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SLEEP MEDICINE PEARLS

"I Can't Sleep at Night" An Unusual Case of Insomnia

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A 77 year old man was referred to the Sleep Disorders Clinic for difficulty with sleeping. The patient had been seen four years previously for complaints of loud snoring, restless sleep, and daytime fatigue. At that time, he had polysomnography, which showed severe obstructive sleep apnea. The apnea-hypopnea index was 59 episodes per hour. Approximately 15% of oximetry quotings were below 90%. The minimum saturation was 82 %. The study was done as a split night study and CPAP at 10 cm of water pressure was found effective at improving his sleep disorder breathing. The patient was prescribed a CPAP unit, which he used regularly since that sleep study. For several years, he slept well at night and experienced increased energy during the daytime. However, for approximately a year prior to the current visit, he experienced disrupted sleep. He slept restlessly at night and felt tired and fatigued during the day. He reported difficulty falling asleep, and once he fell asleep he experienced awakenings during the night and difficulty falling back to sleep.

He had seen his personal physician, who prescribed zolpidem 5 mg and subsequently 10 mg at bedtime for sleep. This had minimal effects on improving his sleep. His personal physician also prescribed fluoxetine 20 mg per day, for presumed symptoms of depression. This also had minimal effects on his sleep

The patient reported that in the prior months, he had developed an unpleasant and uncomfortable sensation in his legs that started in the evening and intensified at bedtime. The unpleasant sensation felt as though he had to move his legs constantly, and interfered with his ability to fall asleep and to stay asleep. His only relief came when he got out of bed and paced the floor in his bedroom, or stretched his legs. The sensation typically resolved by approximately 3 am, allowing him to sleep soundly after this time. He did not experience the sensation during the daytime. The patient's wife reported that his legs seemed especially restless at bedtime and during sleep over several months. She observed that he frequently moved or kicked his legs during sleep and would sometimes strike his spouse. She noted that he tossed and turned excessively throughout the night and he could no longer use his CPAP.

Further history revealed that approximately one month prior to the visit, the patient began to develop recurrent chest pain associated with exertion. His past medical history was significant for coronary artery disease, and approximately three years previously had undergone coronary artery bypass graft surgery. At that point he was referred to a cardiologist. Because of the symptoms of poor sleep, he was also referred for a sleep disorders consultation.

Laboratory studies were pertinent for hemoglobin of 8.6 grams per dL, and hematocrit of 25%. The MCV was 74 fL. The white blood cell count and platelet counts were normal. Serum ferritin level was 18 mcg/L. Iron was 35 micrograms/dL. Percent saturation was 10%. Sedimentation rate was 40. A review of a blood smear showed microcytic red blood cells. Remainder of laboratory studies were unremarkable. Electrocardiogram was normal. A stool study for occult blood was positive. A nuclear MIBI exercise test demonstrated an area of ischemia with exercise in the distribution of the left anterior descending artery. Echocardiography showed an ejection fraction of 50%, hypokinesis of the anterior wall of the left ventricle, mild mitral regurgitation, and mild aortic insufficiency. He was then admitted to the hospital.

What is Your Diagnosis?

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Restless Legs Syndrome Precipitated by Iron Deficiency Anemia from a Slowly Bleeding Colon Cancer

This patient's complaint of disturbed sleep was due to the development of restless leg syndrome (RLS) due to iron deficiency anemia caused by a slowly bleeding colon cancer. The anemia also precipitated angina due to coronary artery disease. Restless leg syndrome is a common condition that causes sleep disturbance and is associated with insomnia. Several studies show its prevelance in the population is approximately 5-10%.[1,2] While it is more common in adults and in the elderly, it can also occur in children.[3] RLS may be primary (idiopathic), or may be secondary to several causes. There is a strong hereditary component; approximately 50% of patients with idiopathic RLS have a positive family history.[4,5] A recent NIH consensus conference defined four main criteria for making the diagnosis of RLS.[6] The four essential criteria are.

1. An urge to move the legs commonly associated with an unpleasant or uncomfortable sensation in the legs.

2. The symptoms begin or worsen with inactivity, such as lying or sitting,

3. The urge to move or unpleasant sensations are partially relieved with activity such as walking or stretching at least as long as the activity continues.

4. The urge to move or unpleasant sensations are worse during the evening or the night compared to the day time. Most patients will not experience restless legs during the day time.

