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Sudden Infant Death After Vaccination

Survey of Forensic Autopsy Files

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Abstract: Sudden infant deaths might be attributable to adverse reaction to vaccination, but separating them from coincidental occurrences is difficult. This study retrospectively investigated vaccination-related details and postmortem findings for 57 cases of sudden death in children 2 years or younger. Data were extracted from autopsy files at the Department of Forensic Medicine, Tokai University School of Medicine. Vaccination histories were available in 50 cases based on the maternity passbook. Of the 32 cases in which any vaccines were administered, 7 infants (21.9%) had received immunization within 7 days of death. The most frequent vaccine cited as the last immunization before death was *Haemophilus influenzae* B. Although a temporal association of vaccines with sudden death was present for two 3-month-old and one 14-month-old infants in whom death occurred within 3 days of receiving the *H. influenzae* type b and other vaccinations, a definitive relationship between the vaccine and death could not be identified. Histopathological examinations revealed pneumonia and upper respiratory infection as contributing to death in their cases. Moreover, all 3 cases showed hemophagocytosis in the spleen and lymph nodes, which are similar features to hemophagocytic lymphohistiocytosis. Judgment of the disorders as truly related to vaccination is difficult, but suspicious cases do exist. Forensic pathologists must devote more attention to vaccination in sudden infant death cases.

Key Words: Hib, *Streptococcus pneumoniae*, forensic autopsy, histopathology, hemophagocytosis

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Sudden infant death (SID) usually occurs during the course of normal development and before revealing clinical symptoms, unlike cases in adults where the cause of death often can be inferred based on the clinical data and history.[1] Therefore, various disorders from abuse to congenital disease must be differentiated in SID cases.[2] To elucidate the etiological background, a sheet of more than 30 check points of settings has been used in Japan.[3] Vaccination history is included among the major points.

For unknown causes of SID, attributable factors have been sought from various approaches. For instance, forensic autopsy cases of unexpected simultaneous twin deaths have been investigated extensively.[4,5] Roberts[6] demonstrated such a twin death, which occurred a couple of hours after diphtheria, tetanus and pertussis (DTP) vaccination, speculating that the immunization potentially gives a clue for the attributable factors. Another case report described twins found dead simultaneously after combined vaccine including DTP.[7] Forensic autopsy has also revealed sudden death after DTP with mast cell increase as a relation to vaccination.[8] By contrast, several large-scale studies have revealed that increased DTP immunization coverage is associated with decreased sudden infant mortality.[9–14] Therefore, most SID syndrome (SIDS) cases are regarded as merely coincident, with no particular relation to DTP vaccination.[15]

Nevertheless, in 2011, 7 fatal incidents occurred in short order after combined immunization with *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* vaccines in Japan.[16] Because some relation was suspected, vaccination was discontinued temporarily. Based on the Preventive Vaccination Act, Japan has a system to notify the Pharmaceuticals and Medical Devices Agency when a critical side effect is suspected. Forensic pathologists receive detailed knowledge about the circumstances preceding death from police officers, but they usually do not devote much attention to the vaccination history unless parents claim adverse effects of vaccination. The number of licensed vaccines has increased to the present day, and they are administrated simultaneously.[17,18] It might be difficult to show evidence of adverse effect despite their potential incidence.[19] Presumably, most SIDS subjects younger than 6 months should inevitably receive vaccination. However, few data have been forthcoming related to how close to the time of death they were vaccinated and which kinds of vaccines were used.

We retrospectively extracted cases of medicolegal autopsy of death after vaccination from infant autopsy reports of the last 5 years. We first present the rate of death within 28 days after vaccination among SID cases, which include subjects younger than 2 years in the present study. In addition, 3 cases in which infants died within 3 days are described. Suspected adverse reactions are highlighted and explored.

