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Clinical Notes

Efficacy of Folic Acid in Children With Migraine, Hyperhomocysteinemia and MTHFR Polymorphisms

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MTHFR gene variants C677T and A1298C seem to be related to an increased risk of migraine. Folates' metabolism could play a role in the pathophysiology of migraine. We supplemented 16 children with migraine, hyperhomocysteinemia, and MTHFR polymorphisms with folic acid and obtained a resolution/reduction of migraine attacks. Although the mechanism leading to these effects has been not made clear, we believe that the use of folic acid needs further investigations in migraineurs with hyperhomocysteinemia and MTHFR variants. A randomized, double-blind, placebo controlled crossover trial is needed to support these findings.

Key words: migraine, homocysteine, MTHFR, folic acid, children

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The C677T and A1298C polymorphisms of 5,10-methylenetetrahydrofolate reductase (MTHFR) gene were associated to a reduced enzyme activity and moderately higher plasma levels of homocysteine (Hcy).[1-3] Hcy is a highly reactive amino acid producing endothelial injury via impaired release of nitric oxide (NO).[4] Hyperhomocysteinemia is an independent risk factor for thrombosis, atherosclerosis, neural tube defects in the offspring of the affected mothers.[5,6] A higher frequency of the 677TT genotype in individuals with migraine with aura (OR = 6.5) was reported in Japanese patients.[1] Kara et al found the association between the genotypes 677TT and 1298CC with migraine (OR = 5.7).[2] An increased risk in patients with migraine with aura (OR = 2.3) compared to those with migraine without aura, bearing the 677TT genotype,[7] was reported. The association between migraine with aura and 677TT genotype in Australian migraineurs was described.[4] Scher et al reported the association between MTHFR C677T polymorphisms and hyperhomocysteinemia with an increased risk of migraine mediated by an impairment of Hcy and folate metabolism.[8] Bottini et al reported an increased risk of migraine in children with 677TT and 1298CC genotypes and suggested that folate metabolism could play a role in the pathophysiology of migraine.[9]

We report 16 migraineurs children with hyperhomocysteinemia and MTHFR polymorphisms supplemented with folic acid.

PATIENTS AND METHODS

Twenty-two young subjects fulfilling the ICHD-II criteria for migraine[10] were consecutively sampled at our

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Children Headache Unit. Those who had a positive family history for cerebral and cardiovascular disorders (16/22) underwent plasma Hcy assessment and other coagulation tests. All presented higher plasma Hcy levels and were screened for MTHFR polymorphisms. All patients presented migraine without aura by chance; they were not pre-selected on the basis of the absence of aura.

We usually assess plasma homocysteine together with other coagulation studies in all children with migraine and a positive family history of cerebral and cardiovascular disorders. Hyperhomocysteinemia and MTHFR polymorphisms are also present in 2% of patients with partial cryptogenic epilepsy followed up at our Unit.

Blood Hcy was assessed by commercially available kit for high-performance liquid chromatography measurements (Bio-Rad, Italy), by fluorimetric detection and isocratic elution. We considered the higher plasma Hcy level in 30 non-migraineurs, 10- to 18-year-old male and female children, as below 9 μmol/L. The reference value of blood Hcy in children for our laboratory is 9 to 9.50 μmol/L.

MTHFR C677T and A1298C genotypes were performed according to previously described methods.[11]

Plasma levels of Hcy ranged from 9.3 to 24.6 μmol/L (see the Table). Other coagulation tests (platelet count, bleeding time, PT, PTT, D-dimers, clotting factors V,VIII, ATIII, protein C, protein S, lupus anticoagulant, antiphospholipid, and anticardiolipin antibodies), and plasma levels of both vitamin B_{12} and folates, were normal. MTHFR 677TT genotype was found in 11 patients, the 677CT genotype in 2 patients; the 1298CA genotype in 2 patients, and 677T/1298C genotype in 1 patient (see the Table).

In sum, the 16 patients (50% males) aged between 8 and 18 years (median 12) with migraine without aura, who were found to have hyperhomocysteinemia and MTHFR polymorphisms, underwent folic acid supplementation.

