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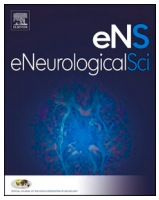

Sertraline treatment for paroxysmal nonkinesigenic dyskinesia comorbid with anxiety and depression

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ABSTRACT

Familial paroxysmal non-kinesigenic dyskinesia, which is a major form of paroxysmal dyskinesias, is characterized by intermittent attacks that include one side, subsequently spreading to the other side, involving the limbs and face, and is triggered by caffeine, alcohol, emotional stress, fatigue, and sleep deprivation, but not by sudden movement. A 26-year-old man had experienced dystonic movements and a choreiform right arm spreading to his arms, legs, and face since the age of one year. Oral dyskinesias and, rarely, dysarthria were also observed. Attacks lasting approximately five minutes occurred several times per day. Over three generations, his family members inherited a c.26C > T (p. Ala9Val) missense mutation in exon 1 of *PNKD/MR-1* in an autosomal dominant manner and reported similar symptoms with clinical manifestations ranging from mild to severe. His scores on the Self-Rating Depression Scale, State–Trait Anxiety Inventory, and Profile of Mood States were high. This suggests that the patient also had comorbidities of anxiety and depression. The patient's attacks decreased from two times per week to once every two months, and his State–Trait Anxiety Inventory score decreased by 5–10 points on treatment with clonazepam and sertraline, allowing his condition to become stable enough that he was able to participate in society. Drug therapy with clonazepam and sertraline is the preferred treatment for reducing attacks in PNKD patients with strong anxiety and depression.

Dear editor

Paroxysmal dyskinesias are a heterogeneous and rare group of episodic and hyperkinetic movement disorders that consist of various combinations of dystonic, choreic, athetotic, and ballistic movements. They are characterized by recurrent and paroxysmal attacks without loss of consciousness, and are classified into four subgroups based on phenomenology according to the duration and frequency of attacks and precipitants. Paroxysmal non-kinesigenic dyskinesia (PNKD) is a clinical subgroup of paroxysmal dyskinesias [1]. Familial PNKD (OMIM No. 11880), also known as dystonia type 8 (DYT8), is a major form of paroxysmal dyskinesias characterized by intermittent attacks that include one side, subsequently spreading to the other side, involving the limbs and face, and is triggered by caffeine, alcohol, emotional stress, fatigue, and sleep deprivation, but not by sudden movement. Involuntary movements occur spontaneously and last from minutes to several hours, or even an entire day. Aura often presents with limb numbness, stiffness, or restlessness. Its onset occurs in infancy or early childhood [2]. Myofibrillogenesis regulator 1 (MR-1) gene mutations mapped to chromosome 2q35 in families of different ethnic origins were recently identified as causative and highly penetrant mutations in PNKD [2].

1. Case description

A 26-year-old man who had experienced dystonic movements and choreiform right arm spreading to his arms, legs, and face visited Kurume University Hospital at the age of one. In addition, oral dyskinesias and rarely dysarthria is also sometimes observed. An aura often presents with limb weakness and stiffness. Attacks lasting approximately five minutes occurred several times per day, often while he was hugged due to becoming fussy during infancy. Treatment with clonazepam (CZP) (0.9–3 mg) from the age of one decreased the frequency of attacks to two times per week, while the response to carbamazepin was poor. Clinical evaluation, including physical and neurological examinations and interviews was conducted at the Department of Pediatrics and Child Health Kurume University School of Medicine. EEG, brain MRI, and CT showed no abnormalities. At 26 years of age, his score on the Self-Rating Depression Scale test (65 points; severe depression 60–80), State–Trait Anxiety Inventory (STAI) score (78 points; cut off = 47.27 ± 10.45 points), and scores on the five mood domains of the Profile of Mood States™, fatigue-inertia, anger-hostility, confusion-bewilderment, depression-dejection, and tension-anxiety revealed current depressed mood and anxiety. A video, recorded on a smartphone of an attack before sertraline treatment is shown in Video 1 (Fig. 1**A, Video 1**). He was forced to quit his job due to relationship difficulties and once attempted suicide, resulting in his attacks increasing to four times a week and the duration of such attacks increasing to one to two hours. He started taking escitalopram 10 mg once a day as an SSRI for depression and anxiety. His mood and attacks remained unstable for one month. He switched to sertraline 25 mg once daily. Fatigue accumulated due to the drastic change in his work environment after a job change, and his depression and anxiety became exacerbated. He sometimes behaved violently, and the frequency and duration of his attacks fluctuated.