MATERIALS AND METHODS

From autopsy cases conducted at the Department of Forensic Medicine, Tokai University School of Medicine, in 5 years (2013–2017), 57 cases of sudden death in infants younger than 2 years were reviewed, excluding deaths that were reasonably attributable to external causes such as abuse or burns. Data from clinical and laboratory examinations done in the emergency department, investigations conducted by police, the maternity record book, and other materials were used. In Japan, a record of received vaccines is noted in a maternity passbook kept by the mother, which includes all medical and welfare records of the mother and her baby. For this study, we obtained vaccination course information from these passbooks, which were available for all but 7 infants. This project was approved by the Ethics Committee of

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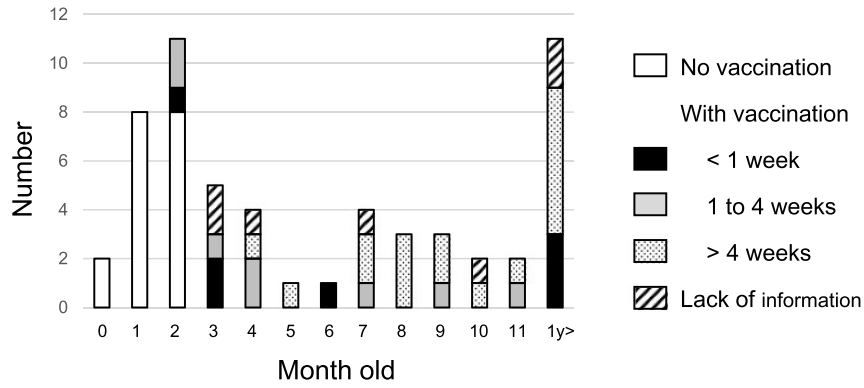

FIGURE 1. Age distribution and days after their last vaccine of 57 SID cases of autopsy for 5 years.

Tokai University School of Medicine as a retrospective clinical study (no. 16-281).

The series of autopsy was performed as reported previously.[20,21] Briefly, tissue examination was performed for formalin-fixed organs using hematoxylin and eosin staining and microscopy, with special staining, such as Gram staining, as appropriate. Biochemical laboratory tests were applied for markers that are stable after death. However, only a few test items could be tested because of the limited amount of samples obtained from autopsy. Viral antibody titer was measured in the serum for adenovirus, influenza A and B viruses, coxsackievirus B, and cytomegalovirus. Bacterial culture was performed using laryngeal swabs, blood in the heart, or a lung section.

RESULTS

Survey of SID Cases in Forensic Autopsy

Fifty-seven cases (33 male, 24 female) of SID, which were subjected to medicolegal autopsy, were extracted, excluding those from extrinsic causes such as abuse. The age distribution is presented in Figure 1. The cause of death, as diagnosed separately by 4 forensic pathologists, was regarded as SIDS suspected in 20 cases, infectious pulmonary disorders including pneumonia in 10 cases, viral encephalopathy in 3 cases, enteritis and ileus in 3 cases, congenital heart anomaly in 2 cases, potential asphyxia in 2 cases, and unknown cause in 17 cases.

Their vaccination history was confirmed in 50 cases based on passbook records, but such data were not available for 7. Eighteen infants younger than 2 months received no immunization. For the remaining 32 cases, the vaccination history was available. Of these, 7 infants (21.9%) received immunization within 7 days of death, and 8 (25.0%) received immunization from 8 to 28 days before death (Table 1). Of 11 infants younger than 6 months who received vaccination, 4 (36.4%) had received some vaccinations within 7 days.

Table 2 summarizes vaccines that infants were administered within the last 7 days and last 28 days before death. It was characterized that the most frequently administered vaccine in single or combined immunizations was Hib, occurring in 5 (71%) of the 7 infants who received vaccines within 3 days of death and 12 (80%) of 15 infants who received vaccines within 28 days of death. Among these cases, a temporal relationship to vaccination was considered at the time of autopsy for 3 infants (cases 1–3) because their death occurred within 3 days after vaccination. Moreover, they all had received Hib as the last vaccination. All exhibited similar courses as described hereinafter.

