

## DOES THE SUCCESSFUL TREATMENT OF VENOUS INSUFFICIENCY CURE SECONDARY RESTLESS LEGS SYNDROME

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### BACKGROUND:

Restless Legs Syndrome (RLS) is a common sensorimotor disorder in which patients experience intense unpleasant sensations deep in the legs that are accompanied by an irresistible urge to move the affected limbs. The sensations are frequently impossible for patients to characterize, but are often described as creeping-crawling, pulling, drawing, boring, wormy, etc. The sensations are painful in about 30% of patients. There is a wide variation in severity. Some patients have only occasional episodes of mild symptoms, while others struggle with disabling episodes on a daily basis<sup>1</sup>. The sensations are usually located in the calf area, but may be felt anywhere from the ankles to the thighs. The arms are rarely involved.

Symptoms of RLS are worse at night and during periods of relaxation and decreased activity, especially while lying down or reclining<sup>1</sup>. Patients often find that they are completely asymptomatic in the morning. Moving the affected limbs, walking, massaging the afflicted area, and stretching bring temporary respite; but the sensations return with cessation of movement. The reason for this is not known<sup>2</sup>. The desire to relieve the symptoms can lead to a compulsion involving excessive limb movements. The sensations and the compulsion to relieve them frequently become quite distressing<sup>2</sup>. As the symptoms of RLS are stronger in the evening, sleep-onset insomnia is quite common. Patients often find they sleep best toward the end of the night or during the morning hours. Patients with severe RLS experience nightly symptoms that lead to chronic sleep-deprivation with all of its accompanying cognitive deficits<sup>3,4,5</sup>.

RLS affects 5%-15% of the general population with a mean age at onset of 27.2 years. Onset is before age 20 in 38.3% of patients. It is frequently unrecognized or misdiagnosed and therefore widely under treated<sup>6</sup>.

The International Restless Legs Study group developed the diagnostic criteria for RLS. Meeting the following 4 criteria is necessary and sufficient for the diagnosis:

1. Urges to move the legs usually associated with abnormal sensations (paresthesias)

2. Motor restlessness, including one or both of two types: a) voluntary movements to reduce symptoms, and b) smooth, short (0.5-10 second) bursts of involuntary, usually periodic, limb movements occurring mostly when the patient is reclining.
3. Onset or exacerbation of symptoms by rest and marked relief by activity, particularly walking.
4. A pronounced circadian (daily) pattern with symptoms significantly greater in the evening during the sleep time (maximal between 10 PM and 2 AM) and much less later in the morning.

A National Institutes of Health (NIH) consensus panel modified these criteria in 2003 to include:

1. An urge to move the limbs with or without sensations
2. Worsening of symptoms at rest
3. Improvement with activity
4. Worsening of symptoms at night.

RLS is divided into Primary or idiopathic RLS and secondary RLS. Primary RLS is the most common form. It most likely represents a heterogeneous group because no single pathophysiologic mechanism explains all the clinical features exhibited<sup>7</sup>. Primary RLS is thought to be associated with central nervous system dysfunction involving abnormal brain iron metabolism and subsequent irregularity of central dopaminergic neurotransmitter pathways<sup>7,8</sup>. Extensive research over the last decade has led to better understanding of primary RLS and to improved relief of symptoms using new drugs of various classes<sup>7</sup>. Despite this research, however, the exact cause of primary RLS remains elusive. Treatment has therefore focused on symptomatic relief rather than cure. None of the drugs used to treat primary RLS have been entirely successful, and all of them are associated with contraindications and side effects.

Secondary RLS is known to occur in and is secondary to such disparate conditions as iron deficiency, renal failure, pregnancy, neuropathy, and venous insufficiency. Various medications such as certain antipsychotics, antihistamines, mirtazapine, tricyclic antidepressants, and serotonergic reuptake inhibitors are known to exacerbate existing RLS or possibly even to precipitate RLS<sup>8</sup>. Other causes are quite likely<sup>9</sup>. Secondary RLS should routinely be ruled out before the diagnosis of Primary RLS is entertained, as this is the patient's only chance for cure rather than ongoing symptomatic treatment.

