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Case Report

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Root Cause Analysis of Queried Covid-Vaccine Induced Psychosis in Single Female Case Study

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Abstract

Background: *Young woman without any prior history of mental illness developed psychotic symptoms shortly after receiving the Astra Zeneca covid-19 vaccine.*
Aims: *The case to be discussed in this paper was chosen due to the rarity of the presenting complaint and to explore all possible avenues of the presenting complaint without agenda to determine most likely cause.*
Method: *Case study of investigations and analysis of treating team looking after the patient.*
Results: *The patient developed encephalitis following administration of AZ CV-19 vaccine which appeared to trigger a psychotic episode. Following treatment of the encephalitis, the psychotic symptoms remained in absence of the suspected organic cause, indicating that the psychosis was present independent of the original trigger.*
Conclusions: *The interpretations of the findings suggested that had the patient not received this vaccine, she would not have experienced the side-effect of encephalitis which resulted in her development of psychosis which required ongoing treatment in the community to treat.*

There are no conflicts of interest to declare and no agenda other than the investigation and reporting of the case on its merits and interest to the researchers.

Background

Mary (pseudonym) is a 22 year old female born outside of the UK. She is a bright, intelligent, multilingual student at university. Other than retinitis pigmentosa, there are no known genetic conditions. No history of epilepsy or mental illness in her family history and has otherwise enjoyed good health with no drug, alcohol or cigarette use.

She presented to the Emergency Department (ED) with a two day history of visual and auditory hallucinations, fever and agitation. According to her family, Mary's personality had also changed acutely in that she became hyper-religious, praying several times a day, whereas before she rarely prayed. It was noted that Mary began to report onset of frontal headaches and vomiting following the second dose of the Astra Zenica COVID 19 vaccination (AZC19), which she received three weeks prior to her presentation to the ED. Due to these headaches she had attended another hospital about a week prior to this presentation but was subsequently discharged as her investigations then were all within normal limits and there was no evidence of vaccine induced thrombosis.

Initially on admission to our ED, Mary was commenced on IV antibiotics for suspected meningoencephalitis but these were stopped the following day as, clinically, this diagnosis did not fit the symptoms. Throughout her admission, Mary was reviewed by Psychiatry colleagues on the ward whilst the Infectious Diseases team investigated any possible organic causes. Her case was also discussed at a specialist neurology Multi-disciplinary team (MDT). Mary had a number of scans and Lumbar punctures, the results of which showed lymphocytic pleocytosis in the CSF. However, the MRI and EEG results were normal. This led to the provisional diagnosis of encephalitis. Unfortunately, since the encephalitis has resolved, Mary has continued to experience symptoms consistent with psychosis independent of any identified organic causes or contributes.

Following no evidence to the contrary, the conclusion from the treating teams involved in the case in the absence of any other suitable explanation, concluded that the AZC19 Vaccine could have contributed to autoimmune encephalitis, manifesting in psychosis and was yellow carded as appropriate.

The aim of this paper is to explore this case in greater detail to try to identify a possible explanation as to why Mary developed psychosis with no family history of mental illness in response to the AZC19 vaccine.

Literature review

The covid vaccine has successfully saved the lives of many vulnerable people who could have become very unwell without it upon contracting covid, and tempered the third wave of infections by reducing the number of hospital admissions and covid deaths [1]. Unfortunately, despite the overwhelming success and evidence of the vaccine's safety in the many millions who have received it, with no or only mild side-effects, there remains a small and unfortunate minority have experienced adverse side-effects which may be why a greater minority are reluctant to accept the vaccine despite the over-whelming body of evidence of its safety.

A cursory glance at the Medicines and Healthcare Regulatory Agency (MHRA) Yellow Card Scheme, where healthcare professionals are expected to report possible side-effects to medication, will reveal a plethora of purported side-effects. Some with vast numbers and others with smaller reported numbers of people reporting these symptoms. These side-effects and numbers must always be taken with a heavy dose of scepticism and scrutiny as there is no research behind these reported side-effects, which are declared if the symptoms emerge shortly after receiving a medication and no other immediate cause is identified. The UK Government publishes weekly reports from the Yellow Card Scheme (Gov.UK [Online]) [2] and in October 2021, there were 43 cases of encephalitis and 44 for psychotic disorder (MHRA) which are specifically relevant to this case study.

