で高く女子で低いとしているが，それは抑うつ障害とも双極性障害とも異なり，いわゆる発達障害と近似している．

年齢に関連した変化も特徴的である．DMDD は青年期前では一般的にみられるが，小児から成人へ移行するにつれて一般的にみられなくなっていくという．これも抑うつ障害や双極性障害とは異なり，いわゆる発達障害の経過と近似している．

鑑別診断

DMDD 診断において最も難しいのは鑑別診断である．DSM-5 でも最も多くの紙数を割いている．特に双極性障害と ODD との鑑別に細心の注意が必要である[1]．

双極性障害との鑑別

小児の双極性障害と DMDD との基本的な相違点は中心となる症状の縦断的な経過である．双極Ⅰ型障害およびⅡ型障害の症状は，子どもの普段の状態とは異なる，明らかに分離したエピソード性の気分の障害である．躁病エピソードのときに起きる気分の障害は，子どもの普通の気分とは明らかに異なるものである．また，躁病エピソードのとき，気分の変化は始まりと同時に，あるいは悪化と同時に，認知的，行動的，生理学的症状として起こる．それは子どもの普通の状態とは明らかに異なっているレベルである．このように，双極性障害では子どもの気分や行動が普通の状態とは明らかに異なる，はっきりと他と区別できる時間を同定することができる．一方，DMDD の症状は持続的であり，何か月にもわたって存在する．ある程度の変動はあるが，重篤な慢性的な易怒性が特徴的な症状なのである．

もう一つの重要な鑑別点は，双極性障害においては，高揚気分あるいは開放気分と誇大気分が存在するかどうかである．これらの症状は双極性障害の最も基本的な症状であるが，DMDD においては存在しないのである．

ODD との鑑別

ODD の症状は DMDD の子どもにも出現するが，DMDD の気分の症状は ODD の子どもに出現することは少ない．つまり，DMDD の診断基準を満たす子どもの多くは ODD の診断も満たすが，逆は真ではないのである．ODD の子どもが DMDD の診断基準も満たすのはわずか 15％である．そのような双方の診断基準を満たす子どもは DMDD のみの診断となるのである．DMDD の子どもは ODD の子どもと比較して，症状のなかにより顕著な気分の要素が含まれているのである．もちろん，DMDD の子どもは気分の問題だけでなく，行動面でも多くの問題を抱えていることはいうまでもない．

ADHD，うつ病/大うつ病性障害，不安症群，自閉スペクトラム症（ASD）との鑑別

DMDD と ADHD，うつ病，不安症群，自閉スペクトラム症（autism spectrum disorder：ASD）は併存診断が可能であるため，明らかに双方が併存する場合もある．しかしながら，その易怒性が ADHD，うつ病，不安症群の文脈においてのみ生じている場合は

DMDDという診断はつかない．また，ASDの子どもがこだわりが妨害されてかんしゃく発作を起こすことがしばしばあるが，そのような場合のかんしゃく発作はASDの二次的な症状と考え，DMDDの診断はつけるべきでない．

間欠爆発症との鑑別

間欠爆発症の症状をもつ子どもは，DMDDの子どもと似ているがより激しいかんしゃく発作を示す．しかしながら，DMDDと異なる点は，かんしゃく発作の間欠期において気分の不調は認められないことである．加えて，間欠爆発症は症状が3か月しか持続しないのに比べてDMDDは12か月以上も持続することである．これらの2つの病態は同じ子どもに同時に診断してはならない．

併存症

DMDDの併存症の割合はきわめて高率である．DMDD単独で診断される子どもはむしろまれである．最も高率に認められる併存症はODDであるが，双方が併存する場合はDMDDのみの診断になる．DMDDにおける併存症の特徴は，それが高率であることだけでなく，その範囲が多様であることである．秩序破壊的行動，抑うつ障害，不安症，そしてASDというように広範囲にわたっている．併存診断ができない疾患は，ODD，双極性障害，間欠爆発症である．また，過去に躁病あるいは軽躁病エピソードを経験している子どもの場合はDMDDの診断をつけるべきではない．

DMDDはDSM-5で初めて採用された概念である．まず，概念成立の経緯について解説した．DMDDは小児双極性障害との鑑別を明確にする目的で，「慢性に持続する重度の非エピソード性の易怒性」をもつ子どもを表現する病態である．次に，DSM-5の診断基準を述べ，臨床的特徴について説明した．

今後の課題は，診断に関しては併存症との関係を明確にしていくことである．DMDD単独で診断されることがむしろまれな病態が，一つの疾患単位として成立するのだろうか．もう一つの課題は治療である．さまざまな薬物療法および心理社会的治療が試みられているが，いまだに明らかに有効性を示すエビデンスは認められない．診断の洗練とともに治療に関するエビデンスが蓄積されることを願いたい．

（傳田健三）

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Regular Article

Increased prefrontal hemodynamic change after atomoxetine administration in pediatric attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy

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Aim: Atomoxetine, approved in Japan for the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD) in April 2009, is a nonstimulant that is thought to act presynaptically via the inhibition of norepinephrine reuptake. Near-infrared spectroscopy is a non-invasive optical tool that can be used to study oxygenation and hemodynamic changes in the cerebral cortex. The present study examined the effects of a clinical dose of atomoxetine on changes in prefrontal hemodynamic activity in children with ADHD, as measured by near-infrared spectroscopy using the Stroop Color–Word Task.

Methods: Ten children with ADHD participated in the present study. We used 24-channel near-infrared spectroscopy to measure the relative concentrations of oxyhemoglobin in the frontal lobes of participants in the drug-naïve condition and those who had received atomoxetine for 8 weeks. Measurements were conducted every 0.1 s during the Stroop Color–Word Task. We used the ADHD Rating Scale-IV-Japanese version (Home Version) to evaluate ADHD symptoms.

Results: We found a significant decrease in ADHD Rating Scale-IV-Japanese version scores, from 30.7 to 22.6 ($P = 0.003$). During the Stroop Color–Word Task, we found significantly higher levels of oxyhemoglobin changes in the prefrontal cortex of participants in the atomoxetine condition compared with those in the drug-naïve condition.

Conclusions: This increase in oxyhemoglobin changes might indicate an intensified prefrontal hemodynamic response induced by atomoxetine. Near-infrared spectroscopy is a sensitive tool for measuring the pharmacological effects of atomoxetine in children with ADHD.

Key words: atomoxetine, functional neuroimaging study, near-infrared spectroscopy, pediatric attention-deficit/hyperactivity disorder, prefrontal hemodynamic response.

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a disorder of the central nervous system that is estimated to occur in 3–7% of school-age children. Neurobiological studies have reported that prefrontal dysfunction is a component of the pathophysiology of ADHD.

