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REVIEW

Is SARS-CoV-2 vaccination safe and effective for elderly individuals with neurodegenerative diseases?

Yan Shi[a*], Minna Guo[a*], Wenjing Yang[a], Shijiang Liu[a], Bin Zhu[b], Ling Yang[c], Chun Yang[a] and Cunming Liu[a]

[a]Department of Anesthesiology and Perioperative Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing China; [b]Department of Critical Care Medicine, The Third Affiliated Hospital of Soochow University, Changzhou China; [c]Department of Cardiology, The Third Affiliated Hospital of Soochow University, Changzhou China

ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) poses a substantial threat to the lives of the elderly, especially those with neurodegenerative diseases, and vaccination against viral infections is recognized as an effective measure to reduce mortality. However, elderly patients with neurodegenerative diseases often suffer from abnormal immune function and take multiple medications, which may complicate the role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. Currently, there is no expert consensus on whether SARS-CoV-2 vaccines are suitable for patients with neurodegenerative diseases.

Areas covered: We searched Pubmed to conduct a systematic review of published studies, case reports, reviews, meta-analyses, and expert guidelines on the impact of SARS-CoV-2 on neurodegenerative diseases and the latest developments in COVID-19 vaccines. We also summarized the interaction between vaccines and age-related neurodegenerative diseases. The compatibility of future SARS-CoV-2 vaccines with neurodegenerative diseases is discussed.

Expert opinion: Vaccines enable the body to produce immunity by activating the body's immune response. The pathogenesis and treatment of neurodegenerative diseases is complex, and these diseases often involve abnormal immune function, which can substantially affect the safety and effectiveness of vaccines. In short, this article provides recommendations for the use of vaccine candidates in patients with neurodegenerative diseases.

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1. Epidemiology of Coronavirus Disease 2019

On 12 March 2020, the World Health Organization (WHO) listed Coronavirus Disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a global pandemic [1]. As of 8 March 2021, the number of COVID-19 patients had exceeded 116 million with a total of 2.5 million deaths, resulting in trillions of dollars in economic loss [2]. The people with the highest COVID-19 mortality rate are the elderly and those with weakened immune systems. Advanced age is a risk factor for COVID-19 death. Compared with people aged 50–59 years, people older than 80 years have more than a 20-fold increased risk of death [3]. Elderly patients often have chronic conditions, such as cardiovascular disease; diabetes; respiratory disease; kidney, liver and nervous system diseases; and autoimmune disease, which are risk factors for death from COVID-19 [3]. Infection with SARS-CoV-2 can cause various forms of organ damage, including acute respiratory distress syndrome (71%), acute kidney injury (20%), heart injury (33%), and liver dysfunction (15%) [4]. Due to the fragile physical condition of the elderly and the complex pathophysiological process of COVID-19, elderly patients are more susceptible to COVID-19 and have worse clinical outcomes.

2. Neurodegenerative diseases and COVID-19

Neurodegenerative diseases are characterized by irreversible neuronal dysfunction caused by the loss of neurons in the brain and spinal cord. They include Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), epilepsy, and others. Aging is a significant risk factor for the onset and development of neurodegenerative diseases [5]. Elderly patients are susceptible to SARS-CoV-2 infection, especially those with primary neurodegenerative diseases [6,7]. There is a growing body of evidence associating neurodegenerative disease with COVID-19, mainly related to susceptibility to the virus and changes in neurological symptoms after infection [8]. The loss of neuronal function in AD patients increases the risk of SARS-CoV-2 infection, and the mortality rate after infection is high [9]. A single-center, retrospective observational study showed that the risk of death from infection may be independent of age but highly related to the severity of

CONTACT Chun Yang chunyang@njmu.edu.cn; Cunming Liu cunmingliu@njmu.edu.cn Department of Anesthesiology and Perioperative Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China
*These authors contributed equally to this study.

