See the corresponding editorial and article in this issue, pp 313–322.

# Neurosurgical forum
## Letters to the editor

### Deep brain stimulation interruption and suicidality

To the Editor: In this issue of the *Journal*, Lozano et al. (Lozano AM, Giacobbe P, Hamani C, et al: A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. Clinical article. *J Neurosurg 116:*315–322, February 2012) illustrate the efficacy of deep brain stimulation (DBS) of the subcallosal gyrus in 21 patients with treatment-resistant major depression. Of these 21, 13 patients had at least a 40% improvement in scores on the 17-item Hamilton Depression Rating Scale–17 (HDRS-17) at 1 year. On two occasions, one patient unknowingly experienced deactivation of the implanted pulse generator. The first time deactivation occurred the individual atempted suicide. The second time, which occurred following submission of Lozano and colleagues' article, provoked a depressive relapse with active suicidal thoughts. This is the first report of suicidality prompted by discontinuation of therapeutic DBS of which we are aware.

The patient is a woman in her late 40s who experienced the first onset of depressive symptoms in her mid-30s. She originally presented with low mood with diurnal variation (morning worsening), poor concentration, anhedonia, low energy, loss of appetite, increased need for sleep, and intermittent suicidal ideation. She described prominent comorbid generalized anxiety. She reported a positive family history of both generalized anxiety and obsessive-compulsive disorder (OCD). Medical comorbidities included hypothyroidism, gastroesophageal reflux disease, chronic temporomandibular joint pain, and a history of deep vein thrombosis and pulmonary embolism. Therapeutic interventions over a period of 12 years included pharmacotherapy with multiple agents including selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, monoamine oxidase inhibitors, and atypical antipsychotics. The patient also underwent several courses of electroconvulsive therapy limited by relapses and memory impairment. Group and individual cognitive-behavioral therapy, in addition to long-term supportive therapy, did not provide a sustained antidepressant response. There were multiple suicide attempts by overdose, usually in response to psychosocial stressors, at a frequency of approximately 2 per year.

The patient gave written informed consent to participate in a pilot study of DBS, approved by the Clinical Research Ethics Board of the University of British Columbia. During implantation of the device and intraoperative testing, she reported a lightening of her mood with the electrode contacts in the target region. Over the initial months following initiation of stimulation of the white matter adjacent to the subcallosal gyrus, she exhibited a gradual response, with symptomatic improvement in her depressive symptoms. At a follow-up appointment 6 months after onset of stimulation, her HDRS-17 score had decreased to 40% of her pre-DBS baseline score. In addition, her cognitive-intellectual function appeared to be gradually improving. Eighteen months following the initiation of stimulation, her HDRS-17 score was 13, putting her in the mildly depressed range, which was an improvement of 63% over a baseline score of 35.

Despite her overall improved mood, she still noted suicidal ideation but only in the context of severe psychosocial stressors. For example, on one occasion in the 1st year of stimulation, when overwhelmed by a number of deadlines and in the context of a family conflict, she took an overdose of acetaminophen, ibuprofen, diphenhydramine, dimenhydrinate, and aspirin. Following the resolution of the stressors, she returned to her overall improved mood state within a number of weeks. However, 26 months following the initiation of stimulation, in the absence of any evident psychosocial stressors, she was taken to the emergency department following an overdose of 250 tablets of clonazepam. One week prior she had seen her regular psychiatrist who noted continual progress with regard to her mood, coping mechanisms, and overall functioning. Five days after the overdose, when the patient's implantable pulse generator for the DBS was assessed, battery depletion was registered and the device was off. Her depressive symptoms improved within 2 weeks of an expedited battery replacement.

Fifty-six months following the initiation of stimulation, the patient was shopping at a store with a magnetic theft detection device. She experienced a rapid mood deterioration characterized by a loss of motivation, social isolation and avoidance, and increased abdominal discomfort, with no significant change in her neurovegetative functioning or any notable increase in anxiety. She became actively suicidal for the first time in many months. She interrogated her device and found it to be deactivated. Her mood stabilized within 24 hours of her reactivating the device.

