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Clinical Presentation of Brain Tumors

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1. Introduction

Understanding the clinical picture and the signs and symptoms produced by brain tumors is complicated by the extreme heterogeneity amongst these patients. This is secondary to the variability in size, location, pathology and rate of growth of the tumor. In general symptoms can be broadly divided into two categories generalized or focal. Most generalized symptoms are caused by the mass effect and resulting increased intracranial pressure or global cerebral dysfunction caused by the lesion [1]. These typically are clues that a neurological abnormality exists, but are not usually helpful in determining lesion localization.

2. Generalized symptoms

The most common generalized symptoms are shown in table 1. Headache is the most frequent symptom and occurs in approximately 48-56% of brain tumor patients [2,3]. Headache patterns and location vary greatly depending on mechanism and pathophysiology and this is described in a subsequent section. In general, headaches can be either localized or global in nature and the intensity and rate of progression may provide insight into the rate of growth of the lesion. Lesions with a long history of slowly worsening symptoms over years tend to be more slow growing and benign whereas acute onset headaches with a rapid crescendo pattern are worrisome for a more ominous course. The classic brain tumor headache is one of a global headache often radiating to the vertex or periorbital region which is associated with nausea and vomiting and worse in the am (secondary to CO_2 retention and subsequent vasodilation during sleep).

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Headache	52%
Memory loss/cognitive dysfunction	35%
Seizures	32%
Personality Changes	23%
Nausea and Vomiting	13%

Table 1. The common generalized symptoms of brain tumor patients [3].

Cognitive changes are not only a common presenting symptom of brain tumors, but also tend to persist even after treatment of the tumor and can affect the patient's overall quality of life and survival [4]. These neurocognitive deficits encompass memory problems, personality changes, and mood disturbances. In some instances, these changes are drastic enough to cause alarm for the patient or family member and lead directly to the diagnosis. These scenarios often include sudden changes, such as the loss of skills related to executive functioning such as paying bills, following directions, job performance or driving and automobile (figure 1).
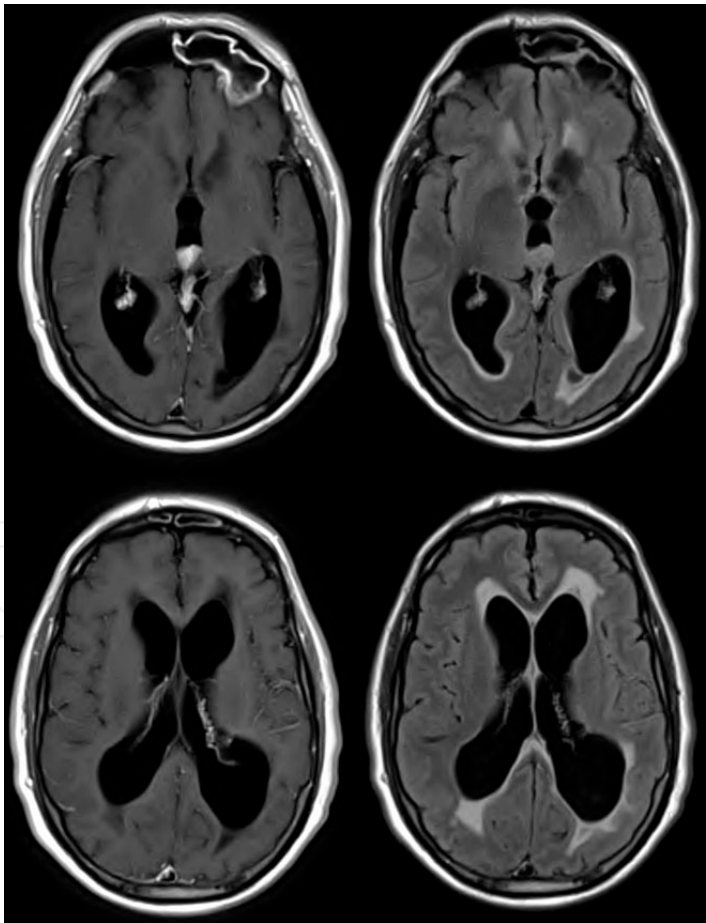

Figure 1. MRI scan from an elderly patient with a pineal mass and associated hydrocephalus who presented with acute confusion consisting of difficulty driving and paying bills.

However, in other cases, these changes are slow and insidious and may often be overlooked or attributed to other causes such as aging or stress. In some instances these issues present only following a visit from a distant family member or friend who has not seen or interacted with the patient recently. It is also not uncommon for these issues to remain completely unrecognized and discovered only after specific questioning and inquiry by a physician or as the result of specialized neuropsychological testing. In fact when formal neuropsychological testing is performed on this population of patients almost all of them show at least mild to moderate dysfunction in at least one cognitive domain [4]. It has only been over the past decade that the magnitude and impact that these cognitive deficits have on such patients has been truly recognized.

A majority of cognitive processes, including planning, motivation, personality, judgment, and abstraction, are controlled by the frontal lobe. However, a significant amount of these processes require input from various other regions of the brain including the parietal and temporal lobes. Therefore, neurocognitive changes are seen with tumors in multiple locations. The tools for evaluation of cognitive deficits will be discussed in a separate section.