The patients had at least a 1-year history of migraine attacks, monthly in 12 out of 16 patients (1 to 3 attacks/month), weekly in 1 patient (1 to 2 attacks/week), and daily in 3 patients (5 to 6 attacks/week). Physical and neurological examination, ophthalmological and cardiological evaluations, and nuclear magnetic resonance, were normal in all of them.

All patients received folic acid 5 mg once daily for 6 months. The attacks' diary during the 3 months preceding folic acid supplementation and during the last 3 months of treatment, was considered. The variations of plasma levels of Hcy were considered after 6 months of treatment.

Two-tailed chi-square for categories comparison, Wilcoxon, and Mann-Whitney tests were used to compare clinical and laboratory characteristics. Significance level was set at $P < .05$.

Table.—Relevant Clinical, Biochemical, and Genetic Findings of the Patients

Patients	Attacks[†]	Hcy[‡]	Genotype[§]
I	Monthly→absent	9.3→6.0	677TT
II	Daily→absent	19.3→8.0	677TT
III	Weekly→50%	10.0→5.0	677TT
IV	Monthly→75%	9.7→6.0	677CT
V	Monthly→absent	9.7→6.0	1298AC
VI	Monthly→absent	12.8→6.0	1298AC
VII	Monthly→75%	9.8→4.7	677CT
VIII	Monthly→75%	24.6→8.0	677TT
IX	Monthly→75%	10.3→8.0	677TT
X	Monthly→absent	17.7→7.7	677TT
XI	Daily→absent	11.5→6.0	677TT
XII	Monthly→absent	9.7→5.0	677TT
XIII	Monthly→absent	10.7→6.0	677TT
XIV	Daily→absent	9.8→5.0	677TT
XV	Monthly→75%	10.9→4.0	677TT
XVI	Monthly→absent	10.6→5.0	677T/1298C

[†]Rate of the attacks during the 3 months before folic acid supplementation and during the last 3 months of the whole 6 months of treatment. The mean frequency is expressed as monthly (1 to 3 attacks/month), weekly (1 to 2 attacks/week), and daily (5 to 6 attacks/week).
[‡]μmol/L, Hcy before and after 6 months of folic acid supplementation.
[§]Patients' genotypes: 677CT heterozygote; 677TT homozygote; 1298AC heterozygote; 677T/1298C compound heterozygote.

RESULTS

Folic acid supplementation was followed by a complete resolution (100%) of the migraine's attacks in 10 out of 16 patients, by a 75% reduction in 5 out of 16 patients, and a 50% reduction in 1 patient. The plasma levels of Hcy dropped to the normal range in 100% of patients (see the Table). Statistical analysis showed a significant variation of Hcy values at follow-up during treatment (–52%; $P < .0001$). Conversely, there were no statistically significant differences between migraine attacks reduction when compared to the plasma levels of Hcy at the beginning and at the end of the treatment, to the extent of plasma Hcy reduction during treatment, and to the patients' genotype.

COMMENTS

The resolution/reduction of migraine attacks after folic acid supplementation in a group of children with migraine and familial vascular disorders, associated to hyperhomocysteinemia and MTHFR polymorphisms, was observed. MTHFR 677TT genotype was commonly found in Southern Italy (26% in Sicily).[12] Although MTHFR 677TT genotype

was associated to migraine with aura,[4] the latter was not present in our patients. An impairment of cerebral blood flow associated with a depolarization wave across the brain cortex (cortical spreading depression: CSD) is thought to be the pathophysiological mechanism of aura.[13] The pain is mediated by the activation of the trigeminovascular system (TVS).[14] The endothelial dysfunction occurring with hyperhomocysteinemia seems to be related to an impaired release of NO, leading to vascular/coagulative dysfunctions.[15] These events may contribute to the variation of cerebral blood flow and activate CSD and TVS. In our patients the reduction of plasma Hcy levels after folic acid supplementation could have interrupted this cascade of biochemical interactions, leading to the clinical improvement. However, lack of correlation between genotype/phenotype and laboratory findings, did not allow us to provide more intriguing pathogenetical hypotheses for these findings.

Folic acid supplementation might be a useful tool to treat migraine in children with hyperhomocysteinemia, since the drug would interact with an impaired biochemical pathway. A randomized, double-blind, placebo controlled crossover trial is needed to further investigate what we observed.

