*Acta Microbiologica et Immunologica Hungarica, 48 (2), pp. 129–141 (2001)*

# DETECTION AND TOXIN PRODUCTION OF *STAPHYLOCOCCUS AUREUS* IN SUDDEN INFANT DEATH CASES IN HUNGARY*

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(Received: 12 January 2000; accepted: 5 April 2000)

The potential role of microbial agents was investigated in 13 cases of Sudden Infant Death Syndrome and in 9 non-SIDS cases in Budapest between September 1996 and May 1998. Autopsy, histological examination and microbiological tests were performed on samples of blood, cerebrospinal fluid, pharyngeal samples and lung tissue from infants under one year died suddenly, without previous diseases. The multifactorial pathomechanism of SIDS was suggested by the isolation of toxin producing *Staphylococcus aureus*-, *Enterobacteriaceae* and *Candida albicans* strains in large number and by the detection of Parainfluenza Type 2 virus antigen. *S. aureus* proved the predominant bacteria in the SIDS cases. Nasopharyngeal microbial flora and *S. aureus* carrier of 100 age matched healthy infants were tested during the same period. *S. aureus* was isolated from 54% of SIDS cases and 37% from healthy infants /OR=1.986 (95% Confidence interval=0.55–7.33), p=0243/. The enterotoxin and TSST-1 toxin producing activity of *S. aureus* showed the characteristic difference. The toxigenic *S. aureus* was detected in 46% of SIDS cases and 16% of healthy infants /OR=4.5 (95% CI=1.15–17.72), p=0.010/. The distribution of toxigenic and nontoxigenic isolates was 86% in SIDS cases and 43% in healthy infants /OR=7.875 (CI=0.78–191.89), p=0.041/.

**Keywords**: sudden infant death syndrome, bacterial toxin production, *Staphylococcus aureus*

Sudden Infant Death Syndrome (SIDS) is an outstanding problem in Hungary There has been a significant decrease in infant mortality rate in the recent decades; however, the incidence of SIDS did not decrease. Between 1980–1996, the SIDS

*This publication belongs to the 10th accredited PhD program of the Semmelweis University Budapest, Hungary

1217-8950/2001/$ 5.00 

incidence was 0.12–0.36 per 1,000 live births [1]. Infectious agents, bacterial exo- and endotoxins can be triggers for sudden infant death. Bacterial toxins exert a powerful effect on the immune system, stimulating T cells, and subsequently induce the formation of large amounts of cytokines. Generation of overwhelming inflammatory response may lead to death by the shock of the cardiac or respiratory system [2].

The purpose of our study was to investigate whether there are correlations between the pathological changes of microbial flora and SIDS.

## Materials and methods

Thirteen infants who died of SIDS between September of 1996 and May of 1998 in Budapest and 9 age matched infants, under one year who died unexpectedly or in accidents in Budapest were examined by detailed autopsy, histological and microbiological tests. Nasopharyngeal microbial flora and isolation of *S. aureus* from 100 under one year old infants were tested during the year 1997 (January–March 24 infants, April–Juny 36 infants, July–September 20 infants, October–December 20 infants). The healthy infants under one year of age were randomly selected from infants considered healthy after a regular control from 3 different primary health care practices, Budapest.

### *Methods*

Medical data of SIDS and non-SIDS infants were collected through the collaboration of parents and pediatricians. (Permission of the Ethical Committee: No: 32/1998.)

### *Autopsy and histological tests*

Samples from various organs (heart-blood, lung, liver, spleen, kidney and segments of small and large intestine) were obtained during the autopsies. The autopsy was done within two days of sudden death. The bodies were stored at 4 °C before the autopsy. Mild infections of the upper respiratory tract or middle ear, or positive bacteriological or virological findings unaccompanied by morphological findings were not considered to be the cause of death. All tissues were fixed in 10% (V/V) buffered formalin for standard period of time (3–6 days). Sections (5 mm thick) were cut from each block of paraffin-embedded tissues and were stained with haematoxylin and eosin (HE). Samples were also used for identifying any degenerative or inflammatory changes present.

