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SPECIAL REPORT

Treatment-related transient splenial lesion of the Corpus Callosum in patients with neuropsychiatric disorders: a literature overview with a case report

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ABSTRACT

Introduction: Transient-localized lesions of the splenium of the corpus callosum (SCC) have been described in various clinical conditions, some of them being attributed to the withdrawal of psychotropic drugs. The pathophysiology of the lesion likely reflects cytotoxic edema and reversible demyelination.

Areas covered: The present article aimed at reviewing cases of transient SCC lesion exclusively related to changes in pharmacological treatment. It also reports the original case of a psychotic patient receiving a complex psychopharmacological therapy who developed a transient SCC lesion investigated by magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and pharmacogenetic profiling.

Expert opinion: To date, only one review on the subject has been published, analyzing 22 cases of transient SCC lesion arising in epileptic patients on antiepileptic therapy. It hypothesized that the nature of the lesion is a cytotoxic edema and the cases described in the subsequent 14 years seem to support this hypothesis. The authors reported the case of an Italian-Egyptian patient who developed a transient SCC lesion after the rapid withdrawal of Carbamazepine and Lurasidone. The lesion completely disappeared from the MRI performed after 1 month. Patient's ethnic group and its specific pharmacogenetic profile were considered as possible causes of altered drug metabolism and, likely, of the SCC lesion.

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KEYWORDS
Pharmacological treatment; splenium of the corpus callosum; transient lesion

1. Introduction

The corpus callosum consists of densely bundled white matter tracts connecting the two cerebral hemispheres. Compared with other brain areas, the neurons of the corpus callosum, particularly of the splenium, have a higher density of receptors, including cytokine receptors, glutamate and other excitatory amino acid receptors, toxin receptors, and drug receptors [1,2]. This characteristic predisposes to a tendency for cytotoxic edema of the corpus callosum in different conditions, including neuropsychopharmacological treatment [3,4,].

The occurrence of cytotoxic lesions of the corpus callosum (CLOCCs) has been increasingly reported in the past years, through various terms including 'RESLES' (reversible splenial lesion syndrome) [5] and 'MERS' (mild encephalopathy with reversible splenial lesions) [6,7,]. A 2017 review suggested naming these lesions 'CLOCCs'[3] and it pointed out that they are frequent findings in clinical practice, even though the actual prevalence has not been estimated yet. The same can be said about drug-related CLOCCs, as the data is even more limited that on CLOCCs in general. CLOCCs are not always reversible [3], thus it is important to recognize them and their known causes so that they can be effectively diagnosed, treated and prevented. Moreover, a misdiagnosis of ischemia can be avoided [3].

The most common lesions of the corpus callosum involve both cerebral hemispheres and are associated with aggressive tumors, demyelination, and traumatic brain injury [8].

Isolated lesions of the corpus callosum are rare and mostly represent the consequence of congenital diseases, like callosal malformations and lipoma, or vascular diseases including infarction, aneurysm, arteriovenous malformation and callosal gliosis [9].

Transient-localized lesions of the splenium of the corpus callosum (SCC) have been reported in various clinical conditions including seizures, viral encephalitis, bacterial and parasitic meningitis, osmotic myelinolysis, Wernicke encephalopathy, hemolytic-uremic syndrome, hypoglycemia, hypernatremia, malnutrition, alcohol poisoning, eclampsia, collagen disease, vitamin B12 deficiency, high-altitude cerebral edema and drug therapy [8]. Ultimately, CLOCCs are more frequently associated with malignant tumors, infections, subarachnoid hemorrhage (SAH), metabolic abnormalities, trauma and drug therapy [3]. There is

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Article highlights

- Transient-localized lesions of the splenium of the corpus callosum (SCC) have been reported in various clinical conditions (e.g. malignancies, infections, metabolic disturbances, etc.) and subsequently to drug withdrawal.
- The hypothesized pathogenetic mechanisms are an inflammatory cascade leading to a reversible cytotoxic edema at glial level.
- Transient isolated SCC lesions have been associated with the administration or withdrawal of antiepileptic drugs (phenytoin, levetiracetam, carbamazepine, lamotrigine, oxcarbazepine, valproic acid, gabapentin, topiramate, lithium), cabergoline, prednisone, and also neuroleptic drugs (risperidone, olanzapine, aripiprazole, clozapine).
- Magnetic resonance imaging (MRI) common features include: location in the central splenium, high signal intensity on T2 weighted and FLAIR sequences, low signal intensity on T1 weighted sequences, restricted diffusion on diffusion-weighted imaging (DWI) sequences and no contrast enhancement. Diagnosis is confirmed by the disappearance of the lesion with time.
- The clinical manifestations of SCC lesions, mostly neurological, can be quite heterogeneous, and require thorough investigation.
- Data from our case report of Schizoaffective patient, who developed a transient SCC lesion after an abrupt cessation of Carbamazepine and Lurasidone, appear consistent with the current literature. Further studies are encouraged in order to better characterize this lesion.

