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Lumbosacral Spinal Cord Epidural Stimulation Enables Recovery of Voluntary Movement After Complete Motor Spinal Cord Injury

Severe spinal cord injury is a devastating problem that results in motor weakness, sensory loss, and bowel/bladder/sexual dysfunction. There are about 12 000 new cases of severe spinal cord injury per year in the United States and almost 300 000 people living with this disease, many of whom are wheelchair bound. Because the majority of patients are young and survive for years after the initial injury, the medical and social consequences of this condition are staggering. There are, unfortunately, no known effective treatments for severe spinal cord injury that might help patients with complete motor lesions regain voluntary movement, although there has been much research in this direction.

Harkema et al[1] previously reported a single case of an individual who suffered an American Spinal Injury Association Impairment Scale grade B injury (motor complete but sensory incomplete) who regained voluntary motor function after 7 months of epidural stimulation and intensive stand training. Because native motor pathways were nonfunctional, it was presumed that the remaining sensory pathways

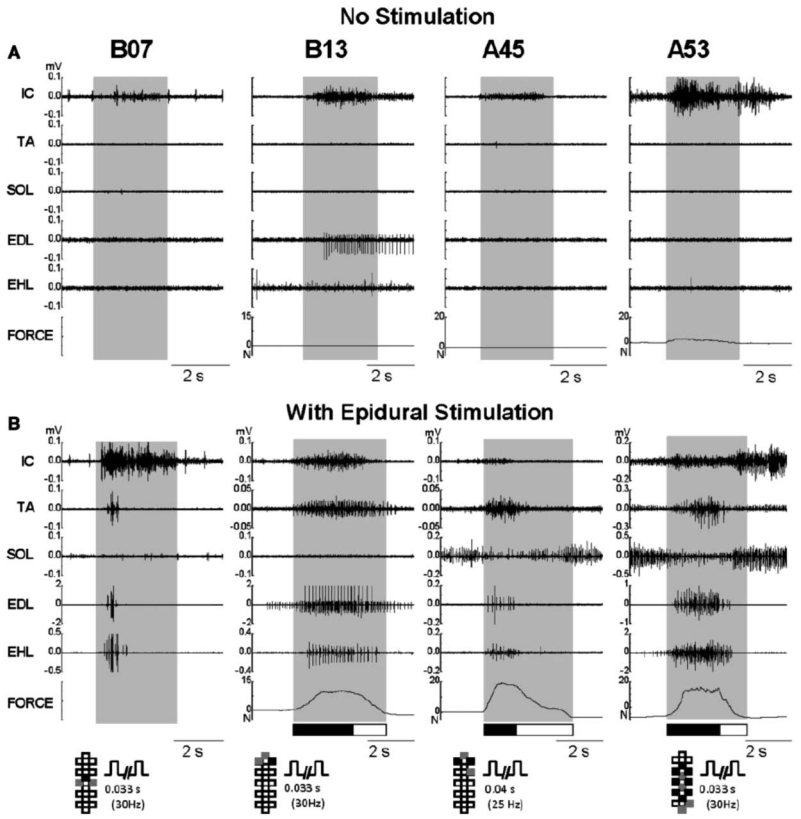

*Figure. Lower-extremity electromyogram during attempted voluntary movement in the 4 subjects without (**A**) and with (**B**) epidural stimulation in various leg muscles groups. All subjects had no voluntary electromyogram responses before epidural stimulator implantation.* Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans, Brain 2014;volume 137 (Pt 5):1394-1409, by permission of Oxford University Press.

and neural plasticity driven by intensive rehabilitation training played a critical role in recovery. The same group recently published a study in *Brain* in which they included 3 additional patients with complete motor lesions, 2 of whom have American Spinal Injury Association Impairment Scale grade A injuries.[2]

This study included 4 male patients with complete motor spinal cord lesions that were at least 2 years after injury who underwent placement of an epidural spinal cord stimulation unit (Medtronics, RestoreADVANCED) and 16-electrode array at vertebral levels T11-12. Three patients were able to generate ankle dorsiflexion and electromyogram activity after epidural stimulation alone before stand or step training. The remaining patient, who was the original individual with American Spinal Injury Association Impairment Scale grade B injury, was only able to generate ankle dorsiflexion and electromyogram activity after 7 months of intensive stand training. The authors go on to demonstrate, through a series of neurophysiological experiments, that with epidural stimulation these patients were able to produce graded levels of force on command and to modulate motor activity according to both visual and auditory cues and that voluntary movement improved over time with daily training.

