

## Commentary: Increased Risk of Cardiovascular Disease in Restless Legs Syndrome Patients: A Call to Action

We have read with great interest the paper by Abuş et al<sup>1</sup> recently published on Alpha Psychiatry. The study's main aim was to evaluate the cardiovascular disease risk in patients with restless leg syndrome (RLS) using laboratory and electrocardiogram (ECG) parameters. They found that concluded that the fQRS-T angle was higher in RLS patients, as well as the C-reactive protein-to-albumin ratio (CAR), neutrophils to lymphocytes ratio (NLR), monocytes to lymphocytes ratio (MLR), and all correlated with the elevated risk of cardiovascular disease (CVD).

RLS, also known as Willis-Ekbom's disease, is a condition in which the main symptom is an uncontrollable need to move the legs because of an intense sensation of discomfort that diminishes or disappears as soon as the person moves the legs.<sup>2</sup> The leg movements typically occur in the evening or at night and when the person is at rest. Although this disorder predominantly affects the legs, it has also been found to affect other body parts, such as the mouth, neck, arms, abdomen and, in some cases, the genitals.<sup>3</sup> Therefore, RLS is a disorder in the category of sleep disorders listed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).<sup>4</sup> To make such a diagnosis, specific symptoms must be observed, such as an intense need to move the legs, often accompanied by/responsive to a sensation of discomfort in the legs, with the characteristics that [1] the need to move the legs occurs or worsens when the individual is at rest, [2] the sensation of discomfort partially or entirely disappears when the legs are moved, and [3] the need to move the legs occurs or worsens only in the evening or during the night.<sup>4</sup> In addition, these symptoms must occur at least three times a week and have been present for at least three months; they must be associated with severe distress or cause difficulties in social, occupational, educational, behavioural or other essential areas of the individual's functioning. In making this diagnosis, it is also imperative to ensure that these symptoms are not caused by other medical conditions (e.g. arthritis, peripheral ischaemia, leg cramps), physiological effects of substances or drugs, other mental disorders, or specific behaviours (e.g. poor posture).<sup>5</sup>

Epidemiological studies have reported that RLS has a prevalence of between 7 and 10% in the general adult population in Europe and America, and it also appears that women are more likely to have the syndrome than men.<sup>6</sup> In addition, the symptoms of RLS appear to be more common in adults over 40, with some studies suggesting that 18-23% of the elderly alone have the disorder, and there seems to be a correlation between symptoms and ageing.<sup>6</sup> Interestingly, RLS also occurs in children and adolescents, affecting about 1-4% of the child population.<sup>7</sup> However, despite the disorder's high prevalence, most people report mild or moderate symptoms, while only 1-3% experience severe or persistent symptoms.<sup>8</sup>

The symptoms of RLS often prevent or make it difficult to maintain normal circadian rhythms, which can negatively affect mood, such as mood swings, and cognitive energy, such as fatigue and slowing down. The severity of the impairment is measured by specific scales such as the International Restless Legs Syndrome Study Group Rating Scale (IRLS), which measures the intensity of symptoms about the patient's mood, daily functioning, sleep quality, frequency of symptoms and discomfort they cause. Some research has also found links with certain physiological conditions such as diabetes, migraine, cardiovascular disease, hypertension and anaemia. RLS also appears to be associated with Parkinson's disease. Iron deficiency has also been identified as significant comorbidity, and as a result of this discovery, some therapies now include iron supplementation, especially in pregnant women.



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However, RLS is even more dangerous than previously thought. People with RLS risk cardiovascular disease more than those without neurological disorders.<sup>9</sup> That means, without mincing words, that they are more likely to die prematurely.<sup>10</sup> The link was found in a study published in *Neurology* by researchers at the University of Pennsylvania, who collected data from more than 57,000 women with an average age of 67 who were part of the Nurses' Health Study, a large prospective study looking at the effects of diet, hormones and environment on the health of nurses, which has become a significant benchmark for many other studies of women.<sup>11</sup> Every two years between 2002 and 2012, they emailed questionnaires to selected women asking about RLS and other health problems. During the ten-year observation period, there were 6,448 deaths. A closer look at the causes showed that women with neurological syndromes had a significantly higher risk of premature death than other women. Specifically, women with RLS were 43% more likely to die from heart disease, while no association was found between RLS and other conditions such as cancer.

This is not the first time that restless legs syndrome has been linked to other health conditions, as it has previously been linked to obesity and high blood pressure, and this may suggest that cardiovascular deaths might also be due to these other comorbid risk factors that need to be treated.<sup>12,13</sup> On the other hand, Gao et al<sup>14</sup> demonstrated successful treatment of RLS (including dopaminergic drugs, anticonvulsants, benzodiazepines, and opiates, but not ergot-dopamine use) might impressively reduce the risk of CVDs.

Eighty per cent of sufferers of RLS have jerks of the lower limbs every 20 to 30 seconds, especially in the early hours of the night. With each jerk, the blood pressure rises, and the heart rate increases.<sup>12</sup> These people accumulate 90-100 jerks per hour for seven hours, so many pressure surges occur.<sup>12</sup> In addition, these jerks of the legs cause small awakenings of the brain, micro-awakenings that the person may not even be aware of, but they occur.

The mechanisms of this association with cardiovascular disease risk are not yet known. However, it is thought that the cause may be vegetative hyperarousal (increased heart rate and systemic blood pressure systemic), associated with periodic limb movements during sleep, repetitive movements of the lower limbs (usually dorsiflexion of the big toe or foot), present in at least 80% of RLS cases.<sup>15</sup> The study by Abuş et al contributes precisely to the knowledge. It makes us aware that cardiovascular disease risk must be carefully evaluated not only in severe neuropsychiatric disorders (such as schizophrenia, multiple sclerosis, Parkinson's disease and bipolar disorders) but also in diseases that would be apparently benign, such as RLS.

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