

Hydroxyzine Hydrochloride in Restless Legs Syndrome

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Citation

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Abstract

Restless legs syndrome (RLS) is a chronic condition, with onset at any age, characterized by urgency to move the legs and unpleasant sensations, worsening at rest and in the evening and relieved by the movement. Pharmacological approaches, including benzodiazepines, dopaminergic agonists, levodopa and antiepileptics, showed substantial inter-individual variability of efficacy and side effects.

We report the case of a woman who did not respond to any previous pharmacological treatment, successfully treated with hydroxyzine hydrochloride.

The efficacy of this first-generation antihistamine with potent anticholinergic properties in our RLS case may resemble the action of several anticholinergic drugs in Parkinson Disease, reasserting the possibility of a common pathophysiological background shared by these two distinct clinical entities.

INTRODUCTION

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

Epidemiological studies have estimated a prevalence of around 4-10% in the general population [1].

Several observations suggest the presence of a dopaminergic dysfunction in RLS [1,2]. The differential diagnosis includes the neuroleptic-induced akathisia, polyneuropathies, the meralgia paresthetica and the nocturnal leg cramps.

While prochlorperazine, metoclopramide, neuroleptics and some antidepressants have been reported to exacerbate RLS, various classes of drugs showed beneficial effects, and ferrum replacement may be effective in iron-deficient patients [2]. No previous reports indicated the potential application of hydroxyzine hydrochloride in RLS. We present the case of a patient suffering from RLS, not responding to common drugs, successfully treated with hydroxyzine hydrochloride.

CASE REPORT

In the last fifteen years a 79-year-old woman developed unpleasant sensations in the legs, occurring at rest, especially at bedtime, accompanied by motor restlessness, and short awakenings to move the limbs with temporary relief of

symptoms, prompting the diagnosis of RLS [1].

The paternal grandfather got remarried with a first-degree cousin and their daughters developed a clinical picture consisting in nocturnal walking urgency and tickling sensation of the legs (Figure 1).

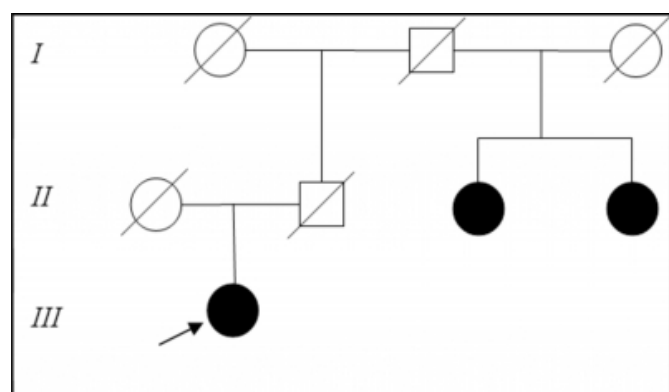
The neurological examination of our patient revealed absent ankle reflexes and no extrapyramidal signs. Blood test showed slightly low amounts of ferritin and iron and initial sideropenic anemia. Electrodiagnostic findings were not significant. Bilateral diffuse areas of hyperintensity of the cerebral white matter on T2-weighted MRI were also detected.

Serological iron and ferritin parameters reversed to normal after three-month supplementation with ferrous gluconate (62.5 mg per os).

Levodopa 200 mg/carbidopa 50 mg twice/day, pramipexole (1.0 mg salt three times/day), prazepam (20 mg/day), lorazepam (2.5 mg/day) and gabapentin (300 mg three times/day) were subsequently prescribed with no effect on RLS or with relevant adverse reactions.

Figure 1

Figure 1: Family of the patient.



Hydroxyzine hydrochloride, at the dosage of 25 mg, caused a striking improvement of symptoms without remarkable side effects.

No disturbances in nocturnal sleep during the four-month therapy were reported and the drug discontinuation was followed by the immediate recurrence of RLS symptoms.

