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## **Rare infections mimicking MS**

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## ***Abstract***

The diagnosis of multiple sclerosis (MS), despite well defined clinical criteria is not always simple. On many occasions it is difficult to differentiate MS from various non-MS idiopathic demyelinating disorders, specific and infectious inflammatory diseases or non-inflammatory demyelinating diseases. Clinicians should be aware of various clinical and MRI “red flags” that may point to the other diagnosis and demand further diagnostic evaluation. It is generally accepted that atypical clinical symptoms or atypical neuroimaging signs determine necessity for broad differential diagnostic work up. Of the infectious diseases that are most commonly mistaken for MS the clinician should take into account Whipple's disease, Lyme disease, Syphilis, HIV/AIDS, Brucellosis, HHV-6 infection, Hepatitis C, Mycoplasma and Creutzfeld-Jacob disease, among others. Cat scratch disease caused by *Bartonella hensellae*, Mediterranean spotted fever caused by *Rickettsia connore* and Leptospirosis caused by different *Leptospira* serovars rarely cause focal neurological deficit and demyelinating MRI changes similar to MS. When atypical clinical and neuroimaging presentations are present, serology on rare infectious diseases that may mimic MS may be warranted. This review will focus on the infectious diseases mimicking MS with presentation of rare illustrative cases.

***Key words:*** Multiple sclerosis, red flags, MRI, infections

## **Introduction**

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system characterized by diffuse areas of demyelination and axonal damage involving the brain and spinal cord white matter. Although there are well developed clinical criteria (1,2), differential diagnosis of multiple sclerosis is still sometimes difficult. The reason is the fact that there are many diseases that may mimic multiple sclerosis clinically, immunologically or radiologically (3,4,5). According to the recently published guidelines on differential diagnosis of suspected MS (3) demyelinating diseases of the central nervous system can be characterized according to the clinical and MRI characteristics. It is generally accepted that the diagnosis of MS can be given when typical clinical symptoms and characteristic paraclinical signs are pointing to the idiopathic inflammatory demyelinating disease, and in the absence of features suggesting an alternative diagnosis. On the other hand, features that are compatible with MS but occur in the presence of other atypical symptoms and signs, the so called "red flags" demand broad diagnostic work up to exclude alternative diagnosis, or eventual coexistence of the two different disease conditions (3,4,5,6). In the broad differential diagnosis of MS many diseases may come into focus. Of the infectious diseases that are most commonly mistaken for MS the clinician should take into account Whipple's disease, Lyme disease, Syphilis, HIV/AIDS, Brucellosis, HHV-6 infection, Hepatitis C, Mycoplasma and Creutzfeld-Jacob disease, among others. (7) This review will focus on the infectious diseases mimicking MS with presentation of rare illustrative cases.

## **Illustrative cases**

## **Case 1.**

A 27-year-old man developed nausea and vomiting. He was admitted to the local hospital and diagnosed with erosive gastritis. Afterwards he had several episodes of severe headaches followed by persistent paresthesiae in the left extremities and diminished visual acuity on both eyes. Brain and spinal cord MRI were reported as normal. Cerebro-spinal fluid (CSF) findings were also normal with negative oligoclonal bands (OCB), as well as antibodies against *Borelia Burgdorferi*, syphilis, HIV, Epstein Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus 1 and 2 (HSV1 and 2). He recovered spontaneously, but after one week he again developed diminished visual acuity on the left eye, double vision and left hemiparesis. In such condition he was referred to our Centre. On admission his visual acuity on the left eye was 20/70 with pronounced oscillations from normal to severely diminished, he had double vision due to the paresis of the left rectus muscle, and left hemiparesis (muscle strength was 4/5) with brisk reflexes. He also had remittent febrile episodes with psychotic reactions. At that time non-tender pustulous eritema on legs was found, with regional lymphadenopathy in lower abdomen, and hepatosplenomegaly detected with the abdominal ultrasound. Repeated brain MRI showed oval subcortical (parietal, insular, commissural and in centrum semiovale) hyperintensities (Figure 1), while cervical and thoracic spinal cord MRI was normal. As the symptoms were pointing to a systemic illness, a broad differential diagnosis had to be considered. Tests for systemic immunological diseases (Antinuclear antibodies - ANA, Anti-Extractable Nuclear Antigen - ENA, Anti-Neutrophil Cytoplasmic Antibodies - ANCA, antiphospholipid antibodies, C3, C4, CH50), as well as for non-inflammatory demyelinating diseases (copper in serum and 24 hours urine, ceruloplasmin, mitochondrial diseases) were negative. Other vascular demyelinating diseases were ruled out by normal biochemistry, no risk factors for vascular diseases, normal

