Clinical data simplified

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Kane and colleagues 12 scoured the electronically catalogued literature to teach us about a rare and controversial entity—the extraventricular neurocytoma (EVN). They discovered information on 85 patients in a total of 35 published articles. They subclassified EVNs as typical or atypical, with atypical lesions having an MIB-1 index of greater than 3% or frequent mitoses, vascular proliferation, or necrosis. Their review suggests that patients with EVN who are greater than or equal to 50 years of age or those harboring atypical lesions had increased rates of recurrence and mortality at 5 years. While this report provides a good review of current literature on this rare and relatively new entity, it also highlights some of the challenges faced in trying to better understand the prognosis and optimal treatment for rare (or more common) disease states by using published literature.

Extraventricular neurocytomas were first defined as a separate entity in the 2007 WHO classification. 14 There has been controversy surrounding this entity over the past decade, however, and its definition has been hotly debated. 1 The lesions are characterized as well-circumscribed, contrast-enhancing masses, often with a cyst and a mural nodule. Histologically, although EVNs resemble the typical neurocytoma, they are more complex, less cellular, and more likely to contain ganglion cells. 1 Importantly, they are difficult to distinguish from more common entities, such as oligodendrogliomas, but also are more rare, with different prognoses and treatment strategies, including clear cell ependymoma, dysembryoplastic neuroepithelial tumor, neurrolipocytoma, and the various other glial-neuronal entities, including cerebral neuroblastoma with maturation. 9 While Kane and colleagues 12 have done a careful and thorough review of the literature, it would have been quite difficult for them to differentiate between these various other entities, given the amount of information that can be lost when patient data is transmitted in the form of publications and the changing definition of this entity over time.

Selection and publication biases may also have affected the authors’ results and conclusions. Selection bias can be defined as a nonrandom sample error of a population that confounds study results and undermines the external validity of a study. In the current study, patients may have been systematically selected for a given treatment based on their disease characteristics, severity of illness, or other factors, and thus, this process may lead to an erroneous association between the treatment and a given outcome. Similarly, another form of selection bias can affect findings when there is unequal follow-up of all subjects due to early termination or attrition. In this context, results may be positively biased if patients are followed up only to a desired outcome, such as tumor response, and then reported on. Alternatively, patients who die of their tumors or are less likely to attend follow-up due to a lack of new tumor-related symptoms may negatively bias study conclusions. There is no doubt that these factors influence what data are available when we review the literature.

Publication bias, however, is generally thought to relate to the tendency of authors and journal editors to differentially submit and accept positive experimental results relative to negative reports. This could include such studies being more likely to be published, published rapidly, published in English, published more than once, and more often cited by others. Research has demonstrated that the studies with positive results are not superior methodologically to those with negative results, 7 and yet are 3 times more likely to be published. 4 This is particularly true of small and nonrandomized clinical case series because of their high susceptibility to systematic error and bias. 7 Such results can then be amplified when several outcomes in this collected patient population are measured and results are reported without an a priori hypothesis being generated. 7 While initial reports such as the one by Kane et al. 12 should not be criticized for such approaches because their work is intentionally exploratory, their conclusions will need to be validated by subsequent analyses that confirm their findings.

While retrospective reviews such as that provided by Kane et al. 12 and guidelines based on expert consensus certainly have value and can inform clinical practice in the absence of other information, increasingly we will be required to perform coordinated clinical investigations to support our therapeutic decision making. Randomized controlled trials (RCTs) are still seen as the gold standard for evidence-based medicine as they can eliminate
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treatment selection bias if well conducted and adequately powered. However, current-day RCTs can also be expensive and challenging to conduct. Such studies are increasingly plagued by regulatory redundancy and excessive data collection and monitoring that slow enrollment and drive up costs. These costs and regulatory hassles have diminished health care systems’ desire to participate in clinical studies if they feel they will affect their practice efficiency. As such, for most studies, a small number of sites enroll the majority of patients, and a large percentage of sites, even those that acquire institutional review board approval, never enroll patients. Moreover, delays related to institutional review board approval or financial contracts and institutional risk aversion have amplified these shortcomings, both for company-sponsored trials and National Cancer Institute–funded cooperative groups. Finally, most of these trials are funded for a single purpose, which results in the repetitive creation and disassembly of the operational infrastructure for such trials. This has dramatically escalated the expense of these trials, made them overly burdensome, reduced enthusiasm for participation, and left us with results that are usually not generalizable to the patients we see every day.

Clinical research doesn’t have to be that hard. Some very simple clinical studies have led to some elegant results, and this tradition dates back to James Lind’s studies on scurvy in the 1700s. Lind performed one of the first prospective and placebo-controlled trials when he investigated the effect of citrus fruits on scurvy. He enrolled only 12 sailors, which he divided among an amazing and ill-advised 6 groups. (Of note, despite his dramatic findings, many of his recommendations took more than 4 decades to be accepted and implemented into routine practice as a result of forceful expert opinion that scurvy was due to putrefaction and could be treated by antiseptic alkaline salts.) While many of the treatments we will investigate will require a larger sample size than Lind’s, the procedural aspects of clinical trials can be simplified and made more practical. In the 1950s, for example, the efficacy of the poliovirus vaccine was demonstrated by such a “practical” trial. This approach has been leveraged by our cardiovascular colleagues, where large trials could be staged as a result of their simplicity and lead to robust information regarding the use of intravenous streptokinase (GISSI), tissue plasminogen activator (GUSTO), and β-blocker treatment in acute myocardial infarction (ISIS). These trials quickly enrolled thousands to tens of thousands of patients with simple randomization schemes and used very simple entry criteria and short data collection forms to address specific but important questions in the context of routine clinical care.

Similarly, clinical registries could help inform our knowledge base, particularly for rare conditions such as EVNs. While many institutions currently expend resources to track patient treatment and outcome data prospectively, these databases are often small and fail to be hypothesis driven. Organizing these databases into a national and international system designed around simple questions could be an important tool for disease study. The evidence derived from these registries could be even more powerful and definitive if augmented by simple randomization strategies for treatment selection. If such strategies were widely adopted in neurosurgery, our field could advance in as rapid a manner as has been seen in infectious disease or cardiovascular disease.

The National Neurosurgery Quality and Outcomes Database (NQOD), sponsored by the American Association of Neurological Surgeons, may just be the right idea to make this happen. Set to launch this fall, NQOD, will provide a national web-based network for any neurosurgery practice to collect and share a multitude of data on pathology, treatment, quality, cost, and outcomes. The primary aim of this data network is to generate national risk-adjusted benchmarks of quality and effectiveness, as well as to objectively demonstrate the value of care we provide. Nevertheless, NQOD will also facilitate collaborations between participating centers for comparative effectiveness research on a scale much larger than achievable in RCTs. This alternative will provide a more feasible, less costly opportunity to address many pressing hypothesis-driven investigations in the setting of real-world health services delivery.

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