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Patient Report

Complex regional pain syndrome by vaccination: A case of complex regional pain syndrome after vaccination of influenza A(H1N1)

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Complex regional pain syndrome (CRPS), a clinical disease characterized by hyperalgesia or allodynia, edema, weakness, and vasomotor malfunction, can be divided into types 1 and 2, according to the inducing cause. The pathologic mechanism is not well known. It is mainly reported to occur after the patient has experienced an external wound and nerve injury, or spontaneously. Many cases of CRPS in children and adolescents occur in girls, usually later in childhood.[1,2] However, the inducing cause cannot be determined in at least 50% of cases.[3]

Reports of CRPS generated after a vaccination are rare; thus, the authors report on a case of CRPS generated in a 17-year-old girl following influenza A (H1N1) vaccination.

Case Report

The patient was a 17-year-old girl with right hand dominance and no history of allergy, including hypersensitivity reaction after vaccination, and who had previously been on medication. She did not suffer from autoimmune disease, and was in good health. On 1 December 2009, she received an influenza A (H1N1) vaccination in the infirmary of her high school. The influenza A (H1N1) vaccination was administered in the form of a group schedule. She received the vaccine (GREEN FLU-S, GREEN CROSS, Yongin, Republic of Korea) with a needle of 25G (2.66 mm outer diameter) and 15 mm length in the deltoid muscle of the left upper arm. Seven hours later, the color of the area of injection had changed, and the patient experienced symptoms that included a tingling sensation; pain and edema were generated from the arm to the fingers. The patient developed weakness of the left upper limb, and she was not able to lift the left upper limb over her shoulder. Edema had subsided a little by the next morning, but rose again in the afternoon. This phenomenon was repeated for 4 days. Pain occurred from the first day after the injection of the vaccine and was ongoing, so that the patient complained of difficulty sleeping. Characteristics of pain included numbness and tingling.

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On the fifth day after vaccination, she went to the doctor's office and was prescribed medications that included non-steroidal anti-inflammatory drugs, anti-histamines, and antacids, which she took for 2 days. No laboratory evaluation was performed. On the seventh day after vaccination, she went to a pediatrician at the hospital. Following evaluation of her history and performance of a physical examination, the physician referred her to a physiatrist. She was found to have edema of the left upper limb, and pain and weakness continued. The visual analogue scale score (VAS: for subjective pain intensity ranging from 0 to 10, with anchors being 0 [no pain] and 10 [most severe pain]) was 7. The entire left upper limb showed dysesthesis that did not match a dermatome on sensory testing. The skin of the area of injection was normal. Muscle weakness was shown on the manual muscle test. Left shoulder flexion and abduction were grade 3, and left wrist flexion was grade 4. Comparison of the arms showed that the circumference of the left arm was 29.5 cm, whereas the right arm was 27 cm in circumference. Left arm had increased 2.5 cm more than the right arm. Compared with the right hand, the left hand, on the whole, was swollen, and cold and dampish with sweat. Capillary refill, pulse, and deep tendon reflex were normal. The left upper limb and shoulder girdle were palpated in order to exclude myofascial pain syndrome; however, a taut band and trigger points were not observed. In addition, abnormal findings were not observed on physical examination and cervical X-rays; cervical magnetic resonance imaging was implemented in order to exclude cervical herniated disk lesions and cervical radiculopathies. No abnormal findings were observed with blood testing, which included white blood cell count, blood chemistry, erythrocyte sedimentation rate, and C-reactive protein. Findings of peripheral nerve injury, including cervical radiculopathies in electrodiagnostic study were not observed. No abnormal findings of the bloodstream were observed on Doppler ultrasonography. In a triple-phase bone scan study, uptake in the left upper extremity was not increased.

