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Niepożądane odczyny poszczepienne u dzieci hospitalizowanych w latach 1999-2009

Vaccine adverse effects of children hospitalized during 1999-2009

Streszczenie

Wstęp. Szczepienia ochronne wiążą się z ryzykiem występowania niepożądanych odczynów poszczepiennych (NOP). W 1991 roku WHO wprowadziło nadzorowanie NOP.

Cel. Celem pracy była analiza epidemiologiczna dokumentacji medycznej wszystkich dzieci hospitalizowanych w Wojewódzkim Specjalistycznym Szpitalu Dziecięcym w Kielcach z rozpoznanym Niepożądanym Odczynem Poszczepiennym.

Materiał i metody. Przeanalizowano dokumentację 29 dzieci hospitalizowanych w latach 1999-2009 z powodu NOP, które otrzymały do trzech szczepionek jednoczasowo o charakterze poliwalentnym. Wyniki opracowano statystycznie.

Wyniki. Stwierdzono, że 64 szczepionki mogły być jego przyczyną: 19 przeciwko Polio; 18 skojarzonych pełno komórkowych przeciwko błonicy, tężcowi, krztuścowi DTP; 10 przeciwko Haemophillus influenzae typu B; oraz po 5 skojarzonych: Infanrix Hexa i DTPa oraz przeciwko Pneumokokom, przeciwko WZW B, przeciwko Rotawirusowi i odrze. Były to drugie i trzecie dawki wg kolejności podawania. Stwierdzono następujące rodzaje NOP: epizod hipotoniczno-hyporeaktywny (HHE) i ciągły płacz dziecka u 7 dzieci, drgawki gorączkowe u 6, drgawki niegorączkowe u 4. U 7 dzieci rozpoznano choroby współistniejące po szczepieniu (zapalenie płuc u 2, zapalenie gardła u 2, zakażenie układu moczowego u 2 oraz u jednego dziecka nieżyt żołądkowo-jelitowy). Wyleczenie pozwoliło kontynuować szczepienia.

Wnioski. Szczepionki Polio, DTP i HiB były najczęstszą przyczyną NOP pod postacią epizodu hipotoniczno-hyporeaktywnego, ciągłego płaczu dziecka i drgawek gorączkowych. Nie stwierdzono dodatniej korelacji między liczbą podanych składników w szczepionkach a częstością NOP. Wszystkie dzieci z NOP wyleczono bez czasowego lub trwałego zdyskwalifikowania z kontynuacji szczepień i zalecono mniej reaktogenną szczepionkę acelularną DTPa. Należy dążyć do rzetelnej rejestracji NOP, również, gdy pacjenci z tego powodu nie wymagają hospitalizacji.

Słowa kluczowe: szczepionka, niepożądany odczyn poszczepienny, bezpieczeństwo szczepień, profilaktyka zakażeń.

Abstract

Introduction. Protective vaccines are linked with the risk of Adverse Events Following Vaccinations (AEFV). In 1991, WHO introduced AEFV supervision.

Aim. The aim of the work was the epidemiological analysis of the medical documentation of all hospitalized children in the Kielce Voivodeship Children's Hospital with diagnosed AEFV.

Material and methods. The documentation of 29 children who received polyvalent vaccinations and were hospitalized due to AEFV from 1999 to 2009 was analyzed and the results were statistically analyzed.

Results. Medical records of 29 patients hospitalized with a diagnosis of AEFV. It was found that 64 of the vaccine may be the cause of AEFV: 19 were against Polio; 18 followed diphtheria, tetanus, and whole-cell pertussis vaccine (DTP); 10 after Haemophilus influenzae type B; five following each, INFANRIX hexa and DTaP and pneumococcus, hepatitis B virus, rotavirus and measles vaccines. These were second and third doses according to the sequence of administration. It was the following types of AEFV: hypotonic-hyporeactive episode (HHE) and continuous crying in seven, febrile convulsions in six, non-febrile convulsions in four. Seven children presented co-existing diseases after vaccination (pneumonia in two, pharyngitis in two, urinary tract infection in two, and viral gastroenteritis in one child). Recuperation allowed further vaccination.

