Association between Tubulointerstitial Nephritis and Uveitis Syndrome and Small-Vessel CNS Vasculitis: A Case of Polyautoimmunity

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Abstract

Introduction We report a case study of two male pediatric patients presenting with anterior uveitis and elevated renal function parameters. Both were diagnosed with tubulointerstitial nephritis and uveitis syndrome and subsequently developed diffuse cerebral symptoms such as headache, fatigue, and diziness.

Methods Magnetic resonance images (MRIs) of the brain showed T2-hyperintense lesions with and without gadolinium enhancement leading to brain biopsy and diagnosis of small-vessel central nervous system (CNS) vasculitis in both cases. Both patients were treated according to BrainWorks small-vessel vasculitis protocol and symptoms vanished over the course of treatment. Follow-up MRIs up to 12 months after initiation of therapy showed no signs of recurrence indicating a monophasic disease.

Conclusion Small-vessel CNS vasculitis can occur simultaneously to other autoimmune diseases (ADs) in the scope of polyautoimmunity. As clinical findings of CNS vasculitis are often unspecific, neurological symptoms in nonneurological ADs should be adressed thoroughly. Under suspicion of small-vessel CNS vasculitis brain biopsy is still the gold standard and only secure way of definitive diagnosis.

Keywords
- TINU syndrome
- small-vessel CNS vasculitis
- polyautoimmunity
- PACNS

Introduction

TINU Syndrome

Tubulointerstitial nephritis and uveitis (TINU) syndrome describes a concomitant presentation of acute kidney inflammation and bilateral uveitis and was first reported in 1975.[1] Usually, symptoms occur sequentially with symptom-free intervals up to 14 months in between.[2] Thereby, TINU syndrome is regarded to be an underdiagnosed entity as symptoms may not be connected to each other by clinician practitioners. The condition affects both children and adults alike; however, children are more likely to have recurrent episodes of ocular manifestation.[3]

Triggers leading to TINU syndrome remain unclear. Association with specific human leukocyte antigen types as well as infectious triggers preceding a TINU is discussed.[4]

Several authors demand a renal biopsy with signs of tubulointerstitial nephritis for diagnosis of TINU syndrome.[4] Histopathological findings of affected kidneys usually show lymphocytic infiltration implying an autoimmune pathogenesis. According to other authors, diagnosis of "probable" TINU can also be diagnosed upon clinical criteria requiring presence of abnormal renal function, abnormal urine analysis, systemic illness, and anterior uveitis.[4]

In general, the clinical outcome of kidney function is good and most of the patients recover spontaneously. Patients

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without spontaneous recovery of renal function benefit from steroid therapy.[5]

Central Nervous System Vasculitis

The term vasculitis summarizes a group of heterogeneous autoimmune diseases (ADs) that are characterized by inflammation of the vessel walls. Clinical features as well as classification of vasculitis depend on affected vessels and organs. According to the most common classifications, vasculitis of the central nervous system (CNS) occurs either as an isolated primary entity or secondary as a symptom of systemic vasculitis.[6]

The term primary angiitis of the CNS (PACNS) refers to disease without inflammation in other organs apart the CNS. First diagnostic criteria were proposed in 1988 as: (1) newly occurred neurologic symptom; (2) feature of CNS vasculitis by angiography and/or tissue examination; and (3) no evidence of a systemic condition resulting in above points.[7] Distinct subtypes of PACNS were defined as angiography-negative small-vessel CNS vasculitis and angiography-positive large- and middle-vessel CNS vasculitis. Clinical manifestation of CNS vasculitis is heterogenic with unspecific symptoms such as headache, fatigue, seizures, neck stiffness, focal motoric deficit, behavioral or concentration changes, or encephalopathy of which none is specific for either subtype of PACNS.[8] Thus, a clinical diagnosis based on observed symptoms is not feasible. To date, there is no specific laboratory finding confirming CNS vasculitis. The main focus of laboratory workup should include possible underlying causes for vasculitis such as systemic infection or AD. At this point, analysis of cerebrospinal fluid (CSF) plays a pivotal role.[8,9]

Histopathological proof of CNS vasculitis is still considered as gold standard. Small-vessel CNS vasculitis presents with intramural or perivascular infiltration of T-cell lymphocytes and endothelial disruption in histopathology.[10]

With improved availability as well as resolution of magnetic resonance imaging (MRI), its diagnostic relevance has been increased over the past decades. In summary, radiological findings are either observed as primary changes in vessels, for example, narrowing diameter, thickening vessel wall, gadolinium enhancement, or secondary effects due to vasculitis such as hemorrhages or edema.[11]

There are published cases of small-vessel CNS vasculitis being accompanied by uveitis[12]; however, to our knowledge, there is no description of an association between TINU syndrome and small-vessel CNS vasculitis, so far.

