Zellweger spectrum disorder in California’s Central Valley: evidence of a founder effect in Mixteco patients affected with a novel PEX6 mutation

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Background
Zellweger spectrum disorders (ZSD) are a group of autosomal recessive disorders caused by mutations in the PEX genes essential for peroxisomal biogenesis. Affected patients have defective lipid metabolism and cell detoxification, resulting in hypotonia, neurologic deficits, congenital malformations, adrenocortical dysfunction, and liver disease. Although variable mutations in the PEX1 and PEX6 genes are most commonly seen, previous studies have shown increased prevalence of specific mutations in distinct regions of the world.1, 2, 4, 5, 6, 7 and founder mutations in these populations have been reported.

Valley Children’s Hospital (VCH), located in California’s Central Valley, cares for a relatively larger Mixteco population compared to other parts of the United States. Many of these families have emigrated from the southern Mexico states of Oaxaca, Guerrero, and Puebla. We have observed an increased frequency of ZSD at our center over the past few years in patients of Mixteco ethnicity. This study reports the spectrum of clinical and genotypic features of ZSD patients at our institution.

Objective
To characterize the genotype, phenotype, and biochemical features of patients diagnosed with Zellweger spectrum disorder, particularly those with PEX6 mutations, and identify any similarities or specific genotype-phenotype correlations seen among ZSD patients at Valley Children’s Hospital.

Methods
We performed a retrospective chart review by searching for ZSD patients seen at our center between 2010 and 2020. Patients with an alternative diagnosis were excluded. Demographic data collected included age of presentation, sex, ethnicity, laboratory parameters, gene sequencing, newborn screening, imaging, and subspecialty notes.

Results
Seven patients with ZSD were identified, all diagnosed over the past four years, presenting at birth with generalized hypotonia and facial dysmorphism with large anterior fontanelles. Two had poor visual response to light, three had lagophthalmos, and four had failed hearing tests. Four patients are now deceased and three died prior to one year of age. Although two were lost to follow-up, they both presented with severe symptoms including worsening hypotonia and poor feeding by three months of age. One patient is currently alive at 10 months of age. Biochemical testing demonstrated characteristic elevations of very long chain fatty acids. Six patients were found to be homozygous for the PEX6 novel variant c.1409G>C (p.Gly470Ala) and one was homozygous for PEX6 c.2095del and was the only patient with parental consanguinity. The patient’s ethnicity is unknown.

Discussion
This over-representation of the novel PEX6 variant affecting ZSD patients of Mixteco ethnicity suggests a founder mutation within this patient population. Further studies analyzing single nucleotide polymorphisms in these patients could provide stronger evidence to support this hypothesis. It would also be worthwhile to collaborate with other children’s hospitals in the southern California region in efforts to identify additional patients.

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