D). Moreover, HME and CD cases showed negative correlations between %bloodMonos and age at surgery (Fig. 4C). Cerebrospinal fluid RBC count

was higher in RE cases than in CD and stroke cases (Fig. 2E). The %CSFMonos was higher in CD cases than in stroke and RE cases (Fig. 2F). Initial analysis for all etiology groups indicated a positive correlation between %CSFLymphs and age at surgery (Table 2 and Fig. 4D), but more detailed assessments showed no significant correlations by individual etiology category.

Repeating the analysis as a univariate study without considering age at surgery (ANOVA) showed the same results by seizure etiology with three added findings (data not shown). The %bloodLymphs was higher in cases of HME and CD than in cases of stroke and RE (p < 0.0001). Cerebrospinal fluid protein levels were higher in CD and RE cases than in stroke cases (p = 0.0075), and the %CSF-

TABLE 2: Results of repeated measures ANCOVA comparing blood and CSF studies according to etiology and age at surgery*

Variable	Etiology		Age at Surgery		Interaction	
	F	p Value	F	p Value	F	p Value
Tmax	8.21	<0.0001	32.7	<0.0001	9.44	<0.0001
blood WBC count	6.44	<0.0001	0.01	0.977	2.60	0.025
%bloodPMNs	3.49	0.0046	1.64	0.202	5.24	0.0001
%bloodLymphs	1.57	0.170	0.04	0.836	1.80	0.114
%bloodMonos	3.25	0.0074	0.88	0.349	4.47	0.0007
%blood eosinophils	2.13	0.062	0.60	0.439	1.96	0.085
%blood basophils	0.17	0.972	0.20	0.657	1.04	0.392
CSF protein	0.58	0.715	0.14	0.704	0.86	0.511
CSF WBC count	1.42	0.216	0.03	0.866	0.576	0.718
CSF RBC count	5.00	0.0002	0.59	0.444	1.69	0.135
CSF RBC/WBC ratio	0.25	0.938	0.04	0.890	1.39	0.229
%CSF PMNs	2.17	0.057	0.50	0.481	1.96	0.083
%CSFLymphs	2.22	0.051	9.83	0.002	2.81	0.017
%CSFMonos	4.28	0.0009	1.00	0.317	2.96	0.012

* Significant values (p < 0.01) are indicated in bold type.

