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Short Communication

Hyperacute reversible encephalopathy related to cytokine storm following COVID-19 vaccine

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ABSTRACT

We describe the first case of hyperacute reversible encephalopathy following COVID-19 vaccination. A patient presented with acute onset encephalopathy, mainly characterized by agitation and confusion, rapidly responsive to high dosage steroid therapy and complete remission within 3 days from onset. The clinical manifestation was related with systemic and CSF cytokine hyperproduction, responsive to steroid therapy. Although the occurrence of encephalopathy after vaccination may be just a casual temporal association, we speculate that the cytokine-storm could be the result of an excessive innate immune response against the vaccine, in a predisposed patient susceptible to autoimmunity.

1. Introduction

As the worldwide mass vaccination is fully operational with more people gaining access to COVID-19 immunization, the reports of accidentally related or causally linked neurological complications are also arising. While jumping to hasty conclusions would be only detrimental for the campaign's success (Lunn et al., 2021), it is essential, as we await solid epidemiological evidence, to pay meticulous attention to neurologic disorders timely related to COVID-19 vaccines.

2. Case

Herein, we report a case of acute encephalopathy temporally proximal to COVID-19 vaccination. A timeline of clinical course, diagnostic investigations and therapies is reported in Fig. 1.

A 77-year-old male with history of sarcoidosis and polymyalgia rheumatica in clinical remission with Methylprednisolone 4 mg/day received the first dose of ChAdOx1 nCoV-19 vaccine (AstraZeneca) (Ramasamy et al., 2021) on April 8, 2021 morning. He recovered from mild COVID-19 five months prior to vaccination. Upon awakening the day after vaccination (April 9, day 1 from vaccination - fv) he presented confusion and agitation consistent with delirium and was referred to our Emergency Department. At admission, he was extremely agitated, needing intravenous sedation, and he presented fever ($T = 38.0$ °C) without meningeal irritation or neurological focal signs. Blood tests revealed slightly increased CRP (3.06 mg/dL, normal value, nv < 0.50) and creatinine levels (1.3 mg/dL, nv 0.5–1.2). Brain contrast-enhanced CT scan, including arteriovenous angiography, was not significant and EEG showed moderate diffuse slowing (Fig. 2a, upper panel). A lumbar puncture was performed the same day, revealing normal white blood cell count and severe increase of the blood–brain barrier permeability (CSF protein = 119 mg/dL, nv < 50; CSF/serum albumin ratio = 20.4, nv < 7.4).

On April 10 (day 2 fv), body temperature was normal, nevertheless the patient was still agitated complaining headache, and he showed periorbicular myokymias and sporadic limb fasciculations. Brain MRI resulted unremarkable (Fig. 2b). Microbiological testing on CSF resulted negative, thus high-dose Iv Methylprednisolone (1 g/day for three days) was started. Meanwhile, other laboratory tests resulted negative: CSF oligoclonal bands, CSF and serum autoimmune encephalitis antibodies, serum onconeural, antinuclear and antineutrophil cytoplasmic antibodies. Conversely, cytokines levels documented significant increase of interleukin (IL)-6 in both CSF and serum (194 and 30.9 pg/mL respectively, nv < 5.9) and IL-8 in CSF (162 pg/mL, nv < 70).

From April 11 afternoon (day 3 fv), the patient presented a normal mental status, though amnesic for the previous 48hours, and neurologic