Article highlights

- Neurodegenerative diseases may change the safety and effectiveness of SARS-CoV-2 vaccines.
- Patients with neurodegenerative diseases are extremely susceptible to SARS-CoV-2, which aggravates neurological symptoms. SARS-CoV -2 vaccines are an effective measure to alleviate this phenomenon.
- Due to special conditions such as advanced age and abnormal immune function in patients with neurodegenerative diseases, the role of candidate vaccines has become extremely complicated.
- Most inactivated vaccines are safe for these patients, whereas other types of vaccines, including live attenuated vaccines, subunit vaccines, and nucleic acid vaccines, still require further clinical research.
- Due to immunosenescence and suppression of immune function, the effectiveness of most candidate vaccines in these patients may be reduced.

dementia symptoms in AD patients [10]. In MS patients, the use of disease-modifying therapies (DMTs) might inhibit the immune system, thereby leading to an increased risk of viral infection [11]. More importantly, the course of MS disease and age have been found to be independent risk factors that affect the severity of COVID-19 [12].

It is widely known that angiotensin-converting enzyme-2 (ACE-2) can produce anti-apoptosis and anti-inflammatory effects by inhibiting the renin-angiotensin system (RAS), thus playing an important protective role in neurodegenerative diseases [13,14]. Kehoe PG et al. found that compared with non-AD patients, the activity of ACE-2 in the brain tissue of AD patients was significantly reduced, and it was related to the increase in Aβ load and p-tau [15]. Therefore, the authors concluded that the reduction in ACE-2 contributes to the occurrence and development of AD. The same conclusion has been confirmed in other neurodegenerative diseases, including PD and MS [16,17]. Unfortunately, ACE-2 is also the key for SARS-CoV-2 to invade human cells [18]. SARS-CoV-2 invades the human body through a combination of spike protein and ACE-2 that are expressed in target tissues, which leads to ACE-2 depletion [14]. These changes cause a decrease in ACE-2 activity and an imbalance in the RAS, thereby promoting neurodegeneration [19]. SARS-CoV-2 infection may lead to further aggravation of neurological symptoms in the elderly with neurodegenerative diseases [19]. Additionally, the virus can directly invade the brain through the olfactory bulb to activate microglia that produce a large amount of inflammatory cytokines, leading to demyelination of the nervous system and promoting the development of neurodegenerative diseases [20]. In PD patients, SARS-CoV-2 infection is associated with dyskinesias and can accelerate the neurodegenerative process [6]. Willis MD et al. proposed that viral infection can cause MS recurrence and deterioration of neurological symptoms, and therefore, MS treatment is challenging in the context of the COVID-19 pandemic [21]. More importantly, the COVID-19 pandemic has also adversely affected cognitive and neuropsychiatric symptoms in AD patients. Isolation measures inhibiting the spread of the virus have led to abnormal cognitive function and behavioral alterations in AD patients [22,23].

3. SARS-CoV-2 vaccines

In addition to the current mitigation measures, vaccines are one of the best strategies for virus prevention and control. Since the SARS-CoV-2 genome was identified [24,25], many vaccines have started to be developed. At the time of our review, there are already 263 vaccines against SARS-CoV-2 under development, of which 182 are in preclinical development, and 81 have entered clinical trials [26]. Here we mainly focus on vaccine candidates that have entered phase 3 clinical trials, including inactivated vaccines, viral vector vaccines, protein subunit vaccines, and nucleic acid vaccines.

3.1. Inactivated vaccines

Inactivated vaccines are made by using physical or chemical methods to inactivate the viruses, which lose the ability to replicate after vaccination but still have antigenicity. The production technology of inactivate vaccines has been well established, and the safety of such vaccines is relatively high, so they can be used in immunocompromised patients [27]. Many inactivated vaccines have been successfully adopted in humans, such as the poliovirus vaccine and rabies vaccine. However, inactivated vaccines have almost no cellular immunity, and the immune response they provoke is weak, often requiring repeated doses to gain immunity. Furthermore, inactivated vaccines have a significant limitation. Due to the existence of non-neutralizing epitopes, inactivated vaccines can induce the body to produce non-neutralizing antibodies, which cannot exert antiviral effects when combined with the virus. Instead, they strengthen the infectious process of the virus, specifically antibody-dependent enhancement, which leads to vaccine-enhanced diseases [28,29]. Most vaccine candidates that have entered phase 3 clinical trials are inactivated vaccines. CoronaVac, an inactivated vaccine developed by Sinovac completed phase 3 recruitment in October 2020, and the relevant data of the phase 3 trial have not been released. However, the previous phase 1/2 data showed good tolerability and immunogenicity, and the adverse reactions were mild, mainly manifested as injection-site pain without significant serious adverse reactions [30].