cardiovascular work up including transeosophageal ultrasound, color Doppler of carotid and vertebral arteries and “bubble test”. Additional serological work-up for toxoplasmosis, brucellosis and Quantiferonal test were negative. As epidemiological history revealed that the patient’s hobby was hunting wild animals and he worked in transport of wild animal meat across Europe. Therefore, serology for fungal infection (cryptococcosis, aspergillosis, candidiasis), leptospirosis, leishmaniasis, listeriosis, Q fever, tularemia and *Mycoplasma pneumoniae* were performed. Digital subtraction angiography was repeated and suggested vasculitis, but all tests for autoimmune vasculitides as well as tests to various infectious agents were negative. Non tender pustules, encephalopathy, regional lymphadenopathy, splenomegaly with oscillations in neurological status finally led us to make serology for Bartonella haensellae which was positive in serum and CSF. We started antibiotic therapy with full recovery. Patient’s clinical status normalized in one month after treatment.

## **Case 2.**

A 30-year-old man with a history of viral meningitis four month before admission to our Center presented with alternative weakness of left and right extremities with the duration of up to 24 hours and continuous paresthesias of the left extremities. Brain MRI performed a month before showed hyperintensive lesion in the right internal capsular region. The diagnosis at the local hospital was MS. Follow-up MRI performed in our Center showed a new lesion with poorly defined borders in the left putaminal region (Figure 2). CSF showed mild pleocytosis without OCB. This patient had several clinical and MRI “red flags”, therefore extensive work-up including Holter-ECG monitoring, heart ECHO, tests on coagulopathies, immunological tests

(ANA, ENA, ANCA, antiphospholipid antibodies, C3,C4 CH50), alpha galactosidase A, long chain fat acids, folic acid and vitamin B12, thyroid hormones, serology for *Borrelia burgdorferi*, hepatitis B, C, HIV, toxoplasmosis, brucellosis was performed and all tests were negative. MRA (magnetic resonance angiography) showed changes on A1 segment of the left anterior cerebral artery and on proximal part (M1) of the middle cerebral artery, which were suspicious of vasculitis. As the patient lived in mediterranean basin serology on *Rickettsia conorii* that cause Mediterranean spotted fever was also done and IgM and IgG were positive in serum and CSF. The antibiotic therapy was started and patient symptoms slowly disappeared.

### **Case 3.**

We have recently reported a 43 year old man who developed progressive unsteadiness and frequent respiratory infections (8). He was diagnosed with obstructive sleep apnea (OSA). At that time he also had ataxia and dysarthria, and after few months he was sent to our Center. MRI showed T2 and FLAIR hyperintensities in the brainstem with partial enhancement on gadolinium. Spectroscopy was highly suspicious of neoplasm, but after further follow-up the clinical status and neuroimaging findings pointed to inflammatory demyelinating lesion. In both serum and CSF oligoclonal bands were positive.

At the beginning our preliminary diagnosis was Behcet disease, because patient had genital and oral ulcerations, but all necessary symptoms and laboratory findings to meet criteria for Behcet disease were not present. After careful re-examination of his history, social and working environment we found out that the patient worked in water canals so we performed serology for leptospira. It was positive for *Leptospira Saxkoebing* in serum and in CSF with titer 1:100.

Patient was diagnosed as chronic leptospiral vasculitis, and treatment with antibiotics started although with limited results. MRI figures after one year follow-up are presented in Figure 3.

## **Discussion**

MRI hyperintensities in the central nervous system in young patients are in most instances the part of the positive paraclinical criteria implicating the diagnosis of multiple sclerosis. However atypical clinical symptoms or atypical paraclinical criteria point to a non-MS demyelinating disease (3,4,5). Demyelinating diseases can be further subdivided into idiopathic inflammatory demyelinating disease (including MS, NMO and ADEM), specific inflammatory demyelinating diseases, infective inflammatory demyelinating diseases and non inflammatory demyelinating diseases (including vascular, metabolic, genetic, toxic etc.) (3). Diagnostic dilemmas in idiopathic inflammatory diseases, especially between MS and non-MS types (ADEM and NMO) are well known (9), as well as demand for broad immunological and other tests necessary to define specific inflammatory demyelinating diseases like vasculitides, sarcoid, etc. On the other hand the group of infectious demyelinating diseases are very rare and are not often broadly investigated in the differential diagnosis of demyelinating diseases of the CNS, except for some more common diseases like AIDS, syphilis, PML, Whipple's disease and Lyme diseases (3,4,5,6,10).