Fevers posthemispherectomy

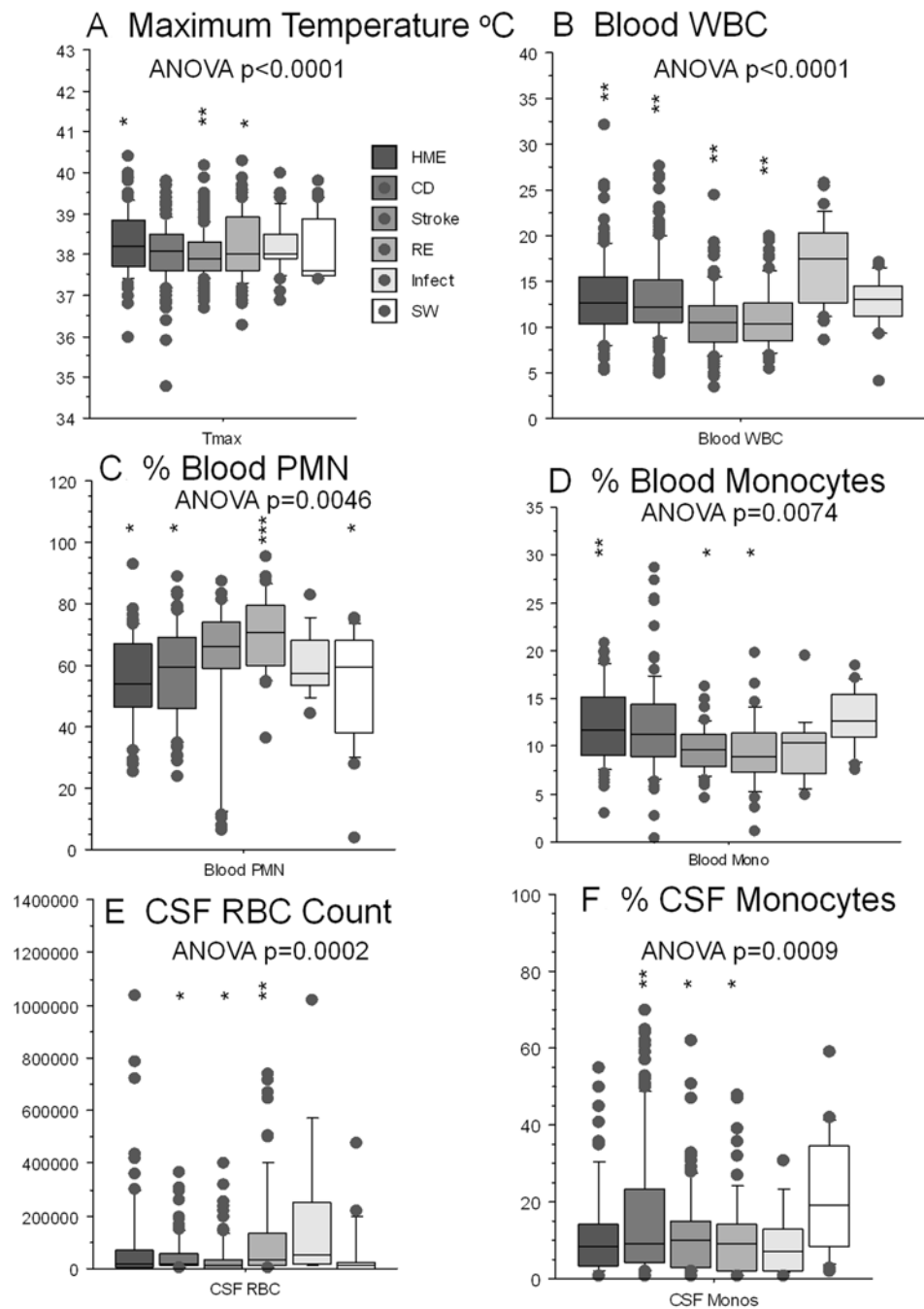


Fig. 2. Box plots for repeated measures ANOVA of data from the first 12 days post-cerebral hemispherectomy, showing by etiology category the Tmax (**A**), blood WBC count (**B**), %bloodPMNs (**C**), %bloodMonos (**D**), CSF RBC count/ μ l (**E**), and %CSF-Monos (**F**). The p values are shown above each graph, and significant post hoc differences ($p < 0.01$) are indicated by asterisks. For Tmax (**A**), post hoc analysis revealed that stroke cases had lower temperatures than HME ($p = 0.0025$) and RE ($p = 0.0005$) cases. For blood WBC counts (**B**), stroke and RE cases had lower counts than HME ($p < 0.0001$) and CD ($p = 0.0003$) cases. For %bloodPMNs (**C**), RE cases had higher levels than HME ($p < 0.0001$), CD ($p = 0.002$), and SWS ($p = 0.0005$) cases. For %bloodMonos (**D**), HME cases had higher levels than stroke ($p = 0.0078$) and RE ($p = 0.0020$) cases. For CSF RBC count (**E**), RE cases had higher levels than CD ($p = 0.0009$) and stroke ($p = 0.0004$) cases. For %CSFMonos (**F**), CD cases had higher levels than stroke ($p = 0.033$) and RE cases ($p = 0.013$).

Lymphs was higher in cases of stroke than in those of HME and RE ($p = 0.0001$). These differences were not statistically different when age at surgery was incorporated into the statistical analysis (ANCOVA; Table 2).

Discussion

In patients who underwent cerebral hemispherectomy at one institution using a standardized resection-discon-

