Dural arteriovenous fistula: a clinical model of thalamic dementia?

TO THE EDITOR: We greatly enjoyed reading the article published by Holekamp et al.2 that reports their experience in the diagnosis and treatment of thalamic dementia caused by a dural arteriovenous fistula (dAVF) in 4 new cases (Holekamp TF, Mollman ME, Murphy RKJ, et al: Dural arteriovenous fistula–induced thalamic dementia: report of 4 cases. J Neurosurg 124:1752–1765, June 2016). In this paper the authors also include a thorough review of the scarce number of similar previously described cases, with an excellent discussion of the results in light of the relevant scientific literature published on this subject to date. In 2014 we had the opportunity to share with the medical community our modest experience in the management of a single case of thalamic venous ischemia caused by a tentorial dAVF, and we would like to remark on some key concepts that may prove useful for the professionals involved in the management of this rare entity.

To begin, it should be noted that the clinical manifestations of thalamic dysfunction could be easily overlooked or misdiagnosed. Arterial ischemia of the thalamus can produce 4 well-defined syndromes (tubero-thalamic, inferolateral, paramedian, and/or lateral posterior choroid) depending on the feeding artery involved. Nevertheless, an impairment of the common venous drainage of deep structures, which occurs in some dAVFs, gives rise to hyperemic changes in the whole thalamus, with bilateral involvement and a variable implication of the caudate nuclei, depending on the individual venous pattern of drainage. Such widespread disturbance often results in a complex constellation of neuropsychological symptoms and signs—including deficits in arousal, attention, memory, cognition, behavior, ocular motility, coordination, and gait—that have been gathered by Holekemp et al. under the term “rapiddly progressive dementia.” Although in our opinion this term entails an excessive simplification, at the same time it rightly highlights the characteristic temporal evolution of the disease in a clinical scenario in which a specific localizing diagnosis can seldom be established. In our patient, the predominance of negative neurological symptoms (hypersomnia, abulia, anergia) led initially to an erroneous diagnosis of major depression, supported by the absence of significant abnormalities on the brain CT scan (Fig. 1A). One month later, the patient was referred to a neurologist because the symptoms were gradually worsening. During the neurological examination, the patient exhibited a marked bradykinesia and an unsteady gait. His verbal language, perseverant and bradypsychic, denoted temporospatial disorientation and unawareness of his illness. He also presented with impairment of vertical gaze. Brain CT and MRI findings (Fig. 1B and C) led us to complete the diagnostic workup with angiography (Fig. 1D and E).

In the review performed by Holekamp et al., almost all cases of dAVF-induced thalamic dementia were caused by lesions involving the tentorial area. This represents a recognized complex subgroup of dAVFs, considering their structure (which frequently includes the presence of multiple arterial feeders), the technical difficulties that may arise during the endovascular navigation of the deep venous system, and the potential impairment of critical neuroanatomical structures involved. In the review performed by Holekamp et al., the endovascular treatment of the dAVF did not cause significant complications, yet the failure rate of this technique reached 25% of cases. Moreover, in the absence of long-term follow-up data, the recurrence rate of dAVFs after embolization cannot be confidently ascertained. In contrast, the cure rate of dAVFs reached 100% following surgery, with only 1 patient developing a postoperative complication (hydrocephalus). It can be concluded from the available data that surgery represents an effective, safe, and definitive modality of treatment, which often constitutes the unique option in this subset of patients. For the purpose of proper surgical planning it is absolutely essential that neurosurgeons become familiar with the excellent systematization of tentorial dAVFs performed by Lawton et al., in which 6 major types of lesions are recognized, each one requiring a specific procedure, from the interruption of a single vein (as occurred in our case) to high-skill, demanding approaches including skeletonization of the major venous sinuses.

Although the neurological symptoms produced by thalamic venous congestion are potentially reversible, a complete recovery was recorded in only 33% of patients. As Holekamp et al. state, early diagnosis and rapid treatment of the dAVF leads to restoration of anterograde venous circulation and cessation of the venous congestion of the brain parenchyma. Nevertheless, sustained venous ischemia may lead to permanent structural changes in both thalami, hence limiting the potential of recovery from...
the neurological deficits. These pathological changes, excellently illustrated by the authors in the pathological photomicrographs obtained from Case 3, include gliosis, petechial hemorrhages, and microinfarctions. From a radiological perspective, although the bithalamic FLAIR hyperintense signal was reported to have been resolved in all cases (as occurred in ours), these underlying structural changes may still become evident in other MRI sequences, such as gradient echo sequences (Fig. 1F–I).