Our first patient presented with encephalopathy, febrile status, non tender-pustulous skin changes, lymphadenopathy, splenomegalia and relapsing neurological symptoms: slight motor weakness of the left extremities, diminished visual acuity and double vision, continuous paresthesia in the left extremities with demyelinating changes on brain MRI. Some of the



mentioned symptoms as non-tender papules on legs, remittent febrile status, regional lymphadenopathy and splenomegalia point to the systemic illness, while on the other side neurological symptoms characterized with remittent encephalopathy, loss of visual acuity and minor left sided hemiparesis together with MR findings could be mistaken for MS. This case showed several “red flags” that strongly argued against the diagnosis of idiopathic inflammatory demyelinating diseases: signs of systemic illness, negative oligoclonal bands in the CSF, encephalopathy and MRI which was more typical for non-inflammatory /vascular demyelinating disorder. The diagnosis in this case was not simple, but due thorough history and extensive differential work-up positive tests for *Bartonella hensellae* were detected. *Bartonella hensellae* is a gram negative bacterium, carried by domestic cats, which are bacteriemic at any one time (11). Our patient had contacts with cats, although he couldn't recall the scratch, and it has been shown that it is not absolutely necessary for the development of the disease (11,12,13). Typically cat scratch disease (CSD) develops 3-10 days after the contact with a bacteriemic cat with a non-tender papule and regional lymphadenopathy (11,12,13). Publications of atypical cases showed that encephalopathy is present in 2% of patients, while seizures were the most common neurological presentation (13,14). MRI changes are usually seen in patients with encephalopathy, but they can be present in other cases with neurological presentation (15,16,17). Our case had atypical presentation with pronounced systemic symptoms, remittent encephalopathy combined with relapsing focal neurological deficit and visual disturbances. High intensity gyriform signal on brain MRI was also observed, a finding previously reported (13,14). Although CSD is generally mild and self limited disease, in some cases it can cause systemic complications and pronounced focal neurological symptoms, as it was seen in presented case

(11,12). Therefore it is important to include serology to *Bartonella hensellae* in differential diagnosis of patients presenting with systemic and neurological symptoms.

Second case presented with alternative weakness of left and right extremities with duration of less than 24 hours, with continuous paraesthesiae of the left extremities and brain MRI hyperintensive lesions that raised suspicion of MS, although clinical course and lesions location were not typical for MS. Therefore more consistent and broad work up was performed. As the patient lived in Mediterranean basin serology on *Rickettsia conorii* was tested and was positive. *Rickettsia conorii* is an intracellular bacterium transmitted by dog tick *Rhipicephalus sanguineus*, causing most common benign disease known as Mediterranean spotted fever (MSF) (18).

Typical manifestation of the disease is benign febrile rash involving palms and soles. However in 5-10% of cases disease occurs as serious or even malignant form causing death in even 32,3% of such cases (19,20). Malignant MSF is characterized with purpuric exantema, coma, hypocalcemia, acute renal failure and rhabdomyolysis. In series of 154 cases different neurological manifestations were reported: meningeal syndrome and meningitis, central nervous system involvement mostly with encephalopathy, seizures and cerebellar symptoms, polyradiculoneuritis and cranial nerve palsies (21). It was found that such fatal rate is most common in conditions as alcoholism, advanced age, diabetes, cardiac insufficiency and other chronic diseases (19,20). Similar observations were reported in Rocky spotted fever due to *Rickettsia rickettsii*, with even more pronounced focal neurological signs similar to those observed in our patient (22). In our patient, in spite of pronounced clinical symptoms the clinical course was benign, probably due to immediate introduction of the antibiotic therapy. This instructive case points to the importance to take into the consideration possibility of this disease in some cases of undetermined demyelinating diseases of the central nervous system.

Neuroleptospirosis is a rare condition and according to the two largest series of patients with neuroleptospirosis the commonest presentation are altered sensorium and seizures followed by meningeal, brain parenchymal, infections or by myelitis or myeloradiculoneuritis, ADEM and stroke (23,24). But all these were acute cases of neuroleptospirosis. Mechanism of chronic neurological manifestations is still unknown, but rare pathological studies mostly explain capillary endothelial damage and vasculitis as prominent factors. The presented patient had pneumonia in a septic phase of the disease, and brainstem involvement, possibly arteritis, in the immunological phase of the disease (8).

