

## Neuroplasticity in play: Outcomes after Hemispherectomy in Rasmussen Encephalitis

Isaiah Baiyekusi<sup>1</sup>, Durga Prasad S.<sup>2\*</sup>

<sup>1</sup>Medical Student, <sup>2</sup>Professor, American University of Antigua, College of Medicine, Coolidge, Antigua

**\*Corresponding Author:**

E-mail: dprasad@auamed.net

### Abstract

**Introduction:** A key property of the brain is its capacity to change after injury to enable at least some behavioral compensation. There are spontaneous reparative changes following injury, some of these changes are sufficient to support significant functional recovery.

**Rasmussen Encephalitis:** Rasmussen Encephalitis is a rare but severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction and intractable seizures. Hemispherectomy in one of its modern variants offers a very high chance of seizure freedom and it is highly probable that the unaffected hemisphere compensates and takes over the functions of the removed hemisphere.

**Outcomes after Hemispherectomy:** We review the some cases of positive outcomes after removal of a hemisphere in patients suffering from Rasmussen encephalitis.

**Discussion:** Neuroplasticity is the key for a functional motor shift to the normal hemisphere to happen. Removal of a hemisphere dramatically illustrates the resilience of the brain to extensive damage.

**Conclusion:** Research on the basic principles of brain plasticity is leading to new approaches to treating the injured brain. The power of neuroplasticity that is play in RE can be harnessed for intervention and rehabilitation in the field of neurology.

**Keywords:** Epilepsia partialis continua, Hemispherectomy, Hemispherotomy, Neuroplasticity, Rasmussen Encephalitis.

### Introduction

For many years, the medical field held the belief that the brain was "hard-wired" with fixed neuronal circuits and that it was constant in its organization and function. Today we know that the brain continually adjusts and reorganizes itself by forming new neural connections throughout life. It has now become clear that the brain is inherently capable of changing after injury to enable at least some behavioral compensation. Researchers in recent decades have revealed that the cerebral cortex, rather than being fixed in structure and function, is highly dynamic<sup>(1)</sup>. This dynamic change to the brain throughout an individual's life course is referred to as neuroplasticity. The term neuroplasticity gained prominence in the latter half of the 20th century, when new research showed many aspects of the brain remain "plastic" even into adulthood<sup>(2,3)</sup>. It allows the neurons to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment, sometimes recovering brain functions. Children have an enhanced capacity for brain plasticity compared to adults as demonstrated by their superior ability to learn a second language or their capacity to recover from brain injuries or radical surgery such as hemispherectomy for epilepsy<sup>(4)</sup>.

There is evidence that neurogenesis occurs in the adult brain as well and such changes can persist well into old age. The evidence for neurogenesis is mainly restricted to the hippocampus and olfactory bulb, but current research has revealed that other parts of the brain, including the cerebellum, may be involved as well<sup>(5)</sup>. The Applications and examples of neuroplasticity

include improvements in functional outcomes with physical therapy after stroke, successful improvements in persons with amblyopia, convergence insufficiency or stereo vision anomalies<sup>(6,7,8)</sup> and positive outcomes after hemispherectomy in Rasmussen Encephalitis. An example neuroplasticity worth mentioning here a case reported in 'Neurology India' describing a patient who had functional hemispherectomy for intractable seizures secondary to right hemispheric cortical dysplasia. This patient presented with mild left-sided weakness with intact gross motor and fine motor activity. An fMRI, however, showed a complete shift of the motor function to normal hemisphere<sup>(9)</sup>.

### Rasmussen's Encephalitis

Neurosurgeon Theodore Rasmussen and his colleagues first made the description of Rasmussen Encephalitis (RE) in 1958<sup>(10)</sup>. RE is a rare but severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction and intractable seizures.

Furthermore, intractable focal motor seizures which later develops into epilepsy partialis continua, gradual hemiparesis, and decline in mental and social domains, homonymous hemianopia and deterioration of language skills have been observed in patients with RE. A Case study describes a 4-year-old child with RE, with the onset at 2 years. Epilepsia partialis continua began at 2.5 years old, progressive left sided hemiparesis was observed. MRI revealed diffused atrophic changes in his right cerebral hemisphere<sup>(11)</sup>.

