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REVIEW ARTICLE

The Influence of Vaccine on Febrile Seizure

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Abstract: ***Background*:** The protective value of vaccines to the public has made vaccines among the major public health prophylactic measures through the entire history. However, there has been some controversy about their safety; particularly concerns have been rising about febrile seizures (FS). Vaccination was found to be the second most common cause of FS.

***Methods*:** We research and collect relative online content for reviewing the effects of vaccine in FS.

***Results*:** there is no causal relationship between FS and vaccination. This relationship is complex by other factors, such as age, genetic inheritance, type of vaccine, combination of different types of vaccines and the timing of vaccination.

***Conclusion*:** In order to reduce FS after vaccination, it is important to understand the mechanism of epilepsy and relationship between specific vaccines and FS. Parents should be informed that some vaccines could be associated with an increased risk of FS, particularly, in children with personal and family history of FS. Children with genetic epilepsy syndrome are prone to seizures and certain vaccinations should be avoided in these children. It is highly recommended to choose vaccines with lower risk of developing FS and to administer these vaccines during the low risk window of immunizations schedule.

Keywords: Vaccine, febrile seizure, genetics, epilepsy, neuron, GABA.

1. INTRODUCTION

Immunization is a very effective public health prophylactic intervention [1]. Childhood vaccinations have reduced the morbidity and mortality attributable to many infectious diseases worldwide [2]. Vaccination was found to be the second most common cause of febrile seizures (FS) [3, 4]. Vaccine-induced FS are defined as seizure occurring within 72 hours of vaccination. Chronic FS have been found to be a risk factor for development of Epilepsy which accounts for 1.16 sudden deaths per 1000 people annually [3]. In addition, there have been concerns about the risk of childhood vaccine-induced encephalopathy and epilepsy [3-5].

The relationship between vaccination and development of epilepsy during infancy has been controversial for a long time. Many studies focused on vaccine-related adverse events [6-8]. Vaccine side effect is an allergic reaction. The common side effects include mild fever, shivering, fatigue, headache, muscle and joint pain. However, none of these studies supported a causal relationship between vaccination and permanent neurologic injury. Although the mechanism of FS remains unclear, animal models are informative, it has been found that elevated brain temperature could affect neuronal functions and cytokine, and cause the seizure. The genetic mutation was also related to the seizure following vaccination in animal model [9, 10].

Owing to concerns of some people about the side effects of vaccination, they refuse to accept vaccination of their children. Consequently, there have been outbreaks of preventable infectious diseases in the developed countries. For instance, few cases of measles were reported in France during 2006 and 2007, but this number has escalated to more than 22000 cases in France during the period of 2008-2011 [11].

Recently, vaccinations have improved extensively. For example, the usage of whole cell vaccines was replaced by cellular vaccines to reduce the risk of the adverse effects. Vaccines are currently much safer than before. Nonetheless, post vaccination seizures remain a debatable side effect. Here, we will review the association of FS with vaccine administration and the other risk factors of FS following vaccination in children.

2. RISK OF FS AFTER VACCINATIONWITH MMR, DTP, TIV AND PCV13 VACCINE

Although, FS episodes are not usually associated with severe neurologic diseases [12], vaccine-induced FS could be a problem, particularly in genetically predisposed children [13-16]. Several types of vaccines were related to increased

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risk of FS, including measles-containing vaccines (MMR) [17, 18], whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTP) [19], some formulation of inactivated influenza vaccines (TIV) [20], and the 13-valent pneumococcal conjugate vaccine (PCV13) [21].

2.1. Relationship between MMR and FS

Measles, mumps, and rubella are common congenital viral infections that are harmful to non-immune pregnant women and have teratogenic effects on fetuses/neonates [22]. These diseases can be effectively prevented by MMR vaccination avoiding their many complications [23].

FS can be induced by viral infections or as an adverse reaction to alive-virus vaccines such as MMR vaccination [24-26]. In previous large epidemiologic studies, MMR vaccine increases the risk of FS, particularly, in two weeks following MMR vaccination [27, 28].

