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Letter to the Editor

Lesser motor disability in adulthood: A ten-year follow-up of a dyskinetic patient with *ADCY5* mutation

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Dear Editor,

Broad phenotypic spectrum has been reported in hereditary dyskinesia associated with mutations in adenylate cyclase 5 gene (*ADCY5*, OMIM 606703). Medication was tried for the disease, including antiepiletpic drugs, propranolol, acetazolamide, trihexyphenidyl, and tetrabenazine, but their efficacy was limited [1]. Partial or moderate response to pallidal deep brain stimulation (DBS) has been reported in medication refractory cases [1,2]; however, therapeutic strategy in consideration of natural disease course remains to be elucidated in *ADCY5*-related dyskinesia. We herein report a case with *ADCY5*-related dyskinesia showing lesser hyperkinetic movements from adolescence to adulthood.

1. Case

The patient is a 25-year-old man, who was born as the third child of non-consanguineous healthy parents. Postpartum adaptation (APGAR 10) was normal. He grew up with mild developmental delay, including stable head and neck at age of 16 months, walking without assistance (*Equinus* gait) at age of 16 months, speaking first “real” word at age of 24 months. Involuntary jerky movements at trunk became noticeable since the age of 1 year and 4 months, which gradually spread to limbs later. He also showed occasional speech difficulty. He underwent Achilles tendon extension surgery at age of 5 years. On neurological examination at that time, he had generalized myoclonus superimposed choreic movements, and brisk reflexes in the lower extremities accompanied by some degree of spasticity. No cerebellar signs were evident. No epileptiform discharges were demonstrated in electroencephalogram. The surface electromyogram (EMG) recordings of the right pectoralis major, sternocleidomastoid, quadriceps femoris, and hamstring muscles showed synchronous EMG discharge of short duration, indicating myoclonic jerks. Continuous EMG discharge superimposed on presumed myoclonic activity was observed at the rectus abdominis muscle, suggesting mixture of dystonia and myoclonus. Neonatal screening tests excluded phenylketonuria, maple syrup urine disease, homocystinuria, and galactosemia. Symptomatic treatment with clonazepam had no effect on the mixed movement disorder including myoclonus. Non-pharmacological therapy, including physiotherapy, was never applied to the patient. Clinical and laboratory evaluation at the age of 14 demonstrated a short stature of 153.2 cm (mean 166.5 cm, Standard Deviation (S.D.) = −2.1) and lower body weight 39.9 kg (mean 56.8 kg, S.D. = −1.6), and intellectual impairment (Wechsler Intelligence Scale for Children-III: F.I.Q. 65, P.I.Q. 74, and V.I.Q. 64). Niemann-Pick disease and mitochondrial diseases were biologically excluded. The patient showed stooped posture in sitting and standing positions, which disappeared in supine position, suggesting axial dystonia. He experienced imbalance and unsteady gait due to the dyskinesias at limbs and axial dystonia; however, he never had falls in his daily life. Neither diurnal nor day-to-day fluctuation of the symptoms was observed during the disease course. He liked playing baseball in his high school days and was good at hitting a baseball. Genetic testing revealed a missense variant, c.1252C > T (p.Arg418Trp), in *ADCY5* (NM_183357.23) [Fig. 1A]. Haplotype analysis suggested the variant arose *de novo* (data available upon request). The patient was videotaped using a standardized recording protocol, including walking, writing, speech (interviewing), Barre test, finger to nose test, and pronation/supination of hands at every half year. Severity of hyperkinetic movements videotaped since 16-year-old was retrospectively analysed and evaluated using the Unified Myoclonus Rating Scale (UMRS) [3] for myoclonic movement, UFMG Sydenham's Chorea Rating Scale (USCRS) [4] for choreic movement, and Disability Subscore for dystonic movement in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMRS) [5]. Hyperkinetic movements became longitudinally lesser, and severe motor disability in adolescence became milder and non-progressive in adulthood (Fig. 1B and Supplementary Video 1). Moreover, his physical growth became almost normalized during young adulthood, presumably after the peak of hyperkinetic movements. Currently his height is 167.5 cm (mean 170.8 cm, S.D. = −0.6) and body weight is 54.6 kg (mean 62.6 kg, S.D. = −0.8). At the age of 24, no significant finding was obtained on the brain magnetic resonance imaging (MRI) and the dopamine transporter (DAT) imaging [Fig. 1C and D]. Localized hypoperfusion at the parietal lobe was shown on N-isopropyl-p-[^{123}I]iodoamphetamine single photon emission computed tomography (^{123}IMP-SPECT) (data available upon request). Scores on Mini-Mental State Examination ranged from 18 to 20, in-