3.2. Live attenuated vaccines

Live attenuated vaccines are a type of vaccine with decreased toxicity that fail to cause disease but induce an immune response in the host body. Immunization with live attenuated vaccines lasts for a long time, and only one dose can usually produce immunity. Interestingly, live attenuated vaccines can also generate mucosal immunity through nasal inoculation to protect the upper respiratory tract [31]. However, because the virus is still alive, there is a risk of reinfection, especially in patients with immunodeficiency. At the time of our review, most live attenuated vaccine candidates were still in preclinical trials.

3.3. Viral vector vaccines

Viral vector vaccines are formed by inserting the gene encoding SARS-CoV-2 exogenous antigen into the virus, which induces the host immune response after vaccination. These vaccines have several advantages, such as high efficacy and specificity. However, because most humans already have neutralizing antibodies against the viral vectors, they can attack the vectors and reduce the effectiveness of the vaccines. More specifically, viral vectors have the potential to increase the risk of human tumors [32]. Currently, many viruses can be selected as vaccine vectors, including adenovirus, adeno-associated virus, and poxvirus. The Ebola vaccine uses the recombinant vesicular stomatitis virus as a vector [33]. The vaccine candidate ChadOx1/AZD1222, jointly developed by Oxford University and AstraZeneca, is an example of the use of this approach. Very recently, AZD1222 released an interim analysis of phase 3 clinical trials, and the results showed that the effective rate against SARS-CoV-2 infection after two doses of the vaccine is up to 70.4%, which has exceeded the minimum WHO standard for vaccine effectiveness [34]. It is worth noting that three reports of adverse reactions of transverse myelitis in AZD1222 have been reported, one of which might be related to an adverse reaction to the vaccine. Further assessment of the unwanted neurological effects of the vaccine is needed [35].

3.4. Nucleic acid vaccines and protein subunit vaccines

Nucleic acid vaccines involve the direct delivery of plasmid DNA or RNA encoding foreign antigens into the human body, and the expression of the antigen activates the body's immune system to induce an immune response. They are very safe and have no immunity against the vectors. However, the issues of weak immunogenicity and low antibody titers remain to be solved. There are currently two nucleic acid vaccines in Phase III clinical trials. Two of the mRNA-based vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer and BioNTech) have shown great efficacy and safety and have obtained Emergency Use Authorization from the Food and Drug Administration (FDA) [36,37]. However, in the phase 3 clinical trials of mRNA-1273 and BNT162b2, Bell's palsy cases were reported, and the safety of these vaccines still needs to be closely monitored.

Protein subunit vaccines are very safe and contain only a few proteins, which prevents the production of irrelevant antibodies, thereby reducing side effects. However, its immunogenicity is relatively lower, and the vaccines need to be used in combination with adjuvants. Currently, five protein subunit vaccines have entered phase 3 clinical trials. Most of them have not yet released a Phase III study report. The recombinant protein subunit vaccine developed by Novavax, NVX-CoV2372, has shown good safety and immunogenicity in Phase 1/2 experiments, and there are no reports of serious adverse reactions [38].

4. Neurodegenerative diseases and SARS-CoV-2 vaccines

Age and immunosuppression often alter the effectiveness and safety of vaccines. The published clinical trial results of multiple vaccines confirm this effect. The Phase 1/2 clinical trial of BBIBP-CorV, an inactivated vaccine developed by the Beijing Institute of Biological Products, shows that compared with the control group, the adverse reactions in the experimental group are mild, mainly manifest as pain and fever, and do not significantly differ between age groups (≥60 years and 18–59 years) [39]. Although older patients (≥60 years) can show a strong humoral immune response after vaccination, the antibody titers are significantly lower than that of adults (18–59 years). The morbidity of elderly patients was significantly reduced after varicella-zoster virus vaccination, but the effectiveness of the vaccine in elderly patients (37.6%) was significantly lower than that of younger patients (63.9%) [40]. A quantitative review of 31 studies on influenza vaccine responsiveness found that compared with young people, the ability of the elderly to respond to the vaccine was significantly lower [41]. This difference may be due to a decline in innate and adaptive immunity in the elderly, that is, immunosenescence [42,43]. This observation suggests that SARS-CoV-2 vaccines are relatively safe for the elderly but may be less effective in this age group. The clinical trial data of the RNA-based SARS-CoV-2 vaccine also confirmed this finding [44]. Although these data are mostly based on healthy elderly, we can infer that the safety and effectiveness of SARS-CoV-2 vaccines for elderly patients with neurodegenerative diseases may also be different (Table 1).

