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GABA TRANSAMINASE DEFICIENCY WITH SURVIVAL INTO ADULTHOOD

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Abstract

GABA-transaminase deficiency is an ultra-rare disorder of GABA metabolism that was described for decades as an early onset epileptic encephalopathy plus movement disorder and hypersomnolence with mortality in early childhood. We report two affected siblings in adolescence and adulthood, both with profound developmental impairment, intractable epilepsy, movement disorder, and behavioral fluctuations. This considerably expands the phenotype and longevity of this inherited neurotransmitter disease.

Keywords

GABA-transaminase deficiency; GABA-T deficiency; ABAT gene; GABA metabolism; India

Introduction

GABA-transaminase deficiency is an extremely rare autosomal recessive disorder of GABA metabolism first reported in 1984.¹ Over the next three decades, this was reported in

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occasional families as an early onset epileptic encephalopathy with mortality within the first two years of life. A recently published spectrum of GABA transaminase deficiency reviewed 10 cases of the disorder, five of which had infantile deaths and the surviving subjects were under 10 years of age.²

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system and is synthesized from glutamic acid in a reaction catalyzed by glutamic acid decarboxylase. The action of GABA transaminase is to convert GABA to succinic semialdehyde, which leads to the oxidative metabolism of GABA through the tricarboxylic acid cycle. GABA transaminase deficiency leads to endogenous GABA elevation. The epileptogenic effects of persistently elevated endogenous GABA remain unexplained. Putative hypotheses have been excessive inhibition of inhibitory interneurons, paradoxical depolarizing effects of GABA as in immature neurons with reversed chloride gradients, and downregulation of GABA receptors due to chronic overuse as demonstrated in deficiency in succinic semialdehyde dehydrogenase (SSADH), the other inherited disorder of GABA metabolism.³

Case Summary

The patients are two brothers from India, now 21 and 15 years, who presented with developmental delay noted from early infancy followed by persistent intractable seizures with psychomotor regression and involuntary movements starting at around 3-4 years of age.

The index patient is the younger sibling who was born at term with an uneventful perinatal course to healthy parents of third degree consanguinity. He had developmental delay; walked at 18 months and spoke a few words at 2 years. He had onset of epileptic spasms at 26 months, which then progressed to head drops, atonic seizures, myoclonic seizures, and atypical absences over the next few years. With the progression of his uncontrolled seizures, he started regressing in his milestones. He stopped walking independently and lost his limited vocabulary to nonspecific vocalizations. He manifested autistic features with a loss of interest in his toys and surroundings. His behavior gradually worsened with episodes of inconsolable crying, dullness, and apathy. Abnormal intermittent involuntary movements were also noted comprising of choreiform, dystonic posturing, and stereotypies such as hand flapping. A characteristic feature was fluctuations in mood, behavior, movements, and functionality. These episodes would last from days to weeks and were usually associated with increased seizure frequency. However, they would settle on their own, with no change in medication or other specific intervention. Overall, his clinical course has been characterized by marked developmental impairment, intractable seizures, challenging behavior, involuntary movements, intellectual disability, and fluctuating clinical condition.

The family history is significant with his elder brother having similar complaints of intractable seizures and intellectual disability. His clinical symptoms and course were similar to those noted in his brother. Presently at 21 years, he is unable to stand, has no speech, and is totally dependent for all daily activities. His seizures, albeit less intractable, were under control from 18 years onwards with sodium valproate and lamotrigine.

Examination of the index child showed that his anthropometrical findings over the years followed normal percentiles. General physical examination showed no obvious dysmorphic features while neurological examination revealed pyramidal signs with hyperreflexia and a positive Babinski reflex along with a mixed movement disorder comprising chorea, dystonic posturing, and motor stereotypies. The remainder of his systemic examination was unremarkable with no evidence of organomegaly, or visual or auditory concerns.