This box summarizes key points contained in the article.

no specific treatment for these lesions except to eliminate the underlying cause [10]. With respect to drug-associated CLOCCs, different case reports mention the association with antiepileptic drugs (AED) [11–13], prolactin inhibitors [14], steroid therapy [15] and antipsychotics [16]. Drug-associated CLOCCs are the only SCC lesion that might be caused by medical intervention rather than an underlying disease. In particular, they often arise after an abrupt drug discontinuation [3]. Therefore, a descriptive analysis of these CLOCCs cases is useful for clinicians to refine the way of handling these drugs and avoid the onset of new cases.

Magnetic resonance imaging (MRI) common features of SCC transient lesions include: location in the central splenium, high signal intensity on T2 weighted and FLAIR sequences, low signal intensity on T1 weighted sequences, restricted diffusion on diffusion-weighted imaging (DWI) sequences and no contrast enhancement [4,8,,17–22]. Their exact pathophysiology remains still unknown but they may be caused by exocitotoxic brain edema (intramyelinic edema) [4,8,,17–22]. Diagnosis is confirmed by the disappearance of the lesion within a few weeks [8]. Magnetic Resonance Spectroscopy (MRS) detects brain metabolites alterations, providing further information about the nature and of the lesions [23–25]. There are few previous studies of MRS of SCC transient lesions which demonstrated a normal spectrum of the main brain metabolites such as N-acetylaspartate (NAA), choline (Cho), and creatine (Cr), but presence of peaks of myoinositol (MI) and lactate (Lac), not detectable in normal brain parenchyma, suggesting hyperosmolar state and increased anaerobic glycolysis in the splenium without irreversible neuroaxonal damage [23–25].

From a clinical point of view, the SCC lesion can be accompanied by neurological symptomatology. Most cases present with epileptic seizures [26]. Cases of alien hand syndrome following corpus callosum infarction [27], along with a transient-localized lesion of SCC in a child [28], have been described. A case report documented the concomitant onset of a neuroleptic malignant syndrome [16]. An in-depth analysis of these cases is needed to understand the role CLOCCs play across various clinical manifestations reported. In the field, data is likely due to the benign nature of transient SCC lesions and the common complete reversion of neurological symptoms, when present. In addition, asymptomatic SCC lesions may not be recognized in clinical practice unless MRI is performed for other reasons. Therefore, it currently does not seem possible to clarify the exact correlation between SCC lesions and neurological symptoms. Finally, although the overall symptoms of most patients with CLOCCs tend to subside with a good outcome, patients with any clinic-radiological features tend to need longer hospitalization for diagnostic investigations with or without neurological sequelae [29].

The objective of the present report was to review transient SCC focal lesions caused by drug initiation or withdrawal in terms of clinical consequences and etiology. Furthermore, we present the case of a 26-year-old man diagnosed with Schizoaffective Disorder who developed a transient SCC lesion in the context of a complex drug therapy.

2. Methods

A literature search was conducted, using PubMed, Embase and PsychInfo databases, to identify clinical studies and other primary literature sources, published up to July 2019, on the transient focal lesions in the SCC, with particular attention to their association with changes in pharmacotherapy. Therefore, the search terms used were the following: 'corpus callosum', 'transient splenial lesion', 'drug induced', 'antiepileptic drug', 'antipsychotic drug', 'abrupt', 'withdrawal', 'intensity changes', 'drug-related', 'drug initiation', 'pharmacology', 'medicine', 'medication', 'polypharmacy', 'psychotropic', 'case report', 'case series', 'review'. Additional references were obtained from the bibliography of the retrieved articles.

Identified articles were evaluated and only English-language reports were included and reviewed. We included all reports describing the onset of transient SCC lesions after treatment changes as shown by MRI that either disappeared or significantly improved on follow-up. Patients with persistent lesions (or with no follow-up) were not included.

Systematic reviews were firstly considered for the purpose of the present article, along with open studies, including also case series and reports.

3. Results

To date, only one single review on transient SCC lesions has been conducted by Prilipko and colleagues et al, in 2005 [26]. The described cases were exclusively caused by AEDs withdrawal. In the last 14 years, 15 additional studies, especially case reports and case series, have been published on drug-related transient SCC lesion. We included and analyzed these cases among those already identified by Prilipko and colleagues [26] and together with other cases not previously reviewed. A few reviews were excluded from the present article because they focus on specific populations such as

children [29], or analyzed different triggering causes [10]. No RCTs were found according to the search criteria used.

In summary, 21 studies meeting our inclusion criteria were included in the review (Figure 1). These studies described 39 different cases that are summarized in Table 1. We also listed patients' countries of origin, clinical symptoms associated with the lesion and related time course through MRI monitoring (Table1).

3.1. Contributing factors

We herein provided a brief analysis of the drugs associated with transient SCC injury in the identified studies and we mentioned related etiopathogenetic hypotheses when it was provided by the authors of the respective studies.

A case-control study by Gurtler and colleagues supported the association between AED withdrawal and appearance of transient SCC lesions [38]. In 2005, Prilipko and coworkers analyzed 22 cases of transient SCC lesion arising in epileptic patients treated with AEDs. Authors focused on the pathophysiological mechanism by which the abrupt interruption of an AED may cause SCC lesions and concluded that their origin was the product of a cytotoxic edema at the glial level. They added that this lesion may be associated with an altered arginine vasopressin (AVP) secretion [26].