*Microbiological studies*

Pharyngeal and nasal secretions were obtained by pharyngeal swabs and cerebrospinal fluid by puncture of the fourth ventricle. The swabs were taken and placed into transport culture medium at the scene within two hours of death was discovered. The parent(s) signed the informed consent and they got detailed information about the purpose of our investigation in SIDS cases. Heart-blood and lung tissues were obtained during autopsy. Virus antigens were detected in paraffin-embedded lung tissue.

*Bacteriological methods*

The specimens were streaked on the surface of blood and chocolate agar, incubated at 37 °C aerobically, anaerobically and at 5% $CO_2$ atmosphere. Plates were examined after 24 hours and 48 hours. The strains were identified by Cowan-Steel methods [3], Gram-negative rods were identified by bio-Merieux ID32E system or ID 32 GN system.

*Yeast cultural methods*

Sabouraud agar containing 10 mg/ml gentamicin was used for the isolation of yeasts. Isolates were identified by bio-Merieux ID32C system.

*Immunohistologic procedures for detection of viral antigenes*

Paraffin-embedded sections were dewaxed in xylene and immersed in 0.1% trypsine in PBS to release the overfixed antigenic sites. The sections were treated with 1% $H_2O_2$ in methanol. These sections were incubated with appropriately diluted monoclonal antibodies against the following viruses: Respiratory Syncytial viruses (Serotypes A, B), Influenza virus A, Influenza virus B, Parainfluenza viruses (Type 1, 2, 3), Adenoviruses (ARGENE, Biosoft, France). After incubation (2 h, 37 °C) bound monoclonal antibodies were detected with peroxidase labelled anti-mouse IgG (Sigma). Peroxidase activity was visualized using 3-Amino-9-Ethylcarbazole (AEC) substrate and sections were slightly counterstained with hemalum.

*Detailed microbiological examinations of* S. aureus *strains*

Isolates from the specimens of SIDS and healthy infants were screened for production of enterotoxin A (SEA), B (SEB), C (SEC), D (SED) and TSST-1 by Oxoid Toxin Detection Kit TD 940 and TD 900 (Unipath Limited, Hampshire, England). The kit may be used to detect staphylococcal entero- and TSST-1 toxins and to measure

semi-quantitative results in the culture filtrates of isolates by reversed passive latex agglutination.

Antibiotic sensitivity of *S. aureus* strains were tested on Müller–Hinton agar by penicillin, oxacillin, ampicillin, amoxicillin + clavulanic-acid, cefuroxim, erythromycin, clindamycin, roxithromycin, vancomycin, ofloxacin, ciprofloxacin, trimethroprim, gentamicin and nethilmycin disks (Oxoid discs). Methicillin resistance of *S. aureus* (MRSA) was detected on Müller–Hinton agar containing 6 μg/ml oxacillin and 4% NaCl incubated at 35 °C.

Phage typing of *S. aureus* was carried out as described by Blair and Wiliams [4].

ORs with 95% confidence intervals were used to evaluate differences in the frequency of bacteria and toxin production in the various categories.