4.1. AD

AD is the most common type of dementia in the elderly, and it is characterized by progressive cognitive dysfunction and behavioral impairment. Although the pathogenesis of AD is still unclear, mounting evidence shows that AD is related to an imbalance of the central and peripheral immune systems [52]. Senescence combined with immune dysfunction makes AD patients highly susceptible to SARS-CoV-2 infection [53]. Vaccination is therefore crucial for AD patients. However, the safety and effectiveness of SARS-CoV-2 vaccines for AD patients is still unclear. Clinical studies have proved that elderly patients with neurodegenerative diseases can elicit an immune response similar to that of normal elderly people after influenza vaccination. Specifically, the effectiveness of the vaccine was not significantly different between the two groups [54]. However, the protective effect of live attenuated herpes zoster vaccine for people ≥70 years is significantly lower than that for people 60–69 years [40]. These data indicate that AD patients can preserve their immune response to the vaccines, but the effectiveness of the vaccines may gradually decrease with age. Animal studies have shown that the systemic immunity induced by influenza vaccination can inhibit the systemic immune suppression caused by Treg cells and restore the ability of microglia to clear Aβ, thus improving

Table 1. Clinical trials on the interaction between neurodegenerative diseases and vaccines.

Neurodegenerative disease	Platform	Vaccines tested	Conclusions	Refs.
Parkinson's disease	Inactivated vaccines	Influenza vaccine	No difference in antibody titers between experimental group and control group and no serious side effects or adverse reactions	[45]
Multiple myelosclerosis	Inactivated vaccines	Influenza vaccine	No increased risk of MS	[46]
		HPV vaccine	No causal relationship between HPV vaccination and MS	[47]
		Rabies vaccine	No increased risk of MS	[48]
	Live attenuated vaccines	BCG	No increased risk of MS	[49]
		MMR vaccine	No significant association between MMR vaccination and MS risk	[50]
	Submit vaccines	Hepatitis B vaccine	No increased risk of MS	[51]
Epilepsy	Inactivated vaccines	DTP vaccine	No evidence of an increased risk of epilepsy following vaccination but earlier onset of DS	[52–54]
		Influenza vaccine	No increased risk of epilepsy	[55–56]
	Live attenuated vaccines	MMR vaccine	An increased rate of seizures but no effect on the course of DS and epilepsy	[57–58]

Abbreviations: BCG: Bacille-Calmatte-Guerin; DTP vaccine: diphtheria-tetanus-pertussis vaccine; DS: Dravet syndrome; HPV vaccine: Human papillomavirus vaccine; MS: Multiple myelosclerosis; MMR vaccine: measles-mumps-rubella vaccine

cognitive dysfunction [55]. No serious adverse reactions from the inactivated influenza vaccine were observed in patients with neurodegenerative diseases compared with a control group [54]. This finding proves the safety of influenza vaccination in elderly patients with neurodegenerative diseases. Although the live attenuated herpes zoster vaccine benefits the elderly, they experience more adverse events [56]. The herpes zoster vaccine is contraindicated in patients with weakened immune function, but it can be used in the elderly with normal immune function [57]. Therefore, we speculate that the inactivated vaccines against SARS-CoV-2 are relatively safe for AD patients. In contrast, immunocompromised patients may experience reinfection even after receiving the live attenuated vaccines. Therefore, live attenuated vaccines should be used with caution in AD patients. Studies have shown that subunit vaccines are relatively safe and effective for such patients. A randomized trial involving 7698 participants showed that compared with placebo, the herpes zoster subunit vaccine significantly reduced the risk of herpes zoster in elderly patients, and there was no significant difference in vaccine effectiveness between the age groups [58]. Compared with the control group, the vaccine group experienced milder adverse reactions. Model studies have also shown that the recombinant subunit zoster vaccine is better than the live attenuated zoster vaccine and is more suitable for Canadian elderly people ≥60 years old [59]. Live attenuated vaccines can still benefit AD patients, as they can induce indirect protection due to herd immunity [60]. Interestingly, the indirect effect of herd immunity, especially in the elderly, is significantly greater than the direct effect of vaccination [61].