Conclusions. Polio, DTaP, and Hib vaccines most frequently caused AEFV (HHE, continuous crying, and febrile convulsions). A positive correlation between the number of vaccine components and AEFV frequency was not evident. All children with AEFV were cured without temporary or permanent disqualification from continued vaccinations, while a less reactogenic DTaP vaccine was recommended. We encourage registration of AEFV, even when patients do not require hospitalization.

Keywords: vaccine, adverse events following vaccination, vaccination safety, infection prophylaxis.

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INTRODUCTION

The basic prophylactic elements for contagious diseases are protective vaccines (a form of active immunization). Vaccines induce immune cells to memory, which produce specific antibodies upon exposure [1].

In Poland, the foremost legal document defining protective vaccine organization is the Act of December 5, 2008, in effect since January 1, 2009. The act defines the rights and duties of providers and beneficiaries, while presenting legal regulations of vaccination. It specifies the types and scopes of vaccines, the principles of production and funding, and distinguishes between compulsory, recommended, and voluntary vaccinations [2,3].

Adverse Events Following Vaccinations (AEFV) is a set of symptoms temporarily associated with a vaccination that occur within 4-weeks of vaccine administration. WHO defines AEFV depending on symptom intensity: mild, moderate, bad, or serious [4].

Specific vaccinations are characterized with specificity in triggering off characteristic adverse events (AE) following vaccinations. Recently, in Poland we observed about 800 cases of AEFV (annual registration), but only some were serious. The risk of AEFV occurrence is incomparably smaller than the risk of falling ill with a contagious disease, which has the possibility of immunization by means of vaccination [5,6].

In 1990, WHO recognized the registration of AEFV as an important part of national health programs and recommended their monitoring. Based on the most recent studies and publications, WHO recommends a list of symptoms and time intervals linked with the occurrence of AEFV and highly recommends reporting [2]. In Poland, a system for monitoring AEFV has been in force since 1994. It entails compulsory reporting of AEFV by doctors to the regional disease control center where preliminary analysis and sending of AEFV reports to the National Hygiene Institute takes place. Early reporting of AEFV may save subsequently vaccinated people from potential threats to life and health, because reporting may be a basis for recalling a faulty vaccine by justification with a great number of AEFV notifications in a short time or a single AEFV of a serious nature [7].

AIM

The aim of the work was the epidemiological analysis of the medical documentation of all hospitalized children in the Kielce Voivodeship Children's Hospital from 1999 to 2009 with diagnosed AEFV.

MATERIAL AND METHODS

In retrospective studies, we used the medical history of 29 hospitalized children with diagnosed AEFV with the consent of the hospital director. We analyzed the causes, character, type, and symptoms of AEFV; hospitalization time; demographic traits (sex, age, and place of living); vaccines suspected of causing AEFV; number of vaccine components; vaccination schedule; irregularities in examinations (physical, additional, coexisting diseases); result and final recommendations of treatment; and continuation of vaccination. AEFV diagnosis and category qualification were based on the Resolution of the Health Minister dated December 23, 2002.

All children qualified to vaccinations were healthy. None had symptoms of acute disease or exacerbation of chronic disease (a contraindication) and no description of a serious chronic disease was made, all of which would increase risk of AEFV occurrence. The results were statistically analyzed using the chi-square test for examining the correlation for non-measurable traits in double classifications (two-part tables) and for examining the distribution diversity of numerousness in case of single classifications. P values <0.05 were adopted as statistically significant.

RESULTS

The 29 examined children with AEFV (100%) were appropriately vaccinated in conformity with recommendations defined in the Protective Vaccinations Program for the given year. Fourteen (48.3%) boys and 15 (51.7%) girls were hospitalized. Fifteen (51.7%) were rural inhabitants and 14 (48.3%) were urban. No statistically important correlation was found between AEFV occurrence and sex or place of living. AEFV occurred before the 3rd month of life in 10 children, between the 4th and 6th month in 11, between 7th and 12th in two, and after 13 months in six. No statistically significant distribution between age groups was found ($p=0.0719$).