The fact that RLS is a "mixed bag" diagnosis has likely complicated research and confounded investigators, as treatments work on only a portion of the test subjects. The authors believe that by "weeding out" those patients suffering from secondary RLS, the treatment of primary RLS will be more successful. In

addition, those patients with secondary causes can frequently be cured of this distressing malady. In this study, the authors will focus on venous insufficiency as a curable cause of RLS<sup>9</sup>.

Venous insufficiency has been defined as “the relative impedance of venous flow back to the heart”<sup>10</sup>. This impedance is caused by outflow obstruction, reflux or a combination of both; and can occur in the deep or superficial veins<sup>11,12</sup>. Deep venous insufficiency results from valvular destruction suffered in deep venous thrombosis. Superficial venous insufficiency frequently occurs when high-pressure deep venous blood refluxes into the superficial venous system via incompetent perforator veins, at the saphenofemoral junction (SFJ), or at the saphenopopliteal junction (SPJ). Superficial venous insufficiency also occurs as a result of sequential failure of valves within the superficial veins<sup>12</sup>. The loss of normal valve function leads to venous hypertension within the affected vein. This high venous pressure is transmitted to the diseased vein’s tributary veins and thus to the venules and ultimately to the entire capillary bed draining into the refluxing vein. These high pressures cause the veins to dilate and become engorged. Eventually the veins may become varicose.

The high venous pressures are ultimately transmitted to the interstitial tissues they drain. According to the Starling concept, most of the fluid forced out of the capillary at the arterial end is returned to the lumen at the venous end. In tissues affected by venous hypertension this delicate balance is disrupted. The high hydrostatic pressure found in the venules and capillaries in these patients causes a net increase in the fluid remaining in the interstitial space. This increased fluid volume in the interstitium overwhelms the lymphatic capacity, resulting in edema formation. As long as the leg is dependant, the interstitial fluid continues to accumulate until the tissue pressure rises to a point at which the Starling equilibrium is restored. Considerable edema can accumulate before this point of equilibrium is reached. Upon elevation of the leg, (such as when the patient is lying down or reclining) the venous pressure diminishes to normal levels, and the lymphatics can drain the engorged interstitial tissues<sup>13</sup>.

Venous insufficiency is quite common. It affects 10% to 15% of adult men and 20% to 25% of adult women<sup>12</sup>. Duplex ultrasound studies have revealed superficial venous insufficiency to be much more common than deep venous insufficiency. Saphenous vein reflux is the most common form of venous insufficiency, and is the underlying condition in most patients suffering with varicose veins<sup>14</sup>.

Duplex ultrasound is the method of choice for the evaluation of lower extremity veins. It is widely available, simple, quick and cost-effective. The deep, superficial, and perforator veins can be quickly and non-invasively scanned for thrombosis or reflux. The results are verifiable and repeatable. The examination is performed with the patient standing. Automatic rapid inflation and deflation cuffs

may be used when a standard stimulus is required<sup>15</sup>. Cutoff values for reflux have been defined<sup>16</sup>.

The clinical signs seen in superficial venous insufficiency are a direct result of high venous pressures. Increased intraluminal pressure leads to engorgement and dilation of the trunk veins and affected tributaries. The capillaries and venules thus become telegectasia and venectasia, while larger veins twist and distort into varicosities<sup>10</sup>. The interstitial edema created by Starling imbalance produces poor tissue oxygenation and nutrition,<sup>10</sup> as well as initiating the inflammatory cascade. This causes acute pain and discomfort and can eventually lead to the spectrum of symptoms known as “venous stasis changes”<sup>12</sup>.

Sclerotherapy in patients with varicose veins and RLS has been shown to be 98% effective in initial relief of RLS with recurrence rate of 8% and 28% at 1 and 2 years, respectively<sup>17</sup>. This leads one to believe that RLS in this population can be effectively cured.