Near-infrared spectroscopy (NIRS) is a non-invasive optical tool for studying oxygenation and hemodynamic changes in the cerebral cortex. NIRS allows researchers to measure changes in oxygenated hemoglobin, and thus, enables functional imaging of brain activity.[1] In addition to measuring changes in the concentration of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), NIRS can be used to measure changes in the redox state of cytochrome-c-oxidase, based on specific spectra in the near-infrared range (i.e., 700–1000 nm). Because of neurovascular coupling,[2,3] brain activation leads to an increase in cerebral blood flow without a proportionate increase in oxygen consumption. Consequently, an increase in the concentration of oxy-Hb is associated with a decrease in the concentration of deoxy-Hb.[1] NIRS is a neuroimaging modality that, according to Matsuo *et al.*,[4] is especially suitable for psychiatric patients for the following reasons. First, NIRS is relatively insensitive to motion artifact, and so it can be used in experiments where motion is expected, such as those involving vocalizations. Second, NIRS can be used to measure participants who are seated in a natural position, with minimal environmental distractions. Third, NIRS has a cheaper running cost than other neuroimaging modalities and is simple to set up and use. Fourth, the high temporal resolution of NIRS is useful for characterizing the time course of prefrontal activity in people with psychiatric disorders.[5,6] Accordingly, NIRS has been used to assess brain function in people with many psychiatric disorders, including schizophrenia, bipolar disorder, depression, obsessive–compulsive disorder, dementia, post-traumatic stress disorder, pervasive developmental disorder, and ADHD.[4–14]

In pediatric ADHD, reduced prefrontal hemodynamic response has been reported as measured by NIRS.[15,16] Negoro *et al.*[17] used NIRS to examine prefrontal hemodynamic activity during the Stroop Color–Word Task in 20 children with ADHD and 20 healthy age- and sex-matched controls. They found that the oxy-Hb changes in the inferior prefrontal cortex in the control group were significantly larger than those in the ADHD group during the Stroop Color–Word Task.

Atomoxetine (ATX), approved in Japan for the treatment of pediatric ADHD in April 2009, is a nonstimulant that is thought to act presynaptically via the inhibition of norepinephrine reuptake. ATX has a limited effect on serotonin and dopamine transporters and has low affinity for dopaminergic, muscarinic-cholinergic, histaminic, serotonergic, and α1- or α2-adrenergic receptors. Multiple reports have indicated that this medication is a safe and well-tolerated intervention for pediatric ADHD.[18,19] In a recent functional magnetic resonance imaging (fMRI) study, ATX was associated with increased activation in the dorsolateral prefrontal cortex, parietal cortex, caudate, and cerebellum of adults with ADHD.[20] In an NIRS study, Araki *et al.*[21] examined the effects of long-term treatment with ATX on prefrontal hemodynamic activity in 12 children with ADHD during a continuous performance task. They found that the oxy-Hb concentration in the right dorsolateral prefrontal cortex in the post-ATX condition was significantly increased compared to the pre-ATX condition.

The Stroop Color–Word Task is one of the most commonly used tools for determining attentional problems. It is also a test of executive function and working memory. The continuous performance task that was used in the previous NIRS study by Araki *et al.*[21] also measures a person's attention. However, the neuropsychological background is different. The continuous performance task mainly measures a person's sustained attention, which is associated with impulsivity. The Stroop Color–Word Task mainly measures a person's selective attention and an effect of interference. Furthermore, in another recent study, there was a different effect on the blood oxygenation level–dependent activity in the prefrontal cortex in a comparison between the Stroop Color–Word Task and the continuous performance task.[22] Thus, it is important to examine the effects of ATX on prefrontal hemodynamic activity in children with ADHD using NIRS during the Stroop Color–Word Task. In addition to these reasons, we used the Stroop Color–Word Task for the following reasons. First, the inferior frontal gyrus has been described as one of the regions most strongly related to Stroop interference.[23] Second, in the NIRS study using the same task, Negoro *et al.*[17] concluded that the word-reading task and the incongruent color-naming task produced suitable prefrontal brain activation in healthy children.

To the best of our knowledge, there are no existing reports on ATX-induced changes in prefrontal hemo-

dynamic activity in pediatric ADHD, as measured by NIRS using the Stroop Color–Word Task. Thus, we used NIRS to examine the effects of a clinical dose of ATX on changes in prefrontal hemodynamic activity during the Stroop Color–Word Task in children with ADHD.

METHODS

Participants

Ten participants (seven boys and three girls), aged 7–13 years and diagnosed with ADHD according to the DSM-IV-TR,[24] participated in the present study. The participants with ADHD, who had no history of treatment for a developmental disorder, had consulted an experienced pediatric psychiatrist at the Department of Psychiatry at Nara Medical University with the chief complaint of inattention, hyperactivity, or impulsiveness. These participants underwent a standard clinical assessment comprising of a psychiatric evaluation, a semi-structured diagnostic interview (the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version),[25] and a medical history assessment. Two experienced pediatric psychiatrists confirmed the diagnosis of ADHD according to the DSM-IV-TR. Intellectual level was assessed using the Wechsler Intelligence Scale for Children–Third Edition, and individuals with full-scale IQ (FIQ) scores below 70 were excluded. We also excluded those who presented with a comorbid Axis I diagnosis, a neurological disorder, a head injury, a serious medical condition, or a history of substance abuse/dependence. Consequentially, two individuals with chronic tic disorder were excluded. In total, 10 participants with ADHD who had no previous medication history were enrolled in the present study. All participants were right-handed and of Japanese descent.

We used NIRS to measure the relative concentrations of oxy-Hb in the participants in the drug-naïve condition (pre-treatment) and after 8 weeks of treatment with ATX (post-treatment). All measurements were conducted at the same time of day (10.00–11.00 hours). We estimated the severity of ADHD symptoms on the same day as NIRS measurement. The participants were treated with ATX as quickly as possible after completing the baseline NIRS measurement. The daily dose of ATX ranged from 10 to 75 mg (mean ± SD, 1.34 ± 0.75 mg/kg). The characteristics of the participants are shown in Table 1. This study was approved by the Institutional Review Board at Nara Medical University (approval number 354). Written informed consent was obtained from all participants and/or their parents prior to the study.

Assessment of ADHD symptoms

We used the ADHD Rating Scale-IV-Japanese version (ADHD RS-IV-J) (Home Version)[26] to evaluate ADHD symptoms in the participants. A higher

Table 1. Participant characteristics

	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	*P*-value
Number [sex ratio: M : F]	10 [7:3]		
Age (years)	9.90 (2.38)		
FIQ (WISC-III)	94.70 (10.30)		
Atomoxetine dose (mg/kg)		1.34 (0.75)	
ADHD RS-IV-J total score	30.70 (10.81)	22.60 (12.27)	0.003
SCWC-1	29.00 (12.82)	37.10 (17.28)	0.005
SCWC-2	31.80 (14.32)	36.00 (15.28)	0.004
SCWC-3	28.60 (12.95)	36.60 (14.01)	0.002

Two-tailed paired *t*-test.
ADHD RS-IV-J, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version; F, female; FIQ (WISC-III), full-scale IQ score on the Wechsler Intelligence Scale for Children–Third Edition; M, male; SCWC-1, Stroop Color–Word Task number of correct answers first time; SCWC-2, Stroop Color–Word Task number of correct answers second time; SCWC-3, Stroop Color–Word Task number of correct answers third time.

ADHD RS-IV-J score is associated with more severe ADHD symptoms. All participants underwent ADHD RS-IV-J assessment pre- and post-treatment (Table 1).