After adding CZP at his own discretion, he became absent-minded and less motivated. In the sixth month of taking sertraline, the CZP dosage was reduced to 3 mg/day, and he began to successfully self-manage his life. One year after taking sertraline, the patient's attacks decreased to 1 every 2 months, and his STAI score decreased by 5–10

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Fig. 1. The pedigree of the Japanese family with paroxysmal non-kinesigenic dyskinesia and the neuroimages of the involuntary movements.
(A) Video neuroimaging of intermittent and involuntary movements. A paroxysmal non-kinesigenic dyskinesia attack began with chorea of the right fingers, followed by chorea of the bilateral fingers, ballisms, cervical dystonia (torticoli), and orofacial dyskinesia. After sitting in a chair to stop the attack, dystonia occurred sequentially in his left arm. The attack lasted approximately 4 min and 30 s without a loss of consciousness. (B) Images of a Sanger sequencing electropherogram showing missense mutations detected in a Japanese family. Over four generations, his family members inherited the c.26C > T (p. Ala9Val) missense mutation in exon 1 of the PNKD/MR-1 gene in an autosomal dominant manner and had similar symptoms with clinical manifestations ranging from mild to severe. (C) Pedigree of the Japanese family with paroxysmal non-kinesigenic dyskinesia and neuroimages. The paternal grandmother (I:2) occasionally had a strained look on her face from unknown causes. His mother (II:3) and older brother (III:2) were unaffected.The arrow indicates the proband, Roman numerals designate the generation of the family, and Arabic numerals designate the subjects who were interviewed in this family. Solid symbols indicate family members with paroxysmal non-kinesigenic dyskinesia. Blank symbols indicate unaffected family members. Gray symbols indicate that the subject had a neurological disorder. Square: male, Circle: female.

points on treatment with CZP and sertraline, allowing his condition to become stable enough that he was able to participate in society further and recognize that he needed to go to counselling. His parents were not consanguineous and had no neurological disorders except for PNKD. His family members inherited the c.26C > T mutation of the PNKD/MR-1 gene in an autosomal dominant manner (Fig. 1B and C).

Rare episodic movement disorders are difficult to distinguish from other neurological disorders (e.g., epilepsy and sleep disorders). He had long-lasting attacks provoked by alcohol, caffeine, or other non-kinesigenic triggers, characterized by intermittent attacks of abnormal involuntary movements without loss of consciousness. To our knowledge, this is the first report of Japanese familial PNKD with the c.26C > T mutation of the MR-1 gene. Japanese middle-aged PNKD patients were treated with bilateral electroconvulsive therapy (ECT) for major depressive episodes [3]. ECT was previously reported to be effective for treating depression in patients with PNKD, but ineffective for treating PNKD attacks.

2. Discussion

The spectrum of heritable mutations in the MR-1 gene varies within movement disorders, including PNKD, migraine, and Tourette's disorder [4]. MR-1 is widely expressed, especially in the substantia nigra pars compacta, which is composed of dopaminergic neurons projecting to the striatum and the substantia nigra pars reticulata. MR-1/PNKD is homologous to HAGH, which encodes an enzyme involved in the detoxification pathway of methylglyoxal, a compound present in coffee and alcoholic beverages, producing a byproduct of oxidative stress [5]. Caffeine, a ryanodine receptor agonist at presynaptic terminals, favors high concentrations of calcium in striatal neurons and enhances hyperexcitability owing to the lack of MR-1 [6]. In the dyskinesia-on state, dopamine signals via the D1- and D2-dopamine receptors enhanced to release movements through the direct pathway and suppressed to halt movements through the indirect pathway [7]. CZP enhances GABA fast inhibition in the basal ganglia via $GABA_A$ receptors, the major inhibitory and metabotropic receptors, is long-acting and high-potency benzodiazepine used for epilepsy and tardive dyskinesia, and it also has serotonergic activity by increasing serotonin synthesis. Sertraline is considered a safe and relatively well-tolerated medication for the treatment of depression and social phobia. Extrapyramidal symptoms, including dyskinesia, may occur as adverse effects of SSRIs. Increased serotonin availability has been proposed to indirectly inhibit dopamine release in the striatum by increasing 5-HT_2 receptors [8]. However, administration of sertraline increases extracellular dopamine concentrations in the nucleus accumbens and striatum [9]. Sertraline also does not affect the pharmacokinetics of CZP [10]. This suggests that sertraline may be potent against PNKD attacks comorbid with anxiety and depression. Drug therapy with CZP and sertraline is therefore the preferred treatment for reducing attacks in PNKD patients with strong anxiety and depression.

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Author contributions

M.H. and T.M. performed the follow-ups and evaluated the patients. M.H. prepared the manuscript. All authors contributed to this study and approved its submission.

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CRediT authorship contribution statement

Munetsugu Hara: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Toyojiro Matsuishi:** Validation, Supervision, Resources, Investigation, Data curation, Conceptualization. **Satoru Takahashi:** Writing – review & editing, Validation, Supervision, Resources, Investigation, Data curation. **Yushiro Yamashita:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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