Information

Restless Legs Syndrome

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IN A SERIES OF ARTICLES from 1944 through 1960, Ekbom brought attention to an odd condition characterized by ill-defined, unpleasant sensations in the legs that produced an irresistible urge to move, which he dubbed "restless legs."[1] Admittedly his was not a novel observation, as earlier accounts of probably the same syndrome can be found scattered in the medical literature. The 17th century neurologist Thomas Willis has generally been credited with the initial description of the restless legs syndrome. In 1880 Beard had written about a state in which "fidgetiness and nervousness, inability to keep still—a sensation that amounts to pain—is sometimes unspeakably distressing. When the legs feel this way, the sufferer must get up and walk or run."[2] Yet, perhaps because of the peculiar and subjective nature of this condition, the symptoms were very often dismissed as psychogenic in origin and the syndrome went ignored.

Even today, the restless legs syndrome frequently goes unrecognized or misinterpreted by primary care physicians, the very people who are most likely to encounter it. Indeed, it has been estimated that 5% of the population will suffer from the syndrome to some degree at some time in their lives. While this figure may be a bit inflated, new therapeutic possibilities make it worth reviewing at this time.

Clinical Features

The restless legs syndrome can be recognized by the clinical triad of unnatural feelings in the legs that only appear when the limbs are at rest and are associated with an irresistible urge to move to obtain relief. Descriptions of these queer sensations vary widely but share an uncomfortable quality. In Ekbom's series the feelings were usually of a deep-seated creeping or crawling nature located in the lower legs (although the thigh and even the upper extremities can be affected). Involvement was bilateral but not always symmetric. Others have found that adjectives such as "aching," "prickling," "tingling" and "pulling" are used just as often and that many patients are unable to differentiate whether the discomfort is superficial or deep.[3]

More distinctive than the quality or location of the sensations are their appearance only at rest and temporary amelioration by movement. While the discomfort is usually most noticeable at night, it can occur anytime a patient must sit still for a long period or is not particularly stimulated. One can often elicit a history of the syndrome being aggravated during a boring movie, reading a dull book or when watching television.

Most patients find daytime symptoms, if present, merely mildly annoying; it is at bedtime that the condition often reaches its most distressing proportions. Commonly, the paresthesias commence or worsen shortly after going to bed and interfere with falling asleep. Some patients report initially falling asleep normally, only to be awakened within hours by the discomfort. Episodes can recur during the night.

With occurrence of the sensations, there is a compulsion to move the legs for relief. Patients may stretch or massage their legs, thrash them about in bed or get up and walk around. While in mild cases the sensations gradually disappear, those more severely afflicted may be up most of the night pacing about. Insomnia can be the predominant complaint in the restless legs syndrome.

Along with their voluntary movements, patients may notice spontaneous jerking of the legs, especially at night. Questioning of bed partners often reveals that these patients kick in their sleep. Polysomnographic studies of patients show repetitive activity occurring before the onset and persisting during the first few hours of sleep.[4] These movements, manifest by dorsiflexion of the foot, along with flexion of the knee and hip, recur with a certain periodicity, such as every 20 to 40 seconds, and are termed periodic movements of sleep. These are not specific for the restless legs syndrome, having been observed in a variety of sleep disorders. Furthermore, periodic movements of sleep are not always present and may be a nonspecific consequence of chronic sleep-wake disturbances.

The syndrome can present in any age group and has allegedly been identified in persons ranging from 1 to 82 years old. Ekbom was unable to detect any age- or sex-related preponderance of the syndrome; a recent survey of 174 patients, however, found about 70% of those affected to be women, with a higher prevalence among middle-aged people.[5] The severity is highly variable, with mild cases often only discovered by specific questioning and not particularly disturbing to the patient. While the syndrome mostly occurs in isolation, it has been seen on a familial basis and in association with a number of other conditions (see below).

The course may extend over years to decades, being punctuated by periods of remission and exacerbation. There is no information on how treatment influences the natural history of the syndrome. In and of itself, the condition is considered benign.

Diagnosis

Identification of the condition is based entirely on the historical findings of unpleasant sensations in the legs appearing at rest that induce an irresistible urge to move to obtain relief. There are no characteristic physical signs nor are there any diagnostic tests.

