# Long-term follow up of an adult with alternating hemiplegia of childhood and a p.Gly755Ser mutation in the *ATP1A3* gene

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【Abstract】

Alternating hemiplegia of childhood (AHC) is a rare neurological disease mainly caused by mutations in the *ATP1A3* gene and showing varied clinical severity according to genotype. Patients with a p.Gly755Ser (p.G755S) mutation, one of minor genotypes for AHC, were recently described as having a mild phenotype, although their long-term outcomes are still unclear due to the lack of long-term follow up. Here, we demonstrate the full clinical course of a 43-year-old female AHC patient with p.G755S mutation. Although her motor dysfunction had been relatively mild into her 30s, she showed a subsequent severe aggravation of symptoms that left her bedridden, concomitant with a recent recurrence of seizure status. The seizures were refractory to anti-epileptic drugs, but administration of flunarizine improved seizures and the paralysis.

Our case suggests that the phenotype of AHC with p.G755S mutation is not necessarily mild, despite such a presentation during the patient's younger years.

## 【Introduction】

Alternating hemiplegia of childhood (AHC) is characterized by recurrent episodes of alternating hemiplegia, dystonic attacks, paroxysmal abnormal ocular movements, epilepsy, involuntary movement, and autonomic disturbances, starting in infancy and present especially during the period from birth to 3 months old [1]. Causative mutations in the *ATP1A3* gene at p.Glu815Lys (p.E815K) and p.Asp801Asn (p.D801N) are the most commonly reported abnormalities with AHC [2] [3] [4], and phenotypes vary in a genotype-dependent manner [5] [6]. For example, patients with the p.E815K mutation show a severe phenotype that deteriorates before adulthood, while the p.D801N mutation results in a moderate to mild form of AHC [4]; however, the clinical course into adulthood of other, low-frequency genotypes such as the p.Gly755Ser (p.G755S) mutation remains largely unknown due to the lack of long-term follow-up reports. Here we show the long-term clinical course of a 43-year-old AHC female patient with the p.G755S mutation.

## 【Case report】

Our patient is a 43-year-old Japanese female with AHC. She was born at full term without any issues during pregnancy or delivery. She showed developmental delay during infancy; she began to talk independently at 18 months and walk at 27 months of age. Her family history was unremarkable. Her symptoms of left transient hemiplegia and epilepsy appeared at 3 months of age, and thereafter she showed recurrent hemiplegia in either the left or right limbs approximately every 4 weeks. The hemiplegia was initially mild and resolved without medication within a few days. After 4 years of age she developed consistent right limb hemiplegia and dysphagia. She was able to walk independently until the age of 37 years.

She was referred to our hospital for further evaluation at 6 years of age. Laboratory testing and imaging by head computed tomography (CT), single photoemission CT (SPECT), and interictal EEG showed no abnormal findings. We diagnosed this patient with AHC after applying the diagnostic criteria, including the presence of repetitive hemiplegia, hemiparesis after hemiplegia, and developmental delay when she was 6-year-old [7].

She initially presented with focal motor seizure, which evolved to

generalized tonic clonic seizures. Various combinations of anti-epileptic drugs did not relieve the seizures completely, but the episodes remained rare until the age of 32 years (Figure 1).

She graduated from a special high school for disabled students and spent her daily life in a care home. In her 20s, she was able to walk by herself, talk with her family, and occasionally enjoy a glass of alcohol at home. As a 19 year old, she scored a full-scale intelligence quotient (IQ) of 41 by the Tanaka-Binet psychological test. After the age of 33 years, her seizure status increased (Figure 1). There were some hypoxic states in seizure status but no ventilator support episode. In spite of using multiple anti-epileptic drugs, it was impossible to stop repetitive seizure status. She lost her muscle power to stand with her legs until 38 years old and became bedridden before 39 years old, but her movement of fingers, toes and wrists preserved. At that stage, she had received flunarizine for 10 years, but this was subsequently discontinued because approval of flunarizine was withdrawn in Japan by the Ministry of Health and Welfare when the patient was aged 25-year-old. We re-prescribed flunarizine without any other change of her therapy on presentation of the worsened symptoms in this patient at 42 years of age,

resulting in some movement in her paralyzed left arm and fingers. Flunarizine was also effective for the epileptic seizures, and 1 year after re-starting the drug administration she had showed only two episodes of status seizure.