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Upright MRI in Spontaneous Spinal Cerebrospinal Fluid Leaks and Intracranial Hypotension

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Orthostatic headaches are the hallmark of spontaneous intracranial hypotension, but MRIs are traditionally obtained in the supine position. We investigated the utility of upright MRI of the brain in 6 patients with spontaneous intracranial hypotension. No discernable differences were noted between the supine and upright images.

Key words: headache, MRI, spontaneous intracranial hypotension

Abbreviations: CSF cerebrospinal fluid, CT computed tomography, MRI magnetic resonance imaging

Spontaneous intracranial hypotension is caused by a spontaneous spinal cerebrospinal fluid (CSF) leak and it has become well established as an important cause of new daily persistent headaches, particularly among young and middle-aged individuals.[1-3] Although a variety of headache patterns and numerous associated symptoms have been reported in patients with spontaneous intracranial hypotension, a positional headache that occurs or worsens shortly after assuming the upright position is the hallmark of spontaneous intracranial hypotension.[1-3] Most patients with spontaneous intracranial hypotension are found to have abnormalities on cranial magnetic resonance imaging (MRI), such as subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperemia, and sagging of the brain (mnemonic, SEEPS), while some have a completely normal MRI.[2] The MRI appearance of spontaneous intracranial hypotension has prognostic implications.[4] MRI scans traditionally have been obtained with individuals in a supine position, but recent technology has allowed MRI to be obtained with the patient in an upright position. We compared the results of upright MRI with that of conventional MRI to investigate possible positional changes in the MRI appearance of spontaneous intracranial hypotension.

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PATIENTS AND METHODS

Supine (conventional) and upright MRIs of the brain were performed in 6 patients with spontaneous intracranial hypotension from a confirmed spinal CSF leak. All patients presented with orthostatic headaches. Imaging sessions were performed within 2 weeks of each other and without any intervening invasive diagnostic studies, such as computed tomographic (CT) myelography, or treatment, such as epidural blood patching. Patients were in an upright position (ie, sitting or standing) for at least 30 minutes prior to upright MRI scanning. Supine MRIs were performed with a conventionally oriented 1.5 or 3.0 Tesla magnet and upright MRIs were performed with a 0.6 Tesla vertically oriented MRI system. All MRIs were obtained with and without gadolinium.

RESULTS

The mean age of the 6 patients (4 women and 2 men) was 43 years (range, 27 to 55 years). The underlying CSF leaks were confirmed with CT-myelography and were located in the cervical spine in 1 patient and the thoracic spine in 5 patients. Three patients had normal findings on MRI, 2 patients had enhancement of the pachymeninges and subdural fluid collections and sagging of the brain, while 1 patient had enhancement of the pachymeninges and pituitary hyperemia and sagging of the brain. No discernible differences were noted between the supine and upright MR images (Figure).

COMMENTS

In this study, no positional changes in cranial MR appearance were demonstrated in a group of patients with spontaneous intracranial hypotension and a confirmed spinal CSF leak, all of whom had presented with orthostatic

Conflict of Interest: The authors report no conflicts of interest.

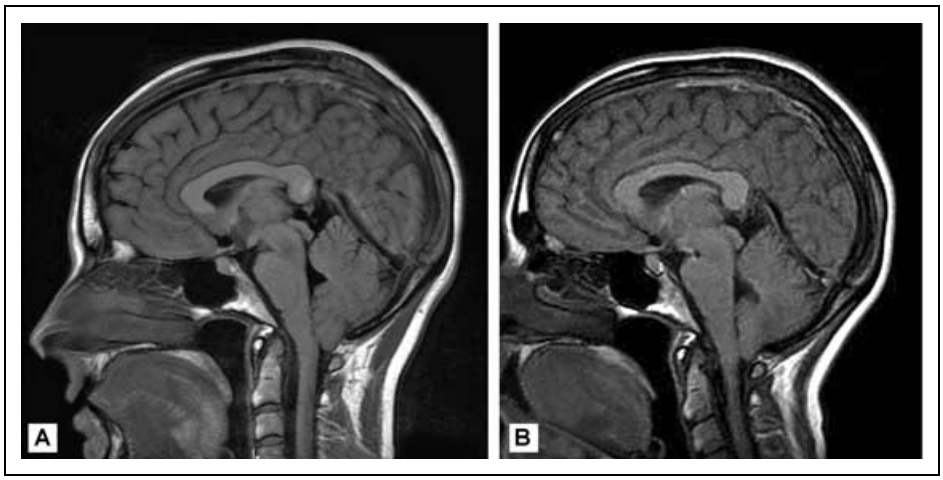

Figure.—Supine (A) and upright (B) sagittal T_1-weighted MRIs in a 49-year-old woman with a thoracic CSF leak show no differences in the severity of brain sagging.

