



# Serial Magnetic Resonance Imaging and <sup>1</sup>H-Magnetic Resonance Spectroscopy in GABA Transaminase Deficiency: A Case Report

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**Abstract** Gamma-aminobutyric acid transaminase (GABA-T) deficiency is a rare, autosomal recessive disorder characterized by severe psychomotor retardation, early-onset epileptic encephalopathy, intractable seizures, hypotonia, and hyperreflexia. The disease is caused by mutation in the 4-aminobutyrate aminotransferase (ABAT) gene, which encodes an enzyme involved in GABA catabolism. In this chapter, a 10-year follow-up of GABA-T deficiency in a rare case of a long-term survivor patient is discussed. The patient showed a progression of clinical phases with increasing age. In infancy, the patient developed psychomotor retardation and recurrent encephalopathic episodes associated with febrile illness. In early childhood, the patient presented with refractory involuntary and hyperkinetic movements and dystonic hypertonicity. In childhood, the patient gradually progressed into the chronic stable phase of the condition. Magnetic resonance imaging demonstrated high signal intensity on diffusion-weighted images involving the internal and external capsules and cerebral white matter in infancy which disappeared gradu-

ally by the age of 3 years, and showed subsequently diffuse brain atrophy in childhood. Using proton magnetic resonance spectroscopy, GABA levels in the basal ganglia were shown to be markedly elevated at the age of 1–2 years, and subsequently decreased with increasing age (toward 5 years). These findings suggest that the encephalopathic episodes in infancy and clinical severity of involuntary and hyperkinetic movements may be correlated with levels of GABA in the basal ganglia. The high levels of GABA in the cerebrospinal fluid remained unaltered, whereas levels of GABA in the serum decreased during childhood. Further investigation of long-term clinical surveillance may improve the understanding of GABA-T deficiency.

## Introduction

Gamma-aminobutyric acid transaminase (GABA-T) deficiency is a rare, autosomal recessive disorder characterized by severe psychomotor retardation, early-onset epileptic encephalopathy, intractable seizures, hypotonia, and hyperreflexia (Jaeken et al. 1984). GABA is metabolized by a combination of GABA-T and succinic semialdehyde dehydrogenase (SSADH) (Parviz et al. 2014). The disease is caused by a mutation in the 4-aminobutyrate aminotransferase (ABAT) gene (OMIM 13715), which encodes an enzyme involved in GABA catabolism and salvage of mitochondrial nucleotides. In GABA-T deficiency, GABA is unable to convert to succinic semialdehyde resulting in a build-up of GABA, beta-alanine, homocarnosine, GABA ketone, and 2-pyrrolidinone.

To date, only ten patients have been diagnosed with GABA-T deficiency worldwide (Louro et al. 2016; Koenig et al. 2017). Of those, five patients have survived for more

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than 3 years, in contrast to the previously reported mortality expected within the first 2 years of life. Currently, there are no studies investigating in detail the clinical information of long-term survivor cases.

Proton magnetic resonance spectroscopy ( $^1\text{H-MRS}$ ) is a noninvasive technique for the investigation of brain metabolites and may also be useful for estimating the levels of in vivo neurotransmitters (Novotny et al. 2003).  $^1\text{H-MRS}$  combined with the LCModel method may facilitate metabolite separation and be applied for the measurement of GABA levels. However, quantifying GABA levels is challenging due to its low concentration masked by the larger peaks of the glutamine–glutamate complex (Provencher 2001).

This report describes the clinical course of a patient with GABA-T deficiency, during a 10-year follow-up, focusing particularly on changes in GABA levels in the brain, serum, and cerebrospinal fluid (CSF).

## Case Report

The patient was a Japanese female aged 10 years who was followed up since infancy. The patient was born without complications, and developed severe psychomotor retardation, with hypotonia and recurrent encephalopathic episodes with intractable seizures during infancy. She was diagnosed with GABA-T deficiency via  $^1\text{H-MRS}$ , based on elevated levels of GABA in the brain. Subsequently, enzyme and molecular studies at 16 months of age confirmed the initial diagnosis. The patient demonstrated compound heterozygosity for a deletion of one exon and a missense mutation 275G>A in the ABAT gene, as well as decreased enzymatic activity of GABA-T in the lymphoblasts. A detailed description of clinical information until the age of 28 months has been reported previously (Tsuji et al. 2010).