We feel that many RLS patients derive their symptoms from the circadian ebb and flow of edema fluid seen in venous insufficiency. The daily accumulation of the soft tissue edema creates unpleasant sensations in the legs such as heaviness, fullness, pain, etc. Our hypothesis is that the nightly receding of that edema can somehow cause the “indescribable” sensations that typically plague RLS patients. This would explain why the typical RLS symptoms occur when the patient is reclining and at night (as the elevation mobilizes edema from the legs), and why symptoms seem to wane in the early morning hours (the edema has largely resolved by that time).

This hypothesis is supported by findings in hemodialysis patients. RLS affects 20%-30% of this population. Despite extensive research of various clinical and biochemical parameters, the cause of RLS remains unknown (of note, the neurological effects of lower extremity fluid shifts have not been studied in these patients)<sup>18</sup>. It has been found that by performing short dialysis 5 days a week (but not changing total weekly hemodialysis times or other parameters), these symptoms resolve<sup>19</sup>. RLS symptoms also disappear in hemodialysis patients who receive a kidney transplant<sup>20</sup>. We suspect that frequent dialysis dampens and renal transplant eliminates the huge volume swings normally seen in these patients, thus minimizing the RLS symptoms.

The purpose of this study is to determine whether the successful treatment of superficial venous insufficiency can alleviate symptoms of restless legs syndrome in patients with RLS who also suffer with symptomatic SVI.

## RESULTS

Results of our study are pending at the time of writing of this abstract (10/01/2006), and will be presented at the American College of Phlebology 20% annual Congress.

## TAKE-HOME POINTS

### INCIDENCE OF RLS:

RLS affects 5%-15% of the general population with a mean age at onset of 27.2 years. Onset is before age 20 in 38.3% of patients. It is frequently unrecognized or misdiagnosed and therefore widely under treated. The percentage of primary versus secondary RLS is unknown.

### DIAGNOSIS OF RLS:

Per the NIH consensus panel of 2003:

1. An urge to move the limbs with or without sensations
2. Worsening of symptoms at rest
3. Improvement with activity
4. Worsening of symptoms at night.

### ETIOLOGY OF PRIMARY RLS:

Primary (idiopathic) RLS is currently felt to be related to the role of dopamine and iron in spinal pathways or the brain. It is familial in 25%-50% of cases and transmitted in an autosomal dominant fashion. Loci with positive linkage have been identified on chromosome 9p, 12q, and 14q.

### RECOGNIZED ETIOLOGIES OF SECONDARY RLS:

1. Deficiency of iron, folate, or B12
2. Polyneuropathy (due to uremia, diabetes, alcohol abuse, rheumatoid arthritis, amyloidosis, Sjogren's Syndrome, radiculopathy, monoclonal gammopathy, Lyme disease, and idiopathic neuropathy)
3. Parkinson's disease
4. Pregnancy
5. Drugs such as lithium, neuroleptics, beta blockers, H2 antagonists, antidepressants, anticonvulsants, spinal anesthetics, etc.
6. Alcohol
7. Caffeine
8. Cigarette smoking
9. History of Gastric Operation
10. Chronic Obstructive Pulmonary Disease
11. Carcinoma
12. Chronic Venous Insufficiency
13. Varicose Veins

14. Arborizing telangiectasia of lower limbs
15. Withdrawal from vasodilators, sedatives, imipramine, or opiates
16. Myelopathy or myelitis
17. Hypothyroidism or hyperthyroidism
18. Acute intermittent porphyria
19. Fibromyalgia syndrome
20. Peripheral cholesterol microemboli

#### TREATMENT/MANAGEMENT OF RLS:

Current treatment of RLS is largely aimed at medical control of symptoms rather than cure. Precipitating factors or drugs are avoided, deficiencies are corrected, and medications (such as Levodopa, Dopamine agonists, Benzodiazepines, Opioids, Anticonvulsants, Clonidine, etc.) are prescribed. We are investigating the effect of curing SVI in RLS patients.

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