The pathological changes associated with sustained thalamic venous ischemia were also reported in the unique fatal case of this series, as a result of the natural evolution of the dAVF. The authors argued that the microscopic findings were similar to those described in so-called subacute diencephalic angioencephalopathy (SDAE), a rare and cryptic entity whose diagnosis is based on pathological findings and only made after exclusion of any other concurrent disease. Interestingly, most of the rare cases of SDAE reported to date lacked an angiographic study, or, when performed, it demonstrated the presence of a dAVF that the authors did not correlate with the disease. All this evidence suggests that an impairment of the deep venous system—including the presence of a nondiagnosed tentorial dAVF—might play a role in the pathogenesis of some cases that were diagnosed with SDAE.

References


**Disclosures**

The authors report no conflict of interest.

**Response**

My colleagues and I appreciate the thoughtful letter provided by Drs. Carrasco and Pascual. They highlight several important aspects and challenges related to the diagnosis and treatment of dAVF-induced thalamic dementia, and they address two additional issues that were not focused on in our original paper. The first issue relates to the optimal treatment approach for tentorial-region dAVFs, in which they note a difference in cure rates between endovascular and surgical approaches (75% vs 100%, respectively). This is an important point to discuss with patients and their families when considering treatment options, although it should be noted that the number of patients included in our analysis (4 in our case series, 15 from the literature) is small and that endovascular techniques available to embolize dAVFs continue to advance. The second issue relates to the completeness of neurological recovery following dAVF treatment. The authors correctly point out that only a minority of patients fully recover from their presenting neurological deficits and that this likely reflects permanent injury from sustained venous hypertension and ischemia. Hopefully, improved understanding and recognition of this rare entity will allow practitioners to diagnose and ultimately treat these patients sooner so that neurological morbidity can be minimized.

Gregory J. Zipfel, MD
Washington University School of Medicine, St. Louis, Missouri

**Endoscopic transsphenoidal pituitary surgery**

TO THE EDITOR: We read with great interest the article by Conrad and colleagues1 (Conrad J, Ayyad A, Wüster C, et al: Binonstral versus monostroral approaches in endoscopic transsphenoidal pituitary surgery: clinical evaluation and cadaver study. *J Neurosurg* 125:334–345, August 2016). The authors compared their experience with 20 patients who underwent surgery using the binonstral approach to their experience with 20 patients who underwent surgery using the monostroral approach for endoscopic resection of pituitary micro- and macroadenomas. After testing their theory on 10 cadaver specimens without pituitary adenomas, they concluded that the binonstral technique is superior for the resection of large tumors with suprasellar expansion, due to improved maneuverability of instruments.

We would like to respectfully present some different opinions. The extent of resection for macroadenomas or giant pituitary adenomas depends more on the anatomical limitations than on instrument maneuverability. The most common limitation of endoscopic transsphenoidal resection is involvement of the cavernous sinus (CS), particularly in cases of tumors located lateral to the internal carotid artery (ICA). For example, the chance of residual tumor after surgery is reported to be greater in cases of Knosp Grade 4 adenoma.5 Furthermore, in our published series of cases of giant pituitary adenomas treated by means of endoscopic transsphenoidal surgery9,10 most of the residual tumors were lateral to the ICA. Suprasellar expansion is usually less problematic in endoscopic transsphenoidal surgery, since it is along the endoscopic working axis, whether a mono- or binonstral approach is used. Even a huge suprasellar pituitary adenoma (up to 7 cm diameter) with CS involvement could be removed completely via a monostroral approach as long as most of the tumor lies medial to the ICA (Fig. 1).