worsening of symptoms. Because of the typically positional symptoms of spontaneous intracranial hypotension, it had been hypothesized that obtaining an MRI in the upright position would show more pronounced abnormalities, such as worsening of the sagging of the brain or the appearance of MR abnormalities in patients with normal findings on conventional MRI obtained in the supine position. Upright MRI of the spine has been shown to demonstrate changes not only in the degree of intervertebral disc herniation or cross-sectional area of intervertebral foramina,[5] but also in the diameter of the lumbar spinal dura.[6] This latter finding would indicate that positional MRI is able to detect the changes related to the redistribution of CSF from the intracranial to the intraspinal compartment that occurs upon assuming the upright position. The MRI findings of spontaneous intracranial hypotension are caused by the loss of intracranial CSF volume by decreasing CSF buoyancy (resulting in sagging of the brain) or by compensatory dilatation of venous structures (resulting in enhancement of the pachymeninges, engorgement of venous structures, or pituitary hyperemia) in order to maintain intracranial volume (Monro-Kellie rule).[7] The exact reason why upright MRI of the brain does not show any changes in patients with spontaneous intracranial hypotension remains to be determined, but it may be that in relationship to the volume of CSF lost by a spontaneous spinal CSF leak the redistribution of CSF from the intracranial to the intraspinal compartment that occurs upon assuming the upright position is relatively minor. In previous investigations, upright MRI of the brain has not been able to demonstrate any positional changes in patients with a variety of neurologic disorders, including patients with severe cerebral atrophy,[8] but its use in spontaneous intracranial hypotension has to our knowledge not been reported previously. Upright MRI of the brain has been able to demonstrate the effect of posture on CSF flow dynamics.[9] In our study, CSF flow dynamics were not measured.

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Headache Associated With Miller Fisher Syndrome

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Miller Fisher syndrome, a variant of Guillain-Barre syndrome, is composed of the clinical triad of ophthalmoplegia, ataxia, and areflexia. A variety of other symptoms and signs have been reported in this syndrome, but headache is not a commonly reported symptom. We report a 35-year-old man with anti-GQ_{1b} antibody-confirmed Miller Fisher syndrome presenting with severe and persistent headache, and we propose that the headache is caused by antibody-mediated effects on the trigeminovascular pain pathway.

Key words: chronic daily headache, Miller Fisher syndrome, polyradiculopathy

Miller Fisher syndrome (MFS) was originally described by Fisher in 1956 as a clinical triad of ophthalmoplegia, ataxia, and areflexia.[1] In addition to the classic triad, a variety of other signs and symptoms have been reported in MFS.[2] However, headache is a symptom which is not commonly associated with MFS. We report a case of prolonged headache with MFS and propose a potential mechanism for the development of headache in a minority of patients with this syndrome.

CASE HISTORY

Two weeks after a gastrointestinal illness, a 35-year-old man awakened with headache, double vision, imbalance, and left-sided paresthesias. Examination on admission the same day revealed a left-eye abduction deficit, bilateral ptosis, and bilateral leg ataxia leading to impaired ambulation. He was areflexic throughout. During the first day of hospitalization his symptoms progressed, leading to near-complete ophthalmoplegia and bilateral facial weakness. Additionally, his speech became dysarthric and he had jaw weakness causing trouble chewing.

The patient had no prior history of headaches. His headache was constant, and radiated up from the neck to the front of the head. It fluctuated in intensity throughout the course of the day, and at times it woke him up from sleep. There was no associated photophobia, phonophobia, nausea, or vomiting. Early in the course, the pain was quite severe and initially narcotics did not provide significant relief.

An MRI of the brain with and without contrast was normal. Additionally, several lumbar punctures were performed, the first showing 1 RBC/μL, 1 WBC/μL, and a protein concentration of 46 mg/dL. One week later, the lumbar puncture was repeated, and it showed 0 RBC/μL, 10 WBC/μL, and a protein concentration of 90 mg/dL. Serum anti-GQ_{1b} antibody was positive. The remainder of his laboratory studies were unremarkable.