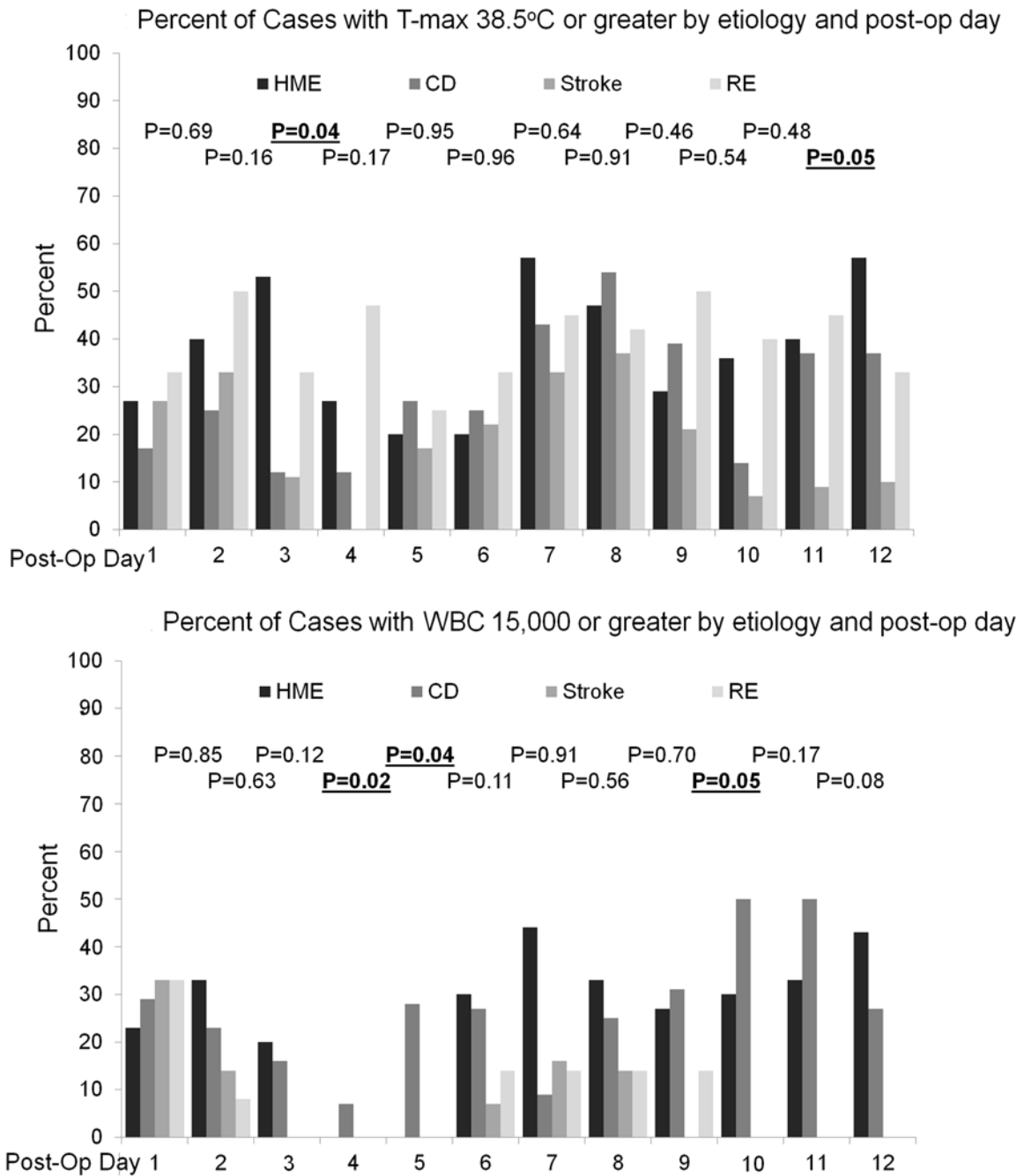


FIG. 3. For the four etiology groups with a sufficient sample size (HME, CD, stroke, and RE), bar graphs show the percentage of patients with a T_{max} ≥ 38.5°C (upper) and blood WBC counts ≥ 15,000 (lower) for the first 12 days posthemispherectomy. Consistent with the repeated measures ANOVA, for T_{max}, stroke cases had lower temperatures than HME cases on posthemispherectomy Days 3, 4, and 10–12 and RE cases on Days 2–4 and 9–12. For blood WBC counts, a higher percentage of HME and CD cases had counts ≥ 15,000 compared with stroke and RE cases on posthemispherectomy Days 3 and 9–12.

nection procedure and perioperative protocol, we identified differences in postsurgery T_{max} and blood and CSF laboratory studies that were associated with seizure etiology and age at surgery (Table 2 and Figs. 2–4). These findings complement those of prior studies by our group showing a limited association of CNS and non-CNS infections with fevers and altered blood and CSF values in all types of pediatric epilepsy surgery cases, as well as an

association between etiology and posthemispherectomy hydrocephalus requiring CSF shunts.^{11,12} Taken together, these findings indicate that multiple clinical variables are associated with the development of fever and altered blood and CSF laboratory studies after cerebral hemispherectomy involving resection-disconnection procedures, including the underlying seizure etiology and age at surgery. For the practicing neurosurgeon, the best predictor of CNS

