CASE REPORT

A CASE OF REVERSIBLE SPLENIAL LESION SYNDROME (RESLES) RELATED TO NEUROLEPTIC MALIGNANT SYNDROME IN A SCHIZOPHRENIC PATIENT

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Abstract

Objective: Reversible splenial lesion syndrome (RESLES) is a rare clinico-radiological condition characterized by a transient lesion in the splenium of the corpus callosum.

Method: A systematic search of the literature has highlighted a possible correlation between this rare condition and neuroleptic malignant syndrome (NMS) despite only few cases have been reported.

Results: This paper reports a case of RESLES syndrome in a 36-years old male patient with NMS who was undergoing psychiatric treatment for schizophrenia.

Conclusions: The reported clinical case highlights the possibility of including NMS as one of the differential diagnosis in RESLES syndrome.

Key words: neuroleptic malignant syndrome, reversible splenial lesion, neuroleptic treatment, schizophrenia, neuropsychiatry

Declaration of interest: none

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Introduction

Reversible splenial lesion syndrome (RESLES) is a rare clinico-radiological entity characterized by a transient, oval-shaped lesion involving the splenium of the corpus callosum (SCC) (Grimm et al. 2015), whose pathophysiology is still not clearly understood. Most cases have been associated with antiepileptic drugs toxicity and withdrawal; furthermore, many reported cases have been found in patient with central nervous system infections. Other aetiologies include collagen disease, high-altitude cerebral oedema, metabolic disturbances, such as hypoglycaemia and hypernatremia (Garcia-Monco et al. 2008). In addition, a systematic search of the literature revealed a possible correlation between this rare condition and neuroleptic malignant syndrome (NMS), although currently only few cases have been reported (Al Edrus et al. 2009, Chieh-Tsung and Chin-Hua 2015, Kaino et al. 2015).

This paper presents a case of RESLES in a 36-years old male patient with NMS who was undergoing neuropsychiatric treatment for schizophrenia.

Case report

The patient was a 36 years old male who was undergoing long-acting treatment with Haloperidol Decanoate 150 mg i.m. every 3 weeks. He was diagnosed with schizophrenia at the age of 23. Two days after the administration of depot therapy, the patient was admitted to General Hospital Psychiatric Ward (SPDC) for worsening of the chronic positive symptoms associated with behavioural abnormalities. On examination, he was conscious, agitated and restless, constantly absorbed in hallucinatory dialogue. His vital signs, laboratory findings and electrocardiography were within normal limits. Treatment with Aripiprazole 20 mg daily and benzodiazepines P.O. was then set. As per our routine, at the time of admission, the expanded version of Brief Psychiatric Rating Scale (Overall and Gorham 1962, Lukoff et al. 1986, Roncone et al. 1999), the Positive and Negative Schizophrenic Symptoms (Kay et al. 1987, Callegari et al. 2005) and the Neuropsychiatric Inventory-Nursing home (Rovner et al. 1994, Baranzini et al. 2013) were administered; total scores were 92, 134 and 82, respectively.

On the 5th day of admission the patient showed himself lethargic but arousable; on neurological examination, his pupils were equally reactive, there was no neck stiffness and motor examination showed a generalized muscular hypertonicity. His blood pressure, pulse rate, and temperature were 180/120 mmHg, 130/min and 38.2°C, respectively. Complete blood count and liver function test were within normal limits; blood chemistries showed a mild hypernatremia (150 mmol/L) and a slightly increased C-reactive protein concentration (72 mg/L). Creatine phosphokinase (CPK) levels were markedly raised and showed an up-going trend, reaching the maximum level of 2862 U/L on the 8th of admission. Chest X-ray and CT scan of

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the brain were normal. Electroencephalography (EEG) revealed diffuse slow waves indicating diffuse cerebral dysfunction which is not specific as to cause. Several aetiologies may provoke generalized background slowing, including CNS infections, metabolic or toxic encephalopathy and even focal structural lesions (Britton et al. 2016). Brain MRI (**figure 1**) showed swollen splenium of corpus callosum and appeared hypointense on T1-weighted image, hyperintense on T2-weighted image and FLAIR. Restriction in diffusion was observed in the diffusion-weighted imaging (DWI) with decreased apparent diffusion coefficient (ADC) values; no enhancement was noted on post- following gadolinium.