The first study demonstrating the efficacy of DBS in treating refractory depression reported that 4 of 6 patients experienced clinical benefit at 6 months following initiation of DBS of the subcallosal gyrus.[4] The investigators attempted, with consent, a blinded discontinuation of stimulation in one patient who then had a subsequent relapse in depressive symptomatology, including a loss of energy and initiative and impaired concentration, which was reversed within 48 hours of reactivation. Similarly, 6 patients receiving DBS of the anterior limb of the internal capsule for refractory OCD disclosed rapid moderate clinical worsening in depressive symptoms while unaware of stimulator battery depletion.[2] Symptom reversal coincided with resumption of stimulation. Finally, in

a patient in whom benefit was reported with DBS of the ventral caudate nucleus for OCD and depression, worsening of his obsessive-compulsive symptomatology and functionality occurred after his pulse generator battery unknowingly failed. Somatic preoccupations and checking compulsions were reported to stabilize 3 months after replacement of the battery.[1]

Controlled studies will be necessary to rigorously demonstrate the efficacy of DBS of the white matter adjacent to the subcallosal gyrus in the treatment of refractory depressive illness. Although we cannot rule out spontaneous worsening of depression, this case offers indirect supportive evidence of the therapeutic effects of subcallosal stimulation reported in the multicenter pilot study in this issue. This patient's unique experiences remind us that, in a population highly susceptible to suicide, it is prudent to regularly and carefully monitor stimulation status. For most cases of DBS used in the treatment of psychiatric conditions, the available data suggest that loss of benefit from pulse generator failure is rapid. Because these individuals are vulnerable to suicidal ideation and self-injurious behavior, a deactivation of the pulse generator, similar to that seen in movement disorders,[3] should be considered a medical emergency.

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## Low-grade gliomas

To The Editor: The interesting retrospective study of Chang and colleagues[2] (Chang EF, Clark A, Smith JS, et al: Functional mapping–guided resection of low-grade gliomas in eloquent areas of the brain: improvement of long-term survival. Clinical article. *J Neurosurg 114:*566–573, March 2011) indicates that functional intraoperative mapping methods may help to identify low-grade gliomas potentially accessible via gross-total resection. In some cases the authors assumed a not-completely-resectable tumor preoperatively and then realized intraoperatively via a functional mapping technique that the tumor was resectable. The variable resectability, as defined by preoperative imaging and/or intraoperative mapping, turned out to be of favorable prognostic influence; that is, patients with resectable tumors fared better in terms of progression-free survival and duration of survival. A finding like this may help to improve classification, prognostic evaluation, and management strategies of a highly heterogeneous disease and should therefore be considered in prognostic models beside other clinical and molecular-genetic covariates. It might be tempting to assume—as suggested in the accompanying editorial by Sampson[4]—that the described prognostic impact of resectability promotes a concept of aggressive resection for all low-grade gliomas. An attempt in this direction, however, is based on a misinterpretation of the data of Chang and colleagues.[2] Resectable tumors are more likely to be anatomically circumscribed, of small size, and located in less eloquent regions, and they might behave in a different manner biologically. They should not be confused with their counterparts, for example, tumors growing diffusely along U-fibers, infiltrating several regions of a hemisphere including eloquent ones. Notably, only 153 of 281 gliomas surgically treated in the series turned out to be resectable gliomas.[2] Given the fact that the median relative extent of resection was only in the range of 30%–60% in the poor prognosis group (as compared with > 90% in the resectable group), one might question the concept of microsurgical volume reduction in terms of the efficacy and risk of the applied procedure. Indeed, histological and molecular-genetic classification could be determined in these patients by partial open tumor resection—although small anaplastic foci might be missed even then unless detected and localized beforehand by sophisticated imaging procedures. However, a similar or even better classification and characterization of these lesions with their complex locations and compositions might be achieved using a minimally invasive molecular stereotactic biopsy technique (as demonstrated previously).[3,5] Thus, inspired by the data of Chang and colleagues,[2] we consider any scientific attempt extremely

useful in elucidating the role of biopsy versus open tumor resection in patients not suitable for complete lesion resection. The evaluation of this reasonable question could be done within the framework of a prospective randomized trial.

From the perspective of further prospective studies on this issue, the data of Chang and colleagues[2] need to be updated. Regrettably, follow-up of the study population was surprisingly short, incomplete, or simply not done for a considerable number of patients. Effects of response bias (those with a favorable outcome are more likely to respond to mail surveys used for follow-up) might have contributed to the extremely favorable outcome scores, particularly for those with resectable tumors. Outcome data turned out to be much better than could be expected from previously published adjusted long-term survival analyses.[1]

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**Disclosure**

The authors report no conflict of interest.