Nevertheless, need for serological work-up in every patient with suspected MS has recently been questioned. For example Lyme disease is one of the most frequently cited diseases that can mimic MS. However, routine screening for Borrelia antibodies in the absence of a specific indication will produce more false positives than true positives. In a study of 283 consecutive patients with MS, 19 had positive Lyme serology and upon further testing, including spinal tap with measurement of intrathecal antiborrelia antibodies, none of these 19 patients had Lyme disease. (25) On the other hand HIV related CNS disorders are varied and may be due to the direct effect of the virus or a consequence of opportunistic infections, neoplasms and vascular diseases, so HIV testing is warranted in most of the patients with demyelinating lesions. It is interesting that out of 78 “red flags” proposed in the consensus approach to the differential diagnosis of suspected MS, only 17 of them refer to the infectious diseases. Most of them, 5 refer to Whipple disease, 4 to Lyme disease, 3 to HTLV-1, 2 to Histiocytosis and Toxoplasmosis and 1 to tuberculosis, Cysticercosis and PML. (3) Extensive work-up for infections in patients with demyelinating lesions on the brain or spinal cord MRI is rarely necessary. However when atypical clinical or MRI features are present, the clinician should not limit the serological work-

up only to the most frequent mimics, but according to the detailed history and clinical signs, order appropriate serologic tests. Detailed epidemiological history is usually crucial in such instances and should not be forgotten in every patient with demyelinating disease.

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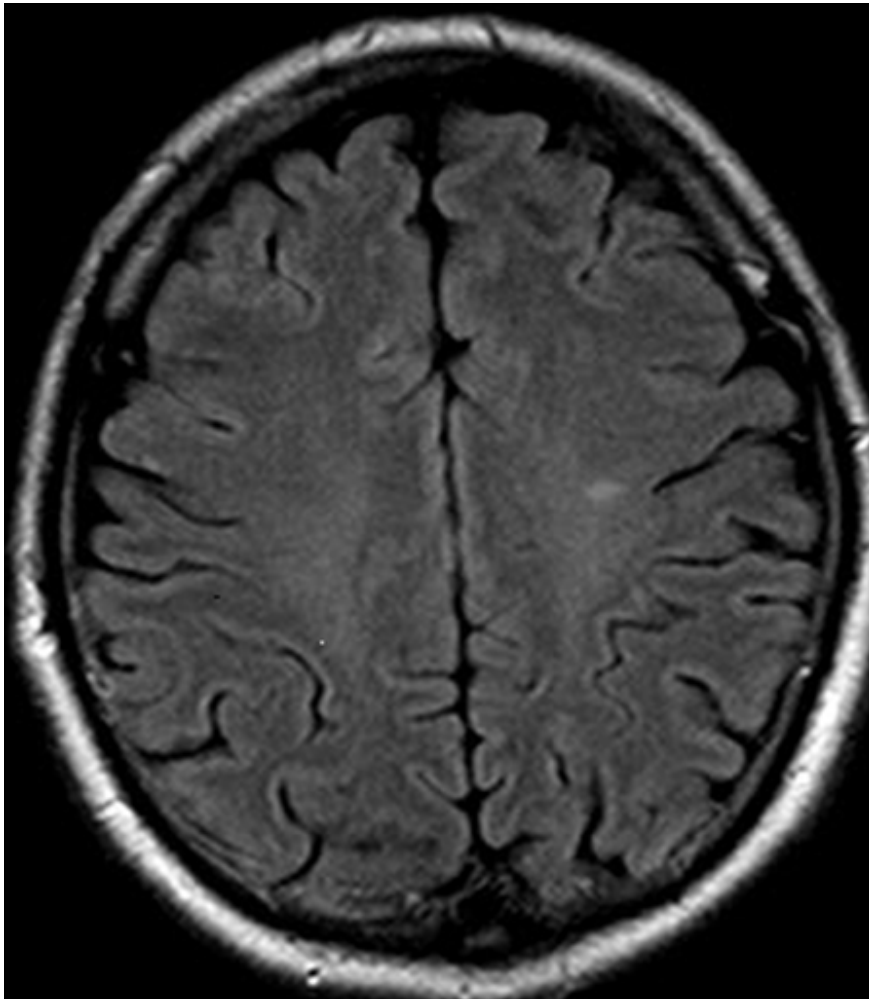
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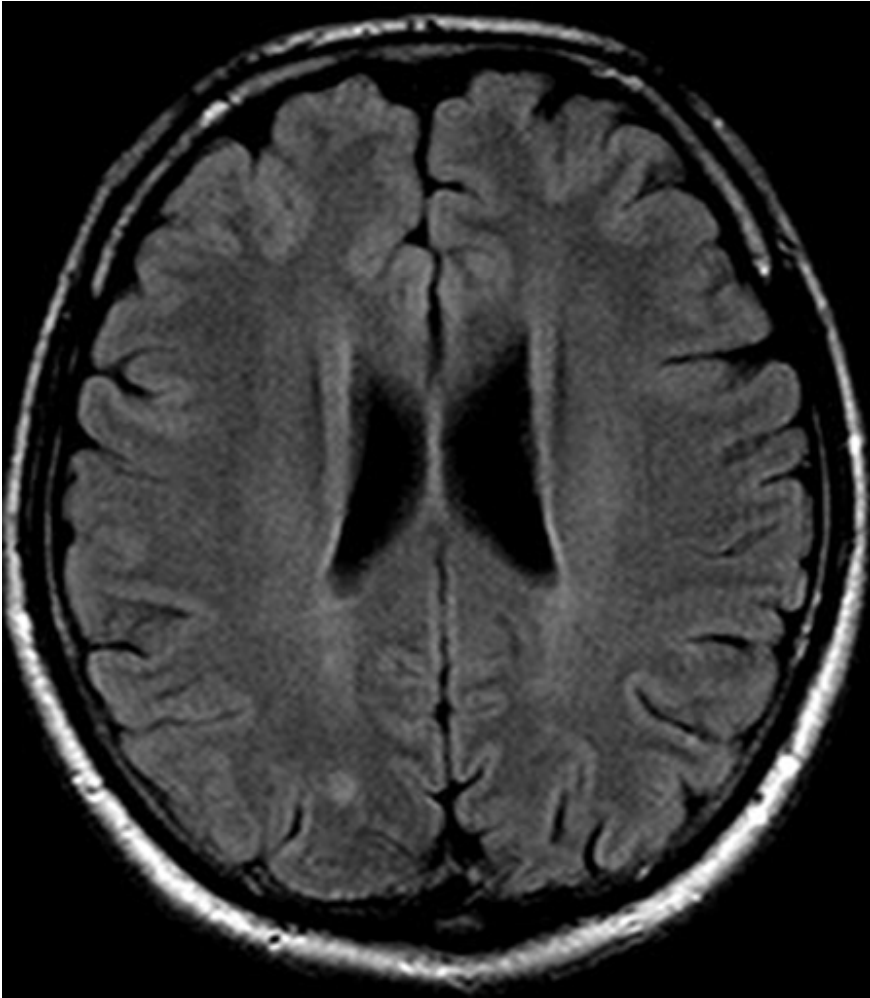
## Figures

