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Letter to the Editor: Guillain-Barré Syndrome Needs to Be Considered as a Cause of Idiopathic Bilateral Vocal Fold Paralysis

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To the Editor:

We read with interest the article by Son et al.[1] about an 82-year-old woman who developed bilateral vocal fold paralysis (VFP) 3 days after the third dose of coronavirus disease 2019 (COVID-19) mRNA vaccine (BNT162b2 Pfizer–BioNTech). The patient underwent tracheostomy for dyspnea and inspiratory stridor due to bilateral VFP. After that, respiratory distress improved, but bilateral VFP still persisted after 2 months. Since there were no abnormal findings in several tests to find the cause of bilateral VFP, the authors considered it as an adverse event of COVID-19 vaccination.[1] This study is an interesting topic for the association between VFP and COVID-19 vaccination. However, in this letter we would like raise under-recognized issues regarding the diagnostic approach and treatment of VFP.

Although there are few reports of VFP associated COVID-19 vaccination so far, most of the reported cases are unilateral.[2-4] In a recent study using the United States Vaccine Adverse Event Reporting System database, 15 of 17 VFP patients (88.2%) following COVID-19 vaccination with information on laterality were unilateral and only the remaining two (11.8%) were bilateral.[2] Moreover, in two recent case reports, 2 cases of VFP after receiving BNT162b2 and 1 case after receiving ChAdOx1 nCoV-19 (AstraZeneca) were all unilateral.[3,4] Therefore, we believe that bilateral VFP requires a more thorough differential diagnosis than unilateral VFP to consider the association with COVID-19 vaccination.

The authors excluded Guillain-Barre syndrome (GBS) as the cause of bilateral VFP because the patient did not manifest limb weakness or other cranial nerve involvement other than VFP. However, this needs further discussion, in depth. Of course, classic GBS is characterized by progressive limb weakness. However, within the spectrum of GBS, there are various variants including Miller Fisher syndrome, acute bulbar palsy, and bifacial weakness with paresthesia, which present only with symptoms such as ophthalmoplegia, bulbar palsy, or facial weakness without limb weakness.[5,6] As an extension of this, there is also a variant of GBS presenting as an isolated bilateral VFP in the absence of limb weakness.[7] Therefore, it is difficult to rule out GBS in this patient based only on the absence of other symptoms, including limb weakness, other than VFP. The authors additionally need to provide information on the presence or absence of cerebrospinal fluid albuminocytologic

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dissociation, anti-ganglioside antibody results including GT1a and GQ1b, and nerve conduction study findings other than laryngeal electromyography.

It is noteworthy to state that 7 days before the onset of VFP, the patient underwent surgery for compression fractures of the 11th and 12th thoracic vertebrae. As the authors correctly pointed out, compression fractures and surgery itself are unlikely to directly cause bilateral VFP considering their location. However, surgery is well known as a potential trigger for GBS.[8,9] Its exact mechanism is not yet known, but autoimmunization against antigens released during surgery and temporary immunosuppression after surgery are thought to induce autoimmune responses to peripheral nerves.[8,9] Post-surgical GBS most often occurs within 2 weeks after surgery, and the most common type of surgery to trigger GBS is orthopedic surgery.[8] Therefore, considering GBS as a potential cause of bilateral VFP in this case is an important issue considering the patient's recent orthopedic surgical history.

In addition to surgery, vaccination can also trigger GBS.[10,11] Recently, studies on the association between COVID-19 vaccination and GBS have been increasingly reported.[12,13]

Finally, we would like to discuss the issue of the patient's treatment. The authors maintained conservative treatment after tracheostomy without steroid treatment due to heart failure and renal and hepatic dysfunction. They need to provide accurate levels of creatinine, aspartate aminotransferase, and alanine aminotransferase. We also believe that it was necessary to consider intravenous immunoglobulin or plasmapheresis treatment in this patient. This is because, as mentioned earlier, it is difficult to completely rule out the possibility of GBS in this patient, given the history of surgery and vaccination. Even if the patient does not have cerebrospinal fluid albuminocytologic dissociation, the anti-ganglioside antibody is negative, and the nerve conduction study results are normal, it is difficult to conclude that the patient is not GBS because these findings may be normal especially in the early stages of GBS. Therefore, if there is any possibility of GBS, it is important to examine the treatment response while attempting treatment such as intravenous immunoglobulin.