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Response: We thank Drs. Kreth, Thon, and Tonn for their interest in our paper, in which we showed that "presumed eloquence" of low-grade gliomas is an important prognostic factor for long-term survival. More importantly, however, intraoperative mapping was found to mitigate the risks of presumed eloquence by determining which tumors were truly eloquent, and thereby facilitating the maximal extent of resection. While our results promote an aggressive resective approach, Kreth et al. instead advocate for a minimally invasive molecular stereotactic biopsy approach.[6]

While using advanced imaging to guide targeted biopsies might improve the accuracy of pathological diagnosis compared with standard biopsy approaches, the central question posed is whether additional resection in high-risk patients confers better long-term survival outcomes. Our experience, along with that of many others now, has demonstrated a clear benefit to aggressive cytoreductive debulking of low-grade gliomas when it can be performed safely.[1,4,5] The preponderance of data now strongly demonstrates that patients undergoing small subtotal resections or biopsies have significantly lower survival estimates. Unfortunately, many poorer outcomes with biopsies could have been averted with mapping to safely facilitate greater resections. Furthermore, biopsies performed in high-risk eloquent areas certainly can be associated with significant morbidity if the functional organization of the sampled areas is not well understood.

Given the current existing data, in our opinion, equipoise does not exist for a randomized controlled trial comparing biopsy and resection. There are no equivalent data in the modern era of MR imaging (including retrospective case series) supporting biopsies with respect to optimal long-term outcomes. There is no theoretical or empiric advantage of a limited approach when both approaches can be performed safely.

With regard to our follow-up data, one needs to take into consideration the large number of patients that was used to power our statistics (281 patients). Using time-dependent analyses with censoring for patients lost to follow-up (Kaplan-Meier), we could minimize the effects of varying follow-up periods (the median follow-up period was more than 5 years). Nonetheless, all retrospective studies do have limitations with regard to bias, as pointed out in our paper.

We recently compared our experience with that of three other major referral centers. In that study, we showed that outcomes across institutions were quite similar when patients were stratified according to the University of California at San Francisco Low-Grade Glioma Prognostic Scoring System (Karnofsky Performance Scale Score ≤ 80, age > 50 years, lesion diameter > 4 cm, and eloquence).[2,3] This was validated as a simple and highly reliable scoring system for prognosticating long-term outcomes, which was quite interesting considering that modern molecular assays were not included. That being said, we agree that more prospective studies will improve our understanding of how specific factors influence long-term survival estimates.

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**Disclosure**

The authors report no conflict of interest.

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## Retinoblastoma

*Make things as simple as possible, but not simpler.*

Albert Einstein

To The Editor: We read with interest the article from Peterson et al. (Peterson EC, Elhammady MS, Quintero-Wolfe S, et al: Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: initial experience with 17 tumors. Clinical article. *J Neurosurg 114:*1603–1608, June 2011). We congratulate the authors on their technical successes and limited extraocular complications. They have also achieved good immediate globe salvage, although the small number of patients and short-term follow-up limit the significance of their results.

Our center initiated intraarterial chemotherapy for advanced intraocular retinoblastoma in the US in 2006. We have performed more than 400 intraarterial chemotherapy treatments in 129 eyes with a follow-up of more than 4.5 years.[1–4,6–8] Our initial goal was globe salvage, but the initial good results encouraged us to aim for the preservation (or restoration) of vision and minimization of the side effects of treatment as well as tumor control and globe retention.

Peterson et al. use the technique that we described in 2006.[1] Our current technique differs: instead of placing a 4 Fr femoral sheath and 4 Fr guide catheter in the carotid artery for guiding the 1.5 Fr microcatheter to the ostium of the ophthalmic artery, we do not use a guide catheter. Instead, we perform catheterization of the ophthalmic artery directly with the microcatheter, from the femoral sheath to the ophthalmic artery. This technical variation minimizes the size of the catheter placed into the internal carotid artery and allows the size of the femoral sheath to be decreased to 3 Fr, which makes the procedure more amenable to young children. We have also used an alternative method of delivering the therapeutic agent to the ophthalmic delivery through the orbital anastomosis with the middle meningeal artery and have used the Japanese balloon technique when necessary.[6]

With intraarterial chemotherapy, the amount of drug delivered to the tumor and surrounding tissues depends on multiple factors, including the size of the arterial territory, which varies greatly as a function of the angioanatomy; the intravascular drug concentration; the capillary transit time; and the passive and active membrane transport—both influx and efflux—mechanisms.[5] We attempt to take all of these factors into account when determining the dosage for intraarterial chemotherapy. We choose the initial dose according to eye size (which grows from birth until the age of approximately 3 years) and angioanatomy of the ophthalmic artery. Then, we systematically use the electroretinogram to judge the toxicity of the previous cycle of chemotherapy and adjust the dose of the next cycle accordingly.[4,6] The electroretinogram quantifies the electrical activity of the retina, and although it is not a perfect surrogate for later measurements of visual acuity, it is the easiest way to repeatedly assess visual function in young children who are not amenable to formal acuity testing.