Course of 3 Suspicious Cases

The time course of vaccination before deaths within 3 days is summarized in Table 3. Parents pointed out that upper airway infectious symptoms occurred within the administered day in all cases except for the last one. Therefore, its causal relation to the

TABLE 1. Immunization Period Preceding Death

Days Immunized Before Death	Cases, n (%)	No.
1 d	0 (0)	
2 d	1 (3.1)	1
3 d	2 (6.3)	2, 3
4 d	2 (6.3)	
5 d	0 (0)	
6 d	1 (3.1)	
7 d	1 (3.1)	
2 wk	4 (12.5)	
3 wk	1 (3.1)	
4 wk	3 (9.4)	
>4 wk	17 (53.1)	
Immunized subtotal	32 (100.0)	
Not immunized	18	
Unknown	7	
Total	57	

TABLE 2. Vaccines in Single and Combined Immunization Given up to 7 Days (n = 7) and up to 28 Days (n = 15) Before Death

	No.	
Vaccines	<7 d (n = 7)	<28 d (n = 15)
Hib	5	12
S. pneumoniae (PCV13)	4	9
Quadruple vaccination for DTP-IPV	3	7
Rotavirus	1	3
Hepatitis B virus	1	3
Varicella	1	1
Influenza virus	0	1
Total	14	36

PCV indicates pneumococcal conjugate vaccine.

TABLE 3. Vaccination Course in 3 Cases With Sudden Death Occurring Within 3 Days

No.	Day After Birth	Received Vaccines
1	63	Hib, PCV7, and rotavirus (initial)
	91	DTP-IPV (initial)
	98	Hib, PCV7, and rotavirus (second)
	100	Sudden death
2	63	Hib, PCV13, HBV, and rotavirus (initial)
	107	Hib, PCV13, HBV, and rotavirus (second) and DTP-IPV (initial)
	110	Sudden death
3	3 mo	Hib, PCV13, and HBV (initial)
	4 mo	Hib, PCV13, and HBV (second), DTP-IPV (initial), BCG
	5 mo	Hib, PCV13 (third), and DTP-IPV (second)
	6 mo	DTP-IPV (third)
	10 mo	HBV (third)
	12 mo	PCV13 (fourth), VZV
	422 (14 mo)	Hib (fourth)
	435	Sudden death

BCG indicates *Bacillus* Calmette-Guérin vaccine; HBV, hepatitis B virus; PCV, pneumococcal conjugate vaccine; VZV, varicella-zoster virus.

deaths came into question. Their respective clinical courses and related postmortem examinations are explained hereinafter.

A 3-month-old female baby (case 1) developed cold symptoms on the day after the second combined immunization for Hib, *S. pneumoniae*, and rotavirus. In addition, the baby had received quadruple vaccination for diphtheria, pertussis, tetanus, and polio (DTP-IPV) 1 week prior. The infant was found limp in the evening, and then was transported by ambulance. The infant was in a state of shallow breathing at arrival, but she was died after 12 hours with little response to resuscitation. Leukocytosis of 23,000/μL and an elevated ferritin level of 16,380 ng/mL were observed in the emergency department.

Another 3-month-old male baby (case 2) received the second combined vaccination of Hib, *S. pneumoniae*, hepatitis B virus, and rotavirus, and simultaneously quadruple DTP-IPV vaccination. The infant showed cold-like symptoms continuously from the immunized day. He was found dead in sleep in the early morning of the third day.

A 1-year, 2-month-old male baby (case 3) received the fourth combined vaccination of Hib. He showed mild cold-like symptoms and high fever of more than 38°C from the following day. He was found dead in sleep in the early morning of the third day.

In these 3 cases, no swelling or callosity was observed on the injected skin, but autopsy showed some characteristically common histopathological findings as described hereinafter.

Histopathological Findings

In all 3 cases, mild inflammatory cell infiltration including neutrophils was visible around the tracheae and the bronchi, indicating tracheitis and bronchitis. In case 1, whole lungs were congested, accompanied by partial patchy pulmonary edema. Inflammatory cell infiltration was observed in alveolar walls and interlobular septa, showing interstitial pneumonia. Moderate inflammation was composed predominantly of mononuclear cells with no cells with intranuclear viral inclusion and antibody reactivity to influenza virus.

