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Clinical case

Brief psychotic disorder revealing a SARS-COV-2 encephalopathy in a patient with myasthenia gravis: A case report

Épisode psychotique bref révélant une encéphalopathie secondaire à une infection par le SARS-COV-2 dans un contexte de myasthénie autoimmune : à propos d'un cas

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1. Case

Mr D., aged 40, had past medical history including an autoimmune hepatitis, discovered and treated with Azathioprine from 2014 to May 2017, a myasthenic crisis revealing myasthenia gravis in February 2021 (anti-RACh positive), a severe obstructive sleep apnea syndrome, and obesity with a BMI over 35. The patient had no personal or familial psychiatric history and was following a daily medication by corticosteroids, Azathioprine and Pyridostigmine. He had not received any dose of COVID vaccine.

He had been hospitalized in Intensive Care Unit (ICU) for a COVID-19 infection in August 2021. RT-PCR was positive to delta variant (mutation L452R). In ICU, he received corticosteroids, two doses of Tolicilizumab, and optiflow oxygenation. Amoxicillin plus clavulanic acid was introduced for an oropharyngeal infection by streptococcus aureus. One week after his admission, he had been discharged from ICU and went home without any residual COVID symptoms.

Twenty-four hours later, Mr D. presented to emergency department for anxiety and psychomotor agitation. The patient exhibited mystical delusions with disorganized speech and behavior. Neurological examination did not reveal an aggravation of myasthenia. Physical examination revealed a febrile temperature at 38.3 °C. Brain CT-scan was normal. Biochemical and immunological analysis of the spinal fluid were performed (see Table 1).

In regards of the recent respiratory failure and myasthenia crisis, Haloperidol 6 mg, an exclusive D2 antagonist was administered in two-steps to treat psychomotor agitation, allowing the patient's admission psychiatric ward. The next day, the patient presented with dystonia, extrapyramidal syndrome, fixed gaze, waxy flexibility, mutism. Body temperature, blood pressure, heart and respiratory rates remained normal. Bush-Francis Catatonia Rating Scale scored at 25/69, raising the hypothesis that Haloperidol has induced catatonia within the context of an autoimmune encephalitis (spinal fluid analysis were underway). We decided to maintain a low daily dose of Haloperidol (2 mg) to reduce the risks if agitation. Given the myasthenia gravis history, Benzodiazepines, which are

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Table 1
Paraclinical results.

Brain-CT	Absence of morphological or focal abnormalities
Biochemical spinal fluid analysis	Normal
Immunological spinal fluid analysis	Absence of: anti-Hu, anti-Ri, anti-Yo, anti-Gad, anti-CV2, anti-Tr, anti-NMDA, anti-AMPA1, anti-AMPA2, anti-VGKC (anti-LGI1, anti-Caspr2), anti-GABArb
Brain-MRI	Non-specific T2 signals without T1 gadolinium signals, localization suggest leukoaraiosis etiology. Absence of inflammatory signs
EEG	Absence of electric abnormalities

central respiratory depressors, were contraindicated and Sodium Valproate up to 750 mg daily was introduced. This decision is discussed below. Medications and doses prescribed are shown in Fig. 1.

Catatonic symptoms rapidly alleviated and disappeared in 48 hours. Psychiatric examination then revealed behavioural oddities, disorganized speech, auditory and verbal hallucinations, passivity symptoms, and anxiety. While speech was disorganized, patient expressed concern and sadness about a friend who died recently. As the biochemical spinal fluid was normal and immunological analysis was still in progress, we made the assumption of a melancholic depression and introduced Fluoxetine 20 mg without excluding the possibility of encephalitis. No anomaly in brain structure and functions were found; results are resumed in Table 1.

Over the course of 15 days, the patient's overall condition improved, with total reduction of symptoms like disorganized speech, hallucinations, and passivity. Immunological spinal fluid analysis did not reveal the presence of antibodies. Residual anxiety symptoms persisted, motivating the introduction of Aripiprazole 10 mg in regard of recent psychotic symptoms, while Haloperidol, Sodium Valproate and Fluoxetine were interrupted.