Case Report Patient 1

Initially, the male patient was admitted at the age of 16 years to our children's hospital due to fatigue, recurrent headaches and limb pain, recurrent episodes of itching eyes over the past months, and weight loss of 5 kg without any dietary restrictions in the past 6 months. The patient is of Caucasian origin, had no history of known chronic medical conditions or exposure to any toxins.

Approximately 2 months prior to admission, there was an episode of oxyuriasis, which was treated accordingly. Upon admission, he already used topic steroids for uveitis in both eyes. Uveitis was diagnosed in an outpatient clinic several days prior to admission. Family history was negative on ADs.

The physical and neurological examination showed no abnormalities. We observed elevated renal function parameters (creatinine 1.5 mg/dL, urea 24 mg/dL, glomerular filtration rate 68 mL/min), microalbuminuria (albumin to creatinine ratio 63 mg/g), elevated eosinophils (1,080/µL), and isolated elevation of immunoglobulin E (3,210 kU/L). Blood cell differentiation showed no signs of malignancy, and antibodies regarding ADs (ANA, ANCA, ds-DNA, SSA, SSB, U1, SCL) were negative. Microbiological tests including toxoplasmosis, Epstein–Barr virus (EBV), cytomegalovirus (CMV), blood culture, tuberculosis, hepatitis A/B/C, human immunodeficiency virus, herpes simplex virus (HSV)1/2, varicella zoster virus (VZV), and borreliosis were negative. Interferon signature in serum, S100 protein in serum, DADA2-enzymatic activity, and genetic testing for familiar Mediterranean fever were normal as well. Once again, he was tested positive on *Enterobius vermicularis* and treated with pyrantel.

Over the next weeks, we saw a spontaneous recovery of renal function; therefore, renal biopsy was not performed. After 2 months, uveitis relapsed in both eyes accompanied by unspecific symptoms such as headache and fatigue without elevation of serum creatinine. Ophthalmologic examination revealed vascular leakage in fluorescein angiography.

In consideration of history of recurrent episodes of headaches, we performed an MRI of the brain. Here, we saw several bihemispheric supratentorial signal altered lesions in basal ganglia and white matter with gadolinium enhancement (►**Fig. 1**). We saw no anomalies in time-of-flight angiography (►**Fig. 2**). These lesions increased in size and number over the next 4 weeks (►**Fig. 3**), which led to a diagnostic stereotactic brain biopsy of a frontal apical lesion in the left hemisphere. The histopathological report confirmed small-vessel vasculitis with lymphocytic infiltration of vessel wall (►**Fig. 4**). There were no signs of demyelination, gliosis, or granulomatous infection. The brain tissue was tested negative for HSV, CMV, JC-virus, and toxoplasmosis. Neuronal antibodies (e.g., MOG, GFAP, Aquaporin-4, CASPR2, LG1, GAD65, NMDA-receptor, $GABA_{A/B}$-receptor, Hu, Ri, Yo, and others) in serum as well as CSF were negative. We performed extensive testing of CSF without signs of autoinflammation or signs of prior infection with HSV1/2, EBV, and CMV. Analysis of oligoclonal bands was negative, and the cell count in CSF was slightly increased with 27/3 cells.

The patient was treated according to *BrainWorks* small-vessel CNS vasculitis protocol with steroids and 7 monthly courses of cyclophosphamide followed by mycophenolate mofetil (MMF) therapy over the course of a year.[9] He recovered swiftly and showed no further clinical signs of CNS vasculitis. Follow-up MRIs showed a decrease of prior described lesions and no gadolinium enhancement, so that treatment was discontinued according to protocol after a total of 18 months. Renal function stayed normal during the follow-up, and there were no clinical signs of uveitis anymore.

