

# Cavitary forms of multiple sclerosis and their clinical and radiological aspects: Observations and revue of literature

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**Abstract-** Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and neurodegeneration. Although classical sclerosing lesions are well described, cavitary forms of MS are of increasing interest due to their potential impact on disease progression and response to treatment. We report two cases of MS with large cavitary brain lesions. Clinical and biological features, progressive form, Expanded Disability Status Scale (EDSS), Mini-mental-State-Exam (MMSE) and radiological features, including magnetic resonance imaging (MRI), of the cavitary lesions were analyzed.

**Keywords:** Multiple sclerosis, Cavitary forms of Multiple sclerosis, Disease progression

## Introduction

Multiple sclerosis (MS) is a heterogeneous disease with varied clinical presentations and an unpredictable course. Cavitary lesions, characterized by fluid spaces in brain tissue, are observed in a subset of MS patients. These lesions pose unique diagnostic and therapeutic challenges, underscoring the need for a thorough understanding of their nature and impact on the disease.

The exact mechanisms underlying cavity formation in MS remain poorly understood. However, several hypotheses have been put forward, including the effects of neuroinflammation, extensive demyelination, neurodegeneration, and the loss of supportive glial cells. Neuropathological studies suggest that cavitary lesions result from a combination of inflammatory and degenerative processes, leading to extensive tissue destruction.

The diagnosis of cavitary forms of MS relies primarily on magnetic resonance imaging (MRI). Cavitary lesions are characterized on T2Flair MRI by poorly delineated hyposignals within hypersignals, probably corresponding to white matter rarefaction [1].

Large cavitary lesions are not typical for MS. Cavitary white matter changes may be seen in megalencephalic leukoencephalopathy with subcortical cysts, Alexander disease, mitochondrial leukoencephalopathies, vanishing white matter disease (VWMD), leukoencephalopathy with calcifications and cysts, cytomegalovirus infection, and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [2–5]. These diseases are mainly observed in young patients and are rare in adults (except CA DASIL), in contrast to MS. The cavitary aspect of these diseases differs depending on the disease type. In megalencephalic leukoencephalopathy with subcortical cysts, cysts show bilateral extensive white-matter changes, with cysts mainly located in the temporal regions [5]. In mitochondrial leukoencephalopathies, cysts may be seen (sometimes with a rim of restricted diffusion around the cysts), most often associated with other MRI abnormalities (e.g., stroke-like lesions, laminar cortical necrosis, basal ganglia necrosis, white matter lesions, atrophy, calcifications, cysts, lacunas, hemorrhages, intracerebral artery stenosis, or Moya Moya syndrome) [3]. In VWMD, abnormal cerebral white matter degenerates, leaving behind a meshwork of better preserved tissue strands, but not well-delineated cysts. VWMD is caused by mutations in either one of the five genes (EIF2B1–5) encoding subunits of the translation initiation factor eIF2B (with EIF2B5 as most frequently involved gene) [1, 4]. Leukoencephalopathy with calcifications and cysts is characterized by asymmetric calcifications, diffuse abnormal white matter signal, parenchymal brain cysts (often showing mass effect and/or contrast enhancement). Therefore, a thorough clinical evaluation and correlation with other MS features are necessary for an accurate diagnosis.

## Observation 1

He is a 38-year-old man admitted with muscle weakness in the lower limbs, imbalance when walking and slowness of speech progressing towards for 1 year " March 2021. Note that the patient had previously suffered 2 relapses, the 1st in 2011 spontaneously regressing in 10 days and the 2nd in 2020 with partial improvement. Neurological examination revealed a stato kinetic cerebellar syndrome with dysarthria and pyramidal syndrome in all 4 limbs. The mean EDSS score was 6.0. Neuropsychological evaluation revealed an MMSE of 22/30 for a university

level of study, attentional problems, slight disturbance of memory capacity, notably impaired verbal episodic memory retrieval (Nine pictures test-93 "TNI 93": Delayed Recall 7/9 with Free Recall 5/9, Indicated Recall 2/4) and working memory problems with an indirect number span of 3. Cerebrospinal fluid (CSF) showed normal cytochemistry, and immunoelectrophoresis revealed an inflammatory profile with intrathecal IgG synthesis. The IgG index was elevated to 7.5, with the presence of oligoclonal IgG bands. HIV, HCV, HBV and syphilis serologies were negative.

Brain MRI revealed multiple T2 hypersignals and T1 hyposignals in the subcortical white matter, periventricular, corpus callosum and deep arcuate fibers, at least 3 of which were active at the level of the frontal convexity, showing incomplete annular enhancement after gadolinium injection (Cf Fig 1 and 2). On T2 FLair there are hypersignal areas centered by a hyposignal of more than 50%, giving a pseudo-cavity appearance (Cf Fig 3). Presence of multiple centro-cerebellar hypersignals and middle cerebellar peduncles on T2 Flair, one of which is annularly enhanced in the left middle cerebellum. Spinal cord MRI revealed multiple T2/ T2 STIR hypersignals of the cervicothoracic medulla without contrast.

