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Sleep disorders in neurology

French consensus: Pharmacoresistant restless legs syndrome

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INFO ARTICLE

Article history:
Received 19 December 2017
Received in revised form
16 April 2018
Accepted 5 June 2018
Available online xxx

Keywords:
Restless legs syndrome
Willis-Ekbom syndrome
Drug resistance
Refractory
Opioids

ABSTRACT

Dopaminergic agonists, α2δ ligands and opioids are, as single-drug therapy, the first line treatment for restless legs syndrome (RLS/Willis-Ekbom disease). However, despite treatment efficacy, exacerbations of RLS may occur with overall worsening in symptoms severity, development of pain and symptoms spreading to other parts of the body, without meeting augmentation syndrome criteria. This development of ''drug-resistant'' RLS can cause pain, severe insomnia and psychiatric disorders that affect considerably patients' quality of life. The lack of French recommendations for this form of RLS leave physicians with few options to help patients with physical and emotional distress. Our group of neurological experts and sleep specialists proposes a diagnostic and therapeutic strategy to provide better care and appropriate treatment through searching for the organic, psychiatric and/or iatrogenic causes of drug resistance. Once a drug-resistant RLS diagnosis has been confirmed, we recommend an obligatory work-up including: a video-polysomnogram, a biological evaluation including iron status, standard numeration and C-reactive protein level. Treatment will be comorbidity-dependent: dopaminergic agonist would be recommended in case of depression or associated periodic leg movements, α2δ ligand in case of insomnia, complaint of pain, or general anxiety, in association with low-dose opioids if necessary. Strong opioids should be preferred for multiresistant RLS.

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https://doi.org/10.1016/j.neurol.2018.06.003
0035-3787/

1. Abbreviations

DA	dopaminergic agonists
AD	antidepressants
EMG	electromyography
SSRI	selective serotonin reuptake inhibitors
SNRIs	serotonin-norepinephrine reuptake inhibitors
IRLS	International Restless Legs Syndrome Study Group rating scale
IRLSSG	International Restless Legs Syndrome Study Group
PLM	periodic limb movements
RLS	restless legs syndrome

2. Introduction

In patients with restless legs syndrome (RLS/Willis-Ekbom disease) the aim of treatment is to reduce symptom severity knowing that only fewpatients require medical treatment [1]. Pharmacological treatments should indeed be restricted only for patients suffering from severe to very severe forms of the disease. However, and despite an initially satisfactory therapeutic response, a large number of patients present a recurrence of symptoms over the long-term related to decrease in treatment efficacy and/or disease's natural progression. For other patients, despite correct compliance, medical treatment may be ineffective.

The absence of French recommendations for drug-resistant forms of RLS, taking into account the characteristics of this population and treatments available in France, leaves physicians in difficulties faced with patients with severe suffering. We propose a consensus for a simple and practical diagnostic and therapeutic strategy to help physicians improve treatment strategies for patients with drug-resistant RLS. The recommendations formulated in this article are based on methodology approved by the European Federation of Neurological Societies (EFNS) [2].

3. Definition of drug-resistant RLS

There is no consensual definition of drug-resistant RLS, also called ''refractory'' or ''intractable'' RLS. Silber et al. propose a practical clinical definition, but this is limited to patients treated with dopaminergic agonists (DAs) [3]. The International Restless Legs Syndrome Study Group (IRLSSG) does not provide a definition of drug resistance in RLS.

It is important to differentiate drug-resistant RLS from augmentation syndrome, from the loss of effect at the end of dose, from the natural evolution of the disease and from mild RLS associated with insomnia, depression or pain as the main complaint. Transient exacerbations and complaints associated with well-treated RLS are covered below. It is also essential to distinguish drug-resistant RLS from the short-term exacerbations of RLS related to contraindicated medication (for example antidepressant, or neuroleptic derived medication), from forced bed rest (e.g. post-surgery) or a drop in iron levels (for example following occult colic bleeding or surgery).

Our definition of drug-resistant RLS is severe to very severe RLS–severity score of $>$ 20/40 on the RLS severity scale (International Restless Legs Syndrome Study Group rating scale, IRLS)–persistent or recurrent over a period of more than 1 month, despite 2 treatments from different classes whose effectiveness is recognised consensually in RLS treatment, taken alone or in combination, with good compliance, sufficient dosage, suitable schedule and for a sufficiently long duration. Drug-resistant RLS must not meet augmentation syndrome criteria.

4. Drug-resistant RLS epidemiology

The frequency of drug-resistant RLS is unknown, but in current clinical practice the reappearance or worsening of pre-existing but tolerable RLS symptoms is frequent in the long-term, particularly with the use of DAs. This can occur despite a treatment taken correctly at optimal dosages. Aggravation lead to an increase in the intensity of unpleasant sensations or their transformation; for example paraesthesia that becomes painful, symptoms spreading to upper limbs or their occurrence during the daytime, without meeting augmentation syndrome criteria. In a cohort of 160 patients monitored over a duration of 8.1 $\pm$ 2.9 years, more than 10% of patients reported aggravated symptoms and 59.4% had benefited from one or several therapeutic modifications [4]. In another series of 2751 RLS patients monitored over a 3 year period, 12.5% of RLS patients had experienced an increase in symptoms severity (increase of 5 points on the International Restless Legs Syndrome Study Group rating scale [IRLS]) [5].

5. Clinical diagnosis of drug-resistant RLS

The clinical diagnosis of RLS is not as easy as it would appear based on the consensual criteria. It is a purely clinical diagnosis and many other pathologies can mirror RLS symptoms (Table 1), misleading physicians and resulting in inappropriate treatment. Therefore it is important to first confirm or disprove diagnosis and subsequently eliminate augmentation syndrome. Fig. 1 summarises the main steps in the diagnosis and treatment of drug-resistant RLS.

5.1. *Is it RLS?*

RLS diagnosis is based on the presence of the 5 essential criteria [6], clinical examination data which must be started over again in the case of drug resistance. In the event of doubt, support criteria can help the physician to establish the diagnosis. We have indicated in italics the specific elements that, during the diagnosis phase, or when the question of diagnosis arises anew when a treated patient is referred for drug resistance, may point to a diagnosis other than RLS.

5.2. *Essential criteria*

5.2.1. *Sensory disorder*

Investigation into the patient's sensory complaint must be clearly identified as described in the ''diagnostic'' article. Sensations of cold (and painful cold) as well as numbness

Please cite this article in press as: Chenini S, et al. French consensus: Pharmacoresistant restless legs syndrome. Revue neurologique (2018), https://doi.org/10.1016/j.neurol.2018.06.003