

Case Report

Adverse Events and Vaccination: Extensive Local Reaction after Anatoxin Vaccine—A Case Report

Maria I. Brumboiu¹, Alexandru M. Durla-Paşca^{1,*}, Irina Iaru²

¹ Department of Community Medicine, Faculty of Medicine, “Iuliu Hatieganu” University of Medicine and Pharmacy, 23 Iuliu Moldovan Str., 400347 Cluj-Napoca, Romania

² Department of Pharmacology, Faculty of Pharmacy, “Iuliu Hatieganu” University of Medicine and Pharmacy, 12 Ion Creanga Str., 400347 Cluj-Napoca, Romania

* Correspondence: durla.alex@yahoo.com; Tel.: +40-756-667025

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Abstract: Post-vaccine adverse reactions are unwanted medical events that concern both the public and healthcare professionals. The objective of this paper is to present a detailed analysis of the case of an extensive local adverse reaction after the administration of a vaccine dose containing diphtheria–tetanus anatoxins. A good knowledge of post-vaccine side effects allows for complete and correct diagnosis, as well as appropriate individualized recommendations. Such an approach contributes to restoring public confidence in vaccines and vaccinations. The patient was a 6-year-old boy, with a history of asthma under chronic treatment with corticosteroids. He developed extensive local inflammatory lesions accompanied by functional disorders of the left arm, which began six hours after the administration of the fifth dose of the diphtheria–tetanus–pertussis–poliomyelitis vaccine. The lesions, which extended to the forearm, were locally treated with antiseptics and systemically treated with hydrocortisone hemisuccinate. They completely remitted within 14 days. Laboratory investigations revealed neutrophilia (6,870 neutrophils/ μ L), which could be related to the long-term treatment with steroids. The investigation needed the plasma concentration of diphtheria and tetanus anatoxins antibodies and the pro-inflammatory cytokines to be complete.

Keywords: local extensive reaction; anatoxin vaccines; case report

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Introduction

Population immunization is recognized as a major factor in reducing the number of illnesses and deaths caused by diseases preventable through vaccination. Due to this, it has contributed to population growth and the improvement of quality of life [1,2].

The presence of fewer cases of severe illness in the vaccinated group of the population has altered the perception of disease-related risk over time. There is an absence of the feeling of danger regarding illness or death, both of which were prevented or made infrequent through vaccination. Therefore, the interest in adverse reactions (ARs) after vaccination has significantly increased, with the occurrence of cases where even

mild or moderate local effects are being hyperbolized [3,4]. At the same time, members of the community such as patients, media personalities and some healthcare professionals have incriminated vaccination against diseases that do not have a well-known etiology [4]. Although no causal relationship has been established through scientific studies, opinions on the existence of such a link still persist. This attitude has created a real trend for either refusing certain vaccines, such as the pertussis or measles vaccines, or for refusing all vaccination in general [4–8].

Thus, cases of diseases that have been previously considered eradicated, such as whooping cough, measles, diphtheria or poliomyelitis, have reappeared, as more and more children and adult individuals are not vaccinated against them [5,8–10]. When such cases arise, the risk of disease is high for the unvaccinated and the people around them, due to the risk of transmitting the infectious disease. On the other hand, the exposure and the risk of disease are also increased for individuals without immune protection, either because they have not been vaccinated due to contraindications or because of the lack of a sufficiently protective immune response even if they have been properly vaccinated [11].

Most medical practitioners do not usually have patients with such diseases and thus their practical experience is limited in these cases. Therefore, diagnosis and treatment could be delayed, which leads to severe cases that threaten patients' lives.

