limited to the NIHSS. Brain imaging is required to safely and completely assess the patient’s status and eligibility for IV tPA. Third, a remote exam does not replace the physical presence of a physician from a clinical point of view and from a physician-patient relationship perspective. That physical presence at bedside is essential to build trust and therefore to allow the patient and the physician alike to make confident assured decisions. In addition, before this technology can be applied on a larger scale a few important issues need to be addressed including reimbursement and legal implications. The telemedicine system needs to be HIPAA compliant. Transfer of patient information has to be done over strictly secure networks with no third party involvement.

Further studies are warranted to improve upon the system presented in this paper. First and above all, a study analyzing the efficacy of telemedicine systems with multiple centers “plugged-in” to one central institution would allow for a more realistic perspective. It would allow for a better understanding of the feasibility and validity of this telemedicine approach with a more complete assessment of potential failings and weak points. Also, incorporating the currently available technology for patient imaging transfer would allow the remote expert physician to look at brain computed tomographic scans and perfusion imaging to rule out intracranial bleeding and possibly clear the patient for IV tPA. In addition, perhaps if the patient could see and talk to the remote physician, it would help build the physician-patient relationship and the trust that comes with it. Finally, the use of handheld devices as educational tools for physicians and patients alike may further enhance stroke care. The next wave of wireless technology adoption is well underway. As devices and applications become more affordable and user-friendly and as wireless and network coverage becomes more widespread, mobile handheld devices will very likely play an increasingly facilitative role in the care of patients with neurological diseases.

The need and potential for telemedicine for stroke care in particular, and for neurosurgical care in general, is becoming clearer. Neurosurgeons and neurosurgical patients could benefit from telemedicine systems if they are applied thoughtfully.

**References**


**Notch Inhibition via Micro-RNA Blocks Glioma Development**

Increasing evidence points to a small subpopulation of cancer stem-like cells (CSCs) within the larger tumor mass as being responsible for the initiation and maintenance of brain tumors, such as gliomas, their resistance to current cancer therapies, and their recurrence (see, for example, reference 1). The Notch signaling pathway appears to play a particularly important role in gliomagenesis by supporting CSCs (see, for example, references 2-5), which is perhaps unsurprising given its essential role in maintaining normal neural stem cells. Along similar lines, emerging evidence implicates microRNAs (miRNAs) as being intimately involved in tumorigenesis, acting as either oncogenes or tumor suppressors (see, for example, reference 6). miRNAs have been increasingly implicated in the
regulation of neural differentiation, and these same miRNAs have also been shown to play a role in glioblastoma multiforme (GBM; see, for example, references 7,8). Recently, Mei and colleagues (Mei J, Bachoo R, Zhang C-L. MicroRNA-146a inhibits glioma development by targeting Notch1. Mol Cell Biol. 2011;31(17):3584-3592) found that a particular microRNA, miR-146a, acts as a tumor suppressor in gliomas through its inhibition of Notch1 when EGFR is high and PTEN is low.9 Using a global expression assay, the authors found that 19 different miRNAs have their expression altered in primary murine astrocytes that had been transformed into tumorigenic and neurosphere-forming glioma stem-like cells (GSCs) through the loss of Ink4a/Arf and PTEN as well as the expression of the constitutively-active EGFRviii mutation. Of these miRNAs, miR-146 expression was particularly elevated by this increased EGFR activation and PTEN inactivation. When these astrocytes-turned-GSCs were transfected with miR-146a and GFP via a lentivirus vector, the resultant sharp increase in miR-146 levels unexpectedly led to a drop in cell proliferation, anchorage-independent colony growth, and migration. Furthermore, these transfected cells showed decreased neurosphere formation, decreased self renewal, and increased differentiation (ie, less Nestin and Sox2 expression and more GFAP expression). These results suggest that miR-146a may be a tumor suppressor that inhibits the formation of GSCs from malignant astrocytes. Consistent with this possible role, NOD/SCID mice injected with the miR-146a overexpressing GSCs had less tumor burden and increased survival relative to those injected with GSCs that had normal levels of miR-146a. This effect was conserved in human glioma cells as ectopic miR-146a expression decreased Notch levels in U87 glioblastoma cells and diminished their ability to form GSCs, and it decreased the tumor burden and increased the overall survival of NOD/SCID mice with U87 intracranial xenografts. Mei et al next set out to determine the mechanism underlying miR-146a’s ability to inhibit the proliferation and oncogenic potential of malignant astrocytes. Using a computer program that predicts miRNA targets and restricting their search to proteins known to be involved with CSCs, tumorigenesis, and neural stem cells, they concluded that miR-146a most likely interacts with Notch. Cos7 cells that had their Notch1 gene linked with the firefly luciferase gene showed decreasing luminescence as they expressed increasing numbers of miR-146a plasmids. A Western blot subsequently confirmed a decrease in Notch1 when ectopic expression of miR-146a induces gliad marker GFAP and suppresses expression of stem cell markers Sox2 and Nestin. E, miR-146a promotes the survival of tumor-bearing mice by reducing the glioma tumor burden. F, A diagram showing the miR-146a-involved signaling network. (Permission to reprint granted by the American Society for Microbiology (Mei J, Bachoo R, Zhang C-L. MicroRNA-146a Inhibits Glioma Development by Targeting Notch1. Mol Cell Biol. 2011;31(17):3584-3592).
mechanism that counteracts the oncogenic potential of dysregulated signaling pathways. Indeed, miR-146 lies downstream of both the EGFR and PTEN pathways, supporting the idea that it is able to integrate information from various pathways to detect whether they are moving in a pro-tumorigenesis direction and then counteract that trend if necessary. Given this data, it would seem that miR-146a specifically and other miRNAs generally may be an attractive target for future cancer therapies, including those directed against GBM. More broadly, Mei et al’s study further elucidates the role Notch signaling plays in cancer and reinforces the importance of understanding this critical pathway.