4.2. MS

MS is an autoimmune disease characterized by inflammatory demyelination of white matter in the central nervous system (CNS). As mentioned earlier, SARS-CoV-2 infection increases the risk of MS progression and recurrence. Therefore, elderly patients with MS are also a priority population for vaccination. However, due to the special pathophysiology of MS and the use of DMTs, the role of vaccines in MS patients has become extremely complicated. In the last century, there was a significant increase in the prevalence of MS after large–scale vaccination for Hepatitis B in France, leading to the misunderstanding that the vaccination would cause MS, although subsequent clinical studies have shown that the Hepatitis B and influenza vaccines are not significantly correlated with the development of MS [62-66]. A cohort study of 3,983,824 patients showed that quadrivalent human papillomavirus (HPV) vaccination does not increase the risk of MS, and a study has even found that HPV vaccination can reduce the risk of MS [67,68]. Bansil S et al. also found that there is no connection between rabies vaccination and the occurrence and development of MS [69].

Additionally, DMTs often affect the effectiveness of vaccines. DMTs mainly include three types: immunomodulators, cell-depleting agents, and anti-tracking agents [70]. In a prospective study, IFN-β was shown to have beneficial antiviral effects on SARS-CoV-2 when combined with lopinavir-ritonair and ribavirin [71]. However, most immunomodulators, including glatiramer acetate and teriflunomide, reduce the effectiveness of inactivated vaccines, but they can still preserve a certain degree of immune response [72,73]. The reactogenicity and safety of live attenuated vaccines in these patients remain unclear. Unfortunately, for MS patients using cell-depleting agents such as ocrelizumab and alemtuzumab, the protective immune response caused by the inactivated vaccines may be suppressed due to the depletion of lymphocytes in the body and immunosuppression [11,74]. More importantly, guidelines encourage avoiding live attenuated vaccines in patients taking immunosuppressive agents [65]. There is limited literature evaluating MS patients who have received viral vector vaccines and nucleic acid vaccines, so we therefore are unable to evaluate the impact of these vaccines on MS and the impact of DMTs on vaccine effectiveness (Table 2).

Table 2. The impact of DMTs on vaccine effectiveness.

DMTs	Example	Vaccines tested	Conclusions	Refs.
Immunomodulators	IFN-β	Inactivated influenza vaccine	No difference in antibody titers between interferon group and control group	[75,76]
	GA	Inactivated influenza vaccine	A reduction in vaccine protection (21.6%)	[77]
	Teriflunomide	Inactivated influenza vaccine	Vaccine response preserved in patients treated with teriflunomide but a diminished in 14 mg group; no serious adverse reactions in treatment group	[73]
		Inactivated rabies vaccine	Antibody titers decreased in the treatment group compared with the control group, but sufficient for seroprotection	[78]
Anti-trafficking agents	Natalizumab	Inactivated influenza vaccine	Immune response reduced in natalizumab group compared to controls but no severe adverse events reported	[77,79]
	Fingolimod	Inactivated influenza vaccine	A decreased immune response to influenza vaccine in treatment group	[72,80]
Cell-depleting agents	Ocrelizumab	Inactivated tetanus vaccine	An attenuated humoral response in ocrelizumab group	[81]

Abbreviations: DMT: disease-modifying therapies; GA: glatiramer acetate; IFN-β: interferon beta.

4.3. PD

PD is a degenerative disease of the elderly mainly characterized by lesions in the substantia nigra and striatum. Because the vaccination rate of elderly patients with PD is very low as compared with other populations, there is limited experience in vaccinating PD patients [82]. It has been reported that a PD patient experienced a sharp deterioration in symptoms after rabies vaccination and died of PD and its complications one month later [74]. In 2012, a patient had an acute exacerbation of PD after H1N1 influenza vaccination, but the prognosis was good, and no obvious sequelae were found during follow-up [83]. Although these studies suggest that vaccines may lead to the progression of PD, they are almost all case reports, and there is a lack of large-scale clinical data to prove that there is a causal relationship. In a prospective study of 239 cases, no significant difference was found in the titers of influenza vaccine between 105 elderly patients with neurodegenerative diseases (cerebrovascular diseases, Parkinson's disease, etc.) and 134 elderly patients, and no serious side effects were observed [54]. A propensity score-matched cohort study showed that even in older patients with PD, the influenza vaccination was associated with a significant reduction in all-cause mortality [82]. Thus, influenza vaccine is effective for PD patients. However, based on these limited clinical data, it is currently impossible to predict the safety of future SARS-CoV-2 vaccines for PD patients. The SARS-CoV-2 vaccines under development need to provide a better clinical basis for future vaccination in PD patients.

