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Herpes simplex virus 2 encephalitis in a patient heterozygous for a TLR3 mutation

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Susceptibility to herpes simplex virus type 1 (HSV-1) encephalitis (HSE-1) in otherwise healthy individuals, in the course of primary infection, can be caused by single-gene inborn errors of Toll-like receptor 3 (TLR3) dependent, interferon (IFN)-α/β-mediated immunity,[1,2] or by single-gene inborn errors of snoRNA31.[3] These variations underlie infections of the forebrain, whereas mutations of *DBR1* underlie infections of the brainstem.[3] HSV-2 encephalitis (HSE-2) is typically observed in neonates, albeit also rarely in older children and adults.[4] Its manifestations include altered level of consciousness, cranial neuropathies or more extensive brainstem encephalitis, hemiparesis, hemisensory loss, and permanent neurologic deficit.[4] MRI in HSE-2 may show normal findings, nonspecific white matter, orbitofrontal, mesial temporal lobe, or brainstem lesions. Inborn errors of immunity underlying HSE-2 have not been described.

A 40-year-old previously healthy woman had suffered from headache and fever of up to 38°C for 6 days when she suddenly developed aphasia. At hospital admission, her body temperature was 37.1°C, blood pressure was 138/90 mm Hg, and vital signs were normal. She was fully conscious and co-operative but aphasic. Her blood hemoglobin level was low (107 g/L, normal range 117–155 g/L), with normal C-reactive protein level, blood white cell and thrombocyte counts, and negative blood and urine cultures. Acute phase brain CT, CT angiography and contrast enhanced MRI were unremarkable. CSF showed elevated mononuclear (98%) white cell count (166×10^6/L; normal $<3 \times 10^6$/L) and high protein concentration (1,192 mg/L; normal range 150–500 mg/L). CSF was positive for HSV-2 and negative for HSV-1 nucleic acid by automated and accredited real-time PCR (artus HSV-1/2 PCR Kits; QIAsymphony SP, Rotor-Gene Q, Qiagen, Hilden, Germany). EEG showed left focal frontotemporobasal 2 Hz slow wave activity consistent with viral encephalitis (figure). She received IV acyclovir for 21 days with improvement in aphasia. Neuropsychological assessment 1 month later revealed poor word fluency, problems with memory interference, and delayed word list memory. The patient continued to suffer from lassitude and mild depression at least for over 12 months after the acute episode. Her presentation was consistent with International the Encephalitis Consortium diagnostic criteria for encephalitis.[5] After the acute episode, she developed frequently recurrent *eczema herpeticum* of lower back tested positive for HSV-2 nucleic acid, suggesting recent primary HSV-2 infection. She did not suffer from genital herpes. This was controlled with peroral prophylactic valacyclovir 500 mg twice daily.

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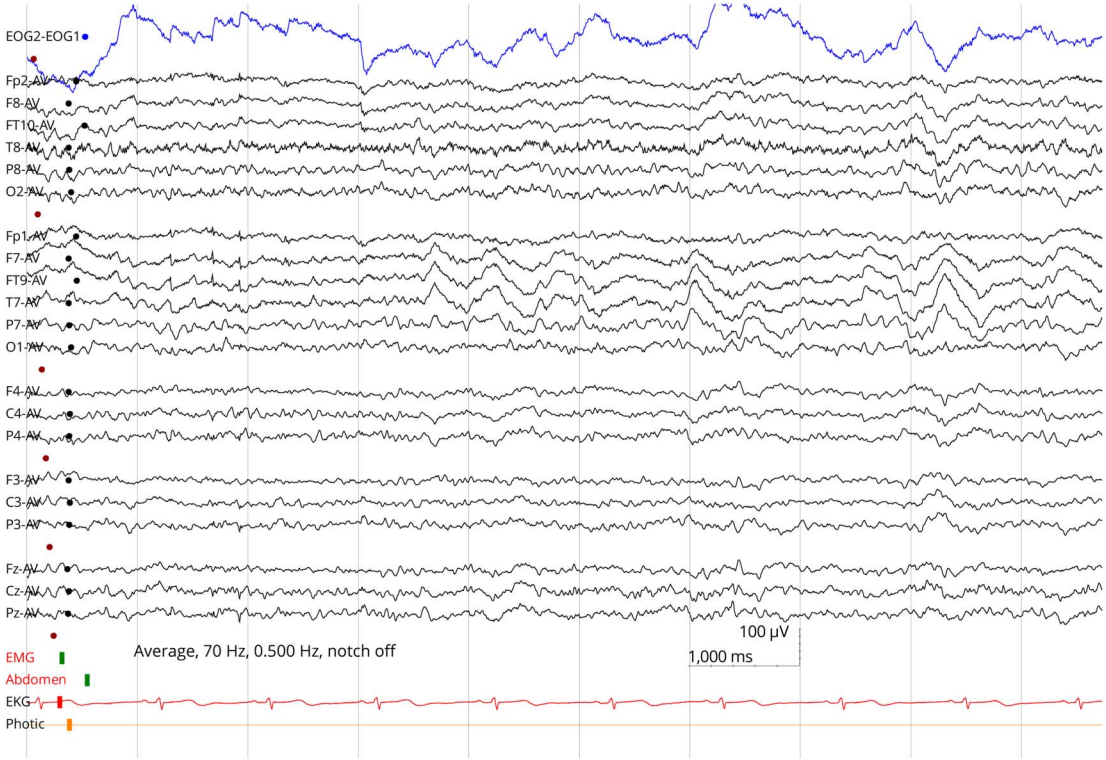
Figure EEG shows focal left frontotemporobasal 2 Hz slow wave activity consistent with encephalitis diagnosis