Farringto *et al.,* showed that the rate of FS episodes following MMR vaccination in children was 33 per 100000 [29]. Barlow *et al.*, in a large cohort study of more than 34000 MMR vaccinations in children younger than six years old, found that FS were most common after 8-14 days post vaccination [30]. They both found that MMR vaccinations resulted in 3-4 additional cases of fever-free seizure or FS per 10000 doses of vaccine.Vestergaard *et al.,* aimed at assessing the incidence and the risk of developing FS following MMR vaccination. They evaluated 53000 children who were immunized with the first dose of MMR at 15 month age, and found that 973 children were ascertained with FS within 2 weeks of vaccination. This rate of FS was higher than the rate in the control group [27]. Miller *et al*., evaluated almost 900 children at the age of 12-23 month, and found that the incidence of FS was increased on the 6-11days following MMR vaccination, with no increased risk in the 15-35 days [31]. They showed that the risk of FS following vaccination was not higher than that caused by other reasons.

Despite that these studies provided some evidence that MMR vaccine might increase the risk of FS, the mechanism of this phenomenon is still not clear. Thus, further research is needed to explain this association and provide solutions to resolve this problem. Meanwhile, it is safer to avoid providing MMR vaccine to children with previous FS.

2.2. Relationship between DTP and FS

Pertussis is an acute infectious disease caused by the bacterium *Bordetella pertussis*, and was a major cause of morbidity and mortality among infants and children before the introduction of vaccination [32]. Since the use of the DTP vaccine, the incidence of pertussis was decreased by more than 80% [33].

Administration of DTP is associated with adverse effects, such as pain, redness, swelling, and even epilepsy [34]. Lately, many studies showed an increased risk of FS following DTP vaccination; Farrington *et al.* showed that FS were three times more frequent in the 3 days after DTP vaccination in a large cohort study [29]. Barlow *et al*., analyzed more than 34000 DTP vaccinations, and demonstrated that FS occurred six times on the same day of vaccination [30].

The whole-cell DTP vaccine is associated with a high frequency of adverse reactions, such as fever and FS, whereas acellular vaccine accounted for a lower rate of adverse reactions. The rate of FS following use of acellular vaccine was 1 per 19496 vaccinations, while the rate for whole-cell vaccine was 1 per 2835 [34]. David *et al*., studied 15069 children who received whole-cell DTP and 23069 children with acellular vaccine. Two in the whole-cell DTP group and one in a cellular vaccine group were identified with FS, respectively [35].

Those data showed that children immunized with DTP had a higher risk of FS, although the mechanism for this was not explained. This increased risk might be related to the high incidence of fever after vaccination [36]. Some studies showed that the risk of FS would decrease if children were immunized with DTP during 2-4 months of age [37].

2.3. Relationship between TIV and FS

Influenza viruses are among the most common causes of human respiratory infections, which may cause high morbidity and mortality [38]. The worst pandemic on record, in 1918, killed approximately 50 million people worldwide [39]. Infants and children are more prone to an increased risk of severe disease from influenza virus infection [40]. Influenza vaccination is a recommended universal-annual vaccination for infants and children aged 6 months and above in many countries [41].

US Vaccine safety datalink program research found only one documented FS in 3 days following administration of 69359 doses of TIV to children under 2 years of age (1.4 per 100000) [42]. Although TIV had a good record of safety, 2010 Southern Hemisphere vaccine, produced by CSL Biotherapies, showed that the risk for FS was up to 9 per 1000 doses in young children [43]. According to these findings, Advisory Committee on Immunization Practices (ACIP) does not recommend the U.S.-licensed CSL Biotherapies TIV for children aged <9 years.

The risk of FS is different following different batches of TIV vaccine.This suggests that the designer of vaccine must reduce the vaccine adverse effect to minimum before clinical utilization.

2.4. Relationship between PCV13 and FS

Pneumococcus is a common cause of invasive bacterial infection [44], it is often mild but can cause serious symptoms, lifelong disability, or death. Children younger than 2 years of age are at a higher risk of this disease [45]. The best way to protect against pneumococcal disease is by pneumococcal vaccine (PCV13) administration [46].

During the period from 2010 to 2011, a study of 497979 PCV13 vaccines was administered among children 6-59 months of age. This study showed that 78 cases were confirmed with FS due to, potentially, exposure to PCV13.The attributable risk estimates for PCV13vaccine were 1.22 per 100000 doses at 260 weeks and 9.23 per 100000 doses at 72 weeks [47].

These studies demonstrated that PCV13 was associated with a significant risk of FS. Probably, a research finding a

new pneumococcal vaccine with a lower risk of FS will provide a solution to this problem.

3. EFFECTS ON THE RISK OF FS FOLLOWING VACCINATION

A number of studies have refuted a causal link between vaccination and seizure [37, 48]. Other studies suggested several factors linked to the increased risk of FS after vaccination, including the age, genetic inheritance, type pf vaccine, time of vaccination, and interactions between different vaccines [12, 15].

