Chapter 35

The Executive with Unusual Visual Aura!

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Case History

A 59-year-old male chief executive officer of a venture capital firm presents with a history of recurring intermittent headaches since his twenties. He is seen urgently after a call from his internist because of an "unusual visual aura."

His headaches have varied in characteristics and frequency over the years, but typically begin in the back of his head or upper neck, more often on the right side than the left, but never both at the same time. The neck pain typically begins as tightness associated with a "band of hard, firm muscle at the bottom of my skull." The muscle is sore to touch, and over 1 to 2 hours, if untreated or treated ineffectively, the temple and/or frontal regions become sore. However, the spread of pain is not contiguous, as the one-sided neck-occipital pain is nearly always accompanied by contralateral temporofrontal pain. A mild anterior pain is squeezing in nature, but with movement, he feels his pulse "bounding" in that temple and an enlarged tender temporal artery. When the process advances to this stage, he cannot concentrate on anything except the pulse itself. If the tenderness is not improved quickly by "an ice pack" and/or additional medication, he goes to bed because only a "long night's sleep with my head encased in ice" ever relieves it. He never vomits, and rarely ever is nauseated. When nausea occurs, "I think that may be due to too much medication."

In his twenties and thirties, the worst headaches occurred monthly, often associated with meeting a deadline. In his forties, they were more infrequent and now occur only about once a year. Lately, he has been most susceptible to headache when he travels. The "muscular" neck pain/headache occurs most often, but never more than three times a week, although once "I can remember having an 11-day episode about 20 years ago." The frequency of milder headache is increased in the last month.

Four days prior to presentation on a Friday evening, while traveling in an airplane, he experienced an episode of right-sided headache. The pain began typically as previously described, except that minutes before the pain, "my vision turned fuzzy followed by unusual shapes which seemed to come in and out of my vision. Then my right hand seemed to twitch and for a minute I felt I couldn't type on my laptop. I am not sure I remember it all. I felt confused. I think everything is fine now, but I did walk into a door jam twice on Saturday, and the same thing happened again yesterday." The vision and hand symptoms resolved in about 2 minutes while he could not treat the neck pain immediately, and since the airplane episode, he has not been able to get rid of a right occipital headache. On two separate occasions in the past, he has experienced visual blurring when a headache was throbbing, and one of these headaches may have involved similar visual, but not hand, symptoms.

He had been under increased travel and job stress. His mother and 2 of his 4 grown children have similar headaches, one of whom has been diagnosed with migraine. "Everyone calls them 'tension headaches'". His past medical history is unremarkable, without known head injury or general medical disorders other than increased cholesterol.

His examination revealed normal blood pressure of 135/82, regular pulse of 77 bpm, and regular respirations without fever. Normal speech, language, affect, and cognition were noted. The only questionable neurologic examination finding was apparent visual extinction to simultaneous finger presentation in the left visual field.

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the author's discussion.

- Is there more than one headache type in the past or the present?
- What differential diagnostic considerations should we consider? Does any diagnosis seem most likely?
- Are there any history or examination features that raise concerns suggesting sinister headaches or offer sufficient comforting features to warrant deferral of testing; that is, when does an individual need a work-up?
- If tests are indicated, which ones should be done?
- How does his care proceed following this visit?

Case Discussion

This man's earliest headaches are self-diagnosed as tension-type headaches. Might these be patient mislabeled? Can there be doubt about a diagnosis of migraine without aura with a history of one-sided headaches (one-sided occipital and temporofrontal), with inhibition of normal cognition and associated need to seek sleep? Nausea is reported with some headaches, and a family history of headache is known. These headaches do meet International Headache Society (IHS) migraine without aura criteria.

There are several differential diagnostic considerations for his preexisting headaches. Could the cervical spine (ie, cervicogenic headache) cause these headaches? There is often an associated minor or major cervical strain or injury preceding the headaches by several weeks to months. Occipital/upper cervical aching, typically chronic, not intermittent, and worsened with sustained or awkward head position, is noted. However, the ipsilateral pain in the neck with contralateral frontotemporal pain is not consistent with the source of pain originating from the cervical spine. The same can be said for paroxysmal hemicranias; additionally, no autonomic symptoms are reported.

