

Elisabeth Schuh, MD
Birgit Ertl-Wagner, MD
Peter Lohse, MD
Waltraud Wolf, MD
Johannes F. Mann, MD
Min Ae Lee-Kirsch, MD
Reinhard Hohlfeld, MD
Tania Kümpfel, MD

*Neurol Neuroimmunol
Neuroinflamm*
2015;2:e55; doi: 10.1212/
NXI.000000000000055

MULTIPLE SCLEROSIS-LIKE LESIONS AND TYPE I INTERFERON SIGNATURE IN A PATIENT WITH RVCL

OPEN

Retinal vasculopathy with cerebral leukodystrophy (RVCL) is a rare late-onset autosomal dominant systemic microvascular disease due to C-terminal truncation mutations in the three prime repair exonuclease 1 gene, *TREX1*.¹ Patients present with varying degrees of progressive bilateral vision loss, renal impairment, and neurologic symptoms. Cerebral MRI shows either confluent tumorlike signal alterations or multiple small white matter lesions.^{2,3} Herein we demonstrate a case of RVCL caused by a novel *TREX1* mutation with distinct lesions on cerebral MRI and type I interferon (IFN) activation.

Level of evidence. This case report provides Class IV evidence that chloroquine did not prevent progression in a patient with RVCL caused by a novel *TREX1* mutation.

Case report. In 2012, a 39-year-old Caucasian man presented to us with the presumed diagnosis of multiple sclerosis (MS) based on multiple white matter lesions on cerebral MRI with partial rim enhancement after administration of gadolinium (Gd) (figure, A and B). Clinically he had mild weakness and hypesthesia of the left arm and face accompanied by mild pulsating headache. CSF examination including oligoclonal bands was normal. Further laboratory investigations revealed normocytic anemia, antinuclear antibodies (1:200), and anti-C1q autoantibodies. High-dose glucocorticoids (GC) improved clinical symptoms but had no effect on Gd enhancement of the cerebral lesions.

His medical history was remarkable for arterial hypertension and proteinuria since the age of 30 years. A renal biopsy demonstrated a thickening of the glomerular basement membrane but no evidence of vasculitis. Subsequently he developed retinal microangiopathy with progressive loss of visual acuity (75%) in the left eye (figure, F). He experienced intermittent episodes of arthralgia and mild pulsating headache for several years. Renal as well as retinal and neurologic abnormalities were regarded as unrelated diseases.

His mother had meningioma and Parkinson disease, while his father died of pleural mesothelioma

at the age of 69 without clinical evidence of RVCL. His younger brother died in early childhood from an unknown brain tumor.