All four are subjective symptoms that the patient describes; there are currently no objective tests in the diagnostic criteria. Other criteria that support a diagnosis of RLS are a family history of RLS, a therapeutic response to dopaminergic drugs, and the finding of periodic leg movements of sleep on polysomnography. Patients may have difficulty describing the uncomfortable sensation that they experience in their legs. It may be described as "creepy crawly" feeling, like "bugs crawling" underneath the skin, an unusual burning sensation, or a pulling or grabbing sensation. It is unusual, but some patients will describe the sensation as painful. Typically, restless leg syndrome involves primarily the legs, but in some patients they may experience this in the arms or the trunk. Restless leg syndrome is associated with disturbed sleep, both initially and in the middle of the night. Neurological examination is typically normal. However there are some reports that there may be subtle EMG abnormalities is some patients with RLS.[7]

RLS should be distinguished from sensory or motor neuropathy of the lower extremities which may produce similar symptoms. However peripheral neuropathy can be diagnosed by neurological examination, EMG and nerve conduction studies. Peripheral neuropathy is not characterized by a primary urge to move the legs, is not relieved by movement, and does not have circadian variation. RLS should also be differentiated from a similar condition known as "painful legs and moving toes" syndrome. In this syndrome, severe pain in one or both feet is characteristic with a burning sensation, and repetitive movements of the toes. However, the symptoms are not characteristically worse at night or relieved by activity. Leg cramps involve a painful contraction of the gastrocnemius muscle that occurs in the middle of the night. The pain can be relieved by strong dorsiflexion of the foot.[8]

RLS may be idiopathic or can be associated with a variety of secondary causes. End-stage renal disease, pregnancy, and iron deficiency anemia have been identified as secondary causes of RLS. RLS occurs in approximately 15-40% of patients with end stage renal disease treated with hemodialysis. RLS appears to be an independent risk factor for mortality in this group, and has been reported to resolve with kidney transplantation.[9,10] RLS also occurs commonly during pregnancy, usually in the third trimester, and usually resolves within several days following delivery.[11,12] Recently, an association of restless leg syndrome with iron deficiency has been identified.[13,14] Both renal failure and pregancy can be associated with iron deficiency anemia. Other conditions associated with iron deficiency such as frequent blood donations, rheumatoid arthritis, and gastric surgery may also be secondary causes of RLS. Iron replacement including intravenous administration can improve or resolve symptoms of RLS.[15,16]

Although the serum level of iron is commonly decreased in these secondary causes, the most sensitive test discovered so far seems to be the ferritin level. A ferritin level of less than 50 mcg/L is associated with restless leg syndrome.[13] However, patients with idiopathic RLS but normal serum iron levels have been found to have abnormal CNS iron levels. One study showed that in patients with idiopathic RLS and normal serum ferritin and iron levels, cerebrospinal fluid ferritin was reduced and transferrin was increased suggesting a deficiency of iron in the central nervous system.[17] MRI studies in patients with idiopathic RLS have shown reduced iron in the area of the substantia nigra (SN) and putamen in patients with RLS compared to controls.[18] An autopsy study of patients with RLS reported a reduced iron content in the substantia nigra.[19] The presumed pathophysiology is that iron is necessary for the synthesis of dopamine,[14] and since the SN contains the cell bodies for the dopaminergic nigrostriatal system, reduction in iron likely reduces synthesis of dopamine in this system. Based on this evidence, it seems probable that RLS involves an abnormality of dopaminergic function in this part of the CNS.

The diagnosis of RLS is based primarily on the clinical history. The typical history supported by a positive family history or a response to treatment with dopaminergic drugs is highly suggestive of the diagnosis. Most cases do not require diagnostic evaluation with polysomnography. Periodic leg movements during sleep occur in approximately 85% of patients with RLS. However, PLMS may occur in patients with other sleep disorders, such as obstructive sleep apnea and narcolepsy, and some RLS patients do not have PLMS,[4] so the finding of PLMS on polysomnography is not diagnostic of RLS.

In some cases, the diagnosis is not clear based on the history, and there is interest in developing objective tests to confirm the diagnosis or to monitor response to treatment.[20] Periodic leg movements while awake (PLMW) may also be observed in association with RLS. PLMWs can be observed and measured using anterior tibialis EMG recordings while the patient is awake lying in bed or sitting prior to sleep during the polysomnogram. PLMWs occurring greater than 15 per hour appears to be accurate in supporting a diagnosis of RLS.[21] A similar test, the suggested immobilization test (SIT) is done an hour before a polysomnogram. The patient is asked to sit reclining in bed at about a 45 degree angle with the legs relaxed but held straight out. The patient is asked to remain awake and to resist moving the legs. The EEG and the EMG are recorded while the patient fills out a diary assessing symptoms and discomfort. A PLM index of greater than 12 per hour during the SIT was found to be supportive of a diagnosis of RLS.[21] These diagnostic tests have been developed, but require more validation

before they are done routinely in most sleep disorders centers.