3.1. Effect of Age on the Risk of FS Following Vaccination

Childhood vaccinations mildly increase the risk of FS in the general pediatric population, during specific risk periods [49]. Owing to concerns of parents about safety of vaccinations, many children were delayed in receiving their immunization schedules recommended by the ACIP [50, 51].

The Vaccine Safety Datalink (VSD) data demonstrated that the highest excess risk of FS appeared to be in children aged 12-23 months who were immunized with the first dose of TIV during the 2010-2011season, and the peak of risk appeared at the age of 16 month following TIV and PCV 13 vaccination [47]. The US advisory committee on immunization practices continues to recommend influenza and pneumococcal conjugate vaccination in young children using the existing schedule [52]. Sun *et al.*, enrolled 378834 children immunized Dta-IPV-Hib, 7811 children were diagnosed with FS before 18 months, found that a higher risk of FS was on the day of first and second vaccination at 3 and 5 months age [37, 53]. A cohort of 323247 US children analyzed the association between the timing of childhood vaccination and the first occurrence of seizure in the first 2 years of life. There was no association between the timing of infant vaccination and post-vaccination seizures in infants. In the second year of life, delaying MMR (MMRV) vaccine past 15 months of age results in a higher risk of seizures [54]. These findings suggest that on-time vaccination is as safe as delayed vaccination in the first year of life, and that delayed vaccination in the second year of life is associated with more post-vaccination seizures than on-time vaccination [55, 56].

These studies emphasized the importance of timely immunization of children, and suggested that the risk of post-immunization FS could be decreased by timely vaccination. ACIP also recommends simultaneous vaccination for age-appropriate vaccines [57].

3.2. Effect of Genetics on the Risk of FS Following Vaccination

Seizures have a familial tendency, suggest that genetic elements may contribute to their generation [58]. Vaccination might precipitate adverse events in children with genetic epilepsy syndrome [59]. In a medical database of 990 children with seizures after vaccination, follow-up was available for 23 of 26 children with epilepsy onset after vaccination. Twelve children developed epileptic encephalopathy, eight had benign epilepsy, and three had encephalopathy before seizure onset. Underlying causes were identified in 15 children (65%) and included *SCN1A*–related Darvet syndrome (DS) or genetic epilepsy with FS plus syndrome (n = 8 and n = 1, respectively), a protocadherin 19 mutation, a 1qter microdeletion, neuronal migration disorders (n = 2), and other monogenic familial epilepsy (n = 2) [60].

In another study, a cohort of 77 children with DS and *SCN1A* mutations, demonstrated that children with vaccination associated seizure onset were significantly younger at first seizure than those without vaccine–association seizure onset [61]. There is a need to select vaccines that carry lower risk of FS in these children who are particularly prone to develop FS.

The general risk gene loci linked to higher risk of seizures in those patients who specifically experienced vaccine-associated seizures. Feenstra *et al.,* analyzed the genotypes of 929 cases of MMR related FS and 1070 MMR-unrelated FS, and identified that common genetic variant was associated with both MMR-related and MMR-unrelated FS.Two loci were specifically associated with MMR-related *FS.IFL44L*, an interferon-stimulated gene, is upregulated by viral infections such as measles; CD46 encodes a membrane protein that has several functions such as a cellular receptor for measles virus.There are additional 4 genetic loci significantly associated with FS: *SCN1A* and *SCN2A* are two potential loci, the third locus is associated with serum magnesium level, and the fourth locus is ANO3, without the gene, rats have low proportion of temperature-sensitive neurons [62].

In order to prevent the potential encephalopathy described in certain patients with gene mutation, it is important to study the interaction between genes and the vaccines which could lead to FS. It does not mean that the children who are prone to develop prolonged FS cannot receive vaccination.They should try and select vaccines that carry a lower risk of seizures.

3.3. Effect of Vaccine Type on the Risk of FS Following Vaccination

In a previous study, it was shown that the risk of FS depends on the vaccine type as well [63]. The risk of FS was increased after whole cell pertussis (DTP), measles containing vaccinations.The rate of FS was approximately 1 per 20000 doses in infants, whereas this figure increased to 6-9 and 25-34 per 100000 children following DTP and MMR vaccinations, respectively [30].

Not all the vaccines associated with elevating risk of seizure, there was no evidence of an increased risk of epileptic seizures after vaccination with a monovalent AS03 adjuvanted pandemic H1N1 influenza vaccine. In a cohort of 373398 people who were vaccinated, 859 people experienced epileptic seizures during the study period. There was no increased risk of seizures in people with previously diagnosed epilepsy [64].

