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CASE REPORT

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Sudden infant death syndrome (SIDS) shortly after hexavalent vaccination: another pathology in suspected SIDS?

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Abstract Experts from panels of the European Agency for the Evaluation of Medical Products have investigated whether there might be a link between hexavalent vaccines and some cases of deaths that occurred. Participants included pathologists with experience in the field of vaccines and sudden infant death syndrome who conducted autopsies. However, to the best of our knowledge, little, if any, attention was paid to examination of the brainstem and the cardiac conduction systems on serial sections, nor was the possibility of a triggering role of the vaccine in these deaths considered. Herein we report the case of a 3-month-old female infant dying suddenly and unexpectedly shortly after being given a hexavalent vaccination. Examination of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus. The cardiac conduction system presented persistent fetal dispersion and resorptive degeneration. This case offers a unique insight into the possible role of hexavalent vaccine in triggering a lethal outcome in a vulnerable baby. Any case of sudden unexpected death occurring perinatally and in infancy, especially soon after a vaccination, should always undergo a full necropsy study according to our guidelines.

Keywords Sudden infant death · SIDS · Hexavalent vaccine · Arcuate nucleus hypoplasia · Cardiac conduction system · Prolonged external cardiac massage

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Introduction

The European Agency for the Evaluation of Medical Products (EMEA) recently reviewed the safety of centrally authorized hexavalent vaccines. During the April 2003 meeting, it was concluded that there was no change in the benefit/risk profile of these products, and, therefore, no changes in the present conditions of use were recommended [4]. The Committee conducted a detailed review, in particular, of five reports of unexplained deaths in children occurring within 24 h of vaccination with a hexavalent vaccine. These reports were received as part of a routine post-marketing safety monitoring (pharmacovigilance) over a period of 2 1/2 years. During this time an estimated 8.7 million doses of vaccines corresponding to the vaccination of some three million children have been used worldwide [4]. Panels of experts investigated whether there might be a link between the vaccines and the deaths observed. Participants included pathologists with experience in the field of vaccines and sudden infant death syndrome (SIDS) who conducted autopsies. The EMEA's conclusions were that the causes of death remained unexplained. SIDS, viral infection, metabolic disorders, allergic reactions or airway obstruction were plausible but were not definitely proven to have been the cause of death [4]. However, to the best of our knowledge, during the mentioned post-mortem investigations, little, if any, attention was paid to examination of the brainstem and the cardiac conduction systems on serial sections, nor was the possibility of a triggering role of the vaccine in the lethal outcome considered.

Case report

A 3-month-old white female infant lost consciousness 1 h after being given a hexavalent vaccination. Emergency help was summoned and arrived quickly. Immediately, resuscitation efforts were attempted by external cardiac massage and assisted ventilation. One hour later the baby reached the hospital, where the resuscitation manoeuvres were

continued, followed by repeated administration of adrenaline and atropine. The baby remained unconscious, with persistent mydriasis, not reacting to light, and was pronounced dead 2 h after arrival at the hospital.

The baby was a firstborn child, born at term in the 42nd week of gestation by Caesarean section, with a birth weight of 3,300 g and an Apgar score of 9–10. The analysis of the placenta after birth was unremarkable. Her parents reported that shortly after birth, the baby had episodes of polypnoea, which was cured spontaneously, and the child continued in apparent good health until the day she received the hexavalent vaccine and then died suddenly. No previous ECG recordings were available. The 35-year-old mother had an unremarkable pregnancy, except for mild hypothyroidism, which required therapy. The baby was bottle-fed. There was no significant family history relevant to the case.

Post-mortem examination was requested with a clinical suspicion of SIDS. The case was analysed at the Institute of Pathology, University of Milan, where more in-depth examinations were performed, including a close study of the cardiac conduction system and the brainstem on serial sections [16, 19–21].

Methods

A complete autopsy was performed according to the autopsy protocol usually followed at our Institute of Pathology in case of sudden death, including careful examination of the cardiac conduction system and of the central and peripheral autonomic nervous structures involved in cardiorespiratory reflexogenesis [16, 19, 21].

The medulla oblongata was divided into three blocks. The first, cranial block, extended from the border between the medulla oblongata and pons up to the upper pole of the olivary nucleus. The second, intermediate block, corresponding to the submedian area of the inferior olivary nucleus, took the obex as the reference point and extended 2–3 mm above and below the obex itself. The third, caudal block, included the lower pole of the inferior olivary nucleus and the lower adjacent area of the medulla oblongata. The first and second blocks were sectioned in a cranial–caudal direction, and the third, in a caudal–cranial direction [13–16]. A fourth block was cut of the brainstem, including the ponto-mesencephalic portion, sectioned in a caudo–rostral direction [14, 16]. From each of these paraffin-embedded blocks, an average of 48 sections were obtained and were alternately stained using haematoxylin–eosin, Bielschowsky, and Klüver-Barrera stains [10, 13]. The pertinent nuclei were outlined, namely, the locus coeruleus, the parabrachial/Kölliker-Fuse complex in the pons; and the arcuate nucleus, the hypoglossus nucleus, the dorsal vagus motor nucleus, the tractus solitarii nucleus, the ambiguus nucleus, the trigeminal tractus and nucleus, and the ventrolateral reticular formation in the medulla oblongata [10, 13–16, 18].