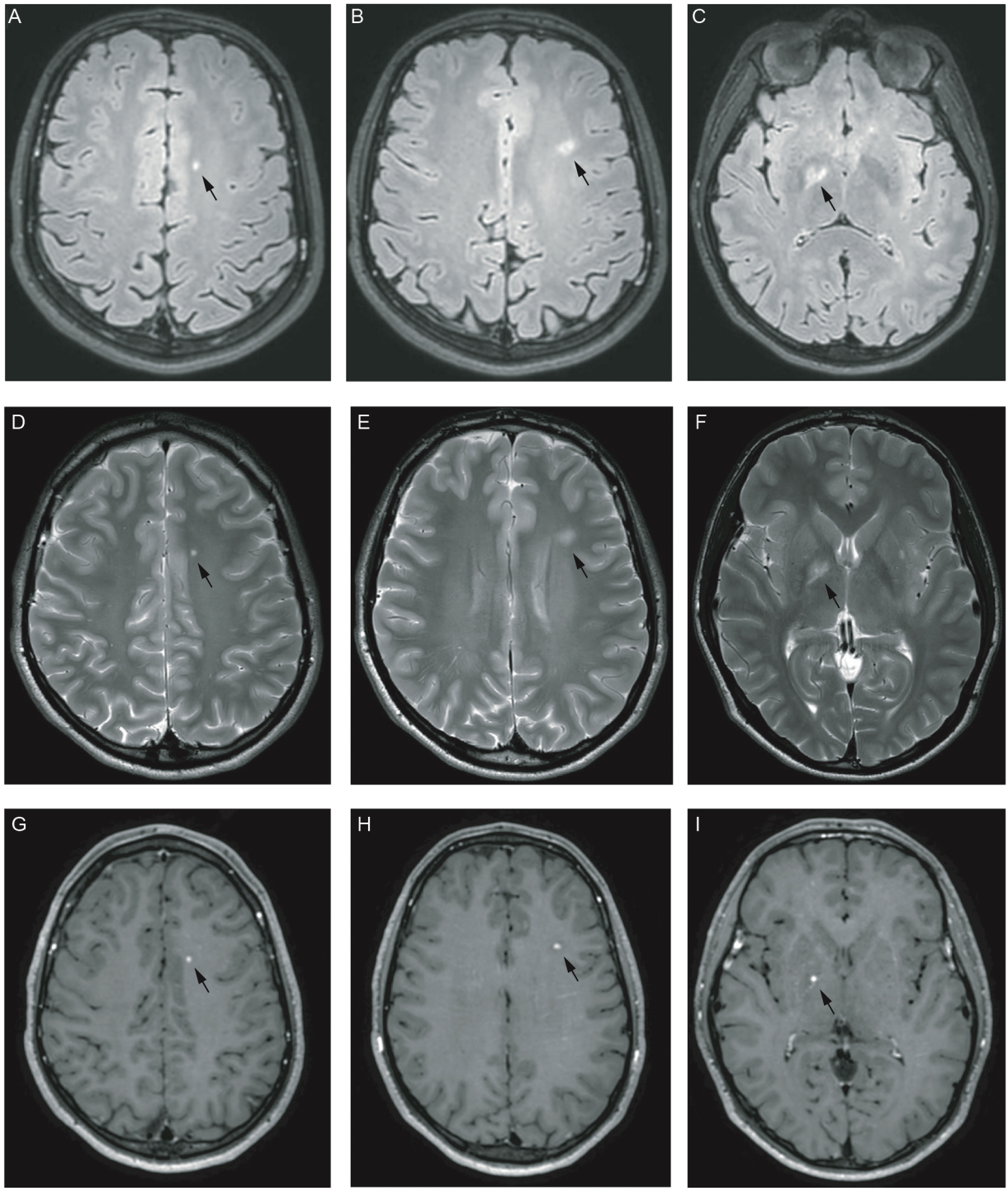

Fig. 1 Magnetic resonance imaging patient 1. Axial fluid-attenuated inversion recovery imaging (**A–C**), T2-weighted imaging (**D–F**), and gadolinium-enhanced imaging (**G–I**) of patient 1 upon diagnosis showed several patchy as well as punctate bihemispheric supratentorial signal altered lesions in basal ganglia and white matter with gadolinium enhancement. Arrows point to lesions.

