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Case Report

Parsonage-Turner Syndrome following axillary nerve injury from an intramuscular injection of COVID-19 vaccine and proposal of the intradermal route as an alternative route of vaccination

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Abstract:

A case of Parsonage-Turner syndrome (brachial plexus neuropathy) occurred following intramuscular (IM) injection of mRNA COVID-19 vaccine into the deltoid muscle. The symptoms were highly suggestive of the needle hitting the anterior branch of the axillary (circumflex) nerve which set up a sequence of distressful events including instant severe pain and palsy of upper limb muscles lasting up to six months. To avoid such adverse events, the intradermal (ID) route is proposed as an alternative to IM injection as no nerve runs in the skin. Review of studies showed that the ID route is the most extensively used route in vaccination. With rare exceptions, it is considerably more effective than the IM route so that smaller doses can be used. When correctly placed in the skin layer, no other structure could be damaged. However, vaccine development is no longer led by physicians and scientists but controlled by pharmaceutical executives who tend to favor the IM route, so that most vaccines today are built on IM trials. Deviation to the ID route incurs extra trials, more expenses and less profit. Yet, to ignore the plight of the unfortunate few who suffer from IM-induced debilitating events is to add fuel to the ongoing trend of vaccine hesitancy. It is hoped, that the authorities should step in and lend support to this issue.

Keywords: parsonage-turner syndrome; covid-19 vaccination; axillary nerve injury; intramuscular injection; intradermal injection

Introduction

One of the fundamental principles to control an epidemic is to enhance the population's immunity, and one of the most effective ways to enhance immunity is vaccination. A vaccine would only work if it is widely accepted in the community and its acceptance has to be gained not only by proven efficacy but also reassured safety. Such confidence is often won not by a one-off roll-out promotion from the producer but by continuous fine-tuning adjustments on the formulation and methodology of administration. In such ways, many epidemics have been brought under control. For the current on-going COVID-19 pandemic we seem to have encountered a different trend of events. In spite of much hyped rhetoric, that the new vaccines were developed with unprecedented speed using unprecedented technology we also encountered unprecedented vaccine hesitancy. To be sure, vaccine hesitancy always happened but usually could be resolved by further research and refinement. This time, such hesitancy seems to have been summarily brushed off as paranoid phobia of statistically insignificant issues. It is the purpose of this study to report on a rare and "statistically insignificant" but extremely traumatizing adverse event following an intramuscular injection (IM) of mRNA COVID-19 vaccine, and to propose a simple and effective method to avoid such complications and win back the confidence of the potential vaccine recipients.

Case illustration

A 23-year-old young man of rather slim stature (BMI 17.73 Kg/M2) received his first dose of IM mRNA COVID-19 vaccine in his right deltoid muscle during the summer of 2021. During the injection he instantly felt excruciating pain over the right shoulder. Over the next few hours, the pain receded to just bearable levels but marked weakness and tenderness was noticed in the right upper limb. Being left-handed, he was able to carry on most daily activities. Remarkably, he was soon able to use his right fingers on the computer keyboard, but the proximal muscles of the right arm remained very weak, to the extent that he could not lift a pile of files with both hands, a handicap which markedly compromised his career which mainly involved clerical work. The pain largely eased off after one month but the palsy relentlessly persisted. Assessment by a neurologist confirmed severe brachial plexus neuropathy or neuralgic amyotrophy, often labelled with the eponym of Parsonage-Turner syndrome (PTS) in honor of the two physicians who first reported a large series of the disorder.1 He was advised to maintain an active living within the limits of his disabilities and patiently wait for a spontaneous recovery. Review at six months showed almost complete recovery with minimal residual muscle weakness. By that time, however, he had lost his job and, given the recession during the pandemic, was unable to get another employment.

Discussion

Parsonage-Turner syndrome may be idiopathic or due to trauma, inflammation, autoimmune reaction or vaccination.2 The sudden sharp pain and palsy during the IM injection is strongly suggestive of a nerve trunk being hit by the needle with the vaccine ingredients delivered into the nerve, or its close vicinity.3 By location, the nerve involved would have been the anterior branch of the axillary nerve, also known as the circumflex nerve, which comes from the brachial plexus and runs deep under the deltoid muscle, passing round the neck of the humerus, and supplying both the

deltoid and the shoulder joint. The vaccine contents might tract along the nerve and spread to the joint and the muscle as well as upstream back to the brachial plexus. The risk would be greater for a vaccine recipient with low BMI as in this case, since a standard IM needle would have reached deeper and closer to the plane of the axillary nerve. The exact incidence of Parsonage-Turner syndrome due to axillary nerve injury from an IM COVID-19 vaccine is not known. Given the fact that 6.9 million people in our city have been vaccinated4 and this is, to our knowledge, the only case known, it is likely to be less than one in a million even after making generous allowance for under-reporting. Still, it is no consolation to tell the patient it was just bad luck that he fell into the wrong side of that 1:1,000,000 ratio. Since no nerve trunk runs in the skin, giving the injection by the intradermal (ID) route would have avoided such a risk altogether. How much better if we could reassure the patient with a positive message, that he had not suffered in vain, and that we had taken the cue from his case and will eliminate such devastating events in future with ID vaccine injection. Ironically, as shown in subsequent sections, hesitancy of vaccine producers to change to ID vaccines proved worse than vaccine hesitancy.