Cognitive assessment with MMSE reached 30/30 on the day of the patient's discharge at day 21. A psychiatric evaluation 10 days later noted a disabling asthenia without any associated psychiatric or neurological symptoms. Hence, Aripiprazole was in turn discontinued at that moment. Given the lack of persistent symptoms and normality of immunological spinal fluid analysis, the final diagnosis, discussed below, was COVID-encephalopathy.

2. Discussion

2.1. Myasthenia gravis and antipsychotics

Myasthenia gravis is a rare disease with an estimated prevalence between 50 and 200 people per million, with 3,000 people affected in France [1]. Several case reports have been published on psychosis associated with myasthenia [2–5], but none focused on COVID-encephalopathy as main comorbidity. Autoimmune myasthenia gravis is characterized by the presence of antibodies, which prevent the binding of acetylcholine to muscarinic receptors of muscle cell. Most neuroleptics have an affinity for muscarinic receptors, and association with myasthenia is theoretically contraindicated as it results in a decrease of acetylcholine transmission. However, some antipsychotics do not have anticholinergic effects: Haloperidol, Aripiprazole and Amisulpride [6]. They have been used successfully in several case reports [5]. In the present case, we did not observe an aggravation of myasthenia when Haloperidol and Aripiprazole were prescribed. It should be noted some drugs with anticholinergic properties have been used successfully with past history of myasthenia, such as Olanzapine and Quetiapine [3]. In addition, the worsening of myasthenia secondary to neuroleptic medication may be misinterpreted as acute dyskinesia leading to usage of anticholinergic drugs and benzodiazepines which may worsen neurological symptoms [5]. In general, exacerbation of neurological symptoms after the introduction of anticholinergic medications should alert clinicians on the risk of a myasthenic syndrome.

2.2. Catatonia and myasthenia

The patient presented an episode of temporary catatonia after Haloperidol injection. We did consider the diagnosis of neuroleptics malignant syndrome (NMS), but no signs of autonomic dysfunction or biological anomalies were found, excluding this hypothesis regarding international recommendations [7]. NMS and catatonia share common clinical features; however, literature does not clearly confirm such a relationship [8,9]. Lowering the daily dose of Haloperidol and frequent clinical examinations were performed to monitor autonomic dysfunction. Both diagnosis and treatment of catatonia are based on GABA agonist drugs; thus, Benzodiazepines

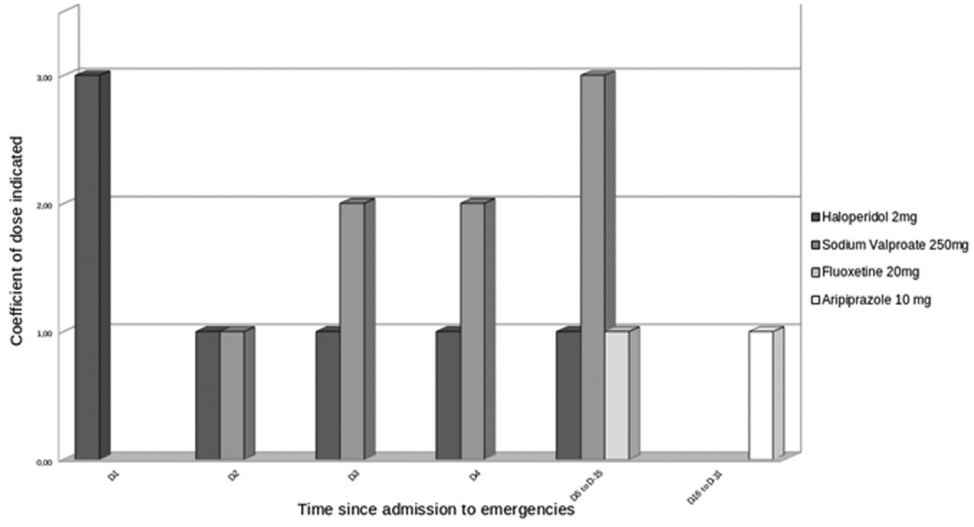

Fig. 1. Medications and doses prescribed. *x*-axis: D-X means Day number X from admission in emergency department. *y*-axis: indicates the number of times the doses in legend were given daily.

