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SHORT COMMUNICATION

Local glucose metabolism is unaltered in reversible splenial lesion syndrome

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Abstract

Background and purpose: Transient splenial oedema, also known as reversible splenial lesion syndrome (RESLES), is a rare magnetic resonance imaging (MRI) finding that presents as a round or ovoid focal oedema in the posterior corpus callosum, and is associated with a wide range of clinical conditions. The aetiology of RESLES is not fully clear. We aimed to investigate conflicting pathophysiological hypotheses by measuring local glucose metabolism in patients with RESLES.

Methods: We retrospectively analysed patients with RESLES after reductions in antiseizure medications during in-hospital video electroencephalography monitoring. We measured local glucose uptake using positron emission tomography/computed tomography and compared matched cohorts of patients with and without MRI evidence of RESLES using nonparametric tests.

Results: Local glucose metabolism in the splenium of seven patients with RESLES was not significantly different from the glucose metabolism of the seven patients in the matched cohort. This was true using both regular and normalized standardized glucose uptake value calculation methods ($p = 0.902$ and $p = 0.535$, respectively).

Conclusion: We found no evidence of local glucose hypometabolism in RESLES, which supports previous pathophysiological considerations that suggest that RESLES is an intercellular, intramyelinic oedema rather than a typical intracellular cytotoxic oedema, which is not reversible.

KEYWORDS
CLOCC, corpus callosum, DWI, encephalopathy, oedema, RESLES

INTRODUCTION

Transient oedema in the splenium of the corpus callosum is a rare finding on magnetic resonance imaging (MRI) [1,2]. However, an increase in the number of MRI examinations being performed revealed this transient oedema in a variety of clinical conditions, resulting in its definition as a distinct radiological entity referred to as reversible splenial lesion syndrome (RESLES) [3,4]. On MRI, RESLES presents with restricted proton diffusion in diffusion-weighted imaging (DWI), with increased intensity in T2-weighted imaging and reduced intensity in T1-weighted imaging, and without gadolinium enhancement [5]. RESLES can appear after reductions in antiseizure medications (especially sodium-channel blockers) [6] and in cases of systemic infections, intoxications and metabolic disorders [1,3,4]. Due to the

broad spectrum of conditions associated with RESLES, its clinical significance and diagnostic consequences remain unclear [7]. In the absence of histological reports [8], the pathophysiological mechanism underlying RESLES is unknown. Although glutamate-mediated excitotoxicity is a plausible common intermediary pathway [2], several explanations have been proposed, and the aetiology of RESLES has been hypothesized to be intracellular cytotoxic [1,9], vasogenic [1], or intercellular intramyelinic [5,10] in nature. The assumption of a cytotoxic mechanism has led to RESLES sometimes being referred to as a cytotoxic lesion of the corpus callosum [8]. However, the reversible nature of RESLES argues against an intracellular cytotoxic aetiology as seen in cerebral ischaemia, and MRI-based diffusion characteristics suggest that vasogenic oedema is also unlikely [10]. Investigations using complementary imaging methods alongside standard MRI allow for a more detailed study of this rare clinical phenomenon [5,10]. For example, 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography with integrated computed tomography (^{18}F-FDG PET/CT) utilizes a radioactive tracer to identify local glucose hypometabolism, and is used to identify epileptogenic areas of the brain [11].

In this retrospective, case–control study, we investigated local glucose metabolism in the splenium during RESLES presentation to further clarify the underlying aetiology of RESLES. To achieve greater validity, we not only compared splenial oedema intraindividually with unaffected regions of the corpus callosum but also compared matched cohorts of patients with and without RESLES.

METHODS

We retrospectively identified patients with RESLES detected on 3-Tesla MRI (Magnetom Verio/Skyra^{fit}; SIEMENS, Erlangen, Germany) acquired during in-hospital presurgical evaluations of pharmacoresistant epilepsy, based on video electroencephalography (VEEG) monitoring [12]. We selected all RESLES patients who also underwent ^{18}F-FDG PET/CT (Biograph 6; SIEMENS). Matched non-RESLES controls were selected based on demographics and clinical presentations (temporal vs. extratemporal epilepsy). A board-certified neuroradiologist evaluated all MRI scans for the presence of RESLES features, including increased hyperintensity of the splenium corporis callosi (SCC) on DWI and a corresponding reduction of the apparent diffusion coefficient. A board-certified nuclear medicine physician evaluated local glucose metabolism using PET/CT measurements after comparison with MRI results. Specifically, we placed regions of interest within the SCC and the genu corporis callosi (GCC) and calculated the mean and maximum standardized uptake values (SUVs) within the regions of interest using proprietary software (Volume Viewer™; GE Healthcare, Solingen, Germany). To account for interindividual baseline differences in cerebral glucose uptake, we normalized the mean SUV in the SCC using the formula $nSUV_{mean} = SUV_{meanSCC}/SUV_{meanGCC} \times 100$, where $nSUV_{mean}$ is the normalized SUV, $SUV_{meanSCC}$ is the mean SUV in the SCC, and $SUV_{meanGCC}$ is the mean SUV in the GCC. All demographic, clinical and imaging variables were compared using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. This analysis was approved by the local ethics committee of the Goethe University Hospital, and informed consent was waived due to the retrospective design.