A few research articles, predominantly case studies, have been published to date, examining the rare and more debilitating side-effects of the vaccines to better understand why these side-effects emerged and whether or not there was another possible cause for the side-effect. One study looked at three case studies whereby patients developed symptoms of possible encephalitis a few days after receiving the AZC19 vaccine and were successfully treated with steroids. Apart from the third case, where steroids were declined. The authors suggested that there appeared to be a link between Astrazeneca and encephalitis (more so than other vaccines), however, larger studies are required to prove causality [3]. The possible reason for the vaccine induced encephalitis has been linked to an auto-immune response. This is not the first time a link between a vaccine and an autoimmune response has been made with various studies claiming an autoimmune response to a vaccination while an equal number appear to refute it [4-7]. However, other researchers suggest that other factors may be involved in adverse side-effects to vaccines and that it may not be the vaccine that is the problem [5].

Speculation as to how a vaccine may cause an autoimmune response suggests one of two possible pathways; Molecular mimicry and bystander activation.

Molecular mimicry is used to describe when microbial molecules such as a foreign microbe (infection) is similar to the antigenic microbes within the host itself. Thus, when the immune response is triggered to respond to the foreign invader, the body's immune response mistakenly targets the host cells that have similar antigenic determinates to the invading microbe. Thereby creating an autoimmune response [8,4,7].

Bystander activation occurs when the immune products from a previous infection are activated into responding to another invading microbe. Unfortunately, this over-abundance of non-specific T-cells to the intended antigen appears to trigger an autoimmune response [9,4,7].

In addition to molecular mimicry and bystander activation, we know that some people are genetically predisposed to autoimmune diseases, which can be triggered in the event of an infection, makes them more susceptible to infection and/or more likely to exhibit symptoms of immune response hyperactivation [4].

In some cases of an infection or an autoimmune response, the brain is affected, causing it to swell and the patient to exhibit a range of distressing symptoms. This is known as meningoencephalitis. People suffering with encephalitis can display a range of symptoms which could potentially lead clinicians down many diagnostic pathways before encephalitis is identified and treated. Symptoms can include nausea, headaches, fever, seizure, cognitive impairment, memory loss, behavioural and personality changes (NHS [online]). In some cases of autoimmune encephalitis, the patient can exhibit symptoms of psychosis which is thought to be caused by autoantibodies targeting and binding against/blocking N-methyl-D-aspartate (NMDA) receptors, necessary in the maintenance of synaptic plasticity which also plays a role in memory; another symptom of encephalitis [10,11]. Expanding on this further, Bergink and colleagues (2014) [12] and Watson and colleagues (2021) [13] cited a growing body of research which suggests an autoimmunity dysfunction in the vulnerability of developing psychosis in some patients. Whereby through a biological mechanism, the brain suffers an autoimmune response which appears to trigger psychosis in some, but not all, patients. While researchers have not been able to identify or agree on the specific mechanisms behind this link. Watson and colleagues (2021) [13] went onto even speculate if psychosocial factors may also play a part in the manifestation of psychosis in people who are unwell and/or vulnerable. Therefore, it is not unreasonable to consider that someone who is genetically susceptible to psychosis, who then suffers from a neurological abnormality such as encephalitis, could trigger not only symptoms of psychosis during the acute phase of the illness, but trigger a psychotic illness which develops and continues independently of the initial catalyst, even once the original trigger has been treated. We speculate that this may be the case for Mary. It is worth noting, that Mary was not knowingly experiencing any psychosocial stressors before becoming unwell which

would not support previous authors speculations in regards to psychosocial stressors as a cause for psychosis following a biological catalyst.

While some research supports the notion of auto-immune vulnerability in the development of psychosis, it is equally important not to assume that psychotic symptoms in the presence of inflammatory markers and antibodies in serum and/or CSF is true psychosis as would be defined with the psychiatric diagnostic community and could be the associated symptoms with the organic brain response to injury and/or infection. Likewise, it should not be assumed that all psychosis is due to the blocking of N-methyl-D-aspartate (NMDA) receptors which can cause both symptoms of psychosis and encephalitis [14] as in Mary's case. A meta-analysis explains the possible pharmacological connection between anti-NMDAR and psychosis in the context of an autoimmune response [15]. There appears to be a connection between these antibodies, encephalitis and schizophrenia, although different studies show different outcomes and autoimmune encephalitis and schizophrenia are different entities [15].