Based on the clinical findings, the patient was diagnosed with CRPS. A small amount (daily 10 mg) of triamcinolone acetonide was used as the medicinal therapy for a period of 2 weeks. Gabapentin 300 mg was used continuously for symptomatic therapy. And, we recommended that the patient undergo physical

therapy, including transcutaneous electrical nerve stimulator. However, physical therapy was not administered. Edema of the left upper limb was gone after 2 weeks, and muscle strength increased. Left shoulder flexion and abduction was grade 4 and left wrist flexion was grade 5. However, pain was reduced to VAS 4, but was still observed. Pain continued after 4 weeks; however, edema and weakness of the left upper limb showed complete improvement. Pain continued for 2 months and Gabapentin was increased to 600 mg. By the third month, pain continued and pain control was easy during the day (VAS 1), but was not easy during the night (VAS 4). One year later, we conducted a telephone interview with the patient. She told us that the pain had not yet disappeared, but that it was tolerable.

Discussion

With the monovalent inactivated split-virus influenza A (H1N1) vaccine, immunity is obtained without serious side-effects. A local response or systemic reaction, including peripheral polyneuropathy, atrial fibrillation, myalgia, arthrodynia, edema, fatigue, headache, fever, gastrointestinal disorder and lassitude have been reported as common side-effects.[4] However, there have been no reports on CRPS. Zhu *et al*.[5] reported that the local reaction was not as strong in vaccines that did not include an adjuvant (alum); however, they did not illustrate a causal correlation between the adjuvant (alum) and generation of side-effects.

In this case, the patient received the monovalent inactivated split-virus influenza A (H1N1) vaccine, in which an adjuvant is not included; therefore, we were able to exclude the possibility that symptoms were generated by an adjuvant.

Nerve injury can be one of the risk factors for CRPS. In an animal experiment, Siegel *et al*.[6] reported on the symptoms and pathological findings of CRPS, including axonal Wallerian degeneration and decreased epidermal neuritis after distal nerve injury by a needle stick. They also mentioned that the pathological findings coincided with the CRPS-1 patient's results and that CRPS-like symptoms could be generated after minor distal nerve injury. Symptoms of autonomic dysfunction might be similar to symptoms of CRPS. Autonomic dysfunction can be generated in lesions or injury to small-diameter nerve fibers (myelinated Aδ, unmyelinated C). In general, small-diameter nerve fibers (myelinated Aδ, unmyelinated C) in the skin of the human body exist with free nerve endings and within 0.1 mm from the surface of the skin. Aδ is 1–5 μm, and C is 0.1–1.3 μm. If the patient incurred damage to the small fibers by a needle stick, the possibility that a CRPS-like reaction was generated cannot be excluded. However, there has been no report of damage to small-diameter nerve fibers, such as free nerve endings, by intramuscular injection. She received an intramuscular injection with a needle of 25G (2.66 mm outer diameter) and 15 mm length on the left arm (deltoid muscle area). When looking at the depth of the needle, the anatomical structure around the left deltoid muscle area, and the fact that there were no symptoms at the time of the injection, we think that direct axillary nerve injury by needle stick did not occur. However, it cannot be completely excluded that physical damage to small fibers below the skin or axon terminal around the neuromuscular junction by needle stick might cause CRPS-like reactions. We regret that in the process of monitoring of her disease we were unable to observe histological changes through skin biopsies around the injection site and left distal upper limb.

Noxious events or trauma, particularly minor trauma, might be risk factors causing CRPS. The definitions of noxious events and trauma, particularly minor trauma, are not clear. Woolf[7] discussed development of continuing pain with noxious skin stimuli, which could result from peripheral and central sensitization. Genc *et al*.,[8] who reported on a case of CRPS generated after a rubella vaccination, suggested injection trauma as the initiating noxious event that caused the reaction. Therefore, we suppose that injection trauma, as a noxious event, is a type of trauma that can cause CRPS.

