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Editorial

COVID-19 vaccine is here: practical considerations for clinical imaging applications

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ABSTRACT

Imaging tools are potentially able to provide valuable data regarding the development of an efficient vaccine against viral diseases. Tracking immune cells *in vivo* by imaging modalities can help us understand the intrinsic behaviors of immune cells in response to vaccine components. Imaging patterns at the vaccination site and draining lymph nodes might provide useful information about the vaccine potency. Besides, serial lung CT imaging has been purposed to evaluate vaccine efficiency regarding its protection against typical lung lesions of viral pneumonias. On the other hand, vaccination causes various confusing radiologic patterns that pose diagnostic challenges for clinicians and pitfalls for reading radiologists. This manuscript reviews potential applications of imaging modalities in the process of vaccine development and also goes over some of the imaging findings/pitfalls following vaccination.

1. Introduction

The novel Coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), represents the first pandemic of the 21st century. The COVID-19 outbreak was first reported in Wuhan (China) as a cluster of cases with pneumonia of unknown etiology, and quickly spread to other regions worldwide. Currently, the virus has caused a global pandemic, with most countries afflicted by COVID-19 and resorting to strict lockdown measures in order to curb further proliferation of the disease. By January 2021, more than 87 million COVID-19 cases with 1.8 million deaths have been reported worldwide.[1]

No specific SARS-CoV-2-specific antiviral agents are present to date. As the COVID-19 pandemic continues, it is profoundly impacting all socio-economic structures across the globe. Regarding the pandemic's global consequences, scientists have been racing to develop safe and effective vaccines for disease prevention. An effective vaccine against SARS-CoV-2 is the only truly global solution to the current crisis.[2,3] Without a vaccine, there will always be a risk that new outbreaks will emerge.

As the world awaits a COVID-19 vaccine, radiologists need to be aware of vaccines' potential implications on imaging studies. Being familiar with these findings and pitfalls will help radiologists prepare for possible imaging challenges in immunized patients in the future. Furthermore, to support research regarding an effective preventive agent/vaccine for COVID-19, we decided to review the available data related to the imaging in the development of vaccines against viral diseases – such as COVID-19.

2. The role of imaging

In-depth knowledge of signaling between vaccines and host body's immune cells may offer a great chance to develop an effective novel vaccine. In this regard, a variety of imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine imaging [*e.g.* positron emission tomography (PET) or single photon emission computed tomography (SPECT)] have been suggested as a non-invasive tool for the evaluation of immune cell kinetics.[4] Youn et al.[4] suggested that monitoring the immune cell dynamics at vaccination site or the draining lymph nodes provides valuable information about the vaccine' efficacy. Lymph node activation following vaccination is closely related to the viral antigen localization, which could be mapped with various imaging probes and reporters. A sustained vaccine response requires locally activated antigens to be accumulated at the injection site that later migrate to the draining nodes. Thus, the post-vaccine FDG PET patterns (presenting nodal activation and injection site activity) adds valuable information about the immune cell dynamic and vaccine efficacy. This might be of great importance, as the *in vivo* tracking of activated immune cells with other tools is challenging, given their small size.

Abbreviations: COVID-19, Novel Coronavirus Disease; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; PET, positron emission tomography; SPECT, Single Photon Emission Computed Tomography; HMPAO, Hexamethyl Propylene Amine Oxime; SUVmax, maximum Standardized Uptake Value; GGOs, ground-glass opacities; ALV, Aerated Lung Volume; SIRV, Shoulder Injuries Related to Vaccines.

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Moreover, other imaging tools such as MRI with Iron, 111In-oxine for SPECT, 99mTc-hexamethyl propylene amine oxime (HMPAO), and FDG PET have also been frequently applied to image the labeled immune and stem cells, which is potentially valuable to monitor the immune cells during vaccine development.[5,6] In a study by Tremblay,[6] after injection of superparamagnetic iron oxide-labeled into mice, MRI scans were obtained to track target cells within the body. MRI can track immune cell populations in response to vaccines or immune therapy, and thus provides insight into the mechanism of action and the potency of these agents.