Like cognitive deficits, seizures are another symptom of brain tumors that may be present on presentation, or may develop later during the disease process. Tumor-related seizures include both general and focal seizures. The seizure semiology (pattern and symptoms) may provide insight into lesion localization especially in cases with focal seizures. There is a distinction that can be made in the incidence of seizures for various types of brain tumors. Patients with primary brain tumors are more likely to present with seizures or subsequently develop them as compared to patients with brain metastases [5]. In addition, patients with low grade gliomas have seizures more commonly than those with high grade gliomas. One study showed as much as a 85% rate of seizures in those with low grade gliomas as compared to 49% in those with glioblastoma multiforme [5].

Seizures occur secondary to irritation of the cerebral cortex either from the brain tumor itself or the surrounding peritumoral edema. Seizures can result from lesions in any area of the cerebral cortex but are more frequently seen in patients with lesions in the frontal or temporal lobes. Lesions in the brainstem and cerebellum almost never cause seizure activity. Seizures in essence occur as a result of this cortical irritation which causes a "short circuit" within the brain where depolarization rapidly spreads to surrounding areas. Seizure types are broken down into several categories based on the symptoms at the time of seizure onset and whether or not the seizure activity remains focused or spreads throughout the brain. Generalized seizures are those where a large portion of the brain is affected at the onset and as a result of this the patient becomes unresponsive at the onset. Secondary generalized seizures such as the classic partial complex seizure are very common and frequently occur with lesions located in the medial temporal lobe. In these cases symptoms typically start with rhythmic movement on the side contralateral to the lesion but then eventually progress to generalized seizure activity resulting in a loss of alertness and tonic and/or clonic movements on both sides of the body. Patients with generalized or secondary generalized seizures almost always lose consciousness during the event and typically have a period of post-ictal confusion that can last for minutes to hours following such events. However, a less common type of generalized

seizure commonly referred to as absence seizures presents with brief starring spells without motor movements. These episodes can occur hundreds of times per day and are not usually associated with post-ictal confusion. Finally, focal seizures occur when the abnormal electrical depolarization remains contained to a small area of the brain. Symptoms with this type of seizure depend on the area involved but usually results in either episodic periods of uncontrolled motor movement and twitching or sensory complaints. The classic Jacksonian March Seizure is commonly seen with lesions in or around the primary motor cortex. These patients exhibit episodes of tonic-clonic activity that typically starts in one area of the contralateral extremity such as the distal leg and the involved activity spreads ("marches") to include a progressively larger area of the body (entire leg and then arm) as the seizure progresses. Patients with focal seizures almost always retain consciousness and awareness during their episodes [1].

Unlike patients with other causes of epilepsy, patients with lesional epilepsy secondary to a brain tumor often progress in frequency, intensity and severity if they remain untreated. It is not uncommon to see a patient with a low-grade glioma who had "a spell" several years ago which was never investigated or brought to the attention of a physician until the patient suffers either repeated or more intense attacks at a later date. The treatment of epilepsy in brain tumor patients varies on a case to case basis. We do not generally recommend prophylactic antiepileptics on these patients for many reasons. Most importantly class I data shows that the routine use of such medications doesn't prevent these patients from having seizures, but does significantly raise the incidence of drug related side effects [6]. In addition, many of these drugs are metabolized through the cytochrome P450 pathway in the liver and can affect the bioavailability of many chemotherapeutic agents and can thus affect the efficacy and side effect profile of these other medications [6]. We typically reserve the use of antiepileptics for patients who present with a seizure or develop one during treatment or for rare instances of "high-risk" patients with temporal lobe lesions who require awake mapping procedures. In these unusual cases we may treat the patient only in the perioperative period. For patients requiring treatment we commonly use leviteracitam unless the use of this is contraindicated. This medication is typically well tolerated by the majority of these patients however in rare instances it can cause or exacerbate headaches or cognitive dysfunction in this patient population. The duration of treatment for patients who present with seizure activity and then do not have any further events remains controversial. In many instances the surgical removal of the epileptogenic trigger may be enough to provide long-term control; however, we recommend continuing antiepileptic medications for at least 6 months or longer and routinely perform EEG prior to considering discontinuation of any antiepileptic medications. If EEG is normal or shows only diffuse changes than medications can usually be stopped safely; however if it shows significant sharp waves or other electrical evidence of cortical irritation than we will routinely advise patients to continue treatment for at least one to two years.