**Figure 1.** Patient 1. A) and B) Brain MRI, FLAIR sequences showing oval, subcortical demyelinating lesions; C) DWI sequences showing diffusion restriction.

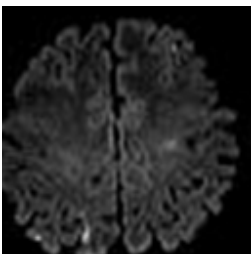


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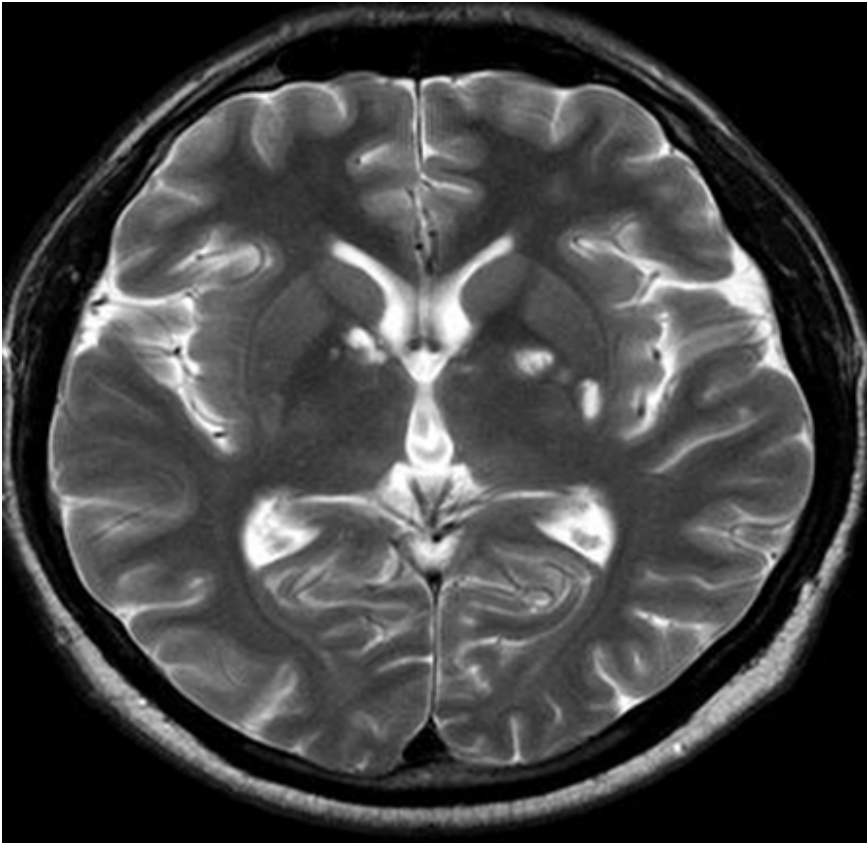


