A patient with a 6q22.1 deletion and a phenotype of non-progressive early-onset generalized epilepsy with tremor

Kazuhiro Haginoya a,b,* ,1, Futoshi Sekiguchi c ,1, Mitsutoshi Munakata a, Hiroyuki Yokoyama a, Naomi Hino-Fukuyo a, Mitsugu Uematsu a, Kazutaka Jin d, Kenichi Nagamatsu e, Tadashi Ando e, Noriko Miyake c, Naomichi Matsumoto c, Shigeo Kure a

a Department of Pediatrics, Tohoku University School of Medicine, Sendai 980-8574, Japan
b Department of Pediatric Neurology, Miyagi Children’s Hospital, Sendai 989-3126, Japan
c Department of Human Genetics, Graduate School of Medicine, Yokohama City University, Yokohama 236-0004, Japan
d Department of Epileptology, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan
e Department of Neurosurgery, National Hospital Organization Miyagi Hospital, Yamamoto 989-2202, Japan

ARTICLE INFO

Article history:
Received 15 May 2020
Revised 15 October 2020
Accepted 17 October 2020
Available online 16 November 2020

Keywords:
6q22.1 deletion
NUS1
Myoclonic tremor
Generalized epilepsy
Deep brain stimulation
DBS

ABSTRACT

We report a patient with a 6q22.1 deletion, who presented with a rare syndrome of generalized epilepsy, myoclonic tremor, and intellectual disability. There was no clinical progression after follow-up for more than 10 years. Our report presents the genetic basis for a phenotype involving a non-progressive generalized epilepsy with tremor. The efficacy of valproic acid for seizure control and the partial efficacy of deep brain stimulation with propranolol for myoclonic tremor is detailed.

© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

INTRODUCTION

Generalized epilepsy and tremor phenotypes have been reported in a few patients with a 6q22.1 microdeletion [1,2], NUS1 variants, or DHDDS variants [3]. Here, we report clinical and genetic studies of a patient with a 6q22.1 microdeletion presenting with a rare syndrome of generalized epilepsy and drug-resistant myoclonic tremor who underwent deep brain stimulation (DBS) of the left thalamic nucleus.

CASE PRESENTATION

The patient was a 28-year-old man born after a full-term pregnancy and without asphyxia to healthy non-consanguineous Japanese parents. His early development was unremarkable. Intention tremor was observed at 3 years of age, and mild intellectual disability at 4 years of age. The patient had two episodes of generalized tonic–clonic seizures at 11 and 15 years of age. Based on the diagnosis of generalized epilepsy, he was treated with valproic acid (VPA), which resulted in no recurrence.

At 16 years of age, he was referred to our hospital for further testing. On examination, he had a resting tremor, which worsened with postural or voluntary tasks, as seen in his handwriting (Fig. 1F). One-foot standing was affected because of continuous tremor in the lower extremities. He spoke fluently and walked without falling. Deep tendon reflexes were normal. He exhibited no spasticity, but had bilateral cogwheel rigidity in his arms. The patient had no nystagmus or swallowing difficulty. His IQ was 43 (Wechsler Intelligence Scale for Children, fourth edition). He had no microcephaly or dysmorphic features. Blood lactate, pyruvate, and amino acid levels and lysosomal enzyme activities in leukocytes were normal. Bone marrow analysis showed no foam cell or sea-blue histiocytes. Ophthalmological examination was unremarkable. A muscle biopsy was normal. The short-latency somatosensory evoked potentials showed no exaggerated cortical responses. Auditory brainstem responses and visual evoked potentials were normal. Electroencephalography showed rare diffuse spike-waves dominant over the bilateral frontal regions and
photosensitive epileptiform responses (Fig. 1A and C). Surface electromyography revealed a myoclonic tremor with co-contraction between active and antagonistic muscles (Fig. 1B). Brain magnetic resonance imaging was normal. Fluorodeoxyglucose position emission tomography (Fig. 1D) and technetium-99m-ethyl cysteinate dimer single photon emission computed tomography (Fig. 1E) showed relatively increased glucose uptake and blood flow in the bilateral basal ganglia.

The patient's tremor was refractory although high-dose propranolol was partially effective. At the age of 23 years, suspecting a pathophysiological similarity to essential tremor, he underwent DBS of the left thalamic ventral intermediate nucleus, which resulted in moderate improvement of the myoclonic tremor of the right hand (Fig. 1G). However, he declined DBS of the right thalamus.

Presently, he has a myoclonic tremor but has shown no clinical progression while taking VPA (1600 mg/day) and propranolol (80 mg/day). He has been working at a welfare center, and DBS is still effective for his daily living.

To analyze the molecular diagnosis and clarify the genetic cause, trio-based whole-exome sequencing was performed as previously described [4]. The exome Hidden Markov Model method and Nord program showed a 2.9-Mb genomic deletion at 6q22.1 involving 25 genes, including NUS1, ROS1, and DCBLD (Fig. 2A). Quantitative polymerase chain reaction validated the de novo deletion of ROS1 and DCBLD1 (data not shown). Other pathogenic variants were not observed.