The binonstral endoscopic approach is advantageous in other pathologies with more extensive skull base invasion, including clival chordomas/chondrosarcomas, anterior skull base carcinomas, and craniovertebral junction (CVJ) anomalies.2,3,11–13 The expanded endonasal approach (EEA) has been described in the treatment of a variety of pathologies involving the skull base and CVJ.4,6–8 How-

FIG. 1. Comparison of preoperative (A and B) and postoperative (C and D) coronal (A and C) and sagittal (B and D) contrast-enhanced T1-weighted MR images obtained before and after monostroral endoscopic transsphenoidal resection of a giant pituitary adenoma demonstrating complete resection of the tumor.
ever, commonly the EEA has not only used 2 nostrils but has also required 2 surgeons (an otolaryngologist to hold the endoscope and a neurosurgeon to operate on the tumor) and resection of middle and lower nasal turbinates bilaterally. Moreover, the rates of hyposmia and anosmia after EEA remain uncertain. Therefore, we recommend the mononostril endoscopic approach for most pituitary macroadenomas.

The authors are to be commended for addressing the efficiency and efficacy of mononostril endoscopic transsphenoidal pituitary surgery. Although not reaching statistical significance, the lower risk of permanent hyposmia in using the mononostril approach should be highlighted. Further studies are warranted to investigate the olfaction, phonation, and long-term changes of the paranasal sinuses after such transnasal endoscopic brain surgery.

**References**


**Response**

We appreciate the observations of Dr. Chang and colleagues and would like to make some comments in response.

Our colleagues from Taiwan estimate that the extent of resection for macroadenomas or giant pituitary adenomas depends more on anatomical limitations than on instrument maneuverability and recommend the mononostril endoscopic approach for most pituitary macroadenomas.

In our series, the maneuverability of instruments was restricted especially by the narrow working channel through the speculum when using the mononostril technique introduced by Joachim Oertel. In our series we did not use a mononostril approach without a nasal retractor. Of course, the surgical corridor can be expanded if one does not use a nasal retractor. It can also be expanded by resection of turbinates. This requires further study.

We fully agree that further studies are warranted to investigate olfaction, phonation, and long-term changes of the paranasal sinuses after transnasal endoscopic surgery. As of this writing, we have a prospective rhinological study underway at our hospital, with data publication planned for 2017.

Jens Conrad, MD
Johannes Gutenberg-Universität Mainz, Mainz, Germany

**Disclosures**

The authors report no conflict of interest.
Role of mutational status of \textit{GNAQ} and \textit{GNA11} in the diagnosis of melanocytic tumors

TO THE EDITOR: We read with great interest the article by Hoffmann and colleagues\(^5\) (Hoffmann M, Koelsche C, Seiz-Rosenhagen M, et al: The \textit{GNAQ} in the haystack: intramedullary meningeal melanocytoma of intermediate grade at T9–10 in a 58-year-old woman. \textit{J Neurosurg} 125:53–56, July 2016). The authors reported an interesting case of an intramedullary intermediate-grade melanocytoma. Histopathological examination revealed a highly cellular tumor composed of epitheliod-shaped tumor cells with scant to moderate cytoplasmic pigmentation and vesicular nuclei with prominent nucleoli. Single mitotic figures and small necrotic areas were present. The proliferation index Ki 67 (MBI1) focally reached 10%. Tumor cells strongly expressed S100 and HMB45, but were negative for BRAF V600E (VE1), pancytokeratin (AE1/3), EMA, and GFAP. Their initial diagnosis was metastatic melanoma, but they changed the diagnosis to melanocytoma after the \textit{GNAQ} mutation was found. We think this diagnosis is incorrect because a \textit{GNAQ} mutation can be found in other tumors such as primary melanoma of the CNS, among others. In addition, they do not mention the possibility of the diagnosis of primary melanoma of the CNS, which we believe is the correct diagnosis in the case presented.

Pigmented (grey, brown, or black) intramedullary tumors are exceedingly rare, with only a few reported cases. When facing a dark intramedullary mass several diagnoses must be considered, including primary melanoma. Other melanin-containing tumors (melanotic neurofibroma and melanotic schwannoma) and melanocyte-containing tumors (melanocytoma, melanoma metastasis) are in the differential diagnosis.\(^2,6,10,13\) Melanoma is the third most common cancer-causing brain metastasis,\(^3,8,11\) but only 12 cases of intramedullary metastases of malignant melanoma have been reported.\(^7\)