are the first line medication. However, they are associated with peripheral muscle relaxation and lower respiratory rate, which may cause secondary respiratory effects or aggravation of myasthenia [10]. Following several case reports [11], treatment with Sodium Valproate was introduced. This is a potent inhibior of GABA-amminotransferase, increasing concentration of GABA inside the brain and without being associated with respiratory depression [12]. In the present case, catatonia was alleviated two days after the introduction of this treatment. While it is not possible to confirm the effect of Sodium Valproate on catatonia, our observation concurs with this hypothesis. Another therapeutic option was electroconvulsive therapy, as it is known treatment of resistant catatonia or in case of therapeutic failure. Some case reports have been published on the safety of ECT with a past history of myasthenia [4,13,14].

2.3. Encephalopathy after Sars-CoV-2 infection

The diagnosis of encephalopathy has been established based on clinical symptoms, negative results to para-clinical examinations and up-to-date scientific knowledge. Considering literature, a window of eight days after first covid symptoms, ICU admission and comorbidities (immunological deficiency and obesity) is positively correlated with apparition of encephalopathy [15–17]. The term "encephalopathy" refers to every pathobiological process in the brain developing in less than 4 weeks [18] not requiring specific para-clinical examinations. The main physiopathological hypothesis the is local destruction of the brain blood barrier secondary to multiple aggression mechanisms: hypoxia, multiple drugs use in ICU, inflammatory process and pro-thrombotic context [19,20]. We did not perform Sars-CoV-2 RT-PCR in spinal fluid; it is a limitation in this report. However, Sars-CoV-2 encephalitis is rare. In a French cohort of 1,979 patients, 249 had, de novo, neuropsychiatric symptoms and only seven fulfilled the diagnosis of encephalitis whom one had reactivation of HSV virus in spinal fluid [16]. Furthermore, international recommendations for diagnosis of encephalitis [21] require one major criteria (encephalopathy) and 3 minor criteria (fever lasting 72 h, seizures, focal neurological signs, biochemical anomalies in spinal fluid, abnormalities of brain parenchyma, abnormalities of EEG) to formally confirm the presence of an encephalitis. In our case, none of the minor criteria were fulfilled, excluding this diagnosis.

3. Conclusion

We present here the case of a patient hospitalized for a brief psychotic disorder following a COVID infection with myasthenia as main comorbidity. The management of such a complex and rare comorbidity required therapeutic adaptation to avoid exacerbation of his autoimmune pathology. Literature on management of psychotropic drugs in myasthenia being scarce, this case report indicates some specific directions to medical practice. In the present case, Sodium Valproate, Fluoxetine, Haloperidol and Aripiprazole have shown to be safe. When taking care of psychiatric patients with myasthenia comorbidity, clinicians should consider these medications first. The episode of catatonia, induced by Haloperidol, rapidly alleviated after introduction of Sodium Valproate. This medication may represent a good alternative to Benzodiazepines in this indication when clinicians are concerned with Benzodiazepines side effects. Encephalopathy after Sars-CoV-2 infection may present as a brief psychotic disorder. In the context of pandemic, psychiatrists should be aware of this hypothesis when taking care of acute psychotic disorder, as it does not require long-term antipsychotics treatment, which may have side effects.

Ethical consideration

The patient received complete information about our project to report his case, prior to the preparation of the present article. He gave his consent and his decision was noted in the medical file.

Disclosure of interest

The authors declare that they have no competing interest.

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