Intraneural ganglion

To The Editor: The recent report of a so-called hypoglossal intraneural cyst by Nonaka et al. is a remarkable one (Nonaka Y, Grossi PM, Filomena CA, et al: Unilateral hypoglossal nerve palsy caused by an intraneural ganglion cyst. Case report. J Neurosurg 113:380–383, August, 2010). Nonaka et al. did not identify a joint connection. They found the tumor “to originate from the hypoglossal canal” (a site without synovium), concluding that the “tumor originated from the hypoglossal nerve rather than the atlantooccipital joint.” They proposed a different mechanism for the formation of their case, one contrary to the unifying articular (synovial) theory. Their paper suggests to us 2 viable explanations: 1) this case would be the first bona fide exception to the articular (synovial) theory, or 2) it follows the rule.

We are grateful to these authors for sharing the complete set of MR images with us after their publication in an effort to not only promote but also advance science. The 2 axial preoperative images immediately caudal to the 1 published figure (selected to demonstrate the mass effect by the cyst) show a joint connection: a small tail can be traced to the medial aspect of the atlantooccipital joint (Fig. 1). The limitations of this imaging study (5-mm slices with a 2.5-mm interslice gap at 1.5 T) make the lack of recognition of this cyst’s subtle caudal extension understandable both on prospective and retrospective review.

Recently we extrapolated the principles of the articular theory from the appendicular skeleton to the axial spine, demonstrating its versatility in explaining extraneural and intraneural cysts. We had previously excluded hypoglossal cysts from our analysis of juxtafacet cysts due to the difficulty of confirming the specifics about previous cases—namely, the intraneural or extraneural nature of these cysts was not always substantiated, remained in doubt, or was controversial. In fact, the previous examples of hypoglossal cysts included in the paper by Nonaka et al. have all been shown or presumed to have an atlantooccipital joint connection. That juxtafacet cysts develop on occasion at the craniovertebral junction appears to be no surprise because both the atlantooccipital joint and atlantoaxial joint are synovial joints; nor is their potential for compression of neighboring nerves (including the hypoglossal nerve) or the spinal cord unanticipated.

The articular connection now established in the case published by Nonaka et al. solidifies the explanation for the formation of these cysts. Unfortunately, the imaging parameters are not detailed enough to allow us to delineate the propagation. Creativity and finesse will be needed to explain an intraneural occurrence: as the hypoglossal nerve, a pure motor nerve, does not have an articular branch to the upper cervical spine, an immediate explanation is not available. We previously postulated that the ansa cervicalis could provide the answer to the link between the hypoglossal and the C-1 and C-2 nerves, a neural communication that could explain the anatomy and perhaps the pathology. Further investigations with high-resolution thin-slice images will undoubtedly unveil the propagation patterns in future patients with this rare condition.

The case presented by Nonaka et al. illustrates the difficulty, even for master surgeons, to establish the diagnosis of an atypical juxtafacet cyst and to identify its joint connection, either preoperatively on imaging or at operation, when it occurs in an unusual location. Just as the cyst itself was originally not identified 7 years earlier when it measured 3–4 mm, the pedicle of these cysts is often small (measuring only 1 mm in this case) and can

Fig. 1. Preoperative axial T2-weighted MR images. Panel D is from the original paper by Nonaka et al. (Fig. 2 in original paper). Panels A and C are immediately caudal to the figure in panel D. Panel B is an enlargement of the slice in panel A. The asterisks on slices C and D indicate the index cyst that was surgically removed. The arrow on slice A demonstrates a focus of increased T2 signal that is the caudal extension of the cyst, which is intimately associated with the posterior aspect of the atlantooccipital articulation; this small tail can be traced on image C (arrow) to the reported image D (asterisk). Panel D is modified with permission from Nonaka et al.: J Neurosurg 113:380–383, 2010.
easily be missed. Likewise, this case illustrates the ease of claiming that the articular theory does not apply without providing definitive evidence to disprove it.

Understanding the pathogenesis of these cysts provides insight into how best to treat the pathology. We are learning that in intraneural and extraneural ganglia the joint is the primary problem; the cyst, which is the secondary problem, and often the more imminent one, need not always be directly addressed if the primary problem is adequately treated. We also know that incorrectly treated, these cysts can recur at alarming rates. Only through such collaborations will we be able to further elucidate the mechanisms and solve these types of clinically relevant problems.