Bolus methylprednisolone was recommended, resulting in a slight improvement, with the EDSS score rising to 5.5 after 2 boluses.

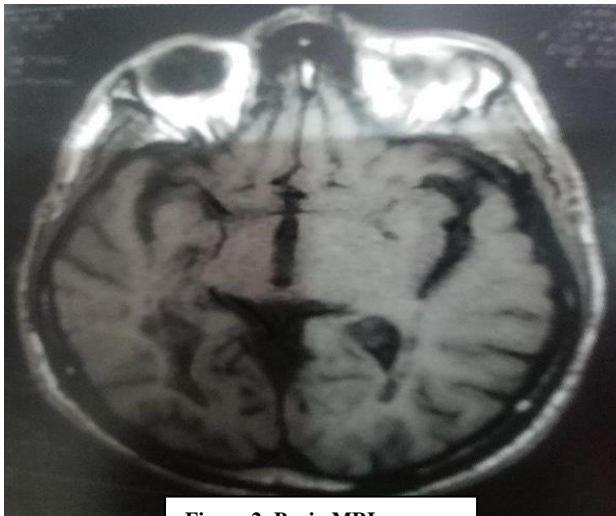


Figure 2: Brain MRI  
T1 cavitations

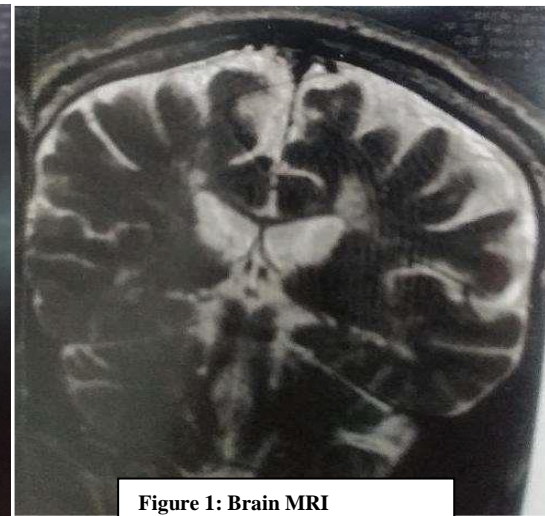


Figure 1: Brain MRI  
T2 hypersignals



Figure 3: Brain MRI  
T2 FLAIR cavitations

### Observation 2

The patient in question was S.A., aged 58, with a history of arterial hypertension and no similar cases in the family. The onset of his disorders dated back a year and was marked by a subacute onset of muscular weakness, tingling paresthesias in the right hemisphere, agueusia, and a speech disorder with a lack of words, leading to hospitalization in a neurology department.

Neurological examination revealed a pyramidal syndrome in all 4 limbs, more marked in the right, a spinothalamic syndrome in the right with a dorsal level, and vesicosphincter disorders such as urinary urgency.

The somatic examination was unremarkable.

The Expanded Disability Status Scale (EDSS) score is 4.5.

Neuropsychological evaluation, in particular of information processing speed using the SDMT, "The Symbol Digit Modalities Test", showed a marked slowdown. The patient returned six correct answers in 90 seconds. There was global cognitive dysfunction on the MMSE (Mini-Mental State Examination) with a score of 16/30 and

dysexecutive syndrome with the FAB (Frontal Assessment Battery) score of 9/15. These include disruption of planning, sensitivity to interference, and loss of inhibitory control.

The ophthalmological workup (visual acuity, slit lamp, fundus) was unremarkable.

Cerebral MRI revealed multiple white matter lesions in the form of T2 hypersignals and, on T2Flair, a cavitory appearance of lesions with poorly demarcated hyposignals within hypersignals and T1 hyposignals. Lesions are periventricular, juxta, and subcortical, left external capsular, and in the left thalamic nucleus. They are nodular in shape. There is discrete para-ventricular enhancement on the right, opposite the posterior horn of the left lateral ventricle with Gadolinium (see Figures 4 and 5). The spinal cord MRI was normal.

Standard laboratory tests and deficiency tests (vitamin B9, B12 and homocysteine levels) came back normal. Viral serologies (HIV, Hepatitis B and C, syphilis) were negative.

Cytochemical study of the CSF revealed a clear fluid and isolated hyperproteinorachia at 0.78g/l, with a normal profile on CSF immunoelectrophoresis. The autoimmunity test was negative. Anti-NMO (Neuromyelitis optica) and anti-MOG (Myelin oligodendrocyte glycoprotein) antibodies were negative. Cerebral evoked potentials were normal. Bolus methylprednisolone was recommended, resulting in a slight improvement, with the EDSS score rising to 4.0 after 2 bolus. Treatment with Tysabri (Natalizumab) was recommended.