This study is definitely an interesting topic, especially in the era of COVID-19. However, considering the patient's history of surgery and vaccination, it is necessary to thoroughly differentiate GBS as a potential cause of bilateral VFP.

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The Author's Response: Reply to the Letter to the Editor

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To the Editor:

Thanks for your very remarkable letter and comments on the previous article, Bilateral Vocal Fold Paralysis After COVID-19 mRNA Vaccination: A Case Report.[1]

We read the letter very carefully, and respond as follows.

We checked whether motor or sensory weakness of limbs was present, however, there was no weakness of limbs. In the case of the lower extremities, because gait was impossible due to compression fracture before surgery, evaluation was done at the bedside, and we checked that motor and sensory function of bilateral lower limbs was normal. Bulbar palsy is controversial. On initial admission to the emergency room, the tracheostomy was done as soon as possible to relieve the symptom of respiratory distress. Therefore, the function of phonation and digestion was not checked meticulously. Immediately after the tracheostomy, although vocal fold paralysis with saliva pooling was observed via laryngoscopy, the sensory of the hypopharynx and the gag reflex was normal. Saliva pooling may have been caused not

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only by bulbar palsy but also by tracheostomy itself. The initial echocardiogram including the heart rate was normal, and there were no gastrointestinal tract complaints throughout the hospitalization period. Comprehensively, all motor nerves to the four extremities, and the sensory nerve and parasympathetic nerve of the vagus nerve were normal. Nerve paralysis was only in the motor nerve of the vagus nerve, the recurrent laryngeal nerve. The external branch of the superior laryngeal nerve also had a possibility of paralysis, but this is not certain.

The stridor started 2 days after vaccination; and 4 days after surgery. If Guillain-Barre Syndrome (GBS) caused bilateral vocal fold paralysis, both vaccination and surgery could be the cause of GBS.[2,3] But, there was a chance that vaccination directly caused vocal fold paralysis. Jeeyune et al.[4] reported one case of bilateral vocal fold paralysis associated with GBS and reviewed 6 cases. A total of 7 cases were reported. However, viral infection also may cause vocal fold paralysis directly.[5] Recently, several reports have been reported that vocal fold paralysis developed after COVID-19 infection or COVID-19 vaccination,[6,7] even though it contains bilateral vocal fold paralysis.[8,9] Of course, those also are caused by GBS, but bilateral vocal fold paralysis is very rare itself, so the cause of bilateral vocal fold paralysis needs more studies.

The cerebrospinal fluid (CSF) study was not performed due to the patient`s obesity and difficulty of positioning the patient due to compression fracture. Steroid therapy is sometimes used in vocal fold paralysis, but is not necessary. In this case, as mentioned in the previous article, steroid therapy was not performed due to heart failure. However, it is very appropriate to point out the CSF study and treatment using steroids or intravenous immune globulin (IVIG), and it seems that it may help the patient recover faster. The patient came to the clinic 6 months after the tracheostomy and her paralysis was almost recovered, she tolerated overnight plugging of the tracheostomy tube, and she showed normal digestion in the modified barium study (MBS). So we removed the tracheostomy tube and she recovered well.

The ultimate purpose of this paper is not to overlook the occurrence of stridor after vaccination and to consider bilateral vocal fold paralysis. Bilateral vocal fold paralysis is a symptomatic diagnosis, not a pathologic diagnosis. In conclusion, when looking at the range of GBS very broadly, this case may be a type of GBS, but according to recent studies, more discussion and studies are needed.

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