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References


RESPONSE: We thank Dr. Spinner and his coworkers for their comments. We are very much aware of their elegant work defining the origin of ganglion cysts in the peripheral nerves. In most cases, the affected nerve has a branch to an adjacent joint. Their papers were very much on our minds when we discovered the cyst at the time of surgery. Because we did not expose the entire nerve from its intracranial origin through its extracranial course, we can not say with certainty that there was not an imperceptible stalk that traveled from the joint along the nerve and then blossomed in the proximal hypoglossal canal. On dissecting the cyst from the fascicles of the hypoglossal canal and the hypoglossal nerve no such stalk was noted (Figs. 1 and 2).

The application of Dr. Spinner’s theory to this case is significant. If Dr. Spinner’s theory is correct, the cyst should recur as the connection with the joint’s synovium is still intact. We know, as does Dr. Spinner, of a description of an articular branch from the hypoglossal nerve to the atlantooccipital joint. The possibility of an ectopic synovial cyst can not be ruled out in this case.

Fig. 1. The inferior portion of the tumor was adherent with the fascicle of the hypoglossal nerve (asterisk). PICA = posterior inferior cerebellar artery. XI = cranial nerve XI.

Fig. 2. Illustration demonstrating the relationship between the tumor and surrounding structures. The tumor was located at the level of the hypoglossal canal with compression of the hypoglossal nerve downward. A-O joint = atlantooccipital joint. Modified with permission from Fukushima T: Manual of Skull Base Dissection, ed. 2. AF-Neurovideo, 2004.
rate of oxygen (CMRO$_2$), and cerebral interstitial levels of related to cerebral energy metabolism: intracranial pressure of oxygen (PO$_2$) level remained significantly elevated in the HBO$_2$ group for more than 5 hours after therapy—an effect not observed in the other 2 groups. Hyperbaric oxygen therapy increases the amount of physically dissolved oxygen in the blood and it is highly unlikely that this effect remains for several hours after therapy. It is known that the brain tissue PO$_2$ primarily reflects the product of CBF and arteriovenous oxygen tension difference. Since in the present study a significant increase in CBV was obtained in the HBO$_2$ group—but not in the 2 other groups—the lasting increase in brain tissue PO$_2$ probably reflects the changes in CBF. Changes in CBF might be explained by variations in sedation and/or stress level as discussed above.

Most of the data discussed previously were deduced from the information presented in Table 4 and Figs. 1 and 3. Our calculated data differ markedly from the percentage changes given in the text. In the text we are informed that CMRO$_2$ increased by 32% and that the L/P ratio decreased by 10% in the HBO$_2$ group when compared with the control group. As far as we can see, the percentage changes in CMRO$_2$ were obtained by adding the percentage increase in the HBO$_2$ group (25%) and the decrease in the control group (7%), and in the L/P ratio were obtained by adding the decrease in the HBO$_2$ group (6%) and the increase in the control group (~3%). In our opinion, presentation of original data in this way is confusing and misleading.

In an editorial$^1$ in the same issue of the Journal of Neurosurgery the article by Rockswold et al. was highly praised, and the editorial’s author stated the study documented that HBO$_2$, 1) substantially changed brain neurochemistry, 2) significantly reduced ICP, 3) reduced extracellular lactate level, 4) increased CMRO$_2$, and 5) decreased the L/P ratio. For the reasons given above we do not agree with any of these statements. We agree that HBO$_2$ therapy may be of interest for intensive care, especially in patients with areas of brain tissue seriously at risk, for example, pericontusional tissue. Whether HBO$_2$ therapy has a substantial effect in these areas remains to be elucidated and we appreciate the magnitude of effort by Rockswold and colleagues in completing this very difficult investigation. However, a major clinical enterprise

Reference

like HBO2 therapy for patients with severe brain trauma must be based on very solid data. The present study unfortunately represents an overinterpretation of minor physiological and biochemical changes.

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References

RESPONSE: We appreciate Drs. Nielsen’s and Nordström’s interest in our study and the opportunity to respond to their concerns.

We agree with the criticism that adding the percentage increase in the HBO2 group (25%) and the decrease in the control group (7%) was “confusing and misleading.” Because the treatment effect of HBO2, improved CMRO2, and over the same time period CMRO2 decreased in the control group, adding the percentages of change is a meaningful, simple, and intuitive way to present the observed treatment difference. The graph is simply a representation of the raw data, and the conclusions are based on the solid statistical model that takes into account the longitudinal nature of the data. In Fig. 1, the changes in CMRO2 from pretreatment to posttreatment for all treatment groups were shown. The information is complete and the presentation is not misleading.