Nausea and vomiting associated with brain tumors is typically a result of the increasing ICP from the space-occupying lesion. However, when occurring in the absence of other symptoms it is often difficult to make the diagnosis which is typically made only after extensive workup for other causes such as gastrointestinal issues have been ruled out. In rare instances lesions
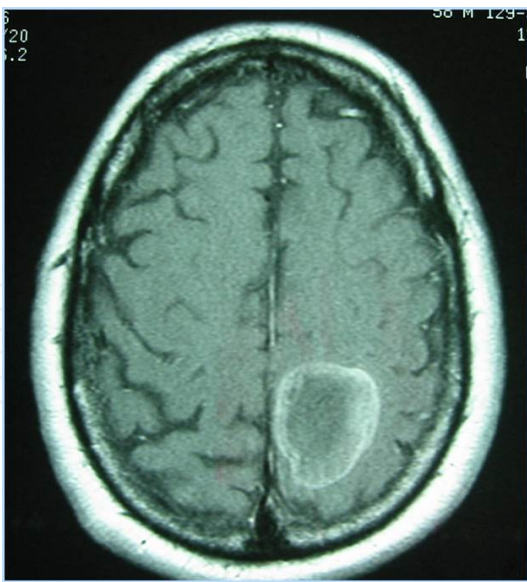
Figure 2. MRI showing lesion in motor cortex in a patient who presented with right sided weakness.

in the brainstem or other parts of the posterior fossa can lead to pure nausea and or vomiting without other complaints.

3. Focal symptoms

Compared to the generalized symptoms described above, focal symptoms of brain tumors can commonly offer clues as to the location of the lesion. This stems from the fact that focal deficits are created from the tumor or resulting edema compressing a specific portion of the brain parenchyma or cranial nerves. Therefore, from the knowledge of the structure and function of the brain, we are able to use the focal deficits found on a patient's exam to predict the location of the tumor.

Motor deficits	33%
Language deficits or aphasia	32%
Visual deficits	22%
Sensory deficits	13%
Dizziness, balance problems or ataxia	9%

Table 2. The common focal symptoms of brain tumor patients [3].

Motor deficits from brain tumors can range from specific weakness in certain extremities to generalized weakness throughout the body. Focal motor deficits occur from a lesion situated in or around the precentral cortex (figure 2).

Lesions in the prefrontal area, caudate or basal ganglia can also cause motor deficits but this is typically more of a coordination or fine motor control issue as opposed to hemiplegia. Deficits can also occur when the lesion affects the descending fibers associated with a specific area of the motor cortex. These types of focal deficits are commonly very noticeable to patients and often lead to them seeking medical attention sooner. In some cases, the tumor itself may not be in a specific motor cortex region, but edema from the tumor extends to that region. In those cases, weakness is typically very responsive to treatment with steroids.

Like focal motor deficits, sensory deficits are also seen when the tumor or associated edema are lying in a region controlling sensory function such as the post-central gyrus or other areas of the parietal lobe. Some of the common sensory deficits that are seen include: graphesthesia abnormalities, stereoagnosis abnormalities, loss of proprioception, and abnormalities in pain and touch sensation. Graphesthesia is the ability to determine a number or letter that is written on the palm of the hand without watching as it is drawn. Stereoagnosis refers to the ability to determine what an object is that is placed in the hand when the eyes are closed. Proprioception refers to the ability to sense where in space a part of the body is. All of these abilities, along with the ability to sense touch, pain, and temperature can be diminished when a brain tumor is affecting the sensory areas of the parietal lobe [1].

When tumors occur in the regions of the brain controlling or contributing to speech and language, specific forms of aphasia and language deficits can be seen. Statistics show that language deficits of some sort occur in 30-53% of brain tumor patients [7,8]. Like all symptoms, language function will be affected differently in brain tumor patients, but most commonly tumors in the fronto-temporal region are responsible for causing aphasia [7].

Two regions of the brain, known as Broca's and Wernicke's area, are the most documented regions for language control. In greater than 85% of people, these areas are located in the left hemisphere, in the temporal region adjacent to the Sylvian fissure. Broca's area is located in the frontal operculum and typifies the expressive language control center, controlling a person's ability to facilitate speech. The location of Wernicke's area is much more variable; however, in most patients it is located in the posterior aspect of the superior or middle temporal gyrus. It is associated with the control of receptive language, a person's ability to understand both written and spoken language.

The four most common types of aphasia include: Broca's aphasia, Wernicke's aphasia, global aphasia and anomic aphasia. A brain tumor causing Broca's aphasia would limit a patient's ability to express their thoughts. These patients understand what they want to say, but the ability to form fluent, sensical words and phrases has been lost. On the other hand, a lesion causing Wernicke's aphasia would cause a patient to create non-sensical, non-meaningful speech. They can speak fluently, but their words and phrases have no meaning. These patients typically are not aware of the meaningless of their speech (figure 3).

When both Broca's and Wernicke's area have been affected, global aphasia results. These patients can neither express nor understand speech and language. This includes spoken language in addition to reading and writing. This can occur with large lesions affecting both the dominant frontal and temporal lobes or from smaller lesions which affect the angular gyrus on the
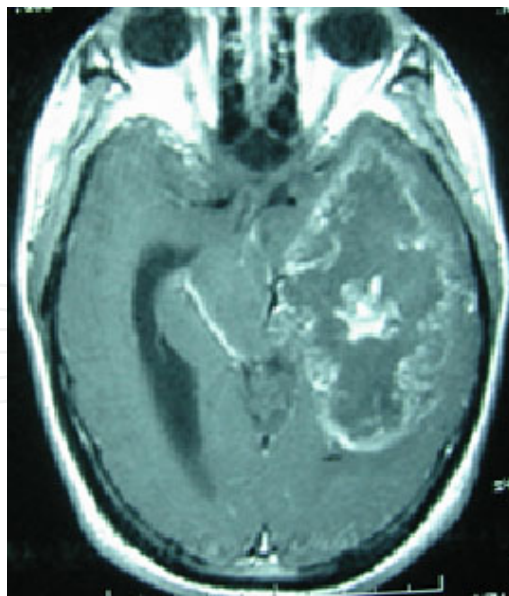
Figure 3. MRI scan of patient presenting with Wernicke's type aphasia.