Stroop Color–Word Task

The traditional Stroop Task was combined with the word-reading task, incongruent color-naming task, and the color-naming task. However, we reconstructed the Stroop Task according to previously described methods.[27] The Stroop Color–Word Task consisted of two pages stapled together: each page had 100 items in five columns of 20 items each and the page size was 210 × 297 mm. On the first page, the words RED, GREEN, and BLUE were printed in black ink. On the second page, the words RED, GREEN, and BLUE were printed in red, green, or blue ink, with the limitation that the word meaning and ink color could not match. The items on both pages were randomly distributed, with the exception that no item could appear directly after the same item within a column.

Before the task, the examiners instructed the participants as follows: 'This is to test how quickly you can read the words on the first page, and say the colors of the words on the second page. After we say "begin," please read the words in the columns, starting at the top left, and say the words/colors as quickly as you can. After you finish reading the words in the first column, go on to the next column, and so on. After you have read the words on the first page for 45 s, we will turn the page. Please repeat this procedure for the second page.'

The entire Stroop Color–Word Task sequence consisted of three cycles of 45 s spent reading the first page and 45 s spent reading the second page (the color–word task). The task ended with 45 s spent reading the first page, which we designated as the baseline task. We recorded the number of correct answers in each cycle, and refer to them as follows: Stroop Color–Word Task number of Correct answers first time (SCWC-1), second time (SCWC-2), and third time (SCWC-3). Examiners who were blind to the diagnoses of the participants administered the Stroop Color–Word Task.

The Stroop Task used in this study was different from the traditional Stroop Task. We made the Stroop Color–Word Task simple because the participants were school-aged children. Furthermore, we excluded the color-naming task (part of the traditional Stroop Task) because we wanted to have only two tasks (baseline task and activation task) for our NIRS study.

NIRS measurements

Increased oxy-Hb and decreased deoxy-Hb, as measured by NIRS, have been shown to reflect cortical activation. In animal studies, oxy-Hb is the most sensitive indicator of regional cerebral blood flow because the direction of change in deoxy-Hb is determined by the degree of changes in venous blood oxygenation and volume.[28] Therefore, we decided to focus on changes in oxy-Hb. We measured oxy-Hb using a 24-channel NIRS machine (Hitachi ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). We measured the absorption of two wavelengths of near-infrared light (760 and 840 nm). Oxy-Hb was calculated as previously described.[29] The inter-probe intervals of the machine were 3.0 cm, and previous reports have established that the machine measures at a point 2–3 cm beneath the scalp, that is, the surface of the cerebral cortex.[10,30]

The participants were asked to adopt a natural sitting position for NIRS measurement. The distance between the eye of the participant and the paper on which items were listed was coordinated from 30 cm to 40 cm. The NIRS probes were placed on the scalp over the prefrontal brain regions, and arranged to measure the relative changes in Hb concentration at 24 measurement points that made up an 8 × 8-cm square. The lowest probes were positioned along the Fp1–Fp2 line according to the international 10/20 system commonly used in electroencephalography. The correspondence between the probe positions and the measurement points in the cerebral cortex were confirmed by superimposing the probe positions onto a three-dimensionally reconstructed cerebral cortex of a representative participant in the control group, obtained via MRI (Fig. 1). The absorption of near-infrared light was measured with a time resolution of 0.1 s. The data were analyzed using the 'integral mode': the pre-task baseline was determined as the mean across the 10 s just before the task period, the post-task baseline was determined as the mean across the 25 s immediately after the task period, and linear fitting was performed on the data between the two baselines. Moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average window, 5 s).

We attempted to exclude motion artifacts by closely monitoring artifact-evoking body move-

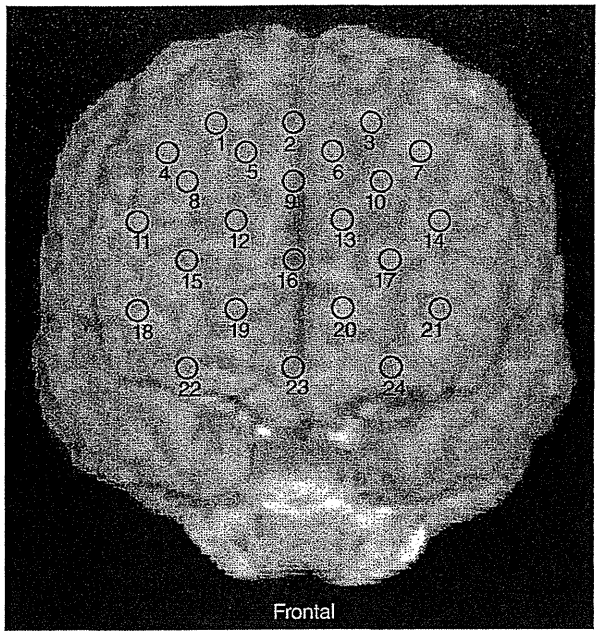

Figure 1. *Near-infrared spectroscopy measurement points.* The points were mapped onto the frontal lobes using MRIcro software (MRIcro was developed by Dr Chris Rorden, and is available at http://www.mricro.com). The numbers denote the channel for each measurement point.

ments, such as neck movements, biting, and blinking (identified as being the most influential in a preliminary artifact-evoking study), and by instructing the participants to avoid these movements during the NIRS measurements. Examiners were blind to the treatment condition of the participants.

Statistical analyses

For statistical comparison of the participant characteristics between the pre- and post-treatment conditions, we used a two-tailed paired *t*-test. Specifically, we compared oxy-Hb changes between the pre- and post-treatment conditions. We used PASW Statistics 18.0 J for Windows (SPSS, Tokyo, Japan) for statistical analysis. To conduct a more detailed comparison of oxy-Hb changes along the time course of the task, we used MATLAB 6.5.2 (Mathworks, Natick, MA, USA) and Topo Signal Processing type-G version 2.05 (Hitachi Medical Corporation, Tokyo, Japan). As we performed 24 paired *t*-tests, the correction for multiple comparisons was made using the false discovery rate (FDR)[31] (two-tailed; we set the value of q specifying the maximum FDR to 0.15, so that there were no more than 15% false positives on average).

RESULTS

As shown in Table 1, the SCWC-1, SCWC-2, and SCWC-3 scores in the post-treatment condition were significantly higher to those in the pre-treatment condition ($t=-3.72$, d.f. $=9$, $P=0.005$; $t=-3.81$, d.f. $=9$, $P=0.004$; $t=-4.28$, d.f. $=9$, $P=0.002$). Additionally, the total ADHD RS-IV-J scores in the post-treatment condition were significantly lower than scores in the pre-treatment condition ($t=4.03$, d.f. $=9$, $P=0.003$).

Figure 2 shows the grand average waveforms of oxy-Hb concentration changes during the Stroop Color–Word Task in the pre- and post-treatment conditions. We found that the amplitude of the grand average waveforms of oxy-Hb concentration changes increased during the task period in the post-treatment condition, although this was not the case in the pre-treatment condition. As shown in Table 2, we found that the difference in mean oxy-Hb measurements between the task and post-task periods was significantly larger in the post-treatment than in the pre-treatment conditions at channels 11 and 21 (FDR-corrected P: 0.0063–0.0125). Figure 3 contains a topographic representation of the t-values representing the difference in oxy-Hb concentration between the pre- and post-treatment conditions during the Stroop Color–Word Task. The oxy-Hb changes in the prefrontal cortex were significantly larger in the post-treatment condition than in the pre-treatment during the task period.