Immunohistochemical markers of melanocytic tumors (such as HMB45, Melan-A, and S100) are not helpful for discerning between pigmented intramedullary tumors because all of them are positive for one or several of these markers.\(^6,12\) Melanocytoma, primary melanoma, and melanoma metastasis are difficult to differentiate. It is not possible to distinguish between primary melanoma of the CNS and metastatic melanoma by pathological examination. Both are histologically identical, displaying cellular atypia, numerous mitoses, and often demonstrating unequivocal tissue invasion or coagulative necrosis.\(^2\) We need to exclude melanoma disease elsewhere (skin or mucous melanoma, and visceral metastasis) to make the final diagnosis of primary melanoma of the CNS.\(^4\) On the other hand, melanocytomas lack cellular atypia, and mitoses are generally absent with a Ki 67 labelling index (a cellular marker of proliferation) of \(<1\%–2\%\) (versus 8\% on average in primary melanoma). Similar to melanocytomas, intermediate-grade melanocytoma also lack cellular atypia; however, occasional mitoses, microscopic CNS invasion, and a Ki 67 labelling index ranging from 1\% to 4\% can be observed.\(^1\)

In the past decade, much has been learned about the genetic alterations in different subtypes of melanomas. Uveal melanoma and primary melanocytic tumors of the CNS are different from cutaneous melanoma. This is because \textit{BRAF} is the most frequent mutation encountered in melanoma metastasis from the skin (50\%), followed by \textit{NRAS} mutation (20\%); however, \textit{BRAF} and \textit{NRAS} are rarely mutated in uveal melanoma (<2\%) and primary melanocytic tumors of the CNS (4\%).\(^2,5\) Instead, mutations on \textit{GNAQ} and \textit{GNA11} are found in 77\% of uveal melanomas and 56\% of primary melanocytic tumors of the CNS, but mutations in \textit{GNAQ} and \textit{GNA11} are only present in 1\% of cutaneous melanomas.\(^3\) In other words, a \textit{GNAQ}- or \textit{GNA11}-mutated intramedullary melanocytic tumor is probably a primary melanoma of the CNS, melanocytoma, or intermediate-grade melanocytoma, depending on histopathological criteria.

\textit{BRAF}-mutated melanoma metastases can be treated with \textit{BRAF} inhibitors. Thus, knowing the mutational status may guide treatment and diagnosis, but is not pathognomonic for any of these tumors. That is, the mutation in \textit{GNAQ}, found in the case presented by Hoffmann et al.,\(^5\) does not exclude the diagnosis of primary melanoma of the CNS. We strongly recommend performing a mutational study in these tumors because very few cases have been analyzed so far, so it is not possible to draw any conclusions. To conclude, even though great advances in molecular aspects of these tumors have been accomplished, a diagnosis based on molecular analysis is not yet possible. Thus, the mainstay of diagnosis should still rest on appropriate histology and the absence of other lesions outside of the CNS.

Yislenz Narváez-Martínez, MD, MPH
University Hospital of Girona Dr. Josep Trueta, Girona, Catalonia, Spain
Marc Sagristà-Garcia, MD
Sant Jaume of Calella Hospital, Calella, Catalonia, Spain
Maria Teresa Fernandez-Figuera, MD, PhD
University Hospital Germans Trias i Pujol, Badalona, Catalonia, Spain

References

Disclosures
The authors report no conflict of interest.

Response
We recently reported a case of a meningeal melanocytoma of intermediate grade, initially believed to be a melanoma of unknown primary, until a mutational screen uncovered a missense mutation in codon 209 of the GNAQ gene. Nárváez-Martínez and colleagues responded to our report, arguing that GNAQ mutations could also occur in primary melanoma of the CNS and suggesting this diagnosis should be considered.

We agree with Nárváez-Martínez and colleagues that primary melanoma of the CNS is a differential diagnosis that should be taken into account. As stated in their response, melanocytic tumors originating in the CNS are rare. The majority of these tumors are benign and diagnosed as melanocytomas or intermediate-grade melanocytomas. Only in rare cases are overt malignant tumors identified and diagnosed as primary melanomas of the CNS.

In an attempt to further characterize the tumor and its malignant potential, an additional genetic analysis of the tumor was performed. A number of recent publications have identified mutations in genes other than GNAQ and GNA11 in primary melanocytic tumors of the CNS. These genes—EIF1AX, SF3B1, and BAP1—were all previously identified as mutated in uveal melanomas, in which EIF1AX and SF3B1 mutations were associated with a favorable prognosis and BAP1 alterations with a poor prognosis (frequent metastasis and death).