Lumbar puncture showed clear cerebrospinal fluid (CSF) with no signs of infections; no bacteria were detected in blood, urine and CSF cultures. While awaiting the results, the patient was treated empirically for possible central nervous system infections with intravenous piperacillin/tazobactam 4.5 g three times a day and subsequently with ceftriaxone 2 g I.V. daily; in addition, therapy with aripiprazole was suspended. Given the rising CPK levels and the presence of myoglobinuria, intravenous fluids were started to avoid renal failure. After two days, the patient has been transferred to Intensive Care Unit and he has undergone oro-tracheal intubation, which was kept for 5 days, due to his impaired level of consciousness.

His body temperature and both the plasma creatine phosphokinase and sodium levels were normalized by the 18th day of admission. His consciousness improved completely, and the abnormal SCC lesion was no longer visible on a follow-up MRI carried out on the 24th day of admission.

In view of the patient's history, clinical presentation, laboratory findings and neuroimaging, a diagnosis of neuroleptic malignant syndrome associated with a reversible lesion of the splenium of the corpus callosum was made.

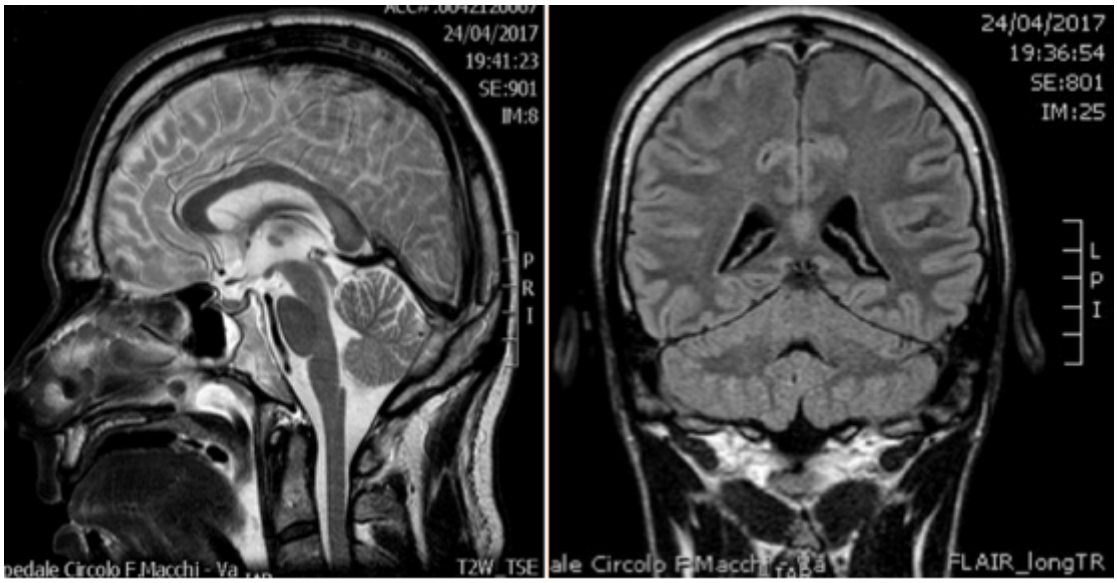
Discussion

Reversible splenial lesion of the corpus callosum is a rare condition which has only been described in recent years. The most commonly reported aetiology was that related to antiepileptic drug withdrawal, followed by central nervous system infections, high-altitude cerebral oedema, and metabolic disorders. In addition, a variety of miscellaneous conditions have also been occasionally associated with RESLES (Gracia-Monco et al. 2008). Clinical presentation is non-specific; the common neurological symptoms include delirious behaviour, followed by consciousness disturbance and seizures, all of which usually resolve completely within a month. In the reported case, EEG showed the slowing of basic cerebral activity which is a common finding in patients with reversible lesion of the corpus callosum (Zhang et al. 2015).

The exact pathophysiology is still not clearly understood; it has been suggested that transient SCC lesions likely reflect rapidly resolving intramyelinic oedema (Zhang et al. 2015). In most of the reported cases brain MRI shows a transient, non-contrast enhancing, T2/ FLAIR hyperintensity associated with diffusion-restriction and low ADC values on DWI, indicating cytotoxic oedema. The exceptions were those cases associated with high altitude cerebral oedema where high ADC values suggested the presence of vasogenic oedema (Garcia-Monco et al. 2008, Al-Edrus et al. 2009). Several authors have suggested that an increase in inflammatory cytokines, such as interleukine-6, may lead to mitochondrial dysfunction and consequently to the destruction of the blood-brain barrier, resulting in vasogenic oedema (Conti et al. 2007, Jain et al. 2015). Supporting this theory, in 2016 Azuma et al. have reported elevated urinary β2-microglobulin levels in four patients with a reversible splenial lesion of the corpus callosum; this finding suggested that an excessive immune response may play a role in the pathophysiology of RESLES (Azuma et al. 2016).