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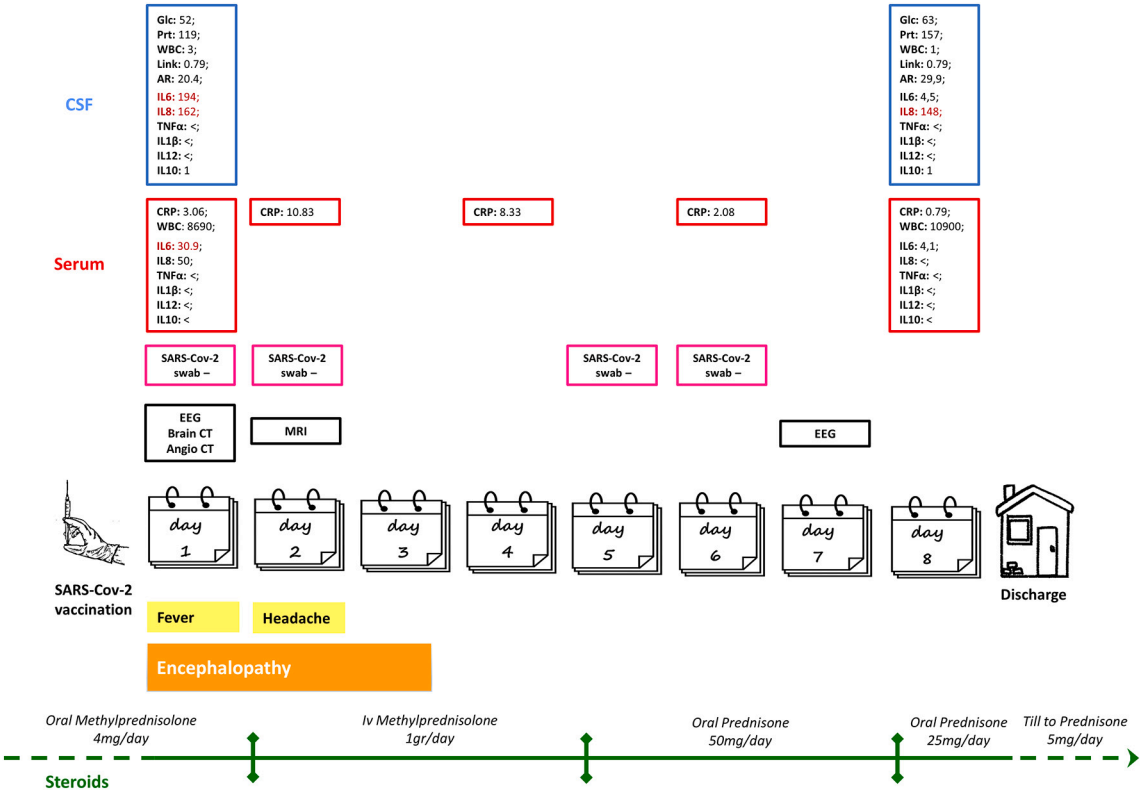

Fig. 1. Time trend of clinical events and diagnostic investigations.
Legend. CSF: cerebrospinal fluid; Glc: glucose (in mg/dL); Prt: proteins (in mg/dL); WBC: white blood cells count (in #/mm^3); Link: Link's index; AR: CSF/serum albumin ratio; IL: interleukin (in pg/mL); TNF: tumor necrosis factor (in pg/mL); CRP: c-reactive protein (in mg/dL); EEG: electroencephalogram; CT: computed tomography; MRI: magnetic resonance imaging; Iv: intravenous.

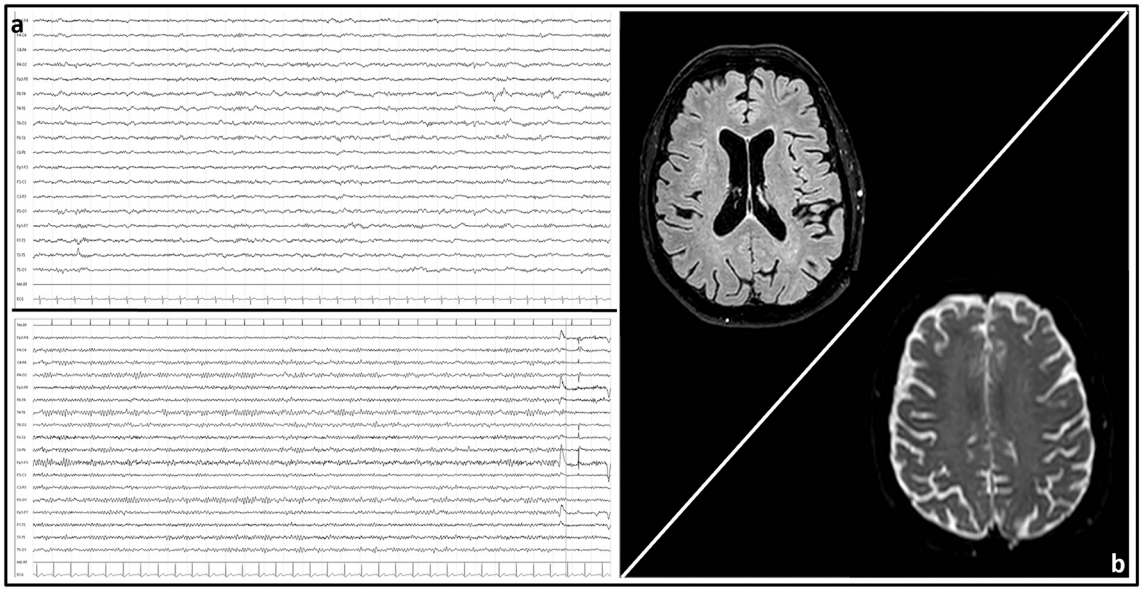

Fig. 2. EEG at onset (a, upper panel) with diffuse slowing partially due to pharmacological effect and at day 7 (a, lower panel) with normal activity. Brain MRI (b) performed at onset did not demonstrate any acute lesion on T2- flair and diffusion weighted images, rare T2 hyperintensities compatible with chronic vessel disease were evident.