## 【Discussion】

In contract to patients with the higher frequency p.E815K or p.D801N mutation, there is limited information about the phenotype of AHC cases with other minor genotypes. In this study, we reviewed the clinical course of a female AHC patient with p.G755S mutation and compared our findings with previous clinical reports of the same mutation (6 patients, Table 1). One adult and two pediatric cases among the six patients were evaluated as mild AHC because there were no further episodes of clinical decline [3]. However, the long-term outcome of these patients is unclear due to the limited follow-up period. To the best of knowledge, we report herein the oldest patient with AHC and a G755S mutation. Our case showing recurrent status epilepticus and sudden deterioration after 35 years of age suggests that the long-term outcome of this minor genotype could be poor even though the effects are moderate at a younger age. This insight is supported by case 1 in

Table 1, who showed rapid deterioration after epileptic status at the age of 12 years [4]. We think the possibility of her deterioration due to not only seizure status but also natural course of this disease. Especially, case 1 and our patient would have seizure status and deterioration after quitting flunarizine. These results might imply that these mutations presented a particular benefit on flunarizine treatment, although it should be confirmed in future additional study. Clinicians should therefore be aware of the potential for aggravated symptoms during adolescence or adulthood, especially in patients with E815K and G755A/S mutations, as Sasaki et al mentioned [4]. Previous reports also indicated that flunarizine in AHC patients prevents paralysis and regression [8], and our case confirms the effectiveness of flunarizine in patients with AHC. In other genotypes of AHC reviewed, some patients regressed after stopping flunarizine [4]. Of note in the current case, the stability of symptoms during the initial 10-year administration of flunarizine suggests that this compound could have preventive effect for neuronal degradation in AHC, although more cases are necessary for meaningful analysis of this proposal.