Comparison of different routes of vaccination

Historically there have been many routes of vaccine administration: percutaneous, intradermal (ID), subcutaneous (SC), intramuscular (IM), oral, nasal and pharyngeal. Such diversity enables scientists and physicians to find the safest and most effective means of giving a particular vaccine. E.g., giving BCG (Bacille Calmette-Guerin) vaccine by IM or SC injections would lead to local abscesses, regional lymphadenitis or even systemic illness,5 so we are now giving it by ID injection. Great pioneers like Jenner, Koch, Pasteur, Salk, Sabin monitored the response of their vaccines and made prompt appropriate adjustments.6 Louis Pasteur for one was reputed to have personally injected his newly developed vaccine subcutaneously to a boy bitten by a rabid dog.7 Come the 21st century, we know more about the basic science of immunology. We know that one of the best sites to introduce an antigen to elicit an immune response is the skin which contains far more resident antigen presenting cells (macrophages/Langerhans cells/dendritic cells) and they instantly and effectively initiate the immune process by presenting the pathogenic antigen sequence to T-cells, which are then carried by an efficient lymphatic system to the regional lymph nodes to activate further steps of immune reaction.8 Subcutaneous tissue and muscle have little or no such resident antigen presenting cells. They have to wait for an inflammatory reaction to set up (which, depending on the potency of the vaccine's adjuvant, usually takes up to a few hours) and attract the phagocytes and macrophages from the circulation.9 Vaccine adjuvants, by definition, are tissue toxic and enhance such reactions. Conceivably, if the vaccine is injected into the axillary nerve an inflammatory reaction will be set up and it might spread upstream to involve the brachial plexus and downstream to involve the deltoid and the shoulder joint. One certain way to avoid such injury is by avoiding the IM and choose the ID route instead.

Subsequent Studies on intradermal vaccination

The worldwide adoption of ID BCG has been mentioned. It has been applied to billions of recipients over many decades with proven safety, efficacy and feasibility. Other more recent studies have repeatedly shown the advantage of ID over IM vaccine injection in the prevention of various other infectious diseases.

Wahl and Hermodsson compared the three methods of vaccination: ID, SC and IM injection of hepatitis B vaccine.10 They administered 20 μg of vaccine for IM and 2 μg for both SM and ID. Seroconversion was obtained in 96% subjects by IM injection, 100% by ID injection and 63% by SC injection. Thus, at 1/10 of the dosage of the IM injection, the ID injection could equal or even surpass the IM injection results. Moreover, if an ID injection is inadvertently delivered subcutaneously, there would still be some protection, albeit at a moderately lower level. Obviously, it was not originally designed for a head-to-head comparison of IM with SC injection, otherwise the dose would have been identical between the two groups. However, the results were misinterpreted or exploited by IM protagonists that SC was inferior to IM injection.

Schnyder et al. used a different approach.11 They reviewed 26 studies of vaccinations on various infectious diseases employing "fractional doses", i.e., with the dose of antigen equally reduced to 20-30% of the standard dose across the three routes of administration, ID, IM or SC injections. In 19 studies, the immune responses were similar across all three routes, while in 7 studies the efficacy of IM and SC routes remained similar, but the ID was clearly superior to the other routes. Notably, Schnyder et al. did not find any trial including the two most extensively administered vaccines, smallpox vaccine and BCG. Such a comparison would have been unethical as the IM route is well-known to be highly deleterious for recipients of these two vaccines.

Migliore et al.8 pleaded for ID injection of COVID-19 vaccines at 1/10 or 1/5 of the standard IM dose to boost vaccine availability to more people. The review covered vaccinations of influenza, hepatitis A and B, poliomyelitis, diphtheria-tetanus-pertussis, human papillomavirus, Japanese encephalitis, meningococcus, yellow fever, varicella zoster virus and rabies. Results uniformly showed that small fractional doses of ID delivered vaccines were equally effective if not superior to the standard full-dose IM vaccines.