**REFERENCES**


**Direct Extracranial to Intracranial Bypass for Stroke Prevention**

In 1969 Yaşargil first described direct extracranial-intracranial (EC-IC) bypass to increase cerebral perfusion. To assess the efficacy of this technique in preventing stroke in patients with athero-occlusive disease, a large multi-center randomized clinical trial was undertaken in 1985. No beneficial effect of surgical intervention was found when comparing the 1377 patients randomized to either surgical or medical therapy. Subgroup analysis failed to demonstrate a beneficial effect of surgery including the 808 patients with carotid artery occlusion.

Limitations of the trial included failure of distinction of etiology of strokes or transient ischemic attacks as being either due to embolic phenomena or hemorrhagic compromise. This could not be assessed through the static imaging of cerebral angiography. Patients with angiographic stenosis may not actually have hemodynamic compromise secondary to adequate collaterals, and EC-IC bypass might provide an additional pathway for emboli. Additionally, the trial included patients with completed infarction. Positron emission tomography (PET) studies have demonstrated that as cerebral blood flow falls, oxygen extraction rises to 100% such that cerebral metabolism becomes flow dependent. This is the optimal hypothesized situation for bypass surgery to increase flow. Once acute infarction has occurred, cerebral oxygen metabolism and arterial oxygen extraction fall to low levels while blood flow paradoxically rises such that surgical intervention to increase cerebral blood flow is ineffective because the tissue is not salvageable and there is no longer low flow.

Over the last 25 years investigators have studied various methods to assess hemodynamic failure. The most common are evaluation of a patient’s dilatation state with an acetazolamide challenge test when coupled with a cerebral blood flow study (Xenon-enhanced CT, TCD, SPECT, IR or MRI). Acetazolamide causes cerebral vasodilator globally increases cerebral blood flow. Vessels that are already maximally dilated are less reactive and show a smaller or no increase in blood flow. In extreme cases, the non-selective global vasodilation can act to decrease the blood flow through the strained vasculature causing a “steal” effect. PET scans may also be used to assess oxygen extraction fraction. When the capacity of vaso-dilation is insufficient, the brain can increase the amount of oxygen extracted from the blood.

Since the publication of the 1985 international bypass study, there have been 3 studies (163 patients) to assess the natural history of patients with altered oxygen extraction measured by PET scan, 16 studies (2320 patients) to assess the natural history of patients with hemodynamic failure assessed through alternative measures, and 23 studies (506 patients) to assess the role of EC-IC bypass in patients with hemodynamic failure. These studies have largely demonstrated significantly increased stroke rates in those patients with significant hemodynamic failure and improved outcomes in patients receiving bypass therapy. These studies had significant limitations including lack of adequate controls, significant publication bias, and primarily surrogate outcome measures (eg, alteration in blood flow) instead of stroke and mortality rates.