CASE REPORT

A fatal infantile case with suspected hyperekplexia

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Abstract : Hyperekplexia is a hereditary disorder characterized by generalized muscle hypertonia and an excessive startle reflexes. It is associated with serious injuries from startle-induced falls ; and risk of sudden death exists due to respiratory arrest induced by muscular stiffness. Hyperekplexia is treatable with clonazepam. However, due to low public awareness of this disease, many cases may remain undiagnosed and untreated. We report the case of a one-day-old male neonate with muscle hypertonia admitted to our hospital. Blood test results and electroencephalography and brain magnetic resonance imaging findings were normal. Hyperekplexia was strongly suspected based on clinical symptoms, family history, and the positive nose-tapping test. Oral clonazepam was administered ; however, the dose could not be increased to a sufficient level due to lack of parental consent ; he was discharged on day 37. After self-interruption of clonazepam, he was transported to our hospital in a state of cardiopulmonary arrest and later died at 2 months of age. Although hyperekplexia is often associated with good prognosis, we encountered a fatal case, highlighting the need for promoting disease awareness and educate patient guardians. J. Med. Invest. 72 : 438-439, August, 2025

Keywords **:** *hyperekplexia, muscle hypertonia, startle reflexes, clonazepam, sudden death*

INTRODUCTION

Hyperekplexia is characterized by core clinical features, including excessive startle reflexes to unexpected sensory stimuli and muscular stiffness (1). Many cases of hyperekplexia follow an autosomal dominant inheritance pattern, suggestive of a large patient population. However, since a definitive diagnosis depends on genetic testing, numerous cases likely remain undiagnosed due to the low public awareness of the disease. The severity of hyperekplexia varies ; however, it can result in fatal outcomes such as respiratory arrest caused by excessive startle reflexes or severe head trauma resulting from startle-induced falls (2). We report the case of an infant who died suddenly of respiratory arrest following an episode of stiffness.

CASE REPORT

A one-day-old male neonate presented with severe muscle hypertonia immediately after birth, along with an absence of Moro and Babinski reflexes, for which he had been transferred to our neonatal intensive care unit. No significant complications occurred during pregnancy. He was born at 40 weeks and 1 day gestation, with birth weight 3150 g by vaginal delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively.

Upon admission to our hospital, sucking reflex was observed ; however, he showed marked muscle hypertonia and an excessive startle reflexes to both auditory and visual stimuli. He demonstrated incomplete Moro reflex ; his arms moved forward with his fists clenched. In addition, apnea with decreased SpO2 was observed during muscle stiffness. Blood test (Table 1) and blood gas analysis (Table2) revealed no significant abnormalities, except for an elevated creatine kinase (CK) level. Since CK decreased nearly to its normal level (200 mg/dl) at discharge, the elevation was considered to be due to perinatal stress. Electroencephalography and head magnetic resonance imaging revealed normal findings. The nose-tapping test was

Table 1. Blood test results on admission

WBC	21100	/μl	UN	15.8	mg/dL
Hb	18.1	g/dL	Cre	0.98	mg/dL
RBC	424	$\times 10^4$/mm	Na	139.3	mEq/L
HCT	52.2	%	K	5.34	mEq/L
PLT	29.9×10^4	/μl	CL	104.2	mEq/L
T-Bil	4.4	mg/dL	Ca	8.9	mg/dL
D-Bil	0.6	mg/dL	P	4.0	mg/dL
AST	72	U/L	Mg	2.1	mg/dL
ALT	16	U/L	TP	6.5	g/dL
ALP	312	U/L	Alb	3.3	g/dL
LDH	840	U/L	CRP	0.55	mg/dL
CK	1582	U/L	IgM	4	mg/dL

Table 2. Blood gas (vein) results on admission

pH	7.375	
pCO2	45.3	mmHg
pO2	40.2	mmHg
$HCO3^-$	26.5	mEq/L
BE(vt)	0.7	mEq/L
Glucose	95	mg/dL
Anion GAP	10.3	mEq/L
Lactate	3.5	mmol/L