Could this recent episode be migraine with aura? Is the aura pattern typical, and does it meet IHS criteria? He reports the minimum number of episodes (total of two attacks) needed to meet IHS aura criteria, but otherwise, these episodes fail other IHS aura criteria. To have typical aura focal visual phenomena, include fully reversible positive and/or negative features with or without dysphasic speech, or positive and/or negative sensory symptoms but no motor weakness lasting greater than 5 minutes. This current event fails to meet IHS aura criteria for duration, and additionally involves atypical characteristics. These include abnormal hand movements; these may represent an episode of motor monoplegia with confusion (ischemic stroke or hemiplegic migraine), or seizure associated with confusion (complex partial seizure). There must be a concern about a valid diagnosis of migraine with aura.

Secondary headache is uncommon in the day-to-day clinical office. But as watchdogs for worrisome/sinister headache, we must be aware that 1) without typical symptoms and at least two identical attacks of aura, whether or not atypical, the cause of aura-like symptoms is suspect and requires assessment; 2) this headache history represents a significant change of pattern in neurologic phenomena and therefore deserves assessment; 3) he is a man over age 50 years with a change in his headache disorder that requires reassessment; 4) he reports a recent constant low-grade headache, and considering other factors, including that his neurologic symptoms are at least as likely to represent seizure related activity as migraine aura; and 5) his neurologic visual exam appears to be abnormal and his recent history suggests a possible visual field cut or agnosis. He requires assessment to rule out several potential underlying secondary causes.

Differential diagnosis requires consideration of a space-occupying lesion, ischemia-related brain injury, posterior fossa abnormalities including Chiari I malformation, vertebral dissection, transverse sinus thrombosis, and infectious/inflammatory processes including giant cell arteritis and isolated central nervous system angiitis. A space-occupying lesion is a strong consideration due to age, recent change in headache, and associated neurologic changes. The same can be said for stroke, although the subacute change in headache makes this a less likely explanation. Chiari I malformation is the herniation of the cerebellar tonsils 5 mm below the level of the foramen magnum, and is typically discovered associated with Valsalva or cough headache. In this age group, cough headache is typically secondary in nature. Vertebral dissection involves similar location of headache and symptoms, but is less likely to be considered without a known precipitating cervical manipulation or injury. Transverse sinus thrombosis is uncommon in this clinical setting, and while isolated central nervous system angiitis must be considered with events including seizures or confusion, this becomes a consideration only after negative work-up for the other diagnoses. Giant cell arteritis is always a consideration for this age group with headache and especially with visual complaints, but is unlikely demographically and due to lack of prior systemic "illness" symptomatology

Clinical Course

For this patient, brain magnetic resonance imaging (MRI) with and without contrast is obtained and found to be abnormal. In the right occipital lobe, there is a 5 mm × 5 mm × 2.5 mm rounded mass lesion, which demonstrates some irregular, somewhat thickened, peripheral enhancement. The

central aspect of the mass does not enhance and is of increased T2 and intermediate T1 signal, suggestive of necrosis. The mass abuts the overlying dura. Some mild associated edema just anterior to the lesion is present. Mild increased signal corresponding with the edema on diffusion-weighted imaging (DWI) either represents shine-through artifact or mild subacute ischemia; the former is favored. DWI otherwise appears within normal limits. MRI confirms the lack of vascular abnormalities. Venous-flow voids on MRI appear normal. Marrow signal appears within normal limits. Computed tomography (CT) scans of chest and abdomen are negative. An electroencephalogram (EEG) was entirely normal. An attempted total resection is performed following histologic confirmation of glioblastoma multiforme.