RESULTS

We included seven patients with RESLES and seven matched controls without RESLES based on their VEEG monitoring results (Table 1). In all patients with RESLES, the presumed cause was the rapid reduction in antiseizure medications for diagnostic reasons. No patient exhibited any overt neurological deficits attributable to splenial oedema, as previously reported [6]. Age, sex, and clinical epilepsy subtypes (temporal vs. extratemporal lobe epilepsy) did not differ significantly between groups (Table 1).

We found no significant differences in the mean SUV values between the RESLES and control groups for either the GCC or the SCC (each $p = 0.902$), and no significant difference was observed for the normalized mean SUV ($p = 0.535$). Figure 1 shows a representative example of SUV region of interest placement.

Due to the likely benign nature of RESLES, no specific MRI follow-up was obtained for any patient. Subsequent MRI scans were performed in four of seven patients with RESLES for other reasons (median time to follow-up: 725 days), and no patient presented with persistent splenial oedema or structural changes in the splenium in the region where RESLES was previously observed.

DISCUSSION

Transient oedema of the callosal splenium is a rare phenomenon observed on MRI but has been detected more frequently in recent years [2]. Transient oedema can occur in a variety of diseases, with unclear pathophysiological basis, and the clinical relevance of RESLES remains unclear [2]. In this retrospective analysis of patients with RESLES following the discontinuation of antiseizure medications, we found that local splenial glucose utilization was not significantly altered compared with a matched cohort, which may clarify competing pathophysiological theories. The lack of change in local energy metabolism strongly supports the hypothesis of intramyelinic oedema, in which fluid accumulates intercellularly between the myelin sheaths without compromising cellular integrity [13]. By contrast, a typical intracellular cytotoxic oedema would be expected to lead to irreversible cell damage, which is not typically detectable in RESLES [4].

A small number of previous case reports have used multimodal or specific methods to investigate the origins of RESLES, and the findings from these extensive examinations of individual patients are generally consistent with the results from our study. Anneken et al. employed diffusion tensor imaging (DTI) at a field strength of 3 Tesla to study the pathophysiology of a transient SCC lesion in

TABLE 1 Clinical, demographic and imaging characteristics of patients with and without splenial oedema

Variable	Splenial oedema (RESLES)	Control	*p* value
N	7	7	
Mean age, years (range; SD)	27.6 (11–46; 12.0)	27.7 (18–42; 9.6)	>0.999
Sex: female, male (n)	2, 5	2, 5	>0.999
Diagnosis: TLE, ETLE (n)	4, 3	4, 3	>0.999
Median number of antiseizure medications (range)	2 (1–3)	2 (1–2)	0.805
Antiseizure medication type	7 of 7 with reduction of sodium-channel blocking agents	5 of 7 with reduction of sodium-channel blocking agents	0.462
Median timepoint MRI, day of monitoring (range)	9 (8–12)	8 (7–9)	0.259
Median timepoint PET/CT, day of monitoring (range)	9 (8–11)	8 (8–10)	0.535
Median time difference MRI–PET/CT, days (range)	1 (0–1)	1 (0–1)	0.710
Median SUV_{mean} in the SCC (range; IQR)	3.2 (2.4–3.7; 0.7)	3.1 (2.2–3.7; 0.7)	0.902
Median SUV_{mean} in the GCC (range; IQR)	2.7 (2.1–3.6; 0.9)	2.8 (2.0–3.5; 0.4)	0.902
Median normalized SUV_{mean} in the SCC[a], % (range; IQR)	114 (88–124; 12.6)	107 (96–146; 15.8)	0.535

Abbreviations: ETLE, extratemporal lobe epilepsy; GCC, genu corporis callosi; IQR, interquartile range; MRI, magnetic resonance imaging; PET/CT, positron emission tomography with integrated computed tomography; RESLES, reversible splenial lesion syndrome; SCC, splenium corporis callosi; SUV, standardized uptake value; TLE, temporal lobe epilepsy.

[a]For normalization method refer to the Methods section.

