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A 24-year-old pregnant woman with headache and behavioral change progressing to
coma

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SECTION 1:

A 24-year-old woman at 21 weeks of gestation developed a subacute, persistent, drug-resistant frontoparietal headache, for which she presented several times to her local emergency department over the course of 20 days. Her physical examination was consistently described as normal, as were routine laboratory parameters and head computed tomography findings, and she was discharged with symptomatic treatment.

Her medical history included depression and alcohol and drug abuse, which she had discontinued two years before. There was no history of migraine or other episodes of headache. This was her third pregnancy and she had two healthy children. Family history was unremarkable.

Three weeks after the initial presentation, she was brought to the emergency department and was described as being disoriented to time, with psychomotor lentification, showing inappropriate behavior and a 'belle indifférence' attitude. The obstetric examination was normal. Her complaints were interpreted as psychosomatic in the context of chronic depression, and she was admitted to the Psychiatry ward, where she was started on sertraline 25 mg id and haloperidol 0.5 mg id. During her stay, she showed infantile behavior with progressively poor communication and lack of interest in group occupational therapy. Sertraline dosage was increased to 100 mg/day, with no clinical benefit.

On day 30 post-admission, the patient developed generalized dystonia and fever (38°C) and was transferred to a tertiary referral hospital. On arrival, the patient was tachycardic, polypneic, diaphoretic, obtunded, had high-grade drug-resistant fever (39°C), and presented right-predominant limb dystonic movements and hyperextension of the trunk, hyperreflexia and bilateral extensor plantar reflexes. Dilated indirect funduscopy revealed no gross abnormalities of the optic disc, macula or retina. Her clinical condition rapidly worsened with depression of consciousness progressing to coma, requiring mechanical ventilation and intensive care unit (ICU) admission.

Questions for consideration:

1. What is your differential diagnosis at this point?
2. What diagnostic testing would you consider?

SECTION 2:

The differential diagnosis for a young pregnant woman with subacute progressive encephalopathy is broad. Given the headache and fever, infectious encephalitis should be the first diagnosis to exclude. Although there was no identified recent environmental context, there was a previous history of alcohol and drug abuse favoring this condition. Autoimmune encephalitis may also present similarly, occasionally with a low-grade fever. Other diagnoses to consider are vascular neurologic conditions associated with pregnancy, namely cerebral venous thrombosis, posterior reversible encephalopathy syndrome, and reversible cerebral vasoconstriction syndrome. Another condition that may be exacerbated during pregnancy is central nervous system (CNS) vasculitis, both primary (primary angiitis of the CNS) and secondary (systemic

inflammatory diseases). Susac syndrome (SuS) is a rare cause of encephalopathy that may also present with migrainous headache and pyramidal signs, and must not be forgotten, despite the absence of the complete triad (encephalopathy, sensorineural hearing loss, and branch retinal artery occlusions (BRAOs)). Other conditions to consider, especially in young women, are other inflammatory demyelinating diseases such as multiple sclerosis (MS) and acute disseminated encephalomyelopathy (ADEM). Taking into account her generalized dystonia and hyperreflexia, fever, and dysautonomia, after exposure to serotonergic and neuroleptic drugs, the serotonergic and neuroleptic malignant syndromes should also be acknowledged.

The evaluation of this patient should therefore be broad, including bloodwork, brain imaging, and cerebrospinal fluid (CSF) examination.

Laboratory examinations revealed mild leukocytosis ($12.9 \times 10^9/L$) with neutrophilia ($10.9 \times 10^9/L$) and PCR (1.55 mg/dL) and CK elevation (3456 U/L).

Brain magnetic resonance imaging (MRI) revealed numerous small T2/FLAIR hyperintense lesions involving the periventricular region, corpus callosum, and internal capsules, with no surrounding edema; and a few more ill-defined and slightly tumefactive lesions in the right middle cerebellar peduncle, adjacent to the left lateral recess of the IV ventricle, periaqueductal, and in the temporo-mesial and insular regions bilaterally. Most lesions were bright on DWI, with ADC values close to the normal parenchyma. Due to pregnancy, gadolinium administration was withheld. (Figure 1A-D)

CSF showed increased protein levels (177 mg/dL) and pleocytosis ($40/mm^3$, mononuclear predominant).