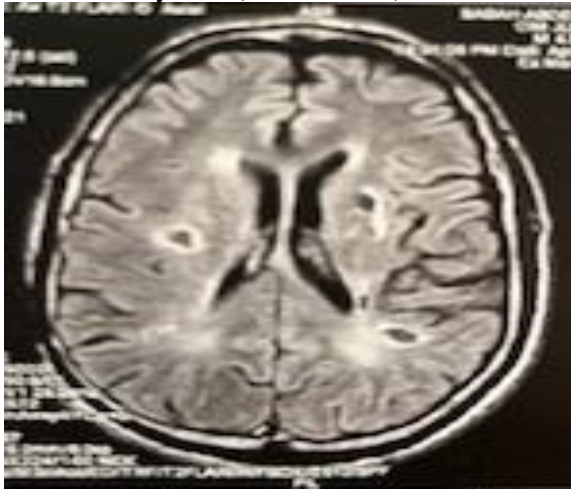


Figure 4: Brain MRI  
T2 FLAIR cavitations

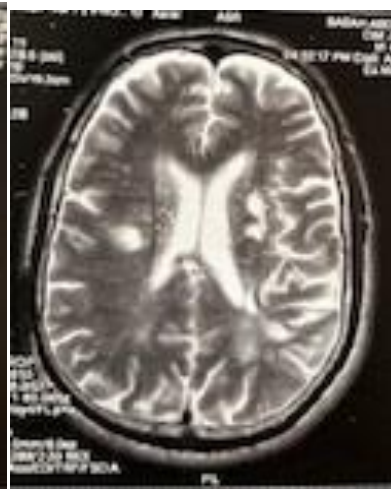


Figure 1: Brain MRI  
T2 hypersignals

## Discussion

MS patients may have atypical brain MRI findings. These cavitory lesions have not been frequently described in MS, even in patients with very long evolution [6,7]. Such cavitory lesions have been mainly described in VWMD, which is an autosomal recessive disorder caused by mutations in one of the five EIF2B genes [4]. Cavitory lesions are characterized by ill-delineated FLAIR weighted hypointensities within the WM hyperintensities, probably corresponding to a rarefaction of this white matter (WM) [1]. Even if cavitory lesions are found, the differential diagnosis between cavitory MS and VWMD is usually simple since clinical findings (relapses, optic neuritis) as well as biological results (oligoclonal bands found in cerebrospinal fluid) found in MS distinguish these two disorders. Nevertheless, it has been described previously that the majority of patients with cavitory MS have an initial progressive onset of cerebellar ataxia and/or spastic paraparesis that is close to symptoms seen in VWMD [8]. Additionally, a recent report has highlighted that VWMD should be considered a differential diagnosis of primary progressive MS in patients with cavitory lesions, highlighting that cavitory MS has to be considered to start treatments early [9]. The distinction between MS with cavitory lesions and VWMD can be difficult in some cases. Our cases clearly show certain MRI features that appear to be MRI features that seem to be specific to cavitory MS and thus help to differentiate these two disorders. Cavitory lesions in hyposignal T1 /FLAIR are strictly supratentorial, well delimited, and located only within areas of abnormal white matter in hypersignal T2 /FLAIR and predominate in the posterior regions.

Indeed, in MS, cavitory lesions generally have a periventricular predominance, whereas they are more frequently anterior in CACH syndrome. In addition, an MRI of the spinal cord in Case 1 showed multiple cervical and thoracic T2 T2 STIR hypersignals, arguing in favor of MS.

Cavitory MS is characterized by a later onset, a more frequently primary progressive form, often high EDSS scores, and severe cognitive impairment, as in our patients.

Cavitory forms of MS present a therapeutic challenge due to their often refractory nature to standard treatments. Therapeutic approaches specifically targeting the mechanisms underlying cavity formation may be required. In addition, strategies aimed at attenuating neuroinflammation and promoting remyelination could offer new therapeutic avenues.

Our two patients define a phenotype of multiple sclerosis patients, characterized by the presence of cavitations within the white matter, a later onset, high EDSS scores, and severe cognitive impairment. These clinical features point to a pathophysiology that begins with a demyelinating process with the disappearance of oligodendrocytes, followed by progressive axonal destruction associated with cortical atrophy. These lesions are different from black holes and are not strictly correlated with the age of the disease.

### Conclusion

MS patients with large cavitory lesions represent an atypical form, posing a diagnostic problem with VWMD. Careful analysis of lesion morphology and location is useful in differentiating these distinct pathologies. The morphology of the hyperintensities (perpendicular to the lateral ventricle lesions and punctuate juxtacortical lesions in MS) as well as their topography (symmetric infratentorial lesions in VMWD) and the topography of the cavitory lesions (periventricular in MS and anterior in VWMD) are very helpful for the diagnosis of these two diseases.

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