Sleep-related hypermotor epilepsy related to *CHRNA4* successfully treated with nicotine and literature review

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INTRODUCTION

CHRNA4 gene variants have been linked to autosomal dominant sleep-related hypermotor epilepsy (ADSHE) or developmental and epileptic encephalopathy (DEE). The pathophysiology of nAChR-related epilepsy makes precision treatment with nicotine a promising option for pharmacoresistant cases.

OBJECTIVES

In this study, we present a case of *CHRNA4*-related early onset DEE and sleep hypermotor seizures that was successfully treated with nicotine and review the literature on the use of nicotine in epilepsy.

MATERIAL AND METHODS

We conducted a literature search using the keywords: *CHRNA4* (or *CHRNA2*, or *CHRNB2*) AND nicotine AND epilep* (or sleep-related hypermotor epilepsy, or SHE); and transdermal nicotine AND epilep* [All Fields]. We included all cases of epilepsies treated with transdermal nicotine and reviewed the clinical data, dose, duration, and response to treatment.

RESULTS

A female patient presented with DEE with sleep hypermotor pharmacoresistant seizures related to an unreported heterozygous likely pathogenic variant in the *CHRNA4* gene (c.860T>G; p.Val287Gly; NM_000744.6). Seizure control was achieved at 19 years old, through transdermal nicotine treatment. The patient later progressed with spontaneous paroxysmal dyskinesia (PD).

The literature review included 21 other cases treated with transdermal nicotine. For these cases, the median age of seizure onset was 7.5 years old, and the use of nicotine patches started at the median age of 19 years. Doses of nicotine varied from 3.5 to 21mg, at a median dose of 7mg per day. All but one case presented seizure reduction and 45.5% became seizure-free. Interestingly, patients with the p.Ser280Phe variant had lower chances of seizure freedom (one out of nine p.Ser280Phe variants versus nine in 13 other variants seizure-free, Fisher exact test, p=0.011).

Continuous variables	**Median (IQ25 - 75)**
Seizures onset (age; years)	7.5 (4.1 - 10.2)
Nicotine treatment onset (age; years)	19 (15.8 – 29.3)
Nicotine dosage (mg/day)	7 (7 -14)
Treatment duration (months)	12 (6 -36)
Categorical variables	**n (%)**
Clinical phenotype (ADSHE/ DEE)	18 (81.8)/ 4 (18.2)
Seizure freedom (yes/no)	10 (45.5)/ 12 (54.5)
Seizure reduction (yes/no)	21 (95.5)/ 1 (0.5)
p.Ser280Phe variant (yes/no)	9 (40.9)/ 13 (59.1)

Table 1. Genetic and clinical features of patients with epilepsy treated with nicotine transdermal patches.

CONCLUSIONS

This study supports the use of nicotine patches in *CHRNA4*-related epilepsy and presents a new variant associated with a phenotype of DEE and PD.

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