Remarkable effect of transdermal nicotine in children with CHRNA4-related autosomal dominant sleep-related hypermotor epilepsy

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Abstract

Objective: Autosomal dominant sleep-related hypermotor epilepsy (ADSHE) is characterized by hypermotor seizures and may be caused by gain-of-function mutations affecting the nicotinic acetylcholine receptor (nAChR). Benefit from nicotine consumption has been reported in adult patients with this disorder. For the first time, the effect of transdermal nicotine is evaluated in children.

Methods: Transdermal nicotine was applied to three boys, two aged 10 years (7 mg/24 h) and one six years (3.5 mg/24 h). Autosomal dominant sleep-related hypermotor epilepsy was caused by the p.S280F-CHRNA4 (cholinergic receptor, nicotinic, alpha polypeptide 4) mutation. The children suffered from frequent, persistent nocturnal seizures and had developed educational and psychosocial problems. Seizure frequency and cognitive and behavioral parameters were assessed before and after treatment.

Results: A striking seizure reduction was reported soon after treatment onset. Hypermotor seizures disappeared; only sporadic arousals, sometimes with minor motor elements, were observed. Psychometric testing documented improvement in cognitive domains such as visuospatial ability, processing speed, memory, and some areas of executive functions.

Significance: Nicotine appears to be a mechanistic treatment for this specific disorder, probably because of desensitization of the mutated receptors. It may control seizures resistant to conventional drugs for epilepsy and impact socioeducational function in children. This mode of precision therapy should receive more attention and should be available to more patients with uncontrolled CHRNA4-related ADSHE across the age span.

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1. Introduction

Autosomal dominant sleep-related hypermotor epilepsy (ADSHE) is characterized by clusters of hypermotor seizures arising from non-rapid eye movement (non-REM) sleep. The disorder was previously denoted autosomal dominant nocturnal frontal lobe epilepsy (ADNFE) [1]. Autosomal dominant sleep-related hypermotor epilepsy follows an autosomal dominant inheritance with incomplete penetrance. The exact prevalence is unknown; the disorder is likely underdiagnosed, and some sporadic cases may also be of genetic origin [2].

Autosomal dominant sleep-related hypermotor epilepsy was the first seizure disorder with a proven monogenic origin [3]. Many
monogenic epilepsies are channelopathies as they are related to genes encoding for ion channels gated by voltage or a neurotransmitter [4]. Several genes associated with ADSHE code for subunits of the nicotinic acetylcholine receptors (nAChRs), which are ion channels gated by acet-
ylcholine and nicotine [5,6]. The most common mutations occur in the CHRNA4 (cholinergic receptor, nicotinic, alpha polypeptide 4) gene, encoding the alpha4 subunit that interacts with various combinations of alpha and beta subunits to form functional nAChRs [5,7,8].

Even though carbamazepine and other antiepileptic drugs (AEDs) are effective in many patients with ADSHE, a large proportion of those carrying the p.S280F-CHRNA4 mutation (previously designated S248F) continue to have seizures [3,8–10]. Treatment with transdermal nicotine appears to be beneficial in some patients with this disorder as first reported in a single Australian patient with this mutation [11]. In two Norwegian pedigrees with p.S280F mutations and p.L291dup-CHRNA4 mutations (previously 776ins3), respectively, seizure control was significantly associated with tobacco consumption [12].

Although nicotine consumption is common as self-medication among patients with ADSHE due to CHRNA4 mutations, the literature on this form of precision therapy has been sparse [12,13]. Because of concerns about the safety profile, nicotine substitution has as yet only been suggested for treatment of adult patients with insufficient effect of established AEDs. However, in underaged patients with severe and intractable ADSHE due to nAChR mutations, targeted treatment with nicotine may also be considered.

For the first time, the effect of transdermal nicotine in children with ADSHE due to the p.S280F-CHRNA4 mutation is reported. We evaluated the impact both on seizure control and on cognitive performance.

- Ethical approval other than written informed consent from the parents of these children was not required by the Regional Committees for Medical and Health Research Ethics.

### 2. Clinical pictures and treatment response

An overview of clinical characteristics and the effect of transdermal nicotine in the three children is given in Tables 1–3.