We examined the correlations between the ADHD RS-IV-J scores and the difference in oxy-Hb concentration at channels 11 and 21. The decreased ADHD RS-IV-J score tended to be negatively correlated with increased oxy-Hb at channel 11 (Spearman's $\rho=-0.626$, $P=0.097$). There was no significant correlation between the ADHD RS-IV-J score and the increased oxy-Hb at channel 21 (Spearman's $\rho=0.427$, $P=0.252$).

DISCUSSION

To the best of our knowledge, there are no other studies using the Stroop Task to examine ATX-induced prefrontal hemodynamic responses in pediatric ADHD as measured by NIRS. We found that oxy-Hb changes in the prefrontal cortex during the Stroop

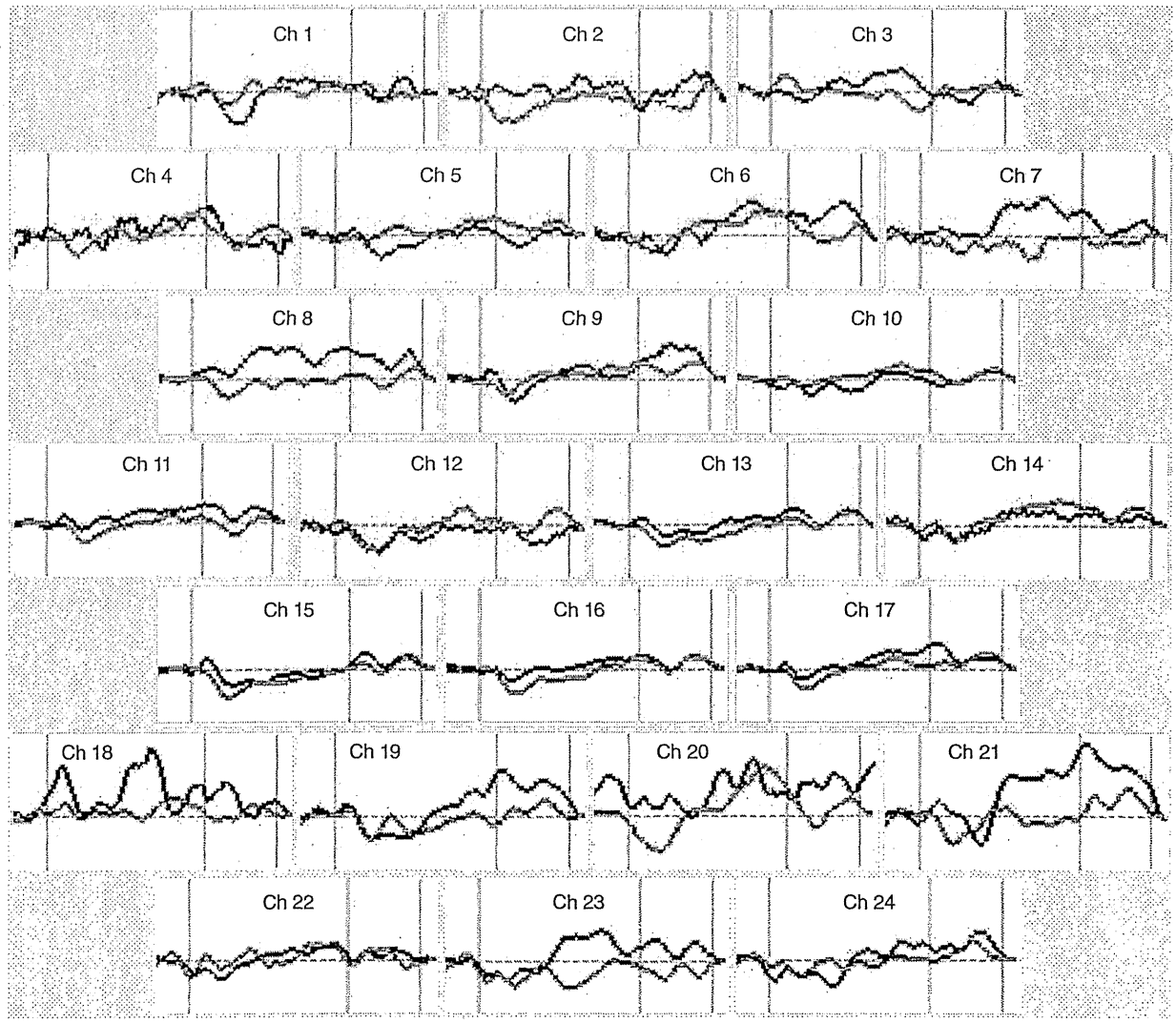

Figure 2. Grand average waveforms of oxyhemoglobin (oxy-Hb) concentration changes during the Stroop Color–Word Task in the pre- and post-treatment conditions. Red lines indicate pre-treatment and blue lines indicate post-treatment. The green lines indicate the beginning and end of each trial.

Color–Word Task were significantly larger in the post-treatment than in the pre-treatment condition. Our findings are consistent with previous NIRS studies. Araki *et al.*[21] examined the effects of long-term (6 months–1 year) treatment with ATX on prefrontal hemodynamic activity in 12 children with ADHD during a continuous performance task. In the ADHD group in the post-ATX condition, significant activation was observed in the right dorsolateral prefrontal cortex and the decrease in oxy-Hb concentration in the left ventrolateral prefrontal cortex disappeared. They concluded that long-term treatment with ATX improved prefrontal hemodynamic activity in ADHD children, and NIRS may be useful for assessment of the prefrontal hemodynamic response to ATX treatment. Furthermore, our findings are consistent with previous fMRI studies. For instance, Bush *et al.*[20] reported that adults with ADHD who had received 6 weeks of ATX treatment exhibited increased activation of the dorsolateral prefrontal cortex, parietal cortex, caudate, and cerebellum during the Multi-Source Interference Task. Similarly, Cubillo *et al.*[32] examined the

Table 2. Difference in mean oxyhemoglobin measurements between the task and post-task periods in the pre- and post-treatment conditions

