55° CONGRESSO SOCIETÀ ITALIANA DI NEUROLOGIA

FOCAL EPILEPSY WITH SENSORY SEIZURES ASSOCIATED WITH ARGININE:GLYCINE AMIDINOTRANSFERASE DEFICIENCY: A CLINICAL AND ADVANCED MAGNETIC RESONANCE IMAGING STUDY

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BACKGROUND AND AIMS

Epilepsy has not been yet associated to pathogenic variants of the arginine:glycine amidinotransferase (AGAT) gene except for one case of febrile seizures and a single isolated seizure [1-3]. With these premises, we ask: (1) Is epilepsy part of AGAT deficiency syndrome? (2) does epilepsy in AGAT deficiency have specific electroclinical signatures? and (3) is there evidence of neurodegeneration in adults with AGAT deficiency despite creatine supplementation?

MATERIALS AND METHODS

We reviewed clinical data from our centre, identifying individuals with AGAT deficiency. Each individual underwent a dedicated epilepsy assessment with electroencephalography and 3-T brain magnetic resonance imaging (MRI). Additionally, 30 age- and sex-matched healthy controls (18 females, 28.2 ± 3.7 years old) were recruited for advanced MRI analysis. A family with four affected members carrying homozygous AGAT NM_001482.3:c.446>A (p.Trp149*) variant was identified. We used the Allen Human Brain Atlas (https://human.brain-map.org) as the primary source of AGAT expression data.

RESULTS

Cohort description

The proband is a 30-year-old woman with moderate intellectual disability. She experienced simple febrile seizures from 12 months to 12 years old. At 30 years, she was referred to our epilepsy clinic for focal seizures, starting with a brief biparietal headache, followed by left arm tingling spreading to the left hemilabial region. Seizures could progress to left hemiface clonic movements, impaired awareness, and postictal confusion. EEG showed right temporoparietal–occipital spike and wave discharges (Figure 1A). She had been on 3 g/day creatine since the age of 4 years.

The proband's 20-year-old brother began creatine therapy at four months. He did not exhibit intellectual disability. He exhibited a similar electroclinical seizure profile (Figure 1C).

The proband's 33-year-old sister had moderate intellectual disability and had been on creatine since the age of 5 years. She never experienced febrile or afebrile seizures. The proband's 24-year-old paternal nephew had mild intellectual disability and started creatine supplementation at the age of 2 years. He had multiple febrile seizures throughout childhood with an unclear age at onset. Brain 3-T MRI of three brothers was unremarkable, except for subtle dysmorphic features of the corpus callosum (Figure 1B, 1D, 1E).

Brain 3- T MRI advanced analysis

We generated three individual brain Z-score maps for the three cases with brain 3- T MRI, comparing them to 30 matched controls (Figure 2). All cases showed reduced mean cortical thickness (IV-2: Z-score = −1.60, IV-1: Z-score = −1.26, IV-3: Z-score = −1.17) and, in epilepsy cases, marked cortical surface reduction (IV-2: Z-score = −3.55, IV- 3: Z-score = −3.78). The postcentral parietal cortex was notably thinner (IV-2: Z-score = −2.69, IV-1: Z- score = −2.65, IV-3: Z-score = −2.40).

The generated three-dimensional brain map of AGAT expression levels showed an anterior–posterior gradient, indicating a lower expression in the parieto-occipital regions (Figure 2D).

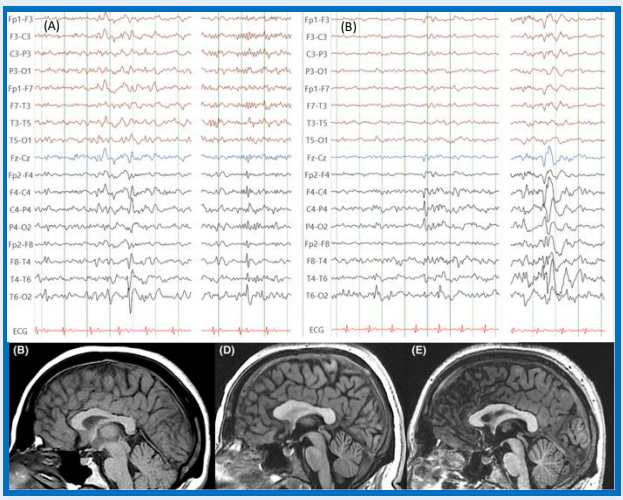

FIGURE 1. EEG and qualitative brain 3-T MRI features.
Interictal bipolar anterior–posterior EEG of the proband (A) and the proband's brother (C) showing prominent temporoparieto-occipital interictal epileptiform discharges. 3D T1-weighted midsagittal brain MRI of the proband (B), the proband's brother (D), and the proband's sister (E) showing subtle dysmorphic features of the corpus callosum.

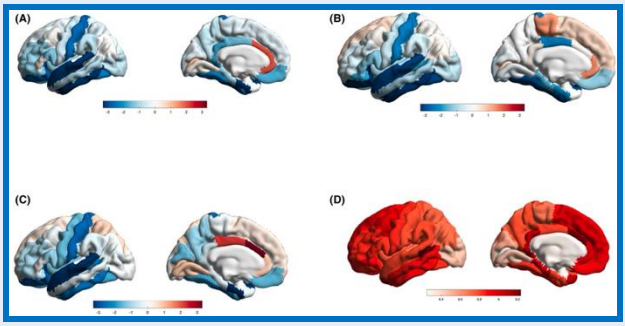

FIGURE 2. 3D brain MRI Z-score maps for the three cases with AGAT deficiency (A–C) and a 3D brain map showing mRNA AGAT expression levels.
The figures were created using MATLAB, and the Desikan–Killiany Atlas was used for all images to generate cortical regions of interest, which were averaged between the left and the right hemispheres. (A–C). Colour scales indicate Z-scores of cortical thickness lower than controls (blue scale) or higher (red scale). (D) Colour scale indicates AGAT mRNA expression levels from the Allen Human Brain Atlas. A more intense red represents higher expression.

DISCUSSION AND CONCLUSION

Our study clearly shows that focal epilepsy and temperature-related seizures may be part of the AGAT-related spectrum. Specifically, in the reported family, we found that three of the four homozygous carriers of the pathogenic variant developed febrile seizures plus and temperature sensitivity. Two of them presented with focal epilepsy with somatosensory seizure semiology with late adolescence or adulthood onset. Notably, no other plausible causes of epilepsy were identified in the affected individuals. This phenotype has strong biological plausibility, as demonstrated by the cortical thickness map (Z-scores) and the cortical levels of AGAT gene expression, which indicate a selective involvement of the postcentral parietal regions. We were able to provide potential answers to the first two research questions of this study. However, we do not claim to fully address the final question: is there evidence of neurodegeneration in adult individuals with AGAT deficiency despite creatine supplementation therapy? Of course, further studies are warranted.

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