Renard and coworkers proposed that an abrupt decrease in Carbamazepine concentration might elevate AVP and destabilize brain water balance [15]. Another hypothesis is that hyponatremia, which occurs during treatment with some AEDs, would be normalized too quickly after rapid withdrawal, leading to osmotic myelinolysis [15]. However, fluctuations in sodium levels have never been reported. This hypothesis is only supported by the case described after the cessation of steroid drug [15]. Corticoids decrease sodium excretion and elevate the osmotic threshold for AVP release with a certain delay [15]. It has been shown that Carbamazepine (CBZ), Phenytoin (PHT), and Phenobarbital (PB) accumulate in white matter due to their lipophilicity [39]. Whether these concentrations are particularly high in the corpus callosum, due to the high fiber density, remains unclear. Anatomic studies in the corpus callosum did not find a different fiber density or composition in the splenium vs other regions of the corpus callosum [40].

Interestingly, recent reports indicated cases of transient splenic lesion with the concomitant introduction or withdrawal of other drugs, including neuroleptics and steroids [14–16,41,42,].

In this regard, various cases of neuroleptic malignant syndrome (NMS) after the administration of antipsychotic therapy (Olanzapine, Clozapine, Haloperidol and Aripiprazole, respectively), showing MRI findings of SCC lesions, have been described [16,41,42]. Elevated plasmatic sodium levels, a common laboratory finding among patients, could be involved in the pathophysiology of the lesion [42]. Even though the mechanism is not clear, NMS might be included in the differential diagnosis of SCC lesions.

Renard and coauthors reported a case of SCC lesion after the introduction of oral Prednisone therapy, with normal plasmatic natremia [15]. Finally, the dopamine agonist Cabergoline has been linked to transient SCC lesion as well [14].

With respect to ethnicity, we identified 6 European (3 German, 1 Swiss, 1 French and 1 Italian), 11 Asian (6 Japanese, 1 Malay, 3 Indian, 1 Chinese), 2 Turkish and 2 American cases. It has been reported that incidental cases of transient lesions of the SCC are more often detected in Japan than in other countries [43]. This is probably due to a comparatively greater availability of MRI and a larger tendency for Japanese physicians to utilize it [12].

3.2. Clinical consequences

The clinical manifestations of transient SCC lesions can be quite heterogeneous [44]. Herein, we reported every clinical element described in conjunction with the SCC lesion after change in therapy.

Among the 39 described cases (Table 1), 24 reported a clinical symptomatology that was concomitant with the lesion. Nineteen patients with epilepsy had presented different types of seizures, one patient with pituitary adenoma

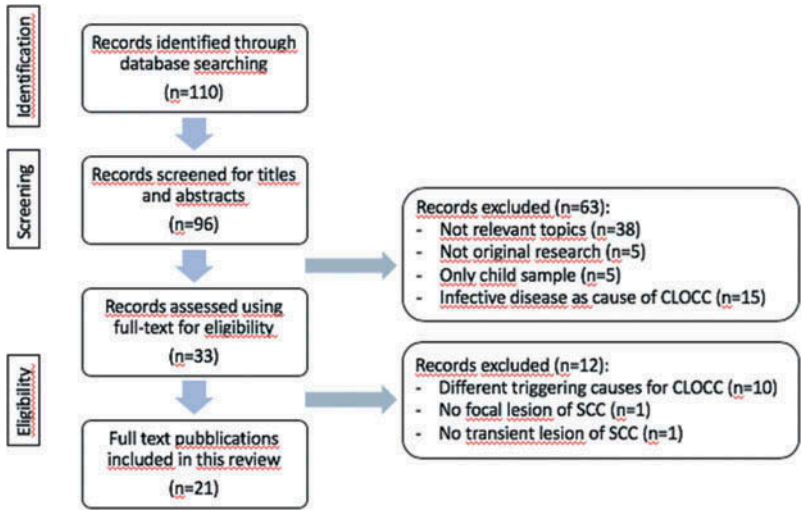

Figure 1. Flow diagram of literature search and study inclusion.

Table 1. Summary of reported cases of transient splenial lesion of the corpus callosum occurred after an initiation or withdrawal of therapy.