Children with AEFV simultaneously received one to three vaccines, most of which were polyvalent, that is why the maximal number of vaccine antigens administered during the vaccination among the analyzed cases amounted to eight. It was established that 64 (100%) vaccines may have caused AEFV – 19 (29.6%) were against Polio; 18 (28.2%) followed diphtheria, tetanus, and whole-cell pertussis vaccine (DTP); 10 (15.6%) after Haemophilus influenzae type B; five (7.8%) following each, INFANRIX hexa and DTaP; three (4.7%) pneumococcus, two (3.1%) hepatitis B virus, and one (1.6%) secondary to each, rotavirus and measles. The analyzed case histories did not differentiate inactivated polio vaccine (IPV) from oral polio vaccine (OPV) since the questionnaire used did not discern them (Figure 1).

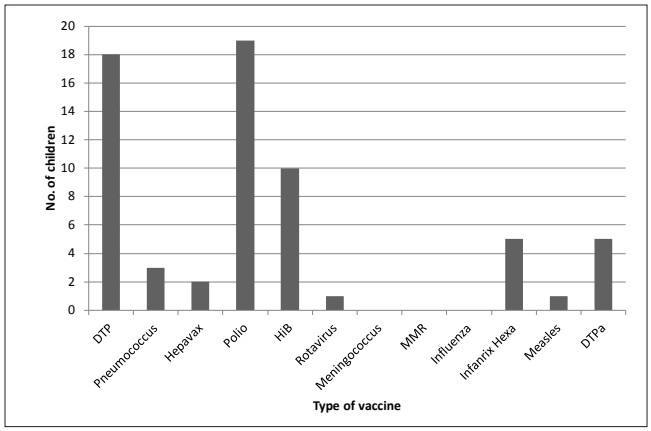

FIGURE 1. Type of vaccines suspected of causing AEFV in children hospitalized in the Kielce Voivodeship Children's Hospital (1999-2009).

When analyzing the correlation between the number of vaccine components and AEFV occurrence in the described children, we found that AEFV were most often caused by four- and five-component vaccines in 13 (45%) and eight (28%) cases, respectively. The distribution of AEFV occurrence and the number of components proved to be statistically significant (p=0.0002) (Table 1).

TABLE 1. Number of components in vaccines suspected of causing AEFV in children hospitalized in the Kielce Voivodeship Children's Hospital (1999-2009).

Number of vaccine components	Number of children (%)
1	1 (30)
2	0 (0)
3	2 (7)
4	13 (45)
5	8 (28)
6	0 (0)
7	4 (14)
8	1 (3)
9	0 (0)
Total	29 (100)
P-value for chi-square test p=0.0002	

We also analyzed AEFV occurrence secondary to dose of a given vaccine. The second dose of a given vaccine led to 11 (38%) cases of AEFV and after the first dose in nine (31%) children. No statistically significant correlation was found (p=0.2108) in the occurrence AEFV and subsequent dose of a given vaccine.

In terms of vaccination order (according to vaccination schedule) we found that the third vaccination caused AEFV 11 (38%) times and the second eight (28%) times.

In the analyses of AEFV types, we found hypotonic-hyporeactive episode (HHE) and continuous crying in seven (24%), febrile convulsions in six (21%), and non-febrile convulsions in four (14%). We found a statistically significant diversification (p=0.0459) of the type of adverse event following vaccination (Figure 2).