The 2005 European consensus proposed formal diagnostic criteria and a therapeutic pathway for the management of RE patients (Table 1)<sup>(12)</sup>. The initial hypothesis of the origin of the syndrome was a viral infection, but has since been researched to be an auto immune disorder<sup>(13,14)</sup>. An important characteristic of RE seizure is that it usually is focal and never spread or diffuse unilaterally or become generalized. As far as treatment of epilepsy is concerned, anti-seizure effect of anti-epilepsy drugs is usually limited to secondarily generalized seizures and complex partial seizures whereas *epilepsia partialis continua* usually is totally refractory. Immunomodulatory treatments seem to slow rather than halt disease progression in RE, without changing the eventual outcome. Hemispherectomy in one of its modern variants offers a very high chance of seizure freedom. Hemispherectomy or hemispherotomy is the definitive treatment of RE<sup>(15)</sup>. The functional outcomes make hemispherectomy the most preferred procedure. Since, RE is localized in only hemisphere, early removal of the affected hemisphere will enable the unaffected hemisphere to compensate the functions of the affected one<sup>(16)</sup>. Hemispherectomy performed in carefully selected pediatric patients with medically intractable epilepsy can be a safe and efficacious surgical procedure<sup>(17)</sup>. Hemispherectomy in children has been used as treatment for refractory epilepsy and for cure of localized focal epilepsy<sup>(18)</sup>. Hemispherectomy offers one of the best chances of making patients with RE seizure free with (70–80%) long-term seizure-free outcome<sup>(19)</sup>. A European consensus statement says hemidissection is the only management option that achieves seizure freedom<sup>(20)</sup>.

### Outcomes after Hemispherectomy

The outcomes of Rasmussen syndrome patients after hemispherectomy are very positive. Most of the patients recovered and consistently showed improvements. Few motor and sensory deficits are observed on the affected side but the unaffected hemisphere compensates and takes over the functions of the removed hemisphere. In the case report of a 4 year old child by Chiang et al cited in the previous section, the *epilepsia partialis continua* disappeared after the surgery. The hemiparesis improved and regained motor function on the affected limbs<sup>(11)</sup>. In a retrospective study published in *Journal of Clinical Neurology*, authors reported that (66.7%) of the children who underwent hemispheric disconnection became seizure-free or showed a more than (90%) reduction in seizure frequency<sup>(21)</sup>. In another study published recently, 136 of 186 hemispherectomized patients (73%) were reported to have achieved either seizure freedom or major reductions in seizure frequency<sup>(22)</sup>. In the Bonn University Medical Center study of 92 pediatric epilepsy patients, 78 of the cases (85%) were reported to be seizure-free at their last follow-up<sup>(23)</sup>. A Brazilian retrospective study reported

the clinical and electrographic analysis, as well as the evolution of 23 patients with RE. Fourteen patients achieved satisfactory seizure control; three patients had partial response to surgery.<sup>(24)</sup> The study conducted at Great Ormond Street Hospital London for Children on the clinical course and outcomes of 33 children who underwent hemispherectomy between 1991 and 1997 showed an excellent seizure outcome with (52%) of children becoming seizure free and a further (39%) experiencing more than (75%) reduction in seizure frequency<sup>(25)</sup>. This compares well with the Johns Hopkins series of 58 children who underwent hemispherectomy<sup>(26)</sup>. Cleveland Clinic study of a cohort of 115 children, (83%) patients walked independently, (73%) had minimal or no behavioral problems, (69.5%) had satisfactory spoken language skills, and (42%) had good reading skills. In (76%) of patients, limitations related to visual field deficits were not perceived as significant<sup>(27)</sup>. A 2004 Harvard Medical School study reported that patients with left-sided disease had worse outcomes with respect to general intelligence, receptive language, and expressive language<sup>(28)</sup>. However, not all patients with dominant-hemisphere disease have poor outcomes. One case report demonstrated new activation of right-sided structures on fMRI after hemispherectomy, demonstrating radiographically that language function can transfer to the contralateral hemisphere in some cases, while other case reports have shown varying findings on late recovery of language function after hemispherectomy<sup>(29-35)</sup>.