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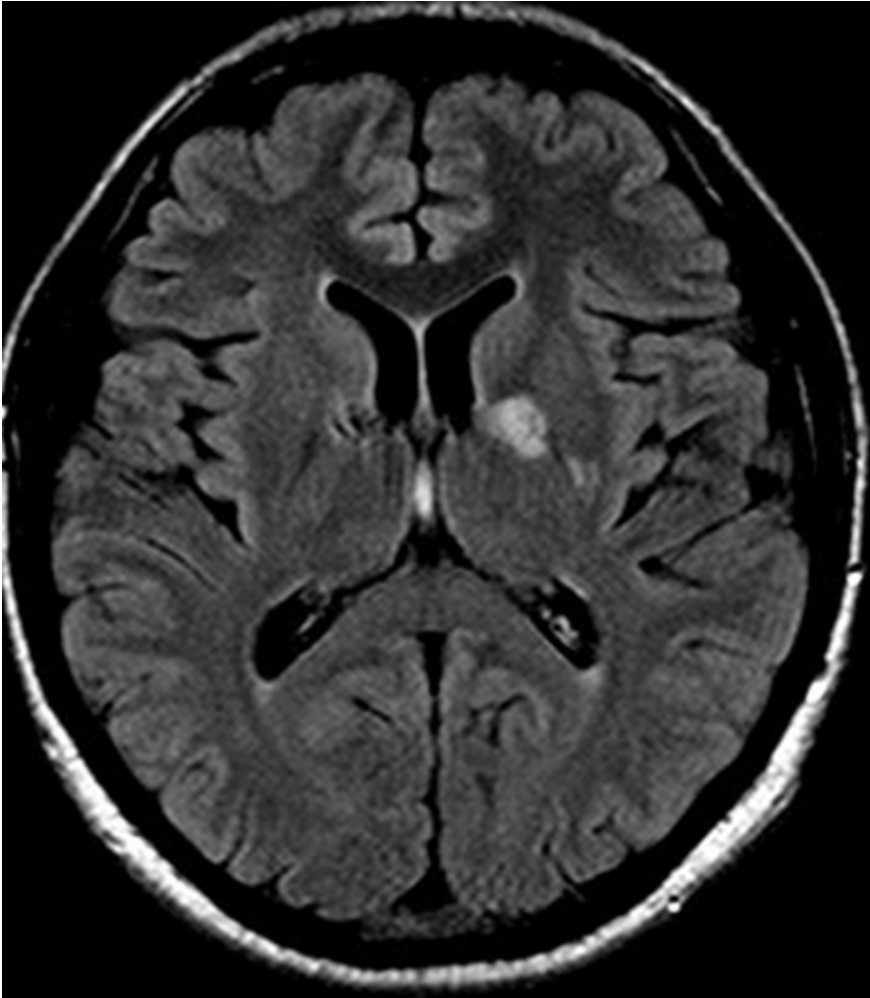


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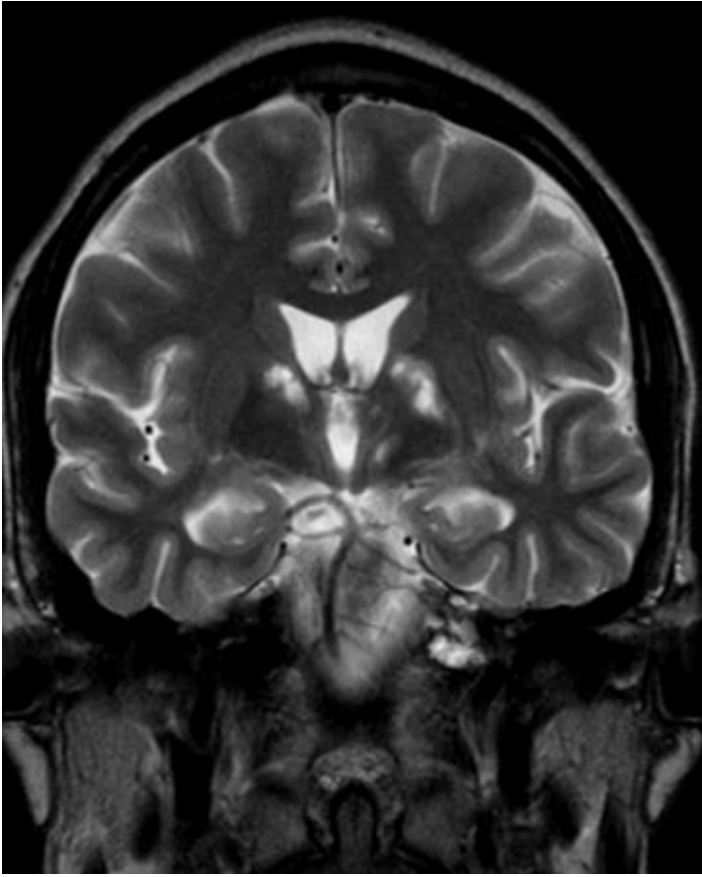
**Figure 2.** Patient 2. A) T2 transversal sequence; B) FLAIR transcersal sequence; C) T2 coronal sequence showing “dirty” putaminal hyperintensities and hyperintensity in right genu capsulae interne.