Fevers posthemispherectomy

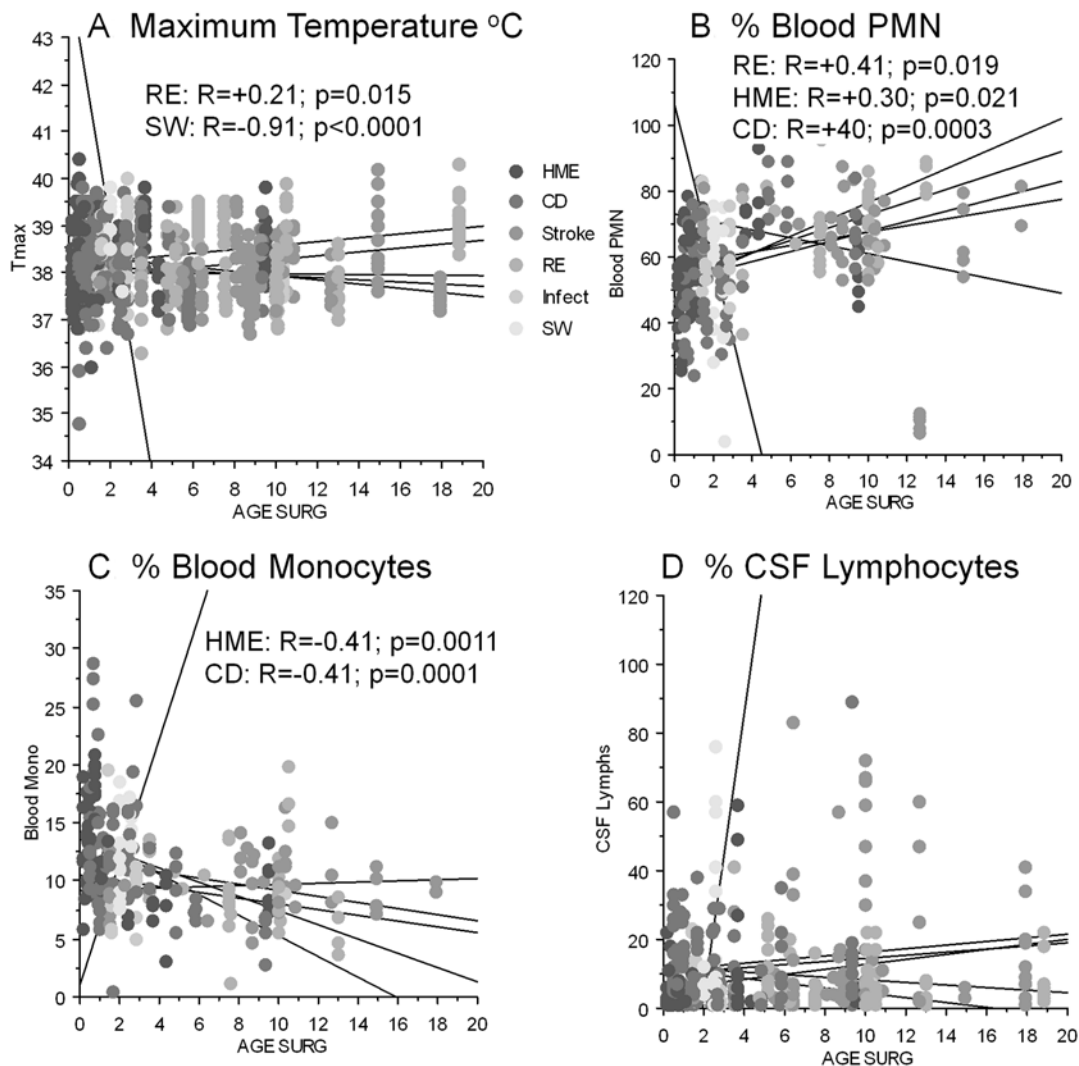


Fig. 4. Line graphs showing the interactions between etiology groups and age at surgery (age surg) in years for Tmax (A), %bloodPMNs (B), %bloodMonos (C), and %CSFLymphs (D). The linear regression r and p value for etiologies that were statistically significant are shown with each graph. For Tmax (A), patients with RE showed increased temperatures that positively correlated with age at surgery, while SWS cases showed a negative correlation with age at surgery. For %bloodPMNs (B), cases of RE, HME, and CD showed positive correlations with age at surgery. For %bloodMonos (C), HME and CD cases showed negative correlations with age. For %CSFLymphs (D), the repeated measures ANCOVA showed a positive correlation with age at surgery for all groups together (Table 2), but there were no significant correlations by individual seizure etiology groups.

and non-CNS infections after cerebral hemispherectomy is a positive culture, and other studies and variables, such as fevers and elevated blood WBC counts, are poorly predictive.