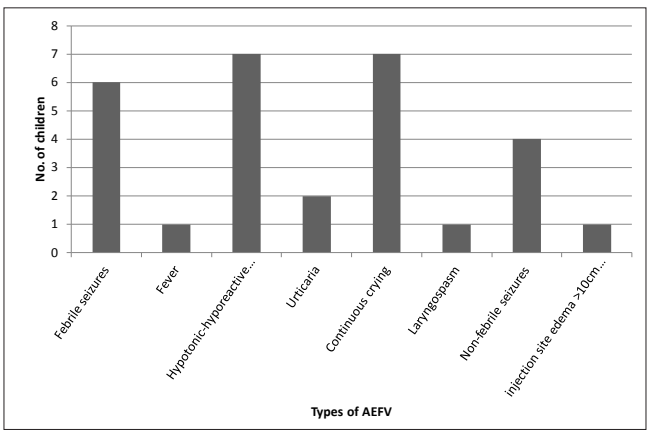

FIGURE 2. Types of AEFV among children hospitalized in the Kielce Voivodeship Children's Hospital (1999-2009).

While evaluating irregularities in physical examinations of 26 (89.7%) children, we found 56 irregularities. The most frequent were anxiety, dehydration requiring parenteral fluids, and fever in 18 (62%), 11 (38%), and eight (28%) children, respectively (Figure 3).

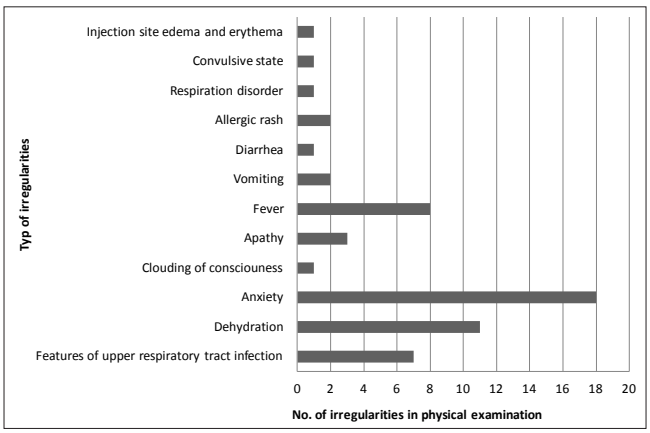

FIGURE 3. Type and number of irregularities occurring in the physical examination of children with AEFV hospitalized in the Kielce Voivodeship Children's Hospital (1999-2009).

Additional examinations revealed abnormalities in 18 (62%) children – altogether 27 abnormalities, most often an elevated level of leukocytes was observed in 17 (59%) (Figure 4).

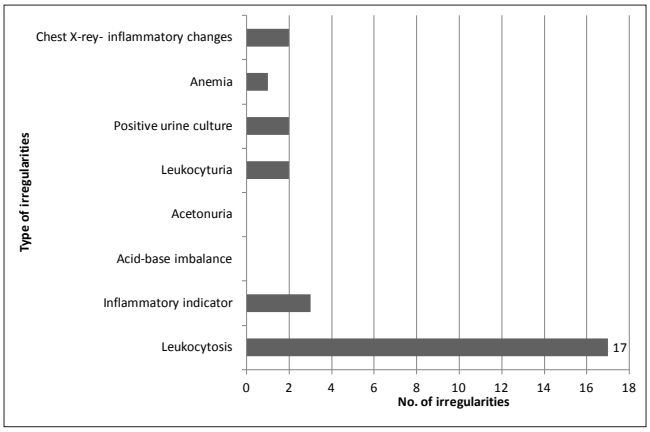

FIGURE 4. Type and number of irregularities occurring in additional examinations of children with AEFV hospitalized in the Kielce Voivodeship Children's Hospital (1999-2009).

In the group of 29 (100%) children with AEFV, seven (24%) had coexisting diseases diagnosed (pneumonia, pharyngitis, urinary tract infection, and viral gastroenteritis in two, two, two, and one respectively). These were acute diseases with symptoms appearing after vaccination. The hospitalization lasted from two to 10 days – most frequently three days in eight (27%) children and four days in six (20%) children (mean 4.5 days). During evaluation of treatment effects there were no deaths and no complications upon hospital discharge. In addition, there were no disqualifications from further vaccinations and no temporary vaccination interruptions. For 18 (62%) children we recommended vaccinations with an acellular pertussis vaccine based on a lower occurrence of AEFV in comparison to the whole-cell variant. In two (7%) children, we recommended continuation of vaccinations in hospital conditions, due to parents' fears about AEFV after subsequent vaccination.