			SUBJECTS						
AUTHORS	STUDY DESIGN	COUNTRY	Age	Sex	PRINCIPAL DIAGNOSIS	THERAPY (dosage)	INITIATION or WITHDRAWAL	CLINICAL SYMPTOMS	RESOLUTION TIME (days)
Polster et al., 2001 [40]	case series	Germany	34	F	epilepsy syndrome with partial and generalized features	PHT (sc 21.8 mg/l)	W	absent	22
			34	M	epilepsy due to right temporal tumor	PHT (sc 9.3 mg/l) LTG (sc 0.47 mg/l)	W	absent	180
			33	M	temporal lobe epilepsy due to right hippocampal sclerosis	CBZ (sc 8.7 mg/l) PRM (sc 2.8 mg/l)	W	six short psychomotor seizures within 24 hours	56
Cohen-Gadol et al., 2002 [30]	case report	USA	27	M	refractory partial seizures	PHT (500 mg/day; sc 13.5 g/ml) VPA (2250 mg/day; sc 42 g/ml) LTG (400 mg/day; sc 4.5 g/ml)	W	generalized seizure	35
Mirsattari et al., 2003 [31]	case report	Canada	28	F	epilepsy	CBZ LTG	W	absent	90
Maeda et al., 2003 [49]	case report	Japan	27	F	Depression Social phobia Binge eating	VPA CBZ Clonazepam Oxazolam Etizolam	I (6 months before)	absent	90
Narita et al., 2003 [32]	case report	Japan	24	F	DOC and epilepsy	CBZ (sc 6.6 mg/L)	W	absent	68
Prilipko et al., 2005 [26]	case series	Switzerland	25	M	epilepsy	CBZ (1200 mg/die) TPR (50 mg/die)	W	absent	10
			12	F	Recurrent seizures	LTG (400 mg/die) TPR (75 mg/die)	W	absent	30
Gurtler et al., 2005 [38]	case control study with 16 patients	Germany	median age 35, range 8 to 57	6 F 10 M	Focal epilepsy	One to four AEDs including LTG, PHT, CBZ, OXC, VPA, PRM, CLB, GBP	W	Fifteen patients developed seizures, one patient remained seizure free	N/A
Honda et al., 2006 [33]	case report	Japan	46	F	schizophrenia with catatonic features	CBZ (600 mg/die)	W	absent	53
Renard et al., 2007 [15]	letter to the editor	France	54	M	lumbar disk herniation in Parkinson's disease	Oral prednisone (60 mg/die)	I (5 days before)	subacute onset confusion, drowsiness and reduced spontaneous speech	42
Anneken et al., 2008 [34]	case report	Germany	48	F	right hemispheric epilepsy secondary to a meningoencephalitis	CBZ (1500 mg/die; sc 12.4 mg/ml) Pregabalin (300 mg/die)	Reduction to half	absent	29
Parikh N. C. et al., 2008 [35]	Case report	India	40	M	epilepsy	PHT	W	seizures	28
Guven et al., 2008 [36]	case report	Turkey	19	F	Psychogenic seizures (?)	CBZ (400 mg/die)	W	visual hallucinations	60
Al-Edrus et al., 2009 [42]	case report	Malaysia	65	F	neuroleptic malignant syndrome in bipolar disorder	Clozapine (10 mg/die) Lithium (900 mg/die) Lorazepam 1 mg	W	absent	56
Achalia et al., 2014 [45]	case report	India	23	M	neuroleptic malignant syndrome in bipolar disorder	Risperidone (6 mg/day) Olanzapine (10 mg/day) Trihexyphenidyl (4 mg/day) VPA (750 mg/day) Lithium (900 mg/day)	W	absent	13
Duberkar et al., 2017 [11]	case report	India	21	M	epilepsy due to a gliotic scar	PHT	W	ataxia	10
Sawagashira et al., 2017 [12]	case report	Japan	18	F	schizophrenia	Levetiracetam	W	absent	45
Fuseja et al., 2017 [13]	case report	Japan	46	F	epilepsy	CBZ	W	anorexia, fatigue and polyuria	30
Kaino et al., 2017 [41]	case report	Japan	27	F	hyperosmolar hyperglycemic state and neuroleptic malignant syndrome in panic disorder	Olanzapine (20 mg/day)	W	absent	26

(*Continued*)

Table 1. (Continued).

AUTHORS	STUDY DESIGN	COUNTRY	SUBJECTS Age	SUBJECTS Sex	PRINCIPAL DIAGNOSIS	THERAPY (dosage)	INITIATION or WITHDRAWAL	CLINICAL SYMPTOMS	RESOLUTION TIME (days)
Ogul et al., 2018 [14]	case report	Turkey	24	M	pituitary microadenoma	Cabergoline	I (8 weeks before)	acute onset of headache	N/A
Gasparini et al., 2018 [16]	letter to the editor	Italy	36	M	neuroleptic malignant syndrome in schizophrenia	Haloperidol decanoate (150 mg IM/3 weeks) Aripiprazole (20 mg/die) OXC	W	absent	19
Chaoyang J et al., 2018 [37]	Case report	China	39	M	epilepsy		W	seizures	150

AEDs: anti-epileptic drugs; F: female; I: initiation; M: male; N/A: not available; NMS: neuroleptic malignant syndrome; NOS: not otherwise specified; sc: serum concentration; W: withdrawal; LTG: lamotrigine; PHT: phenytoin; CBZ: carbamazepine; OXC: oxcarbazepine; VPA: valproic acid; PRM: primidone, CLB: clobazam; GBP: gabapentin; TPR: topiramate.

complained of headache, one patient with psychogenic seizures developed visual hallucinations. Such symptomatology was more attributable to the patient's underlying pathology than to the transient neurological lesion. The remaining three patients with clinical symptoms showed confusion [15], ataxia [11] and anorexia with polyuria [13]. Neurological symptoms, such as confusion and ataxia, might represent the consequence of direct brain damage in the SCC, while polyuria might have resulted from the ADH deficiency caused by abrupt withdrawal of carbamazepine, which boosts the effect of ADH, thereby reducing its endogenous secretion.