Clinical improvement began in 6 to 7 weeks. The headache pain gradually improved, being controlled by simple analgesics, and it resolved completely after 3 months. Four months after his initial symptoms he completely recovered, except for minimal residual diplopia from persistent bilateral abducens weakness.

COMMENTS

MFS is characterized by ataxia, ophthalmoplegia, and areflexia.[1] Other features include paresthesias, ptosis, poorly reactive pupils, facial and mild limb weakness, and micturition disturbances.[2] Pain is common in Guillain-Barre syndrome (GBS), being present in 89% of patients,[3] but is less common in MFS. Two of the 3 patients in Fisher's original report[1] had headaches. One of his reported patients experienced headaches with coughing, and another had a severe headache the day prior to onset of diplopia that persisted for several days, later transforming into a cough-induced headache. In a case series of 27 patients with MFS,[4] 6 patients (22%) reported having pain early in their disease course. Of these patients, 2 had headaches. A review of 50 consecutive patients with MFS did not describe headache or pain,[2]

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though it is unclear whether or not the authors specifically inquired about these symptoms.

The pathogenesis of the headache in certain patients with MFS is uncertain. There are several plausible explanations for the headache. Some authors suggest that MFS may have some central nervous system involvement in addition to the peripheral nervous system involvement typically associated with MFS.[5,6] Lesions seen on brain[7] and spinal[8] MRI in patients with MFS also raise the possibility of a coexisting central process, though the arguments supporting CNS involvement are controversial.[9] However, our patient's brain MRI was normal, so headache directly related to CNS involvement is not a sound explanation in his case unless the lesions were below the resolution of MR imaging.

Effects of increased protein including CSF outflow obstruction at the level of the arachnoid granulations leading to increased intracranial pressure could also be considered as a potential cause of headache in this case. We do not feel that this was likely, as he reported no positional component of the headache, had no nausea, and he had no diminished visual acuity. Additionally, his headache started days before his CSF protein was found to be elevated.

Another potential explanation for headache in this disorder is an activation of the trigeminovascular pain pathway resulting from the serum autoantibodies that cause the disease process. A study investigating the ganglioside composition of the cranial nerves along with the ventral and dorsal roots of the spinal cord did not reveal a significant presence of GQ_{1b} in the dorsal roots.[10] Thus, injury to these nerves directly by anti-GQ_{1b} antibodies is not a satisfactory explanation for headache in MFS. However, the same study also revealed that GD_3 and GD_{1b} are major ganglioside components of all 12 cranial nerves along with the dorsal and ventral nerve roots. Early work in the field by Chiba et al[11] revealed that not only did patients with MFS have IgG antibodies which bind to GQ_{1b}, but in a minority of patients (3 out of 28 patients) the serum also contained antibodies with activity toward either GD_3 or GD_{1b}. It is possible that headache may be caused by antibodies to either GD_3 or GD_{1b} and the low prevalence of these antibodies in MFS patients may explain why pain is uncommon.

In conclusion, the mechanism of headache in GBS patients is uncertain. Demyelination of the cervical sensory nerve roots[12] as a result of antibodies to gangliosides GD_3 and GD_{1b} may take place in the minority of patients who develop anti-GD_3 or GD_{1b} antibodies in conjunction with the typical GQ_{1b} antibodies seen in MFS. This demyelination may serve to activate the trigeminovascular pain pathway, thereby causing headache. Future studies focusing on evaluating the antibody composition of patients with headache in conjunction with MFS will be necessary to confirm this hypothesis.

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CME

Hemicrania Continua-Like Headache due to Nonmetastatic Lung Cancer—A Vagal Cephalalgia

Randolph W. Evans, MD

A 72-year-old man presented with a 7-week history of a new onset constant severe right-sided headache associated with redness and tearing of the right eye, which resolved on indomethacin due to nonmetastatic small cell carcinoma producing a large suprahilar mass. This is the first case report of a hemicrania continua-like headache with autonomic features due to lung cancer. I propose the term "vagal cephalalgia" to include headache and/or facial pain due to nonmetastatic lung cancer and cardiac cephalalgia which result from vagal afferent stimulation.