3. Discussion

To date, 11 patients have been reported to have microdeletions in the same region as our patient (Fig. 2A) [1,2]. Movement disorders, such as myoclonus or tremor, have been reported in 7 of the 12 patients including our patient. Epilepsy was observed in 7 patients; atypical absence or absence seizure in 4, generalized tonic–clonic convulsion in 2, West syndrome in 1, and complex partial seizure in 1 patient. Intellectual disability was observed in 11 patients. Microcephaly was observed in 4 patients, dysmorphic features in 4, and hypotonia in 2. Four patients had ataxia. These findings indicate that a generalized epilepsy and tremor phenotype with intellectual disability is characteristic in patients with a 6q22.1 microdeletion (Fig. 2B).

Szafranski et al. [1] reported an individual with a 6q22.1 microdeletion in a critical 259-bp region that includes only NUS1.
and the SLC35F1 promoter, who exhibited early onset seizures and tremors as well as intellectual disability. Another two patients with missense frameshift variants and an approximately 1.3-kb deletion encompassing the entire exon 2 of NUS1 had the same phenotype [3]. From these findings, NUS1 seems to be the gene causing the generalized epilepsy and tremor phenotype in this patient.

NUS1 encodes the Nogo-B receptor (NgBR), which is a subunit required for dolichol synthesis in yeast, mice, and humans. NgBR forms a complex with dehydrodolichol diphosphate synthase (DHDDS; also known as hCIT) to yield dehydrodolichol diphosphate [3,5]. This process is essential for dolichol monophosphate biosynthesis and global N-linked glycosylation [3,5].

de novo DHDDS variants were recently reported in patients with generalized epilepsy and tremors [3], indicating that NUS1 and DHDDS variants (NgBR/hCIT complex dysfunction) cause similar phenotypes.
Epilepsy with myoclonus during childhood is common in patients with progressive myoclonus epilepsy. However, generalized epilepsy associated with myoclonic tremor is very rare in patients with non-progressive disease. The differential diagnosis includes benign adult familial myoclonus epilepsy, which is adult-onset genetic generalized epilepsy with rare seizures and cortical tremor [6]. However, clinically, onset in our patient was quite different, and intellectual disability was evident.

4. Conclusion

Our report presents the genetic basis of a phenotype of non-progressive generalized epilepsy with tremor, as well as the efficacy of VPA for seizure control and the partial efficacy of DBS with propranolol for myoclonic tremor. DBS of the ventral intermediate thalamic nucleus and propranolol are effective treatment options for patients with essential tremor [7], which implies a pathophysiological similarity between the condition of the present patient with essential tremor.

Conflict of interest

The authors declare no conflict of interest.

Ethical Statement

Written informed consent was obtained from all parents to perform the diagnostic procedures and next-generation sequencing and for publication of this case report. The study was approved by the ethical review boards of Miyagi Children’s Hospital and Tohoku University School of Medicine.

Acknowledgments

We thank the individual and the individual’s family for their participation in this study. This work was supported by Japan Agency for Medical Research and Development (AMED) under grant numbers JP19ek0109280, JP19dm0107090, JP19ek0109301, JP19ek0109348, and JP19kk0205012; by JSPS KAKENHI under grant numbers JP17H01539, JP19H03621 and 17K15630; the Ministry of Health, Labor, and Welfare; and Takeda Science Foundation.

References

[1] Szafranski P, Von Allmen GK, Graham BH, Wilfong AA, Kan SH, Ferreira JA, et al. 6q22.1 microdeletion and susceptibility to pediatric epilepsy. Eur J Hum Genet 2015;23:173–9.
[2] Rosenfeld JA, Amrom D, Andermann E, Andermann F, Veilleux M, Curry C, et al. Genotype-phenotype correlation in interstitial 6q deletions: a report of 12 new cases. Neurogenetics 2012;13:31–47.
[3] Hamdan FF, Myers CT, Cossette P, Lemay P, Spiegelman D, Laporte AD, et al. High rate of recurrent de novo mutations in developmental and epileptic encephalopathies. Am J Hum Genet 2017;101:664–85.
[4] Sekiguchi F, Tsurusaki Y, Okamoto N, Teik KW, Mizuno S, Suzumura H, et al. Genetic abnormalities in a large cohort of Coffin-Siris syndrome patients. J Hum Genet 2019;64:1173–86.
[5] Park EJ, Grabinska KA, Guan Z, Stranecky V, Hartmannova H, Hodanova K, et al. Mutation of Nogo-B receptor, a subunit of cis-prenyltransferase, causes a congenital disorder of glycosylation. Cell Metab 2014;20:448–57.
[6] Kobayashi K, Hitomi T, Matsumoto R, Watanabe M, Takahashi R, Ikeda A. Nationwide survey in Japan endorsed diagnostic criteria of benign adult familial myoclonus epilepsy. Seizure 2018;61:14–22.
[7] Hopfner F, Deuschl G. Managing essential tremor. Neurotherapeutics 2020. https://doi.org/10.1007/s13311-020-00899-3.