Finally, three cases of transient SCC lesion were identified in conjunction with neuroleptic malignant syndrome [41,42,45,]. As can be reconstructed from the clinical-anamnestic data provided in two of these case reports, the most plausible hypothesis is that the NMS was caused by neuroleptic drugs. To solve it, clinicians stopped the entire psychiatric therapy, including the AEDs that had been given as mood stabilizers [42,45,]. The SCC lesion might have arisen as a result of the sudden interruption of AEDs and would not have been a manifestation of the NMS nor this would have caused it. The third reported case is different because no AED was administered [41]. Olanzapine had triggered a NMS and at the same time a hyperosmolar hyperglycemic state (HHS) had arisen. Authors speculated that both HHS and NMS might have contributed to the pathophysiology of SCC lesion by inducing hypernatremia [41].

In conclusion, drug-associated SCC lesions presented with varied and nonspecific neurological and general clinical signs and symptoms, which might result from a transient dysfunction of the SCC, an underlying pathology, or represent the direct consequence of the drug introduction and/or withdrawal. The course of the symptoms was generally transient, with a favorable prognosis [10].

4. Case report

A 26-year-old patient, known to our psychiatric service for six previous hospitalizations, was transferred from a psychiatric rehabilitation community to our inpatient unit after an aggressive act against an operator. Patient's psychopathological onset dated back to the age of 22, when he developed megalomaniac and persecutory delusions in the context of a massive and protracted cannabinoid abuse. Starting from the first hospitalization, a therapy with Olanzapine and Valproic acid was administered. Between the subsequent hospitalizations, Valproic acid was self-suspended by the patient due to side effects. In addition, Olanzapine up to the maximum dosage of 20 mg/day was ineffective in keeping the patient free from psychotic exacerbations. Thus, it was associated with Haloperidol (up to 6 mg/day). During the sixth hospitalization, Olanzapine was replaced with Lurasidone, titrated to the dosage of 120 mg/day. The patient was then transferred to a psychiatric rehabilitation community, in order to strengthen the therapeutic compliance and better control his cannabinoid addiction.

During the community stay, the patient experienced a recrudescence of psychotic symptoms and the dose of Lurasidone was increased up to 150 mg/day with

Carbamazepine being progressively added at a final dose of 800mg/day. The patient became more persecutory and oppositive, leading the community clinicians to rapidly stop Lurasidone and Carbamazepine and reintroduce Olanzapine (20 mg/day) and Haloperidol (9 mg/day). His clinical condition escalated in a threatening and aggressive act on a delusional basis toward a mental health professional. As a consequence, the patient was sent back to our inpatient unit. Given the poor response to both Olanzapine and Lurasidone, Cariprazine was introduced, reaching the maximum dose of 6 mg/day, with a reduction of Haloperidol from 9 to 2 mg/day. In order to better characterize this complex clinical case, brain MRI and MRS were performed.

The MRI scan (1,5 T Intera Philips, Nederland BV, The Netherlands) highlighted a focal well-defined lesion in the central SCC, with T2/FLAIR hyperintense and T1 hypointense signal, markedly reduced diffusivity and no contrast enhancement (Figure 2). No other brain abnormalities were detected. The lesion was suggestive for a transient SCC lesion: further examination and neurological evaluation, in fact, were able to exclude other causes.

MRS of the lesion was performed with SingleVoxel PRESS shortTE technique, with a rectangular voxel (size: 30 mm x 10 mm x 20 mm) placed on the axial T2 sequences on the splenium oriented perpendicular to CC body, including less of 30% of the adjacent gray matter and ventricles, as shown in Figure 3. MRS detected a normal spectrum of NAA, Cho and Cr with a Cho/NAA ratio of 0.41, a significant peak of MI with MI/Cr ratio of 1.093, a small peak of glutamate-glutamine (Glx) with Glx/Cr ratio of 0.543 and a small Lipid (lip)/Lac peak (Figure 3). These results did not support the ischemic, neoplastic or acute demyelinizing nature of the lesion.

A neurological examination did not reveal anything abnormal except for the presence of left-hand movements, characterized by partial, sub-continuous flexion-extension of the fingers and arching of the palm. These movements disappeared in conjunction with the movements of the limb, but they were present at rest and during movements of the contralateral limb, as well as when the patient was distracted. According to the neurologist, these movements could be attributed to stereotypies, but an alien hand phenomenon could not be ruled out. In the following month, we requested an MRI check. That documented the complete resolution of the lesion (Figure 4), while the hand movements were reduced in frequency, though not completely disappeared. From a psychiatric point of view, patient's clinical status had not changed during the follow-up.