	Pre-treatment (mMmm)		Post-treatment (mMmm)		Student's	FDR
	Mean	SD	Mean	SD	*t*-test	correction
Ch 1	0.0004	0.0587	−0.0034	0.0915	NS	NS
Ch 2	−0.0445	0.0889	0.0085	0.1205	NS	NS
Ch 3	−0.0006	0.0535	0.0144	0.1123	NS	NS
Ch 4	0.0004	0.0702	0.0129	0.0654	NS	NS
Ch 5	0.0182	0.0487	−0.0123	0.0687	NS	NS
Ch 6	0.0182	0.0464	0.0434	0.1246	NS	NS
Ch 7	−0.0288	0.0814	0.0516	0.0808	NS	NS
Ch 8	−0.0118	0.0731	0.0690	0.0838	$P = 0.030$	NS
Ch 9	0.0175	0.0743	0.0100	0.1197	NS	NS
Ch 10	0.0109	0.0754	−0.0123	0.0615	NS	NS
Ch 11	−0.0076	0.0858	0.0310	0.0692	$P = 0.011$	*
Ch 12	−0.0051	0.0673	−0.0369	0.0627	NS	NS
Ch 13	−0.0176	0.0716	0.0090	0.0539	NS	NS
Ch 14	0.0341	0.0518	0.0132	0.0730	NS	NS
Ch 15	−0.0224	0.1002	−0.0069	0.0851	NS	NS
Ch 16	−0.0097	0.1155	0.0118	0.0607	NS	NS
Ch 17	0.0063	0.0569	0.0302	0.0451	NS	NS
Ch 18	0.0177	0.0510	0.0835	0.1123	NS	NS
Ch 19	−0.0128	0.0926	0.0361	0.0937	$P = 0.039$	NS
Ch 20	0.0231	0.0994	0.0882	0.2221	NS	NS
Ch 21	0.0004	0.0638	0.1058	0.1254	$P = 0.011$	*
Ch 22	0.0073	0.0697	0.0061	0.0739	NS	NS
Ch 23	−0.0467	0.0460	0.0253	0.1111	NS	NS
Ch 24	−0.0017	0.0943	0.0093	0.0803	NS	NS

Group differences tested with *t*-test and FDR correction.
*$P <$ FDR-corrected P.
FDR, false discovery rate; NS, not significant.

neurofunctional modulation and normalization effects of acute doses of ATX and methylphenidate within medication-naïve ADHD boys during working memory. They found that ATX significantly enhanced activation in the right dorsolateral prefrontal cortex relative to methylphenidate within patients, and significantly normalized underactivation of the right dorsolateral prefrontal relative to controls.

Although several imaging studies have investigated the effects of ATX, these have used a single dose in healthy humans or focused on patients with schizophrenia. In a previous fMRI study, 8 weeks of treatment with ATX produced a significant increase in working memory–related activation of the left dorsolateral prefrontal cortex in people with schizophrenia.[33] Graf *et al.*[34] examined the influence of ATX (80 mg) on the neural correlates of error processing in healthy control participants. Compared with a placebo, they found an increase in error signaling (false minus correct incongruent NoGo responses) in the bilateral inferior frontal cortex. Chamberlain *et al.*[35] used a stop-signal fMRI paradigm to measure the effects of ATX (40 mg) in 19 healthy volunteers in a double-blind placebo-controlled design. They found that ATX increased activation in the right inferior frontal gyrus when volunteers attempted to inhibit their responses. Accordingly, they concluded that ATX produces increased inhibitory control via modulation of right inferior frontal function, and thus it has implications for understanding and treating inhibitory dysfunction in people with ADHD and other disorders. Thus, it appears that ATX increases activation in the prefrontal cortex. Negoro *et al.*[17] used NIRS to examine reduced prefrontal hemody-

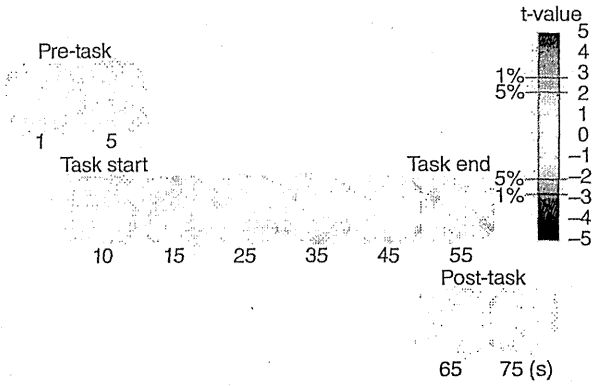

Figure 3. Topographic presentation of the t-value of the oxy-hemoglobin (oxy-Hb) comparison between the pre- and post-treatment conditions during the Stroop Color–Word Task. The t-values of oxy-Hb for the pre- and post-treatment conditions are presented as a topographic map along the time course of the task (from top to bottom). The red, green, and blue areas in the topographs indicate positive, zero, and negative t-values, with ±2.8 and ±2.1 for 1% and 5% statistical significance levels, respectively.

namic responses in ADHD children during the Stroop Color–Word Task, which is the same task used in the present study. They found that oxy-Hb changes in the inferior prefrontal cortex in individuals with pediatric ADHD were significantly lower than those in a control group. Considering the above findings, we suggest that our findings regarding larger oxy-Hb changes in the post-treatment condition indicate that ATX induced an intensified prefrontal hemodynamic response.

In the present study, at channels 11 and 21, the mean oxy-Hb difference of the post-treatment condition was significantly larger than that of the pre-treatment condition. Negoro *et al.*[17] reported a lower increase of the oxy-Hb changes at channels 8, 18, 19, 21, and 22 in individuals with pediatric ADHD compared with controls. Considering this report by Negoro *et al.*,[17] it was expected that improvement of ADHD symptoms with ATX treatment would result in increased change in the oxy-Hb in those regions; and the present finding was in line with that expectation.

In addition to the larger oxy-Hb changes, we found that total ADHD RS-IV-J scores and performance on the Stroop Color–Word Task significantly improved in the post-treatment condition. In a previous study of children with ADHD, post-treatment versus pre-treatment improvements in Stroop Test performance were statistically significant in an ATX group.[36] In a study of adults with ADHD, ATX treatment was associated with improved Stroop Color–Word score.[37] This means that ATX treatment was also associated with improved clinical symptoms in the present ADHD group. If a correlation of clinical symptom and oxy-Hb concentration changes is revealed, it will be possible to evaluate the clinical symptom and the symptomatic improvement with NIRS, which is an objective and biological tool. It is hoped that more research with a larger sample size will be conducted because there was no significant correlation between the clinical symptomatic improvement and the increased oxy-Hb in the present study.

There are three main limitations to our study. First, the spatial resolution for detecting hemodynamic responses from the scalp surface using NIRS is lower than that for fMRI, single-photon emission computed tomography, and positron emission tomography. Although the mean oxy-Hb difference of the post-treatment condition was significantly larger than that of the pre-treatment condition at channels 11 and 21, the present findings indicate that ATX treatment increased hemodynamic response in the broader prefrontal cortex, including the dorsolateral prefrontal, orbitofrontal, and frontopolar cortex, in children with ADHD. However, it is certainly significant that increased prefrontal hemodynamic response in pediatric ADHD after ATX treatment can be shown by NIRS. Second, our sample size was small. As a tentative analysis, the decreased ADHD RS-IV-J score tended to be negatively correlated with increased oxy-Hb at channel 11. However, further investigations with a larger sample size will be helpful. Third, we had no placebo-control participants. Future NIRS studies with large samples and placebo-control participants are required to determine the detailed effects of ATX, especially with respect to an intensified prefrontal hemodynamic response.

In conclusion, to the best of our knowledge, this is the first NIRS study using the Stroop Task to examine ATX-induced prefrontal hemodynamic response in individuals with pediatric ADHD. The results of the present study suggest that multi-channel NIRS systems may have potential in the pharmacotherapeutic evaluation of ATX in children with ADHD.