The patient developed lethargy associated with febrile illness at the age of 8, 10, and 12 months. These encephalopathic episodes were consistently associated with neurological deterioration and led to opisthotonic posturing with generalized dystonia and segmental myoclonic jerks during wakefulness. The patient showed intense involuntary movements such as choreoathetosis, myoclonic jerks, and dystonic opisthotonic posturing in early childhood. These symptoms were refractory to multiple medications such as phenobarbital, clonazepam, diazepam, baclofen, dantrolene, and haloperidol. However, these symptoms gradually improved during childhood.

The patient revealed an accelerated increase in height reaching +3.0 standard deviations from the normal height during late infancy, and remained at the upper limit of

normal height in childhood. At the age of 10 years, the patient was non-verbal, non-ambulatory with spastic quadriplegia and dystonia, and dependent on gastrostomy tube feedings. No further deterioration was reported in childhood.

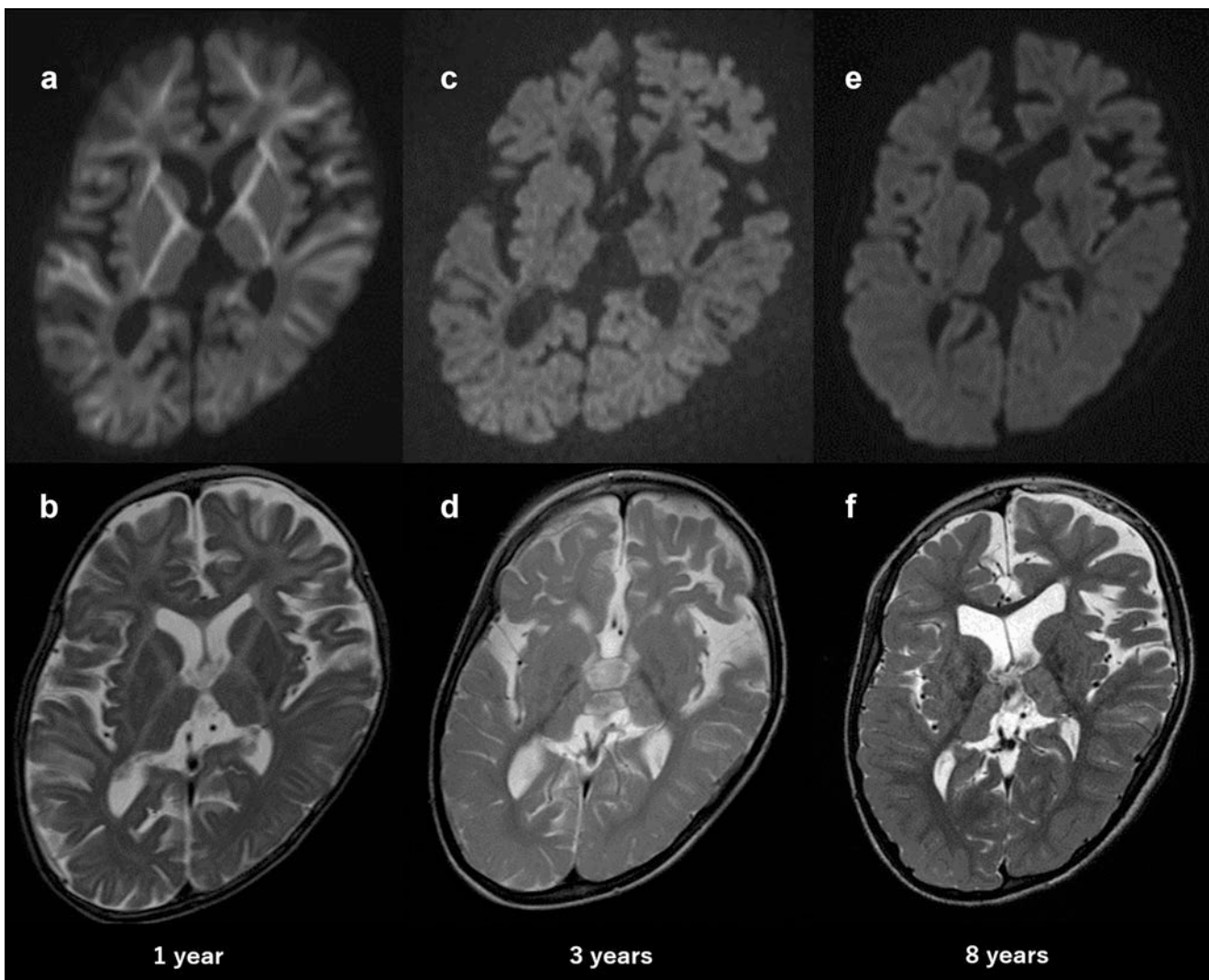
## Radiological Findings

Magnetic resonance imaging (MRI, Siemens 1.5T) at the age of 12 months demonstrated high signal intensity on diffusion-weighted images involving the internal and external capsules and the cerebral white matter with reduced apparent diffusion coefficient. These high-signal intense lesions disappeared gradually by the age of 3 years. MRI (3T, Siemens) at 8 years of age showed diffuse atrophy of the cerebrum and cerebellum and abnormal high-signal intensity in the bilateral thalamus (Fig. 1). The loss of signal of the bilateral globus pallidus on susceptibility-weighted images (SWI) appeared from the age of 2 years and became more apparent at the age of 8 years.

