


Phenotyping GABA transaminase deficiency: a case description and literature review

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Abstract Gamma-aminobutyric acid transaminase (GABA-T) deficiency is an autosomal recessive disorder reported in only three unrelated families. It is caused by mutations in the *ABAT* gene, which encodes 4-aminobutyrate transaminase, an enzyme of GABA catabolism and mitochondrial nucleoside salvage. We report the case of a boy, deceased at 12 months of age, with early-onset epileptic encephalopathy, severe psychomotor retardation, hypotonia, lower-limb hyporeflexia, central hypoventilation, and rapid increase in weight and, to a lesser rate, length and head circumference. He presented signs of premature pubarche, thermal instability, and water–electrolyte imbalance. Serum total testosterone was elevated (43.3 ng/dl; normal range <16), as well as serum growth hormone (7.7 ng/ml; normal range <1). Brain magnetic resonance imaging (MRI) showed decreased myelination and generalized brain atrophy, later confirmed by post-mortem examination. *ABAT* gene sequencing was performed post-mortem, identifying a homozygous variant c.888G > T (p.Gln296His), not previously described. In vitro analysis concluded that this variant is pathogenic. The clinical features of this patient are similar to those reported so far in GABA-T deficiency. However, distinct mutations may have a different effect on enzymatic

activity, which potentially could lead to a variable clinical outcome. Clinical investigation aiming for a diagnosis should not end with the patient's death, as it may allow a more precise genetic counselling for the family.

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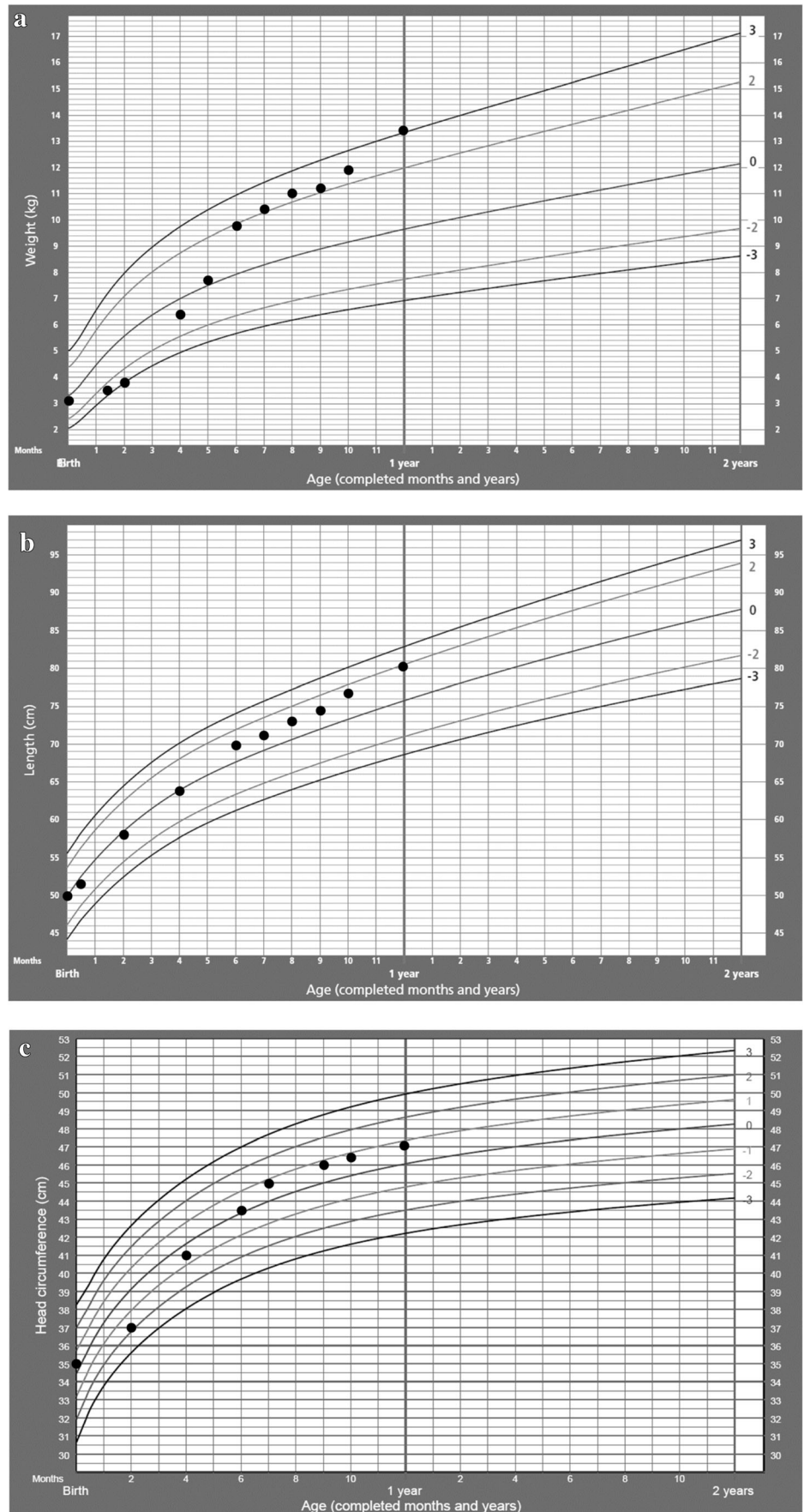
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Fig. 1 Patient's photos (note the increasingly "puffy" appearance) at 2 months (a), 5 months (b), 10 months (c), and 11 months (d) of age