Case Report Patient 2

Our second male patient of Caucasian origin presented with unspecific symptoms of fatigue, headaches, malaise, and itching eyes at the age of 13 years.

Medical history contained diagnosis of common acute lymphoblastic leukemia (c-ALL) at the age of 2 years, and treatment was performed according to CoALL-06-09 low-risk protocol. Upon occurrence of above-described symptoms, chemotherapy had already been completed over 9 years ago, and the patient was still in remission. There were no evident signs of prior or acute infection upon admission. Laboratory testing showed increased serum creatinine (1.53 mg/dL) and albuminuria (218 mg/L) leading to renal biopsy. Here, we saw histopathological signs of TIN, and treatment with oral corticosteroids was initiated over the

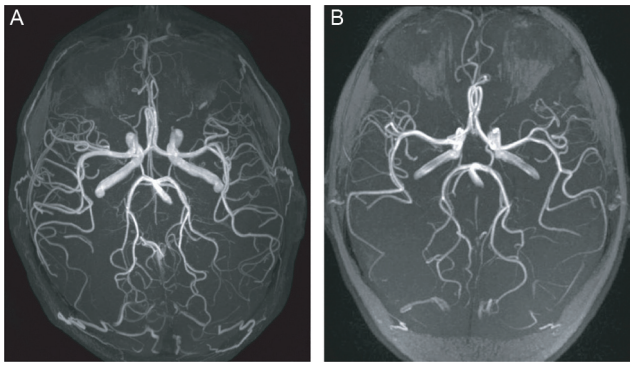

Fig. 2 Time of flight (TOF) angiography patients 1 and 2. TOF images of patient 1 (**A**) and patient 2 (**B**) upon diagnosis showed no abnormalities.

course of 7 weeks. In week 6 of the steroid therapy, the patient suffered from light-sensitive eyes, which led to an immediate ophthalmological examination. Diagnosis of anterior uveitis was labeled, and additional therapy with topic corticosteroid was initiated. Thus, diagnostic criteria of TINU syndrome were fulfilled. Renal function had already recovered after 4 weeks of treatment, and corticosteroid therapy was tapered thereafter. Two months after initial diagnosis of TINU, there was a relapse of uveitis. An ophthalmological examination showed vascular leakage in fluorescein angiography of retina and swollen papilla similar to our first patient. Renal function showed no abnormalities this time, and uveitis responded well to topic corticosteroid treatment. Again, the patient suffered from mild headache and fatigue but showed no hints of severe focal neurologic signs. MRI of the brain was performed to rule out affection of CNS. Here, we saw lesions in turbo inversion recovery magnitude imaging with gadolinium enhancement (►**Fig. 5**) and swiftly performed CNS biopsy of a frontal apical lesion in the left hemisphere under assumption of either relapse of c-ALL or secondary malignoma or CNS vasculitis. Histopathological analysis confirmed small-vessel vasculitis with lymphocytic infiltration of vessel walls (►**Fig. 4**). Again, there were no signs of demyelination, gliosis, or granulomatous infection. Analysis of CSF showed negative results for CMV, EBV, HSV, VZV, HHV6, parvovirus B19, toxoplasmosis, measles, rubella, and mumps virus. Autoantibodies regarding ANA, ANCA, ds-DNA, cardiolipin, and beta2-glycoprotein were also negative as well as oligoclonal bands.

As he had not reached maximum dose of cyclophosphamide during c-ALL treatment, we initiated therapy according to standard *BrainWorks* small-vessel CNS protocol including steroids and cyclophosphamide. The patient showed new bihemispheric T2-hyperintense lesions without contrast enhancement shortly after first application of cyclophosphamide without any new neurological findings. As the newly observed lesions showed no definitive MRI features typical for vasculitis, a cytotoxic effect of cyclophosphamide was assumed in view of the cytotoxic pretreatment due to prior diagnosis of leukemia. According to data indicating a positive effect of B-cell depletion in pediatric patients with CNS vasculitis, we switched treatment to rituximab over the course of 2 years.[13] During the treatment, neurological symptoms vanished, and we have not observed any new CNS lesions during follow-up examinations. There were also no new episodes of impaired renal function or uveitis.