A transthoracic echocardiogram showed no evidence of infective endocarditis.

Questions for consideration:

3. How does this information change your differential diagnosis?
4. What therapy would you initiate?

SECTION 3:

Based on the severe clinical progression, and CSF and imaging changes, treatment for presumed infectious encephalitis was considered a priority. She was started on acyclovir 750 mg every 8 hours, ceftriaxone 2 g every 12 hours, and ampicillin 2 g every 4 hours.

Meanwhile, in the absence of microorganism identification (negative CSF polymerase chain reaction and cultural examination), the patient was also started on intravenous (IV) methylprednisolone 1000 mg id for possible CNS vasculitis. There was no clinical improvement; this prompted the initiation of IV immunoglobulin (IVIg) 20 g id for 5 days. Due to the absence of clinical improvement and considering the potential risks to the fetus of further medications, it was decided to proceed with a cesarean section at 32 weeks of pregnancy. A healthy female newborn was delivered, with no obvious congenital defects and no complications to either the mother or child.

On the following day, a new brain MRI was obtained: the total number of lesions remained stable and there was no gadolinium enhancement. At this time, it was

also noted that the lesions in the corpus callosum affected essentially the central fibers while sparing the callosum-septal interface. (Figure 1E-F) The systemic autoimmune panel, including anti-MOG and anti-AQ4 antibodies and oligoclonal bands, as well as the autoimmune encephalitis and anti-neuronal antibodies panels both on serum and CSF, turned out negative.

The patient was extubated the following day and transferred to the Neurology ward for further workup.

Questions for consideration:

5. What is the most likely diagnosis?
6. What further testing would help to confirm the diagnosis?
7. Which treatment(s) should be considered?

SECTION 4:

Based on clinical and paraclinical findings, SuS was presumed and the patient was started on rituximab two cycles of 500 mg two weeks apart. Even though the typical clinical triad was not complete, brain MRI showed the characteristic centrally located corpus callosum lesions.

Meanwhile, there was a general clinical improvement, and patient became able to undergo thorough ophthalmologic and audiometric assessments. Fluorescein angiography showed BRAO in the left eye temporal periphery with associated late-stage leakage suggestive of occlusive vasculitis. (Figure 2A-B) Pure-tone audiometry revealed mild bilateral neurosensory hearing loss. (Figure 2C)

The patient's neurological status slowly improved and she was finally discharged to a rehabilitation center 123 days after hospital admission. She was kept on rituximab 1000 mg IV every 6 months. Three years after presentation, the patient has presented no relapses, is independent in her daily activities, and has only a mild spastic right hemiparesis. Follow-up brain MRI shows no new lesions and retinal evaluation reveals no signs of vasculitis. Her child has been meeting all developmental milestones.

DISCUSSION

SuS is an autoimmune-mediated endotheliopathy that causes occlusion of the brain, inner ear, and retinal microvessels. It is characterized by the classical triad of encephalopathy, sensorineural hearing loss, and BRAOs.¹ Other common clinical features include migrainous headache, reported in about 80% of patients, and pyramidal and cerebellar dysfunction.^{1,2}

SuS primarily affects women of childbearing age. Given its rarity, the true incidence and prevalence are not well known, but occurrence during pregnancy or post-partum has been described in about 5% of female patients.³

As the classical triad is very rarely noticed on initial presentation, in as few as 13% of patients¹, diagnosis is often challenging. This occurs because eye and ear involvement may be subclinical, and encephalopathy is the presenting symptom in as many as two-thirds of cases¹, precluding the overt expression of

the other symptoms. Therefore, a targeted search for absent components of the triad is essential.

