Chapter 20

The Woman with Never-ending Headaches

Marcelo E. Bigal, MD, PhD

Alan M. Rapoport, MD

Fred D. Sheftell, MD

Stewart J. Tepper, MD

Case History

A 28-year-old previously healthy woman suddenly developed a new onset of chronic daily headache (CDHA). Most of the time, the headache has mild or moderate intensity and is squeezing. Sometimes (4 to 6 times per month), it has severe intensity and is throbbing. The headache is holocephalic. Since its onset 10 months ago, the headache is present most of the time every day. Usually, movement and exercises do not make the headaches worse, and the headaches are not associated with visual, motor, or sensory disturbances, as well as nausea and vomiting. She also denies that loud noise or bright light exacerbates the mild headaches. However, during pain exacerbations, she reports photophobia and phonophobia. During these attacks, movement makes the headache worse. The headaches do not awaken her from sleep.

She was using 2 to 4 ibuprofen tablets (200 mg) 2 days per week to treat her most severe pains. The results were modest.

Because of the abrupt onset of a new headache, her primary-care physician requested a neurologic evaluation. She had a normal neurologic examination, as well as normal magnetic resonance imaging (MRI) scan and lumbar puncture (LP). She used amitriptyline and verapamil, with no improvement.

Six months later, the patient was referred to a headache clinic. She was depressed and feeling tired. She said that the preventive medications she was using were increasing her weight.

She reports that she has been sleeping too much since she was put on amitriptyline. Her current dose of amitriptyline is 75 mg per day. She does not smoke, drinks infrequently, and does not exercise regularly.

Her headaches were very unusual in the past. She does not remember any headache in the previous 6 months before the beginning of her current history. Her family history reveals her mother has migraine.

The patient's physical and neurologic examinations were unremarkable. Her migraine disability assessment (MIDAS) score was 38 (severe disability). Reference to the Minessota Multiphasic Personality Inventory-2 database showed hypomania and depression.

Blood tests showed hypothyroidism. Endocrinologic evaluation was requested.

Questions on the Case

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

- What is the most likely diagnosis?
- What is the correlation between hypothyroidism and headache?
- What is the treatment strategy for this patient?

Case Discussion

The process of classification and diagnosis of headache disorders requires an orderly approach. Usually, the history is the key to diagnosis. The approach is to identify "red flags" that suggest the possibility of secondary headache, to conduct the work-up suggested by those red flags, and to diagnose specific secondary headache disorders, if present. In

the absence of secondary headache, the clinician precedes to diagnose a specific primary headache disorder. The diagnostic algorithm is presented in Figure 20-1. Common red flags, the diagnoses they suggest, and the work-up that should be considered are presented in Table 20-1.

This patient developed a new onset CDHA without any relevant history of previous headache. A new form of a CDHA is a red flag and deserves investigation. Initially, the subsidiary investigation consisted of routine blood tests, an MRI, and an LP. The results did not support a secondary cause.

Thus, the first diagnosis should be new daily persistent headache (NDPHA). According to the Silberstein–Lipton criteria, NDPHA is characterized by the relatively abrupt onset of an unremitting primary CDHA; that is, a patient without a previous headache syndrome develops a chronic headache that does not remit. It is the new onset of this primary daily headache that is the most important feature. The clinical features of the pain are not considered in making the diagnosis, which just requires absence of history of evolution from migraine or episodic tension-type headache. The Silberstein–Lipton classification allows the diagnosis of NDPHA in patients with migraine or episodic tension-type headache, if these disorders do not increase in frequency to give rise to NDPHA. According the 2004 International Headache Society (IHS) classification, NDPHA is classified in those cases where there is a new onset CDHA and the headache features resemble tension-type headache in more than 15 days per month.

Until recently, hypothyroidism was not linked to NDPHA. Previous reports linked hypothyroidism with migraine and other refractory headaches, but not with the new onset of a CDHA. Moreau and colleagues showed that 30% of patients with hypothyroidism reported headaches, improving after thyroid hormone replacement. His population target was hypothyroidism subjects, not headache sufferers. Spierings reported the

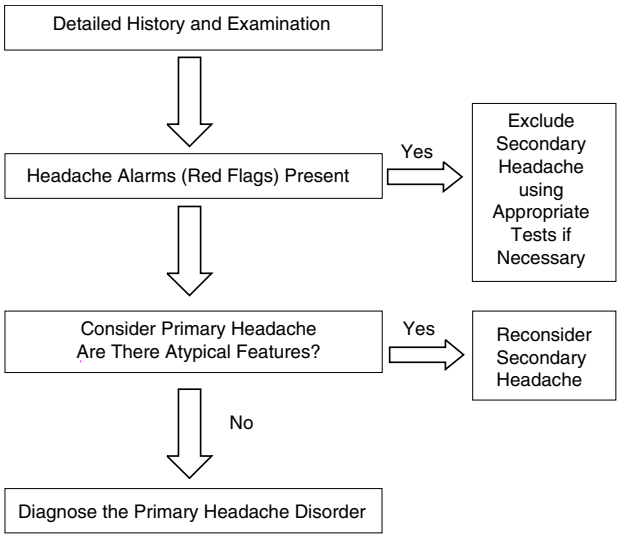

Figure 20-1. Algorithm for headache diagnosis. Adapted from Silberstein et al, 2002.

case of a 51-year-old woman with daily attacks of migraine with visual aura caused by an arteriovenous malformation, of which almost full obliteration resulted in a decrease in frequency of the aura and in intensity of the headache. Subsequent treatment of borderline hypothyroidism with levothyroxine brought about a dramatic improvement in frequency of both the aura and the headache.

