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Authors

Ravenborg, Noah

Kim, Sarah C

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Clinical Reasoning Case

More Than Fatigue, a Case of Narcolepsy Type 2 in a Young Healthy Male

Noah Ravenborg¹, Sarah C. Kim¹¹ Medicine, University of California, Los Angeles<https://doi.org/10.5070/V6.64293>

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Fatigue is a common presenting complaint in primary care and can be a vague concern that requires tailored questioning and a thorough evaluation. This case highlights a 27-year-old male with a past medical history of Anxiety, Depression, Atopic Dermatitis, and Hemorrhoids who presented to primary care clinic complaining of chronic fatigue. He reported long standing worsening fatigue and sleepiness during the day even in the morning upon awakening, in addition to uncontrolled anxiety and depression. On review of systems, he also reported rare intermittent bright red blood per rectum when hemorrhoids were exacerbated, without active bleeding, irritation, weight loss, abdominal pain, or family history of GI malignancy.

WHICH TYPES OF QUESTIONS WOULD YOU ASK DURING THIS HISTORY?

The differential diagnosis for fatigue is long and requires both generic and specific questions regarding the fatigue. I would first clarify the character of fatigue. Is this during exertion that could represent cardiopulmonary disease? Which activities worsen the fatigue, and which improve the fatigue? How long has this been going on for? In this patient with a history of anxiety and depression, clarifying mood is important, typically with a validated mood questionnaire such as a GAD-7 or PHQ-9. Given his history of hemorrhoids, I would want to know if these were active with potential ongoing blood loss that could cause anemia and fatigue. Lastly, asking about sleep is critical. What is your sleep schedule and pattern? How many hours do you sleep? Do you have difficulty falling or staying asleep? How do you feel when you wake up? I typically would obtain a STOP-BANG at this visit as well. Other important historical components include medical history, medications, social history, and family history, to elucidate other potential causes of fatigue.

During this patient's history, he complained of low motivation and regularly experiencing excessive worrying, intrusive thoughts, and rumination. He noted feeling excessively fatigued throughout the day and felt tired in the morning despite feeling he had an adequate night's sleep. He endorsed regularly getting 7-8 hours of sleep nightly with the same bedtime and wake time, with appropriate sleep hygiene and uninterrupted sleep, but would still feel unrested in the morning. He reported chronic snoring and difficulty moving his body upon waking for several minutes.

He was able to exercise regularly without shortness of breath or chest discomfort, or other exertional symptoms. The only medication he was taking at the time was sertraline 50 mg daily, and noted the fatigue started prior to starting sertraline. He denied alcohol or drug use and was sexually active with men, rarely, and had no history of sexually transmitted infections. Family history is notable for his father having a significant smoking history, complicated by COPD and a heart attack at age 58. He reported rare intermittent bright red blood per rectum when he was constipated and hemorrhoids were irritated, but denied regular bleeding, melena, hematochezia, abdominal pain, weight loss, fevers, chills, diarrhea, or family history of IBD or GI malignancies, and at the time of the visit he was not actively having hemorrhoid irritation. At the time of this visit, the patient had a PHQ-9 score of 10 (Moderate depression), GAD-7 score of 9 (mild anxiety), and a STOP-BANG score of 3 (intermediate risk).

On examination, vitals were within normal limits, and complete physical exam was unremarkable including no skin changes, lymphadenopathy, arthritis, pallor, or thyroid abnormalities.

WHAT IS THE DIFFERENTIAL DIAGNOSIS FOR CHRONIC FATIGUE IN THE OUTPATIENT SETTING?

I think it is best to break this up by system:

1. Neurologic – Multiple Sclerosis
2. Psychiatric – Mood disorders, substance use disorders
3. Cardiac – coronary artery disease, valvular disease, arrhythmia, heart failure
4. Pulmonary – COPD, asthma, OSA and other sleep disorders including insomnia
5. Gastroenterology – IBD, Celiac disease, IBS, liver disease
6. Renal – CKD, renal failure, electrolyte abnormalities
7. Rheumatologic – Systemic lupus erythematosus, Rheumatoid arthritis, Connective tissue disease, fibromyalgia, polymyalgia rheumatica, Sjogren's disease, myalgic encephalomyelitis/chronic fatigue syndrome
8. Infectious disease – HIV, syphilis, hepatitis, TB
9. Endocrine – adrenal insufficiency, thyroid disease, diabetes

As mentioned above, the medication list is important to review and consider as a potential cause. This includes over the counter medication such as allergy medications and sleep aids.

WHAT INITIAL WORK UP WOULD YOU ORDER FOR THIS PATIENT?

During the visit I would have the patient complete a STOP-BANG, PHQ-9, and GAD-7 which can help quickly clarify if there is a more likely etiology. A STOP-BANG score greater than or equal to 3 (correlated with intermediate risk) is 93% sensitive for moderate to severe OSA.¹ For laboratory data, a typical work up should include CBC, CMP, TSH. I then consider iron studies, ESR, CRP, ANA, HIV, RPR, HCV, morning cortisol, and vitamin D if relevant to the history and exam. I also ensure that the patient is up to date on all age-appropriate cancer screenings.

Unless there is a specific history or exam finding that warrants it, I do not obtain imaging. For example, if the patient was complaining of fatigue with a B symptom, I would obtain a CT chest/abdomen/pelvis to evaluate for lymphoma or other malignancy as an etiology.

WHAT WERE THE RESULTS OF THIS PATIENT'S INITIAL EVALUATION?

The patient had the following laboratory work up that was unrevealing including thyroid stimulating hormone, complete blood counts, iron studies, C-reactive protein, HIV, RPR, Hepatitis B and C, and Gonorrhea and chlamydia testing. No imaging was ordered given the lack of focal findings or complaints.