Normal background activity and the patient is awake.

The patient was remitted for immunologic evaluation. Family history was unremarkable; she had no history of general infection susceptibility, autoimmunity, or secondary immunodeficiency. Blood white cell and lymphocyte ($CD19^+$ B, $CD4^+$ and $CD8^+$ T, $CD16^+CD56^+$ NK) counts and percentages of T and B lymphocyte subclasses were normal, suggesting normal maturation. She was positive for anti-HSV2 immunoglobulin G (IgG) and negative for anti-HSV1 IgG. Whole exome sequencing showed a heterozygous rs147431766 *TLR3* (chr4: 187005064C>T, ENSG00000164342:ENST00000296795: exon4:c.C2224T:p.L742F) variant, enriched over 23-fold in the Finnish compared with non-Finnish Europeans (allele frequency 0.01621 vs 0.0006819, Genome Aggregation Database; gnomad.broadinstitute.org/). *TLR3* p.L742F variant is in vitro severely hypomorphic based on experiments on TLR3-deficient P2.1 fibrosarcoma cell line, and the production of IFN-λ and interleukin-6 in response to TLR3 activation by poly(I:C) stimulation was impaired in previously tested SV40 immortalized human skin fibroblasts heterozygous for this variation.[6] She was also found to be positive for TRF1-interacting nuclear factor 2 (*TINF2*) variant p.Y312* (rs201677741) previously associated with Ewing sarcoma. Pathogenic *TINF* variants are associated with autosomal dominant dyskeratosis congenita and pathologic telomere lengths (OMIM 604319). However, her telomere length was within the normal interval compared with healthy controls of similar age. Patient's father had died of aggressive cholangiocarcinoma, and her mother has had one episode of varicella zoster skin infection. *TLR3* p.L742F and *TINF2* p.Y312* variants were inherited from the mother. Patient's sister had suffered from recurrent laboratory confirmed cutaneous HSV2 infections. Her targeted testing did not reveal *TLR3* p.L742F or *TINF2* p.Y312* variants.

Previous evidence shows that inborn errors in TLR3-mediated immune response may explain HSE-1 in a subset of patients.[1–3] Our patient suffered an HSE-2 episode associated with impaired TLR3-mediated antiviral response. To our knowledge, this is the first report of a genetic mechanism potentially explaining HSE-2 in immunocompetent patients. The TLR3 p.L742F variant found in our patient is enriched in Finnish population; we can only speculate that this property may associate with HSV-2 CNS infections in Finland.[7] We emphasize that our report does not prove causality between TLR3 deficiency and HSE-2 but suggests that TLR3 signaling defects may need to be contemplated in otherwise healthy HSE-2 patients.

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Terhi Partanen, MD	Oulu University Hospital, Finland	Study design and analysis
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Johanna Lehtonen, PhD	University of Helsinki, Finland	Laboratory analysis
Janna Saarela, MD, PhD	University of Helsinki, Finland	Major role in data analysis
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