EPG5

Patient Description:
This is a 4 year old child with seizures, infantile spasms since 4 months of age, severe global delays, failure to thrive, mild dysmorphia and abnormal brain MRI with commissural agenesis, delayed myelination, and absent corpus callosum. He is repeatedly admitted to the hospital with difficult-to-control seizures.

Disease/Syndrome Features:
Vici syndrome is a rare, recessively inherited and progressive multisystem disorder caused by mutations in *EPG5* [Cullup 2013] with core features that include agenesis of the corpus callosum, bilateral cataracts, cardiomyopathy, oculocutaneous hypopigmentation, combined immunodeficiency, and severe psychomotor and developmental delay [Vici 1988, Cullup 2013]. Additional facial abnormalities in most patients include cleft lip and palate and micrognathia. Severely immunocompromised, patients suffer from recurrent respiratory infections, including bronchopneumonia, as well as chronic mucocutaneous candidiasis. Specific immunologic problems noted include decreased serum IgG, especially IgG2, decreased circulating T cells, especially CD4+ T cells, and a reduced thymic shadow on chest films [Vici 1988]. Additional neurologic complications include seizures which patients begin to experience within the first one to two years of life. Rapidly progressive microcephaly within the first year of life is common and suggests a neurodegenerative component in addition to disrupted neurodevelopmental issues [Bryne 2016]. Muscle biopsies from affected individuals show several features of myopathy including variability in muscle fiber size, prominent central nuclei, glycogen accumulation, duplication of the basal lamina, and mitochondria with abnormal shape and distribution. Most patients reported in the literature die before age three [Cullup 2013, Zhao 2013]. The most important prognostic indicators are the amount of cardiac involvement and degree of immunodeficiency. Vici syndrome is very rare and the incidence is unknown. To date there are only around 50 published cases worldwide since its original description in 1988, though it is likely under-diagnosed [Byrne 2016].

Protein/Pathway:
Vici syndrome is due to recessive mutations in *EPG5* on chromosome 18q12.3, which encodes ectopic P granules protein 5 (EPG5), a protein involved with the regulation of autophagy in higher organisms [Bryne 2016]. Autophagy is a highly conserved cellular pathway that degrades cytosolic components and plays critical roles in numerous processes including embryonic development, the maintenance of post-mitotic cell types, adaptation to starvation and stress, and the removal of pathogens and protein aggregates. Broadly, autophagy proceeds along several steps beginning with the formation of an isolation membrane which elongates and closes to form a double-layered autophagosome around its cargo. Ultimately, this autophagosome fuses with one or more lysosomes to form an autolysosome in which targeted components are broken down. While highly conserved and heavily studied in yeast, a screen of the *C. elegans* genome identified several metazoan-specific autophagy genes including *epg5*, an ortholog of the human gene that was subsequently found to be mutated in most cases of Vici syndrome [Tian 2010].

Nematodes with mutations in *epg5* accumulated products that are typically degraded by autophagy during embryogenesis including PGL granules, SEPA-1 aggregates, and the SEPA-1 family members C35E7.6, and ZK1053.4. Additionally, mammalian cells were shown to have deficits in both basal and starvation-induced autophagy following siRNA knockdown of *EPG5*. Further investigation revealed a specific deficit in late stages of autophagy as knockdown cells accumulated LC3- and LAMP1-positive autolysosomes but were unable to degrade their contents [Tian 2010]. In fibroblasts derived from patients with Vici syndrome, a slightly different late defect was reported. Here, LC3-positive puncta again accumulated but failed to colocalize with LAMP1, which the authors interpreted as a failure of lysosome fusion [Cullup 2013].

Epg5 knockout mice reproduce some of the hallmark features of Vici syndrome. Compared to controls, mutant mice have significantly thinner corpus callosa, muscle atrophy and variations in fiber size, and accumulations of enlarged mitochondria in muscle biopsy. Investigators failed, however, to observe many of the other clinical phenotypes associated with Vici syndrome, including facial dysmorphism, cataract, hypopigmentation, and immunodeficiency [Zhao, Y.G. 2013]. Interestingly, the *Epg5* knockout mice replicate key features of amyotrophic lateral sclerosis (ALS). These include muscle denervation and atrophy, progressive paralysis, and reduced survival. Additionally, mutant mice showed a selective reduction in spinal cord motor neurons and pyramidal neurons of the hippocampus and layer 5 cerebral cortex [Zhao, H 2013].

Publications:

Byrne S, Dionisi-Vici C, Smith L, Gautel M, Jungbluth H (2016). Vici syndrome: a review. *Orphanet Journal of Rare Diseases*, 11:21

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Dionisi Vici, C., Sabetta, G., Gambarara, M., Vigevano, F., Bertini, E., Boldrini, R., … Fiorilli, M. (1988). Agenesis of the Corpus Callosum, Combined Immunodeficiency, Bilateral Cataract, and Hypopigmentation in Two Brothers. *American Journal of Medical Genetics*, *29*, 1–8. Retrieved from https://onlinelibrary-wiley-com.elibrary.einstein.yu.edu/doi/pdf/10.1002/ajmg.1320290102

Tian, Y., Li, Z., Hu, W., Ren, H., Tian, E., Zhao, Y., … Zhang, H. (2010). C. elegans Screen Identifies Autophagy Genes Specific to Multicellular Organisms. *Cell*, *141*(6), 1042–1055. https://doi.org/10.1016/J.CELL.2010.04.034

Zhao, H., Zhao, Y. G., Wang, X., Xu, L., Miao, L., Feng, D., … Zhang, H. (2013). Mice deficient in Epg5 exhibit selective neuronal vulnerability to degeneration. *The Journal of Cell Biology*, *200*(6), 731–741. https://doi.org/10.1083/jcb.201211014

Zhao, Y. G., Zhao, H., Sun, H., & Zhang, H. (2013). Role of Epg5 in selective neurodegeneration and Vici syndrome. *Autophagy*, *9*(8), 1258–1262. https://doi.org/10.4161/auto.24856

Support Groups and Information:

Facebook: Vici Syndrome Family Support Group, private group that serves to connect and support those affected by Vici syndrome, >100 members

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