In practice, vaccines are generally administered to healthy people, reducing the acceptability of ARs [2,4,12]. Nevertheless, it is well known that vaccines, being mostly parenteral pharmaceutical preparations, can cause ARs like any other type of medication. At the same time, an event that appears after vaccination can represent an AR, but it can also appear coincidentally, unrelated to the vaccine administration [2,11]. Differentiation is essential in order to enable the practitioner to establish individualized vaccine recommendations. The system in place to monitor post-vaccine ARs includes AR case investigation, in order to establish the causal relationship between the vaccine and the AR [13]. Unfortunately, few tests so far can confirm that the vaccine is what caused the AR. Vaccine strains such as the Calmette–Guerin bacillus (BCG) and the measles, varicella or poliomyelitis viruses can be identified from cases that present with the side effect, thus confirming the diagnosis as an AR [14]. These practical aspects are solid reasons for improving the investigation of an AR following vaccination and for continuous education in this field. In this context, the aim of this paper is to present a detailed analysis of a post-vaccination AR related to a vaccine containing diphtheria–tetanus anatoxins, in order to improve individual risk assessment for AR and to draw attention to the importance of accurate diagnosis and dissemination of information.

In the case of the DTPa-VPI vaccine, the first dose is administered when the infant is 2 months old, with the booster doses following at 4 months, 11 months and 5 and 14 years of age. According to the National Institute for Public Health, vaccination coverage as of February 2022 did not meet the 95% threshold. This is in part because of patient refusal to be administered either the first or subsequent doses, but also due to a lack of DTPa vaccine [15]. A 2016 analysis of the reported post-vaccine adverse reactions revealed that a majority were local reactions, followed closely by generalized reactions [16].

Case Report

We present the case of an extensive local post-vaccination reaction which was declared to the public health authorities through the specific surveillance system; post-vaccine ARs are reported immediately by telephone, through the national surveillance system, to the local Department of Public Health. A unique standard form is filled out for all events related to communicable diseases [13]. A second form to be filled out is the case report form of the post-vaccine AR, which includes data on the side effect and the investigation steps, mentioning

the need for further investigation. This is jointly completed by the physician and those investigating the AR. Both forms are sent to the National Center for Communicable Disease Surveillance and Control. Those who have performed the vaccination fill out another reporting form and send it to the Romanian National Agency for Medicines and Medical Devices.

The surveillance system defines an undesirable post-vaccine adverse event as any unwanted medical occurrence (unexpected manifestations, abnormal laboratory results, symptoms or illness) that appears within the first 30 days after vaccination and which does not necessarily have a causal relationship with the vaccine administration [11,13].

In the analysis, we included clinical data, vaccine data, medical history, the results of the laboratory investigations that were performed and the parents' attitude.

Patient's Clinical Data

The present case of a 75-month-old (6 years, 3 months) boy living in a rural area was selected during a consultancy working session. The reasons for the case discussion were the extension of the local post-vaccination AR to the upper limb and the high psycho-emotional impact of the clinical manifestation on the parents. They requested numerous medical consultations for this AR, considering it was linked to the vaccination.

The patient was completely vaccinated according to the national vaccination scheme: at 2 and 6 months of age with a dose of hexavaccin for diphtheria–tetanus–pertussis–poliomyelitis–*Haemophilus influenzae* type b–hepatitis B, and at the age of 4 and 12 months with a dose of pentavaccine for diphtheria–tetanus–pertussis–poliomyelitis–*Haemophilus influenzae* type b. The medical history of the patient included a mild form of bronchial asthma and positive allergic tests for pollen, mold and house dust. He was under chronic treatment with glucocorticoids.

The AR occurred after vaccination with the fifth dose (as the second revaccination) of the diphtheria–tetanus vaccination scheme, with a tetravaccine containing the diphtheria–tetanus–pertussis–poliomyelitis components. The vaccine (0.5 mL) was administered in the left deltoid muscle. After about 6 hours, swelling, induration, erythema and pain appeared at the site of administration. Within 48 hours, the swelling extended to the entire arm, from shoulder to elbow, accompanied by functional disorder of the upper left limb. The patient also presented with pale facies, periorbital dark circles and a moderately altered general condition. The swelling continued to extend to the forearm over the next 2 days. Painful axillary adenopathy was also present. Throughout the entire evolution, the patient was afebrile.

