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Sleep disorders in neurology

French consensus: Augmentation syndrome in restless legs syndrome

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ABSTRACT

Augmentation syndrome is one of the most severe complications of RLS. It is characterised by a worsening of treated symptoms; principally an increase in the severity of symptoms and an earlier onset time. Augmentation syndrome occurs primarily with dopaminergic treatments. It is crucial for the patient to be sufficiently well informed to prevent its occurrence and the prescription of too high doses of dopaminergic agonists avoided. In the presence of augmentation syndrome confirmed using the diagnostic criteria, the specialist treating the restless legs syndrome should quickly modify the patient's treatment. In this article, our expert group proposes a practical strategy for the diagnosis, prevention and treatment of augmentation syndrome.

1. Abbreviations

DA	dopaminergic agonist
ASRS	Augmentation Severity Rating Scale
IRLS	International Restless Legs Syndrome Study Group rating scale
IRLSSG	International Restless Legs Syndrome Study Group
PLM	periodic limb movements
PMS	periodic movements in sleep
PSG	polysomnography
AS	augmentation syndrome
RLS	restless legs syndrome

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2. Introduction

For several decades, dopaminergic treatments have been used first line in the treatment of restless legs syndrome (RLS). Their excellent efficacy and good short-term tolerance have been confirmed in numerous double-blind randomised studies of the severe forms of this disease that impact on patients' quality of life.

Initially, L-DOPA then dopaminergic agonists (DAs) were implicated in the origin of augmentation syndrome (AS). According to studies, augmentation syndrome can be found in up to 73% of patients on L-DOPA and between 20 to 30% of patients on dopaminergic agonists. However, the results of these studies do not lend themselves to cross-study comparison due to heterogeneous populations, the fact that diagnostic criteria for AS are evolving over time, the different treatments used, and the doses and length of exposure to the molecule under study. Globally, the annual incidence of AS is 8% in patients treated with dopaminergic agonists [1]. Recent improvements in the understanding of the clinical, physiopathological and therapeutic features of RLS have concentrated attention on the need to improve the prevention and treatment of AS, which is one of RLS' most severe complications.

During 2016, an expert consensus from the International Restless Legs Syndrome Study Group (IRLSSG) and the European Restless Legs Syndrome Study Group (EURLSSG), focusing on the prevention and treatment of AS in RLS was put forward [2]. Our expert group proposes a practical strategy for the diagnosis, prevention and treatment of AS in order to help physicians manage patients.

3. Diagnostic criteria

Augmentation syndrome was first described 20 years ago by Allen & Earley in 46 RLS patients mainly treated with L-DOPA [3]. The symptoms were sufficiently severe to justify a change in treatment in 50% of patients. The defining criteria were the worsening of RLS related to:

- earlier symptom onset in the day, either in the afternoon or the early evening compared to the pre-treatment period;
- symptoms appearing more rapidly at rest;
- more intense symptoms compared to the period without treatment;
- spread of symptoms to other parts of the body (upper limbs, torso) as well as a shorter treatment action.

In 2003 the consensus of the National Institutes of Health subsequently validated the first AS diagnostic criteria principally based on clinical experience due to the lack of published data: symptoms onset 2 hours earlier than usual without medical treatment, or the worsening of at least 2 of the 4 diagnostic criteria of RLS initially described [4].

These criteria were revised in 2006 following empiric data from clinical trials, and were called the Max Planck Institute criteria to identify the criteria used for the AS diagnosis [5].

The diagnostic criteria required to diagnosis are: A + B or A + C or A + B + C:

A. an increase in the severity of symptoms for at least 5 days a week, with good initial response to treatment and no other factors (medical, psychological, change in lifestyle...) explaining the aggravation;
B. a paradoxical response (even if not immediate) to treatment: symptoms worsen on an increase of the dose and improve when the dose is reduced;
C. advanced onset time of symptoms:
   a. either symptoms start 4 hours earlier than before initiation of the dopaminergic treatment,
   b. or symptoms start between 2–4 hours earlier in association with at least one of the following criteria compared to the period without treatment:
      1 shorter latency of symptoms at rest,
      2 symptoms spread proximally to other parts of the body than the lower limbs,
      3 more intense symptoms or increase of periodic limb movement *via* the polysomnography or immobilisation test,
      4 shorter duration of the symptom-free period.

At this time, there is no biomarker to characterise AS. Nevertheless, the clinical criteria defined above enable accurate identification of patients with AS, creating a homogenous population, which allows clinicians to better study its features and management. However, in certain cases, diagnosis can be difficult in clinical practice: for example, there can be a lack of information about the onset time of symptoms at the start of the disease (hence the importance of characterising the RLS phenotype at diagnosis) and evaluating the evolution of symptoms and the efficacy of the treatment is hard if the treatment is split and taken in several doses, or if patients are already treated with a slow release formulation. Moreover, some of these criteria are purely arbitrary, difficult to quantify and therefore merit discussion.

In our experience, paradoxical response to the dopaminergic treatment, defined as the worsening of symptoms when dopaminergic treatment is increased and improvement after its reduction, is both debatable and hard to use in practice. Patients who complain of a partial improvement in symptoms or their appearance earlier in the day sometimes advance the time at which medication is taken or increase doses which may lead to a temporary improvement of symptoms. On the contrary, reduction of the treatment can result in a withdrawal syndrome with a rebound in the symptoms of restless legs syndrome that may last several weeks. The 2 or 4-hour time advance of the onset of symptoms criterion is purely arbitrary and does not take into account the dosage and half-life of the medication. Rotigotine patches as well as extended release forms of pramipexole and ropinirole (sometimes prescribed despite being off-license) make earlier symptom onset time hard to evaluate. Lastly, earlier symptom onset in the day is not always a marker of AS but can signal a fluctuating or slow progression of the disease.

While as yet unvalidated, the IRLSSG recommends four screening questions to guide physicians (one positive response to one of these four questions indicates a possible AS):

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