Fig. 2 Patient’s weight (a), length (b), and head circumference growth (c) (growth charts reproduced with permission from World Health Organization)



Introduction

Gamma-aminobutyric acid transaminase (GABA-T) deficiency (MIM#613163) is an autosomal recessive disorder reported in only three unrelated families (Jaeken et al 1984; Tsuji et al 2010; Besse et al 2015). It is caused by mutations in the *ABAT* gene (HGNC_ID:23), which encodes 4-aminobutyrate transaminase (EC 2.6.1.19), an enzyme of GABA catabolism and mitochondrial nucleoside salvage (Besse et al 2015). GABA-T deficiency is usually characterized by elevated levels of GABA in cerebrospinal fluid (CSF), associated with severe psychomotor retardation, intractable seizures, hypotonia with hyperreflexia, accelerated height growth, and a high-pitched cry (Jaeken et al 1984; Tsuji et al 2010; Besse et al 2015).

Case report

The patient (Fig. 1) was a Portuguese male infant, born full term by caesarean delivery due to cephalopelvic disproportion. He was the first child of healthy parents. Consanguinity was denied but both parents originate from the same Portuguese region. He was admitted at the age of 3 days for generalized hypotonia since birth, progressing to encephalopathy and coma. Electroencephalography (EEG) showed a burst-suppression pattern compatible with early-onset epileptic encephalopathy. Levetiracetam was started, initially reducing the frequency of seizures, but ultimately with no effect. Until his death at the age of 12 months, he presented severe psychomotor retardation, lower-limb hyporeflexia, central hypoventilation, bilateral cryptorchidism, and a rapid increase in weight, as well as in length and head circumference, although to a lesser rate (Fig. 2). He had a general “puffy” appearance, signs of premature pubarche, thermal instability, and water–electrolyte imbalance. He needed noninvasive ventilation and tube feeding.

Serum total testosterone was elevated (43.3 ng/dl; normal range <16), as was serum growth hormone (7.7 ng/ml; normal range <1). Brain magnetic resonance imaging (MRI) showed decreased myelination and generalized cerebral, cerebellar, and brainstem atrophy, later confirmed by post-mortem examination. Diffusion-weighted images revealed bilateral hyperintense areas involving subcortical and periventricular white matter, and globus pallidus (Fig. 3). Magnetic resonance spectroscopy (MRS) showed no abnormalities. Neuropathological examination revealed soft consistency of the white matter. Microscopically, subcortical white matter is seen as a pale-stained/poorly myelinated area on the slide (Fig. 4).

