INTRODUCTION

The majority of patients with periodic paralysis can be classified into hyperkalemic periodic paralysis (HyperPP) and hypokalemic periodic paralysis (HypoPP) according to serum potassium levels during paralytic attacks. Glucose and potassium have opposite effects in HyperPP and HypoPP. Patients with HypoPP tend to have more prolonged and severe attacks of weakness (several hours to days) while patients with HyperPP typically have attacks with a shorter duration, which may be less severe. Symptom onset is typically in the second decades for HypoPP while HyperPP tends to present earlier in childhood. Myotonia is often associated with HyperPP, but is not found in HypoPP.1

Most hereditary HypoPP cases are caused by a mutation in either CACNA1S, encoding the pore-forming α1-subunit of the dihydropyridine receptor Cav1.1 (HypoPP type 1),2,3 or SCN4A, encoding the pore-forming α-subunit of the skeletal muscle voltage-gated sodium channel Nav1.4 (HypoPP type 2).4 The clinical features of type 1 and 2 HypoPP are indistinguishable.5 In Europe, the former is found in 70%–80% of patients, while the latter is observed in 10%. Conversely, up to 10% of men of Southeast Asian background with thyrotoxicosis may have thyrotoxic periodic paralysis (TPP).6 The clinical features of HypoPP and TPP are similar. Carbohydrate-rich meals and rest after exercise can trigger both conditions. Patients with TPP develop attacks only under thyrotoxicosis, regardless of etiology. Nearly all cases of TPP are sporadic,6 although mutations in KCNJ18 are reportedly associated with TPP.7

Here, we report a case with hereditary HypoPP type 2 harboring a c.2015G>A, p.R672H mutation in SCN4A, in whom thyrotoxicosis aggravated his attacks of paralysis. He experienced paralytic attacks several times a year from 24 years of age and was clinically diagnosed with hypokalemic periodic paralysis. At 49 years of age, a laboratory examination showed normal thyroid function. At 57 years of age, transient thyrotoxicosis was accompanied with an increase of the frequency and severity of attacks. Gene analysis revealed a missense mutation (c.2015G>A, p.R672H) in SCN4A, a known pathogenic mutation for hypokalemic paralysis type 2. This case highlights the importance of checking thyroid function when the frequency and severity of attacks are increased in patients with periodic paralysis.

KEYWORDS
hypokalemic periodic paralysis, NAV1.4 voltage-gated sodium channel, thyroid function tests, thyroiditis, thyrotoxicosis
aggravated his attacks. Our patient suggests that thyrotoxicosis can be an exacerbation factor even in hereditary HypoPP.

2 | CASE REPORT

At 24 years of age, the patient experienced his first attack of paralysis and was clinically diagnosed as HypoPP with normal thyroid function. He then experienced severe attacks several times a year. There was no family history of similar attacks. His elder sister had Graves’ disease. At 49 years of age, his thyroid function was normal on the day following a severe attack (Table 1). At 57 years of age, he experienced body weight loss and general fatigue. Approximately 1 month before admission, he had longer and more severe attacks twice; thereafter, he had attacks on 4 consecutive days. He was admitted to our hospital and a laboratory test demonstrated hyperthyroidism (Table 1). On day 4 after admission, at ~8 hour after eating a carbohydrate-rich evening meal, he had another attack. His serum potassium level was 2.2 mmol/L. Therefore, this was considered to be a paralytic attack with hypokalemia, which was the last he experienced under thyrotoxicosis. Blood and urinary examinations demonstrated no electrolyte imbalance secondary to renal or hormonal disease.

He had neither exophthalmos nor goiter. Anti-thyroid-stimulating hormone receptor and anti-thyroid-stimulating antibodies were negative. Technetium-99m pertechnetate thyroid scintigraphy and thyroid echography were normal. In the interictal phase, the electromyography study of the right rectus femoris muscle showed no myotonic discharge and demonstrated a reduced number of motor units. A long exercise test with the right ulnar nerve indicated that the baseline compound muscle action potentials before and after the test for 60 minutes were 6.8 mV and 5.0 mV, respectively, that is, a normal result. His hyperthyroidism changed to hypothyroidism after 9 weeks, and then to euthyroidism at 24 weeks after admission without treatment (Table 1), leading to a diagnosis of painless thyroiditis. Gene analysis was performed after obtaining written informed consent and approval from the ethics committee of Osaka University and Kochi Medical School. Sanger sequencing of CACNA1S and SCN4A was performed, and a heterozygous mutation, c.2015G>A, was found in SCN4A, resulting in the substitution of an arginine with a histidine at position 672, p. R672H, in Nav1.4 (Figure 1).