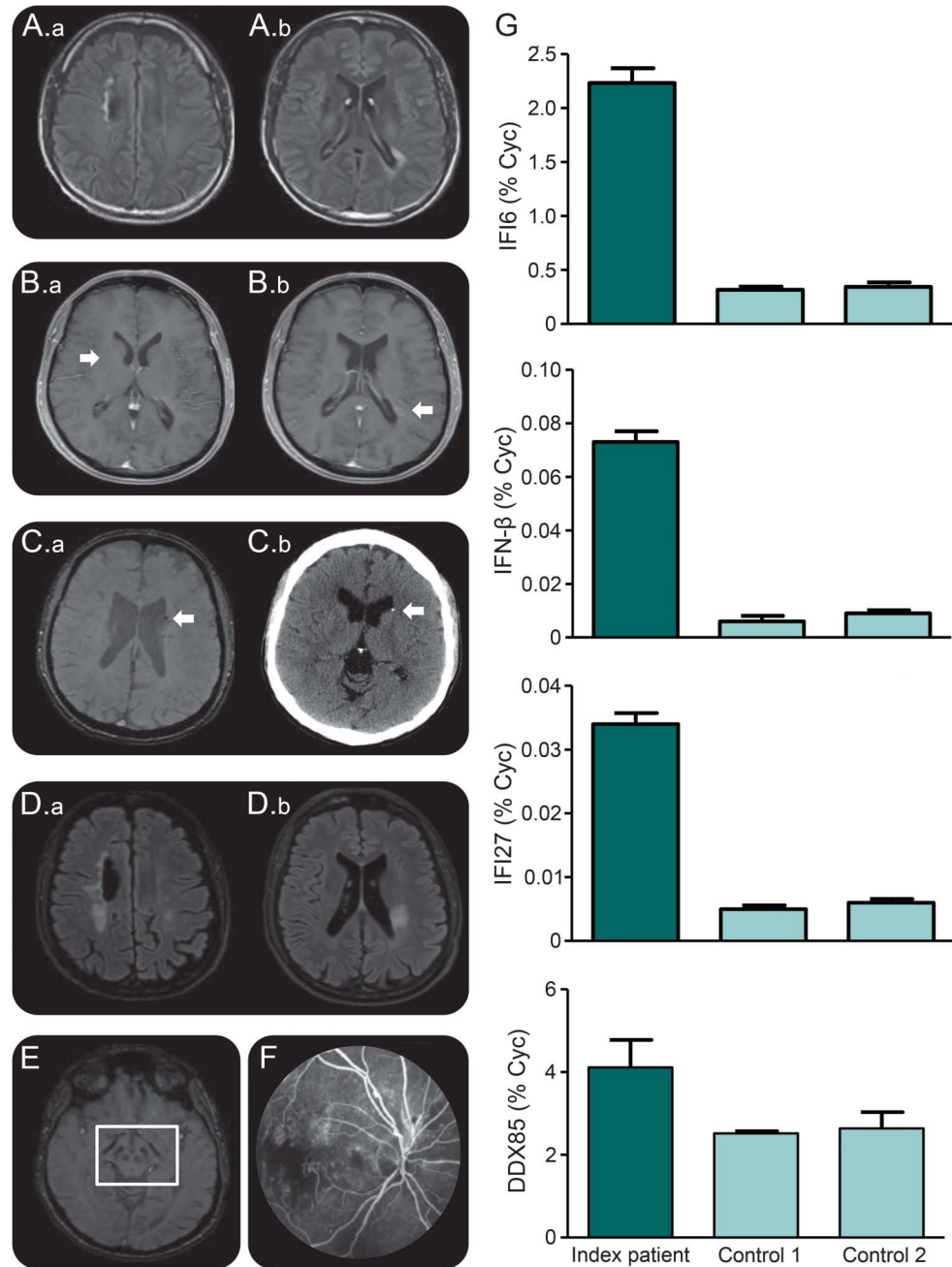
Prompted by the clinical phenotype with the involvement of microvessels in the brain, retina, and kidney, we presumed a hereditary endotheliopathy. Genetic testing of the *TREX1* gene on chromosome 3p21.31 identified a heterozygous novel T deletion (c.822delT) leading to a shift of the reading frame and premature termination of protein translation at amino acid 275 (p.Pro275Glnfs*2), thus confirming the clinical diagnosis of RVCL. The patient's mother tested negative for the respective mutation. Furthermore, despite the absence of increased IFN- α in serum, we identified an upregulation of type I IFN-inducible genes by quantitative reverse transcription PCR of peripheral blood mononuclear cells consistent with innate immune activation (figure, G and supplemental data). Due to its known inhibitory IFN- α effects, therapy with chloroquine was started; however, the patient progressed clinically and on MRI.

Discussion. This case expands the phenotypic spectrum of patients with *TREX1* mutations. Cerebral MRI abnormalities in RVCL can be misdiagnosed as MS, Binswanger disease, CADASIL, multi-infarct dementia, systemic lupus erythematosus (SLE) with vasculitis, and brain tumor.^{2,3} In our patient, MS was initially suggested by the presence of periventricular white matter lesions with partial Gd enhancement, which demonstrated dissemination in time and space on follow-up MRI (figure, D). However, additional detailed MRI analysis revealed features unusual for MS-related imaging patterns: (1) Gd enhancement was patchy and did not respond to GC; (2) small focal signal hypointensities on MRI and CT hyperattenuations were noted in the lesions, indicating calcifications (figure, C); and (3) there was evidence of increased iron depositions in the substantia nigra and nucleus ruber, which might be a distinct feature of RVCL (figure E).