Diagnosing clinicians are encouraged to remain diligent in seeking to rule out diagnosis through appropriate tests rather than seeking to confirm a diagnosis which may over-look the correct diagnosis due to similar presenting symptoms resulting in a missed cause. This was the process followed in Mary's care.

This is not to suggest that the vaccine and having an auto-immune disease is the only risk factor for psychosis. Some research has found that the COVID-19 virus itself can also cause psychosis as well as other neuro-psychiatric difficulties such as depression, brain fog, loss of concentration, memory loss and lack of motivation [16-18]. Therefore, an avoidance of the vaccine will not prevent a susceptible individual from developing psychosis if they go on to contract COVID-19 itself, which can be just as, if not more, likely to develop psychosis than if the vaccine had been administered to protect them from COVID-19 complications.

Specific to Mary who had an existing diagnosis of Retinitis pigmentosa, there has been some research into other case studies, linking this genetic condition with pre-disposition to schizophrenia, including experiences and symptoms that could be associated to schizophrenia such as visual hallucinations. Similarly, these patients were treated with antipsychotics [19]. While none of the research could identify an exact cause for why people with Retinitis pigmentosa were more susceptible to psychotic disorders, common genes and chromosomes thought to be affected in both conditions tentatively suggest a common pathogenic mechanism between these diseases which, when understood, may help find cures for one or both of these conditions [20-22].

Examinations

Table 1. Investigations.

Areas	Investigations
Eyes	Refraction Visual field testing Ophthalmoscopy Tonometry
Limbs	Tone Power Coordination Reflexes Pinprick Vibration sensation Flexor plantar Gait
Imaging	CT head and venogram: with without contrast: report plus images MRI brain: report plus images Chest X-ray ultrasound
Blood	FBC, UE, LFTs, Immunological investigations, Blood cultures, including TB
Other	Lumbar puncture Urine COVID-19

Results

***Eyes*:** On examination, the discs were normal and the visual fields constricted. Eye movements were full in range and facial sensation and power were intact.
Speech was normal and eye contact was good.
Limbs were normal in tone, power, coordination, reflexes, pinprick and vibration sensation with flexor plantars. There was no bradykinesia. Gait was normal.

An initial lumbar puncture did not indicate any unusual symptoms but a second lumbar puncture one week into admission revealed abnormal WCC lymphocyte levels and her cerebrospinal fluid (CSF) was positive for IgO.
All other physical test results were normal. This included test for COVID-19.

***Psychotic symptoms*:** Euphoria, excited about finishing her final exams. But in the early hours she started experiencing visual hallucinations, characterised by dark silhouettes of people surrounding her menacingly. The hallucinations did not disappear if she looked directly at them. They did not speak and she denied auditory hallucinations.

She became increasingly agitated believing evil spirits were after her, that she was being controlled by the devil and that people were trying to abduct her or take her money. She was unable to eat or sleep. Apart from restricted visual fields, neurological examination was intact. She had a single spike in temperature at presentation but was otherwise afebrile during admission. Her condition improved with lorazepam and antipsychotics, initially haloperidol, which was later switched to olanzapine because of haloperidol induced dystonia. Once medically cleared of the organic cause of the psychosis Mary was titrated off of olanzapine. Unfortunately, due to deterioration in her mental state on attempted withdrawal, olanzapine was restarted prior to discharge. Throughout admission her mood was labile and she was hyper-religious, continuously talking to God who she believed was communicating by way of the colour green. She reported auditory hallucinations of the sound of coins pouring into a pot but no voices or any other sounds. There were no seizures, tremor pouring or movement disorder and neurological examination remained normal. She denied any symptoms suggestive of epileptic aura such as epigastric disturbance or sensory symptoms (olfactory, gustatory, etc).

Three weeks into her admission her lumbar puncture and CSF were back to normal.
Following rigorous and thorough testing over an extended period of time, an infective cause for the encephalitis was ruled out. The conclusion was that this was limbic encephalitis most likely caused by the AstraZenica Covid-19 vaccine.