Unfortunately, the medical literature is contaminated by reports that use the term "restless legs" in a more liberal

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sense. For example, some suggest that the syndrome can take a "pure motor" form without sensory symptoms.[6] It is certainly conceivable that partial forms of the syndrome exist, but because accurate classification is essential for meaningful study of the restless legs syndrome and its response to therapy, strict adherence to diagnostic criteria is encouraged.

Other conditions can mimic certain fragments of the syndrome. Uncomfortable sensations, often worse at night, can result from peripheral nerve disease of any cause. These paresthesias, though, do not necessarily produce an impulse to move and are not predictably relieved by movement. Moreover, the sensory and reflex examinations usually elicit abnormalities. Akathisia, that is, involuntary motor restlessness without sensory symptoms, is most commonly seen as a side effect of antipsychotic medications but may occur in encephalopathic states or dementia.[7] While these patients move and fidget constantly, they are usually able to sleep well at night in the absence of other complicating illnesses.

Etiology

As in other syndromes, a variety of disorders may be capable of producing this condition. While most cases are apparently idiopathic, a number of causes have been suggested.

The observed familial occurrence of the syndrome has led some to postulate an hereditary component. Though no systematic genetic study has been done, possibly a third or more cases have a familial incidence. An autosomal-dominant mode of inheritance has been suggested.[8]

Deficiency states have been implicated in producing the restless legs syndrome. In a series of 50 unselected neurologic outpatients with iron deficiency, nearly 25% admitted to the syndrome.[1] Similarly, a fourth of 77 unselected patients with the syndrome had low serum iron levels and in 10 iron-deficient patients with the disorder, symptoms were alleviated with iron therapy.[1] Folate deficiency has also been incriminated as an etiologic factor in both acquired and familial cases.[9] Still, most patients with restless legs have normal iron and folate values, and most patients with these deficiencies do not suffer from the syndrome.

Perhaps the highest incidence occurs in patients with uremia. Reportedly 15% to 20% of uremic patients on dialysis have the syndrome.[10] That dialysis itself is not the causative agent is shown in an earlier study that found 40% of nondialyzed patients with uremia experienced it.[11] Moreover, there appears to be no correlation between clinical evidence of peripheral neuropathy and occurrence of the syndrome.

Pregnancy has long been recognized to precipitate or exacerbate the syndrome. Indeed, its incidence in pregnant women has been said to be from 11% to 27%.[1] Symptoms tend to begin after 20 weeks and disappear soon after delivery. Some women are symptomatic only when pregnant and may experience recurrences with subsequent pregnancies. It has been proposed that a relative folate deficiency (due to increased demands during pregnancy) may contribute to the development of the syndrome.[9]

Emotional factors have been thought by some to be of importance in producing restless legs. Gorman and coworkers were impressed with the high incidence of depression and anxiety in patients with the condition, which they felt were not simply due to chronic discomfort.[3] In contradistinction, Ekbom found most of his patients to be "well-balanced persons without mental disturbances."[1]

Various other conditions have been reported in association with (usually anecdotally) or hypothesized to cause the restless legs syndrome, including cancer, prostatitis, polio, myokymia, barbiturate withdrawal, diabetes, prolonged exposure to cold, avitaminosis, cholesterol-crystal embolization, acute porphyria and following therapy with prochlorperazine or promethazine hydrochloride.[1,3,12] The significance of these relationships is dubious at best.

Pathogenesis

An intriguing and inscrutable aspect of this syndrome is its neurophysiologic basis. There is no obvious thread that ties together the heterogeneous group of disorders. It is possible that more than one pathogenetic mechanism exists; certainly many have been proposed.

Several authors have proposed a peripheral origin. Based on his impression that symptoms could be relieved by vasodilator drugs, fever and movement, Ekbom felt that there might be an accumulation of metabolites in the limbs. Similarly, some have speculated that prolonged muscle contraction may play a role.[3] Callaghan, in his review of the restless legs syndrome in cases of uremia, contended that it may result from irritation or damage to peripheral nerves. Others, though, have been unable to document electrophysiologic findings of neuropathy consistently in patients.[3]

The idea that dysfunction in the central nervous system at either the level of the spinal cord or the brain underlies the syndrome also has it advocates. Motor neuron disease and disturbances in the γ or reticular systems have all been suspected in its pathogenesis. Menninger-Lerchenthal asserted that it is due to iron deficiency in the basal ganglion.[13] Our theory is that the syndrome is due to perturbed sensory processing within the central nervous system. Many of the drugs promoted as beneficial in its treatment (see below) are known to affect various neurotransmitter systems in the brain and spinal cord involved in pain modulation and transmission. Dopaminergic projections, for example, extending from the caudal diencephalon to the dorsal horn of the spinal cord, have been identified in animals and are believed to regulate nociceptive responses.[14]

Unfortunately, there is no convincing evidence for any of these hypotheses. Thus, the pathogenesis must remain obscure until better means of unraveling this mystery are developed.