Management Strategies

- The correct diagnosis is dependent on appreciating the worrisome or sinister aspects of this man's history that differentiate the current headache from the diagnosis of long-standing episodic migraine without aura self-diagnosed as episodic tension-type headache.
- The "minor" abnormality on focused neurologic examination assists in determining the need for neuroimaging and the anticipation that the study(s) will be abnormal. Even if this individual's examination is normal, this case history includes several worrisome features that require neuroimaging. Regardless, the examination for functional symmetry is critical, should the patient's history not tip the balance to testing.
- Should brain MRI with and without contrast not reveal either an anticipated space-occupying lesion or other posterior fossa lesion, then additional testing including magnetic resonance angiography and magnetic resonance venography are indicated. Although an EEG is not typically indicated for headache evaluation, whether neuroimaging is normal or abnormal, a sleep-deprived EEG is appropriate due to the history of hand-twitching and confusion, which raises concern that seizure activity may warrant preventive therapy. Note that a normal EEG should not dissuade other testing. Additional studies should include tests for levels of erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, consideration of a lumbar puncture (spinal fluid pressure, cellular examination, and culture), and possibly thyroid-stimulating hormone.
- Referral to a neurosurgeon and radiation and neuro-oncologists is appropriate. Steroid therapy is optional. The neurosurgeon loaded phenytoin for surgical prophylaxis, despite a normal EEG. The patient did receive rehabilitation therapy postoperatively to assure safety and maximum function at home, and at 9 months post-diagnosis is doing well.

Case Summary

- This individual did have episodic migraine without aura, but self-diagnostic mislabeling of tension-type headaches.
- The patient describes two episodes of visual blurring with vague history about motor symptomatology, creating uncertainty about an IHS diagnosis of episodic migraine with aura. Very likely, the earlier visual symptoms can be attributed to the phenomena of central sensitization.
- Recent history suggests a subacute increase in headache, with the only evident-provoking factor being that of increased stress and travel. He experiences a visual aura not classic for positive followed by negative phenomena of very short duration with associated hand motor features. Both the duration and motor symptoms are rare in aura. The combination should raise concern for either stroke or seizure with an underlying structural lesion.
- The previous diagnosis of headaches with neurologic symptoms could cause the physician to be reassured, and defer evaluation; however, an individual with previous diagnoses of primary benign headache may have multiple causes for headaches and is not exempt from developing a secondary (sinister) headache.

Overview of Brain Tumors as Secondary Headache Subtypes

Primary brain tumors, whether malignant or benign, arise from brain or surrounding tissues. The most common primary brain tumors are glial tumors, classified by cell type or origin. The glial tumors include astrocytomas, oligodendrogliomas, ependymomas, and glioblastoma multiforme.

Oligodendrogliomas likely represent one-third of all gliomas, and are of special interest due to recognized chemosensitivity. Recent genetic markers, such as the *OLIG1/2* gene, and particularly loss of 1p and 19q chromosomes, may predict both treatment response and prognosis. Ependymomas are uncommon neoplasms of the central nervous system, and are best managed with complete resection corroborated by postoperative contrast-enhanced MRI. The role for chemotherapy is undetermined.

Specialized brain areas produce pituitary, pineal gland, and cranial nerve tumors, all of which are less common than gliomas; schwannomas are the most common cranial nerve tumors and involve primarily the fifth, eighth, and ninth cranial nerves. Meningiomas are the second most common primary brain tumors and arise from the coverings of the brain. The best treatment is aggressive surgical resection. Lymphomas are found in the brain and are frequently primary. The most common secondary tumors are metastatic and are the second most common brain tumors. They

primarily arise from breast, lung, the gastrointestine, skin, and kidneys. Metastatic brain tumors represent about 10% of the clinical presentations of systemic primary tumors.

Brain tumors are typically diagnosed upon development of neurologic deficits and not headache. In Forsyth and Posner's series of 111 consecutive patients with brain tumor, headaches were present in 48%, equal for primary and secondary brain tumors. Descriptively, headaches were tension-type in 77%, migraine in 9%, and the remainder of other types. Headache was the presenting worst symptom in only 45% of the individuals. It was typically bifrontal, but worst ipsilaterally. Unlike true tension-type headaches, brain tumor headaches were worsened by bending over in 32% and associated with nausea and vomiting in 40% of individuals. The "classic" early morning brain tumor headache (severe, awakening the patient from sleep with nausea/vomiting) is reported uncommonly and occurred in 17% of Forsyth and Posner's series. Headache is more likely to accompany the presentation of brain tumor if there is raised intracranial pressure, shift/distortion of structures, or if the patient had a previous history of headaches. Interestingly, brain tumor may develop in individuals with primary headache without any change in headache pattern. Typically, brain tumor-associated headaches become more frequent or severe than the previous headaches, and rapidly become associated with physical signs or additional symptoms. On occasion, head trauma is the precipitant for an imaging study that discloses a tumor.