Laboratory Investigations

The laboratory investigations carried out 48 hours after the onset of local lesions showed an increased level of neutrophils (Table 1). The erythrocyte sedimentation rate (ESR) was 16 mm over one hour (normal range: 1–15 mm/h). The hepatic (assessed by serum transaminases) and renal (assessed by urea, creatinine and urinary summary examination) functions were within normal limits (Table 2). The C-reactive protein was within the normal range, reflecting that the local inflammatory process had no systemic resonance. The electrolytes were within normal limits (Table 3).

Table 1. Patient's complete blood count test and reference intervals according to age.

Types of Blood Cells	Number of Cells per μL	Reference Interval (Number/ μL)
White blood cells	9,520	4,000–10,000
Lymphocytes	1,950	500–4,000
Monocytes	360	150–1,300
Neutrophils	6,870	1,500–6,000
Eosinophils	330	0–670
Basophils	10	0–130
Red blood cells	4,800,000	3,900,000–5,700,000
Thrombocytes	319,000	150,000–450,000

(Legend: μL = microliter).**Table 2.** Results of blood tests for liver enzymes, renal function and C-reactive protein.

Tests	Results	Reference Interval
Aspartate transaminase	16 U/L	0–45 U/L
Alanine transaminase	8 U/L	0–45 U/L
C-reactive protein	0.98 mg/dL	0–1 mg/dL
Urea	14 mg/dL	0–50 mg/dL
Creatinine	0.43 mg/dL	0.32–0.59 mg/dL

(Legend: U = units; L = liter; dL = deciliter; mg = milligrams).

Table 3. Results for blood levels of electrolytes.

Tests	Results	Reference Interval
Total calcium	9.7 mg/dL	8.8–10.8 mg/dL
Magnesium	1.92 mg/dL	1.7–2.6 mg/dL
Iron	66 $\mu\text{g/dL}$	33–193 $\mu\text{g/dL}$
Potassium	3.9 mEq/L	3.5–5.1 mEq/L
Sodium	140 mEq/L	136–146 mEq/L

(Legend: dL = deciliter; mg = milligrams; mEq = milliequivalents).

The treatment of the AR was local, with rivanol antiseptic solution compresses, and systemic, with hydrocortisone hemisuccinate 225 g/day for 5 days, followed by oral administration with gradual daily dose reduction. The remission was complete in 14 days.

Discussion

Post-vaccine ARs continue to be a concern for the population and medical personnel, who must continue to recommend and administer the vaccines. There is a need for healthcare professionals to have in-depth knowledge when it comes to vaccination, especially the potential unwanted events that can be associated with it. Furthermore, they must recommend adequate interventions in these cases, in order to be able to conduct an appropriate vaccine practice. All this ensures that there is minimal risk to the patient, while also maintaining the faith and trust of the population when it comes to getting vaccinated.

Vaccination practice against diphtheria and tetanus must be continuously carried out at the population level because they are diseases that cannot be eradicated. The etiological agent *Corynebacterium diphtheriae*

continuously circulates in human populations, and *Clostridium tetani* has herbivorous animals as the source of environmental contamination [17,18].

The surveillance system of ARs has favorably showed up to the present that the extensive local side effects have a low frequency after vaccination with the diphtheria and tetanus components, even after repeated administration [12,19,20]. What remains difficult to achieve is the limited possibility of investigating ARs after administering vaccines containing both or one of the two anatoxins.

For the case we presented, the clinical manifestation was most likely an extended local Arthus-type reaction, a consequence of local immune complexes that stimulated an inflammatory response in the tissues where the vaccine was administered (the left deltoid muscle). The patient probably had high levels of antibodies against the vaccine anatoxins, produced following repeated administrations as required by the national vaccination scheme. In order to confirm this mechanism, we would have needed to at least determine the level of the diphtheria and tetanus anti-anatoxin antibodies. Unfortunately, these tests have not been carried out in the investigation despite being available in practice.