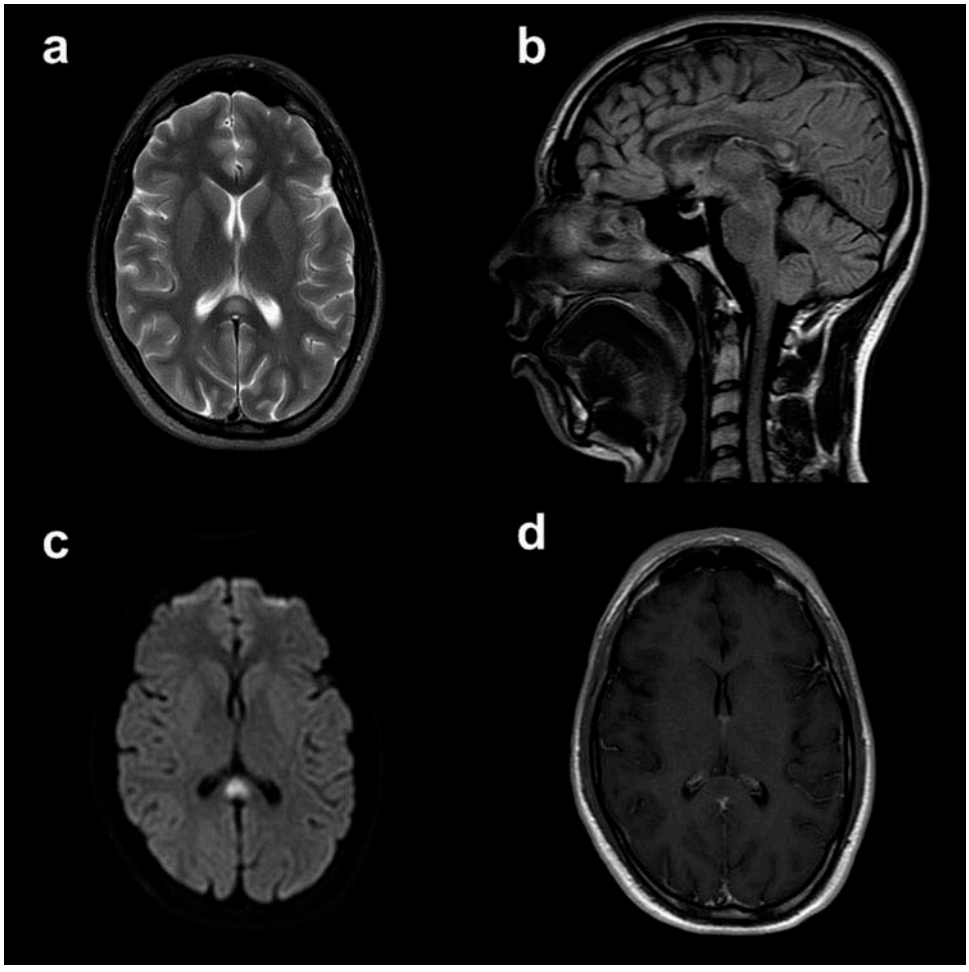

Figure 2. First MRI scan. (a, b) Axial T2 weighted and sagittal FLAIR images showed a well-defined hyperintense lesion in central SCC. (c) Diffusion-weighted image showed hyperintense restricted diffusivity within the lesion. (d) Axial contrast-enhanced T1 weighted image did not show contrast enhancement.

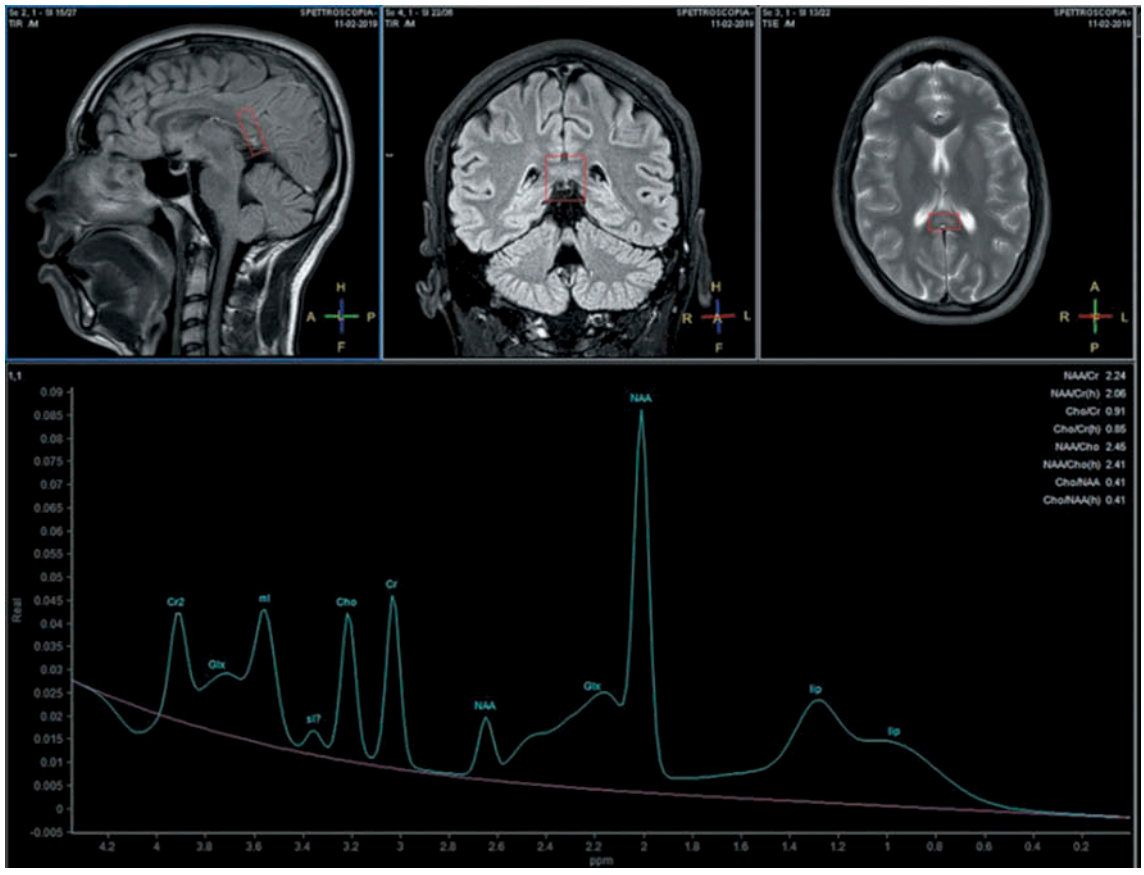

Figure 3. MR Spectroscopy measured from the SCC lesion showed normal spectrum of NAA, Cho, and Cr, a significant peak of MI and small peaks of Glx and Lip.