Discussion

We describe two independent cases of TINU syndrome associated with small-vessel CNS vasculitis. In both patients, TINU syndrome was diagnosed first and diagnosis of CNS vasculitis followed later on. Both patients had evidence of retinal vasculitis due to leakage in fluorescein angiography upon diagnosis of small-vessel CNS vasculitis. There are several cases describing posterior uveitis with retinal vasculitis in TINU syndrome. In those case studies, there were no signs of neurological impairment indicating to a CNS vasculitis, and cerebral imaging was not performed.[14,15] Therefore, it remains unclear if retinal vasculitis is purely TINU related or might be also a sign of CNS vasculitis.

ADs are often described to be triggered by either bacterial or viral infections. In case of TINU syndrome and CNS vasculitis, infectious triggers are also described.[4,8] In patient 1, there was a history of infection with *Enterobius vermicularis*. There is one case report of infiltration of CSF by *E. vermicularis*; however, in our case, microscopy of CSF was normal.[16] Furthermore, there are single reports of cerebral vasculitis in cases of *Toxocara canis*.[17] On the other hand, several authors reported protective effects of parasitic helminth infections on development of autoimmunity due to activation of T-helper cell 2 pathway.[18,19] Furthermore, our second patient showed no hints of a helminth infection.

In our second patient, there is a medical history of leukemia. An association between leukemia and vasculitis is especially well described as paraneoplastic vasculitis or as a drug-induced entity.[20,21] In our case, treatment for c-ALL was already completed 9 years prior without any signs of relapse. Furthermore, patient 1 had no medical history of malignancy.

For several ADs, an association with CNS vasculitis is well known. For example, in inflammatory bowel disease (IBD), there are several cases of histologically proven CNS vasculitis. Occurrence of CNS vasculitis is predominantly described in cases of colitis ulcerosa.[22] However, in these patients, the preceding medication with immunosuppressants as well as biologicals for treatment of IBD are discussed as possible triggers of vasculitis apart from the underlying IBD.[23] Regarding TINU syndrome, there is a study of concomitant diagnosis of Takayasu arteritis.[24]

Leaving TINU syndrome and CNS vasculitis aside, further ADs such as autoimmune thyroid disease or Sjögren's syndrome[25] are described to have higher associations with another AD than the background prevalence. Thus, the terms polyautoimmunity (two concomitant ADs) and multiple autoimmune syndrome (three or more concomitant ADs) were created.[26] The common pathomechanism in all those ADs is regarded as inadequate immunological self-recognition leading to tissue damage. The genetic approach to etiology of polyautoimmunity focuses on shared single-nucleotide polymorphisms (SNPs) between several ADs.