Serial  $^1\text{H-MRS}$  data (echo time/repetition time = 30/5,000 ms) were obtained from the basal ganglia (gray matter region) and the semioval center (white matter region). Concentrations of GABA and N-acetylaspartate (NAA) were quantified via the LCModel method software, using the internal water reference approach (water concentration of 43.30 and 35.88 mol/kg for the basal ganglia and semioval center, respectively). Concentrations of GABA in the basal ganglia at 1, 3, and 8 years of age were 6.35, 5.07, and 3.96 mmol/kg (GABA/Cr were 1.23, 0.67, and 0.50), respectively. Concentrations of GABA in the semioval center at the same ages were 2.03, 2.32, and 2.79 mmol/kg (GABA/Cr were 0.56, 0.53, and 0.56), respectively (Fig. 2a) (normal volunteers  $n = 17$ , 1–9 years: GABA concentrations  $1.43 \pm 0.36$  in the basal ganglia;  $0.82 \pm 0.38$  in the semioval center). NAA concentrations in the basal ganglia at 1, 3, and 8 years of age were 3.60, 5.99, and 6.50 mmol/kg (NAA/Cr were 0.70, 0.79, and 0.81), respectively. Concentrations of NAA in the semioval center were 3.05, 4.61, and 6.45 mmol/kg (NAA/Cr were 0.84, 1.05, and 1.28), respectively (Fig. 2b).

## GABA in the Serum and Cerebrospinal Fluid

Free GABA levels in the serum at 1 and 8 years of age were 2.10 and 0.54  $\mu\text{mol/L}$  (reference range 0.12–0.50  $\mu\text{mol/L}$ ), respectively. Free GABA levels in the CSF at 1 and 8 years of age were 1.261 and 1.133  $\mu\text{mol/L}$  (reference range <2 years; 0.017–0.067  $\mu\text{mol/L}$ , >2 years; 0.032–0.167  $\mu\text{mol/L}$ ), respectively (Fig. 3) (Van Hove and Thomas 2014).