Many reports have suggested that pediatric CRPS is relevant to psychological problems. Galer *et al*.[9] suggested possible involvement of stress and psychological factors at the time of injury in sympathetic nerve system hyperarousal. Bruehl and Carlson[10] argued for a correlation between hyperalgesia and A-adrenergic activity. Increased A-adrenergic activity in patients with nerve injury is associated with anxiety, stress, and depression, which cause sensitization of receptors at the injured site and synaptic plasticity. These changes induce peripheral and central sensitization[11] and contribute to onset and maintenance of symptoms of CRPS. In one report, psychological testing found that 31 of 32 CRPS patients were severely stressed before and after the onset of CRPS.[9] In addition, Stanton *et al*.[12] reported that 83% of CRPS patients showed severe emotional abnormality on psychological tests. Therefore, psychological problems might be a predisposing factor for CRPS and the need for psychological consideration in treatment of CRPS must be emphasized.[1]

In her family history, our patient lived with only her father and a younger sister. She played the role of her mother in the home and suffered from stress in adapting to high school life. Therefore, it is thought that she would have had mental stress. However, we did not consider the question of whether psychological problems were predisposing factors to the illness or not, which remains a disappointment. Ultimately, we think that injection trauma was the initiating noxious event that caused the reaction. In addition, we think that stress or psychological factors are associated with autonomic hyperarousal in patients with noxious stimuli, which lead to onset and maintenance of symptoms of CRPS or central sensitization.

CRPS is a clinical diagnosis. Diagnosis is based on physical examination and medical history. Some diagnostic criteria have been presented. The best-known criteria are those presented by the International Association for the Study of Pain (IASP) (Table 1).[8] When looking at the symptoms, signs and history observed in this case, findings corresponding to diagnostic criteria presented by the IASP[8] were observed. Certain tests, including X-rays, triple-phase bone scan, infrared thermography, and sweat testing, are helpful in diagnosis of CRPS.[9] However, tests used for diagnosis of CRPS are actually performed in order to rule out other diagnoses. Symptoms observed in this case, including edema and muscular weakness, numbness, and pain in the upper limb, can be observed in myofascial pain syndrome, cer-

Table 1 Diagnostic criteria for chronic regional pain syndrome type 1[13]

1. Presence of an initiating noxious event or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia with which pain is disproportionate to any inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4. Diagnosis is excluded by existence of conditions that would otherwise account for the degree of pain and dysfunction

Criteria 2–4 must be satisfied.

vical radiculopathy, or peripheral neuropathy of the upper limb. Although rare, symptoms similar to deep vein thrombosis of the upper limb have been observed. To rule out these diseases, we performed a physical examination, electromyography, and Doppler ultrasonography. However, abnormal findings were not observed, and we were able to exclude the above diseases.

Differentiation of the hypersensitivity reaction is needed. The patient had no history of hypersensitivity reaction to eggs, other vaccines, injections, or drugs, and, despite taking the medications, her symptoms did not show improvement. Therefore, we supposed that the symptoms were not generated by a hypersensitivity reaction to the vaccine.

Kachko *et al*.[1] also insisted that early diagnosis and treatment of pediatric CRPS are the most important elements in the effort to improve the outcome and prevent resistant CRPS. We observed that the time to introduction to us was 1 week and did not perform other non-invasive treatment except for medication. However, the patient's symptoms, except for pain, showed rapid improvement. Therefore we think that early diagnosis and medication are probably helpful to improve the symptoms of CRPS, except for pain. Physiotherapy may help to reduce pain.[14] However, we did not perform physiotherapy, which remains a disappointment.

Conclusion

Frequently, CRPS, a disease whose cause and pathological mechanism are not well known, is clinically diagnosed erroneously as another disease, or is overlooked. When the authors attempted a journal search, only a few cases of CRPS after injection of the rubella vaccine and the hepatitis B vaccine were found.[8,15] The case of CRPS occurring after an influenza A (H1N1) vaccination is considered here for the first time. Thus, we report on a case of CRPS generated after influenza A (H1N1) vaccination with a review of the literature. In this case, we think that injection trauma and stress or psychological factors were associated with the onset and maintenance of symptoms of CRPS.

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