4.4. ALS

ALS is a chronic neurodegenerative disease. The primary manifestations are progressive skeletal muscle weakness and muscle atrophy. Studies have found that adjuvants in the vaccine may have a deleterious effect on the occurrence and development of ALS [84]. Adjuvants are nonspecific immune enhancers that can improve the body's immune response to vaccines. Aluminum hydroxide is currently a commonly used adjuvant in vaccines. However, aluminum is potentially harmful to the CNS and may be associated with neurodegenerative diseases [85]. Mice injected with aluminum hydroxide can induce motor dysfunction and loss of motor neurons, which is similar to ALS [86]. Interestingly, the incidence of ALS among Gulf War veterans may be related to the anthrax vaccine containing aluminum hydroxide, which increases the incidence of ALS and causes a younger onset age [84,87]. It is worth noting that most inactivated vaccines using aluminum hydroxide as an adjuvant, including the CoronaVac developed by Sinovac and the vaccine jointly developed by Sinopharm and Wuhan Institute of Biological Products, are currently under development [39,88]. The impact of the vaccines containing these adjuvants on ALS patients is still unclear, and further evaluation is greatly needed.

4.5. Epilepsy

Epilepsy is one of the most common neurological diseases involving repeated seizures that are caused by the abnormal discharge of brain neurons. It can occur at any age and is one of the most common neurological diseases. Since the idea that the pertussis vaccine may cause encephalopathy was suggested, the relationship between vaccines and neurological diseases has caused substantial social concern. A case–control study showed that the diphtheria, tetanus and pertussis vaccine may be associated with severe acute neurological diseases [89]. It is also believed that people with neurological deficits should not receive pertussis vaccine [90]. However, subsequent studies have shown that there is no causal relationship between vaccination and increased risk of

neurological diseases and epilepsy [91-93]. A large cohort study of 378,834 children in 2012 showed that diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b (DTaP-IPV-Hib) vaccination was associated with febrile seizures, but there was no causal relationship with epilepsy [94]. Therefore, an Italian guideline suggests that vaccination will not cause epilepsy, and past history of epilepsy should not be a contraindication to vaccination because vaccination will not increase the incidence of adverse reactions in such patients [95].

Epilepsy encephalopathy refers to progressive brain dysfunction caused by epilepsy. Dravet syndrome (DS) is an epileptic encephalopathy with symptomatic seizures in infancy. The main cause is the dysfunction of brain neuron cells caused by a SCNT1A gene mutation. Previous studies have suggested that vaccination may cause epileptic encephalopathy, but substantive evidence is lacking. A large retrospective case-control study showed that diphtheria-tetanus-pertussis and measles-mumps-rubella (MMR) vaccination were not associated with an increased risk of epileptic encephalopathy [92]. Epidemiological studies have also failed to confirm the connection between the two [96]. However, vaccination may cause early symptoms in patients with SCN1A mutations who are bound to develop DS. A retrospective study found that the average age of onset of DS in the vaccination group was significantly younger than that of the non-vaccination group, but there was no difference in clinical outcomes between the two groups [97]. Therefore, the author believes that children with epileptic encephalopathy should also be vaccinated because there is no evidence that the vaccines will affect the outcome of the disease. The guidelines also recognize this conclusion and propose that antiepileptic drugs should be appropriately used to prevent seizures in such patients after vaccination [95].

5. Conclusion

SARS-CoV-2 infection has a substantial impact on the safety of elderly patients with neurodegenerative diseases. Vaccination against SARS-CoV-2 infection is one of the most effective strategies for this population. The SARS-CoV-2 vaccines currently under development mainly include inactivated vaccines, live attenuated vaccines, viral vector vaccines, nucleic acid vaccines, and protein subunit vaccines. A large amount of evidence shows that neurodegenerative diseases and their treatments can affect the effectiveness and safety of SARS-CoV-2 vaccine candidates to a certain extent. Therefore, administering these vaccines in elderly patients with neurodegenerative diseases should be performed with caution.

