Paroxysmal dyskinesias with drowsiness and thalamic lesions in GABA transaminase deficiency

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The proband (patient 1), a 25-year-old woman, was the product of normal pregnancy and delivery. Her parents were first cousins from Lebanon. She sat at 6 months and crawled at 12 months. At age 3, she was noted to have developmental delay, hypotonia, and ataxia. The following year, she had a febrile illness and suspected absence seizure. EEG showed 4–5 Hz spike and slow wave complexes and she was treated with sodium valproate. At age 6, seizure frequency increased but improved with the addition of ethosuximide. Brain MRI at age 10 revealed increased T2 signal in both thalami and upper brainstem (figure). Serum and urinary amino acids, white blood cell lysosomal enzymes, serum lactate and pyruvate, liver function, and ammonia were normal. CSF neurotransmitters, glucose, and lactate were normal, although GABA was not measured. Her condition then remained static with occasional absence seizures. At age 22, she developed paroxysmal episodes of chorea in the neck, arms, and trunk associated with drowsiness, triggered by fever or hot weather (video 1). These occurred 4–5 times a year, lasting from 1 to 10 minutes. In all episodes, she remained responsive to verbal stimuli. Prolonged interictal video EEGs showed intermittent 4–6 Hz generalized epileptiform discharges, although no motor events were recorded.

The index patient's sister (patient 2), aged 32, was diagnosed at age 2 with mild motor developmental delay and had 2 febrile illnesses with chorea and fluctuating drowsiness. Following recovery from these episodes, she had gait and limb ataxia. At age 3, she had episodes of abnormal posturing of her right limbs and head lasting 5–10 minutes, precipitated by emotional distress or physical fatigue. These episodes resolved spontaneously. Between ages 7 and 12, she had absence seizures that were controlled with sodium valproate. EEG and MRI brain findings were similar to those of her sister (figure). Both patients achieved reading and writing and attended a vocational school. Interictally, both had hypotonia, hyporeflexia, and ataxia (videos 2–3). Nerve conduction studies were normal.

Whole exome sequencing in both sisters revealed c.275G>A (p.Arg92Gln) pathogenic variants in the *ABAT* gene (supplemental material, doi.org/10.5061/dryad.d6140fj) that were confirmed as homozygous on Sanger sequencing, whereas their parents were heterozygous carriers. ^{1}H magnetic resonance spectroscopy (MRS) demonstrated elevated brain GABA levels (figure), confirming a functional consequence of their mutations (supplemental material).