Remarkably, Rotavirus vaccination may reduce the risk of seizures. In a study based on VSD data of 250601 infants, 186502 of the children were fully vaccinated and 64099 were not vaccinated with Rotavirus vaccine. In comparison with non-vaccinated children, a full course of Rotavirus vaccination was statistically associated with an 18–21% reduction in risk of a seizure requiring hospitalization or emer-

gency department care in the year following vaccination [65]. Consequently, the authors of similar studies suggested that universal infant Rotavirus immunization protects against childhood seizures in the first years after vaccination [66, 67].

3.4. Effect of Combination Vaccine on the Risk of FS Following Vaccination

Different types of vaccines are frequently given on the same day and may be given in combination formulation [68]. For example, Tdap and TIV can be administered simultaneously [69]. The rational for this is to improve vaccine coverage rates and reduce costs [70]. Nonetheless, adverse effects occur frequently after administration of a combination of antigens when compared with administration of them separately.

For example, MMRV vaccination was associated with a twofold-increase in the risk of FS 7-10 days following immunization, when compared with administration of MMR and varicella vaccines separately [28]. In another study by Jacoben, *et al*., they enrolled 31298 children immunized a new MMRV combined vaccine at the age of 1-5 years, with a follow up 30 days after administration for evaluating the risk of FS [71]. This study proved the results of the previous study. Thus, The American Academy of Pediatrics recommended that MMR and varicella vaccines should be administered separately.

In further research by Zanwill *et al*., they compared 61004 infants vaccinated with a combination of Dtap-HepB-IPV with 58251 infants immunized with Dtaponly from 2002 to 2005 [72]. They demonstrated that the incidence of seizures during the 8-day period after the primary doses of Dtap-HepB-IPV (39%) was higher than the Dtap control (29.4%).

Moreover, the VSD showed that there is an increased risk of FS in young children immunized TIV concomitantly with PCV13 [73]. Before the 2010–11 influenza season, an increased risk for FS after TIV administration has not been observed in the United States. During the 2010-11 season, the risk of FS was significantly elevated 0-1 days after vaccination in children aged 6 months through 4 years. This risk was higher in children who received concomitant PCV13. The vaccine information statement for TIV during the 2011-12 season demonstrated an increased risk of FS in young children following concomitant TIV and PCV13 vaccination.

Despite an increased risk of FS following combination vaccination, it has many advantages. Policy-makers need to balance these findings with the potential benefits of administering the combination vaccine or perhaps leave the choice of vaccination timing to clinicians. Clinicians should explain to the parents the risks and benefits of combination of vaccines.

CONCLUSION

Fever is a recognized side effect of vaccination often associated with seizures. Vaccine-induced FS account for the same rate of FS due to other causes, relatively, carry the same consequences. FS are not frequently associated with downstream complications or severe neurologic diseases [12].

The benefits of vaccination still greatly outweigh its side effects, for example, a total of 27550 pertussis cases and 27 pertussis-related deaths were reported in 2010 [74]. The attributable risk of encephalopathy due to pertussis is, currently, estimated to be between 1 in 1200-12000infections, which is higher than any estimated risk of DTP vaccination. Concerns about the side effects of vaccination resulted in lower rates of immunization, and consequently a higher risk of potentially pandemic infections [75].

Though, newer vaccines with better safety profiles have lowered the risk of vaccine-induced FS [76, 77], their management is still a challenging problem [78].

In order to reduce FS after vaccination, it is imperative to improve public awareness of the true risks and safety profiles of the different vaccinations [79]. In addition, it is important to understand the mechanism of epilepsy and relationship between specific vaccines and FS, now many researches focus on developing drug to control epilepsy and FS [80]. During the epileptic process neuroprotective treatment with antioxidants could lead to less sever structural damages, reduced epileptogenesis and milder cognitive deterioration [81]. Different receptor systems may share the common signal transduction pathways or interacting proteins which may be better therapeutic targets for the development of drugs to effectively control epilepsy [82], and inhibition of TRPV1 in the hippocampus may possibly be a novel target for the prevention of epileptic seizures [83].

Parents should be informed that some vaccines could be associated with an increased risk of FS, particularly, in children with personal and family history of FS [13]. Many factors have been associated with increased the risk of FS as well. Children with genetic epilepsy syndrome are prone to seizures and certain vaccinations should be avoided in these children. It is highly recommended to choose vaccines with lower risk of developing FS and to administer these vaccines during the low risk window of immunizations schedule.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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