After excluding the presence of gross cardiac malformations, the origin of the coronary arteries was carefully inspected. The heart chambers were regularly examined for pathologic changes in the atria, septa, ventricles, pericardium, endocardium and coronary arteries. Samples of the myocardium and the major coronary arteries were stained with haematoxylin–eosin and trichromic Heidenhain (Azan).

The cardiac conduction system was removed in two blocks: The first included the sino-atrial node and the crista terminalis, while the second contained the atrioventricular node, from the His bundle down to the bifurcation and bundle branches. These two blocks were serially cut at intervals of 40 μm (levels) and stained alternately with haematoxylin–eosin and Azan [14, 21].

Pathological findings

At autopsy, the baby was described as a well-developed, well-nourished white infant, with a body weight of 5,375 g and body length of 60 cm. Macroscopic examination did not reveal malformations, organ malposition or marks of violence. Results of the gross external and internal examinations were normal for the age and sex.

The study of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus, as confirmed by two-dimensional morphometric reconstruction (Fig. 1). No abnormalities of the other cardiorespiratory medullary nuclei, namely, the dorsal vagus motor, the tractus solitarii, the ambiguus nucleus, the trigeminal nuclei, the ventrolateral reticular formation, locus coeruleus and the parabrachial/Kölliker-Fuse complex, were observed.

The heart weighed 28 g, and the cardiac diameters were the following: longitudinal 4 cm, transverse 4 cm, anteroposterior 3 cm. Gross cardiac examination revealed multiple dyschromic and brownish areas mainly located in the interventricular septum. Histologically, such areas presented wide myofibrillary injury, characterized by anisoinotrpism and contraction band necrosis typical of acute infarction. Myocardial haemorrhage was also detected. The coronaries were normally patent.

Histological examination of the cardiac conduction system showed islands of conduction tissue in the central

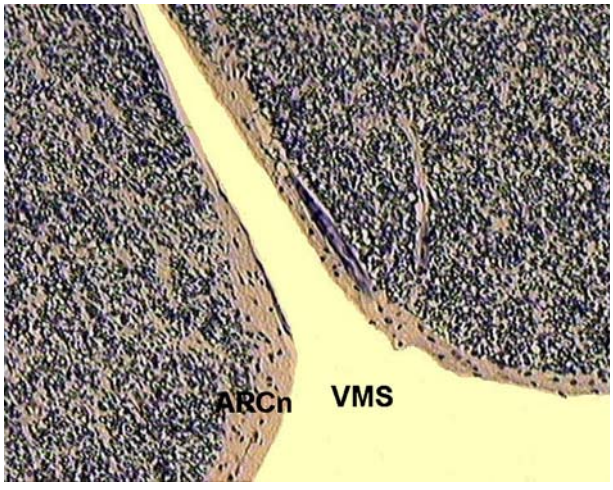

Fig. 1 Bilateral hypoplasia of the arcuate nucleus (ARCn). VMS Ventral medullary surface. Klüver-Barrera stain, ×25

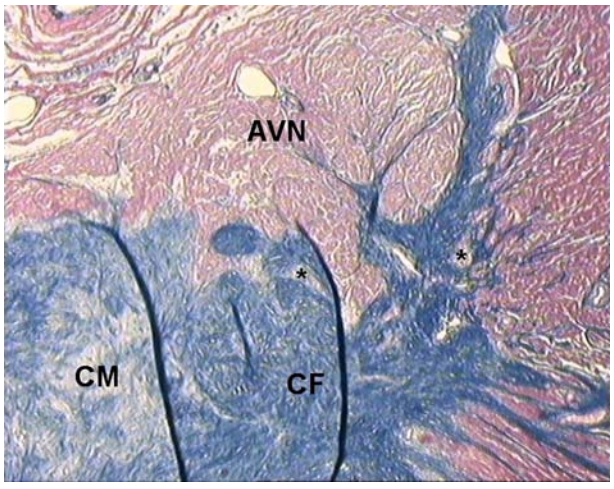

Fig. 2 The atrioventricular node (AVN) presents areas of fetal dispersion and resorptive degeneration. In the central fibrous body (CF), islets of junctional tissue (*) and initial cartilaginous metaplasia (CM) are detectable. Stain, ×25

fibrous body, known as persistent fetal dispersion and areas of resorptive degeneration [7, 21] in the atrioventricular node (Fig. 2).

No other significant pathologic changes were found. The post-mortem gross and microscopic examination corroborated the clinical diagnosis of SIDS.

Discussion

To reduce the number of injections needed to comply with paediatric vaccination requirements, a liquid hexavalent vaccine has been developed for primary booster vaccination of infants against diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* type B and hepatitis B. Seroconversion or seroprotective titres of antibodies against multiple antigens have been achieved in a majority of infants following a primary series of three doses administered at 1- to 2-month intervals from 2 months of age, providing immunity against six important childhood diseases [11].

