

## ANGELMAN SYNDROME: NEED FOR FURTHER ILLUMINATION IN THE THEATER OF THE HAPPY PUPPET

### Analysis of the Characteristics of Epilepsy in 37 Patients with the Molecular Diagnosis of Angelman Syndrome

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Angelman syndrome is a genetic disorder caused by defects in the maternally inherited imprinted domain located on chromosome 15q11–q13. Most patients with Angelman syndrome have severe mental retardation, characteristic physical appearance, behavioral traits, and severe, early-onset epilepsy. We retrospectively reviewed the medical histories of 37 patients, all with the molecular diagnosis of Angelman syndrome and at least 3 years of follow-up in our neurology department, for further information about their epilepsy: age at onset, type of seizures initially and during follow-up, EEG recordings, treatments, and response. The molecular studies showed 87% deletions *de novo*; 8% uniparental, paternal disomy; and 5% imprinting defects. The median age at diagnosis was 6.5 years, with 20% having begun to manifest febrile seizures at an average age

of 1.9 years. Nearly all (95%) had epilepsy, the majority younger than 3 years (76%). The most frequent seizure types were myoclonic, atonic, generalized tonic–clonic, and atypical absences. At onset, two patients exhibited West syndrome. EEG recordings typical of Angelman syndrome were found in 68%. Normalization of EEG appeared in 12 patients after 9 years. Control of epileptic seizures improved after the age of 8.5 years. The most effective treatments were valproic acid and clonazepam. We conclude that epilepsy was present in nearly all of our cases with Angelman syndrome and that the EEG can be a useful diagnostic tool. On comparing the severity of epilepsy with the type of genetic alteration, we did not find any statistically significant correlations.

### COMMENTARY

Angelman syndrome (AS) is a genetic disorder characterized by neurodevelopmental impairment and epilepsy. The neurodevelopmental abnormalities involve cognition and behavior as well as characteristic movements and behavior that resulted in the descriptive term “happy puppet syndrome.” The most common genetic defect described has involved the *de novo* chromosomal deletion of the maternally derived 15q11–q13. This region includes genes coding for several GABA<sub>A</sub>-receptor subunits. In about 25% of AS cases, no deletion, uniparental disomy (UPD), or methylation abnormality is detectable. A functional deficit of the UBE3A gene, which encodes an ubiquitin-protein ligase and shows brain-specific imprinting, has been demonstrated. This defect, in turn, may affect functional GABA<sub>A</sub> receptors. Genotype–phenotype correlations are often problematic, and the challenge is much more daunting when the phenotype is not all that common and involves many facets.

Galván-Manso and colleagues have analyzed the characteristics of epilepsy in children with a molecular diagnosis of AS. None of these patients had demonstrated any deficit attributable to the UBE3A gene. The three most common initial seizure phenotypes were myoclonic (25%), atonic seizures (23%), and generalized tonic–clonic seizures (21%). The presenting seizure type was typical absences for 12%, and the remainder consisted of a small number with infantile spasms or partial seizures. Myoclonic and atonic seizures had an earlier onset (2.1 years on average), whereas generalized tonic–clonic seizures and atypical absences were encountered around 3.1 years of age. During follow-up, atypical absences and myoclonic seizures were each encountered in 57% of the patients. Although most patients had their seizure onset before 3 years of age, development resulted in improved seizure control and EEG background by the end of the first decade of life. High-amplitude delta activity (2–3 Hz) was commonly encountered in the EEG. The authors found valproic acid and clonazepam to be the most efficacious treatments.

How may we attempt a correlation of these clinical findings with results from the laboratory and begin to piece together the pathophysiology of this fascinating disorder? DeLorey and colleagues (1) had reported that mice lacking the  $\beta 3$  subunit of

the GABA<sub>A</sub> receptor exhibited many of the behavioral characteristics and the epilepsy phenotype of AS. Liljelund et al. (2) have extended those initial observations to include parent-of-origin and gender-related observations. Both these reports confirm response of the seizure phenotype and EEG improvement on administration of ethosuximide. Although Galván-Manso and colleagues reported valproic acid and clonazepam to be the most useful medications for patients with AS, beneficial results from high-dose ethosuximide therapy for AS indeed have been reported by Sugiura and associates (3), paralleling the observations with the mice lacking the  $\beta 3$  subunit of the GABA<sub>A</sub> receptor.

A completely satisfying correlation between clinical and laboratory findings will have to account for several important criteria. What do we know about the ontogeny of the  $\beta 3$  subunit? Are developmental as well as anatomic specifications involved in the expression of the  $\beta 3$  subunit? What role does the  $\beta 3$  subunit play in the functioning of the GABA<sub>A</sub> receptor? From a functional standpoint, some data support the notion that the functional activity of GABA<sub>A</sub> receptors is similar whether they contain a  $\beta 2$  or  $\beta 3$  subunit (4). The critical developmental switch appears to be the disappearance of the  $\beta 1$  subunit. Earlier studies of ontogeny have reported  $\beta 2/\beta 3$  subunit immunoreactivity in widespread regions and could not distinguish between  $\beta 2$  and  $\beta 3$  because of the lack of specificity of the antibody (5). Using a more-specific antibody, Miralles and co-workers (6) found that high  $\beta 3$  and low or no  $\beta 2$  in the striatum and the granule cells of the olfactory bulb and considerably higher  $\beta 3$  than  $\beta 2$  in the hippocampus of the rat. Interestingly, high  $\beta 2$  and little or no  $\beta 3$  was found in the thalamus and both isoforms were found in the cortex of these rats. The expectation that something could go awry in the thalamocortical oscillator of the  $\beta 3$ -null mice to give rise to generalized spike-waves and sensitivity to ethosuximide is not sustained in a straightforward fashion based on these regional expression studies. However, a study of subunit mRNAs demonstrated that in the early postnatal cortex and thalamus, high expression of  $\alpha 5$  and  $\beta 3$  (both coded in the same chromosomal region) was found and that the expression of these genes was substantially diminished and superseded by the genes for  $\alpha 1$  and  $\beta 2$  (7). This observation roughly parallels the finding that the seizures in AS develop postnatally but become much more manageable as the child approaches puberty. It has been suggested that GABA<sub>A</sub> receptors containing the  $\beta 3$  subunit are capable of transcytosis and, thus, may play a role in controlling the subcellular (e.g., somatodendritic, axonal) distribution of GABA<sub>A</sub> receptors and in exocytosis (8). Given the importance of GABA<sub>A</sub> transmission in early development of the central nervous system, this role of the  $\beta 3$  subunit may be one reason that the phenotype involves much more than epilepsy.

Many provocative questions remain for the clinician and the scientist. One may wonder whether a drug like zonisamide, which possesses some pharmacologic overlap with ethosuximide on low-threshold (T-type) calcium channels and efficacy in certain syndromes involving myoclonus, may prove to be useful in treating AS. Zonisamide is not licensed yet in many parts of the European Union and, thus, was not commented on by Galván-Manso and colleagues. Equally provocative is the question of whether levetiracetam may be of value in treating AS, as a newly discovered binding site for this drug involves the synaptic vesicle protein SV2A (9). SV2A-null mice have a major deficiency in GABA neurotransmission (10). Further, levetiracetam has shown efficacy against generalized spike-waves in genetic animal models (11) and human studies (12) and has been suggested as a treatment option in myoclonus (13,14). The constant exchange of insights between the bench and the bedside nourishes and sustains both enterprises. Indeed, the stimulation of such interactions is one of the important goals of *Epilepsy Currents*.

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