Digenic *MEFV/TNFRSF1A* autoinflammatory syndrome with relapsing aseptic neutrophilic meningitis and chronic myelitis

Sirs,

A 60-year-old white woman was admitted for recurrent headache, photophobia and high-grade fever. The first episode occurred when she was 49 with bouts lasting 3 to 4 days, occurring every 3 to 6 months. One year before admission, the patient had started to suffer unsteady gait, numbness and tingling in the upper right limb, weakness in the lower right limb and urinary retention. On physical examination during a flare, the patient was in pain with severe headache. Body temperature was 39°. Nuchal rigidity was obvious. Strength was diminished in the right leg with a right Babinsky sign. Routine blood test results were unremarkable besides C-reactive protein (CRP) level at 57 mg/L. CSF analysis disclosed 253 cells/mL, mostly neutrophils (92%) with raised protein level (1g/L), and low glucose (2 mM/l). Spine MRI T2 images showed high-signal lesions of the posterior portion of the spinal cord at C4 and C6 levels. No gadolinium enhancement was observed and conus medullaris was normal. Brain imaging revealed an isolated right occipital periventricular lesion with a moderate increased diffusion weighted image signal. No meningeal enhancement was observed. Comprehensive laboratory, including an exhaustive microbiology panel including CSF PCR for bacteria and virus, and imaging evaluation were negative.

Acute infectious meningoencephalitis was first considered and treated with ampicillin, cefotaxime, gentamicin and acyclovir. CSF analysis and CRP level normalised transiently, until recurrence. Continuous oral low dose acyclovir treatment was prescribed, with no improvement. Because of symptomatic myelitis in the setting of chronic aseptic CNS inflammation, steroid treatment was started. Despite steroid use, CSF analysis confirmed recurrent meningitis (400 cells/mL, 84% of neutrophils). Overtime, immunosuppressive drugs including azathioprine then mycophenolate mofetil were added to steroids with no further efficacy.

An autoinflammatory condition was suspected. Genetic analysis using routine Sanger approach revealed heterozygous R92Q mutation in tumour necrosis factor receptor super family 1A (*TNFRSF1A*) gene and V726A mutation in the Mediterranean fever (*MEFV*) gene. No mutations in mevalonate kinase and cold-induced autoinflammatory syndrome 1 genes were identified. The proband's family members were screened for *MEFV* and *TNFRSF1A* mutations. All relatives were asymptomatic and none shared the proband's genotype (Fig. 1).

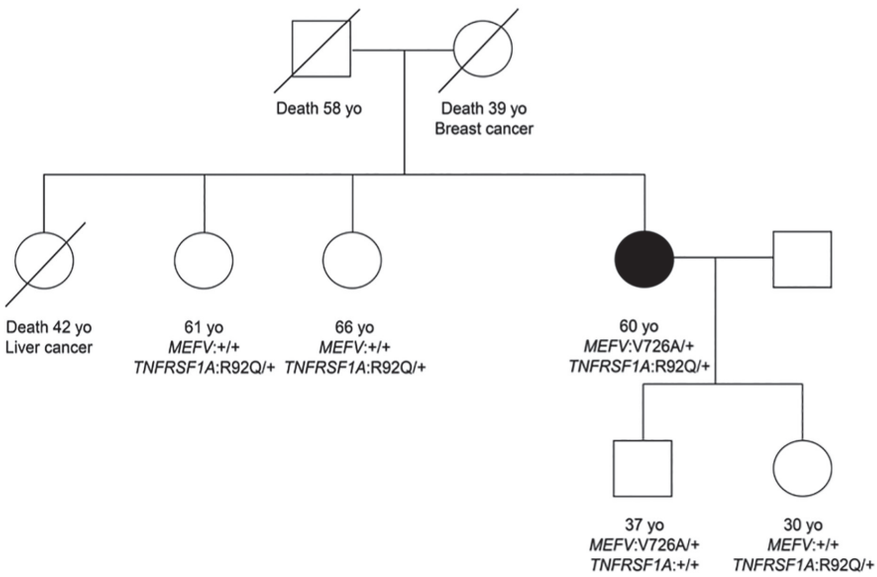

Fig. 1. Segregation analysis study. Sequencing of healthy relatives demonstrated that only the affected proband inherited the two autoinflammatory variants.
MEFV: Mediterranean fever; *TNFRSF1A*: Tumour necrosis factor receptor super family 1A.

Oral colchicine then subcutaneous anakinra, were administered without efficacy. Tocilizumab, a humanised monoclonal antibody against interleukin-6 receptor, was eventually initiated. From the day tocilizumab was started, the patient had no more meningitis. CRP level and CSF normalised. Brain and spinal cord lesions appeared stable on a protracted follow-up with sequential MRI. Prednisone could be stopped. Unfortunately, tocilizumab produced only the suspension of inflammatory attacks, since when it was suspended for hip surgery, meningitis recurred. Thirty-six months after tocilizumab was restarted, the disease is still on sustained remission.

Although the causal relationship remains uncertain between the clinical phenotype and genotype, several lines of evidence support the final diagnosis of autoinflammatory disease. First, late disease onset is possible not only for FMF but also for TRAPS1. Second, CNS inflammation and/or recurrent aseptic meningitis have been reported in both FMF and TRAPS2-5. Third, the association between R92Q *TNFRSF1A* and V726A *MEFV* mutations is exceedingly rare. In France, no other subject (besides our patient) carrying both mutations was identified in the genetic databases of the 3 major genetics departments that received altogether around 1500 samples/year for molecular diagnosis of FMF and TRAPS. Fourth, other causes of recurrent aseptic meningitis such as HSV2 infection or autoimmune/inflammatory systemic diseases have been ruled out over a protracted follow-up. Fifth, the only treatment that clearly prevented acute attacks of the disease specifically targets the inflammatory cytokine IL-6.

In summary, recurrent fever and aseptic neutrophilic meningitis with chronic myelitis may be a specific auto-inflammatory phenotype associated with *TNFRSF1A* R92Q and *MEFV* V726A mutations.

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