dominant side. Finally anomic aphasia occurs when a lesion damages the left temporal region in addition to other lesions in the language pathways. This is best illustrated in a patient who has primarily word finding and naming difficulties. Speech will be fluent to start a sentence, but the patient will then lose the ability to produce the next word. Anomic aphasia is the most common form of language deficit in brain tumor patients [7].

The visual pathway is not specific to one hemisphere or lobe of the brain. Rather it encompasses both hemispheres, multiple cranial nerves, and travels from the retina posteriorly to the occipital lobe. Therefore, there are multiple locations in which visual deficits can be created from a brain tumor. Even compression on the optic nerve creates variability in visual deficits depending on the location along the cranial nerve. When compression occurs at the optic chiasm, bitemporal hemianopsia occurs, meaning that a patient is unable to see temporal peripheral fields out of both eyes. This type of visual loss is very common in patients with tumors in the pituitary region, particularly with non-functioning adenomas that extend into the suprasellar space and cause compression of the optic chiasm [9] (figure 4).

However, if compression from the lesion is only on one side of the optic nerve, than visual impairment is only experienced on the affected side. Patients can also complain of changes related to decreased visual acuity. This can occur with lesions anywhere along the optic system. In addition, it is a frequent complaint among patients with hydrocephalus or increased intracranial pressure in which case it is likely secondary to papilledema. Lesions in the occipital lobe cause a homonymous hemianopsia in which the patient loses vision in the contralateral portion of both eyes (figure 5). The onset of visual deficits is typically very gradual, and may not cause the patient to seek medical attention until the deficits are very severe. In fact in patients with benign slow growing lesions symptoms may not become evident until the patient experiences and accident from running into an object that they didn't visualize secondary to an enlarged blind spot.
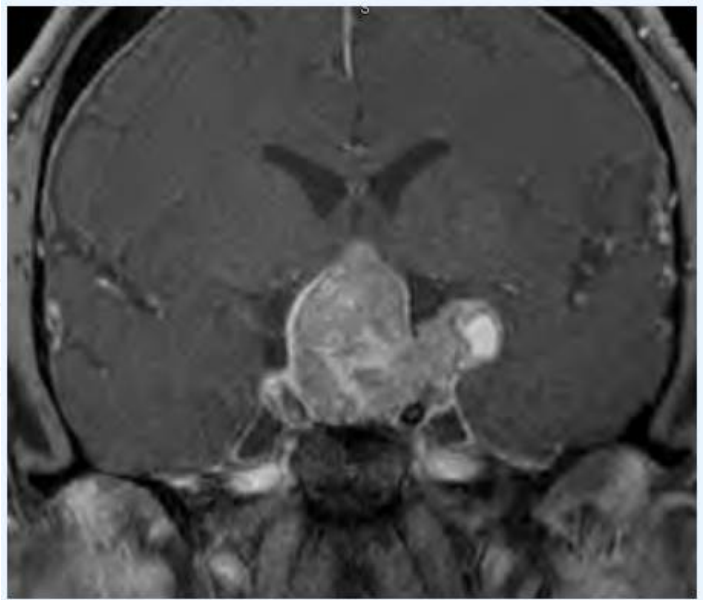
Figure 4. Coronal MRI of a patient with a large pituitary mass compressing the optic chiasm causing bitemporal hemi-anopsia.

Figure 5. MRI scan of patient presenting with a left homonymous hemianopsia from a right occipital lesion.

Cranial nerve dysfunction is much less common than the other above symptoms. These typically occur with lesions affecting the skull base and in many instances multiple cranial nerves may be involved. In general the cranial nerves with pure motor functions (i.e. Facial nerve) are much more resistant to compressive forces than sensory nerves (i.e. Acoustic and vestibular nerves) (figure 6). In patients with metastatic disease the occurrence of multiple cranial neuropathies is an ominous sign and usually signifies the presence of leptomeningeal disease.
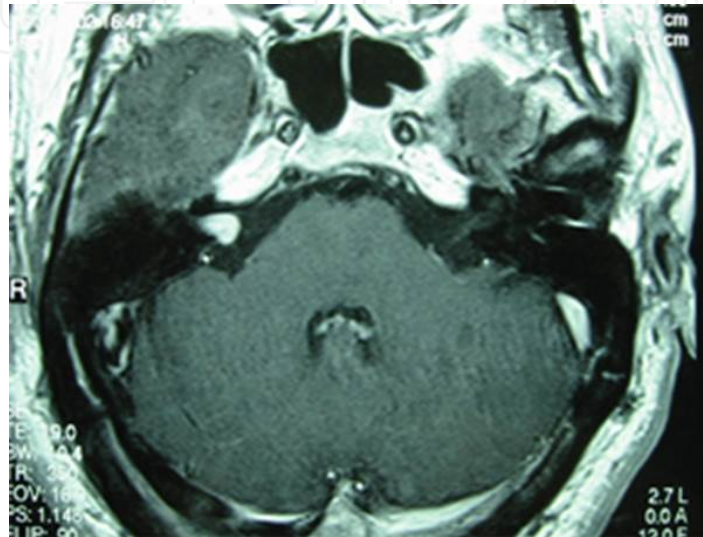

Figure 6. Axial post contrast MRI of patient with a small right acoustic neuroma who presented with hearing loss.