#### 2.1. Case 1

This 14 years old Norwegian boy was born after an uneventful pregnancy and had a normal development prior to seizure onset. His mother had a normal pregnancy and had a normal development prior to seizure onset. His mother complained of headache on the first day, the parents reported a tendency to more severe seizures followed by a striking improvement. He complained of headache on the first evening of treatment, but subsequently, no adverse effects were reported. The parents reported a remarkable improvement with only rare and frequent nocturnal seizures/night.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age</td>
<td>14 years</td>
<td>8 years, 2 months</td>
</tr>
<tr>
<td>Age at seizure onset</td>
<td>3 years</td>
<td>2 years</td>
</tr>
<tr>
<td>Age at onset of nicotine treatment</td>
<td>10 years, 11 months</td>
<td>6 years, 2 months</td>
</tr>
<tr>
<td>Seizures</td>
<td>Hypermotor/asymmetric tonic posturing/paroxysmal arousals</td>
<td>Hypermotor/asymmetric tonic posturing/paroxysmal arousals</td>
</tr>
<tr>
<td>Brain magnetic resonance imaging (MRI)</td>
<td>Normal (1.5 T)</td>
<td>Normal (1.5 T)</td>
</tr>
<tr>
<td>Intercital EEG (awake and sleep)</td>
<td>Normal, apart from centrofrontal sharp activity during non-REM sleep at one occasion</td>
<td>Normal</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>Arousal pattern; no epileptiform activity</td>
<td>Arousal pattern; no epileptiform activity, apart from suspect bifrontal rhythmic sharp activity at two occasions</td>
</tr>
<tr>
<td>Antiepileptic drugs tried</td>
<td>Oxcarbazepine, lamotrigine</td>
<td>Lamotrigine, oxcarbazepine</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of p.S280F-CHRNA4-related epilepsy in three children.
Table 3
Cognitive domain performance levels in three children with p.S280F-CHRNA4-related epilepsy before and during transdermal nicotine treatment.

<table>
<thead>
<tr>
<th>Cognitive domains</th>
<th>Before nicotine treatment</th>
<th>On nicotine treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td>Below average to average</td>
<td>Low average to average</td>
</tr>
<tr>
<td>Memory functions</td>
<td>Below average (verbal)</td>
<td>Average (verbal)</td>
</tr>
<tr>
<td>Verbal/nonverbal reasoning</td>
<td>Average (figurative)</td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive functions</td>
<td>Below average to average</td>
<td>Low average to average</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Low average (verbal)</td>
<td>Average (verbal)</td>
</tr>
<tr>
<td>Verbal/nonverbal reasoning</td>
<td>Low average (nonverbal)</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive functions</td>
<td>Below average (verbal)</td>
<td>Low average to average</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Average</td>
<td>Below average to average</td>
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<td>Memory functions</td>
<td>Low average</td>
<td>Average (verbal)</td>
</tr>
<tr>
<td>Verbal/nonverbal reasoning</td>
<td>Low average (nonverbal)</td>
<td>Below to low average</td>
</tr>
</tbody>
</table>

Cognitive domain performance levels are predominantly based on relevant subtests from the Wechsler Intelligence Scale for Children (WISC), versions IV or V; The Wechsler Preschool and Primary Scale of Intelligence (WPPSI), version IV; A Developmental Neuropsychological Assessment (NEPSY), second version; the Delis–Kaplan Executive Function System (D-KEFS); EpiTrack Junior; and Behavior Rating Inventory of Executive Function (BRIEF).

Performance level is related to average performance range in the reference group (below average = 2 or more standard deviation (SD) below average; low average = 1–2 SD below an average value; average = 1 SD or less below or above average; high average = 1 SD or more above average score).

subtle motor symptoms. Seven months after treatment onset, video-EEG for two nights showed just a few uncharacteristic arousals. After two years, he stopped treatment with oxcarbazepine and continued with transdermal nicotine along with methylphenidate. Hypermotor seizures did not recur; he remained with rare episodes of restless sleep and occasional short-lasting awakenings after stressful events

After application to the Norwegian Health Economics Administration, transdermal nicotine has been accepted for reimbursement for this specific disorder in the two Norwegian siblings.

2.2. Case 2

This boy aged eight years, brother of case 1, had a similar history. Early development was considered normal prior to seizure onset. Maternal treatment with carbamazepine and topiramate had been continued also through this pregnancy.