The diagnosis of GABA-T deficiency was considered post-mortem. *ABAT* gene sequencing identified a homozygous variant c.888G > T (p.Gln296His), previously undescribed. MutationTaster, PolyPhen2 and SIFT predict this variant to be, respectively, “disease causing”, “probably damaging”

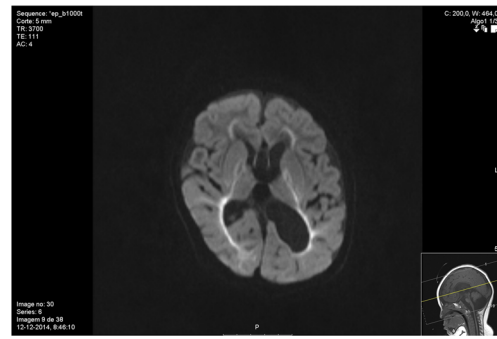


Fig. 3 Brain magnetic resonance imaging (MRI) at 12 months of age. Diffusion-weighted axial images show bilateral hyperintense areas involving subcortical and periventricular white matter, and globus pallidus

and “damaging”. In vitro analysis concluded that this variant is pathogenic (Pop et al 2015). At the time of the diagnosis, the patient’s parents had an 11-weeks’ gestation. Chorionic villus sampling was performed, and molecular analysis confirmed that the fetus was not homozygous for the pathogenic variant.

Discussion

The clinical features of this patient are similar to those reported in GABA-T deficiency cases (Table 1). Interestingly,

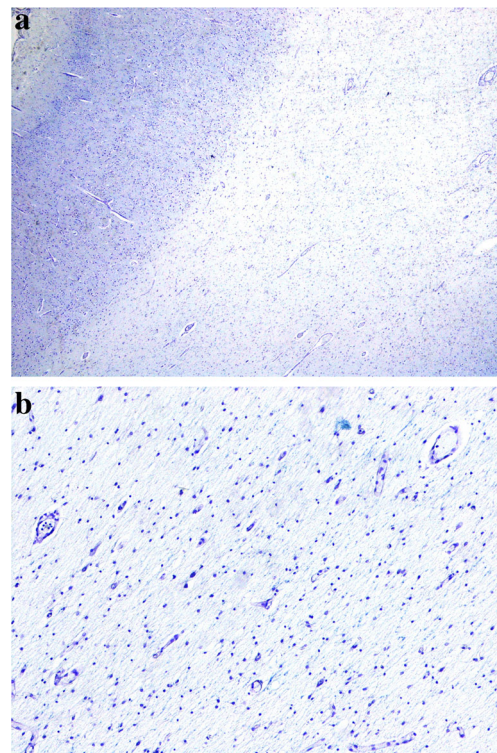


Fig. 4 Cerebral cortex and poorly myelinated subcortical white matter (Paraffin section, Klüver-Barrera staining, $\times 40$) (a). Poorly myelinated subcortical white matter (Paraffin section, Klüver-Barrera staining, $\times 200$) (b)