We recently conducted a case-control study assessing hypothyroidism in subjects with NDPHA ($n = 65$). They were compared with migraine ($n = 100$, an episodic pain syndrome) and chronic posttraumatic headache ($n = 69$, a chronic pain syndrome). Hypothyroidism was extremely more frequent in NDPHA sufferers compared to migraine sufferers (odds ratio, 16; 95% CI, 3.6–72.0) and chronic posttraumatic headache (odds ratio, 10.3; 95% CI, 2.3–46.7). We suggested that hypothyroidism might play a

Table 20-1. Common Red Flags in the Evaluation of Headaches

Red Flag	Consider	Possible Investigation
Sudden-onset headache	Subarachnoid hemorrhage, bleed into a mass or AVM, mass lesion (especially posterior fossa)	Neuroimaging, lumbar puncture (after neuroimaging evaluation)
Worsening-pattern headache	Mass lesion, subdural hematoma, medication overuse	Neuroimaging
Headache with systemic illness (fever, neck stiffness, cutaneous rash)	Meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease	Neuroimaging, lumbar puncture, blood tests
Focal neurologic signs other than typical visual or sensorial aura	Mass lesion, AVM, collagen vascular disease	Neuroimaging, collagen vascular evaluation
Papilledema	Mass lesion, pseudotumor, encephalitis, meningitis	Neuroimaging, lumbar puncture (after the neuroimaging evaluation)
Triggered by cough, exertion, or Valsalva	Subarachnoid hemorrhage, mass lesion	Neuroimaging, consider lumbar puncture

AVM = arteriovenous malformation.

role in the development of NDPHA and should be investigated in such cases.

In a second study, we used a similar design to assess the psychological comorbidity in NDPHA sufferers. We found a higher prevalence of hypomania and depression in the NDPHA group, exactly as reported by the patient presented herein. Since hypomania and depression are very common in hypothyroidism, we assume that all the symptoms the patient reported may be related to the thyroid pathology.

In the case reported herein, the thyroid assessment confirmed that the patient had hypothyroidism. Studies suggest that subclinical thyroid dysfunction has become relatively common over the past few years, perhaps because sensitive serum thyroid-stimulating hormone assays are now readily available. Subclinical hypothyroidism is especially common in elderly women, particularly in those with underlying Hashimoto's thyroiditis, reaching up to 15% in some series. Experts recommend that thyroid peroxidase antibodies should be measured in all patients with subclinical hypothyroidism. L-Thyroxine therapy is recommended in those patients with positive antibodies because they are at greatest risk to progress to overt hypothyroidism. In the absence of positive antibodies, L-thyroxine therapy is more debatable, but might be advisable in the presence of even suggestive symptoms of hypothyroidism. At the least, thyroid function should be closely monitored to determine whether more severe hypothyroidism develops.

If we consider that hypothyroidism is strongly related to the development of this NDPHA, then we assume that we now face a secondary headache. Thus, NDPHA is not the diagnosis anymore. The 1988 IHS classification did not address headaches related to hypothyroidism. The revised version of this classification (2004) classifies headaches secondary to hypothyroidism under Chapter 10 (headaches attributed to disorder of homeostasis). Table 20-2 presents the IHS diagnostic criteria.

The approach for the case reported here was to initiate thyroid hormonal replacement. Amitriptyline was gradually tapered off and topiramate was initiated. After 4 months of therapy, she has headaches 8 days per month (30 days per month before treatment) and her MIDAS grade is III (moderate disability, compared to severe disability before the beginning of the treatment).

Table 20-2. Headache Attributed to Hypothyroidism

Diagnostic criteria:

1. Headache with at least one of the following characteristics: continuous, bilateral, nonpulsatile
2. Hypothyroidism documented by appropriate tests
3. Headache begins within 2 months after the onset of hypothyroidism
4. Headache lasts < 3 months after effective treatment of hypothyroidism

Selected Readings

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Editorial Comments

Dr. Bigal and my editorial colleagues present a very interesting case. Upon first glance, this case could be classified as NDPHA, an entity with multiple causes and relationships to other medical disorders. However, the causation is found to be hypothyroidism, and thus the patient has a true secondary headache disorder and not NDPHA per se. They then go on to describe the pertinent "red flags" in headache disorders, and the approach to diagnosis. Importantly, they highlight the relationship of thyroid disease to headache. This is an important chapter and deserves close study by readers; it introduces new nosology and understanding to the classification of headaches, which was not present in the first classification of 1988.

Final diagnosis:

Headache secondary to hypothyroidism