In the patient described in this case report, after an extensive workout to rule out infection or other possible causes, a clinical diagnosis of neuroleptic malignant syndrome was made, based on the positive history of psychiatric treatment as well as the clinical presentation and laboratory findings. NMS is a relatively rare but potentially fatal side effect of antipsychotic drugs, which was first described by Delay et al in 1960 (Delay et al. 1960). The incidence of NMS ranges between 0.02% to 3.23% of patients receiving neuropsychiatric treatment (Sadock and Sadock 2007). The most obvious risk factor related to the development of NMS is neuroleptic therapy itself. Thus, the time-course of administering the drug, the type of neuroleptic used (high- potency drugs endanger most), rapid titration of the desired therapeutic serum levels, and the oily long-acting depot forms of neuroleptics are well-established risk factors regarding the development of NMS. Previous episodes of NMS, a recent episode of catatonia, and extreme agitation are documented risk factors (Oruch et al. 2017). Furthermore, an intriguing hypothesis, put forward by Poloni et al in 2009, is that gluten encephalopathy can lead to an increased susceptibility to NMS (Poloni et al. 2009). Despite the exact physiopathology of NMS is not completely elucidated, antipsychotic-induced dopamine blockade likely plays a pivotal triggering role in the condition (Mann et al. 2000, Strawn et al. 2007); moreover, sympathoadrenal dysfunction has been suggested as having a contributing role in NMS, based on the autonomic dysfunction described in NMS and the observation that catecholamine levels are elevated in many cases (Feibel and Schiffer 1981, Gurrera 1999). Clinically, NMS is characterized by an abnormal mental status, hyperthermia, "lead-pipe" rigidity, akinesia or dystonia, autonomic instability and rhabdomyolysis, resulting in an increased plasma CPK level. With regards to the treatment, dantrolene has been recommended as a muscle relaxant and dopamine-agonist drugs such as bromocriptine have also proved to be beneficial; in addition, minor tranquilizers such as benzodiazepines are a good choice for treating agitation and catatonia (Oruch et al. 2017). It is important to note that, being a rare condition, most of the published work regarding the guidelines of treatment of NMS are based on case reports, meta-analysis, or opinions of experts in the field (Dell'Osso et al. 2015). In NMS, brain CT and MRI scans did not show any specific neuroimaging features; they are usually done to exclude other structural lesions or infections. At date abnormalities in the corpus callosum have been reported in patients with neuropsychiatric lupus with psychosis (Fogel et al. 2015) and in only few NMS cases (Al-Edrus et al. 2009, Kaino et al. 2015, Chieh-Tsung and Chin-Hua 2015). Another possibility that needs to be considered in this patient is hypernatremia which has been associated with RESLES by several authors (Arnaout et al. 2001, Nells et al. 2006, Maeda et al. 2006). It was stated that hypernatremia can lead to osmotic myelinolysis which might be responsible for the developing of the splenial lesion. Osmotic myelinolysis has been also related to carbamazepine withdrawal and it is possibly due to

Figure 1. . *MRI imaging of the brain on 5th day of admission: an ovoid lesion is seen at the centre of the splenium of the corpus callosum, hyperintense on T2 and FLAIR*



alteration of the arginine-vasopressin (AVP) system (Stephens et al. 1978). It has been demonstrated that the AVP system mediates regional cerebral flow and affects brain hydric content, playing a role in generating oedema (Raichle and Grubb 1978, Doczi et al. 1982).

In this patient hypernatremia, attributed mainly to fever and excessive diaphoresis, could not be entirely excluded as the cause for the reversible splenial lesion.

To date only few cases of NMS with MRI findings have been reported (Jain et al. 2015) these have included hyperintense lesion in parietal and occipital regions (Becker et al. 1992, Sugimoto et al. 1999), multiple contrast enhancing lesion in the cerebellum (Storm et al. 2009) and reversible splenial lesion of the corpus callosum (Al Edrus et al. 2009, Chieh-Tsung and Chin-Hua 2015, Kaino et al. 2015). Establishing a hypothesis for the precise aetiology of the SCC lesion in this patient is difficult; nonetheless, the authors want to highlight the possibility of including NMS as one of the differential diagnosis of reversible splenial lesion of the corpus callosum.

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