In addition, CT scans allow for characterization and quantification of viral-induced pulmonary lesions, and therefore has the potential to be used as a novel indicator of vaccine efficacy: specifically, quantifying alterations in set base-line parameters. In a preclinical study, Veldhuis et al.[7] evaluated the role of consecutive CT imaging in depicting the influenza vaccine efficacy in a group of ferrets exposed to the A/H1N1 influenza virus: the virus responsible for the 2009 pandemic. CT imaging was obtained 6 days prior to the ferrets' inoculation, as well as on a daily basis afterwards, to monitor influenza-induced lung damage. The immunized ferrets were significantly protected against the emergence of pulmonary ground-glass opacities (GGOs), compared to the placebo group. The authors demonstrated that the pulmonary GGOs seen in CT imaging corresponds to alveolar edema, which is a major histological lesion in early influenza-induced pneumonia and can be used to quantify the aerated lung volume (ALV). Other studies have used similar approaches to evaluate the vaccine efficiency, using day to day CT imaging to monitor the appearance of GGOs in the immunized ferrets compared to control group.[8]

3. Post-immunization imaging pitfalls

The recognition of false-positive results is very critical to avoid unnecessary surgical reassessment or medical therapies. Previous studies have demonstrated that vaccination could be a potential source of false-positive results in FDG PET-CT imaging.[9–15] Indeed, the abnormal vaccine-related patterns seen after vaccination (such as increased metabolic activity at the injection site, or abnormal lymphadenopathy related to recent immunization) could cause imaging misinterpretation. Several reports have previously found nodal activation in FDG PET examination following vaccination, presenting various uptake patterns in different locations.[9–15] Axillary lymph node activation following vaccination is the most common reported finding under such circumstances. FDG uptake has been frequently observed in the draining axillary lymph nodes close to the injection site, while low-dose CT revealed normal-sized nodes at the same site.[12] Other studies reported several other active nodes in post-vaccine FDG PET. A case report by Kim et al.[13] found FDG-avid right hilar and paratracheal lymph nodes – post inoculation with the influenza vaccine – in a patient with seminoma: referred for PET-CT examination for post therapy response analysis. Ayati et al.[15] reported generalized lymph node activation in both sides of the diaphragm with no tracer accumulation at the vaccination site, following influenza vaccination the day prior (Fig. 1).

Interestingly, Mingos et al.[16] reported a systemic immune response in the spleen related to the influenza vaccination on FDG PET-CT. They reported a case of lung cancer with new enlarging left axillary and left supraclavicular lymph nodes on CT images with high FDG-uptake, accompanied by intense splenic FDG uptake, 23 days after Influenza vaccination. The finding later resolved in the following FDG PET after a twelve-day gap. This suggests that vaccination might cause both local and systemic immune-mediated responses in FDG PET study. Importantly, observing enlarged axillary nodes in CT was contradictory to the previous reports that have contested the size of post-vaccination axillary nodes to be normal.[12,17,18]

The duration of post-vaccination nodal activation in FDG PET has not been clearly defined yet. Shirone et al.[19] found that only a very recent influenza vaccination before FDG-PET-CT study could cause ipsilateral axillary lymph node accumulations. The team reported abnormal axillary uptake in patients who had been immunized in less than seven days, while patients with a longer interval between vaccination and FDG-PET (more than seven days) displayed no abnormal false-positive results.

