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Letter to the Editor

Unexplained cases of sudden infant death shortly after hexavalent vaccination

Polyvalent vaccines like Hexavac® and Infanrix Hexa® were developed to increase acceptance of vaccinations by decreasing the number of necessary injections [1,2]. Compared to their pentavalent predecessors, these hexavalent vaccines additionally contain hepatitis B serum. They are used for immunisation against diphtheria, pertussis, tetanus, influenza, poliomyelitis and hepatitis B. Hexavac® and Infanrix Hexa® are available in European markets since October 2000. Until April 2003, approximately 3 million children have been vaccinated in this way and about 9 million doses were sold in the European union during this time [3]. Children are to be vaccinated with these vaccines at the age of 2, 4, 6 and 12–14 months.

We report six cases of sudden infant death after hexavalent vaccination that were autopsied and examined at the Munich Institute of Legal Medicine from 2001 to 2004.

Among those investigated children, three were male and three female, ageing between 4 and 17 months. Five children had been vaccinated with Hexavac®, one with Infanrix Hexa® during the past 48 h before death. Shortly after the vaccination, three of the children developed symptoms like tiredness, loss of appetite, fever up to 39 °C and insomnia. All children were found dead without explanation 1–2 days after the vaccination.

These children underwent a forensic post-mortem examination. They were assumed to be typical cases of SID (sudden infant death) because there was no history of a serious illness, and since all children died suddenly and unexpectedly.

In addition to neuropathologic and histologic abnormalities, all of these children showed an extraordinary brain edema, which made them exceptional to other SID cases. After the third of such extraordinary cases had been identified, we decided to further investigate the pathological findings.

Abnormal neuropathologic findings were acute congestion, defective blood–brain barrier, slight infiltration of the leptomeninx by macrophages and lymphocytes, perivascular lymphocytic infiltration, diffuse infiltration of the pons, mesencephalon and cortex by T-lymphocytes, microglia in the hippocampus and pons, and in one case a necrosis in the cerebellum.

In four cases, a slight infiltration of the liver by lymphocytes and eosinophile granulocytes was diagnosed, in two cases also in the lung, and in one case in the spleen.

We were able to do histological examinations at the cutaneous injection site in one child and found an infiltration of the cutaneous and subcutaneous layer by lymphocytes and eosinophile granulocytes.

Three of these six cases could be investigated concerning increased serum levels of mast cell tryptase and IgE. Mast cell-tryptase concentration was slightly above normal in one, and markedly elevated in the other two children (18, 100 and 108 μg/l). On the other hand, IgE levels were normal and specific IgE against tetanus toxoid and latex could not be detected.

Autopsy and all further investigations did not reveal other serious abnormalities that could have lead to the deaths of the children.

The neuropathological findings in the investigated cases are unlikely to explain the deaths, since early post-vaccinal encephalopathy is mostly associated with a congestive and edematous brain without relevant inflammatory infiltration. Post-vaccinal encephalopathies are mentioned especially in relation with vaccinations against pertussis [4,5]. Such cases, however, typically show clinical symptoms like somnolence, convulsion, headache or paresis [4]. Such or similar symptoms could not be found in any of the examined cases.

Increased brain weights either which result from edema or hyperemia, and in which clinical symptoms are lacking, are described as “benign intracranial hypertension”, and are reported mainly after DTP-vaccinations [6].

At the moment, to our knowledge, there are no reference values available regarding mast cell-tryptase plasma concentrations in children up to the age of 12 years. For older children the 95.0 percentile is 11.4 μg/l. Increased tryptase levels were repeatedly described in SID [7,8]. It is unlikely that our children had a predisposition for an atopic diathesis, since mast cell-tryptase plasma concentrations were increased while IgE levels were normal. The increased tryptase levels and numbers of eosinophile granulocytes suggest that an anaphylactic reaction developed after the vaccination. As time to death seems comparably long for an acute anaphylactic reaction, a delayed immune reaction has to be discussed.

Prior to the release of hexavalent sera (in the years 1994–2000), we observed only one child out of 198 cases

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with sudden unexplained infant death who died shortly after vaccination (DTP). However, between 2001 and 2004 five of such cases were identified in our institution among 74 children with SID. This would indicate a 13-fold increase (the local autopsy rate for infants is about 70%). A recent analysis of all cases known to German authorities [9] showed death rates that were to be expected statistically for the first day after vaccination. As four of those 10 cases were autopsied at Munich, although the Munich institute represents just 7.8% of the German population, a real number of about 50 cases might be expected, that is, 500% of the statistic figures to be expected.

We reported these six cases to direct attention to a possibly serious vaccination side effect. So far, there is no way to proof that these infant deaths are caused by vaccination. Therefore, the relation between the vaccinations and the death of the children must remain uncertain. Nevertheless, we feel that it is important to inform vaccinating physicians and pediatricians as well as parents about such possibly fatal complications after application of hexavalent vaccines. Especially, physicians and pediatricians should be also informed about the possibility of using pentavalent vaccines, which seem to be associated with lesser complications.

Finally, if broad use of hexavalent vaccines continues, extensive studies are most likely required to assess or exclude a relation between vaccination and death in infants.

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