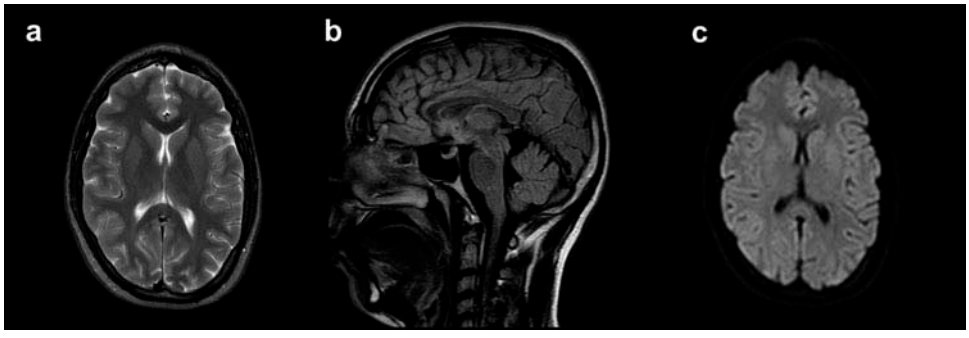

Figure 4. MRI scan performed at 1 month. (a, b) At axial T2 weighted and sagittal FLAIR images there was no more evidence of the lesion within SCC (c) Diffusion-weighted image did not show areas of hyperintense restricted diffusivity within SCC.

5. Discussion

Our decision to obtain brain imaging was due to patient's lack of treatment response and to exclude brain morphological alterations. MRI showed an isolated ovoid lesion at the SCC. The MR metabolites spectrum did not support the ischemic hypothesis, as in ischemia the NAA peak is usually reduced with elevated peaks of Lac/Lip, nor the neoplastic or acute demyelinizing hypotheses, as in tumors and multiple sclerosis acute plaques the Cho peak is usually elevated, with Cho/NAA ratio >1 [23–25].

Our results were similar to those reported for multiple sclerosis quiescent demyelinating lesions with normal peaks of the principal brain metabolites and increased MI, a marker for astrocytic reactions to noxious factors. Normal NAA and no significant peaks of lip and Glx suggested that normal neuronal integrity was preserved, without evidence of irreversible neuro-axonal damage [23,25,]. These results are consistent with the limited available MRS studies of transient SCC lesions, suggesting that a reversible intramyelinic citotoxic edema could represent the main pathophysiologic mechanism [19,46–48].

Transient SCC lesions have been associated with the administration/withdrawal of antiepileptic drugs, including Carbamazepine [38,40,49,,], but also with neuroleptic malignant syndrome [45] caused by Olanzapine [41].

The clinical course of our case suggests that abrupt cessation of Carbamazepine might have induced the SCC lesion observed on MRI. However, we cannot exclude the implication of Lurasidone withdrawal or Haloperidol reduction.

Indeed, when polypharmacotherapy is used, there is a potential risk of drug interactions (DIs) [50]. DIs represent a frequent complication associated with the use of AEDs [51]. In this regard, AEDs are used in psychiatric patients as mood stabilizers, in combination with other psychotropic medications. The majority of clinically important pharmacokinetic DIs between AEDs and new psychotropic drugs occur at a metabolic level and involve the hepatic cytochrome P450 (CYP) system and, to a lesser extent, the uridine diphosphate glucuronosyltransferase (UGT) system [52]. Traditional AEDs are potent inducers of several drug-metabolizing enzymes including CYPs, specifically CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4 [50]. Carbamazepine has been reported to cause a clinically significant decrease in plasma concentration of many second-generation antipsychotics [53]. In our case, Carbamazepine and Lurasidone were co-administered and Carbamazepine was expected to induce the metabolism of Cariprazine and Lurasidone, mainly metabolized by CYP3A4 [53]. Indeed, it is possible that the lack of efficacy of Lurasidone had been caused by the effect of Carbamazepine on its pharmacokinetics. Therefore, we decided to analyze patient's pharmacogenetic profile, after his written informed consent was obtained. As shown in the table (Table 2), his hepatic metabolism was abnormal in our case, confirming our hypothesis.

6. Conclusion

We found the present case of great interest in clinical, diagnostic and therapeutic aspects. In case of pharmacoresistance, neuroimaging can represent an element of good clinical practice: first, to exclude brain morphological alterations [54] and, secondly, to detect lesions caused by drug therapy or other cause. In this regard, especially when polypharmacotherapy is used, particular attention must be paid to drug and dosage change, in particular to the interruption of AEDs. Finally, it may be useful to carry out an investigation of the patient's metabolic profile in order to have a prediction of the plasma level of the drug. In conclusion, clinicians must be aware of transient lesions of the SCC following an abrupt change in psychotropic drugs, as the etiology, pathophysiology and clinical outcome of such events can manifest with different symptoms and remain to be further characterized.