For all of these reasons, we caution readers against the one-size-fits-all approach of the uniform dose of 7.5 mg of melphalan proposed by the authors. In our experience, 7.5 mg of melphalan can be safely given only to older children (older than 3 years), when the ophthalmic artery had large extraocular branches; this dose is otherwise retinotoxic (and causes significant electroretinogram decrements), especially following radiation therapy. Furthermore, we have encountered significant hematological complications when a dose of melphalan exceeding 0.5 mg/kg is given, and we would expect a dose of 7.5 mg to be toxic (neutropenia) in children weighing < 15 kg.

We also caution against the hope that only 1 cycle of intraarterial chemotherapy will adequately treat an eye with advanced retinoblastoma. In our extensive experience with long-term follow-up, 1 cycle was the exception, not the rule, and should not be the goal of therapy. The number of treatment cycles required for tumor control varies among individuals, and in our hands at least, 3 cycles of intraarterial treatment have usually been necessary.

Vitreous hemorrhage rarely occurs as a complication of retinoblastoma unless radiation is used as part of the treatment regimen. We are surprised by the high rate of vitreous hemorrhage reported by the authors. All 4 vitreous hemorrhages reported led to enucleation. These 4 hemorrhages occurred among the 9 eyes that were retreated with a second cycle of intraarterial melphalan at a dose of 7.5 mg, resulting in a very high complication rate (44%) in this cohort. On the other hand, using the dosage algorithm we developed,[6] we have been able to perform multiple treatment cycles to achieve tumor control while preserving electroretinographic retinal activity, and we have seen this complication in only 3% of eyes.

We think that a uniform regimen of 1—or 2—cycles of intraarterial chemotherapy at a high dose may not be optimal and may carry a high risk of adverse vascular events. We think that the initial dose of intraarterial chemotherapy should be individualized and that further

cycles should be adjusted according to observed tumor response and retinal toxicity.

Intraarterial chemotherapy is a powerful but still novel treatment for retinoblastoma, and we look forward to future investigations from this group and others who will help to identify more potent and less toxic regimens, a better understanding of the optimal dosage and cycle intervals, and the role of combining intraarterial chemotherapy with local therapies such as laser treatment and cryoablation.

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Response: We appreciate the interest of Gobin et al. in our recent description of 15 children treated with selective ophthalmic artery infusion of melphalan chemotherapy (intraarterial chemotherapy [IAC]) for the management of advanced retinoblastoma. This pioneering work, originally described by the Japanese group including Kaneko and Yamane,[9] has revolutionized our approach to advanced intraocular retinoblastoma. Our clinical ocular oncology service and ocular oncology laboratory have been focused on targeted treatment for retinoblastoma aimed at eliminating systemic toxicity risk while enhancing local tumor control. This approach has led our research team to evaluate periocular chemotherapy delivery (including juxtascleral and intravitreal chemotherapy).[4,5] Currently, the Children's Oncology Group (COG) is evaluating systemic chemotherapy with local injection of supplemental juxtascleral carboplatin to achieve enhanced tumor control in advanced retinoblastoma (COG protocol).

In contrast to Gobin et al., we directed our initial exploration of IAC to children with advanced retinoblastoma, specifically those having progressive clinical disease despite being exhaustively treated with systemic 4-drug chemotherapy (carboplatin, vincristine, etoposide, and cyclosporine) and aggressive local laser, and thus scheduled for enucleation surgery. Nine children were treated with melphalan dosing between 5 and 7.5 mg. The dose in those requiring retreatment was escalated to 7.5 mg with the next IAC treatment. Virtually all children in the series received 7.5-mg melphalan dosing either primarily or in secondary retreatment. Remarkably, the globe salvage rate in eyes scheduled for removal was 76.5%. Notably, all eyes requiring enucleation were initially treated with a lower dose, typically < 5 mg of melphalan. Finally, orbital vascular alterations were documented in eyes that had been treated using combinations of systemic chemotherapy with either focal carboplatin chemotherapy or external beam radiotherapy.[1,7] These vascular alterations, we believe, may decrease intraocular delivery of melphalan during IAC.[8]

With these data in mind, we strongly recommend targeted treatment seeking an ocular delivery dose between 5 and 7.5 mg of melphalan. Currently, for "salvage" therapy we begin with IAC at 7.5 mg of melphalan. In eyes undergoing upfront IAC or those with a lower tumor burden, we are now using 5 mg of melphalan delivered via 3 planned repetitive therapies at 4-week intervals. Currently, the COG is initiating a multicentered clinical trial to evaluate IAC in advanced retinoblastoma. The proposed protocol will utilize IAC of 5 mg of melphalan delivered in 3 planned treatments and will incorporate local tumor laser consolidation in treating children 2 years of age or older (Chintagumpala et al., COG, 2011). We continue to focus on minimizing any treatment-related radiation exposure (including fluoroscopy). Further, in these patients, as in our systemically treated children, all tumors are evaluated pre-IAC treatment and receive intraoperative indirect laser tumor therapy as a consolidation to improve local tumor control.

