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# Diffusion Restricted Lesions in the Splenium of the Corpus Callosum

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**Abstract.** *Background/Aim: Various neurological disorders are associated with lesions predominantly or exclusively affecting the splenium of the corpus callosum (CC), such as Marchiafava-Bignami syndrome (MBS), reversible splenium lesion (RSL), and ischemic stroke (IS). The spectrum of symptoms is broad and clinical presentations may be indistinguishable. Therefore, we aimed to investigate the additional value of diffusion-weighted imaging (DWI) findings of splenial lesions in patients with MBS, RSL, and IS. Patients and Methods: Overall, 23 patients (4 patients with MBS, 10 patients with RSL, and 9 patients with isolated IS in the splenium) were identified from a magnetic resonance imaging report database and analyzed with focus on lesion localization, shape, and size on DWI, as well as relative apparent diffusion coefficient (ADC). Results: A focal hyperintensity in the splenium was observed on DWI in all patients. In MBS symmetrical boomerang-shaped lesions, in RSL central oval or round lesions, and in IS eccentric irregular lesions in the splenium were found. The median lesion size in MBS [6.25 (IQR=2.04-8.62) ml] was significantly larger than that in RSL [0.38 (IQR=0.09-0.92) ml, p=0.01], and in IS [0.09 (IQR=0.05-0.94) ml; p=0.01]. Regarding relative ADC values, no significant differences between MBS [0.32 (IQR=0.19-0.62)], RSL [0.22 (IQR=0.14-0.30)], and IS [0.27 (IQR=0.20-1.19)] were found. Conclusion: Diffusion restricted lesions in the splenium of the CC are best classified by localization, shape, and size, whereas relative ADC values are of limited value for differentiation of different neurological disorders.*

The splenium (Greek for bandage or patch) is the most dorsal and thickest part of the corpus callosum (CC) (1) and connects occipital, parietal as well as inferior and medial temporal cortex regions (2). On sagittal anatomical sections on magnetic resonance imaging (MRI) the splenium may seem inseparable from the CC at first glance. However, on transverse anatomical sections on MRI, the complexity of its anatomical structure and its connections to other anatomical brain regions can easily be recognized. The splenium obtains arterial supply in particular from the posterior cerebral artery (PCA) (3). Various neurological disorders are associated with lesions predominantly or exclusively affecting the splenium of the corpus callosum (CC), such as Marchiafava-Bignami syndrome (MBS), reversible splenium lesion (RSL), and ischemic stroke (IS) (4). The spectrum of symptoms is broad and clinical presentations may be indistinguishable. Consequently, it might be crucial to know the characteristic neuroimaging features of splenial changes in differentiating the underlying pathological condition.

Diffusion-weighted imaging (DWI) was developed in the 1980s and implemented as a standard imaging procedure in acute ischemic stroke in the 1990s (5). Although diffusion restriction often reflects a vascular etiology, it may occur in many other neurological disorders such as seizures and status epilepticus (6), transient global amnesia (7), brain tumors (8), encephalopathies of different etiology (9), as well as pontine and extrapontine myelinolysis (10). Thus, in particular DWI might be of additional value for the evaluation and differentiation lesions in the splenium of the CC caused by different etiologies.

Therefore, we investigated the usefulness of DWI findings of splenial lesions in patients with MBS, RSL, and IS.

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*Key Words:* Splenium lesion, Marchiafava-Bignami syndrome, ischemic stroke, diffusion-weighted imaging.

Table I. *Predisposing illnesses and comorbidities, clinical presentation, and MRI findings in Marchiafava-Bigami syndrome (MBS), reversible splenium lesion (RSL), and ischemic stroke (IS) in the splenium of the corpus callosum.*