This study is important for the field of spinal cord injury research because it demonstrates that patients diagnosed with complete motor lesions can regain some voluntary movement even years after the injury. The exact mechanism of these results, however, remains unclear. It could be that epidural stimulation enhances pre-existing anatomic connections that persisted after the initial injury but were clinically silent; alternatively, it is possible that epidural stimulation encourages the growth of new axons across the level of injury. The authors report that each of the 4 patients in this study have found a way to incorporate their newfound ability to voluntarily move their trunk and legs into daily activities, which results in greater strength and less fatigue. These results are highly encouraging, and perhaps a better understanding of the underlying mechanism will enable us to develop therapeutic interventions in the future that will help patients with complete motor injuries regain the ability to ambulate.

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The Regulatory Network of Proneural Glioma in Tumor Progression

Significant time and expenditure have been devoted to revealing the pathophysiology of glioblastoma multiforme (GBM). Despite tremendous advances in our understanding of disease initiation and progression, overall outcomes have not improved. This is partially attributable to universal recurrence despite surgery, radiotherapy, and chemotherapy. It has become clearer that GBMs are not a homogeneous group of lesions and that subdivisions of GBMs may require individual treatment. This has provided an impetus to further understand the molecular events that define GBM phenotypes and genotypes.

Subgroups of GBMs have been based on differences in gene expression, molecular classification, and signaling profiles. In molecule-based schemes of classification, the classic, mesenchymal, and proneural subtypes have been defined on the basis of alterations in EGFR, NF1, and PDGFRA/IDH1, respectively, and on lineage-related expression patterns.[1-3] The numerous genetic alterations found within GBMs may help further define primary vs secondary GBMs that originate from primordial low-grade gliomas. The implications would be to help develop subtype-specific treatments that provide individual tumor therapeutic options. Recently, large randomized clinical trials have begun to substratify lesions according to molecular alterations in an effort to better define treatment responsive cohorts,[4,5] but trials may not have found favorable results in part as a result of an incomplete understanding of the regulatory network behind tumor progression among the various subtypes.

Although much of the diversity of GBMs may be attributable to genetic heterogeneity, the sequence of events that define this remains unclear. Acquisition of mutations during tumor progression is likely a defining element rather than a random sequence and is likely regulated by multiple epigenetic alterations. Furthermore, heterogeneity may be influenced by pre-existent genetic background,[6] differences in cell origin,[2,7] age,[8] and environment.[9]

The proneural subtype of GBM is defined by a gene expression profile that resembles that of oligodendrocyte progenitor cells, a potential cell of origin for these tumors.[7] These gliomas are characterized by genetic alterations, including TP53 and IDH1 mutations, and PDGFRA amplification.[2] The proneural phenotype represents the majority of low-grade gliomas and secondary GBMs.[2]

To better define the dependent sequential events leading to the development of the proneural subtype, Lei et al[7] and Sonabend et al[10] assessed the events behind the development of a murine model of proneural glioma induced through overexpression of the platelet-derived growth factor (PDGF) oncogene and inactivation of the PTEN tumor suppressor. Overexpression of PDGF induces proliferation of oligodendrocyte progenitor cells,[11] which is implicated in the development of proneural gliomas.[2,7] In their model, tumor formation results from injecting PDGF-B-IRES-Cre retrovirus into the subcortical white matter of adult Pten$^{lox/lox}$ transgenic mice.[7,10] A small collection of retrovirus-infected glial progenitors then develop into tumors that recapitulate the histological features of low-grade glioma and then progress to GBM.

The authors used cross-species comparison with human GBMs from The Cancer Genome Atlas that revealed that this model similarly matches the proneural gene expression profile.[7,10] The authors then assessed sequential changes in gene expression, histological appearance, and gene copy number alterations that develop within the initiation and lineage of murine proneural gliomas. This helped define the critical steps behind tumor progression while allowing control of confounding variables including age, cell origin, environmental exposure, and genetic alterations. Furthermore, this demonstrated consistency in the sequential events of spontaneously occurring chromosome copy number alterations, including a subset of genes deleted in both human and murine proneural tumors.

The authors identified that p53 is a significant transcription regulator during early and late progression of the proneural gliomas.[10] Upfront deletion of p53 allowed glioma progression, without the necessity of accumulation of additional proneural specific genetic deletions. These results provide experimental support for a functional link between the pre-existing cellular phenotype and the acquisition of specific genetic alterations.

This type of approach may be beneficial in determining the sequential events behind specific phenotypic and genetic alterations in