4. Headaches

Headaches are probably the most common complaint among brain tumor patients. Headaches can arise from many different pathological reasons. In some instances the headaches are unrelated to the imaging abnormalities and thus may not improve with treatment whereas in others the headaches are directly related to the pathological abnormalities.

In many instances the headaches are the result of increased intracranial pressure. This headache pattern is often associated with either large tumors or those lesions that have significant surrounding peritumoral edema (figure 7). The skull is a fixed rigid space with a limited volume. Therefore any changes in that volume directly affect the pressure within the skull. During early stages or with slowly growing lesions the CNS has the ability to autoregulate and compensate for these changes in tumor or edema volume by decreasing spinal fluid or changes in venous engorgement. However, sudden rapid changes in tumor size or edema can cause changes that cannot be overcome by these typical compensatory mechanisms and thus cause a dramatic change in intracranial pressure (ICP). This relationship of pressure and volume in the skull is referred to as the Monroe-Kelli Doctrine [1].
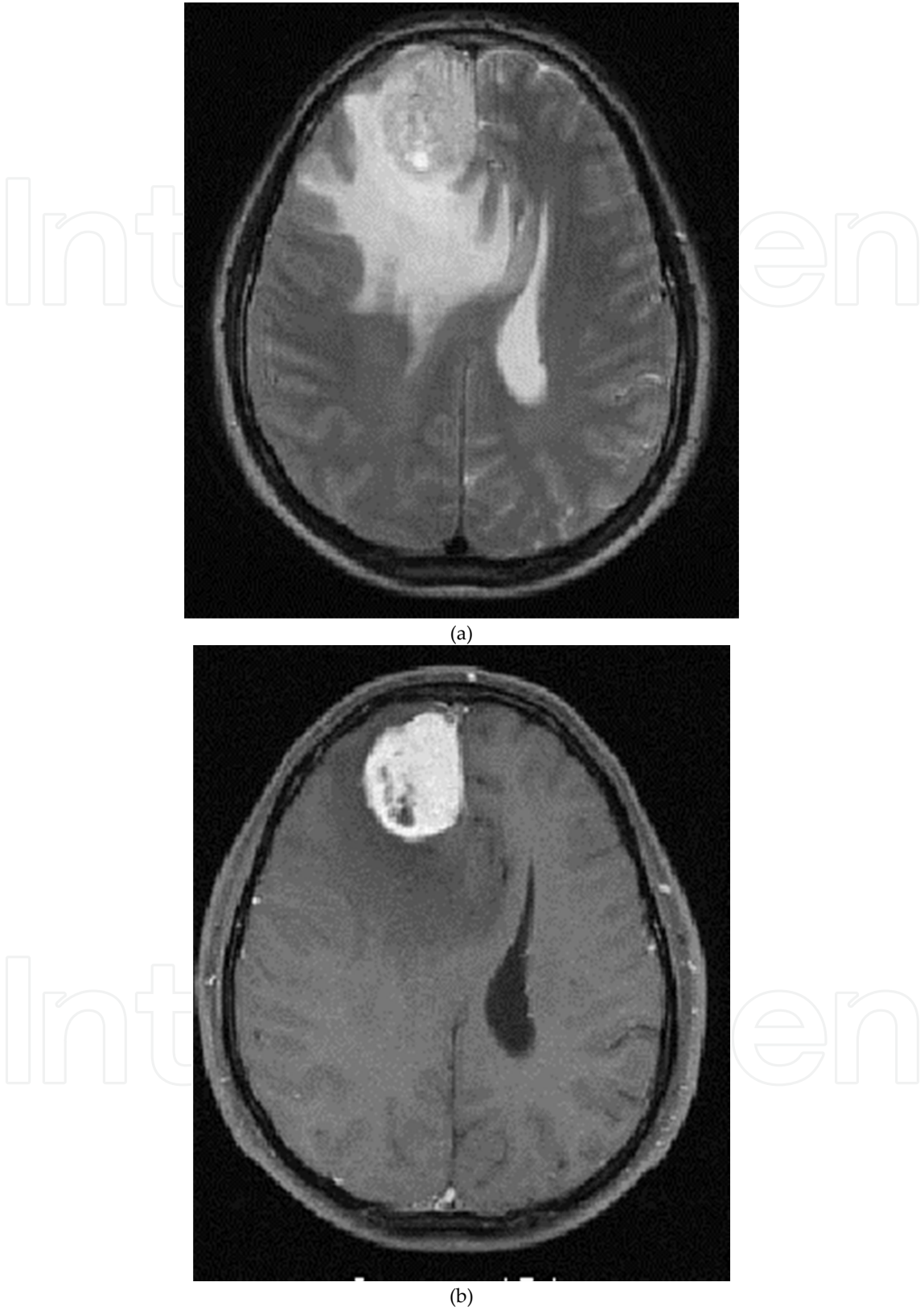
(a)