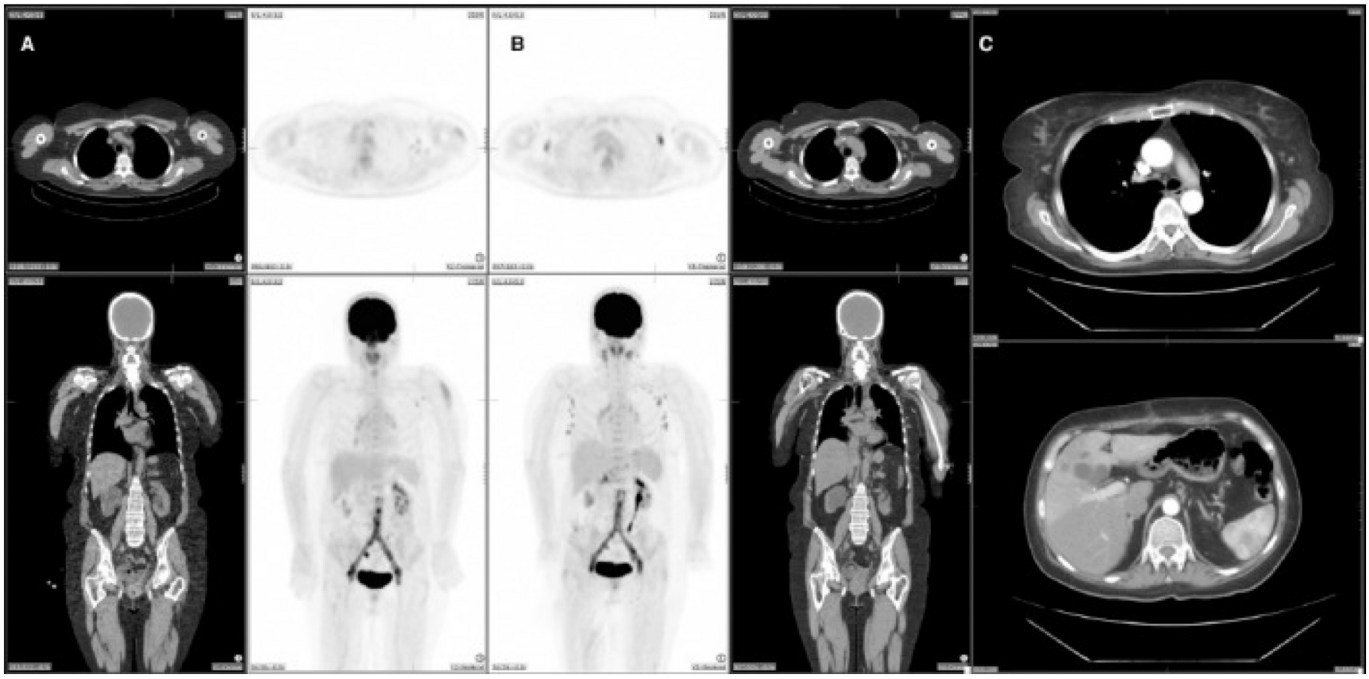

Fig. 1. Generalized lymph node activation in FDG PET-CT, following influenza vaccination, in a patient who was referred for investigation of an infected graft. The first FDG PET/CT study (A) reveals increased activity in the left deltoid and ipsilateral axillary lymph nodes. The second study (B) demonstrates multiple FDG-avid lymph nodes on both sides of the diaphragm, including bilateral cervical, bilateral axillary, coeliac, porta hepatis, and left femoral regions (B). The patient underwent CT angiogram (C) three months after removal of the infected graft, which shows no lymphadenopathy above or below diaphragm. Images are obtained from Ayati N et al.[41]

This contradicts Coates report,[21] which found that contralateral lymph node activation may be detected up to 1 month after the first vaccination in Cervarix recipients (against human papillomavirus vaccine). Burger studied 58 patients who had been vaccinated for the H1N1 virus, of which 17 (29.3%) patients had FDG-positive lymph nodes (mean SUV, 1.43 ± 1.06), with an interval of 1 to 14 days (between the vaccination date and PET examination).[20]

Youn[4] suggested that the type of vaccine formulation (the adjuvant component) and the time to deliver to the draining nodes might somehow explain the different patterns of lymph node activation observed after immunization. As a tangible example, Coates et al.[21] compared PET results following two different vaccine types for human papillomavirus: Gardasil and Cervarix. They found no significant difference between the duration or intensity of uptake (SUV) between Cervarix and Gardasil recipients in ipsilateral axillary lymph nodes, but there was a significant long-lasting contralateral nodal activation only in Cervarix receivers, possibly indicating the differences in vaccine adjuvant formulation. This suggests that the addition of adjuvants to vaccines can further enhance the immune response, and causes different nodal variations in nodal activation patterns.

The aforementioned findings emphasize the need to take vaccination history before the FDG PET and other imaging examinations, even when no evidence of tracer activity or imaging sign of inflammation/edema is present at the vaccination/injection site. Serial imaging might also help to differentiate between reactive *versus* neoplastic lymphadenopathy or splenomegaly.

