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Case Report

Prevention and Treatment of Long-Term Neuropsychiatric Sequelae of COVID-19 by the BNT162b2 mRNA Vaccine

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Abstract

Background: Neuropsychiatric manifestations of post-acute sequelae of COVID-19 (PASC) produce substantial morbidity and have frequently fallen to psychiatrists for management. PASC pathology may be caused by a virally-activated, dysregulated immune response. Epidemiologic studies have shown prevention of PASC by BNT162b2 mRNA vaccination. In the clinical setting, reports of patients with PASC endorsing improvement and resolution of symptoms following vaccination are increasingly apparent. These clinical events may have an immunologic basis.

Objective and Methods: We present here two distinct cases of patients with neuropsychiatric symptoms of PASC seen in our hospital. We use these examples to review current immunological hypotheses about causes of PASC neuropsychopathology, and how vaccination may both prevent and treat symptoms of PASC.

Results: We report cases of a 45-year-old woman without past medical history, and a 66-year-old woman with hypothyroidism, type II diabetes and post-traumatic stress, demonstrating improvement in neuropsychiatric symptoms of PASC within 1-2 weeks of vaccination.

Conclusion: These cases illustrate how neuropsychiatric manifestations of PASC may remit quickly and decisively following vaccination. Dysregulated innate immune activation may drive PASC pathogenesis via production of autoantibodies and cytokines with neuroinvasive potential, and viral reservoirs in brain, lung and other tissue. If so, organization of the immune system towards a more coordinated adaptive response may reflect the mechanisms underlying PASC prevention and treatment by vaccination.

Keywords: Post-acute sequelae of COVID-19 (PASC); Immune dysregulation; mRNA vaccination

Introduction

Viral infection can produce a clinical picture of chronic symptomology persisting beyond the acute phase, with or without laboratory evidence of ongoing infection [1-3]. The novel coronavirus SARS-CoV-2 joins a group of viral pathogens, including influenza, Ebola and other coronaviruses, whose ability to produce chronic illness is established [1-5]. Increased severity of acute infection appears to confer elevated risk for development of post-acute sequelae of COVID-19 (PASC) [6-8], suggesting that intensity and/or organization of the immune response may play a role in driving long-term symptoms. That is, the link between severe acute illness and chronic illness by SARS-CoV-2 infection may lie in the architecture of the host immune response. As in severe acute

illness, PASC pathology and its neuropsychiatric manifestations may be caused by a virally-activated, dysregulated immune response. Research is just beginning to characterize the components of this immune dysregulation and its neuropathological effects. In the meantime, patients with PASC are presenting to emergency rooms, urgent care clinics and their primary care physicians, with little known about how to treat them. Many are referred to psychiatrists and neurologists. Neuropsychiatric sequelae occur in both acute and chronic illness. Acutely and in more severely ill patients, infection may cause anosmia, ageusia, headache, delirium, encephalopathy, seizures, and stroke [4,9]. Chronically, neuropsychiatric symptoms of PASC include headache, fatigue, neurocognitive complaints and diminished neuropsychological performance, depression and anxiety symptoms [2,5,10]. Along with symptomatic management strategies that do not target infection, antiviral prevention and treatments are likely to be the primary weapon against the neuropsychiatric symptoms of PASC. Vaccination has led to reductions in SARS-Co-V2 infection and associated morbidity and mortality [11]. Perhaps not surprisingly, early reports suggest vaccination also reduces the incidence and severity of PASC, though impact on specific symptoms, including neuropsychiatric sequelae, is not yet well characterized. In the clinical setting, reports of patients with PASC endorsing improvement and resolution of symptoms following BNT162b2 mRNA vaccination are increasingly apparent. These clinical events may have an immunologic basis. We present here two cases of patients seen in our hospital reporting improvement in neuropsychiatric symptoms of PASC following vaccination. We use these examples to review current immunological hypotheses about causes of PASC neuropsychopathology, and how vaccination may both prevent and treat symptoms via activation of a coordinated and more targeted adaptive immune response.

Case I

A 45-year-old woman was referred for neuropsychological evaluation because of difficulty with attention and concentration. Fourteen months previously, the patient developed mild-moderate symptoms of COVID-19, including dyspnea, chills, headache, anosmia and ageusia. Acute infectious symptoms largely improved after two weeks. Over the following month, the patient began experiencing fatigue, forgetfulness, myalgias, weakness and reduced exercise tolerance. She developed significant difficulty with reading, attending to household care, and managing her business. The patient was in good health prior to SARS-CoV-2 infection. She reported periods of fatigue, thinning hair and weight gain in her 20s and 30s that improved with dietary modification. Although she was never diagnosed with thyroid illness, several family members, including her mother, had hypothyroidism and thyroid cancer. The patient consulted with an endocrinologist and thyroid function tests were within normal range. She was seen by a pulmonologist for persistent dyspnea and was prescribed modafinil, which offered mild improvement in alertness. A neurologist ordered magnetic resonance imaging (MRI) of the brain which was unremarkable, and referred her for neuropsychological testing. The patient also started seeing a psychotherapist to develop skills for coping with her reduced level of function. No acute psychopathology was diagnosed. One year following development of symptoms, the patient received a first dose of the mRNA vaccine and within one week experienced improvements in fatigue, headache and dyspnea. She was able to discontinue modafinil without ill effect. By the time of presentation for neuropsychological evaluation, she had already received two-dose vaccination and was reporting a return to 90-95 percent of her previous level of function, with some subjective residual forgetfulness and inattention. Neuropsychological testing did not reveal significant deficits.