Key words: hemicrania continua, lung cancer, vagal cephalalgia, facial pain, cardiac cephalalgia

There are 36 case reports[1-3] of current or former smokers with intrathoracic nonmetastatic to head lung cancer causing unilateral facial pain presumably due to direct tumor invasion or compression of the vagus nerve by malignant lymph nodes.[4] The pain, which is usually continuous, aching, and may be severe, has been reported in various unilateral facial locations including the maxilla, cheek, jaw, teeth, nose, eye, orbit, forehead as well as the temporal region, ear, oropharynx, throat, and neck. The most common locations are the ear, jaw, and temporal region. Ipsilateral eye tearing and redness can be associated.[3] The erythrocyte sedimentation rate (ESR) is usually elevated. Chest x-rays may not reveal the pathology in up to 20% of the cases.[2] The delay between the onset of symptoms and diagnosis may be up to 48 months.[4]

I present the first case report of a hemicrania continua-like headache with autonomic symptoms responsive to indomethacin.

CASE REPORT

This 72-year-old man was seen for a headache consultation with a 7-week history of headaches without any prior history of significant headaches. He described a right nuchal-occipital and side of the head to the temporal area (but not the frontal or orbital area) constant pressure with an intensity of 10/10. There was no associated nausea, light or noise sensitivity, or visual symptoms. He had no nares congestion or drainage. Several times daily, he would have redness and tearing of the right eye lasting a few minutes but had not observed ptosis or miosis. He had no jaw claudication or shoulder or hip girdle pain. Treatment with metaxalone and naproxen and then with levofloxacin and mometasone furoate monohydrate nasal spray did not help the pain. He was then placed on amitriptyline 10 mg at bedtime for a week but the baseline pain was still a 10/10. Tramadol 50 mg every 4 hours as necessary resulted in a mild reduction in the pain.

An MRI of the brain with and without contrast 4 weeks previously was normal fMRI except for nonspecific periventricular white matter abnormalities A chemistry profile was normal and a complete blood count was normal except for a hemoglobin of 12.6 g/dL and a hematocrit of 37.7% with a mean corpuscular volume of 87.7. Examination by an ENT physician was normal. A CT scan of the sinuses was normal. A cervical spine MRI study revealed a C5-6 disc protrusion. He then saw a neurologist 1 week prior who recommended a headache consultation.

For the prior 10 days, he reported frequent shortness of breath and intermittent anterior chest pressure, both of which were present at rest. He also reported fatigue, decreased appetite, and a 12-pound weight loss over 2 months. He had no visual complaints.

There was a past medical history of hypertension and hyperlipidemia. His other medications were aspirin, atorvastatin, and nifedipine. He had smoked 1 pack per day for 60 years but had stopped 5 months previously.

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On examination, vital signs were normal. The superficial temporal arteries were nontender with good pulses. Neurological examination was normal.

On hospital admission that day, a Westergren ESR rate was 57 mm/hour (reference range 0 to 40) and a C-reactive protein was 1.4 mg/dL (reference range 0 to 1.0). Prednisone 60 mg was given that evening and again the next morning for a presumptive diagnosis of temporal arteritis.

The prednisone was discontinued the next morning when the admission chest X-ray revealed a large mid-to-upper half mass of the right thorax. A CT scan of the chest the next morning demonstrated a 15 cm × 12 cm × 12 cm large right suprahilar soft tissue mass extending in the anterior and middle mediastinum involving the peritracheal and subcarninal spaces encasing the superior vena cava, azygos vein, right pulmonary artery, and right mainstem bronchus. There was lymphadenopathy along the right side of the pericardium, a moderate right-sided pleural effusion, and partial collapse of the right lung secondary to mechanical compression and passive atelectasis. Cytopathology of a fine needle aspiration of the lung mass revealed small cell carcinoma. Two days later, an oncologist started chemotherapy with etoposide for 3 days and the next day a single treatment with carboplatinum.

One day after the second dose of prednisone, the headache had decreased from a 10/10 in intensity to a 3.5/10. The next day, the headache was a 4/10 and the patient was started on indomethacin 50 mg 3 times daily. After 2 days on indomethacin, the headache was a 1.5/10. The headache continued to improve and was gone after 5 days on indomethacin. The indomethacin was discontinued after 6 days. The headache was then constant with an intensity of 4/10 and gradually decreased over the next several weeks to an occasional minimal pain as follow-up chest x-rays revealed a significant reduction in the size of the neoplasm.