4. Imaging of vaccine-induced complications

4.1. Local inflammatory reaction

The local inflammatory reaction at the injection site is a common side effect of vaccination, which is more prominent with inactivated vaccines, given the use of adjuvants. Indeed, every vaccine induces a different extent of local reaction at the vaccination site. Although most cases are mild and transient, severe or prolonged injuries may also emerge; these cases may still necessitate further evaluation with imaging of the affected region. Imaging methods could visualize soft tissue changes under such parameters. MRI or ultrasonography has been used frequently to evaluate the local reaction at the injection site, in order to detect or follow-up on vaccine-induced inflammatory lesions (*e.g.* an infected abscess). Due to higher sensitivity, better spatial resolution, and non-ionizing radiation, MRI is the method of choice for soft tissue imaging.[22]

In non-human models, the usefulness of MRI to measure vaccine reactivity has already been established.[23–26] The extent or frequency of vaccine-induced side effects – like pain, swelling, granulomas, and abscess – needs to be evaluated in preclinical field trials. MRI has been successfully applied in animals as an ideal method to measure and quantify vaccine-induced tissue reactions over time: an identical part of the licensing procedure for veterinary vaccines.[25,26] The signal intensity changes resulting from trauma, inflammation, edema, or infection could be detected using MRI.[27]

In humans, a few case reports of vaccine-induced myositis and/or intramuscular sterile abscess formation have been reported.[28–30] McMillan et al.[29] reported an 8-month infant (with routine vaccination history at 2, 4, and 6 months), who presented with a large soft-tissue mass in the anterior aspect of his left thigh. The mass was initially diagnosed as sarcoma, but pre-operative MRI evaluation confirmed a circumscribed lesion in the deep subcutaneous tissues of the anterolateral thigh, at the vaccination site. This turned out to be a delayed-onset sterile abscess.

Local vaccine-induced reactions can sometimes mimic a soft-tissue mass as their clinical presentation. Hence, both clinicians and radiologists should be familiar with these entities, their clinical and imaging spectrum, as well as proper follow-up strategies.

4.2. Musculoskeletal complications

While local reactions related to vaccinations are usually mild and self-limited, several cases of bursitis and other shoulder injuries have been described in the literature. Shoulder injuries related to vaccines (SIRV) is a rare complication and indicates a periarticular inflammatory reaction. Several case reports detailed shoulder pain and dysfunction, persisting as a complication of deltoid muscle vaccination.[31–34] In a systematic review on vaccine-related shoulder injuries,[34] the most frequent vaccines inducing complications were influenza and pneumococcal vaccines; furthermore, the most frequent injury was bursitis. Most of the vaccine-associated shoulder injuries were related to poor technical injections: albeit, the inflammatory reaction due to chemical constitutes is also an important factor in many cases.

In this situation, MRI might be performed to characterize the lesions. Focal subcortical bone marrow edema with no apparent cortical destruction, periosseous soft tissue inflammatory changes, bursal fluid in various amounts, and focal subcutaneous signal intensity at the injection have been reported in these cases.[35] Physicians need to be aware of the potential complications and maintain a high index of suspicion when evaluating patients with post-vaccination shoulder complaints.

4.3. Neurological complications

Although rare, CNS complications of vaccination against H1N1 influenza or Japanese encephalitis (JE) may occur, presenting with diverse clinical and imaging manifestations.[36,37] A few cases with different types of encephalitis and myelitis, including acute disseminated encephalomyelitis (ADEM) have been reported after vaccination. These syndromes might present with various neurological symptoms, such as seizure, altered mental status, headache, paralysis, and behavioral changes. Neuroimaging methods using MRI is of great value to detect these neurological symptoms, specifically when performed serially.[37] The imaging patterns, vaccination history, and good response to steroids will help to recognize the vaccine-induced neurological complications.

In addition, SPECT imaging is potentially able to depict the functional changes even before MRI changes.[38–40] Previous studies have reported persistent hypoperfusion observed in SPECT remained even after the disappearance of lesions in MRI, reflecting the impairment of cognitive abilities. Thus, MRI and SPECT studies (preferable with serial imaging) will offer complementary diagnostic information in different stages of the illness, thus assisting clinicians detect and follow-up neurological complications – such as pots-immunization encephalomyelitis. Albeit, the awareness of the patient vaccination history is the key element in these cases, to improve patient care.

5. Conclusion

As the world is waiting for an effective preventative agent against COVID-19, the role of imaging provides a valuable asset for diagnostic observations. Firstly, molecular imaging enables us to track the immune cell dynamics within the host body, which holds valuable research attention in the vaccination field. Secondly, serial CT imaging might be a great indicator of vaccine efficiency in research setting, as the immunized patients will be presumably protected against the appearance of pulmonary GGOs. Thirdly, lymph node activation observed in post-vaccination FDG PET might offer a useful parameter of activated immune cells, representing a sustainable immune response and vaccine efficacy. Lastly, as the local and systemic inflammatory immune response following immunization might mimic various confusing imaging patterns, taking vaccination history before imaging acquisition is of great importance to avoid unnecessary therapy intervention secondary to reactive and false positive findings. The clinical value of current imaging technology on the study of vaccine efficacy is a pertinent field of concern and, as demonstrated, a valuable asset for diagnostic medicine.