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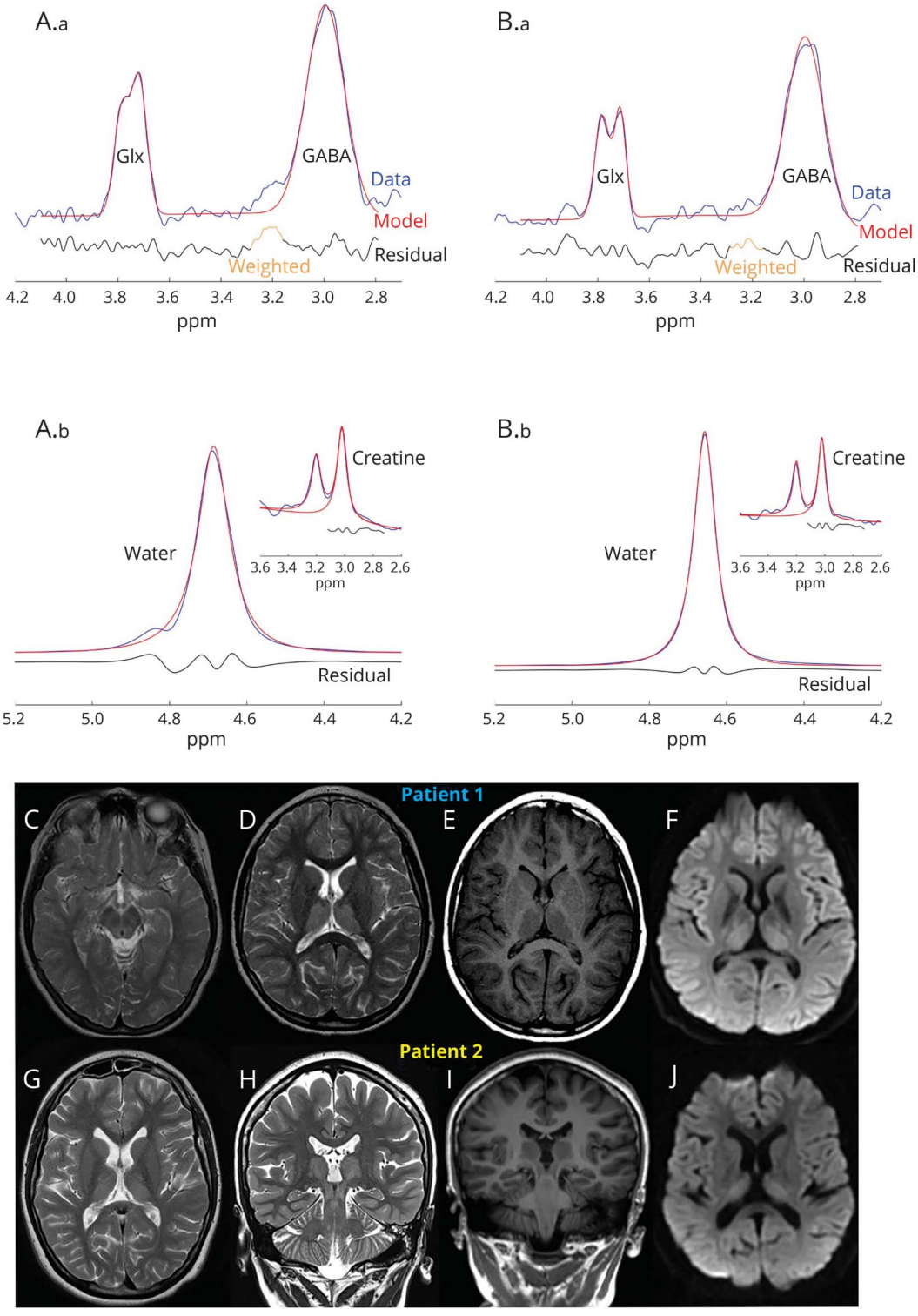
Figure [1]H magnetic resonance spectroscopy (MRS) quantification of GABA and MRI of the patients with GABA transaminase deficiency



(A.a, B.a) (Patients 1 and 2, respectively) modeled data (red), raw GABA + signal (blue), and residuals (black) exemplifying the accuracy of the GABA spectroscopy data fit. Representative water data (insert: unedited raw data at 3.0 ppm highlighting creatine and choline peaks) (A.b, B.b). The [1]H-MRS quantification of GABA (not shown in figure) showed increased levels in the thalamus (patient 1, GABA = 3.99 mM; patient 2, GABA = 4.46 mM) and occipital lobe (patient 1, GABA = 3.72 mM; patient 2, GABA = 2.79 mM) in both patients (normal range 0.5–2.0 mM). See also data supplemental material (doi.org/10.5061/dryad.d6140fj) for [1]H-MRS acquisition and analysis protocol. The MRI of patient 1 at age 10 years shows T2 sequence upper midbrain (C) and thalamic hyperintensities (D) and T1 hypointensity (E). Diffusion-weighted imaging (DWI) restriction is seen in the thalamus (F). MRI of patient 2 at age 19 years demonstrates similar findings with symmetric hyperintense signals in thalamus (G) and midbrain (H) in the T2 sequences that are also hypointense in T1 sequences (I). DWI sequences show diffusion restriction in the thalamus (J).

