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Letter to the editor

Biallelic SZT2 mutation with early onset of focal status epilepticus: Useful diagnostic clues other than epilepsy, intellectual disability and macrocephaly

Dear Editor,

We read with great interest the paper entitled "Compound heterozygous SZT2 mutations in two siblings with early-onset epilepsy, intellectual disability and macrocephaly" by Domingues et al. [1].

SZT2 is expressed during embryonic development and tranlated in many tissues, with the highest expression in brain. The scientific interest in SZT2 protein function started in 2009, when the influence of the SZT2 gene on seizure threshold and epileptogenesis in mice was discovered [2]. After first reporting on the role of SZT2 protein in generating human epilepsy, it was demonstrated that the functional protein tunes GATOR control of mTORC1 signal [3]. At present, only 10 subjects from six different studies have been documented to carry homozygous or compound heterozygous mutations on SZT2 gene as a cause of their epilepsy, primarily expressing with early onset epileptic encephalopathy [1]. In this paper the authors propose epilepsy, intellectual disability and macrocepahly as common features suggesting SZT2 biallelic mutations. Unfortunately, information on the onset, evolution and type of epilepsy in subjects with SZT2 mutation is heterogeneous and lacks specificity, since they were frequently described just as focal epilepsy or pharmacoresistant epilepsy.

We would like to share our experience with biallelic SZT2 mutation by reporting on a ukrainian girl with severe hypotonia and psychomotor delay since the first year of life. At 30 months of age she presented with a cluster of afebrile focal clonic seizures, starting from the right cerebral hemisphere, initially treated with levetiracetam. Frequency and severity of seizures increased with a crescendo pattern and progressively evolved into a right temporal status epilepticus (SE), time-related with psychomotor regression (*See Supplement 1,2*). Established SE was successfully treated with administration of intravenous midazolam and repeated boluses of phenytoin. Levetiracetam was then switched to valproic acid, whereas intravenous phenytoin was replaced by oral administration and stopped one month later due to progressive leukopenia. From the clinical point of view, she evolved towards epileptic encephalopathy with a Lennox-Gastaut-like pattern on EEG, with atypical absences and tonic seizures during sleep. Seizure control was achieved with a combination of valproic acid, rufinamide and clobazam for almost one year. Brain MRI documented thick and short corpus callosum besides right hippocampal atrophy, probably due to the prolonged focal seizures. Next generation testing with targeted resequencing platform (Paired-End 150 bp on MiSeq) identified the SZT2 gene biallelic mutations c.3632G > A [p.Arg1211Gln] and c8435delC [p.Ser2812Leufs*41]. At last evaluation (6 years old) rare seizures (at times clustered) were reported, mostly during sleep, and neurological evaluation confirmed macrocephaly, severe axial hypotonia, global developmental delay with absent speech, in agreement with previous reports describing poor or no speech together with intellectual disability. Although no other study reported focal status epilepticus, we think that it might be a pretty specific feature because of the rarity of such an onset besides epileptic encephalopathies [1]. In our patient we recognized an evolution towards Lennox-Gastaut syndrome. The same epileptic pattern can be presumed in three subjects from the literature [1,4]. Neuroradiological features are quite heterogeneous, nevertheless dysmorphic, thick corpus callosum might be a common finding as it was present in our patient as well as in at least 5 previously described subjects [4]. We believe that our observation further supports additional specific clues to identify subjects with biallelic SZT2 mutations. We think that pursuing genotype–phenotype correlations will be a worthwhile endeavour to better understand pathophysiologic mechanisms behind seizures and to drive towards new therapeutic options.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.05.015.

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