Diagnosis may be supported by brain MRI, which typically shows multiple small T2/FLAIR hyperintense, sometimes with restricted diffusion, and usually contrast-enhancing lesions, throughout both deep gray and white matter, in callosal, periventricular, and subcortical localization, although the cerebellum, cerebellar peduncles and brainstem may also be involved. Corpus callosum lesions, described as “snowballs”, typically involve the central fibers, sparing the periphery, and are best seen on sagittal sections.^{1,2,4} CSF often shows mild lymphocytic pleocytosis and moderate elevation of protein levels, and may present oligoclonal bands.^{1,2} No specific biomarkers are available to support the diagnosis; although anti-endothelial cell antibodies have been proposed, more research is required to determine their role in the diagnosis of these patients.⁵

The initial treatment consists of pulsed IV methylprednisolone (1000 mg daily for 3-7 days) followed by tapering oral prednisolone (1 mg/kg/day). IVIg (2 g/kg divided in 5 days) and plasmapheresis (3-10 exchanges) may also be an option in severe cases refractory to steroids. Steroid-sparing immunosuppressive therapy [mycophenolate mofetil (3000 mg/day), rituximab (two cycles of 1000 mg 14 days apart, followed by 1000 mg every 6 months), or cyclophosphamide (two cycles of 10-15 mg/day mg 2 weeks apart, followed by monthly cycles)] is recommended to prevent relapses.^{2,6}

There are currently no guidelines for the treatment of SuS during pregnancy. Steroids, IVIg and plasmapheresis seem to be safe, whereas mycophenolate mofetil and cyclophosphamide are teratotoxic. Although harmful effects cannot be ruled out definitively, rituximab may be considered in severe cases.³

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Figure 1 – Brain MRI on presentation (A-D). Axial fluid attenuated inversion recovery (FLAIR) shows hyperintense lesions in the periventricular white matter and internal capsule (A), as well as infratentorial lesions (B), with high signal on axial diffusion-weighted imaging (DWI) (C). Additional T2 hyperintense lesions are seen in the corpus callosum, corona radiata, and subcortical white matter (D). Follow-up brain MRI (E-F) highlights corpus callosum lesions involving central fibers while sparing peripheral fibers, with hyperintense signal on FLAIR (E) and corresponding marked hypointensity on T1 (F) – “snowball” lesions.