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Declaration of competing interest

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References

1. https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1.
2. Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, Santos MR, Schuitemaker H, Watson M, Arvin A. Prospects for a safe COVID-19 vaccine. Sci Transl Med. 2020;12(568): eabe094.

[3] Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: the current state of play. Paediatr Respir Rev 2020;35:43–9.
[4] Youn H, Hong KJ. Non-invasive molecular imaging of immune cell dynamics for vaccine research. Clin Exp Vaccine Res 2019;8(2):89–93.
[5] Gholamrezanezhad A, Mirpour S, Bagheri M, et al. In vivo tracking of 111In-oxine labeled mesenchymal stem cells following infusion in patients with advanced cirrhosis. Nucl Med Biol 2011;38(7):961–7.
[6] Tremblay ML, Davis C, Bowen CV, et al. Using MRI cell tracking to monitor immune cell recruitment in response to a peptide-based cancer vaccine. Magn Reson Med 2018;80(1):304–16.
[7] Veldhuis Kroeze EJ, Stittelaar KJ, Teeuwsen VJ, et al. Consecutive CT in vivo lung imaging as quantitative parameter of influenza vaccine efficacy in the ferret model. Vaccine. 2012;30(51):7391–4.
[8] Maltais AK, Stittelaar KJ, Veldhuis Kroeze EJ, et al. Intranasally administered Endocine formulated 2009 pandemic influenza H1N1 vaccine induces broad specific antibody responses and confers protection in ferrets. Vaccine. 2014;32(26): 3307–15.
[9] Sheehy N, Drubach L. (18) F-FDG uptake at vaccination site. Pediatr Radiol. 2008; 38:246.
[10] Prosch H, Mirzaei S, Oschatz E, Strasser G, Huber M, Mostbeck G. Gluteal injection site granulomas: false positive finding on FDG-PET in patients with non-small cell lung cancer. Br J Radiol 2005;78:758–61.
[11] Burger IA, Husmann L, Hany TF, Schmid DT, Schaefer NG. Incidence and intensity of F-18 FDG uptake after vaccination with H1N1 vaccine. Clin Nucl Med 2011;36. 848–5.
[12] Panagiotidis E, Exarhos D, Housianakou I, Bournazos A, Datseris I. FDG uptake in axillary lymph nodes after vaccination against pandemic (H1N1). Eur Radiol 2010; 20:1251.
[13] Kim JE, Kim EK, Lee DH, Kim SW, Suh C, Lee JS. False-positive hypermetabolic lesions on post-treatment PET-CT after influenza vaccination. Korean J Intern Med 2011;26(2):210–2.
[14] Galloway TL, Johnston MJ, Starsiak MD, Silverman ED. A unique case of increased 18F-FDG metabolic activity in the soft tissues of the bilateral upper thighs due to immunizations in a pediatric patient. World J Nucl Med 2017;16(1):59–61.
[15] Ayati N, Jesudason S, Berlangieri SU, Scott AM. Generalized lymph node activation after influenza vaccination on 18F FDG-PET/CT imaging, an important pitfall in PET interpretation. Asia Ocean J Nucl Med Biol 2017;5(2):148–50.
[16] Mingos M, Howard S, Giacalone N, Kozono D, Jacene H. Systemic immune response to vaccination on FDG-PET/CT. Nucl Med Mol Imaging 2016;50(4): 358–61.
[17] Thomassen A, Lerberg Nielsen A, Gerke O, et al. Duration of 18 F-FDG avidity in lymph nodes after pandemic H1N1v and seasonal influenza vaccination. Eur J Nucl Med Mol Imaging 2011;38:894–8.
[18] Williams G, Joyce RM, Parker JA. False-positive axillary lymph node on FDG-PET/CT scan resulting from immunization. Clin Nucl Med 2006;31:731–2.
[19] Shirone N, Shinkai T, Yamane T, et al. Axillary lymph node accumulation on FDG-PET/CT after influenza vaccination. Ann Nucl Med 2012;26(3):248–52.
[20] Burger IA, Husmann L, Hany TF, Schmid DT, Schaefer NG. Incidence and intensity of F-18 FDG uptake after vaccination with H1N1 vaccine. Clin Nucl Med 2011;36 (10):848–53.
21. Coates EE, Costner PJ, Nason MC, et al. Lymph node activation by PET/CT following vaccination with licensed vaccines for human papillomaviruses. Clinical Nuclear Medicine. 2017;42(5):329–34.

