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LETTER TO THE EDITOR

Reply: Rational therapy with vigabatrin and a ketogenic diet in a patient with GAD1 deficiency

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In their letter, von Hardenberg *et al.* (2020) describe a female infant with mild malformations and neonatal onset seizures with a burst-suppression pattern on EEG, in whom they identified a novel homozygous splice-site variant in the glutamate decarboxylase 1 gene *GAD1*. After genetic diagnosis and in the second month of life, they began a precision therapy with a combination of vigabatrin and ketogenic diet. This combination treatment not only resulted in clinical cessation of seizures within 2 days, but at 7 months of age, growth and psychomotor development were unremarkable.

The authors provide further support to our recent publication (Chatron *et al.*, 2020), in which we reported 11 patients with a syndrome caused by bi-allelic loss-of-function mutations in *GAD1*. All individuals reported in our study had an early onset developmental and epileptic encephalopathy with frequent malformations such as cleft palate and joint contractures. We welcome the identification of additional cases, which contribute to a better understanding of the phenotypic spectrum associated with *GAD1* variants. The seizure onset age and type, and the malformations of the patient reported in the study of von Hardenberg *et al.* (2020), nicely reproduce our findings. Their study also provides independent support for our suggestion of a therapeutic benefit from vigabatrin. In our report, five of seven patients who tried vigabatrin showed a remarkably good seizure response. We nevertheless cautioned that the effect of vigabatrin might be driven by seizure type, given that a response was seen particularly in patients with epileptic spasms. The patient in von Hardenberg *et al.* (2020) indeed also had predominant infantile spasms. What is more remarkable than the seizure response though, is the normal developmental trajectory of the patient. The presence of a neonatal burst-suppression pattern on EEG generally has a dire prognosis, and all families reported in our study indeed had a profound developmental delay. The authors claim that this good clinical outcome relates to the early start of the combination of ketogenic diet and vigabatrin, which was not simultaneously tried in any of the patients in our study. Both treatment strategies are thought to increase the available pool of GABA, and combined they might compensate for the severely impaired GABA synthesis. While this is certainly a reasonable hypothesis, one should be cautious drawing conclusions from one single observation. In this regard, it is interesting to read the recent published paper by Neuray *et al.* (2020), which describes an additional six cases with bi-allelic *GAD1* variants. One patient (Patient C) also appears to take a combination of ketogenic diet and vigabatrin at the age of 28 months, and still has refractory seizures and severe delay. Unfortunately, the paper does not provide a full description of seizure history and drug response, so that it is not clear at what age these respective treatments were started.

Whereas we do not agree with von Hardenberg *et al.* (2020) that there is large phenotypic variability within our families (one sibling of Family E died shortly after a

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premature birth at 29 weeks, and therefore cannot be compared to his term-born brother), there is indeed no strict genotype-phenotype correlation, as illustrated by the phenotypic variability among individuals with *GAD1* variants predicted to lead to a total loss-of-function. Von Hardenberg *et al.* rightfully refer to potential genetic modifiers. We are sorry that our presentation of results on molecular genetics and clinical evaluations may have been overlooked by the authors. Detailed results of whole exome or genome sequencing in all families are presented in the Supplementary material of Chatron *et al.* (2020). None of the families carried any other (likely) pathogenic variants, although this obviously does not exclude the possibility of less disruptive variants influencing drug response and phenotype. We indeed discussed that the phenotype may be influenced by variability in genetic backgrounds or environmental factors that might modulate movement *in utero*. Also, one should take into account that many genes, including *GAD1*, have several different transcript isoforms. Variants with a seemingly similar effect on the full transcript, might differentially affect shorter ones. Interestingly, several embryonal expressed transcripts, including the widespread and non-enzymatically active *GAD25*, do not include exon 11 (Tao *et al.*, 2018), the exon that was skipped in the patient in von Hardenberg *et al.* (2020). Further elucidation of the role of these alternative transcripts during early neurodevelopment, and concomitant description of additional patients carrying pathogenic *GAD1* variants throughout the gene, may shed further light on the full range of *GAD1* functionality.

Overall, these independent reports confirm our finding that bi-allelic *GAD1* mutations cause a developmental epileptic encephalopathy with frequent malformations. Von Hardenberg *et al.* also propose a combination of vigabatrin and ketogenic diet as a precision approach for *GAD1*-related recessive pathology. While their observation is without doubt promising, additional evidence is needed to prove that starting this combination therapy early not only targets seizures, but also improves developmental outcome.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

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