Laboratory investigations on the proband were normal and included complete blood count, routine chemistries including liver and kidney functions, ammonia, lactate, pyruvate, cholesterol, uric acid, urine GC/MS for organic and amino acids, karyotype, comparative genomic hybridization, sequencing for Rett and Angelman syndromes, methylation for Angelman syndrome, and antibody testing for NMDA, VGKC, and GAD. Brain MRI on two occasions at 4 and 13 years showed stable increased T2 signal in the subinsular white matter and subcortical white matter of the temporal poles, decreased undulations of the hippocampal heads, mild prominence of the temporal horns of the lateral ventricles and a thin corpus callosum with abnormal increased T2 prolongation in bilateral centrum semiovale at 4 years that resolves by 13 years (Figures 1 and 2). There is no evidence of interval brain volume loss. Electroencephalography (EEG) done initially at 2.4 years showed hypsarrhythmia which evolved to diffuse slow spike and wave discharges (< 2.5 Hz) along with brief generalized paroxysms of fast activity suggestive of Lennox Gastaut syndrome. Multiple antiseizure medicines ranging from ACTH injections to vigabatrin, sodium valproate, clobazam, and nitrazepam were administered when he had hypsarrhythmia. Levetiracetam, topiramate, zonisamide, and lamotrigine were subsequently administered but with minimum benefit. The ketogenic diet was tried with partial improvement but was not maintained.

In view of inconclusive investigations, a deteriorating and refractory course over several years, supported by a history of consanguinity in parents and similar phenotype in the elder sibling, whole exome sequencing was obtained. This revealed a homozygous missense variation in exon 16 of the 4-aminobutyrate aminotransferase (ABAT) gene (chr16:8875215;G>A) that results in the amino acid substitution of histidine for arginine at codon 497. A homozygous missense variation in exon 16 of the ABAT gene was also detected in the elder brother with both parents confirmed as heterozygous carriers (Table 1).

Discussion

GABA transaminase deficiency has been characterized by early onset seizures and lethality within two years but a broader phenotypic spectrum is now suggested.² All patients from the prior literature presented with neurodevelopmental impairment and intractable seizures. A prominent choreoathetoid movement disorder and hypersomnolence have been noted.⁴

Our cases of GABA-transaminase deficiency are the first recorded to survive into adolescence and adulthood. The two brothers presented with epileptic spasms at two years of age, and had a similar picture of developmental regression along with intractable epilepsy and fluctuating episodes of behavior, seizures, and movement disorder. Accelerated length, a feature observed in some patients and attributed to growth hormone promoting effects of

GABA, has not been seen uniformly including in our cases. Over the years, we observed that the seizures became less active with age. The seizures in the older sibling stabilized after 18 years but there was not much functional improvement subsequently. This could be suggestive of a pseudo-stationary or a plateau stage.

The disorder is characterized by high levels of GABA in CSF, plasma and urine.⁵ GABA-transaminase deficiency may be diagnosed through accurate determination of elevated CSF GABA and beta-alanine, with confirmation by either enzymatic quantification or molecular testing. The differential diagnosis includes SSADH deficiency, cerebral gigantism, globoid cell leukodystrophy, and Pelizaeus-Merzbacher disease.⁶ MR spectroscopy with special editing for small molecules has been shown to be a useful test in making this diagnosis.⁷ MR spectroscopy with GABA editing and CSF GABA quantification were not available in the case of this family.

GABA-transaminase deficiency is caused by homozygous or compound heterozygous mutations in the ABAT gene on chromosome 16p13 and has autosomal recessive inheritance. Table 2 presents an updated series of 7 patients of confirmed GABA transaminase deficiency with survival beyond infancy with different genetic mutations. With the advent and availability of genetic panels, we anticipate an increase in the number of reported cases.

Recently flumazenil, a benzodiazepine antagonist, was administered in one patient who showed clinical improvement in seizure control, alertness, and adventitious movements with no adverse effects over a period of 11 months.^{2, 8} However, no benefit was noted in another reported case.^{2, 9} Flumazenil, being an antagonist of the benzodiazepine binding site of the GABA_A receptor, was implemented as targeted therapy in an attempt to decrease GABAergic innervation.

In conclusion, GABA transaminase deficiency should be considered in children presenting with developmental delay, refractory seizures, movement disorder, hypersomnolence, and a fluctuating clinical picture. We anticipate more cases to be diagnosed with the use of next generation gene sequencing. Efficacy of flumazenil as targeted therapy in this disorder is yet to be determined. Our cases establish survival past childhood and a widened spectrum of phenotype and longevity.

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Figure 1.

MRI at 4 years of age. Axial T2 weighted images A and B show increased T2 signal in the subinsular region and subcortical white matter of the temporal pole (arrows). Axial T2 weighted image C shows abnormal increased T2 signal in the centrum semiovale (arrows). Coronal T2 weighted image D shows decreased undulations of the hippocampal heads (arrows) and prominent temporal horns of the lateral ventricles.