Treatment

Lacking any clear understanding of the disorder's pathophysiology, the treatment of patients with it has been empiric. A wide variety of pharmacologically diverse agents has been tried with variable responses.

Certainly in view of the reported association with iron or folate deficiency, it would make sense to check these values in all cases and correct when necessary. In fact, one may want to routinely prescribe a daily multivitamin that contains folate and iron.

Where no deficiency state is demonstrable, clinicians have a number of medications to choose from. Regrettably, the scientific data on which one might base a therapeutic decision are feeble. There have not been any controlled clinical drug trials of significant size or duration; the fluctuating nature of

the syndrome and known placebo effect make interpretation of anecdotal reports difficult.[5]

In the earlier literature, various presumed "vasodilators" were recommended. Other therapies that are said to be helpful include intravenous injections of dextran, propranolol hydrochloride at doses of 5 to 30 mg at night, methysergide maleate, clonidine and baclofen.[1,15-17] The use of carbamazepine was concluded to be more effective than a placebo in a recent short-term study.[5] Narcotic analgesics at low doses may reduce symptoms in some patients but should be avoided due to the risk of addiction.[18] Benzodiazepines have been used, with conflicting results. Some clinicians have found diazepam and chlordiazepoxide hydrochloride of value.[1,15] There have been recent reports, though, that 1 to 2 mg of clonazepam at bedtime or in split doses, alone among the benzodiazepines, suppressed the symptoms of the syndrome.[10] Administering dopaminergic agents also may be efficacious. Akpinar was able to abolish symptoms of the syndrome in five patients with the use of levodopa combined with benserazide (a dopa decarboxylase inhibitor); similar results were obtained using bromocriptine mesylate, 2.5 to 5 mg a night, in three patients.[19] Likewise, we have found the combination carbidopa/levodopa at doses from 25/100 to 25/250 mg twice a day to be beneficial in uremic patients with the restless legs syndrome.

As anyone who has treated many patients with this syndrome will attest, certain patients will be resistant to all of the previously mentioned medications. With these patients, we emphatically advise restraint before embarking on aggressive (and potentially harmful) therapy for this benign condition.

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California Birth Defects Monitoring Program

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THE California Birth Defects Monitoring Program (CBDMP) operates a large, population-based registry of children with structural congenital anomalies. The conditions being monitored (generally included within the *International Classification of Diseases, 9th Rev—Clinical Modification* codes 740-0 to 759.9) encompass disabilities due to irregularities in the development of internal and external organs and limbs, chromosomal anomalies and syndromes. The program, run by the California State Department of Health Services and the Health Officers Association of California, collects data to provide information on the prevalence of structural anomalies and to determine whether birth defects are related to suspected etiologic agents.

The program currently operates in 16 counties of California, with 165,000 births annually (Alameda, Contra Costa, San Francisco, San Mateo and Santa Clara counties for births beginning January 1, 1983, and Fresno, Merced, Monterey, Napa, Orange, Sacramento, San Joaquin, Santa Cruz, Stanislaus, Tulare and Yolo counties for births beginning January 1, 1986). On January 1, 1987, the program will be expanded to an additional 21 counties throughout California.

The program requires no reporting of congenital anomalies by either physicians or hospitals. Instead, program staff visit all hospitals and other data sources that serve children in the eligible counties. They have the legislative authority to abstract information on children and to enter this data in a confidential computer file at the State Department of Health Services. Only statistical summaries are released. Nonconfidential data will be readily available to any qualified scientist who submits a research protocol to the CBDMP.

Data from 1983 show an overall prevalence rate of severe congenital anomalies in the San Francisco Bay Area of 2.4%, and 60% of the cases were in male infants. Condition-specific rates were remarkably similar to prevalence rates in Atlanta where the Centers for Disease Control operate a similar, but much smaller, birth defects registry.

The causes of most birth defects are not known. The CBDMP represents the largest comprehensive effort to systematically collect data on children with congenital anomalies in the United States. As such, it serves as an important epidemiologic resource to help identify causes and to ease fears about suspected agents.

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