(b)

Figure 7. Axial T2-weighted and post contrast T1-weighted MRI scan showing significant edema and midline shift secondary to a tumor and surrounding edemawhich resulted in headache secondary to increased ICP

Typically headaches associated with this type of pathology are reported as global or frequently refer pain to the convexity or bifrontal/periorbital region. These headaches are usually progressive with time and are crescendo in nature. The speed at which they worsen varies depending on the rate of change in ICP. These headaches are usually worse in the morning and often associated with nausea and or vomiting. Vague visual complaints, likely the result of increased pressure in the optic nerve sheath, are often common.

Some lesions result in obstructive hydrocephalus (figure 1). The pattern and disease progression are often similar to headaches from more general increased ICP. These patients often have cognitive deficits as a result of involvement of the lateral ventricles and frontal horns. In severe cases alterations in mental status can occur and at times rapidly progress to death if emergent interventions are not instituted.

Headaches as the result of dural inflammation or irritation tend to me more focal. This can be the result of focal involvement of the dura by lesions such as meningiomas or metastasis or from stretching of the dura from tumor growth. A majority of the dura in innervated by the trigeminal nerve. As a result pain can at times be referred to the face, preauricular or periorbital region.

However, in most cases the headaches are located unilaterally ipsilateral to the pathology and in some instances directly correlated with lesion location. In my experience headaches that are directly correlated with the location of imaging abnormalities almost always improve with surgical resection.

Tumors in the sellar region can commonly cause stretching of the diaphragm sella (figure 8). These headaches commonly radiate to the periorbital or bifrontal region. The intensity and frequency of these types of headaches commonly fluctuate and can be sporadic in nature likely do to transient changes in local inflammation or pressure in the lesion itself.

Tumors that invade or compress the trigeminal nerve typically cause a very classic headache syndrome. Many of these patients experience facial pain syndromes similar to classic trigeminal neuralgia. This can often be dysesthetic in nature and frequently can become very severe and debilitating. The pain is always on the side of the lesion unless there is involvement of the brainstem. Unlike classic trigeminal neuralgia patients pain related to these lesions typically does not respond to medical management (gabapentin, pregabalin or carbamazepine) (figure 9).

In rare instances tumors can be large enough to compress or stretch the large arteries in the brain. Headaches from this cause are infrequent and vary in nature and symptomatology. On the other hand headaches as the result of tumor bleeding tend to be very classic. These headaches are often thunderclap or sudden onset in nature and occur instantaneously with a high intensity. Mental status changes and nausea and vomiting may accompany this type of headache depending on the volume and degree of hemorrhage (figure 10). Table three shows the most common histologies for brain metastasis which result in hemorrhage.
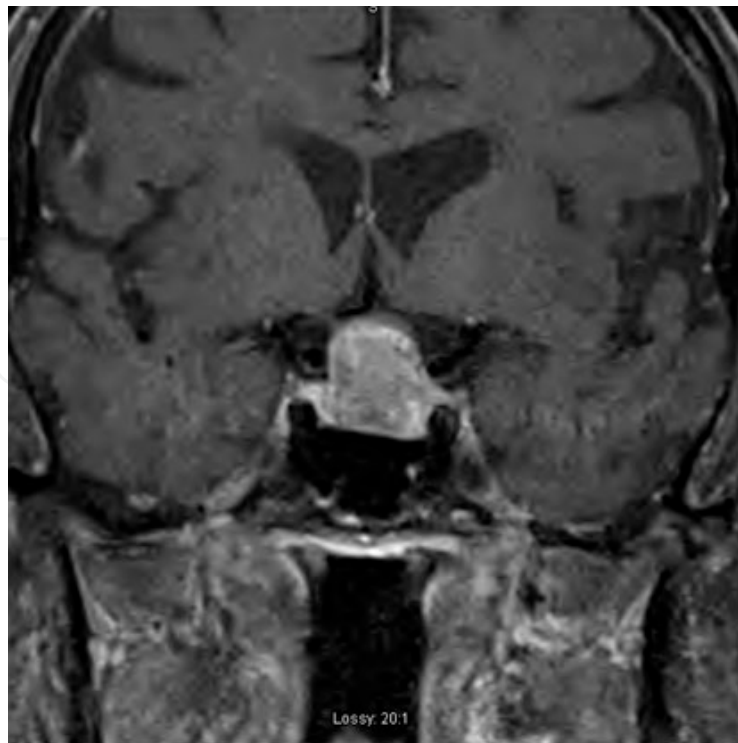
Figure 8. Coronal MRI of a patient with a small pituitary macroadenoma who presented with headache likely the result of stretching of the diaphragm sella.
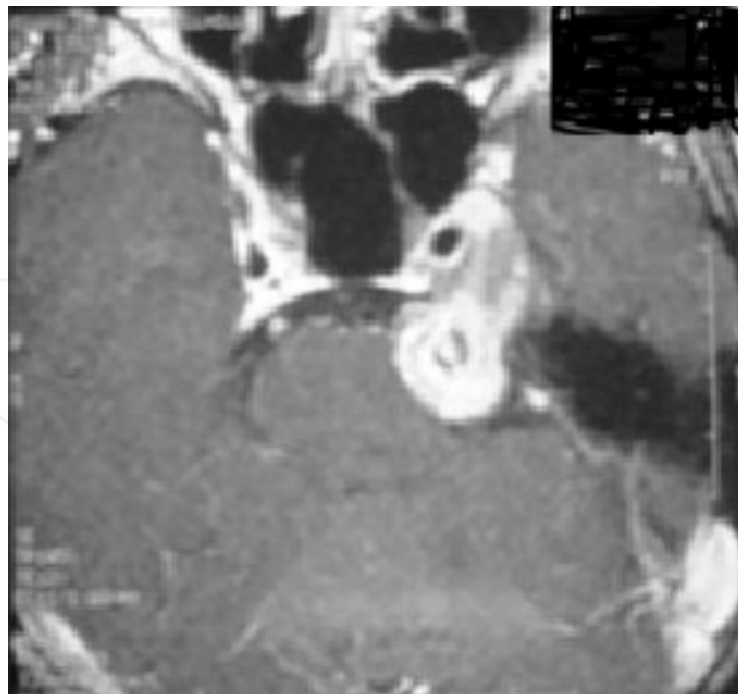

