# Disputes & Debates: Editors' Choice



## Editors' Note: Teaching NeuroImage: Partially Reversible Widespread Leukoencephalopathy Associated With Atypical Hemolytic Uremic Syndrome

In "Teaching NeuroImage: Partially Reversible Widespread Leukoencephalopathy Associated With Atypical Hemolytic Uremic Syndrome," Cani et al. presented a patient with altered mental status and leukoencephalopathy in the setting of hemolytic uremic syndrome, which improved after treatment with eculizumab and dialysis. Although genetic testing was unremarkable, the authors suspected a genetic etiology because the patient's brother had a history of anemia and renal failure. Dr. Graber asked whether testing was performed for a *TREX1* mutation, noting this can cause retinal vasculopathy with cerebral leukoencephalopathy (RVCL), which can present as episodic renal failure and leukoencephalopathy that is partially reversed by immunosuppressants. Foschi et al. responded on behalf of the authors that *TREX1* analysis was not included in the genetic panel, but that they felt RVCL was unlikely, given the response to eculizumab (leukoencephalopathy associated with a *TREX1* mutation is understood to be independent of complement, so would not be expected to improve with anticomplement treatment). In addition, the patient did not have other episodes of leukoencephalopathy in the 14 months after treatment and was able to stop dialysis. However, they agreed that it is appropriate to consider *TREX1* analysis in patients with leukoencephalopathy and small vessel kidney disease and emphasized the need for neurologists to collaborate with nephrologists to diagnose and treat patients with this type of presentation.

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## Reader Response: Teaching NeuroImage: Partially Reversible Widespread Leukoencephalopathy Associated With Atypical Hemolytic Uremic Syndrome

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I read the Teaching NeuroImage by Cani et al. with great interest.[1] I wonder whether the genetic testing assessed for *TREX1* mutations that cause retinal vasculopathy with cerebral leukoencephalopathy can cause similar familial renal and cerebral manifestations to those reported in this case. The episodes are partially reversible with steroids and other immune suppressants. In some cases, punctate calcifications are present in bilateral frontal white matter changes.

1. Cani I, Righini M, Cenni P, Foschi M. Teaching NeuroImage: Partially reversible widespread leukoencephalopathy associated with atypical hemolytic uremic syndrome. *Neurology*. 2022;99(24):1128-1129. doi:10.1212/WNL.0000000000201378



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# Author Response: Teaching NeuroImage: Partially Reversible Widespread Leukoencephalopathy Associated With Atypical Hemolytic Uremic Syndrome

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We greatly appreciated the comment by Dr. Graber on our case.[1] To date, kidney involvement associated with *TREX1* sequence variations has been sparsely reported in the context of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S). Specifically, different subtypes of kidney involvement have been described in RVCL-S, including thrombotic microangiopathy (TMA) and glomerulosclerosis.[2-4]

As for our case, unfortunately, *TREX1* analysis was not included in the genetic panel. However, a diagnosis of RVCL-S was unlikely, given the optimal response to eculizumab. Indeed, *TREX1*-related TMA and leukoencephalopathy have been suggested to be driven by dysregulated type-1 interferon pathways.[5] Therefore, the pathophysiologic association between *TREX1* sequence variations and endothelial damage is supposed to be independent of complement and should not improve after anticomplement treatment. In addition, after 14 months from onset, no other episodes of leukoencephalopathy occurred in our patient, and she was totally weaned from hemodialysis.

To sum up, even if in our case RVCL-S was a remote possibility, we agree with Dr. Graber's suggestion to consider *TREX-1* analysis in patients presenting with acute leukoencephalopathy and small vessel kidney disease. Close collaboration between neurologists and nephrologists remains the key point to promptly recognize such a critical condition.

1. Cani I, Righini M, Cenni P, Foschi M. Teaching NeuroImage: Partially reversible widespread leukoencephalopathy associated with atypical hemolytic uremic syndrome. *Neurology*. 2022;99(24):1128-1129. doi:10.1212/WNL.0000000000201378
2. Gulati A, Bale AE, Dykas DJ, et al. TREX1 mutation causing autosomal dominant thrombotic microangiopathy and CKD - a novel presentation. *Am J Kidney Dis*. 2018;72(6):895-899. doi:10.1053/j.ajkd.2018.05.006
3. De Boer I, Van den Maagdenberg AMJM, Terwindt GM. TREX1 mutation causing autosomal dominant thrombotic microangiopathy and CKD Is in fact a case of RVCL-S presenting with renal features. *Am J Kidney Dis*. 2019;73(6):893. doi:10.1053/j.ajkd.2018.12.041
4. Vodopivec I, Oakley DH, Perugino CA, Venna N, Hedley-Whyte ET, Stone JH. A 44-year-old man with eye, kidney, and brain dysfunction. *Ann Neurol*. 2016;79(4):507-519. doi:10.1002/ana.24583
5. Schuh E, Ertl-Wagner B, Lohse P, et al. Multiple sclerosis-like lesions and type I interferon signature in a patient with RVCL. *Neurol Neuroimmunol Neuroinflamm*. 2014;2(1):e55. doi:10.1212/nxi.0000000000000055





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