Table of outcome from investigations

	Outcomes
Diagnosis	limbic encephalitis
Differential diagnosis	First episode psychosis Drug (AZ vaccine) induced psychosis
Treatment	Olanzapine for psychosis

Outcome

At One Week:
When interviewed in the week following her discharge from hospital, Mary reported that she felt rather "down" in comparison to prior to discharge from hospital although not tearful. In retrospect, she felt she had been rather "manic" but had enjoyed the close communication with God during the last two weeks of her admission. Mary was now "talking to God" less than before, but still more than was normal for her, and the green hallucinations continued to be experienced a few times per day, although less than on admission. Mary is sleeping well and is more tired than normal. She gets up and dresses herself every day and is eating well. She has not socialised with her friends since returning home which she used to do prior to going into hospital. She is also spending more time alone in her room than previously; reading and watching television, although has been out for walks on her own. Mary is looking forward to going on holiday and to studying again and wants to be a Physician's Assistant. Mary and her mother agree there is no cognitive impairment, although her recollection of the first week of admission is very limited. Otherwise her memory has fully recovered. There have been no unresponsive episodes, absences or seizures and no involuntary movements, tremor, stiffness or slowing down.

At One Month:
When reviewed by a community mental health team a month after discharge, Mary was still exhibiting some symptoms of psychosis which were being treated and reduced through the use of oral olanzapine. Due to a formal physical health diagnosis (encephalitis) being given on discharge from hospital, Mary was not given a formal diagnosis of psychosis and subsequently was not accepted into Early Intervention Services (EIS) for First Episode Psychosis (FEP). The rationale in avoiding a formal psychotic diagnosis was to avoid prejudice and discrimination against a very talented young woman. The disadvantage of this meant that Mary was denied access to a service specifically designed to support people experiencing FEP with the view to preventing further relapse, thereby improving patient outcome. Another disadvantage to not providing a formal psychiatric diagnosis meant that the link to an autoimmune response and drug-induced psychosis is not formally recorded for prevalence and research purposes. The consensus of the authors is that Mary regrettably suffered an auto-immune response to the vaccine which may be due to her underlying auto-immune disease retina pigmentosa, that triggered a psychotic response which she was genetically pre-disposed to.

Discussion

This case was chosen due to the current interest in this vaccine and its impact on the NHS at present. The prevailing situation of the ongoing COVID crisis means that vaccines remain at the forefront of governmental responses to manage and contain this infection. As such, serious side effects that impact the patient are a concern for the whole medical profession, in terms of the severity of the side effects and the likelihood of the side effects.

We need to be aware of the relevant genetic factors of this patient that played a part in predisposing her to experience these side effects and while we are at present unable to quantify these risks, it was clear to us during our literature search that autoimmune abnormalities play a large part in the experience of adverse side effects of vaccines in general, not just the AZ vaccine. Therefore, all we can do at this stage is to highlight that patients with a personal or familial history of autoimmune abnormalities are at greater risk of adverse side effects after receiving an AZ vaccine, and we are clearly NOT generalising this case to the wider population without autoimmune abnormalities.

There is NO finding or basis to conclude that the vaccine itself causes psychosis. Rather, that Mary could have suffered an autoimmune response to any number of other prescribed or recreational drugs, including alternative vaccines, that may have triggered the same neurological response. Because she is a fit and healthy young woman who does not drink or use recreational drugs, the opportunity for the auto-immune response was reduced until the time came for her to accept the AZ vaccine which triggered the events documented above.

In this case, the patient remains with residual symptoms that continue to impact on her lifestyle and relationships, and it is clear that she experienced this as a direct consequence of receiving the vaccine. Her psychosis continues but at a reduced level of deficit than when she was admitted. The hope is that over time her psychosis will continue to go into remission. If Mary continues to follow a healthy lifestyle, it would be expected that it is unlikely for the psychosis to relapse. This suggests that Mary could still enjoy a healthy and happy life and pursue her dream of becoming a healthcare professional herself without any residual deficits or impact on her cognitive abilities.

When considering universal vaccinations, the risk of potential side effects needs to be borne in mind when seeking informed consent from patients who are considering accepting a vaccine, and balanced against the risks of not receiving the vaccine to determine the best course of action. In Mary's case, there would not have been any prior awareness of underlying susceptibility to encephalitis or psychosis prior to receiving the AZ vaccine. Mary's childhood inoculations were administered without incident so her history did not identify any risk factors. Additionally, should Mary have contracted COVID-19 there is no guarantee that she would not have developed similar or entirely new symptoms than what was brought about by the vaccine. At this stage, it can be not be identified if Mary was safer for receiving the vaccine or not. We cannot generalise Mary's experience to the general population. We ask professionals to be aware of these unique and rare cases to best consider appropriate treatments for those affected by or at risk of harm from vaccines.

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