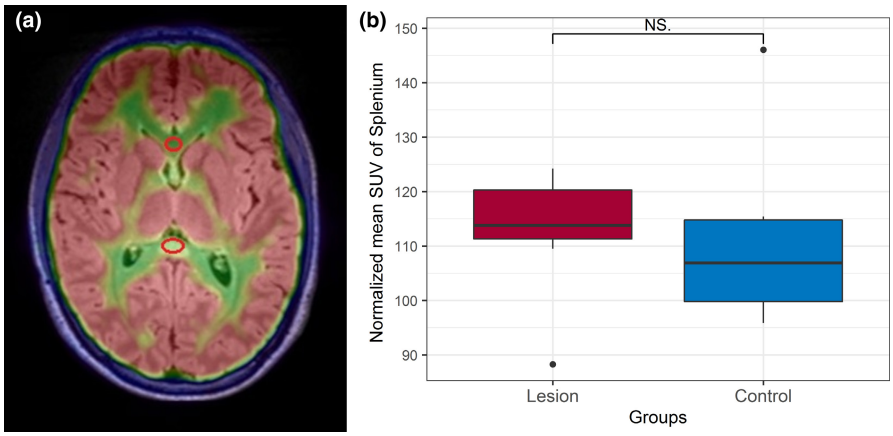

FIGURE 1 (a) Representative depiction of the regions of interest used to calculate standardized uptake values (SUVs) in a single patient. Regions of interest are marked with red circles and are located in the genu and splenium of the corpus callosum. The attenuation-corrected positron emission tomography image is overlayed on a coregistered diffusion-weighted axial magnetic resonance image showing oedema in the splenium. (b) Boxplot showing no significant difference (NS) in the normalized SUV_{mean} values in the callosal splenium between patients with and without a reversible splenial lesion syndrome ($p = 0.535$) [Colour figure can be viewed at wileyonlinelibrary.com]

a single individual [5]. Their fully automated quantitative fractional anisotropy analysis found a reversible loss in the directional fibre organization in the splenium, which is morphologically consistent with intramyelinic oedema. Using a similar methodology, Shimizu et al. also found DTI evidence suggesting intramyelinic oedema [10]. This group additionally employed proton magnetic resonance spectroscopy, and the unaltered levels of N-acetyl-aspartate in the affected splenium detected by Shimizu et al. are inconsistent with intracellular cytotoxic oedema, in which N-acetyl-aspartate levels are typically reduced, reflecting the loss of structural integrity [14].

Further insights into the probable pathophysiology of RESLES can be obtained from a purely clinical perspective. Typically, intracellular cytotoxic but not intercellular intramyelinic oedema compromises gross neuronal functional integrity, and clinical experience suggests a lack of overt neurological deficits in RESLES [6,15], despite the central role played by the corpus callosum in interhemispheric communication. The appearance of RESLES in the context of acute encephalitic or encephalopathic diseases can make determining the contributions of RESLES to neurological deficits challenging. However, the occurrence of RESLES following the discontinuation

of antiseizure medication is not associated with any specific overt neurological deficits [6,15].

The present study should be considered as another piece of the puzzle contributing to the pathophysiological elucidation of RESLES. Ultimate certainty regarding RESLES pathophysiology would only be achieved through histological examination; however, invasive histological sampling is conceptually impossible for RESLES due to the inevitable postoperative oedema, limiting RESLES study to indirect methods. Multimodal imaging methods currently represent the best approach to studying the aetiology and pathophysiology of RESLES [5,10].

This study has some important limitations. Follow-up imaging was not available for the reliable detection of reversibility in all patients. However, the typical pattern associated with no clinical neurological deficits argues for typical, reversible RESLES. Although PET/CT was not performed on the same day as the MRI in all cases, the maximum interval was 1 day for all cases, allowing for the assumption of essentially identical local metabolism. Studying patients with combined PET-MRI seems a promising method to further substantiate the lack of an association between DWI changes and local glucose metabolism in RESLES.

In conclusion, isolated RESLES should be interpreted as an essentially benign phenomenon. No current evidence suggests the existence of a specific overt clinical correlate for RESLES, and patients should be informed of the relatively benign nature of an isolated RESLES finding to avoid unnecessary follow-up investigations. In addition, neurological deficits should not be hastily attributed to the appearance of an isolated RESLES, and such cases warrant further investigations.

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CONFLICT OF INTEREST

J.P.Z. reports speaker's honoraria from Eisai, GW Pharmaceuticals companies, and Desitin Arzneimittel. S.S.-B. reports personal fees from Eisai, Desitin Pharma, GW Pharmaceuticals, Ethypharm, UCB Pharma, and Zogenix. F.R. reports personal fees from Angelini Pharma, Arvelle Therapeutics, Eisai GmbH, GW Pharmaceuticals companies and UCB, and grants from the Detlev-Wrobel-Fonds for Epilepsy Research, the Deutsche Forschungsgemeinschaft, the LOEWE Programme of the State of Hesse, and the European Union. A.S. reports personal fees or grants from Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals companies, Marinus Pharma, UCB Pharma, UNEEG medical, and Zogenix. J.W. and E.H. report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Johann Philipp Zöllner: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Visualization (lead); Writing – original draft (lead); Writing – review and editing (equal). **Jennifer Wichert:** Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Software (equal); Visualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Susanne Schubert-Bast:** Data curation (equal); Formal analysis (supporting); Investigation (supporting); Supervision (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Elke Hattingen:** Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Writing – original draft (supporting); Writing – review and editing (equal). **Felix Rosenow:** Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Resources (equal); Supervision (equal); Writing – original draft (supporting); Writing – review and editing (equal). **Adam Strzelczyk:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Supervision (equal); Visualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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