Case II

A 66-year-old woman presented to the psychiatric clinic reporting five months of daily headache, fatigue, inattention, low energy and myalgias. Symptoms developed following breakthrough infection with SARS-CoV-2 with mild-moderate symptoms, despite two-dose mRNA vaccination. She experienced difficulty with previously pleasurable activities, including reading books and walking around her neighborhood. Her past medical history included obesity, hypothyroidism, type II diabetes, fibromyalgia, post-traumatic stress and depression. In the 1980s the patient developed a similar set of chronic neurologic symptoms following contraction of Lyme disease, which subsequently remitted. The patient's primary physician found elevated serum thyroid stimulating hormone (TSH) and increased her levothyroxine dosage. She was referred to her rheumatologist for mild elevation in rheumatoid factor, though further workup was negative for rheumatoid arthritis. For headache and facial pain the patient sought care from an otolaryngologist. She underwent computed tomography (CT) imaging of brain and sinuses which were unremarkable, and was prescribed nasal decongestant. The patient had been receiving psychiatric care at this clinic for several years. Depressive and post-traumatic symptoms were stable with escitalopram and psychotherapy. Psychosocial stressors included caring for her 83-year-old husband, and isolation secondary to pandemic lockdowns. Despite substantial impairment in daily activities, the patient denied significant decline in mood or other acute symptoms of a major depressive episode. She maintained hopefulness towards recovery. A diagnosis of PASC was made in the clinic. The patient continued to attend monthly medication management and supportive therapy sessions and her PASC symptoms were tracked. Her psychotropic medication regimen was not changed. Nine months after development of symptoms, the patient reported significant improvement two weeks after booster

vaccination. She was subsequently able to resume activities of daily living at her baseline level of functioning.

Discussion

These cases illustrate how neuropsychiatric manifestations of PASC may remit quickly and decisively following vaccination. To understand this, it is important to review how the virus may cause these neuropsychiatric symptoms by immune dysregulation, and how immunoregulatory effects by vaccination may reverse such symptoms. While varying across strains, acute symptoms of COVID-19 are driven primarily by the innate immune system [12]. Viral infection, wherein the S1 spike protein and other antigenic components bind angiotensin converting enzyme (ACE)-2 receptors highly concentrated in respiratory tissue (including nasal and alveolar epithelium), stimulates a broad inflammatory response [13,5] with release of cytokines, monocytes, macrophages and neutrophils [14]. When immune activation is excessive and/or dyssynchronous, increased expression of interleukin (IL)-10 and pro-inflammatory cytokines (IL-1, IL-6 and tumor necrosis factor [TNF]-alpha) produce severe respiratory and multi-organ illness and mortality [5,15-17]. Also known as cytokine storm, this dysregulated immune response is elicited by other viral infections, including human immunodeficiency virus (HIV) [15]. Weak or delayed activation of interferons [13,16-18] and mixed lymphocytopenia with proliferation of $CD8^+$ T cells of the adaptive branch [19-21] are also present in severe COVID-19 illness. Dysregulated innate immune activation may underlie the pathogenesis of PASC [3,5]. Research suggests that inflammatory activation results in downstream generation of autoantibodies lingering past resolution of initial infection [22-23]. These antibodies may also be elicited by molecular mimicry involving viral antigens (i.e., the spike protein) and host peptides [24]. The ability of these autoantibodies to cross the blood-brain barrier poses a possible explanation for the neuropsychiatric pathology [25] (cytokines [26] and the S1 spike protein [27] also have neuroinvasive potential). Furthermore, diffuse viral spread with evasion of the innate line of defense may yield viral reservoirs in tissue, including brain [25], intestine [28] and lung [29]. The mRNA vaccine has been shown to protect against PASC [11,30-31]. Its ability to do so likely reflects the vaccine's relationship to the dysregulated immune response implicated in severe illness and PASC pathogenesis. Reduced risk of severe illness and shorter disease course, which have both been associated with vaccination [11], may reasonably translate into reduced likelihood and duration of this problematic immune response. Furthermore, immunity conferred by vaccination (in addition to prior infection) primes the immune system for coordinated activation of its adaptive arm [32-33]. The adaptive immune system generally involves antibody production by B cells with support by T cells, reflecting its humoral and cellular branches, respectively. Operating based on memory of past antigenic experience, the adaptive response is targeted and organized, in contrast to the aforementioned broad, dysregulated immune activation and cytokine storm. The adaptive response induced by vaccination includes early activation of $CD8^+$ T cells, and production of high-affinity antibodies supported by $CD4^+$ T cells exhibiting a T_H1 phenotype [19].