DISCUSSION

WHO, in its evaluation of vaccinations worldwide, stated an elevated proportion of vaccinated people in Poland compared to other countries. European Union data from 2003 and 2004 substantiated that Poland and Denmark had the highest indicator of vaccinations. Vaccinations provide potential for community resistance and programs require eradication of particular contagious diseases [8]. Safe vaccination preparations are applied fearlessly and confidently motivate for vaccinating healthcare workers and the parents of the children. In Poland, vaccine safety relies on the full cooperation of institutions responsible for their organization, performance, and supervision [9].

In our studies concerning AEFV in children, it was shown that only 29 children presented the necessity for hospitalization. However, one should remember that some events following vaccinations meet the criteria of AEFV, but due to their mild character do not require hospitalization and therefore are very often not reported. Most AEFV are of a mild course and do not leave permanent outcomes, however, they should not be ignored. Serious AE occur very rarely, but their character and intensity may cause a threat to life. Consequently, in the process of reporting AEFV, one should pay more attention to the classification of these AE due to their severity.

It was stated that among 64 vaccines suspected of triggering AEFV, the most suspected ones were polio vaccine in 19 (29.6%) and DTP in 18 (28%) cases. When analyzing the number of AE following polio vaccine we were unable to differentiate reactions caused by OPV or IPV, because the questionnaire used until December 2010 did not discern them. In the subject literature, there is an emphasis put on AE following poliomyelitis vaccines, especially OPV containing attenuated poliovirus. One complication after its application may be flaccid paraplegia, qualified in 1997 by WHO as Vaccine-Associated Paralytic Polio (VAPP). Annually, between 1980-1996, 8-9 cases of VAPP were reported to the Centers for Disease Control and Prevention (CDC). According to CDC, the frequency of VAPP occurrence in USA and other well-developed countries is one case per 2.3 million OPV doses. They occur most frequently after the first dose of OPV [10]. In Poland, between 1996-2000, 18 general AEFV were reported to the Department of Epidemiology of the National Institute of Hygiene after application of OPV; eight febrile AE; 17 cases of acute diarrhea and one case of VAPP in the form of flaccid paraplegia. In 2000, WHO reported five serious AEFV after administering OPV. In 1996, the Advisory Committee on Immunization Practices (ACIP) took into consideration the number of VAPP and the lack of poliomyelitis illnesses to recommend a change in the vaccination schedule to IPV then OPV, because IPV does not cause VAPP. More often, however, there is a need to substitute the whole schedule with the safer IPV [11,12].

The most frequent cause of AEFV, besides polio vaccine, was associated with the diphtheria, tetanus, and whole-cell pertussis vaccine (DTP). This vaccine was suspected of causing AEFV in 18 children (62%). It should be mentioned that, in the studied group, vaccines containing the acellular pertussis antigen (DTaP and INFANRIX hexa) caused only five (17%) cases of AEFV each. In Poland, DTP containing whole-cell Bordetella pertussis killed with formaldehyde was introduced in 1960. To date, it plays a fundamental role in pertussis prevention in children; distinguished by high immunogenicity but contains endotoxins and other antigens of B.pertussis that contribute to AEFV occurrence. In 2006, the total number of vaccinated people in Poland amounted to 204,035, in which AEFV occurred in 183 after DTP administration. Two of these cases were in the Świętokrzyskie Voivodeship. Whereas in 2007, among 210,943 vaccinated in Poland, 234 presented AEFV after DTP, eight of which were reported in the Świętokrzyskie Voivodeship [13]. Australians consider DTP especially reactogenic; it contains whole-cell pertussis. In a group of 469 children with AEFV, they reported as many as 90% linked to DTP. Between 1992 and 1995, the studies carried out in Sweden revealed that both local and general AE are less intense after application of DTaP in pertussis prophylaxis [2,13].