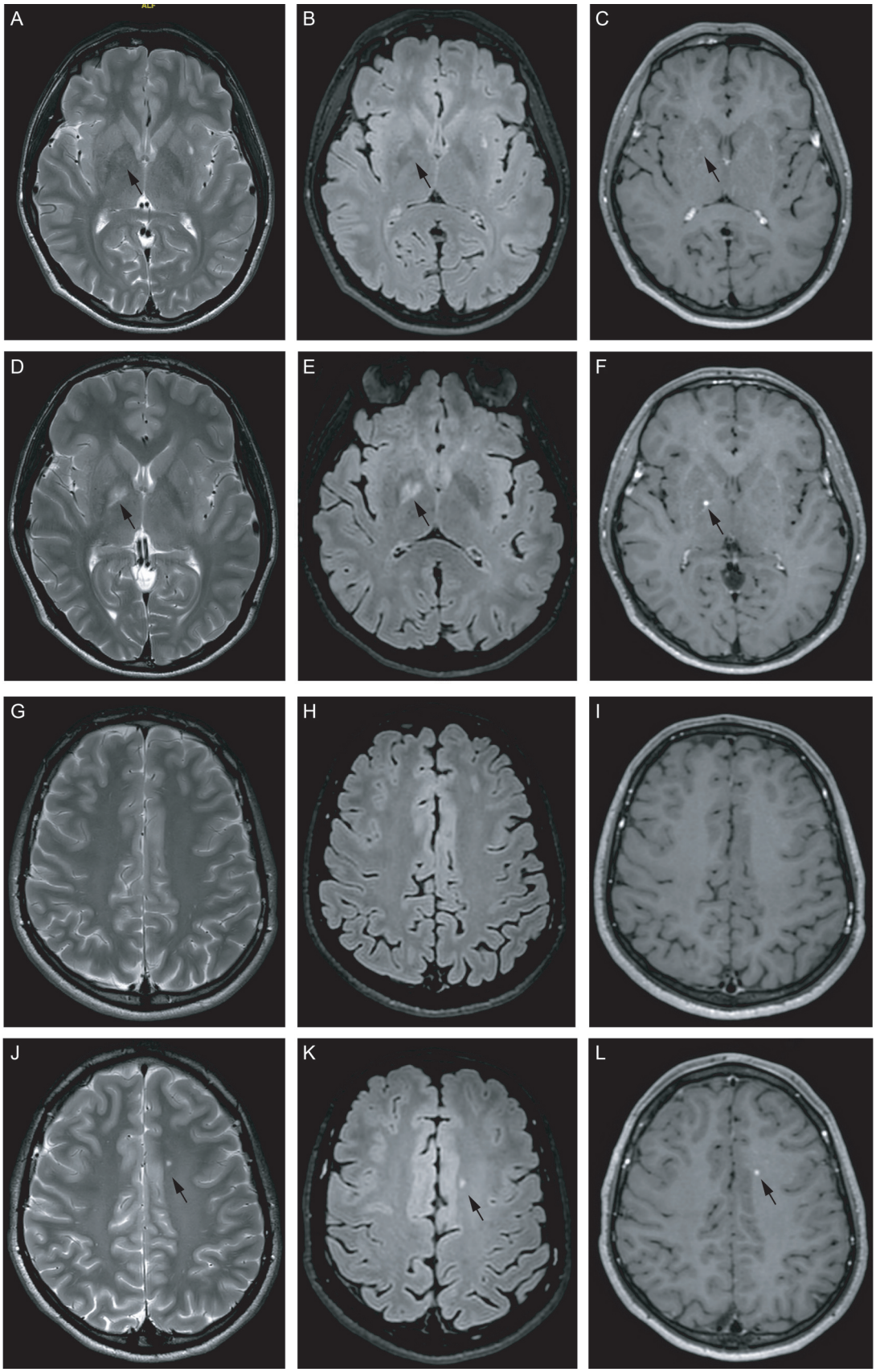

Fig. 3 Repeated magnetic resonance imaging of patient 1 after 4 weeks. Comparison of MR images upon first admission (**A–C; G–I**) and after 4 weeks (**D–F; J–I**). In basal ganglia (**A–F**) increase in size of signal altered lesions with gadolinium enhancement. In white matter (**G–L**) occurrence of new signal altered lesions with gadolinium enhancement. Arrows point to lesions. T2-weighed imaging (**A, D, G, J**); fluid-attenuated inversion recovery imaging (**B, E, H, K**) and gadolinium-enhanced imaging (**C, F, I, L**). Arrows point to lesions.