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ANNALS OF GENERAL PSYCHIATRY

CASE REPORT Open Access

Levetiracetam improves disinhibitory behavior in nonconvulsive status epilepticus

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Abstract

Background: Nonconvulsive status epilepticus (NCSE) is a severe medical condition and heterogeneous disorder defined by different seizure types and diverse etiologies. NCSE occurs commonly in the elderly and is potentially misdiagnosed as a psychiatric disorder. Current treatment options for NCSE are still unsatisfactory.

Case presentation: We report a case of NCSE in a 55-year-old epileptic male patient with a history of infectious encephalitis, disinhibitory behavior, and a suspected diagnosis of frontotemporal dementia. Add-on levetiracetam (LEV) to carbamazepine treatment improved clinical manifestations and abnormal electroencephalographic discharge.

Conclusion: With disinhibitory behavior in the elderly, the possibility of NCSE should be considered. Moreover, LEV may be an effective and well-tolerated pharmacotherapy for elderly NCSE patients.

Keywords: Disinhibitory behavior, Levetiracetam, Nonconvulsive status epilepticus, Psychiatric disorder, Infectious encephalitis

Introduction

Nonconvulsive status epilepticus (NCSE) is common and often manifests as altered consciousness accompanied by subtle motor twitches or ambiguous behavior changes [1], although there are subtypes of NCSE without altered consciousness. Diagnosis is based on electroencephalographic (EEG) recordings and is defined by continuous or repeated EEG epileptic discharges beyond 10 min [2]; and continuous EEG-video monitoring is preferred to increase detection rate of NCSE [3]. Without evidence of continuous EEG epileptiform activities, NCSE without altered consciousness is easily misdiagnosed, leading to delays in treatment or loss of opportunity for proper treatment [4].

Levetiracetam (LEV) is a newer antiseizure drug (ASD), with an approved oral formulation that can be administered at doses effective in controlling seizures [5]. LEV is known to be well-tolerated, even in the elderly [6].

This report focuses on the use of LEV as an add-on therapy in the treatment of NCSE in an epileptic patient with disinhibitory behavior, as our survey of the literature did not identify any current report related to LEV used in this context. We found add-on LEV to carbamazepine (CBZ) treatment reversed clinical and EEG manifestations. Moreover, we highlight the importance of differential NCSE diagnosis in elderly patients with abnormal behavior, such as disinhibition, and the high tolerability and efficacy of LEV about elderly NCSE patients.

Case report

A 47-year-old man was admitted to the hospital with headache and fever and diagnosed with infectious encephalitis (virus not determined/bacteria not detected). He has suffered from tonic-clonic seizures since 50 years of age, with a seizure frequency of one per year, and consequently been administered with CBZ (600 mg/day). At 55 years of age, he suddenly started to show socially inappropriate behavior, often disappearing during work, and taking pictures of unknown woman on the train, culminating in a police warning. To treat his disinhibitory behavior, he was referred to our hospital. His consciousness was normal and his vital signs are stable. There were no focal neurological signs except blepharospasm and there was no obvious convulsion. Admission laboratory work was normal except for elevated γ-GTP (77 U/l). Blood CBZ levels were in the normal range (4.3 mcg/ml). First, we suspected a psychiatric disorder with disinhibition, specifically

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frontotemporal lobar degeneration. However, we did not observe any abnormal findings in the magnetic resonance imaging and single photon emission computed tomography, whereas EEG examination identified epileptiform discharges with components resembling spikes of 'spike and slow wave' complexes, and which occurred at a frequency of 5 Hz in the right frontal region (Figure 1A). Based on a diagnosis of NCSE, he began 1,000 mg/day LEV, which was increased to 2,000 mg/day the following month. Two months later, his disinhibitory behavior and abnormal EEG discharge disappeared, with few side effects (Figure 1B).

Discussion

To the best of our knowledge, the case presented here is the first report showing the therapeutic effect of add-on LEV for treatment of NCSE with disinhibitory behavior.

Previously, complex partial status epilepticus (CPSE) was thought to be rare [7]; however, subsequent studies have shown CPSE amounts to 16%–43% of all status epilepticus cases [8,9]. CPSE is characterized by clouding of consciousness and is a heterogeneous condition that may be related to ictal disorganization of various temporal or extratemporal epileptogenic networks, mainly involving frontal lesions [10,11]. NCSE of frontal origin occurs frequently without overt confusion [12,13]. Thomas et al. [13] reported that NCSE of frontal origin can be identified by two types. First, type 1 is characterized by mood and behavior, either a hypomanic state related to right frontal focus with affective disinhibition and increased verbal fluency or conversely, a state of emotional indifference related to left frontal focus with diminished facial expression, reduced verbal fluency, and decreased emotion and spontaneous activity, without clear alteration