Table 1 Clinical features of reported patients

Main features	Patient 1 ^a Male	Patient 2 ^a (sib of patient 1) Female	Patient 3 ^b Female	Patient 4 ^c Female	Patient 5 ^c (sib of patient 4) Male	Our patient Male
Psychomotor delay	+	+	+	+	+	+
Refractory seizures	+	+	+	+	+	+
Hypotonia	+	+	+	+	+	+
Hyperreflexia	+	+	+	+	+	-
High-pitched cry	+	+	+	?	?	+
Adiposity	+	+	-	?	?	+
Accelerated length growth	+	+	+	?	?	+
CT/MRI structural anomalies	Greatly enlarged ventricles, cisternae, and cortical sulci	Greatly enlarged ventricles, cisternae, and cortical sulci	-	Generalized cerebral, cerebellar, and brainstem atrophy	Generalized atrophy of the right cerebral hemisphere	Generalized cerebral, cerebellar, and brainstem atrophy
Serum growth hormone (ng/ml)	ND	7.9–38.4 (nl <5)	8.84 (nl 0.28–1.64)	?	?	7.7 (nl <1)
CSF free GABA ($\mu\text{mol/L}$)	ND	4.8 (nl 0.04–0.12)	1.26 (nl 0.04–0.12)	?	?	ND
Lymphoblasts GABA-T (pmol/h/mg)	ND	1.2 (nl 20–58)	2 (nl 23–64)	?	?	ND
Genotype ^d	ND	c.[659G > A];[1433 T > C]	c.[275G > A];[199- ?_316 + ?del]	c.[631C > T];[c.631C > T]	c.[631C > T];[c.631C > T]	c.[888G > T];[888G > T]
Deduced effect	ND	p.[Arg220Lys];[Leu478Pro]	p.[Arg92Gln];[p.Asn67Valfs*8]	p.[Leu211Phe];[p.Leu211Phe]	p.[Leu211Phe];[p.Leu211Phe]	p.[Gln296His];[Gln296His]
Age at death	12 months	25 months	Alive at 8 years	Unknown (alive at 5 years)	Alive at 5 years	12 months
Post-mortem examination of the brain	Dilated ventricles White matter with a soft consistency	Spongy leukodystrophy	ND	?	ND	Dilated ventricles White matter with a soft consistency
	Poor myelination of gyral white matter					Generalized leukodystrophy

CT computed tomography, MRI magnetic resonance imaging, CSF cerebrospinal fluid, GABA-T gamma-aminobutyric acid transaminase, nl normal range, + present, - absent, ND not determined

^a Jaeken et al. 1984; ^b Tsuji et al. 2010; ^c Besse et al. 2015

^d Reference sequence NM_000663.3

hyperreflexia was not present in our patient. His weight gain almost overshadowed length growth. These growth alterations seem to be related with the abnormally high levels of growth hormone, while the signs of premature pubarche are likely to be related with the high testosterone levels, which may also have contributed to the patient's "puffy" appearance. High GABA levels probably contributed to this hormone imbalance (Jaeken et al 1990; Ritta et al 1998).

Certain mutations express a residual enzymatic activity (Pop et al 2015), which potentially could lead to a variable clinical outcome. However, other (epi)genetic factors could also have an effect. CSF amino acid analysis was performed but did not include free GABA measurement; when GABA-T deficiency was considered, it could not be performed due to the lack of a CSF sample. This reinforces the need for the rigorous implementation of sample collection and storing protocols, mostly in severely affected patients, during life and even at post-mortem. However, lumbar puncture is an invasive procedure, and sampling is not always easy. In our case, collected CSF volume was not enough to store.

Detection of brain GABA elevation by MRS is difficult and usually requires a technical modification (Levy and Degnan 2013), which was not considered in this patient while he was alive. GABA-T is also involved in the mitochondrial nucleoside salvage pathway. Mitochondrial DNA (mtDNA) copy number measurement was not performed in our case, but an mtDNA depletion was previously demonstrated in fibroblasts from other patients (Besse et al. 2015). Evidence of a depletion would probably have misled us to disorders with phenotypic overlap, such as the mtDNA depletion syndromes caused by mutations in *SUCLG1* and *SUCLA2* genes (Besse et al 2015). Clinical investigation aiming a diagnosis should

not end with the patient's death, as it may allow a more precise genetic counselling for the families. In our case, it allowed us to offer our patient's parents a molecular prenatal diagnosis.

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Compliance with ethical standards

Conflict of interest None.

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