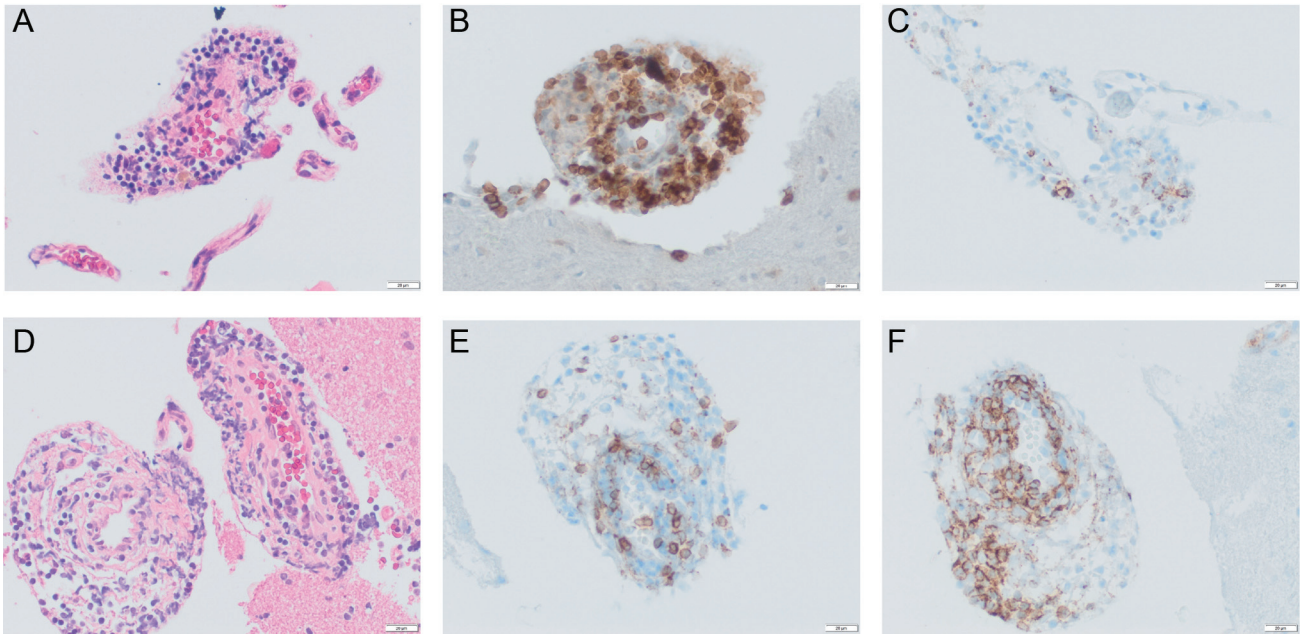

Fig. 4 Histopathology of brain biopsies positive of small-vessel vasculitis. Biopsies of patient 1 (**A–C**) and patient 2 (**D–F**) were stained with hematoxylin and eosin (**A, D**), brown anti-CD3 (**B, E**), and brown anti-CD20 (**C, F**) staining. We observed thickening and lymphocytic infiltration of predominantly small vessels. Detection of CD3-positive T-cells as well as CD20-positive B-cells was successful. Original magnification ×20.

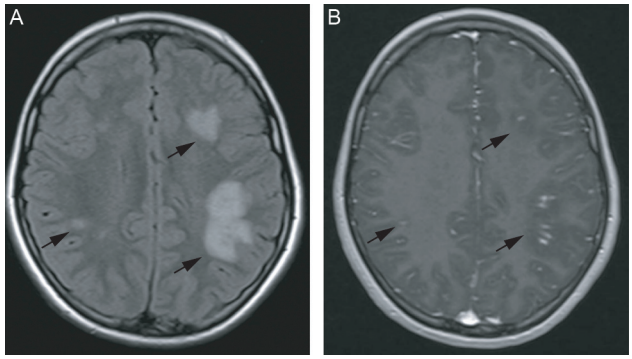

Fig. 5 Magnetic resonance imaging patient 2. Turbo inversion recovery magnitude imaging (**A**) and gadolinium-enhanced imaging (**B**) of patient 2 upon diagnosis showed several patchy bihemispheric supratentorial signal altered lesions in white matter with gadolinium enhancement. Arrows point to lesions.

These are often located in genome parts regulating expression of proteins for T-cell differentiation, immune-cell signaling, and the innate immune response.[27] Concerning TINU syndrome and CNS vasculitis separately, there are data suggesting associated SNPs with each disease;[28,29] however, as far as we know, there are no data of shared SNPs, yet. In case of more documented associations between TINU syndrome and CNS vasculitis, a shared genetic etiology should be considered. We did not perform genetic analysis on presented cases.

The treatment was conducted according to the *BrainWorks* protocol valid at the given time. In patient 2, treatment was changed due to suspected cumulative toxicity of cyclophosphamide in consideration of prior chemotherapy. Rituximab was chosen to avoid further organ toxicity in this particular case and showed therapeutic success. MMF was discussed and would have been chosen in case of a medical history free of chemotherapy.

Conclusion

We report two cases of histologically proven small-vessel CNS vasculitis after diagnosis and treatment of TINU syndrome. Clinical findings as well as MRI are often unspecific, thus hampering the diagnosis of small-vessel CNS vasculitis. We conclude that unspecific neurological symptoms in patients suffering from primary nonneurological ADs such as TINU syndrome should be taken seriously and addressed by brain MRI under suspicion of small-vessel vasculitis as possibly additional underlying disorder.

Upon occurrence of unclear MRI lesions in patients with unspecific symptoms, a noninvasive diagnostic workup should be performed thoroughly. However, under assumption of a small-vessel CNS vasculitis, the gold standard and only secure way of diagnosis is still a brain biopsy.

Conflict of Interest

None declared.

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