Seizures were suspected already from the age of two years. He developed the same seizure semiology as his brother. Language testing at the age of three years confirmed language delay, in particular expressive language.

Whole-night sleep video-EEG recordings at the age of four and six years showed multiple stereotypical paroxysmal arousals and hypermotor seizures without corresponding ictal EEG activity, similar to his brother (Table 2). Abrupt jerking and stiffening were sometimes accompanied by vocalization.

He also had a tendency to hyperactivity, impulsivity, and inattention. Neuropsychological testing at six years, including Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition (WPPSI-IV), showed a general performance at low-average level for his age.

Treatment with lamotrigine had dubious benefit on seizure control and behavioral adverse effects. Oxcarbazepine was discontinued because of nausea after a few weeks. The hypermotor seizures disappeared with transdermal nicotine 3.5 mg/24 h (approximately 0.15 mg/kg/24 h). After six months, 24-h video-EEG recording was normal with no clinical signs of nocturnal seizure activity. In particular circumstances, such as febrile illness and after stressful events, he may have rare, subtle seizures with awakenings and minimal motor elements. At eight years, such symptoms were associated with ictal EEG activity in the form of bifrontal rhythmic sharp waves. Currently, the exposure to nicotine appears to be variable as he has a tendency to scratch off the patch because of itching during daytime. He remains with a tendency to impulsive and hyperactive behavior.

Neuropsychological testing at the age of eight years showed a low-average ability level with no significant change compared with the testing before nicotine treatment. However, the results indicated improvement in verbal and nonverbal reasoning with scores classified as average. Fine motor speed was impaired, and verbal learning and memory tests indicated deficits. Although some scores on tests of executive functions were considered normal, his parents reported problems consistent with severe executive dysfunction.

2.3. Case 3

This French boy was born after an uneventful pregnancy. Early developmental milestones were normally achieved. His parents and his older brother are healthy.

At the age of five years, hypermotor seizures occurred during sleep. The first video-EEG recorded a motor seizure with right limb dystonia accompanied by left frontal delta activity. Interictal EEG showed left frontal spike-and-waves. Valproate and lamotrigine were ineffective. Levetiracetam and topiramate induced adverse effects, but he had some effect from carbamazepine.

Repeated nocturnal video-EEGs recorded 10 to 30 motor seizures/night with right limb dystonia, sometimes extended to both limbs and associated with frontal polyspikes, and interictal left frontal slow activity. Some seizures were more subtle arousals with eye opening and mild tonic posturing accompanied by bifrontal polyspikes.

Progressive behavioral deterioration with hyperactivity and attention-deficit held him back at school. Psychometric testing at seven years showed a working memory deficit but normal verbal and visual processing. Neuropsychological testing confirmed severe executive problems.

An intracerebral EEG recording (stereo-EEG) at the age of eight showed a widespread epileptogenic network, which excluded resective surgery. Despite additional drug trials with oxcarbazepine and zonisamide, the epilepsy worsened with more than 20 seizures/night. At the age of nine, the behavior deteriorated with anxiety and impulsiveness. His condition was treated with risperidone, and he received
special education. Psychometric testing showed worsening of the visual processing index (VPI) and the working memory index (WMI).

Transdermal nicotine 7 mg/24 h was introduced at the age of 10 years, while he was treated with carbamazepine and oxcarbazepine. Dramatic improvement with rapid decrease of seizure frequency was reported, together with a reduction of impulsiveness and anxiety. Nocturnal video-EEG recordings were performed two days before nicotine introduction and two months afterwards. The frequency of seizures had decreased by >70%, from 50 seizures/night with hypermotor elements to eight seizures/night with only auras and mild posturing. Neuropsychological and psychometric testing performed four months after nicotine introduction evidenced an improvement in control and attention and a normalization of VPI. Executive functioning was still impaired, but improvement was observed for verbal fluency and memory tests. The Child Behavior Checklist (CBCL) had also improved.

One year after introduction of transdermal nicotine, the boy is able to attend secondary school with educational support. Antiepileptic drug treatment has been reduced to carbamazepine monotherapy, and risperidone was lowered. Nicotine treatment is well tolerated. The parents only observe seizures very occasionally during stressful periods. They report a better daily social functioning. The CBCL score remains abnormal, and neuropsychological testing still shows impulsiveness and executive deficits one year after onset of nicotine treatment.