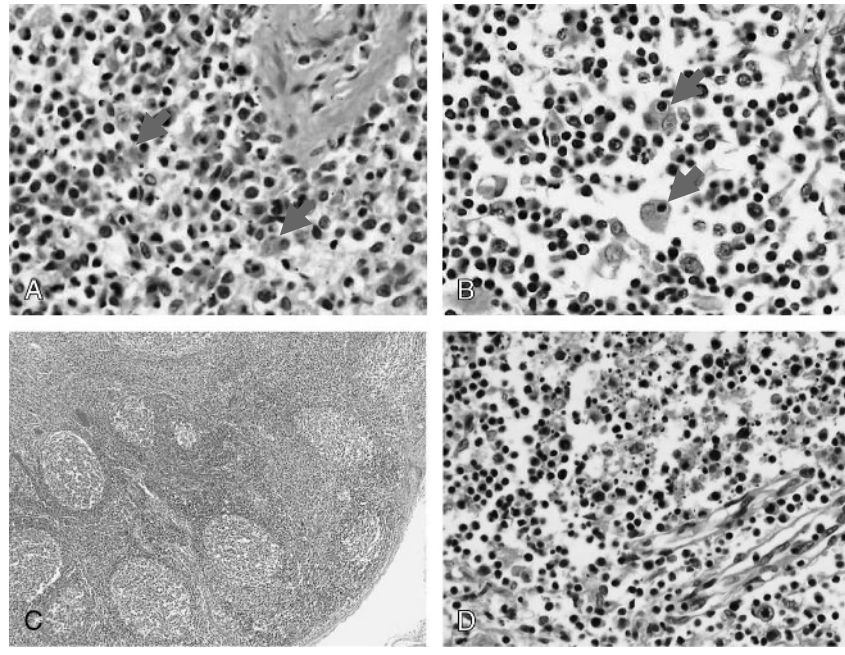

FIGURE 2. Hematoxylin and eosin–stained sections. A, The spleen of case 1 (original magnification ×400). B, The lymph node of case 2 (×400). C, The lymph node of case 3 (×20). D, The lymph node of case 1 (×400). In panels A and B, the hemophagocytosis was observed, as erythrocytes, leukocytes, and platelets were engulfed by activated macrophages in tissues of the spleen and the lymph node (arrows). In panel C, the cortex of lymph node expands with an increase of the number and size of secondary follicles. The follicles vary in size, but they exhibit polarized germinal centers including tingible body macrophages. In panel D, the apoptotic lymphocytes are evident as small, basophilic, and pyknotic (or fragmented) nuclei. Macrophages are present with engulfed cytoplasmic apoptotic bodies.

All 3 cases showed acute splenitis characterized by infiltration of neutrophils and congestion within the red pulp of the spleen. Moreover, extensive hemophagocytosis was visible in the spleen, liver, and lymph nodes (Fig. 2, A and B). In case 3, swollen lymph nodes were visible in the whole body such as cervical lymph nodes and mesentery lymph nodes. Histopathology showed reactive follicular hyperplasia (Fig. 2C). In case 1, numerous instances of lymphocyte apoptosis and abundant nuclear debris were found in the lymphoid tissue of the whole body, such as the lymph nodes, white pulp of the spleen, gut-associated lymphoid tissue, and bronchus-associated lymphoid tissue. Similar findings were visible in the lymph nodes and bronchus-associated lymphoid tissue of case 2 (Fig. 2D).

Laboratory Data

Influenza A virus was detected in our postmortem examination of case 1. Otherwise, no vital infectious sign was evident in other cases. Biochemistry indicated no increased C-reactive protein at postmortem. The cause of death was judged as pneumonia or upper respiratory infection at autopsy for all 3 cases.

Tryptase was measured for cases 2 and 3 at postmortem. Those levels were 5.8 and 2.8 μg/L, indicating no anaphylactic reaction potentially related to the SID cases.