DISCUSSION

Restless legs syndrome is a common disorder mainly observed in the elderly [1,2,3]. The pharmacological treatment includes several molecules and substantial inter-individual variability exists with regard to side effects [2].

It is communis opinio that benzodiazepines are not the elective molecules in old patients, neither for RLS, nor for sleep disturbances, as they may cause excessive sedation or paradoxical reaction [2,3]. In our case benzodiazepines did not show beneficial effects on RLS.

Similarly, we did not notice any modification of the restlessness with the no-ergot dopamine agonist pramipexole, increased up to 3.0 mg/day, as well a four-month treatment with gabapentin was useless [2]. Unfortunately, levodopa plus carbidopa for three months was ineffective in our patient and accompanied by nausea and hypotension.

The possible sedative action of antihistamines has been thus taken into consideration with the purpose of reducing nocturnal discomfort in this patient.

Hydroxyzine hydrochloride is a first-generation-piperazine derivative- antihistaminic drug, used to treat allergic reactions and seasonal allergic rhinitis [4,5]. As a consequence of the favourable pharmacokinetic profile, the effects being observed within one hour of administration

with short half-life, hydroxyzine also represents an aid in insomnia and in inducing sedation before several diagnostic or therapeutic procedures [4]. Although working mainly as anti H₁-agents, the first-generation antihistamines are also potent muscarinic acetylcholine-receptor antagonists and slightly active on the α -adrenergic and the 5-HT receptors, showing various side effects due to this low receptor selectivity.

Cetirizine, the main active metabolite of hydroxyzine, belongs to the second-generation antihistamines, does not produce noticeable cholinergic antagonism in vitro and does not exhibit anticholinergic effects in vivo, because of the substitution on the nitrogen in piperazine side chain with polar or electronegative groups [5].

In the reported case, a previous treatment of urticaria with cetirizine (10 mg for one month) did not cause any change of RLS. Contrary to cetirizine, which does not have any anticholinergic action, hydroxyzine promptly improved the RLS symptoms in this woman and the low dosage we administered prevented any relevant side effect.

As hydroxyzine shows also a sedative profile, one may assume that the clinical benefit obtained in this patient could be a consequence of the sleep induction and the reduction of anxiety due to this drug. Even if we cannot exclude tout court that the sedative action of hydroxyzine hydrochloride may play a role in the clinical outcome, it is of some interest that the other hypnotic drugs, such as the short-acting benzodiazepines, were completely ineffective in this patient, reinforcing the hypothesis that the improvement on RLS symptoms may be mediated by the anticholinergic effect of hydroxyzine.

RLS pathophysiology still remains obscure, but dopaminergic pathways are believed to be involved [6]. As an example, in the management of the drug induced akathisia, a clinical condition which seems to share a pathophysiological substrate with RLS, the anticholinergic molecules 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 [7].

Moreover, several epidemiological and neurophysiological reports showed an association between RLS and Parkinson Disease (PD) [2,8,9]. In this light, it should be reminded that the pure anticholinergics like procyclidine, bengtropine, orphenadrine have been using in young PD patients for a

long time. Orphenadrine has been tested in RLS, successfully [10].

Conversely, although having an anticholinergic profile, hydroxyzine shows minimal anticholinergic side effects in vivo, such as hypotension or cognitive impairment, as a result of the scarce interaction of this molecule with M₃ muscarinic receptors [5].

Contrary to the previous treatments, hydroxyzine showed an excellent compliance and no side effects in this woman.

Hydroxyzine, an antihistamine with anticholinergic properties, may represent a convincing option in the clinical management of drug-resistant RLS subjects.

Contrary to pure anticholinergics employed in Parkinson Disease, hydroxyzine seems to have no significant side effects even in aged patients.

The anticholinergic profile of hydroxyzine hydrochloride may disclose a potential application in drug-resistant cases of RLS, even if the extrapyramidal involvement is not clinically evident.

A case-control study could point out the possible role of hydroxyzine, a safe and inexpensive first-generation

antihistamine, in the treatment of this disabling syndrome.

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