学 位 論 文 の 要 旨

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学　位　論　文　名　　Clinical and Genetic Investigation of 17 Japanese Patients with Hyperekplexia

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論 文 内 容 の 要 旨

INTRODUCTION

Hyperekplexia is clinically characterized by neonatal hypertonia and an exaggerated startle response. The excessive startle reflex may occasionally cause traumatic injury or arrest of breathing. Positive nose-tapping test is considered to be characteristic of hyperekplexia. No abnormalities are usually observed in routine blood tests, imaging studies, or physiological examination of the patients. Clonazepam is often used. It has been reported that hyperekplexia is caused by gene mutations related to glycinergic neurotransmission. The common disease-causing gene is the *GLRA1* gene which encodes the postsynaptic glycine receptor (GlyR) α1 subunit, the *SLC6A5* gene encoding the presynaptic glycine transporter GlyT2 and the *GLRB* gene encoding the GlyR βsubunit. Mutations in the above glycinergic neurotransmission-related genes impair inhibitory neurotransmission pathways, and stimulate excitatory transmission systems, resulting in hyperekplexia.

Until now, there have been few reports of large-scale clinical and genetic studies of hyperekplexia patients. We investigated clinical and genetic features in 17 Japanese patients with hyperekplexia.

MATERIALS AND METHODS

Patient recruitment was performed by self-referral. We investigated ages at onset and diagnosis, familial and perinatal history, symptoms, clinical courses, complications, blood and imaging tests, responses to medications, neurological outcomes, and gene mutations (*GLRA1*,*GLRB,* and *SLC6A5*) in 17 Japanese patients (from 12 families) with hyperekplexia.

Clinical diagnosis of hyperekplexia was based on the following manifestations: exaggerated startle reflex, muscle stiffness, and a positive nose-tapping test. Genetic analysis was performed direct sequencing and PCR-RFLP. Informed consent for genetic analysis was obtained from each patient and/or their parents.

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

1. Clinical features

In all patients, muscle stiffness and startle responses appeared soon after birth. Only seven patients were diagnosed with hyperekplexia before 1 year of age. This is the first article to highlight this delay in diagnosis. Seven patients had been misdiagnosed with other disorders including epilepsy, dystonia or cerebral palsy. The cause of misdiagnosis might be due to the low recognition rate of hyperekplexia. Umbilical/inguinal hernias were seen in 10 patients. In Japanese patients, the frequency of umbilical hernia was very high, suggesting that umbilical hernia is an important factor for diagnosis of hyperekplexia. The nose tapping test was positive in all cases, and may be useful for early detection of hyperekplexia. No notable abnormalities were observed in routine laboratory tests or by imaging examinations, whereas electroencephalographical abnormality was found in 3 patients.

2. Gene mutations

Mutations in *GLRA1* and *GLRB* genes were identified in 16 and 1 patient(s), respectively. Fourteen patients showed autosomal dominant inheritance, while 3 were autosomal recessive. p.R271Q of *GLRA1* was the most frequent mutation and found in 10 patients. Novel mutations,

p.A272P and p.A384P of *GLRA1*, were detected in this study. Regarding genotype-phenotype correlation, umbilical hernia was frequently found in patients with p.R271Q of *GLRA1* although clinical severity and outcome varied even in the same family.

3. Medications and response

Clonazepam was likely effective in 12 patients given, whereas clobazam and valproate may have also been effective in 3 cases used, suggesting that drugs that modulate gamma-aminobutyric acid (GABA) transmission may be effective for hyperekplexia.

4. Outcomes

Muscle stiffness disappeared before 5 years of age in 12 patients. The startle response disappeared or remitted in 12 (70%) of 17 patients between infancy to adolescence., although startle response recurred in one case during adulthood. These suggest that attention to startle response is required even after remission although GABA transmission modifiers ameliorate startle response.

CONCLUSIONS

This is the largest report of Japanese patients with hyperekplexia and the first to highlight potential delays in diagnosis. Delayed diagnosis of hyperekplexia due to an incorrect diagnosis, such as epilepsy, may result in improper treatment and/or unnecessary examination. Consistent with previous reports, all hyperekplexia patients in the present study demonstrated a neonatal onset. Muscle stiffness, startle responses, and a positive nose tapping test from the neonatal period may be important points for early detection. Clonazepam will be most effective although the outcome of the startle responses varied. The majority of Japanese patients have *GLRA1* mutations. Genetic analysis of glycinergic neurotransmission-associated genes could provide an appropriate diagnosis of hyperekplexia. Genotype/phenotype correlations are partially observed although other factors may regulate their clinical course.