K.N. Ramesha, et al of Sree Chitra Tirunal Institute for Medical Sciences and Technology reported that out of 10 RE patients who underwent either hemispherotomy (n=6), hemispherectomy (n=3) or focal resection (n=1), all except 1 patient was ambulant at last follow-up, either independently or with minimum support<sup>(36)</sup>. Therefore by looking at these scientific studies, we can say that the outcomes of hemispherectomy in RE are consistent, with about (65%) been seizure-free. In few cases, mild episodes of residue seizures were observed. The restoration of motor function was observed in most of the patients, some of them walking and running without braces.

### Discussion

Evidently, neuroplasticity enables the brain to compensate for damage. It is the key for a functional motor shift to the normal hemisphere to happen. Removal of a hemisphere dramatically illustrates the resilience of the brain to extensive damage. The scientific articles on hemispherectomy in RE cited above demonstrate the fact that the brain can sometimes not just generate new neurons, but also make new connections, and that these new neurons can sometimes “migrate” within the brain. There is a possibility that, under certain conditions, these new neurons could migrate to damaged areas, form new connections, and restore some or all lost functions. Brain plasticity brings

about increase in new synapses besides strengthening and expansion of influence by dendritic branching<sup>(37)</sup>. After hemispherectomy the inhibition of the corpus callosum is stopped, hence the ipsilateral pathways open up. In addition, there is an overall hyperexcitability and increase in neuromodulators and neurotrophins after such cortical damage. This overall hyperexcitability helps neuroplasticity. The involvement one such neurotrophin, brain-derived neurotrophic factor (BDNF), represents one of the major mediators of neuroplasticity<sup>(38)</sup>. The capacity of the brain for plasticity has a limited window of opportunity and it is believed to occur until 7 years for language, between 5 and 16 years for frontal lobe functions and between 1 and 11 years for occipital functions<sup>(39,40)</sup>. In RE progressive extensive hemispheric deficits occur. Hence, early hemispherectomy is indicated before maximal deficit occurs and for better neurocognitive outcomes<sup>(41,42)</sup>.

### Conclusions

Neuroplasticity is the key mechanism in the recovery after hemispherectomy in RE. Future studies, involving larger numbers of hemispherectomized patients, will be necessary to have a greater knowledge of how cerebral reorganization can contribute to residual sensorimotor function. As we gain more and more clear understanding of the principles that control plasticity in the normal brain, novel treatment strategies can be developed to stimulate recovery after cerebral injury. The power of neuroplasticity can be harnessed for intervention and rehabilitation in the field of neurology. A significant challenge in the coming decade is to devise ways to apply the knowledge generated in the studies mentioned here to develop successful rehabilitation strategies.