H. influenzae and *S. pneumoniae* were not detected in the bacterial culture. However, α-hemolytic *Streptococcus* was detected in the lung section or in the blood in cases 1 and 2, respectively.

Other Similar Cases

Lymphadenopathy, splenomegaly, and pneumonia similar to these cases were found in 2 other cases in a review of extracted data for the other 54 cases. Severe infection and sudden death occurred in 1 case of a 4-month-old infant at 27 days after first immunization for Hib and *S. pneumoniae*. A 1-year, 9-month-old infant child died 4 months after the last *Bacillus* Calmette-Guérin vaccine, suggesting little or no relation.

DISCUSSION

In this study, we examined vaccination course in SID cases of children younger than 2 years. Among the 32 cases for which vaccination, vaccine, and timing data were available, 7 infants were immunized within 7 days of their death. During postmortem investigation, the relation to vaccination was assessed for 3 cases in which infants received immunization within 3 days of their death.

The antemortem point that is common among these 3 infant cases is that the condition immediately before death was associated with mild cold-like symptoms accompanied by fever. Their parents inferred some relation of the infant death with vaccination because cold-like symptoms appeared during the day after the vaccination. Moreover, their condition deteriorated suddenly at home, which consequently shows no apparent differences from the general situation of discovery of SIDS.[22]

All 3 deaths occurred after vaccination of Hib and *S. pneumoniae.* Four repetitions of combined immunization are recommended in Japan.[18] The safety of that recommendation has been confirmed etiologically.[23] Moreover, case 2 received 8 vaccines in 1 day. Simultaneous immunization of many sorts might affect the physical condition, as Ottaviani et al[24] and von Kries et al[19] reported cases of fatality after combined immunization of 6 vaccines.

Among the 3 cases reported here, features at postmortem examinations were heterogeneous, but similar findings related to the immune system were observed to some degree. Particularly, neutrophil infiltration in the spleen was evident, suggesting that the subjects were affected by hypercytokinemia deriving from an immunological reaction by some infection. The pathological features in lymphoid tissue and spleen demonstrated the presence of uncontrolled activated lymphocytes, histocytes, and macrophages. Blood culture developed the *Streptococcus* in 2 cases, but identifying the pathogenic bacteria of infection is generally difficult at the postmortem phase.[25] The important question of whether the disorders are truly related to vaccination remains.

Common features such as splenitis and hemophagocytosis were also evident among the 3 cases. The uncontrollable immune overreaction mainly caused by the activated lymphocytes and histiocytes/macrophages reminded us of hemophagocytic lymphohistiocytosis (HLH), which is clinically similar to macrophage activation syndrome (MAS). Actually, MAS/HLH is characterized by an overwhelming inflammatory reaction attributable to dysfunction of the immune system, accompanied by the continual activation and expression of T lymphocytes and macrophages.[26,27] This activation and expression leads to hypersecretion of proinflammatory cytokines, so-called cytokine storm, which might create unfavorable immunological conditions in infants who are affected by inflammation.[28] The case reports of MAS/HLH after immunization were limited, but some have been published.[29] As another instance, Otagiri et al[30] reported that a 19-month-old infant died of HLH after measles vaccination. The cause of death was determined as pneumonia or upper respiratory infection for the presented cases, but we thought that their fatality might be also attributable to MAS/HLH in some degree.

Concerning deaths after vaccination, estimation of coincident timing was performed based on epidemiological data obtained over a long period.[6] Brotherton et al[15] simulated the probability of death coincident with vaccination using vaccination-encountered age in a population of vaccination resisters and the age distribution of SIDS deaths in Australia. They estimated that 1.3% and 2.6% of the infant victims would be expected, by chance, to have some vaccination during the prior 24 and 48 hours, respectively. In the present study, 3 infants (9.4%) were found to have died within 3 days among 32 cases, and 7 (21.9%) were within 7 days, for whom a history of similar repetitive vaccinations was confirmed. We are not sure whether the present frequency is significantly different from their estimation. It is, anyhow, difficult to ascertain whether these were merely coincidental.