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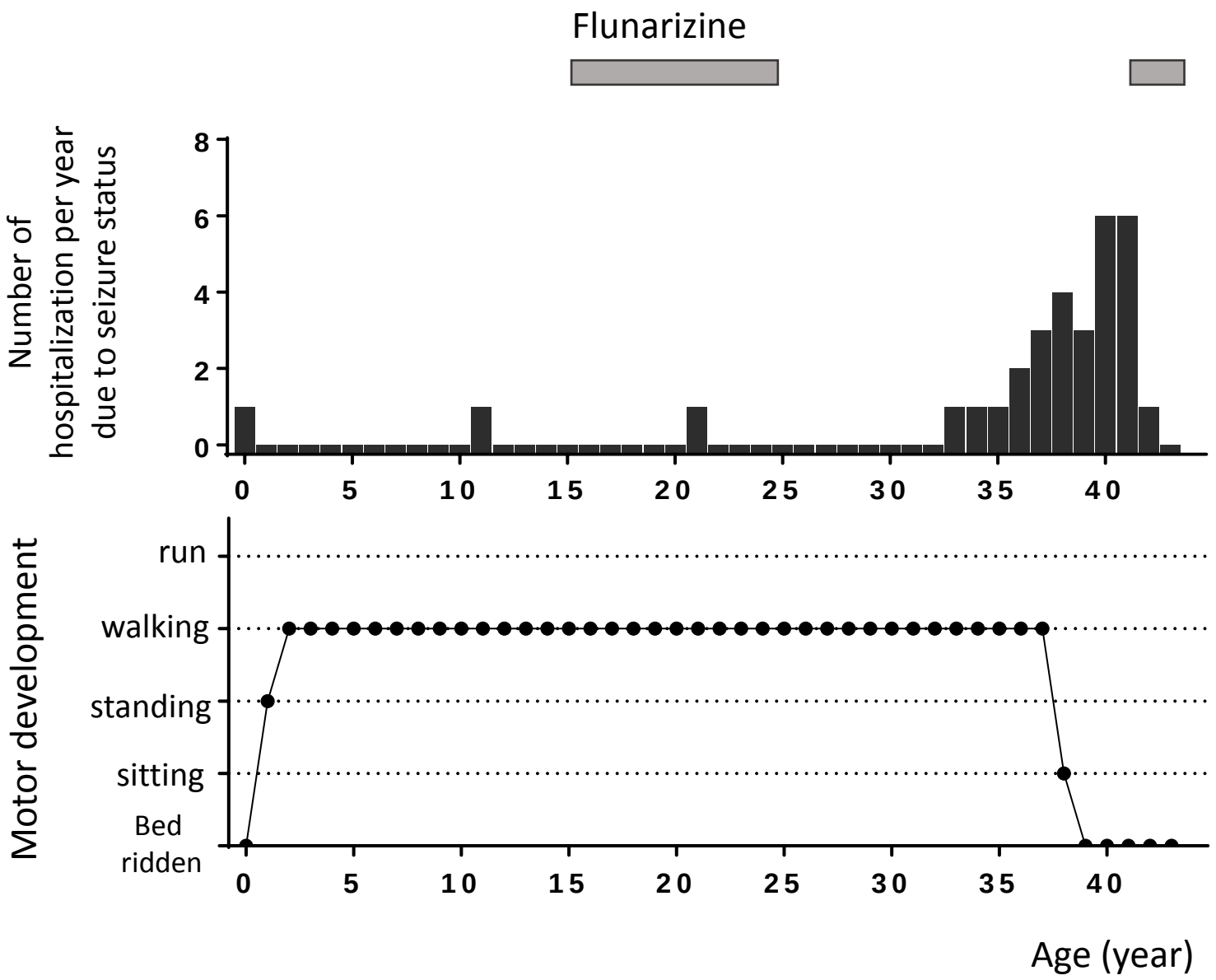
## Figure legends

Figure 1. long time course of our patient of AHC with p.G755S mutation

Upper and lower graph show admission frequency due to epileptic seizure and time curse of motor dysfunction, respectively. In her 30s, she suffered frequent epileptic statuses, then, she regressed to bedridden.


Flunarizine
Number of hospitalization per year due to seizure status
8
6
4
2
0
0
5
10
15
20
25
30
35
40
Motor development
run
walking
standing
sitting
Bed ridden
0
5
10
15
20
25
30
35
40
Age (year)

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In her 30s, she suffered frequent epileptic statuses, then, she regressed to bedridden.

Table 1. AHC with p.Gly755Ser (p.G755S) mutation in ATP1A3 gene in previous reports and our case.

| | Age<br>Onset / last follow | MR | Epilepsy | Respiratory support | Tube feeding | Phenotype |
|---|---|---|---|---|---|---|
| Sasaki M, et al, 2014 [4] (n=35) | 0y4m / 13y | (+) | (+) | (+) | (+) | severe |
| Panagiotakaki E, et al, 2015 [3] (n=155) | 0y4m / 24y | (-) | improved | N/A | N/A | mild |
| | 0y6m / 8y | (+) | (+) | N/A | N/A | mild |
| | 0y6m / 8y | unknown | (-) | N/A | N/A | mild |
| Yang X, et al, 2014 [9] (n=52) | 0y3m / 1y4m | (+) | (-) | N/A | N/A | N/A |
| Rosenwich H, et al, 2014 [10] (n=16) | 0y3m / 12y9m | (+) | (+) | N/A | N/A | N/A |
| Our patient | 0y3m / 41y | (+) | (+) | (-) | (+) | mild?? |

MR: Mental Retardation, N/A: not assessed