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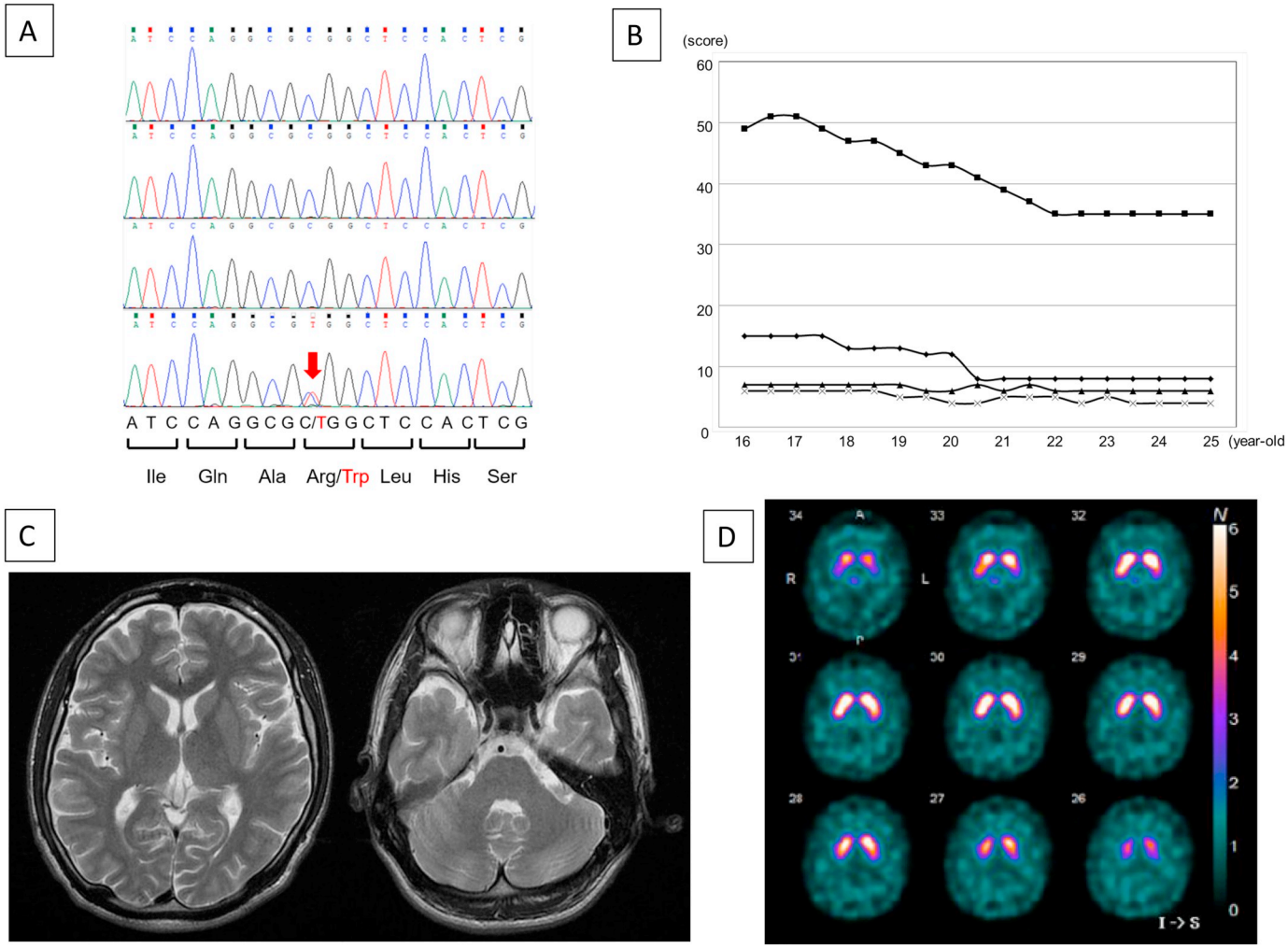