Discussion

Recessive mutations in the *ABAT* gene cause GABA transaminase (GABA-T) deficiency, the neurochemical hallmark of which is increased brain GABA levels.[1] Our patients have a distinctive phenotype with mild developmental delay, absence epilepsy, paroxysmal dyskinesia, and nonprogressive ataxia. To date, only 10 infants with GABA-T deficiency have been described, with the longest survivor aged 10.[1,2] Universal findings are severe epileptic encephalopathy, developmental delay, drowsiness, hypotonia, and cortical visual impairment. Secondary hypomyelination, T2 hyperintensities, or diffusion-weighted imaging restriction in the internal capsule or brainstem tegmentum are seen on MRI. The T2 thalamic hyperintensities in our patients have not previously been reported. The occurrence of paroxysmal dyskinesia with drowsiness in our patients is an unreported feature of GABA-T deficiency. Drowsiness may be a diagnostic clue as this feature is present in 90% of reported patients.[1] Three cases with an otherwise classical presentation of *ABAT* mutations have also had persistent chorea.[1] One of these cases had gradual stabilization of symptoms over a 10-year follow-up despite sustained high GABA levels.[2] Movement disorders in other conditions of GABA metabolism have been reported. Patients with succinic semialdehyde dehydrogenase deficiency develop choreoathetosis, dystonia, myoclonus, and paroxysmal dyskinesias.[3] Furthermore, patients treated with vigabatrin—a GABA-T inhibitor—rarely develop hyperkinetic movement disorders and thalamic and pallidal T2 hyperintensities.[4] Enhanced GABA neurotransmission has been implicated in absence epilepsy pathophysiology; however, how this may predispose to hyperkinetic disorders remains unknown.

Our patients were homozygous for the c.275G>A (p.Arg92Gln) variant, previously reported as pathogenic as part of a compound heterozygous state with a c.199-231del, causing a severe phenotype, although interestingly with the longest survival reported thus far in GABA-T deficiency.[5] Each of these alleles individually conferred enzymatic activity of 63% and 15%, respectively.[6] Thus the relatively milder phenotype in our patients might be attributed to higher residual enzymatic function.

The diagnosis of GABA-T deficiency has potential therapeutic implications because GABAergic medications are potentially harmful and treatment with flumazenil has been shown to improve neurologic function.[1,7] In addition to GABA levels and ^{1}H MRS,[5] 2-pyrrolidinone is a surrogate biomarker for GABA-T deficiency and can be detected in plasma and CSF.[7] Our patients show that GABA-T deficiency can cause paroxysmal dyskinesia with epilepsy and should be added to the differential diagnosis of this syndrome.

Author contributions

Dr. Morales-Briceño: study concept and design, acquisition and interpretation of data, writing first draft and final version of the manuscript. F. Chang: study concept and design, acquisition and interpretation of data, writing first draft, critical revision of final manuscript for intellectual content. Dr. Wong: study concept and design, acquisition and interpretation of data, writing first draft, critical revision of final manuscript for intellectual content. A. Mallawaarachchi: study concept and design, acquisition and interpretation of data, writing first draft, critical revision of final manuscript for intellectual content. N. Wolfe: study concept and design, acquisition and interpretation of data, writing first draft, critical revision of final manuscript for intellectual content. Dr. Pellegrino da Silva: study concept and design, acquisition and interpretation of data, writing first draft, critical revision of final manuscript for intellectual content. Dr. Hakonarson: study concept and design, acquisition and interpretation of data, writing first draft, critical revision of final manuscript for intellectual content. S.A. Sandaradura: study concept and design, interpretation of data, study supervision, critical revision of final manuscript for intellectual content. Dr. Guo: study concept and design, interpretation of data, study supervision, critical revision of final manuscript for intellectual content. Dr. Christodoulou: study concept and design, interpretation of data, study supervision, critical revision of final manuscript for intellectual content. Dr. Lagopouloss: study concept, interpretation of data, critical revision of final manuscript for intellectual content. P. Grattan-Smith: study concept, interpretation of data, critical revision of final manuscript for intellectual content. Dr. Fung: study concept and design, interpretation of data, study supervision, critical revision of final manuscript for intellectual content.

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Disclosure

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