Copy number variation analysis and targeted next-generation sequencing of tumor DNA were performed. No alterations of BAP1 (sequencing showed no mutation, copy number analysis showed no loss of the gene on chromosome 3, and immunohistochemistry demonstrating normal protein expression) or EIF1AX were detected (Fig. 1). However, in addition to the previously recognized GNAQ Q209L (c.626A>T) mutation, a SF3B1 R625H (c.1874G>A) mutation was identified. SF3B1 R625 mutations, recurrent in nonmetastasizing uveal melanomas, were also recently reported in a total of 3 cases of primary melanocytic tumors of the CNS.

The diagnostic implications of the detected SF3B1 R625H mutation are a matter of debate. Of the 3 tumors reported previously, 2 were diagnosed as melanomas, and 1 as an intermediate grade melanocytoma. The latter, however, was reported to cause disease-related death due to leptomeningeal seeding. For comparison, the only primary CNS melanocytic tumor published to date to have a loss of function BAP1 mutation was also diagnosed as an intermediate-grade melanocytoma. This is somewhat surprising, as other melanocytic tumors (uveal melanomas and malignant blue nevi) harboring BAP1 mutations are clearly malignant and have a poor prognosis. Whether the BAP1 mutant intermediate-grade melanocytoma tumor led to patient death is unclear, yet it is documented that the tumor recurred. Unfortunately, the existing data is too sparse to allow general statements on the implications of different gene mutations in the malignant potential of primary CNS melanocytic tumors. EIF1AX mutations were reported in all tumor types (melanocytoma, intermediate-grade melanocytomas, and melanomas), SF3B1 and BAP1 mutations were less frequent and identified only in melanomas (2 tumors) or intermediate-grade melanocytomas (2 tumors) that either recurred or led to patient death. Although very preliminary, these data imply that these mutations may be associated with a more aggressive tumor phenotype. Future studies will be required to demonstrate if this initial observation proves to be true in larger cohorts.

Currently, diagnosing primary CNS melanocytic tumors is based solely on histopathological criteria. As the present case illustrates, the differential diagnosis of intermediate-grade melanocytoma and primary CNS melanoma remains challenging when applying these criteria. The existing preliminary genetic evidence implying SF3B1 R625 and loss of function BAP1 mutations are associated with tumors displaying a more aggressive phenotype in leptomeningeal melanocytic tumors will be considered if further treatment of this specific patient is required. We believe our and other recent reports strongly argue that larger genetic studies are needed to assess if the current histopathological-based diagnostic approach should be refined to include genetic results for determining tumor dignity.

Klaus G. Griebank, MD1
Christian Koelsche, MD2
Frederik Wenz, MD2
Frank A. Giordano, MD3
Christoffer Gebhardt, MD4
1University Hospital Essen, West German Cancer Center, University Duisburg-Essen and the German Cancer Consortium (DKTK), Essen, Germany
2Ruprecht-Karls-University Heidelberg, and Clinical Cooperation Unit Neuropathology, and DKTK, DKFZ, Heidelberg, Germany
3Universitätsmedizin Mannheim, Medical Faculty, Mannheim, Heidelberg University, Mannheim, Germany
4Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany
TO THE EDITOR: We read with keen interest the article by Brat et al. (1) reporting on the genetic analysis of melanocytic neoplasms of the central nervous system. Their findings highlight the importance of genetic alterations in the pathogenesis of these tumors. We would like to draw attention to a recent study by Harbour et al. (2) which demonstrated the frequent mutation of BAP1 in metastasizing uveal melanomas. This finding is consistent with our observations in a primary leptomeningeal melanoma, where we identified a SF3B1 mutation in addition to GNAQ and NF1 mutations. (3) The genetic and immunohistochemical analysis of our case is illustrated in Figure 1.

FIG. 1. Genetic and immunohistochemical tumor analysis results. A: Targeted next-generation sequencing results demonstrating the identified GNAQ Q209L, c.626A>T mutation (left) and SF3B1 R625H, c.1874G>A mutation (right). Annotation is according to human genome assembly 19 (hg19). B: Immunohistochemical results demonstrate a strong nuclear expression of BAP1. Original magnification ×400. C: Copy number alteration profile of the tumor, showing a number of gains and losses. No losses of chromosome 3 were observed.