Hung and Yuen12 observed that for influenza vaccination the ID route at reduced dosage was equivalent to the IM route. With a new device they were able to deliver larger volumes of vaccine accurately into the skin's epidermis and proved beyond all doubts that with the same standard dose, the ID route proved significantly superior to the IM route. They also showed that prior topical application of imiquimod to the ID injection site further enhanced the immunogenicity and clinical protection value of the vaccine.

As often happens, one size does not fit all. Leung et al.13, studying on influenza vaccine, showed that among atopic dermatitis patients with skin colonized by Staphylococcus aureus, the ID route has lost its immunological advantage and the vaccine is best given by IM route. This is no surprise as S aureus produced superantigens and proteins such as SpA which tend to down regulate the skin's immune elements, depleting the Langerhans cells, suppressing the B-cells and reducing the antibody response.14 Unfortunately, this study was not endowed with the same or a similar ID injection device as used by Hung and Yuen, so that no standard IM dose could be delivered into the skin for a fair comparison; otherwise it might be able to show whether Staphylococcal skin colonization merely deprived the skin of its immunological advantage over other tissues like the muscle or rendered the skin immunologically incompetent altogether.

The problem with changing the IM stereotype

Vaccine producers today almost uniformly adhere to the stereotype method of IM injection. All suggestions of trying alternative methods have fallen on deaf ears. Whereas vaccine development was led by medical scientists in the past, it is now controlled by gigantic business enterprises with profit as the prime aim. Most of the time, drug developers are dealing with agents that directly produce certain desirable effects e.g., antibiotics against bacteria, cytotoxic drugs and targeted agents against cancer, immune suppressants to put down autoimmune reactions, and so on. For this purpose, the IM route seems simpler, easier, faster and more effective. This "antibiotic mentality" has been carried over to the executive planning for vaccine development and taken a toll on vaccination decisions. But do we really want vaccines to be quickly absorbed into the blood stream like antibotics and reach various organs in the body to expedite immune reaction. Vaccination involves a very different discipline from antibiotics. A vaccine does not directly fight the infective agent. Instead, it mimics the infective agent and train the body's own immune system to recognize the invader and fight against it. The best place to start such training is not in the muscle or the blood stream, but in the skin with its large constituent of resident antigen presenting cells ready for initiating such training. However, to divulge into further trials of ID vaccination would incur more labor, more time and higher cost, without bringing in more revenue. In fact, revenue might diminish because the ID route, being more efficient, will

end up consuming less vaccine. Such prospects are far from attractive to the business executive.

Can the physician independently proceed with ID vaccination? Nowadays, the answer is likely "no". Formerly a physician has more liberty to try out new methods of treatment. Over the years, in the name of patient safety and public interest, everything is tightly regulated. The physician needs to follow guidelines. Any new proposition has to be "evidence based" and approved by the authority, and the authority today needs extensive and expensive Phase III trials to consider the approval. No physician could afford hundreds of millions of dollars to conduct such trials. Furthermore, with the increasing litigation trend in society, any new move by a physician might present an attractive target for seekers of astronomical compensations.

Conclusion and projection into the future

Our society has "advanced" to the present situation in which vaccine development is almost entirely in the hands of big pharmaceutical corporates. To maximize profit, trials are often stripped down to the bare minimum just to gain authority's approval. Further trials to explore the possibility of avoiding serious side effects but without bringing more revenue would not easily gain acceptance. In this brief presentation of a rare adverse event following IM injection, the Parsonage-Turner syndrome, we have proposed a simple solution of substituting the IM with the ID route. Many problems are foreseen in carrying out such trials. The authority should take the lead to support such trials, since the best way to overcome vaccine hesitancy is not by brushing the adverse events aside as being statistically insignificant but by eliminating them altogether with a safer alternative.

Limitations

This study is limited by the typical constraints of a single case report. It is narrowly focused on a rare subgroup of a direct hit of the IM needle at the axillary nerve and depositing its payload into the nerve and the immediate vicinity. The pain and palsy occurred immediately and stretched over the next few months. Switching to ID injection would almost certainly prevent such a event. Most other cases had a time gap of a few days to a few weeks between the IM vaccination and the onset of acute pain and palsy,15 the needle was unlikely to make a direct hit and the vaccine was probably deposited only around the nerve and not into it. Switching to ID might still provide prevention as there would be no reaction nearby to affect the nerve. In a third subgroup, there was a wide spatial gap between the injection site and the affected nerves, e.g., the vaccine may be injected to the left deltoid but the right brachial plexus would be affected or vice versa. For such cases, the preventive value of switching to ID might be less certain. Still, since ID vaccination would be using a much smaller dose, there would be a good chance that any side effect might be mitigated.

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