7. Expert opinion

According to the literature, callosal lesions are caused by inflammatory cascade and consequent cytotoxic edema [26]. The higher density of cytokine, toxin and neurotransmitters receptors compared to other brain regions may explain the greater vulnerability to cytokinopathy and glutamate excitotoxicity of the corpus callosum [3]. Drug initiation and withdrawal may cause cytotoxic lesions in the corpus callosum influencing cellular fluid control and cytokines balance [55,56,]. The splenium is by far the most common site of ischemic infarction in the corpus callosum [57]. Its structure, a thick bundle of closely packed myelinated fibers, may explain (at least partly) its vulnerability to cytotoxicity. Moreover, splenial lesions are probably more often symptomatic compared to lesions in the genu and body, thus increasing the rate of diagnosis with brain MRI.

We also analyzed the country of origin of the patients with SCC, as reported in literature, and reflected on the possible involvement of an altered drug metabolism related to a particular pharmacogenetic profile in the etiology of the lesion under examination. Inter-ethnic differences in drug response and tolerability are actually well known [58]. Yet, no previous studies presented transient lesions of SCC in a drug-resistant Italian-Egyptian subject.

In this regard, we analyzed pharmacogenetic variation at CYP2D6 and CYP3A4-5, describing their worldwide distribution and pointing out the genetics variant characterizing our patient.

Genetic polymorphism in cytochrome P450 (CYP) genes can result in altered metabolic activity. Drug response is highly variable between patients, resulting in 40-70% of subjects showing lack of efficacy of drug therapy or adverse drug reaction [59,60,]. It is estimated that 15-30% of this variability is due to genetic polymorphisms [59].

The distribution of CYP alleles has been studied in multiple ethnically and geographically diverse groups and significant differences in allele frequencies have been found [61]. The CYP2D6 gene locus is complex and highly polymorphic, harboring a multitude of common genetic variants with

Table 2. Patient's pharmacogenetic profile.

Variant	Result	Reference	Metabolism
CYP1A2 rs762551 C > A	C**A**	CC	The presence of the A allele could be associated with an **increased inducibility** of the enzyme
CYP1A2 rs2069514 G > A	GG	GG	
CYP2D6*3 (rs35742686 delA)	absent	absent	The presence of gene duplication could result in an **ultrarapid metabolism**
CYP2D6*4 (rs3892097 G > A)	absent	absent	
CYP2D6*5 (gene deletion)	absent	absent	
CYP2D6*6 (rs5030655 delT)	absent	absent	
CYP2D6 (**gene duplication**)	**present**	absent	
CYP2D6*9 (rs5030656 del AAG)	absent	absent	
CYP2D6*10 (rs1065852 C > T)	absent	absent	
CYP2D6*41 (rs28371725 G > A)	absent	absent	
CYP3A4*22 rs35599367 C > T	**CT**	CC	**Poor metabolizer**
CYP3A5*3 rs776746 A > G	**GG**	AA	

CYP: cytochrome P450; rs: reference single nucleotide polymorphism (SNP); C: Cytosine; A: adenosine; G: guanine; T: thymine; del: deletion.

clinical relevance. CYP2D6 constitutes the most variable gene [62]. Moreover, in regard to CYP2D6, among the various polymorphic positions, whole-gene deletions and duplications have been considered as well. In our case, the patient showed a duplication of CYP2D6 gene that could result in an increased enzyme activity. The phenotypic consequence of this variation is ultra rapid metabolism (<*https://www.pharmgkb.org/page/pgxGeneRef*>). Duplications of CYP2D6 occur with frequencies of 1-2% in Whites and Asians, but are more common in certain African populations, in which their frequency can be up to 29% [63,64,]. Genetic polymorphisms that result in increased CYP2D6 metabolic capacities, mainly observed in Africans, have been linked to a decreased drug response. Of note, our patient had an African parent. The enzymes encoded by the two major genes in the CYP3A family, CYP3A4, and CYP3A5, exhibit similar metabolic capabilities but different variation profiles [65]. CYP3A4 is the most conserved variable gene [61]. In Americans and Europeans, CYP3A4*22 is the major allele. CYP3A5 harbors only a few common genetic variants and we analyzed CYP3A5*3 that results in CYP 3A5 inactive function [66]. This allele shows high frequencies in Europeans, admixed in Americans, East Asians, and South Asians (respectively, 94.3%, 79.7%, 71.3%, 66.8%) [67]. By contrast, in Africans *3 variant allele is much lower [61].

Our patient exhibited a poor metabolism: this finding was not easily predictable considering his dual Caucasian and African origin, but certainly provides a further element to be considered in the management of complex poly-therapies, in terms of effectiveness and tolerability.

Author contributions

Conception and design: G Cirnigliaro, I Di Bernardo, V Caricasole, B Scaramelli, and B Dell'Oss. Analysis and interpretation of the data: G Cirnigliaro, I Di Bernardo, V Caricasole, E Piccoli, L Pomati, C Villa and B Dell'Osso. Drafting and revision of the paper: S Pantoni and B Dell'Osso.

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