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.

論文審査及び最終試験又は学力の確認の結果の要旨

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論文審査の結果の要旨

驚愕病は、新生児期より予期できない刺激に対して全身を硬直させる過度の驚愕反応や、持続性の筋緊張亢進などを呈する疾患である。原因は、グリシン受容体の遺伝子変異に基づく機能異常による抑制性神経伝達障害と考えられている。筋緊張亢進は成長とともに改善する傾向があるが、驚愕反応は残存することが多い。驚愕反応による呼吸停止や転倒は事故につながることもあり、早期診断と適切な治療が重要である。また一般検査（血液、画像検査、脳波等）では異常を示さないため、誤診されて不必要な治療が行われていることも少なくない。さらに成人後の臨床像についても不明な点が多い。これまで本症に対する認知度は低く症例報告も少ない。

申請者は日本人症例17例の遺伝子変異と発症形態、臨床経過、治療効果等について検討した。その結果、①全例が新生児期にNose tapping テスト陽性を示すこと、②てんかんと誤診されて診断が遅れやすいこと、③臍ヘルニアの合併が多いこと、④治療としてクロナゼパムが有効なこと、⑤筋緊張亢進は5歳までに全例消失すること、⑥驚愕反応は比較的長期に持続し、成人期に再燃することもあること、⑦17症例の遺伝子変異は、Glycine receptor subunit alpha-1(*GLRA1*)遺伝子変異16例およびGlycine receptor subunit beta(*GLRB*) 遺伝子変異1例であったこと、⑧遺伝形式は優性遺伝14例および劣性遺伝3例であったこと等を明らかにした。本研究は、日本人の驚愕病の多数例の臨床像・治療経過/遺伝的特徴を解明した初めての報告であり、驚愕病患者の早期診断、治療および合併症の予防、生活の質の向上に貢献するものである。

最終試験又は学力の確認の結果の要旨

申請者は、日本人における驚愕病についての広範な調査を行い、本症が実際的には誤診されて診断が遅れること等から早期の鑑別診断と適切な治療の重要性を導き、さらに日本人全症例の遺伝子変異部位も特定した。さらなる応用や今後の発展性についても明確であり、博士の学位に値すると判断した。（主査：竹下　治男）

申請者は、グリシン受容体の遺伝子変異に由来する驚愕病17例について精査し、変異部位や遺伝形式が様々あり、発症形態、臨床像も多様であるが、クロナゼパムが有効で、てんかんとの鑑別が重要であることを示した。グリシン受容体に関する基本知識も充実しており、学位授与に値すると判断した。（副査：廣田　秋彦）

申請者は、本邦においてまだ認知度の低い驚愕病を17例収集し、その臨床的特徴と遺伝子学的背景を明らかにした。本研究は我が国での最初の多数例での検討であり、本症の病態解明に大きく貢献する。豊富な関連知識も有しており学位授与に値すると判断した。（副査：山口　修平）

（備考）要旨は、それぞれ４００字程度とする。