In RVCL, *TREX1* mutations alter the perinuclear localization of the *TREX1* protein while the exonuclease activity remains intact, indicating a critical functional role of the subcellular localization of *TREX1*.¹ It is interesting that C-terminal truncating *TREX1* mutations have also been described in

Supplemental data
at Neurology.org/nn

Figure MRIs, fluorescence angiography, and measurements of IFN- α -inducible genes in the patient carrying a novel mutation in the TREX1 gene



Initial cerebral MRI demonstrated focal patchy lesions in the subependymal areas of the frontal white matter and in the peritrigonal regions with a signal hyperintensity on T2-weighted and fluid-attenuated inversion recovery sequences (A.a and A.b) and with a partial rim enhancement of the lesions after IV gadolinium administration (B.a and B.b). On T2*-weighted gradient echo sequences and susceptibility-weighted imaging (SWI), focal small signal hypointensities were noted in the areas of the lesions (C.a), which corresponded to areas of hyperattenuation on CT (C.b) and most likely represent areas of calcification. A follow-up examination 5 months later showed dissemination in time and space by new partially confluent T2 lesions (D.a and D.b). (E) The substantia nigra and nucleus ruber demonstrated a markedly decreased signal in T2*-weighted and SWI sequences, which potentially corresponds to increased iron depositions. (F) Fluorescence angiography of the right eye showed typical cotton-wool spots, focal leakage, and telangiectasias. (G) Upregulation of type I IFN-dependent genes, including the IFN- α -inducible protein 6 (*IFI6*) gene, the interferon- β (*IFN- β*) gene, the interferon- α -inducible protein 27 (*IFI27*) gene, and the DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 (*DDX58*) gene, compared to the 2 housekeeping genes cyclophilin (% Cyc) and glyceraldehyde-3-phosphate dehydrogenase (% GAPDH) (data not shown) in peripheral blood mononuclear cells of the index patient in comparison with 2 healthy controls (control 1 and 2). Shown is one representative experiment run in triplicates. The error bars indicate SD.

patients with SLE.⁴ Mutations that disrupt the enzymatic exonuclease function of the *TREX1* protein may cause familial chilblain lupus or Aicardi-Goutières syndrome (AGS), a leukoencephalopathy with elevated IFN- α levels in the CSF and characteristic calcifications on cerebral MRI beginning in early childhood.⁵ Both disorders are characterized by signs of inflammation and autoimmunity.

Recently, a distinct type I IFN signature in the blood of patients with mutation-proven AGS and chilblain lupus has been described, identifying type I IFN as a key factor in the pathogenesis of the inflammatory phenotype.^{6,7} The observed upregulation of type I IFN-dependent genes, the formation of autoantibodies, and the history of intermittent arthralgia suggest an overlapping autoimmune component in our patient, which has not been reported so far for RVCL. Whether the type I IFN signature is a distinct feature of RVCL has to be further investigated. However, these findings suggest that patients with RVCL may therapeutically benefit from IFN- α blockade.

From the Institute of Clinical Neuroimmunology (E.S., R.H., T.K.) and Institute of Clinical Radiology (B.E.-W.), Ludwig-Maximilians University, Munich, Germany; Department of Neuroimmunology (E.S.), Center of Brain Research, Vienna, Austria; Institute of Laboratory Medicine and Human Genetics (P.L.), Singen, Germany; Department of Ophthalmology (W.W.), Outpatient Clinic Neubann, Munich, Germany; Department of Nephrology (J.F.M.), Clinical Centre Schwabing, Munich, Germany; Department of Pediatrics (M.A.L.-K.), Technische Universität Dresden, Germany; and Munich Cluster for Systems Neurology (SyNergy) (R.H.), Munich, Germany.

