HEMISPHERECTOMY AND EPILEPTIC ENCEPHALOPATHY

Cerebral Hemispherectomy: Hospital Course, Seizure, Developmental, Language, and Motor Outcomes

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Neurology 2004;62(10):1712–1721

OBJECTIVE: To compare hemispherectomy patients with different pathologic substrates for hospital course, seizure, developmental, language, and motor outcomes.
METHODS: The authors compared hemispherectomy patients ($n = 115$) with hemimegalencephaly (HME; $n = 16$), hemispheric cortical dysplasia (hemi CD; $n = 39$), Rasmussen encephalitis (RE; $n = 21$), infarct/ischemia ($n = 27$), and other/miscellaneous ($n = 12$) for differences in operative management, postsurgery seizure control, and antiepilepsy drug (AED) use. In addition, Vineland Adaptive Behavior Scale (VABS) developmental quotients (DQ), language, and motor assessments were performed before or after surgery, or both.
RESULTS: Surgically, HME patients had the greatest perioperative blood loss and the longest surgery time. Fewer HME patients were seizure free or not taking AEDs 1 to 5 years after surgery, but the differences between pathologic groups were not significant. After surgery, 66% of HME patients had little or no language and worse motor scores in the paretic limbs. By contrast, 40% to 50% of hemi-CD children showed near-normal language and motor assessments, similar to RE and infarct/ischemia cases. VABS DQ scores showed +5 points or more improvement after surgery in 57% of patients, and hemi-CD (+12.7) and HME (+9.1) children showed the most progress compared with RE (+4.6) and infarct/ischemia (–0.6) cases. Postsurgery VABS DQ scores correlated with seizure duration, seizure control, and presurgery DQ scores.
CONCLUSIONS: The pathologic substrate predicted pre- and postsurgery differences in outcomes, with hemimegalencephaly (but not hemispheric cortical dysplasia) patients doing worse in several domains. Furthermore, shorter seizure durations, seizure control, and greater presurgery developmental quotients predicted better postsurgery developmental quotients in all patients, irrespective of pathology.

COMMENTARY

More than a half century ago, Roland Krynauw (1) reported his experience with hemispherectomy in the management of infantile hemiplegia. Epilepsy was the primary indication for surgery in 10 of his cases, and all patients became seizure free in conjunction with their gains in motor functioning. Of perhaps greater scientific significance, however, were Krynauw's subjective observations of overall improvement in neurobehavioral status. He remarked, "Disorders of behavior and personality are a marked feature of this group of cases, and the profound betterment in respect of mentality in all cases exceeds our best expectations. It should be pointed out that this improvement in the mental sphere, presupposes, and is dependent upon, the integrity of the remaining hemisphere and its ability to function normally once it has been released from abnormal influences from the pathological side" (1).

Subsequent studies of hemispherectomized patients have largely confirmed Krynauw's early clinical observations, and examples of above-average intelligence after left or right hemispherectomy are now well documented (2,3). Lindsay et al. (4) described 17 patients, followed up for 36 years, whose progressive declines in intellect were abruptly halted by hemispherectomy, whereas their IQ scores uniformly improved. Gains in neurocognitive status have been noted after hemispherectomy for late-onset seizures due to Rasmussen syndrome (5) and early-onset seizures in patients with hemimegalencephaly (6). These results collectively confirm the ability of the unoperated-on hemisphere to support function previously residing in the operative hemisphere, if contralateral structures are intact. Immediate postoperative and serial neuropsychological assessments further suggest that the reorganization process begins very early after surgery but can continue for as long as 1 year (5).

How does a radical surgical procedure, such as hemispherectomy, contribute to the improved neuropsychological status of so many patients, and why is it that all patients do not benefit to an equal degree? The absolute anatomic and functional integrity of the remaining hemisphere is probably a key factor in the recovery process—plasticity of higher cortical function cannot proceed unless functional processes can relocate to contralateral regions with well-preserved and integrated neural networks. Patients with anatomically and functionally normal contralateral tissue would be expected to achieve the most dramatic gains, whereas contralateral damage, especially within homologous regions, would be expected to impede recovery.

Age at which surgery occurs is a second consideration, given the potential of more-immature, less-dedicated neural tissue to take on functional tasks not ordinarily assigned to that hemisphere. Neural plasticity considerations are often invoked as a rationale for performing earlier surgery in patients with medically resistant seizures. However, the absolute contribution of earlier age at surgery is imprecisely known, and the capacity of the brain to remodel itself after injury persists well into adult life (7).

A third consideration regarding improved neuropsychological status with hemispherectomy involves the role of the pathologic substrate. Certain pathologies, such as hemimegalencephaly, are known to have a poorer long-term prognosis, even after successful surgery. In these cases, however, the contribution of pathologic substrate to outcome may be confounded by variables such as age of seizure onset or the erroneous presumption of full integrity of the contralateral hemisphere.