6. Expert opinion

In December 2019, Wuhan reported the first case of COVID-19, which soon swept across countries and became a global pandemic. COVID-19 is a respiratory infectious disease caused by SARS-CoV-2. Patients with neurodegenerative diseases are highly susceptible to the virus due to advanced age, abnormal immune function, and the use of immunosuppressive agents. A multi-database study showed that MS patients have a significantly increased risk of infection compared to non-MS patients. Additionally, SARS-CoV-2 has neurotropic and neuro-invasive properties and can affect the CNS in various ways, such as directly entering the brain through the olfactory bulb or invading the CNS through vagus nerve endings after infecting the lung. Studies have confirmed that SARS-CoV-2 can be detected in the cerebrospinal fluid of patients with neurodegenerative diseases after infection. Viral infection can cause varying degrees of neurological damage, leading to aggravation of neurological symptoms in patients with neurodegenerative diseases and an increased risk of death. The total mortality of patients with dementia after being infected with SARS-CoV-2 is approximately 62.2%, which is much higher than that of non-dementia patients (26.2%).

Vaccination is the most promising measure to reduce infection rates and mortality in patients with neurodegenerative diseases. After completing SARS-CoV-2 sequencing, several SARS-CoV-2 vaccine candidates began research and development. After SARS-CoV-2 vaccination, the body can produce an immune response against the vaccine antigen, including cellular and/or humoral immunity, and generate memory immune cells, thereby gaining antiviral ability. As patients with neurodegenerative diseases often have complex conditions such as advanced age and poor immune function, we must consider the safety and effectiveness of vaccines in these patients. Unfortunately, most SARS-CoV-2 vaccine candidates exclude elderly patients in clinical trials, and we are unable to obtain relevant clinical data. Based on previous vaccination data, we speculate that most inactivated vaccines are relatively safe for patients with neurodegenerative diseases. There is not sufficient data to prove the safety of live attenuated vaccines, viral vector vaccines, and nucleic acid vaccines. Because neurodegenerative diseases are often associated with immunosuppression, live attenuated vaccines should be avoided. Furthermore, vaccines containing aluminum hydroxide as an adjuvant should be used with caution in these patients.

The abnormal immune function often associated with neurodegenerative diseases significantly reduces the effectiveness of the vaccines against SARS-CoV-2. Additionally, treatment with immunosuppressants and/or immunomodulators may even inhibit the protective effect of COVID-19 vaccines, resulting in a decrease in the effectiveness of the vaccines. Due to immunosenescence, the response to SARS-CoV-2 vaccines in the elderly is significantly lower than that in younger populations. Therefore, the elderly may need higher doses or immunogenic vaccines to obtain the best antibody titers. For example, high-dose influenza vaccine is more effective than standard-dose influenza vaccine in improving the clinical outcomes of elderly patients. However, whether elderly patients with neurodegenerative diseases are suitable for such vaccines still needs to be determined. Multiple studies on the safety and effectiveness of SARS-CoV-2 vaccination in patients with neurodegenerative diseases are needed to provide better clinical evidence for subsequent vaccination of these patients. It is worth noting that there is a lack of antibodies and cytokines in the nerves, so the vaccines cannot directly act on the nerves

to produce an immune response. However, recent studies have shown that immune cells and nerve cells communicate with each other to form a neuroimmune unit, which regulates the body's defense functions. After exposure to antigenic components, the nervous system is activated, thereby regulating the body's immune response through innervation, neurotransmitters, and various hormones. In patients with neurodegenerative diseases, demyelination of neurons may change the neuroimmune function and further affect the effectiveness of the vaccines.

In the next five years, a SARS-CoV-2 vaccine that is safer and more effective for elderly patients and patients with abnormal immune function should be developed. In any case, for these immunocompromised patients, vaccination should be approached with caution. Clinicians need to closely observe the responsiveness of patients with neurodegenerative diseases to vaccine candidates. At the same time, thorough discussions are needed to reach a consensus on vaccinating patients with neurodegenerative diseases.

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Author contributions

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