| | Age, years | Male sex (n, %) | Predisposing illness | Comorbidities | Clinical presentation | MRI findings |
|---|---|---|---|---|---|---|
| MBS, n=4 | 50 (IQR=31-81) | 4 (100%) | Alcoholism with malnutrition and vitamin B6 deficiency<br>Malnutrition and vitamin B6 deficiency in combination with myelodysplastic syndrome | Cigarette smoking, arterial hypertension, atrial fibrillation, gastroesophageal reflux disease | Aphasia, seizures | Symmetrical boomerang-shaped lesions |
| RSL, n=10 | 42 (IQR=17.5-44) | 5 (62.5%) | Seizures<br>viral meningitis<br>hypoglycemia<br>hypernatremia<br>carbamazepine withdrawal | Diabetes mellitus, trigeminal neuralgia, septic abortion | Headaches, nausea and vomiting, diarrhea, fever, dizziness, sensorimotor hemiparesis | Central oval or round lesions |
| IS, n=9 | 65 (IQR=37.5-79.5) | 5 (55.6%) | After interventional treatment of a vein of Galen malformation<br>Cerebellar hemorrhage due to aneurysm of a vertebral artery | Arterial hypertension, hyperlipidemia, diabetes mellitus, history of stroke, history of coronary heart disease, atrial fibrillation, adipositas, Alzheimer's disease | Headaches, dizziness, nausea and vomiting, aphasia, dysarthria, hemiparesis | Eccentric irregular lesions |

## Patients and Methods

*Patients*. This retrospective single-center study was approved by the local institutional review board and performed in accordance with the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. The need for written informed consent was waived due to the retrospective nature of the study. We identified all patients with a DWI lesion solely or predominantly affecting the splenium (n=23) from a combined inpatient and outpatient radiology database with more than 60,000 neuroradiological MRI reports (2002-2019). There were 211 positive radiology reports identified in the database with diffusion restriction in the CC. We excluded all patients with history of recent neurosurgical procedures, head trauma or history of CNS malignancy. Consequently, 188 patients were further excluded due to documentation of central nervous system instrumentation/neurosurgical procedures, head trauma or history of malignancy (*e.g.*, lymphoma, glioblastoma). Finally, we included 4 patients with MBS, 10 patients with RSL, and 9 patients with isolated IS of the splenium in the final cohort for further analysis. The diagnosis of MBS, RSL, and IS was based on the clinical symptoms at presentation and during hospitalization corroborated by imaging and laboratory findings. The demographic details, clinical presentation, predisposing illnesses, and comorbidities were abstracted from the hospitals case records in each case. Additionally, the patients' laboratory test results were reviewed with a special focus on vitamin B1, B6, and B12 levels. Patient records, medical images, and other data were not anonymized before access for this study.

*MRI studies*. MRI was performed on a 1.5-T or a 3-T MR system (Magnetom Sonata/Avanto/Trio, Siemens Healthineers, Erlangen, Germany). A standardized protocol was used in all patients including DWI (field of view 230×230 mm, matrix 128×128/192×192/192×192 mm, TR 4,200/4,000/4,000 ms, TE 101/96/91 ms, b values 0 and 1,000 s/mm$^2$, 24 slices, slice thickness 5 mm), T1- and T2-weighted as well as fluid attenuated inversion recovery (FLAIR) images.

*Data processing and analysis*. All MRI scans were independently reviewed by two readers (blinded) with regard to lesion location and signal characteristics on transverse DWI. Lesion size was measured on DWI by a manually delineated region of interest (ROI), summation of these areas in cm$^2$ on each section, and multiplication with the slice thickness, to determine the volume in cm$^3$ using a multidimensional image navigation and display software (OsiriX; Pixmeo SARL, Bernex, Switzerland) (11). Furthermore, apparent diffusion coefficient ADC maps were quantitatively assessed. Ratios between the ADC values of 1) a manually defined ROI in the hyperintense area in the splenium on DWI and 2) a second manually defined ROI in the ipsilateral corona radiata were determined. Normal white matter in the ipsilateral corona radiata was chosen as reference tissue for the quantitative comparison of ADC since it has been shown to have comparable ADC values as the splenium of the CC (12).

*Statistical analysis*. Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) statistics for Windows (Release 17.0; SPSS, Chicago, IL, USA). Chi-square, Mann-Whitney U, or Kruskal-Wallis tests were used to analyze descriptive data as appropriate. Comparison of lesion size on DWI and rADC was performed using the Mann-Whitney *U*-test. All statistics was performed with a 0.05 level of significance.

## Results

*MBS*.