Fig. 1. Sequence chromatograms, longitudinal analysis of hyperkinetic movements, and neuroimaging.
(A) Sequence of the normal *ADCY5* exon 2 sequence detected in unaffected members as well as the mutation in the proband are presented. Top: unaffected father, Middle: unaffected brothers, and Bottom: proband. The missense variant, c.1252C > T (p.Arg418Trp), is indicated by a red arrow. The nucleotide number is based on the longest *ADCY5* transcript (NM_183357.23). The corresponding amino acid sequence is also shown, Ile (Isoleucine), Gln (Glutamine), Ala (Alanine), Arg (Arginine), Trp (Tryptophan), Leu (Leucine), His (Histidine), and Ser (Serine).
(B) Graph to show longitudinal scores of myoclonus with action in the UMRS (rectangle:■), myoclonus at rest in the UMRS (diamond:◆), BFMRS Disability Subscore (triangle:▲), and Behaviour score in USCRS (cross:×). Clinical follow-up was conducted almost every six months. Videotape exam protocols were utilized and two blinded raters (T.K. and A.O.) scored videotapes of the patient. The raters were blinded to genotype.
(C) No abnormal white matter intensity is evident in T2-weighted axial MRI image of the brain. The basal ganglia and cerebellum are not atrophied.
(D) Neurotransmission SPECT using [^{123}I]-labeled dopamine transporter ligands (FP-CIT, DaTSCAN; Nihon Medi-Physics Co. Ltd., Tokyo, Japan) showed no decreased striatal binding. Average value of the right and left specific binding ratios is 8.65, which is within normal age-specific range in our in-house data (average = 9.51, S.D. = 1.36). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dicating moderate cognitive impairment.

2. Discussion

The missense variant, p.Arg418Trp, is the most frequently discovered in dyskinesia patients with *ADCY5*-associated disease. The variant, c.1252C > T, was found to be present in many sporadic cases, indicating the allele is vulnerable to *de novo* mutation. Various phenotypes have been reported, including benign hereditary chorea, paroxysmal day and night time dyskinesia and facial twitches [6,7]. Our case had mix movement disorders, comprising of chorea, myoclonus, facial twitching, and dystonia.

No severe interference with voluntary motion was seen in the patient although he had hyperkinetic involuntary movements. Mechanisms for spontaneous decreasing of the dyskinesia seen in the patients remain to be elucidated. Neuronal network, including motor cortex and basal ganglia, might have been modulated to decrease myoclonic and choreic movements, or relative activity of striatal direct/indirect pathway might have been altered to ameliorate dyskinesia.

Increased energy expenditure due to hyperkinetic movements would interfere with physical development in childhood. Gaining body weight by combination of nutritional supplementation and DBS placement was previously reported in a case with *ADCY5*-related dyskinesia [2]. Investigation of natural disease course is a prerequisite for determining the therapeutic strategy in patients' lives. A previous review of DYT-*SGCE* showed spontaneous improvement of myoclonus and dystonia (5% and 20%, respectively) in childhood or adolescence [8]. Alteration of tic severity was previously analysed in Tourette syndrome and a mathematical model was proposed. The most severe period was observed around 10 years of age, followed by a steady decline of tic severity [9]. Clinical course and prognosis would be predicted in hyperkinetic movement disorders. Possibility of spontaneous

improvement of hyperkinetic movements and normalization of physical development should be taken into account, especially, for paediatric patients with *ADCY5*-related disease. Further accumulation of disease course and response to therapy would contribute to optimal therapeutic choice depending on age.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.001.

Disclosure

The authors report no conflicts of interest relevant to the manuscript.

Ethical standards

The authors hereby declare that the research documented in the submitted manuscript has been carried out in accordance with ethical standards laid down in the 1964 declaration of Helsinki and approved by the Institutional Review Boards (IRBs) of the Tokushima University.

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Authors' contributions

T. K. and R.K. were the attending doctors of the present case. T.K. drafted the manuscript. A.O. participated in data analysis and interpretation, and helped to draft the manuscript. All authors read and approved the final manuscript.

Relevant conflicts of interests/financial disclosures

Nothing to report.

Declaration of Competing Interest

The authors report no conflicts of interest.

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