examination was unremarkable. Over the following days, steroid therapy was reduced to oral Prednisone 50 mg/day (from day 5), then tapered until a 5 mg/day target. Nasopharyngeal SARS-CoV-2 swabs tested always negative. A follow-up EEG on April 15 (day 7 fv) was within norm (Fig. 2a, lower box). A second lumbar puncture performed on April 16 (day 8 fv) detected the persistence of increased blood–brain barrier permeability (CSF protein = 157 mg/dL; CSF/serum albumin ratio = 29.9), but significant reduction of cytokines levels, with normalization of serum and CSF IL-6. The patient was discharged the same day (day 8 fv) in good clinical conditions.

3. Discussion

In our case, the acute onset after vaccination in absence of other documented etiologies, the overproduction of intrathecal neuro-inflammatory mediators, the downward trend of cytokines with normalization of IL-6 as well as the prompt recovery after corticosteroid therapy, seem to point beyond the typical picture of fever-related delirium of the elderly, suggesting a brain dysfunction associated to cytokine storm (Fajgenbaum and June, 2020; Pensato et al., 2021).

Cytokine storm neurotoxicity has been related to immune effector cell-associated neurotoxicity syndrome in chimeric antigen receptor T-cell therapies, COVID-19 infection (Cani et al., 2021), iatrogenic and autoimmune conditions. Recently, a unifying definition of cytokine storm-associated encephalopathy (CySE) was proposed (Pensato et al., 2021). CySE origins from the massive release of cytokines promoting blood–brain barrier disruption and microglia/astrocyte activation which support neuroinflammation in a synergistic act (Pensato et al., 2021).

It is plausible that CySE could constitute a common denominator also for COVID-19 vaccine-related acute reversible encephalopathy. Albeit the association of CySE with COVID-19 vaccine is only temporal, we could speculate that, in our case, the cytokine-storm represents an excessive innate immune response (Fajgenbaum and June, 2020), either against the Sars-Cov-2 coding DNA, or towards the viral vector or adjuvants, in a patient with previous exposure to Sars-Cov-2 and documented predisposition to autoimmunity, which could have fostered an unbridled immune response. Indeed, few cases of acute encephalopathy occurring within 3 days from vaccine administration are reported among USA's Vaccine Adverse Event Reporting System (Centers for Disease Control and Prevention, 2021) and Europe's EudraVigilance database (EMA, 2021), although without evidence of elevated cytokine levels.

In conclusion, although further data are needed to confirm this association, we documented the first hyperacute reversible encephalopathy following COVID-19 vaccination, suggesting cytokine storm as its causative mechanism, and highlighting the need to deepen our knowledge on this immune-mediated phenomenon.

Guidelines

The case report presentation followed CARE guidelines where appropriate.

Standard protocol approvals, registrations, and patient consents

The report of this case was exempt from ethics board approval.

Written informed consent was collected from the patient for the inclusion of deidentified clinical data in a scientific publication, in accordance with the Declaration of Helsinki.

Data availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Authors contribution

Name and Degree	Location	Contribution
Luca Baldelli, MD	University of Bologna, Bologna, Italy	Drafted and revised the manuscript for intellectual content; had a major role in the acquisition of data; analyzed and interpreted the data.
Giulia Amore, MD	University of Bologna, Bologna, Italy and IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy	Drafted and revised the manuscript for intellectual content; had a major role in the acquisition of data; analyzed and interpreted the data.
Angelica Montini, MD	University of Bologna, Bologna, Italy	Drafted and revised the manuscript for intellectual content; had a major role in the acquisition of data; analyzed and interpreted the data.
Ivan Panzera, MD	University of Bologna, Bologna, Italy	Interpreted the data; drafted and revised the manuscript for intellectual content.
Simone Rossi, MD	University of Bologna, Bologna, Italy	Interpreted the data; drafted and revised the manuscript for intellectual content.
Pietro Cortelli, MD PhD	University of Bologna, Bologna, Italy and IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy	Revised the manuscript for intellectual content; interpreted the data.
Maria Guarino, MD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy	Revised the manuscript for intellectual content; interpreted the data.
Rita Rinaldi, MD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy	Revised the manuscript for intellectual content; interpreted the data.
Roberto D'Angelo, MD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy	Revised the manuscript for intellectual content; interpreted the data.

Declaration of Competing Interest

None.

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