*Patient demographics and clinical presentation*. The median age of the 4 patients with MBS was 50 (IQR=31-81) years; all 4 patients (100%) were male. The suspected underlying causes of MBS were malnutrition and vitamin B6 deficiency in

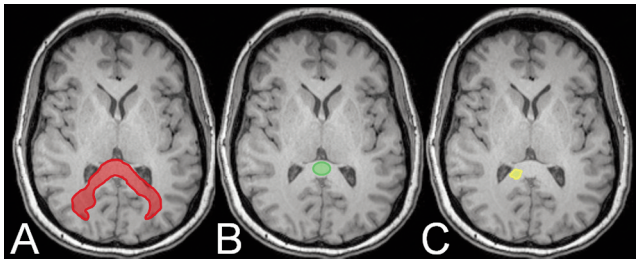


Figure 1. *Schematic illustration of diffusion-weighted imaging findings in A) Marchiafava-Bignami syndrome B) Reversible splenium lesion and C) ischemic infarction in the splenium.*

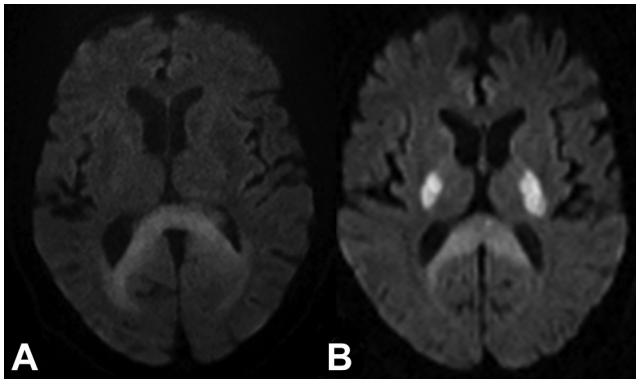


Figure 2. *Examples of two patients with Marchiafava-Bignami disease. A) and B) DWI shows symmetrical boomerang-shaped diffusion restricted lesions in the splenium of the corpus callosum. B) Note additional symmetrical diffusion restricted lesions in the corona radiata.*

combination with alcoholism in one patient, malnutrition, and vitamin B6 deficiency in combination with myelodysplastic syndrome in one patient, and unclear in two patients. Comorbidities included alcoholism, cigarette smoking, seizures, arterial hypertension, atrial fibrillation, gastroesophageal reflux disease, and myelodysplastic syndrome. Clinical symptoms are shown in Table I.

*MRI analysis*. All patients with MBS presented with symmetrical "boomerang"-shaped lesions (Figure 1 and Figure 2; Table I). On DWI, splenial lesions had a median volume of 6.25 (IQR=2.04-8.62) ml with a median rADC value of 0.32 (IQR=0.19-0.62).

*RSL*.

*Patient demographics and clinical presentation*. The median age of the 10 patients with RSL was 42 (IQR=15-45) years; 7 patients (70%) were male. The suspected underlying causes of RSL were seizures in three patients, viral meningitis in three patients, hypoglycemia in one patient, septic abortion, and hypernatremia in one patient, and carbamazepine withdrawal in a patient with trigeminal neuralgia. Clinical symptoms are shown in Table I.

*MRI analysis*. In RSL, DWI demonstrated central oval or round lesions in the splenium (Figure 1 and Figure 3; Table I). In one patient additional lesions were observed in the corona radiata. The median lesion size was 0.38 (IQR=0.09-0.92) ml. In these lesions, rADC was decreased to 0.22 (IQR=0.14-0.30). Follow-up MRI was performed in all patients and demonstrated complete resolution of the splenial lesions.

*IS*.

*Patient demographics and clinical presentation*. The median age of the 9 patients with IS was 65 (IQR=37.5-79.5) years; 5 patients (55.6%) were male. Clinical symptoms included headaches, dizziness, nausea and vomiting, aphasia, dysarthria, and hemiparesis. Comorbidities comprised arterial hypertension, hyperlipidemia, diabetes mellitus, history of stroke, history of coronary heart disease, atrial fibrillation, adiposities, and Alzheimer`s disease. In one patient, IS in the splenium occurred after interventional treatment of a vein of Galen malformation. In another patient, IS in the splenium was an incidental finding after cerebellar hemorrhage due to an aneurysm of a vertebral artery.