HOW WOULD YOU INITIALLY MANAGE THIS PATIENT'S FATIGUE?

Given there was a component of anxiety and depression that the patient endorsed and was confirmed by PHQ-9 and GAD-7, increasing the sertraline dose is a reasonable next step in the absence of significant SSRI side effects. Sertraline was changed to bedtime dosing and increased to 100 mg nightly. Although sertraline can contribute to fatigue, it was helping to treat his mood disorder and he did not complain of side effects, and it was changed to bedtime dosing to reduce the risk for medication induced daytime fatigue. I also counsel on lifestyle modifications including maintain regularly physical activity, appropriate sleep hygiene, and avoiding substances and alcohol. Given this patient also complained of chronic intermittent constipation and hemorrhoids, psyllium husk powder with water was recommended to start in addition to lifestyle modifications (avoiding straining and lingering on the toilet), with strict return precautions to discuss referring to GI and/or colorectal surgery if needed.

WHAT ARE THE "CANNOT MISS" DIAGNOSES FOR FATIGUE IN PRIMARY CARE?

When I think of "cannot miss" diagnoses for fatigue, I first think of cardiovascular disease. I would typically think of this in an older patient who complains of nonspecific fatigue with risk factors for cardiovascular disease. I would order an EKG and have a low threshold of obtain stress testing to rule out stable angina as cause of fatigue. Furthermore, fatigue can be a symptom of malignancy, albeit nonspecific. This is why basic laboratory studies and inflammatory markers can be helpful in a patient with nonspecific fatigue and more objective assessment is needed. As a PCP, I would use this opportunity to confirm the patient is up to date on age-appropriate cancer screenings. This patient did not have red flags in his history, exam, or laboratory data.

WHAT WAS THE PATIENT ULTIMATELY DIAGNOSED WITH?

After a trial of higher sertraline dose, the patient was referred to sleep medicine given fatigue persisted, with ongoing unrefreshing sleep and snoring. The sleep specialist ordered an in lab polysomnogram (PSG). The PSG did not demonstrate significant sleep-disordered breathing but did show reduced latency to primary REM. Reduced REM latency has several causes, including OSA, depression, antidepressants, and narcolepsy.² Of note, the patient's SSRI dose had been increased prior to the sleep study. Subsequently, multiple sleep latency test (MLST) was completed and demonstrated latencies to sleep onset ranging from 0 to 4 minutes, with a mean sleep-onset latency of 1.2 minutes, which is consistent with pathologic sleepiness. The patient was ultimately diagnosed with Narcolepsy Type 2.

WHAT ARE THE KEY POINTS FOR A PCP TO KNOW ABOUT NARCOLEPSY?

There are two different types of narcolepsy. Narcolepsy type 1 is defined as narcolepsy with cataplexy, which usually presents as daytime fatigue and cataplexy. Patients with type 1 narcolepsy have low CSF hypocretin levels. Type 2 is narcolepsy is defined as excessive sleepiness without cataplexy, and patients have normal CSF hypocretin levels.

WHAT IS THE ROLE OF A PCP IN NARCOLEPSY MANAGEMENT?

For type 2 narcolepsy, sleep specialists usually treat symptoms with wake promoting medications to control sleepiness. This usually includes medications such as modafinil, armodafinil, pitolisant, solriamfetol, methylphenidate, or dextroamphetamine. The role of the PCP in caring for patients with narcolepsy is critical. This should include collaborating with the sleep specialists, monitoring for side effects from wake-fulness promoting agents (eg, blood

pressure monitoring with amphetamine), educating patients on non-pharmacologic management, and evaluating for co-occur disorders. Non-pharmacologic management for narcolepsy include scheduling naps to reduce sleepiness, appropriate sleep hygiene, and lifestyle modifications including exercise, healthy diet, and reducing stress.^{3,4} Patients with narcolepsy frequently suffer from co-occurring psychiatric disorders including depression, anxiety, ADHD.⁵ Given that many of the medications used for narcolepsy are stimulants, they may worsen mood related symptoms. Other co-occurring disorders include other sleep disorders like OSA, RLS, and REM behavior disorder,⁶ and lastly patients with narcolepsy are at higher risk for cardio-metabolic disease.⁷ Patients with narcolepsy are more likely to struggle with obesity, diabetes, and hypertension.⁴ Therefore, PCPs should be vigilant in screening for and managing these comorbidities.

WHAT WAS THE MANAGEMENT AND OUTCOME FOR THIS PATIENT?

After the diagnosis of Narcolepsy Type 2, the sleep specialist worked with the patient on various pharmacotherapies to mitigate excessive daytime sleepiness. Treatment first

started with sodium oxybate which eventually caused anxiety and low appetite and was discontinued and replaced by modafinil. This was up titrated for hypersomnolence and then pitolisant was added for sleep stability. He was eventually titrated to modafinil 250 mg daily and pitolisant 35.6 mg daily with relief of daytime sleepiness.

SUMMARY

Chronic fatigue is a complex and common complaint in primary care.⁸ PCPs should remain vigilant to consider life limiting diagnoses such as cardiovascular disease or malignancy, while evaluating for more common causes. Sleep disorders are common causes of fatigue and should be considered high on the differential.^{9,10} PCPs should consider a referral to a sleep specialist when evaluating chronic fatigue to help clarify if the patient has a sleep or wakefulness disorder. Sleep specialists and PCPs should collaborate in supporting their patients with sleep disorders. Narcolepsy is not a common disorder and is often delayed in its diagnosis¹¹ and requires inter-disciplinary collaboration to help manage these patients and improve their quality of life.



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