

Hydroxyzine Hydrochloride in Familial Restless Legs Syndrome

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Restless legs syndrome (RLS) is a common neurological disorder characterized by nocturnal motor restlessness accompanied by lower limb paresthesias usually alleviated by activity.¹

A dopaminergic dysfunction has been hypothesized.^{1,2} Several classes of drugs showed beneficial effects on RLS, and ferrum replacement may be effective in iron-deficient patients.² Here, we present the case of three related patients suffering from RLS, successfully treated with hydroxyzine hydrochloride, an antihistamine with anticholinergic properties.

CASE REPORT

Case 1 is a 79-year-old woman who has been complaining of irresistible urge to move the legs at rest and at night, for eight years.¹ She reported that the urgency was alleviated only by the movement of the legs, so that every night she was forced to get up and walk all over the room.

Her neurological examination was normal and the RLS rating scale score was 26.³

In order to exclude ischemic involvement of the basal ganglia, a condition rarely associated with RLS,⁴ we performed brain MR, which showed bilateral diffuse areas of hyperintensity of the cerebral white matter on T2-weighted images, and no lesions in the basal ganglia. The EMG with nerve conduction study was not significant.

Slightly low ferritin was replaced after supplementation, but no changes on RLS symptoms were noted.

Pramipexole (1.0mg salt three times/day for two months) and levodopa/carbidopa (200mg/50mg twice/day for two months) were subsequently prescribed with no effect on RLS. Gabapentin (300mg three times/day for approximately three months) and carbamazepine (200mg/day for three months) were useless and caused side effects: poor concentration and weakness; benzodiazepines, such as prazepam (20 mg/day for two months) and lorazepam (2.5mg/day for one month), were ineffective.⁵

Hydroxyzine hydrochloride, at the dosage of 25 mg, was started, without remarkable side effects.⁶ Only slight disturbances in nocturnal sleep during the four-month therapy were reported (score 6 on the RLS scale) and the drug discontinuation was followed by the immediate recurrence of RLS symptoms.

The paternal grandfather of Case 1 married, for a second time, a first-degree cousin and their daughters (Case 2 and Case 3) showed a clinical picture consisting of nocturnal walking urgency and tickling sensation of the legs.

Case 2, a 65-year-old woman, did not show any remarkable diseases in her clinical history, except for primary insomnia. One year before our examination, she started complaining of two or three awakenings, due to motor restlessness and legs discomfort

every night and a diagnosis of RLS had been made. She had also a worsening of symptoms at rest, partially relieved by leg movements.

The neurological examination was normal, with the exception of slight anxiety, and the RLS scale score was 24. Blood tests, including iron and ferritin, were normal. Treatment with gabapentin (300mg three times/day for two months) had not been effective.

Case 3 was a 63-year-old woman with a long history of sleep disturbances, consisting mainly in difficulty in falling asleep. In the last five years, she additionally reported an impulse to move the legs, when resting. Her symptoms worsened at night and were accompanied by creeping sensations in the lower limbs, which were reduced only when walking. She also had excessive, exaggerated anxiety and worry about everyday life events. The remaining neurological examination was normal and the RLS scale score was 26. A full blood analysis was not significant. In this case, alprazolam (0.5mg twice a day) had been prescribed with discrete efficacy on insomnia and anxiety, but no effects on RLS.

Hydroxyzine, a medication with sedative properties,⁶⁻⁸ had been effective on RLS symptoms in Case 1. Since sleep disturbances and anxiety were present in both Case 2 and Case 3, we decided to administer the same drug in both patients at the dosage of 25mg at bedtime, before trying any alternative treatment for RLS. We observed a prompt remission of RLS symptoms (score 5 and 4 at the RLS scale, respectively). In both patients, the discontinuation of therapy after two months caused a recurrence of RLS symptoms.

DISCUSSION

Several classes of medications have been utilized in restless legs syndrome, an annoying disease which may impair patients' quality of life.^{1,2}

Here, we reported three related women, affected by RLS, who responded to hydroxyzine hydrochloride, a first-generation-piperazine derivative-antihistaminic drug generally used to treat allergic reactions and seasonal rhinitis,⁹ and to induce sedation.⁶⁻⁸

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Although working mainly as anti H1-agents, the first-generation antihistamines are also potent muscarinic acetylcholine-receptor antagonists.¹⁰

Hydroxyzine hydrochloride is one of the less sedative first-generation antihistamines and it is of some interest that the other hypnotic drugs, such as the short-acting benzodiazepines, were ineffective in Case 1 and Case 3.

Hence, we hypothesized that the anticholinergic profile of hydroxyzine may contribute to its efficacy in the treatment of the patients with RLS here described.

It is also relevant that a treatment of urticaria with cetirizine (10mg for one month) was not effective on RLS symptoms in Case 1. Cetirizine, the main active metabolite of hydroxyzine, belongs to the second-generation antihistamines but, contrary to hydroxyzine, does not produce noticeable cholinergic antagonism *in vitro* and does not exhibit anticholinergic effects *in vivo*.¹⁰

Therefore, the pharmacodynamic differences between hydroxyzine and cetirizine support the hypothesis that the improvement of RLS in these subjects may be mediated by the anticholinergic profile of hydroxyzine.

Moreover, pure anticholinergics -such as orphenadrine- proved to be useful in the treatment of RLS, although their regular application in clinical practice has been made difficult because of the side effects, such as constipation, hypotension or cognitive impairment.^{11,12}

The exact pathophysiology of RLS still remains obscure, but dopaminergic pathways are believed to be involved.¹³

As an example, in the management of the drug induced akathisia, a clinical condition which seems to share a pathophysiological substrate with RLS, anticholinergics may be of some utility, probably lowering the overactivity of striatal cholinergic interneurons and eventually levelling the relative imbalance between the dopaminergic and the cholinergic neurological pathways.¹⁴

Contrary to the previous treatments, in particular in Case 1, hydroxyzine showed an excellent compliance, no side effects and good efficacy in our patients.

However, since the cases here described were related, we cannot exclude that a genetic factor may influence their response to the pharmacological treatment. Moreover, we do not know the usefulness of this drug in a long-term treatment.

Restless legs syndrome may benefit from dopaminoagonists such as pramipexole and ropinirole and, recently, rotigotine showed to be helpful. Levodopa and anticonvulsivants such as gabapentin, valproic acid and carbamazepine may be considered good alternatives, while benzodiazepine-receptor agonists are still considered investigational for RLS.⁵

On the other hand, in the general population, the percentage of RLS patients not-responding to the pharmacological treatment approaches 30%.¹⁵ No clinical or diagnostic clue can indicate *a priori* whether a patient will be a responder to treatment or not, and whether a medication will be more appropriate than another.^{5,15}

Hydroxyzine hydrochloride, an inexpensive antihistamine with anticholinergic properties, may represent a potential drug option in the clinical management of patients with RLS associated with anxiety or in patients with poor response to conventional medications.

A further study testing hydroxyzine in a larger population would be of great interest, especially with the option of using cetirizine as a pharmacological control.

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