The analysis of vaccine components studies did not prove correlation between them and the frequency of AEFV occurrence with special consideration for multicomponent vaccines. Some authors state that, since adequate vaccination requires numerous doses (most often injected) of a given vaccine requiring more than 30 vaccinations, the application of combined vaccines allows a decrease the number and frequency of applications. It also decreases stress in the child and parent, but does not influence the decrease in AEFV occurrence frequency [2].

The most frequently reported forms of AEFV in our study were hypotonic-hyporeactive episode (HHE), continuous crying, and febrile convulsions. The studies of authors from Italy and Sweden also stated the most frequent forms as HHE, febrile convulsions above 40˚C, and continuous crying [14]. The statistics of AEFV in the Cracow Voivodeship Clinic of Protective Vaccinations from 1997 to 2002 also described HHE as dominating, especially after vaccination with a whole-cell DTP [15]. According to the data of the Protective Vaccinations Consulting Clinic of the Mother and Child Healthcare facilities in Łódź, AEFV dominated in the form of local AE and fever, but the patients did not require hospitalization. However, those requiring hospitalization had AEFV in the form of febrile convulsions, continuous crying, and HHE [13]. At present, in the Świętokrzyskie Voivodeship, there is no Protective Vaccinations Consulting Clinic. Undoubtedly, this makes registration of mild post-vaccination reactions and AEFV difficult, which creates difficulty when conducting comparative studies with other centers in Poland.

Among the 29 (100%) children with AEFV, 18 (62%) showed abnormalities in additional studies; most frequently leukocytosis. However, since the level of leukocytes may increase secondary to stress, infection, and/or convulsions it is difficult to discern whether the cause of the resulting leukocytosis was the vaccination or the consequent AEFV.

In seven out of 29 children with AEFV, we diagnosed coexisting diseases: pneumonia, pharyngitis, urinary tract infection, or viral gastroenteritis, in two, two, two, and one, respectively. We may expect that the accompanying infectious symptoms, which occur independently from the vaccination, may speed up AEFV development. In scientific

literature, however, we have not found convincing data confirming this thesis. Until December 31, 2010, the AEFV questionnaire lacked distinction between OPV and IPV complicated the retrospective analysis of AEFV.

After treatment, all hospitalized children were discharged without complications. However, revaccination in hospital conditions was recommended for two children because of parents' concern about the consequences of subsequent vaccination. The majority, 18 (62%), of children continued vaccinations with the less reactogenic acellular pertussis variants. The Advisory Committee on Immunization, American Academy of Pediatrics, and American Academy of General Practitioners make similar recommendations. They also recommend acellular pertussis vaccinations in children with central nervous system damage and those in whom AEFV occurred after previous administration of DPT and polio vaccine [13].

On January 1, 2011 the directive of the Ministry of Health dated as of December 21, 2010 became binding, on the issues of undesirable AE following vaccinations and criteria of their diagnosis. Changes concern among others the type and criteria of diagnosis of undesirable AE following vaccinations and a new reporting form was introduced. In the new form of reporting AEFV, in the part concerning vaccines suspected of triggering the AE, we applied a division of vaccines into OPV and IPV vaccines. The lack of this division in the previous form made analysis of AE following the polio vaccination difficult. The severity of AEFV progression was also introduced and divided into three types: serious, bad, and mild. This verification is recommended by WHO. Before the latest regulations, it was difficult to retrospectively analyze severity of AEFV progression [2,4,16].

CONCLUSIONS

1. Polio, DTaP and Hib vaccines most frequently caused AEFV (HHE, continuous crying, and febrile convulsions).
2. A positive correlation between the number of vaccine components and AEFV frequency was not evident.
3. All children with AEFV were cured without temporary or permanent disqualification from continued vaccinations, while a less reactogenic DTaP vaccine was recommended.
4. We encourage registration of AEFV, even when patients do not require hospitalization.

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