Figure 2.

MRI at 13 years of age. Axial T2 weighted images A and B show increased T2 signal in the subinsular region and subcortical white matter of the temporal pole (arrows). Axial T2 weighted image C shows abnormal increased T2 signal in the centrum semiovale (arrows). Coronal T2 weighted image D shows decreased undulations of the hippocampal heads (arrows) and prominent temporal horns of the lateral ventricles.

Table 1.

Mutation status in the proband family

	Family Member	Gene	Genomic position	Mutation status in family member	Clinical condition of family member
1	Index Case	ABAT (+)	Chr16:8875215; G>A(HOM);c.1490G>A;p.R497H	<i>Present Homozygous</i>	<i>Symptomatic</i>
2	Father	ABAT (+)	Chr16:8875215; G>A(HOM);c.1490G>A;p.R497H	Present Heterozygous	Asymptomatic
3	Mother	ABAT (+)	Chr16:8875215; G>A(HOM);c.1490G>A;p.R497H	Present Heterozygous	Asymptomatic
4	Sibling	ABAT (+)	Chr16:8875215; G>A(HOM);c.1490G>A;p.R497H	<i>Present Homozygous</i>	<i>Symptomatic</i>

Table 2.

GABA-T deficiency subjects with survival past infancy

Patients	<i>Present case 1</i>	<i>Present case 2</i>	Patient 1 ²	Patient 2 ⁷	Patient 3 ⁸	Patient 4 ⁹	Patient 5 ⁴
Age at last follow up	15 years	21 years	8 years	9 ½ years	3½ years	8 years	1½ years
Gender	Male	Male	Male	Female	Male	Male	Female
Population	Indian	Indian	Mexican	Japanese	---	---	Indian
Onset (months)	18 months	18 months	5 months	7 months	6 months	3 months	Neonate
Features	Profound neurodevelopmental impairment, Hypotonia, somnolence, epilepsy, Choreoathetosis	Profound neurodevelopmental impairment, Hypotonia, somnolence, epilepsy, Choreoathetosis	Profound neurodevelopmental impairment, Hypotonia, somnolence, epilepsy, Choreoathetosis, Failure to thrive	Profound neurodevelopmental impairment, Hypotonia, somnolence, epilepsy, Failure to thrive, Accelerated growth	Mild neurodevelopmental impairment, hypotonia, choreoathetosis, Hypersomnolence, Failure to thrive	Profound neurodevelopmental impairment, Hypotonia, somnolence	Profound neurodevelopmental impairment, Hypotonia, somnolence, Choreoathetosis, Failure to thrive
EEG	Spike and slow wave at 1.5 Hz	Multifocal spikes; Diffuse slowing	Multifocal spikes, diffuse Slowing	Slow spike-wave	Modified hypsarrhythmia	Multifocal spikes; diffuse slowing	Multifocal spikes
MRI Brain	Thinning of corpus callosum ; Decrease in bulk of grey and white matter	Not done	Dysmyelination, atrophy	Dysmyelination, atrophy	Dysmyelination, atrophy	Dysmyelination, atrophy	Dysmyelination
CSF GABA (micromolar)	NA	NA	NA	1.26 (0.04–0.12)	0.25 (0.02–0.07)	3.1 (0.8–1.4)	NA
Genetics	c.1490G>A, p.Arg497His	c.1490G>A, p.Arg497His	c.1129C.T, p.Arg377Trp	c.275G.A, p.Arg92Gln 1 c.199-?_3161?del, p.Asn67ValfsTer8	c.454C.T, p.Pro152Ser 1 c.1393G.C, p.Gly465Arg	c.631C.T, p.Leu211Phe	c.862-2A.G; c.1505T.C, p.Leu502Pro
Treatment	Valproate, Lamotrigine, Ketogenic Diet, Vigabatrin, Clobazam, Nitrazepam, Zonisamide, Topiramate, Tetrabenazine	Valproate, Lamotrigine, Tetrabenazine	Ketogenic diet, levetiracetam, lacosamide, tetrabenazine, clonazepam	BS, clonazepam, diazepam, baclofen, dantrolene, haloperidol	Flumazenil	Flumazenil	Levetiracetam, clonazepam