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# French Consensus: How to diagnose restless legs syndrome

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ABSTRACT

Correct diagnosis of restless legs syndrome (RLS) is essential to patient care and treatment. Diagnosis is most often clinical and based on diagnostic criteria: the need to move the legs accompanied to varying degrees by unpleasant sensations, predominantly during the evening and improved by movement. In rare cases, clinical examination is insufficient and a polysomnography is necessary. Once a positive diagnosis has been made, a neurological examination and an assessment of iron status are required. The severity of the RLS must be evaluated to determine whether a specific treatment is necessary. Before treatment, it is essential to ensure that a definite diagnosis of RLS has been made and the phenotype characterised. This enables a personal treatment plan and limits the risk of augmentation syndrome.



## 1. Abbreviations

| | |
|---|---|
| VAS | visual analogue scale |
| IRLS | IRLSSG rating scale |
| IRLSSG | International Restless Legs Syndrome Study Group |
| PLM | periodic limb movements |
| RLS | restless legs syndrome |

## 2. Introduction

Restless legs syndrome (RLS) is a frequent neurological sensorimotor disease [1] characterised by an urge to move the limbs, modulated by activity and the time of day.

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### 2.1. The history of RLS

Sir Thomas Willis first described RLS in 1675 and then again in 1685, at which time he already recommended opioid treatment. A century later, the pathology was mentioned in F. Boissier de Sauvages de La Croix's descriptions of neurological diseases, described by G. Gilles de la Tourette in 1898 and F. Gerard Allison in 1943. However credit goes to K.-A. Ekbom for charting the clinical presentation of RLS in many publications between 1944 and 1966, emphasising its high prevalence, heredity, normality of clinical examination and the role of iron deficiency. Cases of anaemia- and renal insufficiency-related RLS were reported in 1953 and 1966. E. Lugaresi subsequently established the connection between RLS and periodic limb movements. At this point, the efficacy of L-DOPA was demonstrated. In 1990, the diagnostic criteria for the syndrome were published in the *International Classification of Sleep Disorders* (ICSD), revised in 1995 under the impetus of the *International Restless Leg Syndrome Study Group* (IRLSSG), and reiterated in 2003 by the *National Institutes of Health* (NIH). Finally, the diagnostic criteria were reviewed in the ICSD-3 in 2014, with the addition of criteria for children [1,2]. This history explains the name given to RLS in 2011: Willis-Ekbom disease.

### 2.2. Epidemiological data

General population prevalence, in cross-sectional studies, in the United States and Western Europe, is estimated to be between 4 and 29% (14.5% average) [3]. Prevalence is higher in primary care $19.5 \pm 7.9\%$ (compared with $12.3 \pm 7.2\%$ in geographically defined or targeted cohorts). Prevalence varies according to sex (sex-ratio: 2 female/1 male), age (increase in prevalence with age), disease severity and comorbidity. In France the prevalence of RLS is estimated to be 8.5% (10.8% female, 5.8% male), and it is estimated that 3.1% of the population presents RLS symptoms monthly, 2.5% weekly and 1.9% daily [4,5].

Prevalence in the paediatric population is 2 to 4% (15 to 35% in the case of attention deficit and hyperactivity disorder) [6]. In children, a family history of restless legs is very frequent, and is seen in 71 to 80% of cases.

The presence of sensorimotor symptoms, their impact on sleep and day time vigilance [7], and their psychological repercussions [8,9], have a profound effect on patients' quality of life and considerable socio-economic impact [9]. Compared to the general population, patients with RLS have a 2- to 5-fold risk of anxiety and/or depressive disorders [10–12].

### 2.3. RLS physiopathology

The physiopathology of RLS is complex and involves both genetic factors, the dopaminergic system and iron metabolism.

#### 2.3.1. Genetic factors

A positive family history is found in more than 40% of individuals with RLS. Transmission can be autosomal dominant or recessive. Several studies have highlighted genetic predisposing factors. RLS is associated with an intronic variant in the genes *MEIS1*, *BTBD9*, *MAP2K5* and/or *LBXCOR1* [10].

#### 2.3.2. The dopaminergic system

Since RLS improves with dopaminergic treatments the dopaminergic system has been studied. There is no difference in dopamine levels in the cerebrospinal liquid of RLS patients and controls [11]. However an increase in ortho-methyl-dopamine (3-OMD) and homovanillic acid (HVA) seen in one study supports an increase in tyrosine hydroxylase activity leading to an increase in the synthesis, liberation and turnover of dopamine [12,13]. This data has been confirmed on a neuropathological level with post-mortem demonstration of a reduction in the D2 receptors associated with an increase of tyrosine hydroxylase in the substantia nigra, as in the iron deficiency animal model. This implies a presynaptic hyper-dopaminergic state associated with an iron deficiency in certain targeted areas that could lead to post-synaptic internalisation of D2 receptors.

#### 2.3.3. Iron

In the brain, iron is involved in the hydroxylation of tyrosine to form dopamine and also in the stabilisation of D2 dopaminergic receptors. A low level of iron leads to a deregulation of monoaminergic systems (both dopaminergic and serotoninergic) probably causing RLS symptoms [12]. Several studies using specific magnetic resonance imagery sequences have demonstrated a reduction in the cerebral iron rate in patients with RLS compared to healthy controls [12]. This suggests a disturbance in the transport of iron firstly at the blood–brain barrier and then at neuronal level, through a decrease of neuronal transferrin receptors [14].

## 3. Positive diagnosis of restless legs syndrome

Diagnosis of RLS is clinical. It is recommended that a neurologist or sleep specialist confirm the diagnosis. It is important to let the patient spontaneously describe the symptoms and their everyday consequences. A guided examination then completes the clinical picture.

A RLS diagnosis is based on the presence of 5 criteria [1]. The first four enable a positive diagnosis to be made, the fifth enables differential diagnosis to be eliminated:

- the urge to move the legs, generally accompanied by or related to uncomfortable sensations in the legs;
- during a period of rest or inactivity (for example when lying down or sitting), the urge to move the legs occurs or worsens accompanied by uncomfortable and unpleasant sensations;
- partial or complete improvement of the urge to move through a movement, such as stretching or walking, for at least as long at the activity lasts, of the urge to move the legs and the uncomfortable and unpleasant sensations;
- the occurrence or worsening of the urge to move the legs and uncomfortable and unpleasant sensations during the evening or night time rather than during the day.

These four diagnostic criteria provide good sensitivity (86%) but low specificity (45%), the addition of the fifth criterion increases diagnostic specificity to over 90%.

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