A fourth issue, which has received less attention in the hemispherectomy literature, centers on the ability of successful hemispherectomy to alleviate the burden of epilepsy on the developing brain. This consideration presupposes that severe hemispheric epilepsy causes an epileptic encephalopathy that ultimately involves both cerebral hemispheres. In this scenario, any plasticity-induced developmental progress that requires one functioning hemisphere would cease in the face of bilateral cerebral involvement, ultimately leading to deterioration of higher cortical functioning. It is known, for example, that even in the absence of clinical or electrographic seizures, continuous unilateral interictal epileptiform discharges in the dominant hemisphere can delay language acquisition, whereas successful hemispherectomy can reverse this process (8).

Working with a large population of patients undergoing hemispherectomy, Jonas et al. (9) analyzed the effect of several critical pre- and postoperative variables on long-term developmental and seizure status. The study design used a single-procedure, single-center pediatric surgical population and analyzed postsurgery seizure, motor, developmental, and language status as a function of preoperative risk factors and pathologic substrate. This study design minimizes the influence of variability in surgical technique, as well as multicenter referral and selection biases. Limiting the study population to children with medically resistant seizures further assures that a high proportion of candidates will have prenatally acquired etiologies and that surgery will be performed in patients with developmental potential. Of the patients, 58% were seizure free at 5 years—a finding consistent with other hemispherectomy series. Although not statistically significant, patients with hemimegalencephaly experienced the lowest incidence of seizure freedom. From a surgical standpoint, hemimegalencephaly patients required greater operative time and experienced more blood loss. Hemimegalencephaly patients also had the poorest prognosis for postoperative language and motor status compared with other pathologic groups.

In the Jonas et al. study, no child undergoing hemispherectomy deteriorated after surgery, and most achieved modest developmental improvement. The lack of more substantial neurocognitive gain is not entirely unexpected, as the degree of preexistent brain damage is often severe in the early-onset seizure population and is more likely to involve the non–operated-on hemisphere. However, the authors found that the greatest gains in postoperative development correlated with higher preoperative developmental attainment, shorter preoperative seizure duration, and better postoperative seizure control. Improvement was independent of pathologic substrate, suggesting that a surgical patient's premorbid pathologic substrate is unlikely to be the sole determinant of neurodevelopmental outcome. This finding in no way implies that pathologic substrate and laterality of seizure origin are not important variables, as both are known to be important predictors of outcome (10). They strongly suggest that children with severe unilateral, medically resistant seizures are at significant risk for acquiring an epileptic encephalopathy and should be referred promptly for surgical evaluation. To delay could further worsen long-term neurodevelopmental status.

The findings reported by Jonas et al. thus lend scientific credibility to Krynauw's historic clinical observations and provide important confirmation that surgical intervention is capable of reversing an epileptic encephalopathic state. Although not discounting the potential contribution of underlying substrate, age at seizure onset, or age at surgery for long-term prognosis, the findings suggest that seizure control, both before and after hemispherectomy, may be critical to the recovery process. A reversible encephalopathic process mandates a prompt and definitive solution.

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References

1. Krynauw RA. Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatry 1950;13:243–267.
2. Smith A, Sugar O. Development of above normal language and intelligence 21 years after left hemispherectomy. Neurology 1975;25:813–818.

3. Damasio AR, Lima A, Damasio H. Nervous function after right hemispherectomy. Neurology 1975;25:89–93.
4. Lindsay J, Ounsted C, Richards P. Hemispherectomy for childhood epilepsy: a 36 year study. Dev Med Child Neurol 1987;29:592–600.
5. Boatman D, Freeman J, Vining E, Pulsifer M, Miglioretti D, Minahan R, Carson B, Brandt J, McKhann G. Language recovery after left hemispherectomy in children with late-onset seizures. Ann Neurol 1999;46:579–566.
6. Battaglia D, DiRocco C, Iuvone L, Acquafondata C, Ianelli A, Lettori D, Guzzetta F. Neuro-cognitive development and epilepsy outcome in children with surgically treated hemimegalencephaly. Neuropediatrics 1999;30:307–313.
7. Kaas JH, Merzinich MM, Killackey HP. The reorganization of somatosensory cortex following peripheralnerve damage in adult and developing mammals. Ann Review Neurosci 1983;6:325–365.
8. Rosenblatt B, Vernet O, Montes JL, Andermann F, Schwartz S, Taylor LB, Villemure J-G, Farmer J-P. Continuous unilateral epileptiform discharge and language delay: effect of functional hemispherectomy on language acquisition. Epilepsia 1998;39:787–792.
9. Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, de Bode S, Yudovin S, Shields WD, Vinters HV, Mathern G. Cerebral hemispherectomy: hospital course, seizure, developmental, language and motor outcomes. Neurology 2004;62:1712–1721.
10. Pulsifer MB, Brandt J, Salorio C, Vining EPG, Carson BS, Freeman JM: The cognitive outcome of hemispherectomy in 71 children. Epilepsia 2004;45:243–254.