Naturally, vaccination induces protection via the immune response; however, this may represent the pathogenic substrate of some ARs [21]. For pathological manifestations, the investigation of post-vaccine anaphylaxis showed an increased amount of IgE against different components or antigens present in the vaccine, which is a type I or immediate hypersensitivity reaction [20]. An investigation of extensive local reactions revealed the involvement of type III hypersensitivity reactions, mediated by immune complexes, or type IV, mediated by local infiltrates with T lymphocytes identified at the vaccine administration site [12]. The differentiation of the pathogenic substrate is the criterion used in subsequent recommendations to contraindicate further vaccination. For immediate hypersensitivity reactions, vaccination must be subsequently contraindicated, while for manifestations of delayed hypersensitivity, vaccination may be continued, but with vaccine doses distanced over a period of 10 years [17,18,20]. The extent of the local inflammatory process can also be investigated by evaluating the pro-inflammatory cytokines that are locally released and which contribute to the extension of the local process [21]. These tests, which depend on the laboratory equipment, were not performed for the present case.

We consider it essential to investigate the pathogenic substrate of the extended local adverse reaction and to consequently achieve a comprehensive diagnosis, justified both for the medical aspect, but also for making the most appropriate medical decisions for the patient based on medical evidence. The recommendation is to individualize the medical decision according to the specifics of each case. The investigation should also include documentation of other possible causes for the clinical manifestation than the vaccine or vaccination, in the form of a well-structured differential diagnosis [11–14].

For the present case, the mild neutrophilia and the local axillary adenopathy supported the extent of the immune response developed by the patient after vaccination. At the same time, the patient's medical history included clinical manifestations of immediate hypersensitivity, and he was under chronic treatment with corticosteroids. Mild neutrophilia may have been secondary to chronic corticosteroid treatment. There are several factors that have been found to be associated with neutrophilia following corticosteroid treatment: specific bacterial species that excessively recruit neutrophils, chemokines and pro-inflammatory cytokines that increase the recruitment of neutrophils, high levels of leukotriene B₄, with chemoattractant and pro-survival properties for neutrophils, and the inhibition of neutrophil apoptosis [22]. However, in medical practice neutrophilia is mostly associated with an underlying disease rather than corticosteroid treatment in

hospitalized patients [23]. In order to establish this, it would have been necessary to repeat the blood tests and to monitor the patient for a longer period.

The advantages of the analysis and discussion conducted through multidisciplinary consultation are objectivity in data interpretation, the disponibility of all medical data on the case, including the results of the investigations from the preliminary stages. On the other hand, the limits of such an analysis are the inability to clinically check for local lesions and to carry out further investigations for a complete diagnosis. Only investigations that are made available to the multidisciplinary committee are evaluated, and it may be that other investigations have been carried out or other medical events have been present without being made available.

These aspects suggest the need for a larger-scale investigation than the routine ones, of each post-vaccine AR case, in order to gain sufficient evidence to scientifically support the actual causal relationship.

Conclusions

We presented the case of an extended local AR associated with vaccination with diphtheria and tetanus anatoxins. The investigation should have included supplementary laboratory tests (plasma concentration of antibodies against diphtheria and tetanus anatoxins and the level of pro-inflammatory cytokines).

It is highly important that post-vaccination adverse effects are properly reported and analyzed. Having a solid understanding of these events can help improve both the immunization process and the product itself, lowering the risks associated with such an act even more. Vaccine recommendations must be personalized for the patient according to the investigation results of the individualized case. Only a good knowledge on the post-vaccine AR leads to a correct and complete diagnosis and a proper medical attitude, and thus helps to restore public confidence in vaccines and vaccinations.

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