### References

1. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve*. 2001 Aug; 24(8):1000-19.
2. Livingston R.B. (1966). "Brain mechanisms in conditioning and learning". *Neurosciences Research Program Bulletin*. 4(3):349-354.
3. Rakic, P. Neurogenesis in adult primate neocortex: an evaluation of the evidence. *Nature Reviews Neuroscience*. 3(1):65-71.
4. Johnston MV. Clinical disorders of brain plasticity. *Brain Dev*. 2004 Mar; 26(2):73-80.
5. Ponti, Giovanna; Peretto, Paolo; Bonfanti, Luca; Reh, Thomas A. (2008). Reh, Thomas A., ed. "Genesis of Neuronal and Glial Progenitors in the Cerebellar Cortex of Peripuberal and Adult Rabbits". *PLoS ONE*. 3(6):e2366.
6. Young J. A., Tolentino M.; Tolentino (2011). Neuroplasticity and its Applications for Rehabilitation. *American Journal of Therapeutics*. 18(1):70-80.
7. Indu Vedamurthy; Samuel J. Huang; Dennis M. Levi; Daphne Bavelier; David C. Knill (27 December 2012). "Recovery of stereopsis in adults through training in a virtual reality task". *Journal of Vision*. 12(14).
8. Robert F. Hess; Benjamin Thompson (February 2013). "New insights into amblyopia: binocular therapy and noninvasive brain stimulation". *Journal of AAPOS*. 17(1).pp.89-93.
9. Krishnan SS, Panigrahi M, Jayalakshmi S, Varma DR. Neuroplasticity in hemispheric syndrome: An interesting case report. *Neurol India*. 2011 Jul-Aug; 59(4):601-4.
10. Rasmussen T, Olszewski J, Lloydsmith D: Focal seizures due to chronic localized encephalitis. *Neurology* 1958; 8:435-445.
11. Chiang KL, Wong TT, Kwan SY, Hsu TR, Wang CH, Chang KP. Finding on brain MRI mimicking focal cortical dysplasia in early Rasmussen's encephalitis: a case report and review. *Childs Nerv Syst*. 2009 Nov;25(11):1501-6
12. Bien CG1, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, Lassmann H, Mantegazza R, Villemure JG, Spreafico R, Elger CE. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain*. 2005 Mar;128(Pt 3):454-71.
13. Pardo CA1, Vining EP, Guo L, Skolasky RL, Carson BS, Freeman JM. The pathology of Rasmussen syndrome: stages of cortical involvement and neuropathological studies in 45 hemispherectomies. *Epilepsia*. 2004 May;45(5):516-26.
14. Takahashi Y, Mori H, Mishina M, et al. (2005). Autoantibodies and cell-mediated autoimmunity to NMDA-type GluRepsilon2 in patients with Rasmussen's encephalitis (RE) and chronic progressive epilepsy partialis continua. *Epilepsia* 46 (Suppl 5):152-158.
15. J.M. Freeman. Rasmussen's syndrome: progressive autoimmune multi-focal encephalopathy. *Pediatric Neurology*, 32(2005), pp.295-299.
16. Daniel RT, Joseph TP, Gnanamuthu C, Chandy MJ. Hemispherotomy for pediatric hemispheric epilepsy. *Stereotact Funct Neurosurg*. 2001;77(1-4):219-22.
17. Fountas KN1, Smith JR, Robinson JS, Tamburrini G, Pietrini D, Di Rocco C. Anatomical hemispherectomy. *Childs Nerv Syst*. 2006 Aug;22(8):982-91.
18. Ramey WL, Martirosyan NL, Lieu CM, Hasham HA, Lemole GM Jr, Weinand ME. Current management and surgical outcomes of medically intractable epilepsy. *Clin Neurol Neurosurg*. 2013 Dec;115(12):2411-8.
19. Bien CG, Schramm J. Treatment of Rasmussen encephalitis half a century after its initial description: promising prospects and a dilemma. *Epilepsy Res*. 2009 Oct;86(2-3):101-12.
20. Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, Lassmann H, Mantegazza R, Villemure JG, Spreafico R, Elger CE. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: A European consensus statement. *Brain* 2005;128(pt 3):454-471.
21. Yun-Jeong Lee, Eun-Hee Kim, Mi-Sun Yum,, Jung Kyo Lee, Seokho Hong, Tae-Sung Ko. Long-Term Outcomes of Hemispheric Disconnection in Pediatric Patients with Intractable Epilepsy. *J Clin Neurol*. 2014 Apr;10(2):101-107.
22. Moosa AN, Gupta A, Jehi L, Marashly A, Cosmo G, Lachhwani D, et al. Longitudinal seizure outcome and prognostic predictors after hemispherectomy in 170 children. *Neurology*. 2013;80:253-260.
23. Schramm J, Kuczaty S, Sassen R, Elger CE, von Lehe M. Pediatric functional hemispherectomy: outcome in 92 patients. *Acta Neurochir (Wien)* 2012;154:2017-2028.
24. Terra-Bustamante VC, Machado HR, dos Santos Oliveira R, Serafini L et al. Rasmussen Encephalitis: Long term outcome after surgery. *Childs Nerv Syst*. 2009 May; 25(5):583-9.