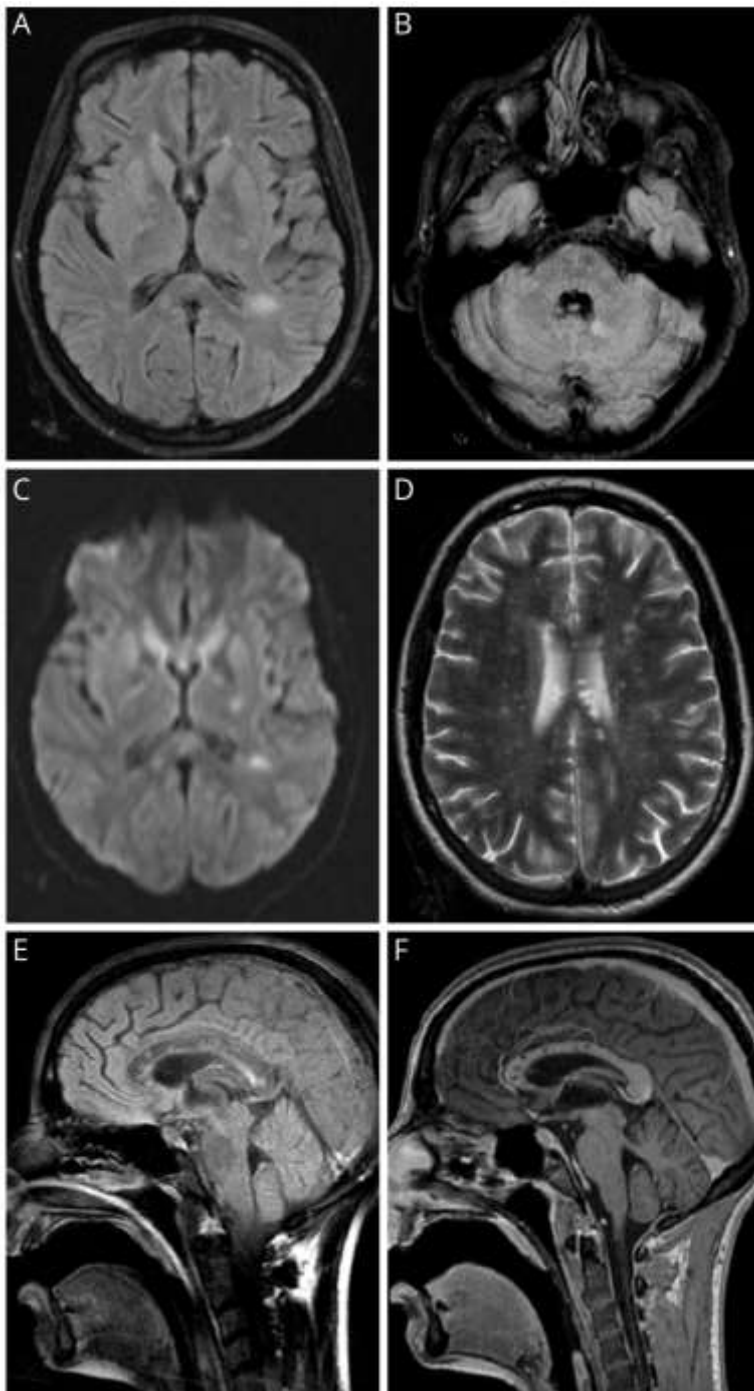
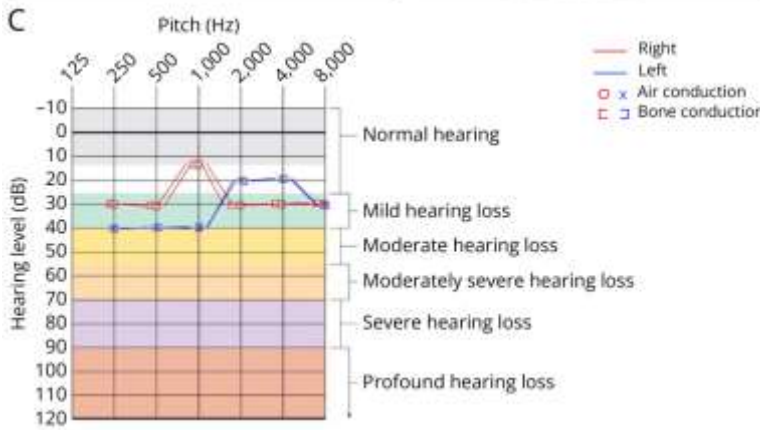
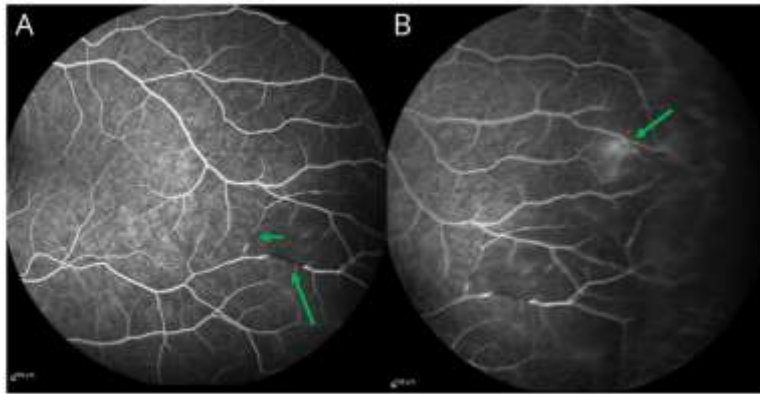


Figure 2 – A and B) Fluorescein angiography of the left eye demonstrating branch retinal artery occlusions (A, arrows) as a fluid void and hyperfluorescence due to leakage from inflamed arterioles (B, arrow). C) Pure-tone audiometry showing mild bilateral sensorineural hearing loss.



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