Author contributions: E.S.: performed experiments, was involved in patient care and evaluation, analysis and interpretation of the data, manuscript writing and editing. B.E.-W.: acquisition and interpretation of MRI data, manuscript writing and editing. P.L.: molecular genetic testing, manuscript writing and editing. W.W.: patient care and contribution to clinical data. J.F.M.: patient care and contribution to clinical data. M.A.L.-K.: contribution to the analysis and interpretation of PCR data. R.H.: supervision of patient care, manuscript writing and editing. T.K.: patient care and evaluation, analysis and interpretation of data, manuscript writing and editing. All authors discussed results and commented on the manuscript.

Disclosure: E. Schub received travel expenses from Novartis. B. Ertl-Wagner is on the scientific advisory boards for Phillips, Bracco, and Springer Medical Publisher; has received travel funding or speaker honoraria from Siemens, Philips, Bracco, and Bayer-Schering; is an associate international editor for Journal of the American College of Radiology; receives royalties from Springer Medical Publisher and Thieme Medical Publisher; has consulted for Munich Medical International and Philips

Healthcare; and received research support from Guerbet, Eli Lilly, Merck-Serono, Novartis, and Bayer-Schering. P. Lohse reports no disclosures. W. Wolf has received travel funding from Bayer AG. J.F. Mann and M.A. Lee-Kirsch report no disclosures. R. Hohlfeld has served on the scientific advisory board for Novartis, Biogen-Idec, Bayer-Schering, Merck-Serono, Sanofi-Aventis, and Teva; has served on the data safety monitoring board for Novartis, Merck-Serono, and CSL Behring; has received travel funding from Novartis, Biogen-Idec, Bayer-Schering, Merck-Serono, Sanofi-Aventis, Teva, and Genzyme; has consulted for Novartis, Biogen-Idec, Bayer-Schering, Merck-Serono, Sanofi-Aventis, Teva, and Genzyme; and received grant support from Novartis, Biogen-Idec, Bayer-Schering, and Teva. T. Kümpfel has received travel funding and/or speaker honoraria from Bayer-Schering Pharma, Teva, Merck-Serono, Genzyme, Novartis Pharma, and Biogen-Idec and research support from Novartis Pharma. Go to Neurology.org/nn for full disclosures. The Article Processing Charge was paid by the Institute of Clinical Neuroimmunology, Ludwig-Maximilians University, Munich, Germany.

This is an open access article distributed under the terms of the Creative Commons Attribution-Noncommercial No Derivative 3.0 License, which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received August 30, 2014. Accepted in final form October 31, 2014.

Correspondence to Dr. Kümpfel: tania.kuempfel@med.uni-muenchen.de

1. Richards A, van den Maagdenberg AM, Jen JC, et al. C-terminal truncations in human 3'-5' DNA exonuclease *TREX1* cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. *Nat Genet* 2007;39:1068–1070.
2. Weil S, Reifenberger G, Dudel C, Yousry TA, Schriever S, Noachtar S. Cerebroretinal vasculopathy mimicking a brain tumor: a case of a rare hereditary syndrome. *Neurology* 1999;53:629.
3. Mateen FJ, Krecke K, Younge BR, et al. Evolution of a tumor-like lesion in cerebroretinal vasculopathy and *TREX1* mutation. *Neurology* 2010;75:1211–1213.
4. Lee-Kirsch MA, Gong M, Chowdhury D, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease *TREX1* are associated with systemic lupus erythematosus. *Nat Genet* 2007;39:1065–1067.
5. Rice G, Patrick T, Parmar R, et al. Clinical and molecular phenotype of Aicardi-Goutières syndrome. *Am J Hum Genet* 2007;81:713–725.
6. Rice GI, Forte GM, Szykiewicz M, et al. Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, and *ADAR*: a case-control study. *Lancet Neurol* 2013;12:1159–1169.
7. Cuadrado E, Jansen MH, Anink J, et al. Chronic exposure of astrocytes to interferon- α reveals molecular changes related to Aicardi-Goutières syndrome. *Brain* 2013;136:245–258.