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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IS NOT ASSOCIATED WITH MUTATIONS IN AQUAPORIN-4

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Posterior reversible encephalopathy syndrome (PRES) is characterized by acute reversible subcortical vasogenic edema that is typically bilateral and self-limiting. It preferentially affects posterior regions of the brain. Clinical manifestations include encephalopathy, seizures, headache, and cortical blindness. PRES may be precipitated by hypertensive crises such as eclampsia and by immunosuppressive agents. The pathophysiology of PRES is incompletely understood. Disordered cerebral autoregulation leading to protein and fluid extravasation is thought to be important.[1] Other theories implicate endothelial dysfunction or vasospasm.[2]

Aquaporin-4 (AQP4) is the most abundant water channel in the CNS. AQP4-null mice are less susceptible to cytotoxic cerebral edema following brain insults and have improved neurologic outcome after focal cerebral ischemia and bacterial meningitis compared with wild-type mice. However, brain swelling and clinical outcome are worse in AQP4-null mice after insults producing vasogenic edema, probably due to impaired AQP4-dependent brain water clearance.[3]

Four *AQP4* single nucleotide polymorphisms (SNPs) found in healthy humans have been linked with reduced water permeability.[4] We have reported an association between PRES and neuromyelitis optica, a disease characterized by autoimmunity against AQP4 that ultimately results in reduced immunoreactivity for this channel protein and reduced water transport.[5] Here we investigate whether mutations in *AQP4* are present in patients who had PRES and did not have neuromyelitis optica.

Methods. All patients had given written informed consent. Patients with a diagnosis of PRES were identified during admission to Saint Mary's Hospital, Mayo Clinic, Rochester, MN, from October 1, 2005, through April 30, 2009. Three criteria were required for inclusion: (1) clinical history of acute neurologic change, including headache, encephalopathy, seizure, visual disturbance, or focal deficit; (2) brain imaging findings of focal vasogenic edema; and (3) clinical or radiologic proof of reversibility. Patient records were assessed for demographic data, clinical presentation, comorbid and predisposing conditions, PRES recurrence, and family history. Patients with neuromyelitis optica who had similar comprehensive sequencing of *AQP4* but did not have an episode of PRES served as controls, and they were matched to patients with PRES based on ethnicity.[6]

DNA was obtained from blood samples. The human *AQP4* gene maps to 18q11.2—q12.1 and is encoded by 5 exons. We sequenced *AQP4* in both downstream and upstream orientations after amplification of genomic DNA in 4 fragments that included 1,000 base pairs upstream of the exon 0, exons 0–4, 5′ and 3′ untranslated regions, and splice consensus sequences flanking the exons. Chromatograms were analyzed using mutation detection software (Mutation Surveyor V3.12, Softgenetics, State College, PA).

Results. DNA was isolated from 23 patients, 14 of whom were women (60.9%). The median age at PRES onset was 52.5 years (range 25–78 years). Eight-seven percent (n = 20) of the patients were white, 1 was Asian, and 2 did not disclose their ethnicity. No patients had a family history of PRES.

One patient (4.3%) had recurrent PRES 15 months after her initial episode. Most patients (78.2%, n = 18) experienced the characteristic manifestations of PRES, including headache, mental status changes, seizure, cortical blindness, visual hallucinations, and focal motor, sensory, or coordination deficits in various combinations. Atypical presentations were status epilepticus in 2 cases, coma in 2, and isolated confusion in 1. Precipitating factors for PRES included hypertension (n = 11, 47.8%), renal failure (n = 5, 21.7%), cytotoxic medications (n = 4, 17.4%), and sepsis (n = 3, 13%).

We did not find any novel coding mutations in patients with PRES, nor did we identify variants previously reported to be associated with impairment of water transport. Sixteen previously reported SNPs (National Center for Biotechnology Information) were polymorphic in patients with PRES (table). The minor allele frequencies of these SNPs were similar to those detected in matched controls.

Discussion. In this comprehensive genomic sequencing study of *AQP4* in a cohort of patients with PRES, we found no evidence for the association of genetic

Table Minor allele frequencies of SNPs in patients with PRES and control subjects

SNP rs; alleles	MAF in PRES	MAF in controls	MAF (Genbank)	*p*
rs162006 G/A	0.2	0.145	0.194	0.80
rs2075575 C/T	0.375	0.364	0.260	0.86
rs56282359-/AAA	0.35	0.406	0.452	0.84
rs162007 C/T	0.2	0.177	0.207	0.92
rs162008 G/A	0.2	0.177	0.206	0.92
rs35248760 G/T	0.071	0.138	0.044	0.66
rs72557968 G/A	0.023	0.020	0.031	0.42
rs61731042 T/A or T/G	0	0.01	0.003	0.29
rs1839318 G/A	0.023	0	0.041	0.68
rs9807747 T/C	0	0	0.012	—
rs3763043 G/A	0.261	0.316	0.318	0.84
rs335929 T/G	0.227	0.153	0.201	0.65
rs1058424 T/A	0.125	0.204	0.229	0.62
rs14393 C/A	0.325	0.260	0.292	0.76
rs1058427 C/A	0.125	0.163	0.044	0.94
rs11557239 G/T	0	0.02	NA	0.68
rs61327137 C/T	0.025	0	0.050	0.68
rs7240333 C/T	0.125	0.061	0.057	0.63

Abbreviations: MAF = minor allele frequency; NA = not available; PRES = posterior reversible encephalopathy syndrome; SNP = single nucleotide polymorphism.
p Values calculated based on the comparison of cases and controls (comparison of 2 proportions from independent samples).

variation of *AQP4* with susceptibility to PRES, allowing for the power of this study. We did not detect novel allelic mutations that could disrupt the water transport properties of AQP4.

Four rare coding SNPs (I128T, D184E, I205L, and M224T) were previously reported[4] to alter water permeability by 26%–48% compared with the wild-type AQP4 in cellular assays. These variants had been detected in otherwise healthy individuals and were not found in the patients we studied. It is unclear whether they might be susceptibility factors for PRES.

Recently it was noted that a high percentage of patients with PRES have autoimmune disorders,[7] and it was suggested that PRES may be associated with inflammatory endothelial dysfunction. We have previously tested 17 patients with PRES for anti-AQP4 antibodies; none was positive.[5]

Study limitations include small sample size and limited evaluation of nonwhite patients; we did not assess copy number variations. Based on our sample, *AQP4* genomic variations affecting protein structure or expression are unlikely to be major contributors to the development of typical PRES.

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