In the past there was concern that vaccinations might have a causal relationship with SIDS, particularly considering that the peak age for SIDS is 2–4 months, coincidental with the age for vaccinations. Many studies have shown that vaccines are not associated with an increased risk of SIDS [8, 24]. Some studies have even shown a reduced risk of SIDS associated with vaccinations [5]. Despite this, from time to time this controversy is reopened [3].

Recently, Brotherton et al. [2], considering that SIDS peaks at 2 months of age, when vaccination encounters are frequent, estimated the probability of vaccination within the last 24 h for a child who has died of SIDS as 1.3% and as 2.6% in the last 48 h. With the average number of SIDS deaths equal to 130 patients per year in Australia, they estimated that a case of SIDS will occur when vaccination was given in the last 24 h in 1.7 patients per year and within 48 h in 3.5 patients per year.

In 2003, the EMEA, through its scientific Committee for Proprietary Medicinal Products (CPMP), reviewed the safety of the centrally authorized hexavalent vaccines Hexavac and Infarix Hexa [4]. During the March and April 2003 meeting, the CPMP concluded the following:

1. Vaccination offers benefits to the individual child and to the general population.
2. The causes of death of the five children dead within 24 h of vaccination with a hexavalent vaccine remain unexplained, and it is not possible to establish a cause and effect association with hexavalent vaccines [4].

SIDS or crib death is defined as the sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation including performance of a complete autopsy, examination of the death scene, and a review of the clinical history [25].

The identification of a possible pathological basis of reflexogenic mechanisms in sudden, unexpected infant death necessarily requires examination of the brainstem nuclei and of the cardiac conduction system on serial sections according to the procedures described in the "Methods" section. The neuropathological and cardiovascular study necessary for the objective identification of the nature and location of each lesion, likely morphological substrata of death, requires examination of a large number of patients according to homogeneous and standardized criteria [15, 16]. It was proposed at the 7th International Conference on SIDS [12] that the current definition of SIDS as "the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including the performance of a complete autopsy, examination of the death scene, and review of the clinical history" be modified to include the words "a complete autopsy with an in-depth histopathologic analysis of the cardiorespiratory innervation and specialized myocardium, performed only by an experienced, reliable pathologist".

More recently, Krous et al. [9] underlined that since the definition of SIDS originally appeared, an enormous amount of additional information has emerged, justifying the additional refinement of the definition of SIDS to incorporate epidemiologic features, risk factors, pathologic features, and ancillary test findings and that the definition of SIDS will be modified in the future to accommodate new understanding of sudden infant death.

Taken together, the abnormalities of the autonomous nervous and cardiac conduction systems described in the present case, as well as the review of the clinical history, represent a plausible basis for the diagnosis of SIDS [6, 13, 15].

Abnormalities in the morphological findings of the brainstem (Fig. 1) and cardiac conduction system (Fig. 2) similar to those detected in this case have already been proposed in infants dying suddenly and unexpectedly as possible morphological substrates for sudden reflexogenic infant death [6, 7, 13, 15, 16, 19, 21].

In this case, histological examination of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus. In term fetuses, newborns and infants dying suddenly and unexpectedly, we have recently demonstrated a variety of structural defects of the arcuate nucleus, ranging from neuronal immaturity in a well-shaped structure to total agenesis [6, 13, 15, 16].

On one hand, the unexpected death of this vulnerable baby (infant with bilateral hypoplasia of the arcuate nucleus) could have been triggered by the hexavalent vaccination. This case is consistent with the triple-risk model of SIDS, a hypothesis comprising an underlying biological vulnerability to exogenous stressors and some triggering factors in a critical developmental period [6]. On the other hand, this case could be classified as a SIDS "gray zone" or borderline case, defined as a case in which it is difficult to establish whether the pathological findings are sufficiently severe to have caused the death. Recently, our examination of the brainstem of 103 patients of SIDS disclosed five SIDS gray zone cases in which only our further investigations on serial sections successfully identified anatomo-pathological findings likely representing the morphological substrates for a sudden reflexogenic death [20, 23].

Regarding the infarct-like myocardial lesions detected in this patient, two of the present authors have already pointed out, among the disadvantages of external cardiac massage, the not infrequent occurrence of damage to the myocardium and the cardiac conduction system [17, 22]. The compression of the heart between the spine and the sternum exerted by this maneuver causes a direct vertical pressure perpendicular to both the atrial and ventricular septa [17, 22]. In this case, the overinsistent external cardiac massage is responsible for the findings of the wide myofibrillary injury in the interventricular septum, as is typically seen in the contraction band degeneration of hyperacute infarction and as in many examples of myocardial biopsy [1].

In conclusion, the careful examination of the heart, cardiac conduction system and brainstem on serial sections was crucial to classify this case as SIDS and to identify the possible morphological substrates responsible for this lethal reflexogenic sudden death, that is, arcuate nucleus hypoplasia in the brainstem and persistent fetal dispersion and resorptive degeneration in the cardiac conduction system. All cases of sudden unexpected death occurring in infancy and perinatal age, especially soon after a vaccination, should always undergo an investigated necropsy study, according to our guidelines [14].

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