If PASC is driven by immune dysregulation, organization of the immune system towards a more coordinated adaptive response may reflect the mechanism by which vaccinated patients with breakthrough infection become less likely to develop symptoms [34]. This mechanism may further underlie the symptom improvement and remittance reported by patients with PASC following vaccination [35]. That is, these patients may feel better as a result of immunoregulatory effects offered by immunization. Furthermore, suppression of adaptive T cell responses by co-morbid conditions and age [19,36] may necessitate additional vaccination dosages (i.e., boosters) to achieve sufficiency, in terms of protective and salutary effects. The cases presented here demonstrate neuropsychiatric symptoms of PASC improving after a first dose of the mRNA vaccine in a 45-year-old female patient, while a 66-year-old female patient with comorbid conditions experienced breakthrough infection and subsequent development of PASC despite two-dose vaccination. In the latter case, symptom improvement occurred following booster vaccination, possibly suggesting the need for increased immune stimulation to mount an adequate adaptive response. However, the extent to which these observations translate to the general population remains to be seen. Of further interest is the shared history of thyroid dysfunction, both clinical and subclinical, among these cases. There is evidence for thyroid illness (i.e., autoimmune thyroiditis) and anti-thyroglobulin and anti-thyroid peroxidase (TPO) antibodies developing out of the dysregulated immune response in acute SARS-CoV-2 infection, in addition to elevated anti-TPO antibodies in PASC [37]. However, the existence of a relationship between COVID-19 and thyroid dysfunction may not be surprising given the infection's propensity for multi-organ damage, and the ability of thyroid disease to predispose towards severe acute COVID-19 or PASC has not been observed. The more salient point may lie in the role of autoimmunity in acute and chronic symptomology. Indeed, in addition to anti-TPO antibodies, numerous additional autoantibodies have been identified in COVID-19 and linked to clinical severity in the acute phase [38]. Antiphospholipid antibodies have been observed and are thought to contribute to the hypercoaguability seen in acute illness [24]. Autoantibodies against G protein-coupled receptors (GPCR) of the autonomic nervous system, including adrenergic and muscarinic receptors, have been suggested as possible effectors of neuropsychiatric manifestations of PASC [24]. Anti-GPCR antibodies have further been detected in chronic fatigue syndrome, which shares clinical similarities with PASC and may also be triggered by viral infection, in this case

Epstein-Barr virus [24]. Moreover, while autoantibodies elicited by dysregulated immune activation may persist beyond the acute phase to drive symptoms of PASC, there is further evidence for the development of autoimmunity in the post-acute phase [24]. Taken together, these observations suggest a role for autoimmunity in PASC. While thyroid disease does not appear to increase the risk of PASC [39], a genetic predisposition to autoimmunity may be important, especially when combined with a virally-induced dysregulated immune response. Ultimately, the emerging picture depicts vaccine-induced organization of a previously disorganized immune response resulting in resolution and prevention of PASC symptoms. Should this be apt, the activity of the specific components of this vaccine-induced adaptive response, namely antibodies, T cells and cytokines, would require elucidation. Still unknown are the processes by which these immune players could mediate improvement of symptoms, especially over the fairly rapid timeline patients are reporting. For instance, if viral reservoirs in brain tissue contribute to neuropsychiatric sequelae, would symptom improvement occur via vaccine-induced neutralizing antibodies and cytotoxic T cells crossing the blood-brain barrier? Furthermore, what vaccine effects address the pathology produced by autoantibodies? Iwasaki, who has prominently speculated on immunologic mechanisms of PASC pathogenesis and vaccine-induced treatment, is undertaking the investigation of these specific processes [40].

Numerous etiologies for long-term neuropsychiatric sequelae of SARS-CoV-2 infection have been suggested, including dysautonomia, microvascular thrombosis and post-traumatic stress [5], none of which is mutually exclusive. Nevertheless, the likelihood of a key role for immune dysregulation in driving symptomology is emphasized by the volume of patients reporting symptom improvement post-vaccination, including the patients presented here. Producing some confusion are reports of a minority of patients with worsening of symptoms post-vaccination [40], and these troubling observations warrant further investigation. Certainly, the need for fuller understanding of the immunologic underpinnings of PASC pathogenesis, prevention and treatment is evident. Such a need is bolstered by the substantial morbidity of PASC, likely endemicity of its causative virus, and stigmatization experienced by its sufferers. Given the preponderance of neuropsychiatric manifestations of PASC, psychiatrists and neurologists share an important role in addressing this need.

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