Figure 9. Axial post contrast MRI of patient with left sided facial pain who was found to have a small trigeminal neuroma compressing the trigeminal nerve.
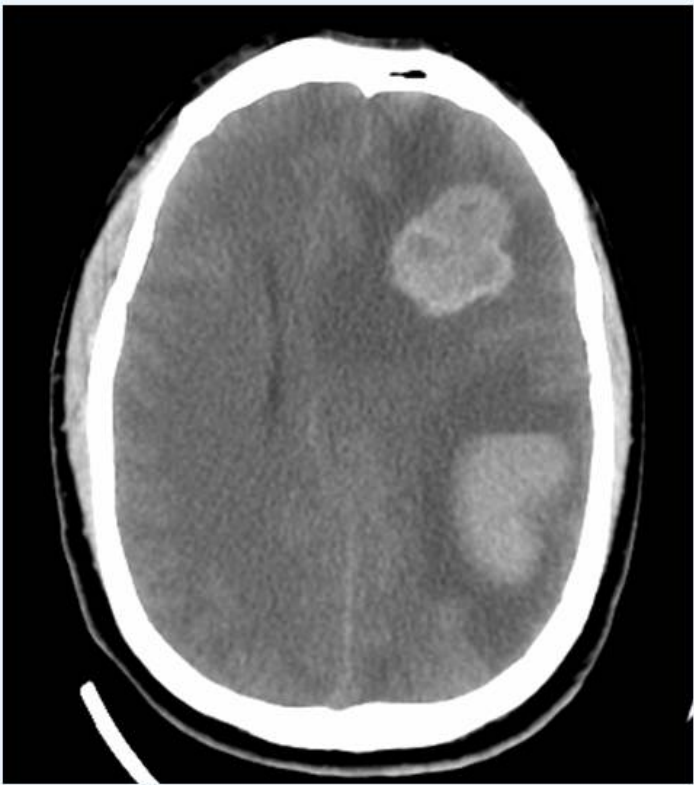
Figure 10. CT scan from a patient with remote history of melanoma who presented with thunderclap headache.

Lung adenocarcinoma
Melanoma
Renal cell Carcinoma
Choriocarcinoma
Papillary Thyroid

Table 3. Most common histologies for brain metastasis that result in hemorrhage

Lesions located in the posterior fossa can cause headaches that refer pain to the vertex especially if there is associated hydrocephalus. In addition, pain may also be referred to the auricular and post auricular region secondary to innervation of the petrous dura and tentorium. These patients may also complain of pain in the suboccipital region. In rare instances of tonsilar herniation either from posterior fossa lesions or hydrocephalus patients may complain of severe neck pain at the base of the skull which worsens with extension.

The determination of which headache patient to image is always a difficult decision for the primary care or emergency room doctor as there are many more patients who complain of headaches who don't have intracranial pathology that those who do. My recommendations have always been that for adult patients who previously have not had significant headaches