*MRI analysis*. In IS, DWI demonstrated eccentric irregular lesions in all patients (Figure 1 and Figure 4, Table I). The median lesion size was 0.09 (IQR=0.05-0.94) ml. In these lesions, rADC was decreased to 0.27 (IQR=0.20-01.19).

Comparisons between MBS, RSL, and IS. MBS showed the largest median lesion size with 6.25 (IQR=2.04-8.62) ml, which was significantly larger than that in RSL [0.38 (IQR=0.09-0.92) ml, $p$=0.006], and IS [0.09 (IQR=0.05-0.94) ml; $p$=0.01]. There was no significant difference in lesion size between RSL and IS ($p$=0.144). Regarding rADC values, there were also no significant differences neither between RSL [0.22 (IQR=0.14-0.30)] and IS [0.27 (IQR=0.20-1.19)], MBS [0.32 (IQR=0.19-0.62)] and RSL nor between MBS and IS ($p$>0.05).

## Discussion

Focal imaging abnormalities of the splenium of the CC are rare and have been described in a variety of neurological disorders such as MBS, RSL, and IS. In the present study, we report two novel and essential findings: 1) diffusion restricted lesions in the splenium of the CC are best classified by localization, shape, and size, whereas 2) relative ADC values are of limited value for differentiation of these disorders.

MBS is a rare potentially fatal disease found in chronic alcoholics or poorly nourished non-drinkers, which primarily

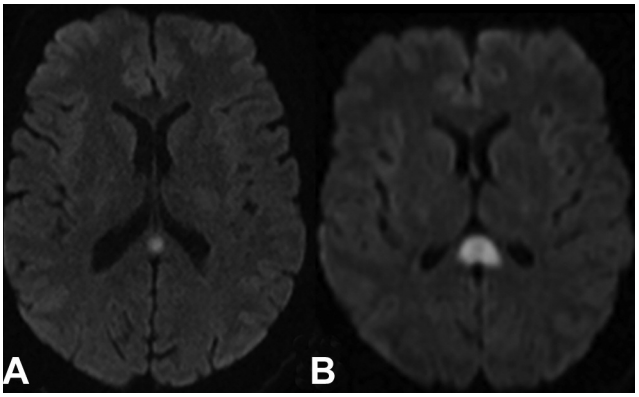


Figure 3. *Examples of two patients (A, B) with reversible splenium lesion presenting with central oval diffusion-weighted imaging lesion in the splenium of the corpus callosum.*

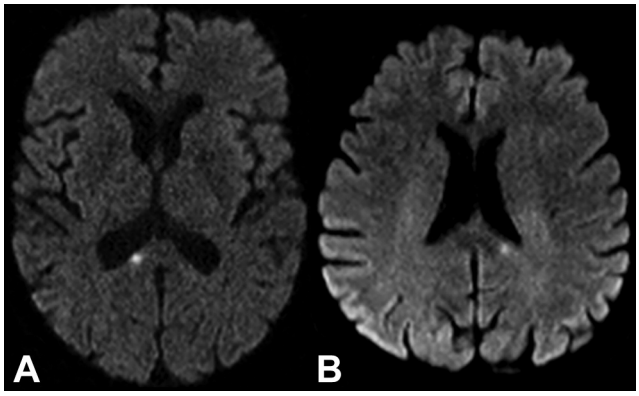


Figure 4. *Examples of two patients (A, B) with acute ischemic lesion in the splenium of the corpus callosum with irregular shape and eccentric location.*

affects the CC. Even though MBD was originally only referred to malnutrition and/or chronic alcoholism, recently MBD was also discussed to be related to paraneoplastic syndromes or to occur after surgery (13, 14). The most frequently reported risk factors for MBD remain alcoholism and malnutrition (15). In the present study, the suspected underlying causes of MBS in the current study were malnutrition and vitamin B6 deficiency in combination with alcoholism or myelodysplastic syndrome. Clinical presentations of MBS may be highly variable. In the present study, patients presented with aphasia and seizures, which is in line with the literature. Typical neuroimaging findings include symmetrical hyperintensity and swelling of parts or the complete CC on T2-weighted images with low signal intensity in T1-weighted images (15-17). DWI frequently shows a hyperintensity of the CC extending into the adjacent white matter usually sparing the subcortical U-fibers (15) with decreased ADC in the early phase, and hyperintense lesions with increased ADC in the late phase of the disease (18). In the present study, DWI demonstrated symmetrical boomerang-shaped diffusion restricted lesions, which were significantly larger than the lesions found in RSL or IS. However, there were no significant differences in relative ADC values comparing MBS, RSL, and IS.

