Psychiatric pathology potentially induced by COVID-19 vaccine

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Vaccines are the predominant biological management measure for controlling the COVID-19 pandemic, and aim to break the chain between disease status and hospitalisation. Unseen or rare side-effects are being reported via the COVID-19-specific Yellow Card reporting site, including mania, psychosis and encephalitis of various subtypes. This article presents a patient displaying a range of psychiatric pathologies that occurred within 10 days of AstraZeneca COVID-19 vaccination and resolved spontaneously without antipsychotic medication. The possibility of a vaccine-related autoimmune encephalitis (AE) is tentatively raised.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) gave authorisation for the first COVID-19 vaccines in December 2020 as part of their 'rolling review' process that assessed the safety and efficacy of the medicines.[1] As of 12 August 2021, three vaccines have been approved for UK use: the BioNTech Pfizer vaccine; the Oxford University AstraZeneca vaccine, and, most recently, the Moderna vaccine.

Vaccination, in general, is a safe procedure designed to prevent the outbreak of communicable disease and to protect vulnerable groups; but, like all pharmaceutical agents, side-effects associated with vaccines are common. While the majority of side-effects are minor, significant complications are possible. Indeed, the AstraZeneca vaccine trials were halted in phase 3 by a case of transverse myelitis, and people under 40 years of age will no longer be offered this vaccine due to an association with blood clots.[2,3,4] Furthermore, the neurological sequelae of COVID-19 infection itself are increasingly common and include cases of encephalitis.[5,6] A recent systematic review and meta-analysis of outcomes in 129 008 patients across 23 studies with radiologically- or biochemically-confirmed encephalitis as a complication of COVID-19 infection indicated an incidence of 0.215% and an average mortality rate of 13.4%.[7]

The COVID-19-specific Yellow Card reporting site records suspected side-effects of medications, vaccines or procedural adverse incidents to ensure continuing safe use.[8] They produce an analysis print of the reported side-effects of all available COVID-19 vaccines, and up until the 28 July 2021, had identified a large range of neuropsychiatric complications.[9] Of the approximate total of 23.4 million people who received a second dose of the AstraZeneca vaccine, this included 54 potential cases of encephalitis of varying subtypes; but there are also reports of new-onset bipolar disorder, psychosis and confusional states.

There have been further cases of encephalitis of varying forms reported in those who received the Pfizer/BioNTech vaccine, with a total of 23 cases identified from the approximate figure of 13.8 million people to have had both doses.[10] There was, at the time of writing, a single association between administration of the Moderna vaccine and a case of Japanese B encephalitis, with the important caveat that considerably fewer people have had two doses of the Moderna vaccine than either of the other preparations, at approximately 400 000.[11]

As yet, there are no COVID-19 case reports on encephalitis as a result of vaccination. Herein, we present a patient displaying a range of psychiatric pathologies. Symptoms occurred within 10 days of AstraZeneca vaccination and resolved spontaneously without the need for antipsychotic medication. We tentatively raise the possibility of a vaccine-related autoimmune encephalitis (AE).

Presentation

The patient is a 51-year-old Caucasian male, who is married with no children. There is no family history of mental illness to suggest any genetic susceptibility to psychiatric morbidity. There were no perinatal complications or neurodevelopmental delays in his infancy. His early life experiences were very good; he lived in a caring and supportive family environment, with no significant traumatic experiences. This likely underpins his resourceful personality, with no significant maladaptive personality traits observed during his inpatient stay.

This is demonstrated in good functioning in terms of both occupation (with a successful job) and relationships (with one serious long-term relationship). Prior to admission, he had had no previous contact with psychiatric services. He had only a single contact with his GP in January 2021 for anxiety symptoms following an episode of chest pain. He was prescribed sertraline, but he took one dose only because he felt sedated and unilaterally discontinued the medication.

The patient had his first dose of AstraZeneca COVID-19 vaccine in mid March 2021. No other precipitating factors were identified, such as illicit substance use or significant stressors. In the days after administration of this initial dose, he developed flu-like symptoms that included a severe 'splitting' headache. Ten days later, his wife observed that he was becoming confused, with a significant change in his behaviour. He was taken to the accident and emergency department of the local general hospital by ambulance after he stopped eating, drinking and communicating. Physical assessment, including a CT head scan and routine blood tests, found no abnormalities. Therefore, two days later he was referred to psychiatric services and was subsequently admitted to the adult mental health inpatient unit under Section 2 of the Mental Health Act 1983.