COMMENTS

The presentation was initially a mimic of temporal arteritis. The patient met 3 of the 5 American College of Rheumatology criteria (age over 50 years, localized headache of new onset, and ESR greater than 50 mm/hour) which are associated with a 93.5% sensitivity and a 91.2% specificity for the diagnosis.[5] The mild normochromic anemia, weight loss, and rapid improvement in the headache after 2 doses of prednisone within 12 hours were also consistent with temporal arteritis.

The headache was also a hemicrania continua mimic meeting most of the International Headache Society 2nd edition criteria: unilateral pain without side-shift; daily and continuous, without pain-free periods; at least 1 autonomic feature (nasal congestion and/or rhinorrhea); and a complete response to therapeutic doses of indomethacin.[6] (It is extremely unlikely that the chemotherapy would have resulted in the reduction in the headache intensity.[2]) The headache did not meet the criteria because it had not been present for more than 3 months (7 weeks) and was not of moderate intensity with exacerbations of severe pain (always a 10/10).

Other secondary causes or associations of hemicrania continua reported include the following: mesenchymal tumor of the sphenoid;[7] sphenoid sinusitis;[8] HIV;[9] right brainstem ischemic lesion with secondary hemorrhage (ipsilateral headache);[10] internal carotid artery dissection;[11,12] unruptured cavernous internal carotid artery aneurysm;[13] prolactinoma;[14] pineal cyst;[15] head trauma;[16] and venous malformation of the right masseter.[17]

Only 1 similar case has been reported.[18] A 61-year-old smoker presented with a 6-month history of continuous right-sided headaches with superimposed severe attacks lasting hours to days completely responsive to indomethacin 50 mg 3 times daily. All of the criteria for hemicrania continua were met with the exception of associated autonomic symptoms. An MRI of the head and neck was normal. The chest x-ray was negative but the CT of the chest revealed a 2.5-cm right hilar mass on biopsy shown to be adenocarcinoma.

Several mechanisms have been postulated for the referred headache and facial pain and eye tearing and redness with vagal nerve tumor invasion or compression.[1,2,4] Sensation from the pharynx, larynx, thorax and abdomen is conveyed through general visceral afferents (GVA) of the vagal nerve to the nodose ganglion and then to the nucleus solitarius in the medulla. Sensation from the dura mater of the posterior fossa, the pharynx, and a portion of the tympanic membrane and concha of the ear via the auricular ramus is transmitted by general somatic afferents (GSA) through the jugular ganglion. Vagal afferents also converge with somatic afferents in the descending trigeminal tract and nucleus. Ear pain may result from convergence of the GVA and GSA in the medulla. Facial pain may result from convergence of the GVA at the level of the descending nucleus of the trigeminal system. Ipsilateral headache may occur because the descending trigeminal nucleus extends to the dorsal horn of the high cervical region and is a referral center for head pain.[18] The ipsilateral eye tearing and redness is due to activation of the trigemino-autonomic reflex (a connection between the nucleus caudalis and the superior salivary nucleus) by severe pain.[18]

There are now 2 reported cases of hemicrania continua-like headaches responsive to indomethacin due to lung cancer with vagal nerve involvement. When older patients, especially smokers, present with undiagnosed unilateral headache or facial pain with normal brain imaging and an elevated ESR, undiagnosed lung cancer should be considered as well as other possibilities such as temporal arteritis. If the chest x-ray is negative, a CT scan of the chest may lead to the diagnosis.

Cardiac cephalalgia or anginal headache is myocardial ischemia manifesting as a bilateral or unilateral headache.[19] Angina can also cause referred pain to the jaw, nose, tongue, mastoid, teeth/gums, palate, and ear.[20] A proposed mechanism is partial mediation of anginal pain in a minority of people from vagal afferents[21] which could account for the headache or facial pain through central convergence[22] as described previously.

I suggest a new term, "vagal cephalalgia," for these presentations, which include unilateral headache, unilateral facial pain, and cardiac cephalalgia and facial pain. The introduction of this term may increase awareness of these rare presentations.

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