Written informed consent for participation in the study was provided from the parents of the three children.

3. Inheritance

3.1. Cases 1 and 2

These brothers belong to a large Norwegian family with ADSHE caused by the p.S280F-CHRNA4 variant (c.839C>T). Both boys and their mother carry the mutation. Genetic testing was limited to analysis of the eight mutations provided from the parents of the three children.

3.2. Case 3

This French boy also carries the heterozygous p.S280F-CHRNA4 mutation, revealed by next-generation sequencing using a large epilepsy panel. He was first considered to be a sporadic case, but both his father and brother were shown to carry the same mutation. At a detailed interview, the father recalled recurrent ‘nightmares’ during childhood but had never been aware of hypermotor seizures. His wife had not observed nocturnal attacks. His older brother did neither experience auras nor hypermotor seizures and had a normal cognitive function. This case illustrates the incomplete clinical penetrance and the high intrafamilial phenotypic heterogeneity of this mutation.

There is no known relationship between the Norwegian and the French family.

4. Discussion

Transdermal nicotine is established as an experimental therapy in adults with ADSHE due to CHRNA4 mutations. The novelty of this contribution is the young age of the patients and the impact of treatment on cognitive development. Our case series suggests that nicotine treatment may be safe and efficacious also in children.

4.1. Seizure control

In the three present boys with p.S280F-CHRNA4 mutations and multiple nocturnal seizures, there was an impressive effect on seizure frequency and severity, which is in line with previous reports in adults [11,12]. Two of the children stopped AED treatment because of side effects and maintained seizure control with nicotine monotherapy, whereas the third child continued with concomitant carbamazepine. With unchanged treatment, the effect remained stable after a follow-up time of one to three years although poor adherence to the patch administration appeared to be associated with restless sleep and subtle attacks in the youngest Norwegian boy.

4.2. Encephalopathic features

Mutations in the nAChRs may have wider consequences than just the seizure disorder. Cognitive impairment involving executive and memory functions has been demonstrated among adult patients with ADSHE, including patients with the p.S280F-CHRNA4 mutation [8,15,16]. It has been suggested that these cognitive dysfunctions predominantly are due to the central nervous cholinergic abnormality [17]. The findings highlight the discussion on the differentiation between a ‘developmental encephalopathy’ and an ‘epileptic encephalopathy’, in which the epileptic activity itself contributes to neuropsychological impairment [18]. In two of the children, behavioral problems decreased after the introduction of nicotine, whereas cognitive impairment slightly improved in all. The present findings cannot determine whether nicotine exposure directly improves the cognitive and behavioral dysfunction or if seizure control itself and abolished ictal sleep fragmentation are crucial factors [16]. If the latter is true, intense antiseizure treatment might have the potential to reduce the overall clinical consequences of the disorder, corroborating the importance of early nicotine treatment in children with uncontrolled epilepsy. Moreover, this precision therapy may allow for a reduced adverse effect burden from AEDs.

An intriguing, yet hypothetical question is whether early nicotine treatment even can interact with brain development. A study based on positron emission tomography (PET) showed that patients with ADSHE had a higher density of nAChR in the brainstem along with decreased density in the forebrain compared with controls [17]. These findings challenged the channelopathy concept as they may suggest an architectural abnormality, conceivably acquired during brain development, although an alternative hypothesis is an upregulation of the gain-of-function mutated receptors in a region known to have a particularly high receptor density. In cases 1 and 2, an additional environmental effect on neurodevelopment from the fetal exposure to AEDs cannot be excluded [19]. Also, genetic complexity may influence comorbidity profiles in seizure disorders thought to be purely monogenic [20,21].