A number of clinical features were reported by the patient's wife and subsequently observed by the nursing staff during his psychiatric inpatient admission. He was confused and disoriented in time and place. His communication ranged from speaking in short sentences, sometimes whispering or mumbling to being completely mute. He was thought disordered. When he was given some paper to write down his thoughts, he was unable to write anything meaningful and was drawing lines only. He stated that he was hearing voices, both male and female, saying the word '*Covid*' to him, but he could not elaborate any further. His mood was labile and informed his behaviour, which was bizarre and at times very disinhibited. On one occasion he was incontinent of urine. Physical examination was unremarkable; aside from the aforementioned confusion and disorientation, there were no abnormalities that suggested neurological symptomatology. Physical investigations, including routine bloods, were all normal.

Based on the absence of risk factors, the age of onset, the acute onset and the fluctuating clinical picture and predominating confusion, an organic cause was suspected by the clinical team. The onset of symptoms following the first dose of COVID-19 vaccine was thought to be significant. An MRI and a blood screen for autoimmune encephalitis (NMDA receptor antibodies, anti-Caspr2 antibody, anti-Lgi1 antibodies, anti-AMPA1 antibodies, anti-AMPA2 antibodies and anti-GABAb receptor antibodies) were requested. On a regular basis, he was prescribed only lorazepam 1mg, twice daily. Antipsychotic medication in the form of haloperidol 5mg twice daily, was prescribed on an unscheduled, *pro re nata* basis only. There were no doses administered during his stay on the ward.

He did not report any fever, or symptoms of autonomic dysfunction. He did not report vomiting or symptoms suggestive of focal seizures. He did not report any swallowing difficulties or abnormal eye movements. He was sleeping well during his stay on the ward.

The patient's mental state improved in the four days following admission leading to a complete resolution of all symptoms described. He was discharged on 7 April 2021. One month post-discharge, he reported feeling very well with no recurrence of symptoms.

At the time of writing this report, an MRI head was awaited. The results of the autoimmune encephalitis screen were all negative.

Discussion

Autoimmune encephalitis (AE) comprises a group of non-infectious, immune-mediated inflammatory disorders of the brain.[12] It is a debilitating neurological disorder, characteristically developing as a rapidly progressive encephalopathy secondary to brain inflammation that creates a diffuse, poly-syndromic clinical picture with a complex differential diagnosis.[13]

Original cases were classically from paraneoplastic-derived antibodies against intracellular onco-neuronal antigens that were not directly pathogenic; their immune-mediated T-cell responses against the tumour invoked a secondary nervous system response.

More recently, pathogenic antibodies against neuronal surface or synaptic antigens have been identified that also provoke immune-mediated diseases, some of which have a characteristic clinical presentation.

There is also a subset of patients with a seronegative AE, likely to have been provoked by T-cell response or as yet unidentified antibodies. This highlights both the gap in progress between the research and clinical settings in recent years and the considerable diagnostic challenge posed by this disease and its diffuse range of presentations in the absence of a confirmatory test result.[14] Supplementary tests, such as EEG and MRI, are rarely pathognomonic and not always abnormal.

The negative sequelae of the above within psychiatric settings is that diagnoses of AE are often delayed as the psychiatric symptoms of disease are assessed and treatments are attempted, potentially compromising outcomes for patients.[15]

When deliberating the patient described here, a seronegative AE is a tentative possibility despite considerable diagnostic ambiguity. Investigations are incomplete but negative results, as above, would not preclude a diagnosis of AE.

Consideration around the potential role of the COVID-19 vaccine in this case is necessary. Vaccines are the predominant biological management measure for controlling the pandemic, and aim to break the chain between disease status and hospitalisation. Vaccine rollout has been necessarily rapid. Unseen or rare side-effects, including AE, are being reported.

In the absence of other causative explanations and in the context of the short period between vaccine administration and onset of psychopathology, as well as the resolution of symptoms without psychotropic medication, a tentative hypothesis is that the presentation could have been provoked as a result of complications relating to COVID-19 vaccination.

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Declaration of interests

No conflicts of interest were declared.

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