

Toll-Like Receptor 3 Immune Deficiency May Be Causative for HSV-2-Associated Mollaret Meningitis

Olaf Willmann^a Parviz Ahmad-Nejad^b Michael Neumaier^b Michael G. Hennerici^a
Marc Fatar^a

^aDepartment of Neurology, and ^bInstitute of Clinical Chemistry, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim, Germany

Dear Sir,

A 47-year-old man without fever was referred to our neurology department with cumulative headache, sensitivity to light and neck stiffness since the previous day. On the day of admission, nausea occurred and the patient had vomited several times. At this time point headache was most intense and he described the impression of water rushing in his ears. The patient had already experienced two similar episodes diagnosed as meningitis 3 and 6 years before. Several years prior to the first episode, he remembered untreated small genital blisters with spontaneous recovery. An infectious focus in the ear, nose or throat could not be determined; there was also no history of any other disease, like migraine, head trauma, any relation to drug treatment or a stay abroad. Beside his neck stiffness physical and neurologic examination was always normal – as it was on admission. No skin lesions were obtained. A spinal and cerebral MRI (1.5 T using T1, T2, T2* and DWI sequences including MR angiography) showed neither structural lesions nor meningeal enhancement. Lumbar puncture confirmed the diagnosis ‘vi-

ral meningitis’. Early cytology showed the characteristics, but not specific mononuclear endothelial Mollaret cells (fig. 1). Laboratory findings of cerebrospinal fluid (CSF) using enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA), Western blot or polymerase chain reaction (PCR) for a pathogenic agent (e.g. *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *enteroviruses*, *herpes simplex type 1*, *human herpes type 6*, *cytomegalovirus*, *varizella zoster*, *Epstein-Barr*, *mumps*, *human immunodeficiency virus* and *Cryptococcus*) were negative. There was no sign of a systemic disease or CSF shunt.

History of CSF is presented in table 1. HSV-specific PCR revealed a positive result for herpes simplex virus type 2 (HSV-2) in all three episodes with acute symptoms during the first 2 days. Genotyping for functionally relevant sequence variations in the *toll-like receptor 3* (*TLR-3*) and the *UNC-93B* genes which have previously been associated with susceptibility to herpes simplex encephalitis revealed the homozygous Phe variant (encoded by the T allele at rs3775291) for TLR3 p.Leu412Phe (p.L412F) by pyrosequencing [1–3]. No other sequence variation investigated (TLR3 p.Asn284Ile, TLR3 p.Pro554Ser, UNC-93B 1034del4 or 781G>A) could be detected.

All episodes were treated with intravenous acyclovir 3 × 10 mg/kg/day for two weeks and the headache relieved continuously during the first 4–5 days of treatment. After the third actual presentation, we started a prophylactic medication with valacyclovir 500 mg/day. Since then, normal CSF results were found for 6 months. The prophylactic on-going medication was well tolerated without any side effects.

Discussion

Recurrent lymphocytic meningitis was first described and named by Pierre Mollaret in 1944 and clinical and diagnostic criteria allowed the diagnosis in our case [4]. Besides the CSF pleocytosis with characteristic mononuclear endothelial cells nucleic acid testing revealed a positive result for HSV-2. HSV-2 is known to induce recurrent meningitis as it was the case in our patient [5, 6]. Cases without fever were also reported earlier by Galdi et al. [7]. Other agents causing recurrent meningitis or a systemic disease such as systemic lupus erythematoses or spinal or cerebral lesions were not identified in our case.

