Dear Editor,

The association between autism spectrum disorder (ASD) and epilepsy has been known for several decades. Epilepsy recurs in individuals with ASD more frequently than in the general population, although with percentages that vary greatly (2.4–46%) depending on the studies, mainly due to methodologic differences (1).

From a historical perspective, this association in the past was an important finding favoring neurobiologic theories about autism etiopathogenesis, due to the indisputable neurologic nature of epilepsy, when psychogenetic theories about autism were still very widespread in the world.

From a clinical perspective, the possible scenarios of this association are very heterogeneous. The first and most frequent scenario is represented by an individual with ASD presenting epilepsy with very heterogeneous features (with two onset peaks, respectively in early childhood and towards adolescence): focal forms prevail, often benign, with good response to antiepileptic drugs and high chances of suspending the therapy without seizure relapse. Note that epilepsy diagnosis can be complex in individuals with ASD, particularly if an intellectual disability coexists, due to the difficulties in history taking. The main factor favoring the appearance of epilepsy in these individuals is the comorbidity with an intellectual disability. Other favoring factors include cerebral lesions, comorbid rare diseases, and pre-/peri-/neonatal personal antecedents. In this scenario, seizures impact negatively on the quality of life of affected individuals and their families, but do not substantially modify ASD evolution.

Another scenario is that of a child with early onset (first months of life) epileptic encephalopathy (e.g. West syndrome), whose modern definition states that the epileptic activity itself, shown on electroencephalogram (EEG), may lead to severe impairments of cognitive development and behavior beyond what might be expected from the possible underlying pathologies (e.g. cerebral lesions), and that these impairments can worsen over time (2). In these children, psychomotor development is compromised, and an autistic-like behavior may develop. Usually seizures are drug-resistant and development prognosis is poor.

A further, rare scenario is continuous spike-waves on EEG during sleep, clinically characterized during childhood by a dramatic skill regression, limited to language (Landau-Kleffner syndrome: LKS) or may be more widespread (electrical status epilepticus during slow Sleep: ESES). Also, an autistic-like behavior may develop. Clinical seizures of heterogeneous type are inconsistently present. Based on the aforementioned definition, these are now considered as epileptic encephalopathies. Prompt treatment with corticosteroids is often effective on EEG and on the clinical picture. Considering that about 25% of children with ASD show a seemingly normal initial development and then (before 3 years) without apparent reason lose skills (autistic regression) (3), it is essential to distinguish between this skill loss, whose cause remains unknown, and the skill loss related to rare but potentially treatable conditions such as LKS or ESES, in which autistic regression results from epilepsy/epileptiform EEG activity. This strongly underlines the importance of sleep EEG in all children with autistic regression (4).

The association between ASD and epilepsy leads us to hypothesize shared neurobiologic mechanisms, as suggested by numerous genetic mutations found in ASD.
and epilepsy indicating abnormal synapse formation and function, altering the balance between excitatory and inhibitory neurons (5). Modern molecular techniques such as candidate gene panels and whole-exome sequencing could help to find the etiology of these two disorders and to understand their frequent coexistence.

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