Nielsen and Nordström state that the “brain tissue PO2 primarily reflects the product of CBF and arteriovenous oxygen tension difference.” They further state, “Since in the present study a significant increase in CBF was obtained in the HBO2—but not in the other 2 groups—the lasting increase in brain tissue PO2 probably reflects the changes in CBF.” We would agree with the statement with the addition that it is actually the increase in CMRO2 that is important, as CBF and CMRO2 are metabolically linked. Cerebral blood flow increased in response to improvement in mitochondrial function and oxidative metabolism as the arteriovenous differences in oxygen remained relatively constant during the study period. Nielsen and Nordström state, “Changes in CBF might be explained by variations in sedation and/or stress level as discussed above.” In actuality, great effort was made to have a uniform protocol for standard treatment between the patient groups. Patient sedation and/or stress level should be the same among groups.

Another important finding of this study was a persistent significant reduction in the microdialysate L/P ratio following HBO2 therapy with a smaller effect produced by NBH. Nielsen and Nordström state that the control group had a microdialysate L/P ratio that was normal (26.5). We disagree that 26.5 is a normal value. In patients with severe brain trauma, Engström et al. found a microdialysate L/P ratio of 19 ± 0.2 in ipsilateral normal tissue and 20 ± 0.3 in contralateral normal tissue to a contusion. The authors state that the baseline difference among the 3 groups was significantly different when comparing the HBO2 and the control group. The treatment effect was measured by post-/pretreatment ratio that corrects for any difference in baseline measurements. The baseline difference might affect the degree of treatment effect, but the microdialysate L/P ratio decreased in the HBO2 group and increased in the control group. That should not be caused by the baseline differences. The authors state that the decrease in the microdialysate L/P ratio obtained in the HBO2 and NBH groups is often observed in TBI patients in the absence of any specific oxygen therapy. That may be true, but we were comparing changes between treatment groups, not testing changes over time.

Nielson and Nordström point out that the change in the ICP values was relatively small in terms of the raw data, with which we agree. The analysis included patients who had relatively normal ICP as well as those with intracranial hypertension. In our previous work we have seen the largest reductions in ICP using HBO2 in patients with elevated ICP (> 15 mm Hg). In retrospect, a statistical analysis should have been performed using only patients with elevated ICP.

We agree with the statement, “a major clinical enterprise like HBO2 therapy for patients with severe brain trauma must be based on very solid data.” The data is solid. It was collected prospectively from 3 groups of patients treated with the same clinical protocol. Mixed-effects linear modeling was used to test differences between the treatment arms as well as changes from pretreatment to posttreatment in this study. The mixed-effects model controls for the interrelatedness of sequential hourly values within each subject. Statistical methods used were the
most rigorous and appropriate available for the nature of the investigation. Our results are based on solid data and the appropriate statistical modeling.

It is important that this clinical investigation not be taken in isolation but rather in the context of previous preclinical and clinical work on hyperoxia. We would refer the readers to the extensive bibliography quoted in our article. Also, the findings in this study that indicate improved oxidative metabolism—that is, improved CMRO₂, CBF, microdialysate L/P ratio, and brain tissue PO₂, as well as decreased levels of CSF and microdialysate lactate—must be taken as a whole. To our knowledge, HBO₂ is the first therapy that has consistently improved oxidative cerebral metabolism for an extended period of time following treatment. In addition, HBO₂ is not only effective in the early hours following injury but for many days following injury. In multiple animal TBI models, as well as multiple clinical investigations, HBO₂ has consistently reduced intracranial hypertension. Our finding that a brain tissue PO₂ greater than 200 mm Hg was required to produce a significantly more robust effect in oxidative cerebral metabolism is an important finding. Achieving this level of brain tissue PO₂ will be important in future trials. We conclude that this clinical investigation was a significant contribution to the literature regarding oxygen and cerebral metabolism and provides important preliminary data for a multicenter clinical trial.