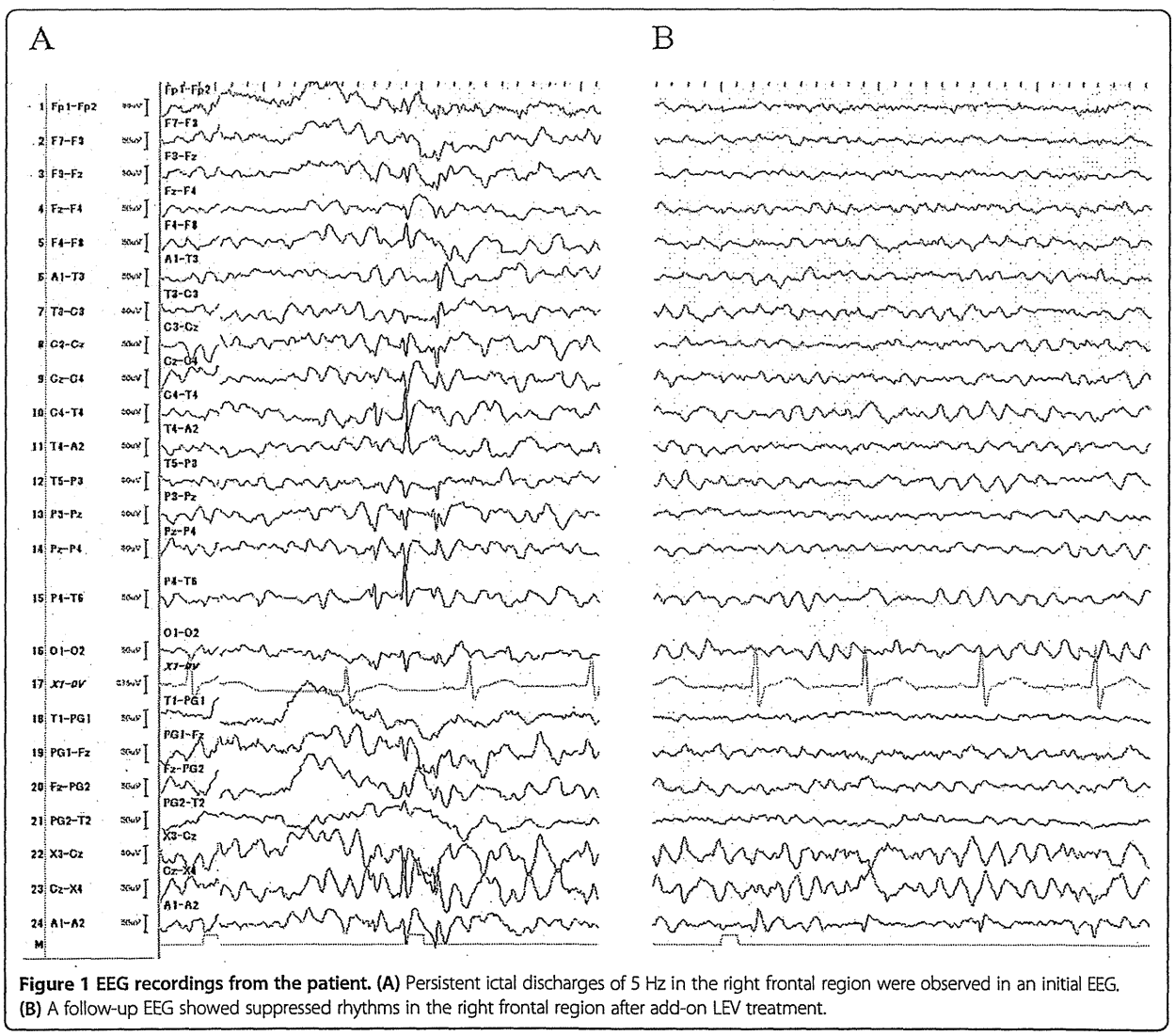

Figure 1 EEG recordings from the patient. (A) Persistent ictal discharges of 5 Hz in the right frontal region were observed in an initial EEG. **(B)** A follow-up EEG showed suppressed rhythms in the right frontal region after add-on LEV treatment.

of consciousness, and most patients are able to recall the episode. EEG patterns consist of unilateral frontal ictal activity. Second, type 2 is characterized by temporospatial disorientation and evident behavioral disorder with a confusional state. EEG patterns consist of bilateral frontal ictal activity. Based on these findings, we classified our present case as type 1 NCSE with right frontal lesion.

LEV's mechanism of action as an ASD involves binding to a synaptic vesicle glycoprotein, SV2A [14], inhibition of presynaptic calcium channels [15], reducing excitatory neurotransmitter release [16], and thereby acting as a neuromodulator. Although LEV requires cautious use for patients with frontal lesions and might bring substantial fatigue and drowsiness for elderly patients [17,18], LEV is relatively well-tolerated and has few side effects [6,19]. Furthermore, previous reports have demonstrated the efficacy of LEV as a co-medication in treatment of status epilepticus and refractory status epilepticus, including patients with NCSE [20,21]. LEV may also serve as an advantageous pharmacotherapy for the treatment of elderly NCSE with disinhibitory behavior.

Conclusions

NCSE is a heterogeneous disorder including a number of subtypes with varied electroclinical feature manifestations. NCSE should always be considered with the sudden appearance of behavioral and/or cognitive changes in elderly patients, especially those with a past history of organic brain disease. As LEV is effective and well-tolerated, even in the elderly, it may be a better option with fewer side effects, to treat elderly NCSE patients with abnormal behavior.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Abbreviations

NCSE: nonconvulsive status epilepticus; LEV: levetiracetam; EEG: electroencephalographic; CBZ: carbamazepine; CPSE: complex partial status epilepticus; ASD: antiseizure drug.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KY was involved in the collection of the data and wrote the first draft of the manuscript. HY, KT, TO, and TK supervised the entire project and was critically involved in the design and contributed to the editing of the final manuscript. All authors read and approved the final manuscript.

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ANNALS OF GENERAL PSYCHIATRY

CASE REPORT Open Access

Paliperidone extended release for the treatment of pediatric and adolescent patients with Tourette's disorder

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Abstract

Objective: A subgroup of patients with Tourette's disorder (TD) has symptoms refractory to haloperidol, a standard therapeutic drug for TD.

Methods: We report on three cases of pediatric and adolescent patients who were treated with paliperidone extended release.

Results: In two cases, TD symptoms were remarkably improved by switching from haloperidol to paliperidone extended release, and in another case, paliperidone extended release showed significant efficacy in treating TD symptoms as the first-line drug. In all cases, no significant adverse side effects were detected.

Conclusion: Paliperidone extended release may be a strong candidate for the treatment of pediatric and adolescent patients with TD.

Keywords: Tourette's disorder, Paliperidone extended release, Haloperidol, Tics

Introduction

Tourette's disorder (TD) is a neurodevelopmental disorder commonly associated with the presence of multiple vocal and/or motor tics. The onset of TD occurs in childhood and the prevalence is higher in males than in females (4.3: 1) [1,2]. Of school-aged children, 6%–20% experience transient tics and 0.5%–1% suffer from chronic tics or TD [3]. TD usually has a familial component [2]. The majority of patients with TD also meet the criteria for one or more comorbid psychiatric disorders, including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), mood disorder, and non-OCD anxiety disorder [4]. Since there are several biological hypotheses relating to TD that highlight dopaminergic function, typical antipsychotics such as haloperidol and pimozide have been prescribed to control tic symptoms [5]. More recently, clinical opportunities for prescribing atypical antipsychotics such as risperidone, quetiapine, aripiprazole, and olanzapine have increased owing to the enhanced efficacy and more tolerable side effect profiles relative to classical antipsychotics [1,6-8]. Considering all antipsychotics, risperidone is commonly recommended by experts [9,10].

This report focuses on the utilization of the atypical antipsychotic, paliperidone extended release (ER), which chemically is a major active metabolite of risperidone (9-hydroxyrisperidone), in the treatment of child and adolescent patients with TD since our survey of the literature has failed to identify any current reports related to its use in this setting. The three cases showed reductions in TD symptom severity over a relatively short time period and an improvement in the Yale Global Tic Severity Scale (YGTSS) [11], a clinician-rated, semistructured interview useful for determining both the effects of treatment as well as providing an assessment of tic severity (0–50 scale range, impairment score not included). Motor and phonic tics were rated separately according to number, frequency, intensity, complexity, and interference.

According to the World Medical Association Declaration of Helsinki, a statement of ethical principles for medical research in human patients, we provided

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patients and patients' parents with thorough monitoring information and any serious adverse events.

Case presentation

Case A

Patient A is a 10-year-old boy who developed facial motor tics such as blinking and grimacing at 8 years of age. He also began to express involuntary utterances consisting of the vowel sound 'a' and excessive shoulder shrugging when he was 9 years old. At the age of 10, the abnormal 'a' vocalization was replaced with very loud snoring. Subsequently, he began to display involuntary coprolalia using words such as 'kill' and 'die.' Treatment with haloperidol (1.5 mg/day) failed to improve the tic symptoms while being followed at a local clinic. Since the tics had a significant negative impact on his activities of daily living and social relationships, he was referred to our hospital when he was 10 years old. TD was diagnosed in accordance with DSM-IV-TR and his YGTSS was 27. He did not have ADHD, OCD, or other behavioral or psychiatric disorders. He was prescribed with 3 mg of paliperidone ER to improve tic symptoms and scheduled for weekly visits to our hospital to monitor side effects. One week after initiation of paliperidone ER, the occurrence of coprolalia had dramatically improved, although he still displayed motor and vocal tics (YGTSS 20), which were gradually improved with few side effects. Within 2 months, his vocal tic symptoms had nearly disappeared, but slight shoulder shrugging remained (YGTSS 7).