25. A. M. Devlin, J. H. Cross, W. Harkness, W. K. Chong, B. Harding, F. Vargha-Khadem, B. G. R. Neville. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain*. 2003 Mar;126(Pt 3):556-66.
26. Vining EP, Freeman JM, Pillas DJ, Uematsu S, Carson BS, Brandt J, Boatman D, Pulsifer MB, Zuckerberg A. Why would you remove half a brain? The outcome of 58 children after hemispherectomy-the Johns Hopkins experience: 1968 to 1996. *Pediatrics*. 1997;100(pt1):163-171.
27. Moosa AN1, Jehi L, Marashly A, Cosmo G, Lachhwani D, Wyllie E, Kotagal P, Bingaman W, Gupta A. Long-term functional outcomes and their predictors after hemispherectomy in 115 children. *Epilepsia*. 2013 Oct;54(10):1771-9.
28. Pulsifer MB, Brandt J, Salorio CF, Vining EP, Carson BS, Freeman JM. The cognitive outcome of hemispherectomy in 71 children. *Epilepsia*. 2004;45:243-254.
29. Ogden JA. Language and memory functions after long recovery periods in left-hemispherectomized subjects. *Neuropsychologia*. 1988;26:645-659.
30. Stark RE, Bleile K, Brandt J, Freeman J, Vining EP. Speech-language outcomes of hemispherectomy in children and young adults. *Brain Lang*. 1995;51:406-421.
31. Stark RE, McGregor KK. Follow-up study of a right- and a left-hemispherectomized child: Implications for localization and impairment of language in children. *Brain Lang*. 1997;60:222-242.
32. Hertz-Pannier L, Chiron C, Jambaque I, Renaux-Kieffer V, Van de Moortele PF, et al. Late plasticity for language in a child's non-dominant hemisphere: A pre- and postsurgery fMRI study. *Brain* 2002;125(pt 2):361-372.
33. Telfeian AE, Berqvist C, Danielak C, Simon, Duhaime AC. Recovery of language after left hemispherectomy in a sixteen-year-old girl with late-onset seizures. *Pediatr Neurosurg* 2002;37:19-21.
34. Voets NL, Adcock JE, Flitney DE, Behrens TE, Hart Y, Stacey R, Carpenter K, Matthews PM. Distinct right frontal lobe activation in language processing following left hemisphere injury. *Brain*. 2006;129(pt 3):754-766.
35. Liegeois F, Connelly A, Baldeweg T, Vargha-Khadem F. Speaking with a single cerebral hemisphere: fMRI language organization after hemispherectomy in childhood. *Brain Lang*. 2008;106:195-203.
36. Ramesha KN1, Rajesh B, Ashalatha R, Kesavadas C, Abraham M, Radhakrishnan VV, Sarma PS, Radhakrishnan K. Rasmussen's encephalitis: experience from a developing country based on a group of medically and surgically treated patients. *Seizure*. 2009 Oct;18(8):567-72.
37. Anatomical and physiological basis of Neural Plasticity. In: Moller AR. *Neural Plasticity and Disorders of the Nervous System*. 1st Ed. Cambridge: Cambridge University Press. 2006.p.7-41.
38. Barbay S, Zoubina E, Nudo RJ. Neural Plasticity in Adult Motor Cortex. In: Ebner FF, Editor. *Neural Plasticity In Adult Somatic Sensory-Motors Systems*. 1st ed., Boca Raton, FL: CRC division of Taylor and Francis. 2005;p.155-88.
39. Graveline C, Hwang P, Bone G, Shikolka C, Wade S, Crawley A. Evaluation of gross and fine motor functions in children with hemidecortication: Predictors of outcomes and timing of surgery. *J Child Neurol*. 1999;14:304-15.
40. Hertz-Pannier L, Chiron C, Jambaqué I, Renaux-Kieffer V, Van de Moortele PF, Delalande O. Late plasticity for language in a child's non-dominant hemisphere: A pre- and post-surgery fMRI study. *Brain*. 2002;125:361-72.
41. Villemure JG. Functional Hemispherotomy and Periinsular Hemispherotomy. In: Baltuch GH, Villemure JG, Editor. *Operative Techniques in Epilepsy Surgery*. New York: Thieme Medical Publishers. 2009;p.138-45.
42. Daniel RT, Thomas SG, Thomas M. Role of surgery in pediatric epilepsy. *Indian Paediatr*. 2007;44:263-73.