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Seizures in Angelman and 15q Duplication syndromes

Angelman syndrome (AS) and 15q Duplication syndrome (Dup15q) both arise from alterations of the genes in the 15q11.2-q13.3 region. AS is due to an under expression of UBE3A, through a deletion of the region, uniparental disomy, an imprinting center defect, or mutation of the gene. Those with deletions have a more severe phenotype than those with gene mutations, indicating that the loss of function of other genes in the region exacerbates the phenotype. Dup15q is due to an over expression of genes in this region – likely UBE3A, as well as others such as GABRB3.

Over expression vs under expression results in phenotypes that differ in many ways, but both syndromes cause symptoms in the same domains. For example, both syndromes cause developmental delays with abnormal social interactions – individuals with AS tend to be overly social, whereas those with Dup15q tend to have a more typical autism spectrum disorder. Both also lead to motor difficulties – those with Dup15q have more impressive hypotonia and those with AS have a movement disorder, including tremor and ataxia. Both syndromes also typically result in anxiety, GI dysfunction and disordered sleep, which can vary in terms of frequency and intensity (i.e. sleep issues are more frequent in AS).

Seizures are common in both disorders, with 80+% of those with AS and 50+% of those with Dup15q having epilepsy. The epilepsy in AS is a generalized epilepsy with generalized slow spike and wave activity on EEG, though focal spikes are also present for ~30% of those with seizures. The most common seizure types include atonic, myoclonic, atypical absence, and tonic-clonic seizures. Focal seizures can also occur, but since it is overall a generalized epilepsy, broad-spectrum anti-epileptic drugs (AED) must be used. The epilepsy in Dup15q, however, is a multi-focal epilepsy with focal and tonic-clonic seizures being common. Unlike AS, pathology has shown multiple areas of dysplastic brain, so epileptic (typically infantile) spasms are common, occurring in as many as 40% of those with Dup15q and seizures. Some of these individuals will go on to develop a secondarily generalized epilepsy syndrome consistent with Lennox-Gastaut. These seizures are typically refractory and include tonic, atonic and tonic-clonic seizures, as well as spasms. For those with spasms, ACTH/steroids tend to be much more effective than vigabatrin.