Case B

Patient B is an 11-year-old boy who developed motor tics such as blinking and coughing at 9 years old. He began to express an involuntary vocal utterance as a very loud 'a' sound at the age of 11. Since both the frequency and severity of these motor and vocal tics worsened, he was referred to our hospital. His was diagnosed with TD in accordance with DSM-IV-TR and his YGTSS was 21. He did not have ADHD, OCD, or other behavioral or psychiatric disorders. First, he was prescribed with 3 mg/day of paliperidone ER to improve the tic symptoms. While the volume of his vocal tics became lower after three weeks of paliperidone ER treatment, his overall tic symptoms were not improved (YGTSS 17). After having been on 3 mg/day of paliperidone ER for 6 weeks, his dosage was increased to 6 mg/day. Two weeks after initiating the 6 mg/day paliperidone ER treatment, both the motor and vocal tic symptoms had substantially improved with few side effects (YGTSS 7).

Case C

Patient C is 13-year-old boy who developed motor tics such as violent neck shaking, repeated jumping, and sniffing as well as vocal tics beginning at 8 years of age. He visited our hospital when he was 11 years old and was diagnosed with TS in accordance with DSM-IV-TR and his YGTSS was 18. While there was a family history of TD, neither ADHD, OCD, nor other behavioral or psychiatric disorders were identified. He had been treated with haloperidol (1.5 mg/day) for approximately 2 years and showed only mild improvement while the presence of drowsiness prevented further dosage titration. He was prescribed with 3 mg/day of paliperidone ER and showed no improvement in his tic symptoms over the course of 3 weeks following initiation of therapy (YGTSS 16). Subsequently, the dosage of paliperidone ER was increased to 6 mg/day. After 5 weeks of higher dosage of paliperidone ER, he did experience mild drowsiness but significant improvement of the tic symptoms was observed (YGTSS 6). Due to the presence of the mild drowsiness, the dosage of paliperidone ER was then reduced to 3 mg/day and, despite this reduction, his tic symptoms did not recur over the following 4 months (YGTSS 7).

Discussion

To the best of our knowledge, only a single case study has reported beneficial effects of paliperidone ER for the treatment of an adult patient who was diagnosed with TD and comorbid schizophrenia [12]. The cases presented here are the first reports showing the therapeutic effects of paliperidone ER in treating child and adolescent patients with TD.

While the exact pathobiology of TD remains unknown, several hypotheses have been proposed. Dysfunction in the cortico-striatal-thalamo-cortical (CSTC) circuits has been suggested as a potential cause of TD [13]. Previous studies using single-photon emission computed tomography (SPECT) have suggested higher levels of dopamine transporter binding in the caudate and putamen nuclei in TD patients as compared to healthy controls [14]. Furthermore, greater putamen dopamine release was observed in TD in comparison to healthy controls using positron emission tomography (PET) [15]. These findings are supportive of abnormalities in dopaminergic function as potential participants in the pathophysiology of TD. Therefore, typical or atypical antipsychotics, which generally block dopaminergic signaling, have been prescribed to control its tic symptoms. Of all antipsychotics, currently risperidone is recommended by the experts to treat tic symptoms [9,10]. Risperidone has potent dopamine-2 (D_2) and 5-hydroxytryptamine (5-HT2A) receptor blocking properties, and it has been proven to be as effective for the treatment of TD as haloperidol and relatively safer compared to haloperidol in terms of side effects (e.g., high frequency of extrapyramidal symptoms by haloperidol) [16,17]. While the

major anti-tic efficacy of risperidone is probably due to the blocking of dopaminergic neurotransmission, the serotonergic action might give additional effects by indirectly attenuating mesolimbic and/or mesocortical dopaminergic pathways [18]. Therefore, risperidone could be a better pharmacotherapeutic agent for the treatment of TD than other typical antipsychotics such as haloperidol. However, resperidone also has its own problematic side effects including oversedation and weight gain, and here we would like to suggest the possibility that paliperidone ER, the extended-release form of the major metabolite of risperidone, could be used to avoid these adverse events especially since blood concentration of paliperidone ER is relatively stable [19] leading to less daytime somnolence [20] and it can produce fewer extrapyramidal symptoms as compared to risperidone [21]. As daytime somnolence and extrapyramidal symptoms substantially disturb children's life; study, exercise, friendship, and so on, paliperidone ER may serve as an advantageous pharmacotherapy for the treatment of child and adolescent TD.

Conclusion

These cases suggest that paliperidone ER might serve as an efficacious therapy in child and adolescent patients with TD and present few side effects. Further information and details provided by studies using larger sample sizes are needed to validate the apparent efficacy, safety, and tolerability of paliperidone ER in the treatment of child and adolescent patients with TD.

Consent

Written informed consent was obtained from the patient's parents for the publication of this report and any accompanying images.

Abbreviations

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TD: Tourette's disorder; YGTSS: Yale Global Tic Severity Scale.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KY was involved in the collection of the data and wrote the first draft of the manuscript. MM, TO, JI and TK supervised the entire project and was critically involved in the design, and contributed to the editing of the final manuscript. All authors have read and approved the final manuscript.

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■臨床経験

Paliperidone徐放剤が奏効した10歳トゥレット障害患児の1例

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抄録：学童期にチック症状が出現し，次第に運動チックと音声チックが慢性的に経過したトゥレット障害患児にpaliperidone徐放剤が奏効した1例を経験した。症例は10歳男児であり，X－2年より断続的にチック症状を認めていたが，X年2月より音声チックが悪化するとともに，コプロラリアが出現し，不登校状態となったため，X年2月21日に当科初診となった。Paliperidone徐放剤服薬後，徐々に症状は改善し，X年4月中旬には，若干の単純運動チックは残存するが，有害事象もなくおおむね安定して経過した。今後，paliperidone徐放剤が学童期のトゥレット障害の薬物治療の選択肢の1つになりえる可能性が考えられた。　精神科治療学　29(3)；399-403，2014

Key words：*paliperidone, Tourette's disorder, tic, atypical antipsychotics*

Ⅰ．はじめに

チック障害は一過性チック障害からトゥレット障害まで幅広いが連続性があると考えらており，チックという運動症状で定義される症候群である。多くはチックの持続が1年以内の一過性チック障害であり，たとえ慢性化しても10歳から10歳半ば過ぎにピークを迎え，それ以降はチックが軽快の方向に向かうことが多い。トゥレット障害においても80から90％が成人期の始まりまでに消失もしくは軽快に転じるといわれている。トゥレット障害は，多様性の運動チックと1つ以上の音声チックが慢性に持続する症候群である[1]。また，トゥレット障害は，Gilles de la Tourettの報告ではコプロラリア（汚言症）およびエコラリア（反響言語）という複雑音声チックが重要な特徴とされたが，それらは現在では診断に必須ではない。

今回，トゥレット障害患児にpaliperidone徐放剤が奏効した1例を経験したので報告する。なお，paliperidone徐放剤の使用にあたり，本邦においてはpaliperidone徐放剤が本疾患に対して保険適応外であることや，効能や副作用等を本人および家族に十分に説明し同意を得た。また，本報告について本人および家族の同意を得ているが，プライバシー保護のため症例提示の中で本質的でない部分については一部改変を行った。

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