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positive. The interview revealed that his mother also experienced marked muscle hypertonia since infancy. Additionally, a family history of similar symptoms was noted on the maternal side. Thus, the possibility of hyperekplexia was considered. However, the parents did not want a genetic testing to be performed. Oxygen therapy for apnea was initiated on Day 1. Clonazepam (CZP ; 0.02 mg/kg/day) was initiated on Day 6 and increased to 0.03 mg/kg/day on Day 11, leading to a noticeable reduction in muscle hypertonia. However, an increase in muscle hypertonia was observed again on Day 16. Although an increased dose of CZP was considered, parental consent could not be obtained. It was suspected that the mother also had hyperekplexia ; however, she had matured without pharmacological intervention, this may have contributed to her reluctance to initiate medication for her child. Also she showed resistance to administer antiepileptic drugs even though the infant did not have epilepsy.

Following the discontinuation of oxygen therapy on Day 22, transient decreases in oxygen saturation were observed during episodes of muscle hypertonia. However, from approximately Day 31, muscle hypertonia began to improve ; the patient was discharged on Day 37. Upon discharge, the parents were instructed to continuously monitor his SpO2 levels and administer home oxygen therapy or perform manual ventilation using a bag-valve mask in the event of oxygen desaturation.

Following discharge, he gradually developed hypertonia, accompanied by an umbilical hernia and developmental dysplasia of the hip joint. Although the need to increase the CZP dosage was repeatedly communicated to the parents ; however, consent could not be obtained.

At 2 months of age, he was in cardiopulmonary arrest at home and was transported to our hospital. Resuscitation was initiated ; but there was no response, and the patient died. Postmortem computed tomography imaging for autopsy revealed ground-glass opacities in both lungs. Upon autopsy, a diffuse alveolar hemorrhage was observed in all lung lobes. Given the underlying condition, it was thought that upper airway obstruction caused by muscle hypertonia due to hyperekplexia led to negative-pressure alveolar hemorrhage.

DISCUSSION

As mentioned above, hyperekplexia is characterized by muscle hypertonia and startle reflexes. Complications such as apnea, abdominal hernia, developmental dysplasia of the hip joint, delayed language acquisition, and epilepsy have been reported (3). In our case, an umbilical hernia and developmental dysplasia of the hip joint were observed.

Hyperekplexia typically shows no specific findings in blood or urine tests, head imaging, electroencephalography, or electrophysiological examinations. Hyperekplexia is predominantly caused by mutations in the genes encoding the postsynaptic inhibitory glycine receptor (GlyR ; GLRA1 and GLRB) and presynaptic glycine transport (GlyT2 ; SLC6A5). Therefore, definitive diagnosis is established through genetic testing (1). The variability in clinical features of hyperekplexia is due to differences in these mutations (4). Furthermore, the severity of symptoms varies depending on the type of mutation even within the same GLRA1 gene (3). In addition, small degree of variability in clinical features within families is frequently encountered in clinical practice. Most cases follow an autosomal dominant inheritance pattern ; however, autosomal recessive inheritance also exists. Revealing the normality in routine examinations and then performing genetic testing are necessary to identify this disease at an early stage. However, genetic testing takes long time. The nose-tapping test is simple, non-invasive, and specific to this disease, making it a useful diagnostic tool. This study has a limitation. We were unable to make a definitive diagnosis of hyperekplexia because genetic testing was not performed. However, the development of diagnostic criteria is currently underway (3). Since the patient showed three main symptoms, three secondary symptoms, and the positive nose-tapping test, he could be diagnosed as a "probable" case of hyperekplexia. Several other drugs such as valproic acid, clobazam, and fluoxetine have been considered but their effectiveness has not been well established (5). In animal studies, drugs that potentiate GlyR responses have been investigated (6), expecting further applications.

However, owing to low public awareness of this disease, it is often misdiagnosed as refractory epilepsy or other conditions (7). Even if diagnosed correctly, hyperekplexia is generally associated with good prognosis because muscle stiffness typically resolves during infancy. Although the startle reflexes often persists throughout life (1), its severity varies among individuals.

To ensure an appropriate diagnosis and treatment, increasing public awareness of this disease and educate patients are urgently needed.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this article.

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