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that hypofractionated SRS has minimized the incidence of morbidity while maintaining an excellent local control rate and minimizing medicolegal risk. Even though GKS displayed a marvelous local tumor control rate of 99% at 3 years, a clinician would be disappointed with the longer follow-up outcome of a 7-year local control rate dropping to 92%, despite the highest dose of 36 Gy delivered to WHO Grade I benign meningiomas in their series. Third, other limitations of GKS include frame-based fixation of skull to deliver high-dose radiosurgery in single fraction. Therefore, it increases the morbidity to critical intracranial neurovascular structures. This has become a fundamental consideration to seek adequate therapies targeting skull base meningiomas while minimizing morbidity and discomfort in all settings.

In spite of these limitations, their study does draw attention to the optimal choice of SRS facility, such as hypofractionated CyberKnife radiosurgery, which has allowed the radiosurgeons to manage skull base meningiomas based on the technique of robotic arm to deliver hypofractionated radiation beams through global angle around the lesion. Further studies are necessary to target large-volume skull base meningiomas by using hypofractionated CyberKnife radiosurgery.

References


Response: Proponents of multisession intracranial SRS have discussed the theoretical advantages of this technique compared to single-session procedures for many years. However, there is no quality evidence to support the clinical benefits of this radiation delivery method despite widespread clinical usage for more than 10 years. Conversely, advances in our knowledge of the radiation tolerance of the cranial nerves and other neural structures after single-session radiosurgery has continued to improve patient outcomes for a large number of disorders. For example, it is now recognized that the radiation dose to the cochlea as well the radiation exposure of the vestibulocochlear nerve relates to the probability of hearing preservation in patients with vestibular schwannomas. Contemporary studies on GKS using tumor margin doses of 12–13 Gy have documented preservation of serviceable hearing (Gardner-Robson Grade I–II) in 71%–78% of patients. This compares favorably to the CyberKnife se-

ries of Chang et al. who noted a 74% (26 of 35 patients) hearing preservation rate using a dose fraction scheme of 18–21 Gy in 3 fractions. Recent studies have also found that the radiation tolerance of the anterior visual pathways is clearly greater than previously thought. Hasegawa et al. reviewed the outcomes of 100 patients having single-session radiosurgery for craniopharyngiomas and found the risk of new visual deficits was very low if the maximum radiation dose to the optic apparatus did not exceed 14 Gy. Thus, the accepted notion that the dose tolerance of these structures is 8 Gy is overly restrictive and limits the number of patients with periopitoc lesions who are candidates for single-session radiosurgery. In our current practice we frequently perform single-session radiosurgery for asymptomatic patients with meningiomas, craniopharyngiomas, and nonfunctioning pituitary adenomas that abut the optic nerves and chiasm. We generally recommend surgical decompression for the majority of patients with visual loss related to tumor compression of the anterior visual pathways rather than multisession radiosurgery or radiation therapy as the best method to restore visual function.

In their letter, Hueng and Ju cite 3 factors that argue against single-session radiosurgery to manage patients with large-volume, benign skull base meningiomas based on our recent paper. First, they state that our morbidity rate was unacceptably high for the skull base group (18%). However, our series included patients from our early radiosurgery experience (dating back to 1990) when dose planning was crude and dose prescription was higher than commonly used today. Complications for this group were primarily minor (new facial numbness or diploria) and did not interfere with patients’ day-to-day functional status. Our more recent experience has been that cranial nerve morbidity is rare using highly conformal dose plans and marginal tumor doses of 13–15 Gy. Second, they state that our 7-year tumor control rate (92%) is disappointing despite the high radiation doses used in these patients. While it is correct that our overall 7-year tumor control rate was 92%, the 7-year in-field tumor control rate was 98%. The majority of our failures related to tumor progression outside the irradiated volume in patients who had undergone previous surgery. Consequently, performance of multisession versus single-session radiosurgery would not reduce these failures assuming that volumes treated were similar. This point is illustrated by the results in the recent paper by Colombo and colleagues on CyberKnife radiosurgery of benign meningiomas. They demonstrated a 94% progression-free survival rate at 5 years, with a much shorter follow-up (30 months vs 70 months) and significantly smaller tumors (6.8 cm³ vs 17.5 cm³) than in our series. Third, it is true that placement of a stereotactic head frame has been required to perform GKS. However, the discomfort associated with proper placement of stereotactic head frames is often greatly exaggerated and should not be a significant factor in deciding between single-session or multisession radiosurgery. Conversely, it could be argued that the convenience and simplicity of a 1-day procedure is preferable over the time commitment required for multisession radiosurgery (typically 3–5 days).
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