Specific signs on neurologic examination very often are referable to the region affected, unless non-eloquent brain is involved, such as the right frontal lobe. In eloquent areas of the brain, such as the visual and somesthetic cortex, the motor strip, brainstem, and cranial nerves, symptoms occur relatively early. In less eloquent areas, tumors may grow relatively large before becoming clinically symptomatic. Headache is typically a nonspecific symptom whose characteristics rarely suggest a specific tumor type or location. Seizures or specific symptoms, such as loss of hearing, facial numbness, or galactorrhea, point to tumor location. Imaging typically demonstrates related brain swelling, displacement of normal neural tissues, and involvement of regional blood vessels and adjacent bone. MRI with and without gadolinium is the superior imaging technique to assess size, composition, and total tumor location. It is often difficult to tell without previous history of malignancy whether the visualized tumor on either MRI or CT scan is primary or metastatic (secondary) in nature. Multiple lesions increase the likelihood of the latter. Metastasic tumors may display well-demarcated margins and induce considerably more edema than primary tumors. Characteristic patterns, such as the "butterfly" involvement of both frontal lobes and corpus callosum, or location, such as pituitary gland, indicate primary glioma. Histologic confirmation by biopsy or resection is usually necessary in the absence of a history of other malignancy.

Most brain tumors demonstrate no gender, age, race, and geographic or socioeconomic preference. The incidence of nonmalignant tumors is uncertain, but malignant brain tumor incidence worldwide is 0.5 to 2% of all malignancies. Other general trends include the following:

- Relative increase in children less than 10 years of age
- Relative decrease between 10 and 40 years of age
- Sharp, significant increase beyond 50 years of age, particularly malignant brain tumors and meningiomas
- Minor increase in males versus females
- Significant female predominance with meningiomas

Current brain tumor treatment involves surgery, radiation therapy, or chemotherapy. Often, these options are combined. Besides tumor type, residual disease, recurrence and change in tumor histology, the age of the patient, the functional status, and treatment preference and tolerance influence management planning. Surgery varies from complete resection in less eloquent brain areas to stereotactic biopsies in the most eloquent areas. With histologic determination, malignant tumors usually receive whole brain or regional radiation, whereas stereotactic radiosurgery is applied to localized tumors of 5 mm or less in size. Implantation of radioactive seeds or local brachytherapy of certain cystic lesions is least often applied. Chemotherapy is an adjuvant therapy, with histology determining the protocol of current research choice.

Generally, prognosis is very good for most brain tumors with complete resection of benign tumors. Benign glial tumors are an exception, secondary to a tendency to degenerate histologically, thereby altering the survival rates. Five-year survival rates for malignant primary glial tumors is a poor 10% overall. With treatment, 1-year survival is 50%, whereas 2-year survival is 25%. Without treatment, patients with malignant gliomas survive less than 20% of the time at 1 year and 50% for 6 months.

Conclusions

When individuals develop new, different, or atypical headache or neurologic symptoms, and/or have abnormal sign(s) on neurologic examination, even if subtle, then diagnostic testing is required. Patient mislabeling of headache is common, and particular attention is required on the practitioner's part to review vital signs, systemic medical disorders, and to ascertain subacute headache changes and sudden onset of headache, and any different, atypical historic symptoms and physical examination signs. The threshold for testing must be extremely low in these circumstances, as our first order in diagnosis is to play an appropriate "watchdog" role for secondary headache.

Selected Readings

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Editorial Comments

Cerebral neoplasms are in the differential diagnosis of any patient presenting with headache; fortunately, the vast majority of patients will not have a tumor, especially if they have a long history of a primary headache disorder, with stereotypical features and a stable course. Nevertheless, it is prudent to investigate any patient with atypical features in symptoms or signs ("investigate the atypical"), changing headache ("investigate change of pattern"), or other red flags ("investigate focal neurologic signs"), as pointed out in this excellent case and discussion. Some patients will turn out to have incurable disease, but many will also have several therapeutic options open to them, based on advances in neuro-oncologic care and therapy. Therefore, diagnosis is still important and nothing, including advanced neuroimaging, replaces a good neurologic history and physical in the first instance.

Final diagnosis:

Headache secondary to glioblastoma multiforme