**Fig. 1** Axial MRI at 1, 3, and 8 years of age (top: diffusion-weighted images, bottom: T2-weighted images). MRI at 1 year of age showing high signal intensity involving the internal and external capsules and cerebral white matter (**a**, **b**). MRI at 3 years of age showing the

disappearance of high signal intensity in a diffusion-weighted image (**c**, **d**). MRI at 8 years of age showing diffuse brain atrophy and symmetrical high signal in the bilateral thalamus (**e**, **f**)

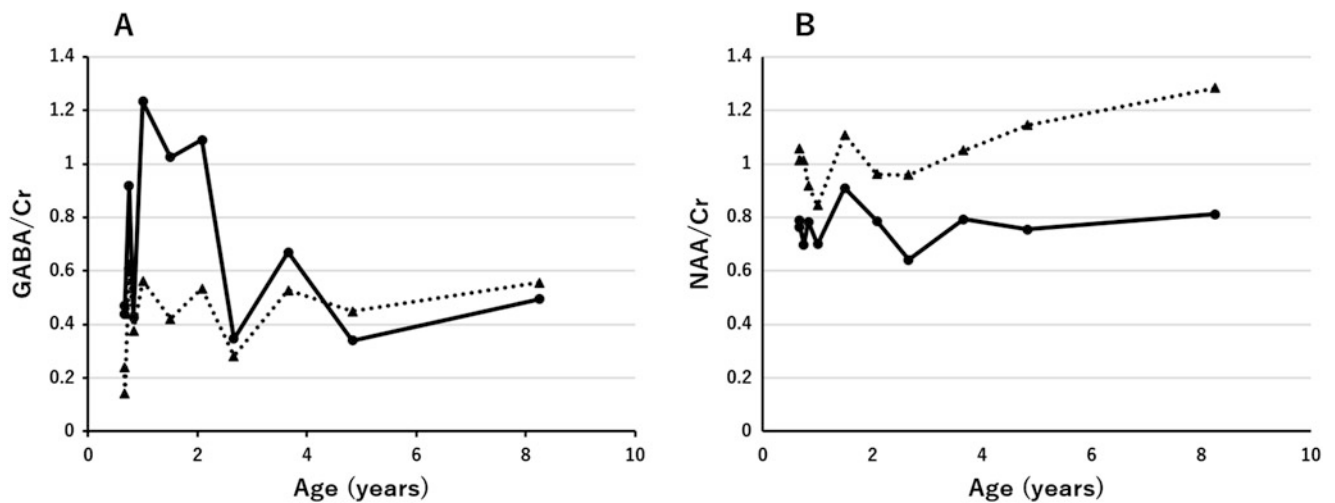
### Electroencephalography (EEG)

EEG revealed a diffuse slow spike and wave discharges with 1–2 s suppression during encephalopathic episodes in infancy. This examination at 3 years of age showed diffuse occipital dominant 2.5–3 Hz slow activities on background, occasionally containing paroxysmal sharp waves and diffuse polyspike and slow waves. EEG at 8 years of age revealed 13–14 Hz occipital dominant rhythmic activities on background having 4–5 Hz slow waves on the centro-occipital area, and demonstrated sporadic focal spikes. In contrast to the patient's infancy, childhood was characterized by infrequent seizures such as myoclonic or complex partial seizures.

### Discussion

The patient showed a progression of clinical phases with increasing age. In infancy, the patient developed psychomotor retardation and recurrent encephalopathic episodes associated with febrile illness. In early childhood, she presented refractory involuntary and hyperkinetic movements and dystonic hypertonicity through encephalopathic episodes. In childhood, the patient gradually progressed into the chronic stable phase of the condition.

Using  $^1\text{H-MRS}$ , GABA/Cr levels in the basal ganglia were shown to be markedly elevated at 1–2 years of age, and subsequently decreased with increasing age (toward 5 years). Levels of GABA/Cr in the semioval center



**Fig. 2** Changes in the level ratio of GABA to Cr and NAA to Cr with increasing age (years) quantified by the LCMoel method. Basal ganglia (solid line); semioval center (dotted line)



**Fig. 3** Changes in GABA levels in the serum and cerebrospinal fluid

remained slightly elevated over time. These findings suggest that the levels of GABA in the basal ganglia were highest during the encephalopathic phase in infancy. Moreover, it is suggested that the clinical severity of involuntary and hyperkinetic movements in early childhood may be correlated with the levels of GABA in the basal ganglia. Levels of NAA/Cr in the basal ganglia remained

low over time, whereas those in the semioval center increased slightly from the age of 3 years onwards. This finding suggests that neuronal loss of the cerebrum, particularly in the semioval center, may not progress during childhood.