3 | DISCUSSION

Except for thyrotoxic symptoms, the clinical features of HypoPP and TPP are similar.6 The mutation identified in this case (c.2015G>A, p.R672H) has been reported as a common pathogenic mutation for HypoPP type 2.1,8 A patient with TPP associated with an SCN4A mutation, presenting with body weight loss prior to the recognition of hyperthyroidism, has been reported.9 In our patient, disease history and thyroid function tests aided the recognition of transient thyrotoxicosis. No aggravated attacks have occurred since day 4 after admission.

Once a potential trigger effects, extracellular potassium levels are reduced in patients with HypoPP. In patients with SCN4A mutations, the two outmost arginine residues in domain II of Nav1.4 cause a leak current, which only manifests at hyperpolarized resting membrane potentials, is very small, and lead to a minor shift of resting muscle membrane potential.1,8 However, it has a marked

| Normal range | 8 years earlier | On admission | Day 13 | 5 weeks | 9 weeks | 16 weeks | 24 weeks |
|--------------|----------------|--------------|--------|---------|---------|----------|----------|
| TSH          | 0.38 – 4.30 µIU/mL | 1.160 | <0.005 | <0.005 | <0.005 | 0.205 | 4.73 | 4.03 |
| Free T3      | 2.4 – 4.0 pg/mL | 3.20 | 7.27 | 7.41 | 4.47 | 2.75 | 2.84 | 3.03 |
| Free T4      | 0.94 – 1.60 ng/dL | 1.10 | 3.26 | 2.88 | 1.87 | 1.02 | 1.00 | 1.05 |

Abbreviations: TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.
effect on the muscle membrane during hypokalemia by increasing the potassium concentration, at which point paradoxical depolarization occurs. At extremely low potassium levels, the majority of fibers partially depolarize. Activated \(3\text{Na}^+/2\text{K}^+\) ATPase pumps could be involved in worsening hypokalemia and increasing the percentage of fibers undergoing paradoxical depolarization.

In TPP patients, excess triiodothyronine, increased activity of \(3\text{Na}^+/2\text{K}^+\) ATPase pumps, and/or insulin can exert additional alterations to sodium channel behavior during thyrotoxicosis.

In conclusion, we reported a patient with hereditary HypoPP type 2 in whom repeated thyroid function tests revealed that transient thyrotoxicosis aggravated his attacks.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report relevant to the paper.

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REFERENCES

1. Fialho D, Griggs RC, Matthews E. Periodic paralysis. *Handb Clin Neurol*. 2018;148:505-520.
2. Junkar-Rott K, Lehmann-Horn F, Elbaz A, et al. A calcium channel mutation causing hypokalemic periodic paralysis. *Hum Mol Genet*. 1994;3:1415-1419.
3. Ptacek LJ, Tawil R, Griggs RC, et al. Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. *Cell*. 1994;77:863-868.
4. Bulman DE, Scoggin KA, van Oene MD, et al. A novel sodium channel mutation in a family with hypokalemic periodic paralysis. *Neurology*. 1999;53:1932-1936.
5. Cannon SC. Sodium channelopathies of skeletal muscle. *Handb Exp Pharmacol*. 2018;246:309-330.
6. Maciel R, Lindsey SC, Dias da Silva MR. Novel etiopathophysiological aspects of thyrotoxic periodic paralysis. *Nat Rev Endocrinol*. 2011;7:657-667.
7. Ryan DP, Dias da Silva MR, Soong TW, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. *Cell*. 2010;140:88-98.
8. Matthews E, Labrum R, Sweeney MG, et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. *Neurology*. 2009;72:1544-1547.
9. Lane AH, Markarian K, Brazinene I. Thyrotoxic periodic paralysis associated with a mutation in the sodium channel gene *SCN4A*. *J Pediatr Endocrinol Metab*. 2004;17:1679-1682.

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