References

INCLUDE WHEN CITING
Published online January 20, 2017; DOI: 10.3171/2016.7.JNS161756.
©AANS, 2017

Beta-blocker therapy

TO THE EDITOR: We read with keen interest the ar-
article by Chalouhi et al.2 (Chalouhi N, Daou B, Okabe T, et al: Beta-blocker therapy and impact on outcome after aneurysmal subarachnoid hemorrhage: a cohort study. J Neurosurg 125:730–736, September 2016). In the authors’ study, the cohort consisted of 210 patients with aneurysmal subarachnoid hemorrhage (SAH) with Hunt and Hess (HH) Grades I–V. Of these 210 patients, only 13% (27/210) were exposed to beta-blocker (BB) therapy before admission. Compared to these patients, a higher percentage of patients without exposure to BB therapy had transcranial Doppler mean flow velocity > 120 cm/sec (59% vs 22%, p = 0.003). The authors found a significant association between left ventricular (LV) dysfunction and medically refractory cerebral vasospasm (cVSP) and in-hospital mortality. We commend the authors for their work. However, there are a few points that we would like the readers to pay attention to.

An echocardiogram was performed in only 82% (174/210) of the patients. However, while analyzing the proportion of patients with cardiac dysfunction, 210 rather than 174 was used as the denominator, which led to an underestimation of the true incidence of cardiac dysfunction in the study population. Also, the authors do not mention how many patients in the BB-exposed group had undergone an echocardiogram. So we do not have the true incidence of cardiac dysfunction in the 2 groups. As the authors have concluded that cardiac dysfunction is a statistically significant independent predictor of cVSP and in-hospital mortality, it is important to know the exact percentage of patients with cardiac dysfunction in the 2 groups at admission.

One hundred twenty patients were hypertensive, 27 of whom were on BBs. While analyzing the data, the authors grouped the patients taking antihypertensive medications other than BBs with the hypertensive patients not on antihypertensive medications and with the non-hypertensive patients. Twenty-one hypertensive patients in the non–BB-exposed group were not on any hypertensive medications. As uncontrolled hypertension is a risk factor for cardiac dysfunction, it is important to know how many of these 21 patients had cardiac dysfunction at admission and what the rate of cVSP and mortality was among these patients. Left ventricular dysfunction after SAH is an independent risk factor for the development of vasospasm and cerebral infarction.3 Hypertensive patients who are on regular antihypertensive treatment carry a lower risk of developing LV dysfunction. In a recent study, Temes et al.2 found that none of the patients with LV dysfunction after aneurysmal SAH were on pre-admission antihypertensive medications, as compared to 35% of those without LV dysfunction. Thus, the non–BB-exposed group is a heterogeneous group. It is important to know the details of cardiac dysfunction in the 2 subgroups in the non–BB-exposed group.

Hyperdynamic therapy/induced hypertension has been shown to improve cerebral blood flow.1,3 As the antihypertensive medications were stopped, it would be interesting to know whether the mean blood pressure among the hypertensive patients was higher than in the normotensive patients after the aneurysm was secured. A higher mean blood pressure among the BB-exposed group would act as a confounding factor in determining the correlation between BB exposure and the incidence of cVSP.

Though the number of patients with the different HH and Fisher grades has been mentioned, it is not clear whether the groups in the study were uniform in terms of the severity of SAH as assessed by the HH and Fisher classifications. As the severity of SAH is a statistically significant independent predictor of cVSP and medically refractory VSP,4 the presence of good-grade SAH patients in one group would definitely lead to a lower incidence of cVSP and consequently a better outcome in that particular group. Hence, to compare the rates of vasospasm between the 2 groups, the authors need to have similar patient populations in terms of the severity of SAH. The possibility of this selection bias needs to be considered, and the authors must declare the proportion of patients with different grades of SAH in both the BB-exposed and non–BB-exposed groups.

References

Disclosures
The authors report no conflict of interest.

Response
No response was received from the authors of the original article.

INCLUDE WHEN CITING
Published online January 20, 2017; DOI: 10.3171/2016.10.JNS162509.
©AANS, 2017