4.3. Pathophysiological considerations

Conceivably, the seizure reducing effect of nicotine relates to the pathophysiology of nAChR mutations. Typically, an increased acetylcholine sensitivity is observed in vitro in this form of ADSHE, hence, gain-of-function of nAChR appears to be the underlying mechanism [22,23]. The main hypotheses postulate that the mutated receptors cause altered γ-aminobutyric acid (GABA)-ergic interneuron activity leading to seizure generation [24]. It has been suggested that desensitization of the mutated receptors, ‘normalizing’ the receptor physiology, explains the effect of nicotine in ADSHE [12]. We postulate that nicotine may have a potential beneficial effect not only in patients with p.S280F-CHRNA4 mutations but in most patients with nAChR mutations as an increased sensitivity to acetylcholine has been identified in most functionally characterized mutations [24,25]. In one single adult patient with uncontrolled epilepsy carrying the p.S284L-CHRNA4 mutation, transdermal nicotine also provided seizure control [26]. A study in adults has also suggested benefit from nicotine in patients with the p.L291dup-CHRNA4 mutation [12]. However, electrophysiological studies have demonstrated major differences regarding the sensitivity to nicotine in various nAChR mutations, suggesting variations in pharmacogenomic properties not readily correlating with increased acetylcholine affinity [25]. Therefore, it is currently not possible to predict which patients will benefit from nicotine intervention; even a worsening effect cannot
be excluded in some mutations. Nicotine treatment should be initiated with care. More studies are needed to elucidate these issues further in relevant mutations, but clinical experience speaks for itself.

4.4. Risks of nicotine treatment

The safety of continuous nicotine exposure in children is obscure. Long-term health effects of nicotine itself are difficult to estimate as nicotine replacement therapy typically is used by previously heavy smokers [27]. However, there are concerns about hemodynamic effects of nicotine, which may have implications for risk of cardiovascular disease. Smokeless tobacco consumption in the form of snuffing (‘snus’) is widely used in the Scandinavian countries, even in the absence of former smoking. Swedish studies did neither find an association with ischemic heart disease [28] nor with stroke [29]. Nevertheless, future epidemiological studies should be kept under surveillance, and the balance between benefit and risk should be carefully weighed.

4.5. Nicotine treatment in ADSHE

Importantly, only a minority of patients with sleep-related hypermotor epilepsy (SHE) have mutations in nAChRs. Most cases are considered ‘sporadic’ without a clear family history [1,13]. Moreover, some patients have mutations in the sodium-activated potassium channel encoded by KCNT1 (potassium channel subfamily T member 1) [30] in the DEPDC5 (DEP domain containing 5, GATOR1 subcomplex unit) gene which encodes a repressor of the mammalian target of rapamycin (mTOR) pathway [31] and in the CABP4 (Ca²⁺ binding protein 4) gene encoding the neuronal CaBP4 [32]. Interestingly, transdermal nicotine led to a complete resolution of the seizures in an adolescent with severe nonstructural frontal lobe epilepsy in the absence of CHRNA4 or CHRNB2 (cholinergic receptor, nicotinic, beta polypeptide 2) mutations [33], suggesting a similar mechanistic pathway in this patient. However, a case-control family study on sporadic cases of SHE did not show a significantly higher tendency to tobacco consumption in patients compared with controls [34]. Only empirical and anecdotal data yet support the efficacy of transdermal nicotine in ADSHE due to nAChR mutations. In this study, the number of treated patients was low, and the follow-up time was short. From the outset, this study was retrospective; various neuropyschological tests were applied at different points in time, and we could not consider the natural course or inherent fluctuations of the disorder in individual. Unfortunately, the rarity of the disorder limits the opportunity to perform controlled trials in a large number of patients. Complete and reliable seizure diaries are usually impossible to obtain for sleep-related hypermotor seizures. Notwithstanding, we believe that the currently available clinical experience is sufficiently convincing to suggest that nicotine may be a mechanistic therapy in this specific type of seizure disorder as opposed to the symptomatic treatments used for most epilepsies. The effect on seizure control was remarkable in this series. For the first time, we have been able to demonstrate that cognitive and behavioral function also may improve, suggesting that this treatment approach may reduce the educational and psychosocial consequences of the disorder in young children. Children with SHE without known cause should all be tested for nAChR mutations.

5. Conclusion

Nicotine treatment for AED-resistant ADSHE should receive more attention as it may control seizures resistant to conventional AEDs and impact socioeducational function in children. This potential precision therapy should be available to more patients across the age span after a careful genetic and clinical selection as well as a thorough risk/benefit assessment. When prudently tried and effective, this mode of treatment should be reimbursed for this specific disorder by health authorities and medical insurance programs in line with standard AEDs.

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Declaration of competing interest

None of the authors has any conflict of interest to disclose.

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