RSL of the CC is an infrequent finding on MRI and has been reported in only a few studies to date. This might, besides its rarity, also be caused by an overall inconsistent nomenclature across the literature. Different terms have been used for "RSL" such as MERS (mild encephalitis/encephalopathy with a reversible lesion in the splenium) or RESLES (reversible splenial lesion syndrome) (4, 19). While different hypotheses have been generated, its pathophysiology is still not well understood (20, 21). MRI is the imaging method for the initial diagnosis as well as follow-up (22). The prognosis of RSL is mostly excellent. The majority of reported cases have been found in neuroleptic malignant syndrome, patients undergoing antiepileptic treatment (rapid and relatively long-lasting reduction of antiepileptic drugs) (23-25), and in patients with encephalitis or encephalopathy caused by varicella-zoster virus, adenovirus, rotavirus, mumps virus, *Salmonella enteritidis*, O-157 *Escherichia coli*, measles virus, and influenza A virus (20, 26, 27). Correspondingly, we could identify several predisposing factors such as seizures, viral meningitis, hypoglycemia, hypernatremia, or carbamazepine withdrawal. Clinical symptoms included headaches, nausea, vomiting and diarrhea, fever, dizziness, visual disturbances, and sensorimotor hemiparesis. Regarding neuroimaging findings, lesions in RSL are typically reported as round or oval lesions located in the midline in the medical literature. In the present study, nearly all patients with RSL demonstrated round or oval diffusion restricted lesions centrally located in the splenium of the CC, while one patient showed additional lesions in the corona radiata. The lesions size in RSL was significantly smaller than that in MBS but comparable to that in IS in the splenium of the CC.

Isolated acute IS in the splenium of the CC is very rare and most reports remain anecdotal (4, 28-32). To the best of our knowledge, no case series has been published until today. In the present study, we report the findings of nine patients with isolated acute IS in the splenium of the CC. Clinical symptoms comprised headaches, dizziness, nausea and vomiting, aphasia, dysarthria, and hemiparesis. Comorbidities included typical cerebrovascular risk factors such as arterial hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, adiposities, history of stroke, as well as history of coronary heart disease. Regarding MRI findings, diffusion restricted lesions were eccentric, located in the splenium of the CC, and irregular in shape. These observations are also in line with previous reports of IS in the splenium.

The present study has some limitations. First, this is a retrospective study of moderate size. However, reports on distinctions and differences of splenial lesions are limited and have not been well documented in the radiologic literature. Second, as our cohorts' patients often underwent acute MRI at the treating physician's discretion, we cannot exclude a selection bias. Third, the study was performed with different MRI scanners. However, the DWI sequences have been customized for optimal comparability across all scanners. Finally, some cases of diffusion restricted lesions in the splenium of the CC may have been missed leading to ascertainment bias, although the search terms used were very broad and inclusive.

In conclusion, a diffusion restricted lesion of the splenium of the CC does not necessarily indicate an acute IS, the actual cause might be another pathology such as RSL or MBS. Neuroimaging findings such as exact localization, shape, and size might be helpful to distinguish nonvascular from vascular etiologies, whereas relative ADC values are of limited value for differentiation of different neurological disorders. Knowledge and awareness of these is essential to avoid misdiagnosis and unnecessary diagnostic and therapeutic procedures.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

A. Förster, design of the study, analysis of the data, drafting and revising the manuscript; P. Apfaltrer, analysis and interpretation of the data, revising the manuscript; M. Al-Zghloul, acquisition of the data, revising the manuscript; H. Wenz, acquisition of the data, revising the manuscript; A. Alonso, analysis, and interpretation of the data, revising the manuscript; C. Groden, interpretation of the data, revising the manuscript.

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