Results from the current study extend findings from previous reports on patients undergoing cerebral hemispherectomy. For example, prior reports have revealed that elevated fevers are associated with larger anatomical resections and RE etiology.^{3,8} Our study data extend these findings by showing that fevers and abnormal blood and CSF studies are associated with seizure etiology after cerebral hemispherectomy using resection-disconnection procedures. These findings indicate that elevated temperatures and abnormal blood and CSF studies are poor predictors of CNS infections after large cranial procedures, especially in children.^{12,14} It should be recognized that our

clinicolaboratory associations could be related to other variables strongly linked with etiology, such as perioperative blood loss and intravenous fluid management, as previously reported.³

Why some seizure etiologies are associated with differential changes in blood and CSF studies rather than other etiologies is unclear and not a component of the present study design. For example, one could speculate that smaller cortical excisions in larger and older patients explain why stroke cases had a lower Tmax than other seizure etiology cases. Similarly, elevated %bloodPMNs and CSF RBC counts in patients with RE could be related to the chronic brain inflammation associated with this syndrome and the effect that inflammation may have on the meninges.¹⁵ Likewise, increased blood WBC counts in children with HME could be related to the larger resec-

tions relative to body size and associated blood replacement necessary for hemispherectomy or possible alterations in the mammalian target of rapamycin (mTOR) signaling pathway that affects the immune system associated with this disease.^{10,16} The associations identified in our study will require further investigation to identify the reasons they relate to seizure etiology.

The association of changes in Tmax and blood and CSF studies with age at surgery, to our knowledge, has not been reported for patients who have undergone cerebral hemispherectomy. If this finding were related to cerebral maturation, we would expect most of the correlations to be uniformly positive or negative with age at surgery for all seizure etiologies and tests. Instead, we found differing positive and negative associations that varied by test and pathology. This finding suggests that the associations with age at surgery are probably related to developmental maturation that varies by etiology.² How seizure etiology might have a differential impact on producing fever and changes in laboratory studies in older patients after cerebral hemispherectomy is unknown and will require further study.

The reader should be aware of the inherent limitations of this study. It is a retrospective analysis, and blood laboratory studies were not performed daily for every patient as part of the perioperative protocol. After the first few days, blood studies were sent as clinically indicated (mostly for elevated temperatures), and we estimate that blood work was obtained from 90% of the patients in the first 3 days postsurgery, declining to about 50% of patients from Day 4 onward. Future prospective studies should include daily blood laboratory studies as part of the research protocol. Daily CSF studies from Day 2 onward were part of the clinical protocol and are therefore more reliable. Furthermore, our results are most pertinent for pediatric patients undergoing cerebral hemispherectomy for intractable epilepsy. It is unclear if similar results would be found for other types of large and small pediatric and adult neurosurgical nonepilepsy procedures.

Conclusions

This study provides new and useful information related to the chance of developing fevers and abnormal blood and CSF values after cerebral hemispherectomy involving resection-disconnection procedures in infants and children. With current prophylactic clinical protocols, the risk of CNS infection was 5% even though most patients had fevers and abnormal laboratory studies in the first 12 days after surgery. These fevers and altered blood and CSF values were related to seizure etiology and age at surgery. Clinically, interpreting fevers and abnormal blood and CSF studies becomes very challenging in this patient population. The main predictor of CNS and non-CNS infections is a positive culture. For this patient population the benefit of obtaining repeated blood and CSF studies other than cultures should be evaluated, since according to our data their clinical utility is limited and they increase costs unnecessarily.

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Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Mathern. Acquisition of data: Phung, Krogstad. Analysis and interpretation of data: Mathern, Krogstad. Drafting the article: Mathern. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mathern. Statistical analysis: Mathern.

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Fevers posthemispherectomy

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