There is a range of options of treatment for restless leg syndrome.[22,23] Dopaminergic agents generally are believed to be the most effective therapy for restless leg syndrome. These include levodopa, pergolide, pramipexole, and ropinirole. Ropinirole is currently the only drug with specific FDA approval for the indication of treatment of restless leg syndrome. Pergolide has been associated with heart valve abnormalities and is not commonly used.[24] Levodopa is generally formulated as a combination with carbidopa and there has been extensive study using carbidopa/levodopa in the treatment of RLS. The response to dopaminergic agents can be quite dramatic and virtually all patients experience relief when treatment is initiated at doses much smaller than is typically required for treatment of Parkinson's Disease. However, one complication of the dopaminergic agents, especially carbidopa/levodopa is the development of augmentation of RLS. Augmentation occurs when the symptoms of RLS become more severe and begin to occur earlier in the day than before treatment. Augmentation may become severe enough to require discontinuation of the medication.

Anticonvulsants such as gabapentin and carbamazepine have also been found to be effective. Gabapentin is generally effective and well tolerated. However, it is usually employed as the second-line treatment in patients intolerant of dopaminergic agents or who have developed augmentation and require an alternative therapy. Opioids, such as codeine, propoxyphene, methadone, fentanyl and tramadol have been studied and found to be effective in treating RLS. Benzodiazepines such as clonazepam, triazolam, and temazepam have also been used frequently. It is not clear that the benzodiazepines actually suppress the restless legs, or more likely suppress the arousal associated with the restless legs, and facilitate sleep via the latter mechanism.

In evaluating a patient with restless leg syndrome, it is important to perform an evaluation for conditions which may lead to a state of iron deficiency. Measuring the complete blood count, iron level, and a serum ferritin level are often important in evaluating these individuals. If the patient's serum ferritin level is reduced or even borderline reduced, there should be an evaluation for iron deficiency. Treatment with supplemental iron has been shown in some studies to be effective in the treatment of restless legs.

FOLLOW-UP

A blood transfusion was administered and supplemental iron therapy was started for iron deficiency anemia associated with angina and dyspnea. The patient underwent cardiac catheterization and was found to have narrowing of the graft that supplied the distal left anterior descending artery. Percutaneous coronary intervention was performed and stenotic area was dilated and a coronary stent placed. Subsequent to this procedure, the patient noticed marked improvement in angina and dyspnea with exertion.

Following his cardiovascular evaluation and successful treatment, a barium colon radiograph demonstrated a 5 cm lobulated mass arising from the lateral wall of the ascending colon near the level of the cecum. Colonoscopy confirmed that this was an adenocarcinoma. The patient underwent a right hemicolectomy and was found to have a stage 2 colon cancer. He had an uneventful recovery from surgery.

Postoperatively, he was given further oral iron supplementation. When seen in follow-up, the hemoglobin level had improved to 12.6 grams per dL. The serum ferritin level had increased to 58 mcg/ L. The iron level had increased to 95 mcg/dL and the percent saturation had increased to 40%. The patient noticed a significant improvement in his sleep. The sense of restlessness in his legs had markedly decreased. He continued zolpidem 5 mg at bedtime which helped improve his sleep onset and improved his ability to tolerate CPAP. Three months later, his sleep was much more consolidated. The restless leg syndrome had improved markedly. He continued to use CPAP and used intermittently zolpidem 5 mg at bedtime.

CLINICAL PEARLS

1. In evaluating a patient with a complaint of insomnia or disrupted sleep at night maintain an open mind for potentially serious causes of the complaint of insomnia.
2. Restless leg syndrome is a common condition occurring in up to 10% of the adult population and is a common complaint associated with insomnia.
3. RLS may be idiopathic and is often associated with a positive family history.
4. Restless leg syndrome can be secondary and is associated with iron deficiency anemia, pregnancy, and uremia; the latter two conditions often associated with iron deficiency anemia. In patients complaining of restless leg syndrome, a complete blood count, iron level and serum ferritin level should be measured. If iron deficiency anemia is found, a search for secondary causes should be undertaken. Iron replacement therapy is often effective at treating RLS.
5. Dopamine agonist drugs are the most effective drugs in the treatment of RLS. Alternative medications include gabapentin, opiods, and benzodiazepines.

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