[22] Fisher MR, Dooms GC, Hricak H, Reinhold C, Higgins CB. Magnetic resonance imaging of the normal and pathologic muscular system. Magn Reson Imaging 1986;4(6):491–6.
[23] Bernau M, Liesner BG, Schwanitz S, et al. Vaccine safety testing using magnetic resonance imaging in suckling pigs. Vaccine. 2018;36(13):1789–95.
[24] Bernau M, Kremer-Rücker PV, Kreuzer LS, et al. Magnetic resonance imaging to detect local tissue reactions after vaccination in sheep in vivo. Vet Rec Open 2017; 4(1):e000200.
25. Bernd G. How magnetic resonance imaging can determine vaccine reactivity. 2017.

[26] Bernau M, Kremer PV, Kreuzer LS, et al. Assessment of local reaction to vaccines in live piglets with magnetic resonance imaging compared to histopathology. ALTEX. 2016;33(1):29–36.
[27] Lovitt S, Moore SL, Marden FA. The use of MRI in the evaluation of myopathy. Clin Neurophysiol 2006;117(3):486–95.
[28] Polat AV, Bekci T, Dabak N, Ulu EM, Selcuk MB. Vaccine-induced myositis with intramuscular sterile abscess formation: MRI and ultrasound findings. Skeletal Radiol 2015;44(12):1849–52.
[29] McMillan CS, Spouge AR, Hammerberg O, Thain LM. Magnetic resonance imaging for differentiating delayed-onset sterile abscess complicating vaccination from soft-tissue neoplasm: case report. Can Assoc Radiol J 2000;51(1):28–9.
[30] Katz LD. Vaccination-induced myositis with intramuscular sterile abscess formation. Skeletal Radiol 2011;40(8):1099–101.
[31] Atanasoff S, Ryan T, Lightfoot R, Johann-Liang R. Shoulder injury related to vaccine administration (SIRVA). Vaccine. 2010;28(51):8049–52.
[32] Bodor M, Montalvo E. Vaccination-related shoulder dysfunction. Vaccine. 2007;25 (4):585–7.
[33] Degreef I, Debeer P. Post-vaccination frozen shoulder syndrome. Report of 3 cases. Acta Chir Belg 2012;112(6):447–9.
[34] Martín Arias LH, Sanz Fadrique R, Sáinz Gil M, Salgueiro-Vazquez ME. Risk of bursitis and other injuries and dysfunctions of the shoulder following vaccinations. Vaccine. 2017;35(37):4870–6.
[35] Okur G, Chaney KA, Lomasney LM. Magnetic resonance imaging of abnormal shoulder pain following influenza vaccination. Skeletal Radiol 2014;43(9): 1325–31.
[36] Lessa R, Castillo M, Azevedo R, Azevedo F, Azevedo H. Neurological complications after H1N1 influenza vaccination: magnetic resonance imaging findings. Arq Neuropsiquiatr 2014;72(7):496–9.
[37] Ohya T, Nagamitsu S, Yamashita Y, Matsuishi T. Serial magnetic resonance imaging and single photon emission computed tomography study of acute disseminated encephalomyelitis patient after Japanese encephalitis vaccination. Kurume Med J 2007;54(3–4):95–9.
[38] Hung KL, Liao HT, Tsai ML. Postinfectious encephalomyelitis: etiologic and diagnostic trends. J Child Neurol 2000;15(10):666–70.
[39] Okamoto M, Ashida KI, Imaizumi M. Hypoperfusion following encephalitis: SPECT with acetazolamide. Eur J Neurol 2001;8(5):471–4.
[40] Broich K, Horwich D, Alavi A. HMPAO-SPECT and MRI in acute disseminated encephalomyelitis. J Nucl Med 1991;32(10):1897–900.
[41] Ayati N, et al. Permission to use was granted by the Asia Oceania Journal of Nuclear Medicine & Biology. Asia Ocean J Nucl Med Biol 2017;5(2):148–50.

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