but then start having gradually progressive headaches that imaging should be strongly considered. Patients with rapidly deteriorating headaches or those with thunderclap onset deserve more urgent evaluation. A strong index of suspicion should also be entertained when new headaches occur with nausea and vomiting and persist despite routine headache management. Headaches associated with any other neurological finding or seizure activity also demand urgent imaging. In most instances MRI with and without contrast is the gold standard as CT scanning even when performed with contrast can have significant false negative rates. CT scanning may be adequate when intracranial hemorrhage or hydrocephalus are of concern based on clinical suspicion.
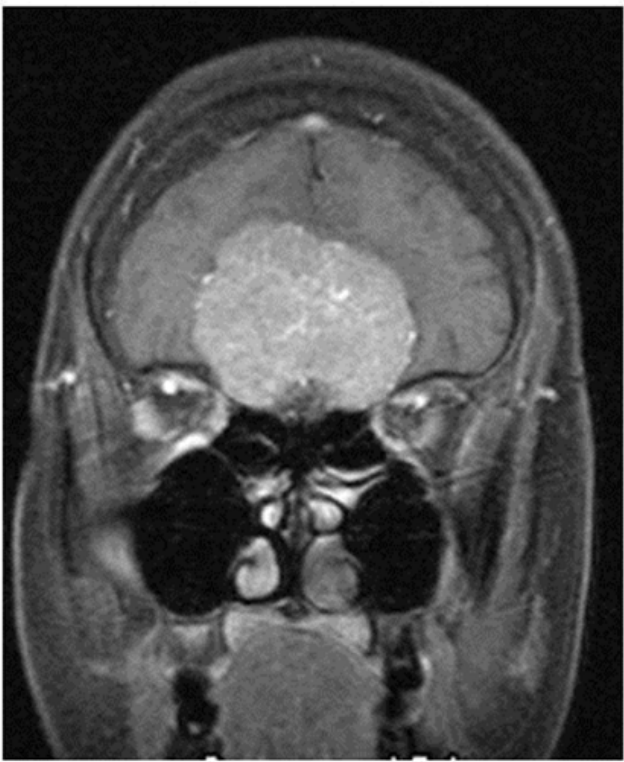
5. Cognitive evaluation for brain tumor patients

A majority of patients harboring brain tumors experience changes in cognitive or high level executive functioning [10-14]. Many patients may complain of subjective deficits which often are difficult to characterize, while others can slowly develop large abnormalities and be unaware of the slowly progressive changes (figure 11).

Unless patients are exhibiting major confusion and disorientation these complaints often go unassessed and unaddressed for these patients. In addition, most will exhibit at least partial improvement if a cognitive rehabilitation program is instituted before symptoms become too devastating [15].

Objective screening tests are limited and vary in efficacy in this patient population. Extensive neuropsychological batteries are time consumptive and require a trained neuropsychologist which is not available at most major brain tumor centers or smaller community treatment facilities. In addition, these deficits can change with time and are affected by all treatment modalities: surgery, radiation and chemotherapy. Therefore any reliable screening tool must also take into account the effect of "learning" from prior administrations.

Not until the past decade has the importance of assessing cognitive function and evaluating the impact of treatment on such function come into the forefront, despite the known association with cognitive functioning on quality of life and overall survival [16-18]. Only recently have prospective studies incorporated some aspect of cognitive evaluation in their study design. The mini-mental status evaluation (MMSE) is the most frequently used tool in clinical practice as well as for many large research studies. This test has numerous drawbacks including extremely low sensitivity and specificity in this patient population. In addition a "ceiling effect" exists [4]. Many patients score normal results on this test despite having significant cognitive impairments.

For the past five years I have been using the Montreal Cognitive Assessment Tool (MoCA) with my tumor patients. This is a free screening tool (available at www.mocatest.org) can be administered by office staff or physicians with minimal training and excellent inter-observer reliability. This tool assesses several aspects of cognitive function including: executive function, visuo-spatial function, naming, memory, attention, abstraction, language, orienta-

(a)

(b)

Figure 11. Axial post-contrast T1-weighted and FLAIR MRI in patient with a large olfactory groove meningioma who presented with cognitive dysfunction.

tion; and has been used extensively as a screening tool and for serial examinations for numerous different pathological conditions from dementia to heart failure.

The MoCA is more sensitive than the MMSE for detecting mild cognitive impairment (MCI) [19-21]. Olson compared the efficacy of MoCA vs MMSE in a group of patients with brain metastasis by administering both tests to patients at a similar time point after diagnosis of their brain metastasis. Ninety-eight percent of patients completed the test in less than 15 minutes, and 88% of patients took less than 10 minutes. Based on the results of the study (using normal cutoff scores for both tests) 80% of patients were classified as having at least mild cognitive impairment on the MoCA (score <26) vs. 30% using the MMSE (score <26) [22].

In 2011 the same group reported the results of 58 brain metastasis patients who were studied prospectively [4]. Once again both groups were administered MoCA and MMSE tests, 67% of the patients also underwent formal neuropsychological assessment (NPA) which consisted of a battery of tests taking 3-4 hours to complete. This formal testing was performed within 2 weeks of administration of the screening tests. Study analysis showed that only 7% of patients scored normal on the NPA and an additional 38% had borderline results, the remainder of the patients had cognitive impairment in greater than two domains. MMSE results showed abnormal cognitive function in only 12.8% and MoCA showed impairment in 53.8%. Thus it is clearly illustrated based on the poor sensitivity that the MMSE is a poor screening tool for determining cognitive impairment in these patients and has limited value. The MoCA was more sensitive in determining mild cognitive impairment but still failed to illustrate all cases [4]. Finally, in yet another study they were able to show that the results of the MoCA were highly correlated with overall survival in patients undergoing treatment for brain metastasis but failed to show a relationship of survival to MMSE results [22].

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