One cannot determine which vaccination affected the body adversely or in what way because the infants had received many vaccinations. This study found that the most frequent vaccine used before death was Hib. However, combined immunization of Hib and *S. pneumoniae* is recommend on 4 occasions before 2 years of age. More opportunities for exposure might affect the results. In Japan, fatal incidents occurred after combined immunization with Hib and *S. pneumoniae* vaccines in 2011.[16] Because some relation was suspected, vaccination was discontinued temporarily but was restarted soon thereafter. As described in the overview of the cases reported at that time, the cases are similar to the present cases: death occurred within 3 days after vaccination.

However, we concluded that the causal relationship of vaccination to the SID subjects was unknown in the reports because of the unclear mechanism how the 2 nonactive vaccines affect the mortality of infants and because of the difficulty to exclude potential coincidental occurrence. It is therefore necessary to consider it carefully at postmortem, along with the circumstances of death and autopsy findings, as many forensic pathologists may overlook this potential contributing factor.

The safety of Hib vaccine combined with other vaccines has been confirmed in general.[23,31,32] Moro et al[33] comprehensively analyzed numerous Hib vaccination cases including autopsy reports and death certificates for a total of 749 death cases. They

conclude that the review did not identify any new or unexpected safety concern for Hib vaccines. However, death certificates are usually written within a day of autopsy because of administrative purposes like burial. Detailed examinations should be completed within a couple of months. Therefore, we regard surveys based solely on death certificates as unproductive. In this point of view, reports of extensive analysis in forensic pathology are expected to be valuable.

Disorder after repetitive immunization, such as the second time in cases 1 and 2 and the fourth time in case 3, suggests the possibility of anaphylaxis. Vaccine-associated anaphylaxis is a rare event, with only a few cases reported despite the millions of doses administered, representing incidence of 0.65 cases per million doses.[34] By contrast, elevated tryptase activities were demonstrated in a part of forensic SIDS autopsy cases, in which tryptase is known as the most valuable marker at postmortem.[35,36] D'Errico et al[9] reported the fatal case of a 3-month-old infant who died within 24 hours of vaccination with hexavalent vaccine with postmortem findings such as acute pulmonary edema and a high level of β-tryptase, 43 mg/L, in serum. Similar cases have been reported for which anaphylaxis after immunization was suspected.[23] In this study, 2 of 3 cases showed no elevation of tryptase level at postmortem, in accordance with no relation of SIDS cases to tryptase elevation reported by Nishio and Suzuki.[37]

An adverse reaction to vaccination was suspected only because the parents had pointed it out. The role of infection and inflammation in SIDS cases has been investigated for a long time.[38] It is otherwise unlikely for a forensic pathologist to consider the vaccination history seriously. In fact, another case of sudden death (case 3) was found in which similar observations and adverse reactions should be suspected from reviewing other cases in the past. The possibility that the death resulted from vaccination effects should have received more attention.

A collaboration between forensic pathologists and pediatricians is important. In cases 1 and 2, we had contact with the pediatricians who administered vaccinations to the infants. The effects of vaccination were not considered at all for case 3 before the present survey. However, under the present circumstances, it takes 2 or 3 months at least before all autopsy test results are available. That period invariably leads physicians to hesitate to reconsider a case at that time and judge if the case should be notified to the agency. Although the autopsy rate in cases of infant death in Kanagawa Prefecture is higher than 80% at present, no child death review by experts has yet been performed in Japan. It is hoped that future studies will include general multiscriptual reviews conducted for acute infant death.[39]

In conclusion, there were a couple of SID cases in which the relations to vaccination was suspicious. Particularly, such a relation was observed after combined vaccination of Hib and *S. pneumoniae*, exhibiting histopathological features similar to MAS/HLH. However, it cannot be stated conclusively that they are related or coincidental deaths. We expect extensive postmortem examinations for SID cases to assess vaccination effects in infants.

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