High levels of GABA in the CSF remained unaltered, whereas GABA levels in the serum decreased in childhood.

GABA levels in the CSF may reflect those of the semioval center. The pathophysiology of the decrease in the serum levels of GABA could not be disclosed in this study.

In the developing brain, elevated GABA levels have been associated with an excitatory effect. However, in the mature brain, GABA exerts an inhibitory effect (Kilb 2012). Moreover, it has been suggested that supraphysiological levels of GABA result in a neurotoxic effect. Inhibition of GABA-T by the irreversible inhibitor vigabatrin has been shown to induce intramyelinic edema via elevation of GABA levels in dogs (Peyster et al. 1995). In the case described herein, the paradoxical excitatory effect of GABA was manifested prominently until 5 years of age particularly in the basal ganglia, in terms of the correlation between GABA levels and the severity of involuntary movement. The disappearance of the restricted diffusion as shown through MRI also suggested withdrawal of the neurotoxic effect of GABA. The relief of hyperkinetic movements with increasing age may be due to a decrease in the levels of GABA in the basal ganglia or GABAergic postsynaptic changes resulting in the resolution of excitatory/neurotoxic effects. Regional differences in GABA metabolism in the brain coupled with age-dependent susceptibility of the developing brain may also be responsible for movement disorder.

Although loss of signal of the globus pallidus was shown on SWI, its pathophysiology could not be disclosed in this study. This finding may be correlated with the abnormal elevation in GABA levels and involuntary movement such as SSADH deficiency and vigabatrin-associated brain abnormality. SSADH deficiency is the most prevalent among GABA degeneration disorders leading to accumulation of  $\gamma$ -hydroxybutyric acid and GABA, and reveals an increased hyperintense signal of the globus pallidus as shown on MRI (Ziyeh et al. 2002). Furthermore, vigabatrin may induce reversible MRI signal changes and restricted diffusion in the globus pallidus, thalamus, brainstem, and dentate nucleus, with an increase in GABA levels in the brain during treatment of infantile spasms (Dracopoulos et al. 2010).

A limitation of this study was that the control individuals of GABA concentration were not completely age-matched between the three ages that the MRS scans obtained from the patient. In addition, the natural history of GABA concentrations in the brain with age has remained to be elucidated in GABA-T deficiency. This study included only a patient with GABA-T deficiency. Therefore, the meaning of the lowering GABA is unclear and is uncertain as to whether unique to GABA-T deficiency. Decrease of GABA levels in the plasma and urine was also reported even in SSADH deficiency (Jansen et al. 2016).

In this report, a 10-year follow-up of GABA-T deficiency in a rare case of a long-term survivor patient is discussed. Encephalopathic episodes as well as hyperkinetic and involuntary movements seemed to correlate with the levels of GABA in the basal ganglia.  $^1\text{H}$ -MRS combined with the LCModel method may be clinically applicable to measure region-specific GABA levels. The pathophysiology of GABA-T deficiency remains to be elucidated. Investigation of additional patients with long-term follow-up data may improve the understanding of GABA-T deficiency. The findings discussed in this chapter may provide important insights into the pathogenesis of GABA-T deficiency and the role of the GABAergic system in human brain development.

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### Authors' Contributions

K.I. wrote the manuscript and provided medical care for the patient; Y.T. and M.T. provided medical care for the patient; M.T. performed the analysis of magnetic resonance spectroscopy and interpreted the results; N.A. interpreted magnetic resonance images; T.G. approved the final manuscript. All authors read and approved the final version of the manuscript.

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### Conflict of Interest

Kazushi Ichikawa, Megumi Tsuji, Yu Tsuyusaki, Moyoko Tomiyasu, Noriko Aida, and Tomohide Goto declare that they have no conflict of interest.

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### Compliance with Ethics Guideline

#### Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki

Declaration of 1975, as revised in 2000. Informed consent was obtained from the patient's parents for being included in the study.

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