As regards Gobin and colleagues' concerns about the systemic effects of the chemotherapy, interestingly, our experience has revealed a unique profile of IAC treatment-related events that differ significantly from those seen with systemic chemotherapy, periocular chemotherapy, or external beam radiotherapy. From our series and others' (Bianciotto and Muen, personal communication,

2010), we believe that, with the exception of neutropenia, treatment issues do not appear to be agent- (melphalan) or dose- (5–7.5 mg) dependent but instead appear related to the procedure itself. These complications include vitreous hemorrhage, Purtscher-like retinopathy, retinal/choroidal embolization, orbital inflammation including myositis, and optic neuropathy. These complications are in addition to those previously reported by Marr et al.[6] to include periocular erythema and ciliary madarosis. In our initial series of 4 eyes failing therapy and undergoing enucleation after IAC, all eyes exhibited histopathological confirmation of viable retinoblastoma, vitreous hemorrhage, and vitreous tumor seeding. No eye showed evidence of vasoocclusion or vasoobliteration of the ocular vasculature.

Currently, we are beginning to utilize a novel approach that delivers relatively targeted, high-dose chemotherapy to the involved eye(s) of children with retinoblastoma. This therapy, like all treatments before, requires an understanding of the unique anatomy of the eye, the pathophysiology of retinoblastoma, and the balance between risk and benefit. This editorial highlights the difficulties in managing a "rare" disease in which the initial evaluation of drug, dose, and delivery schedule is begun in patients. Our laboratory is finalizing studies that will directly address the evaluation of IAC as regards drug, dose, and delivery selection by using the murine transgenic model of retinoblastoma.[2,3] These data will ultimately establish a framework for ongoing clinical discussions to enhance the utilization of IAC in children with retinoblastoma. We thank Gobin et al. for their pioneering work and look forward to multicentered collaborations (such as the COG trial) to assist in bringing world-class care to children with this life- and vision-threatening disease.

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## Normal pressure hydrocephalus

To The Editor: We read with interest the article by Gupta and Lang (Gupta A, Lang AE: Potential placebo effect in assessing idiopathic normal pressure hydrocephalus. Case report. *J Neurosurg 114:*1428–1431, May 2011)[3] and editorial by Roberto Heros (Heros H: Editorial. Normal pressure hydrocephalus. *J Neurosurg 114:*1426–1427, May 2011). Drs. Gupta and Lang should rightfully be circumspect concerning potential candidates for ventriculoperitoneal shunt (VPS) placement for idiopathic normal pressure hydrocephalus (INPH), and their observation of the placebo effect should be taken as a cautionary note. We have seen the corollary to this in the patient who has undergone VPS placement and about whom family members (and sometimes the patient) say the patient is "better," but objective testing of mental status and gait are unchanged. As emphasized by Gupta and Lang, VPS placement is not a benign procedure:[4] it has a costly and frequent revision rate and a highly variable success rate, regardless of the screening procedures performed. Unlike Dr. Heros, we do not accept the diagnosis of INPH until we complete a more detailed evaluation to determine if the patient is a candidate for endoscopic third ventriculostomy (ETV)[2,4] instead of a VPS. In all patients referred with a diagnosis of hydrocephalus, we seek to establish the possible causation of their enlarged ventricular systems; the possible causes include unrecognized aqueductal stenosis and abnormalities in cisternal flow dynamics. A large-volume lumber puncture is performed frequently, but the findings are interpreted with caution. In addition,

we have performed brain biopsy at the time of VPS placement in patients with even moderate dementia and have found Alzheimer disease. This avoids future revisions when deterioration occurs later on and investigation indicates a nonfunctioning VPS. The cost and complication rates of VPS placement are significant,[5] and, as the population ages, both will probably increase. Adult hydrocephalus has proven to be much more complex than previously thought and causation may overlap with the effects of cerebral blood flow, cisternal CSF flow, CSF translocation dynamics, and the physics of cerebral ventricular wall movement.[1,6,7] The high-volume lumbar puncture is only one modality of evaluation in adult hydrocephalus and needs to be interpreted carefully, but ultimately, the more sophisticated analysis of CSF flow dynamics will yield the best insight into which adult patients will respond to VPS placement or, as an alternative, ETV.

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