Since molecular biology-based methods have become widely used, the number of HSV-2-positive Mollaret meningitis patients have increased. Dylewski et al. [8]

O. Willmann and P. Ahmad-Nejad contributed equally.

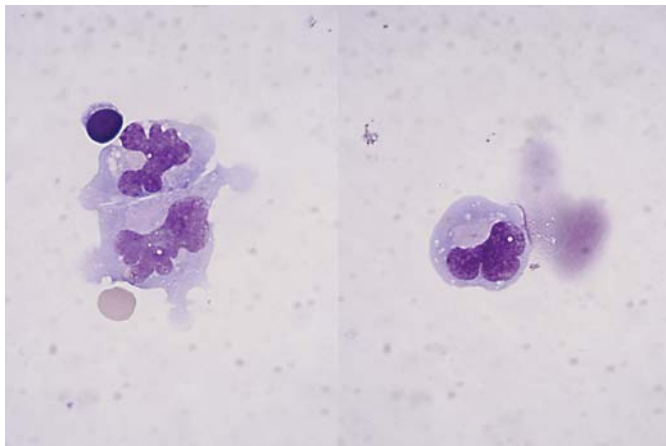


Fig. 1. May-Grunwald-Giemsa staining of CSF shows large monocytes with pseudopods and bean-shaped bilobed nuclei sometimes presenting in aggregates.

Color version available online

Table 1. History of CSF results

Follow-up days	Cells n/ μ l [0–5]	Protein, mg/l [150–450]	Glucose mg/dl [45–70]	HSV-2 PCR
First episode at 41 years of age				
0	353	872	64	positive
6	195	273	61	negative
9	15	204	59	negative
Second episode at 44.5 years of age				
0	555	857	60	positive
12	57	280	52	negative
60	19	287	62	negative
90	9	303	58	negative
Third episode at 47.5 years of age				
0	582	1,325	50	positive
10	169	357	53	positive
45	14	292	56	negative
180	1	312	61	negative

demonstrated 49 (84%) HSV-2-positive cases in a collective review of 58 patients with recurrent lymphocytic meningitis. A recent study reviewing 49 patients with HSV-2 affecting the central nervous system revealed 43 (88%) meningitis cases of which 8 (19%) patients had recurrent lymphocytic meningitis [9].

The phenomenon why patients suffer recurrence of meningitis instead of genital herpes or vice versa or both might be explained by genetic aspects or different virus strains. TLR3 is located primarily in intracellular vesicles of many cells and recognizes double-stranded virus RNA and polyinosine-polycytidylic acid (poly I:C), a synthetic double-stranded RNA analogue predominantly used in studies [10]. TLR3 triggering can induce innate immune responses by stimulating the production of interferons and activating a variety of cytokines and chemokines. The nonsynonymous and frequent p.L412F sequence variation is present in around 20% of the human population. Biochemically the p.L412F displayed a reduced receptor activ-

ity upon stimulation which could not be restored by increasing poly I:C concentrations [3]. By analyzing p.L412F sequence variation, our patient was homozygous for this allele. We therefore postulate a deficient immune response against HSV-2, because TLR3 is vital for natural immunity in HSV-1 encephalitis patients and TLR3 agonists are known to elicit protective immune response for genital HSV-2 infection [1, 11].

Our patient had only one suspicious untreated episode of genital herpes before the onset of recurrent meningitis, although asymptomatic episodes are known of in HSV-2. Aurelious et al. [12] suggested that the absence of apparent genital infection may be the more common presentation at the time of meningeal involvement. In accordance with other reports our patient experienced a quick recovery of symptoms and long symptom-free intervals by acute intravenous treatment with acyclovir. Some experts doubt the need of treatment according to known spontaneous benign course with long symptom-free intervals and regarded long-term antiviral

prophylaxis not to be appropriate, but it could be a beneficial option in cases with high frequency [13]. For prophylaxis, we chose oral valacyclovir therapy known to be effective in suppression of recurrent genital herpes [14]. Under this treatment for 22 months the patient developed no further meningitis so far. But how long a prophylactic treatment should be given and when a complete eradication of HSV-2 in the central nervous system could be achieved still remains unclear.

Conclusion

In this case report, we demonstrate a patient with recurrent lymphocytic meningitis, who suffered from deficiency in TLR3 due to homozygous p.L412F sequence variation (encoded by the T allele at rs3775291). To gain further information on the possible relevance of TLR3 deficiency for recurrent lymphocytic meningitis, TLR3 alleles should be tested in such cases.

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