A

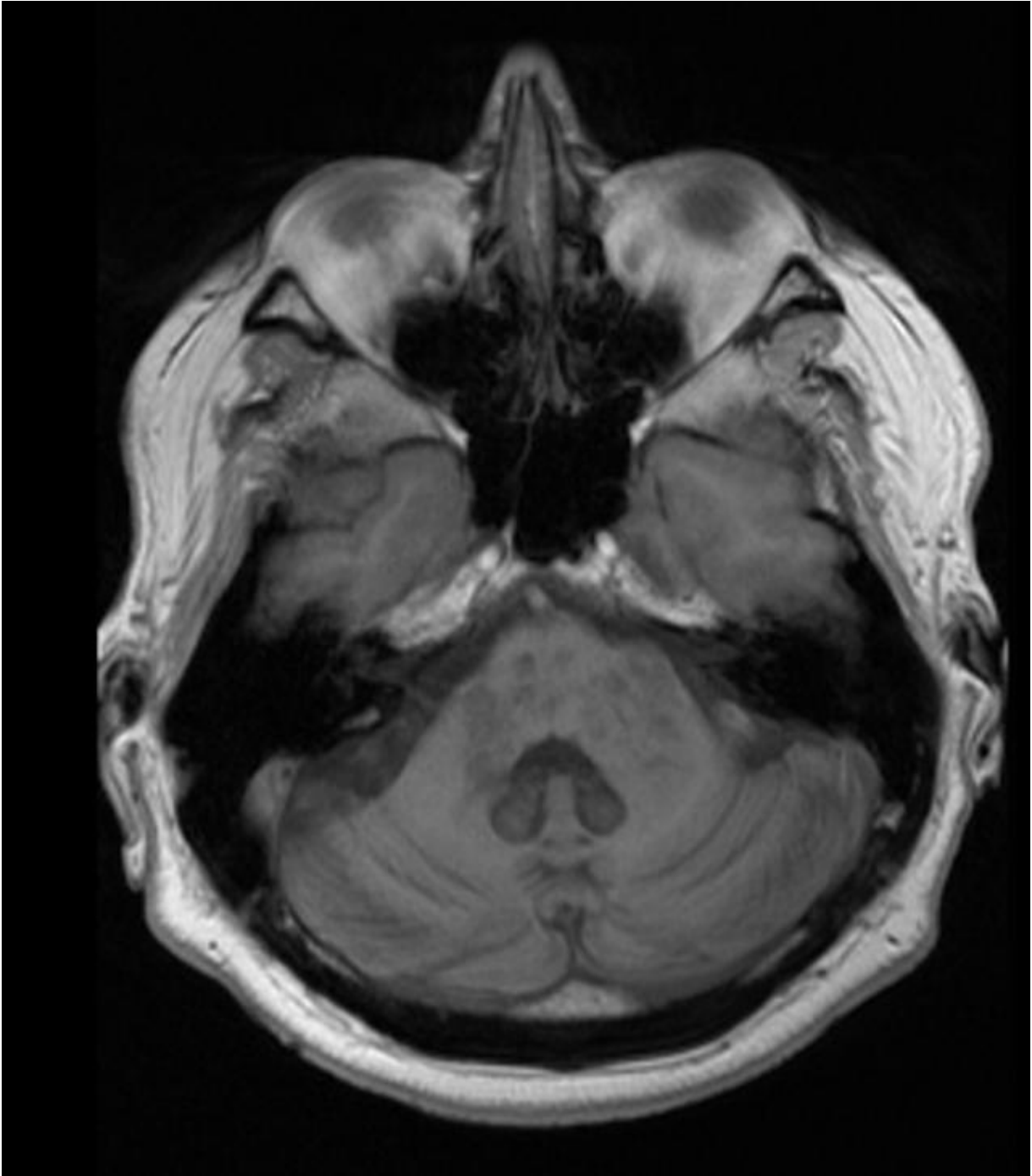


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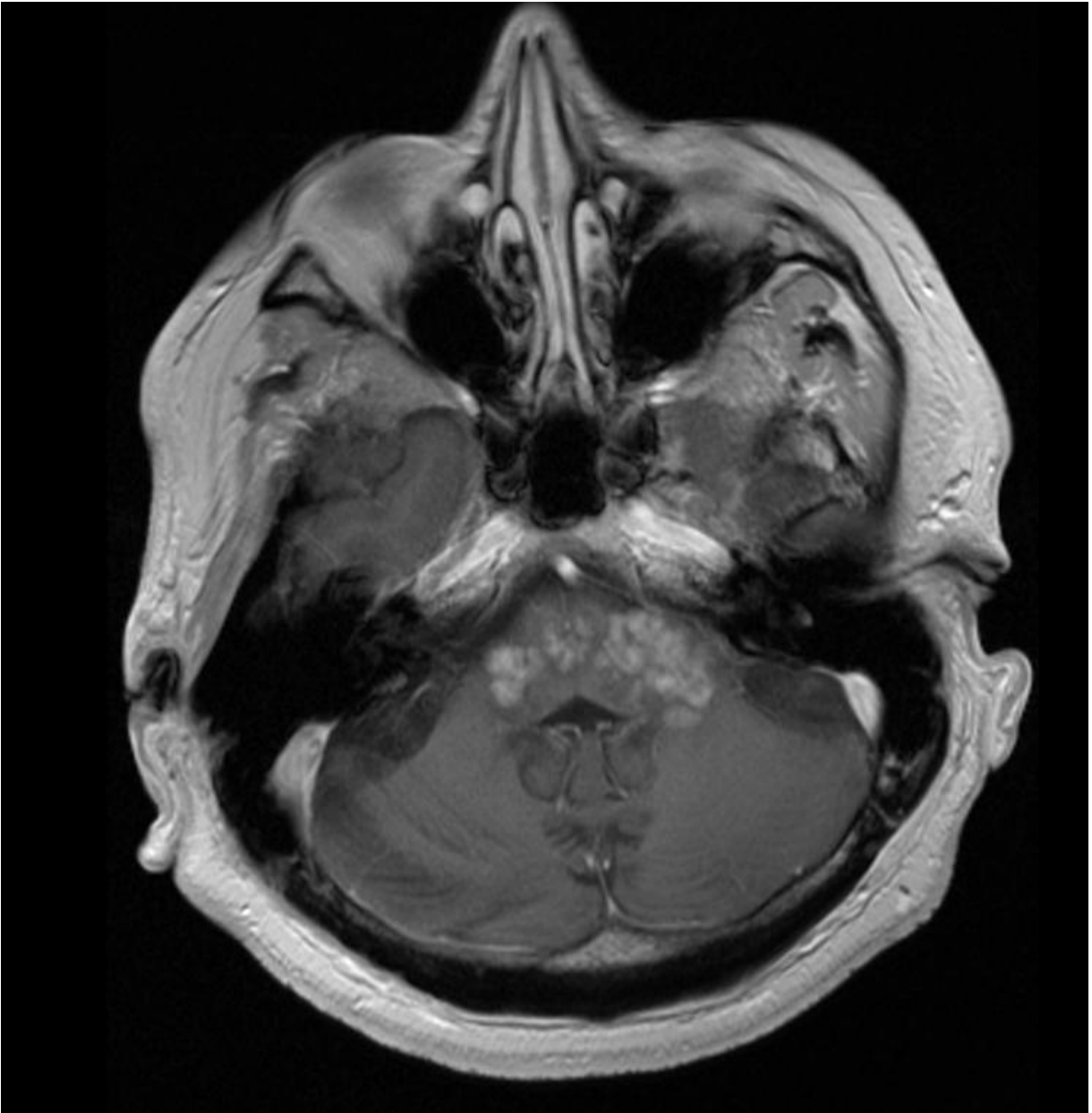
**Figure 3.** Patient 3. A) T1 transversal sequence; B) T2 transversal sequence; C) T1 postcontrast transversal sequence: Brain MRI showing large patchy hyperintensities in both pontine region with enhancement after contrast administration.



A



B



C