**Table I**

*Relevant clinical details of 13 SIDS cases*

| No. | Sex | Age | Anamnestic data | Birth weight (g) | Time of death | Site of death |
|---|---|---|---|---|---|---|
| Case 1 | F | 2 months | mild cold | 2600 | 5.00 | home |
| Case 2 | F | 6 months | mild cold, cysta colli with *Staphylococcus aureus* | 3200 | 16.00 | home |
| Case 3 | F | 4 months | mild cold | 2800 | 3.00 | home |
| Case 4 | M | 4 months | negative | 2620 | 5.30 | home |
| Case 5 | M | 2 months | mild cold | 3250 | 11.40 | home |
| Case 6 | M | 3 months | negative | 2770 | 10.00 | home |
| Case 7 | M | 2 months | negative | 3300 | 6.00 | home |
| Case 8 | M | 11 months | high fever without medical treatment in 6 months of age | 2800 | 8.00 | home |
| Case 9 | M | 10 months | high fever in 3 months of age | 2950 | 0.30 | home |
| Case 10 | M | 6 months | anus atresia at birth, cold, high fever for 3 weeks before death, resuscitation | 2700 | 5.10 | hospital |
| Case 11 | M | 5 months | negative | 3000 | 23.25 | ambulance |
| Case 12 | F | 2 months | pneumonia in 2 weeks of age | 3100 | 16.32 | hospital |
| Case 13 | M | 5 months | soor oris | 3200 | 7.00 | home |

## Results

Thirteen SIDS cases, 4 female and 9 male infants, were under one year of age, the majority were under the age of three months. They were found dead at their homes, and only 2 infant died in hospital. In most of the cases the time of death was the early morning hours (from midnight to 8 a.m.). Four infants had showed symptoms of mild cold before death and 3 infants had high fever, 5 months (case 8), 7 months (case 9) and 3 weeks (case 10) before death. In 8 cases the infants were lower than the average Hungarian birth weight (3,100 g). SIDS cases were found in spring, autumn and winter months. In one of the cases a twin with low birth weight was the victim of SIDS (Table I).

*Autopsy and histology*. Intrathoracic, subpleural, subepicardial and subcapsular thymic petechiae were found in SIDS cases. Subconjunctival petechiae were not detected in any SIDS case. Mild or severe pulmonary edema was found in most of the cases. Lymphoid cells or macrophages in the upper respiratory tract were detected in about half of the cases.

*Microbiology*. The following microbes were isolated from the autopsy specimen.

Bacteriology: In 2 cases *S. aureus,* in 6 cases different *Enterobacteriaceae* species, in 4 cases *S. aureus* and *Enterobacteriaceae* strains and in 1 case *S. aureus* and *S. pyogenes* were isolated. In case 1. *E. coli* 0:8 H:999, a non-enteropathogen serotype, was isolated from blood, cerebrospinal fluid and throat specimen of a newborn. The results of bacteriological cultures are shown in Table II. Yeast isolates were *Candida albicans*. High number of *C. albicans* was cultured from pharyngeal secretions in case 1, from lung tissue in case 3, from pharyngeal secretions and lung tissue in case 5, and from pharyngeal specimen of case 13 (Table II).

Virus antigens were detected: In case 7. *Parainfluenza Type 2 virus* antigen with previous negative clinical symptoms and very mild pathological changes. All other SIDS cases were negative (Table II).

*S. aureus* was the predominant isolate from specimens of SIDS cases, 7/13 (53%) (Table III).

SEA, SEB and/or TSST-1 toxins were identified only in 6 SIDS cases 6/13 (46%) (Table IV). Different amounts of SEA, SEB and TSST-1 were produced by these staphylococcus strains. Large quantities of SEA were produced by *S. aureus* isolated from Case 1. At the same time two or three different types of pyrogenic and TSST-1 toxins were produced by these *S. aureus* strains (Table V).

Among the 9 infants who died of other cause, different pathogens or normal microbial flora were isolated; however *S. aureus* was not cultured.

**Table II**

*Results of microbiological examination of 13 SIDS cases*

| No. | Throat specimen | Pulmonary tissue | Blood culture | Cerebrospinal fluid |
|---|---|---|---|---|
| Case 1 | *Staphylococcus aureus*<br>*Escherichia coli*<br>*Candida albicans* | *Staphylococcus aureus* | *Escherichia coli* | *Escherichia coli* |
| Case 2 | *Staphylococcus aureus* | *Staphylococcus aureus* | *Staphylococcus aureus* | sterile |
| Case 3 | *Escherichia coli* | *Staphylococcus aureus*<br>*Candida albicans* | sterile | sterile |
| Case 4 | *Staphylococcus aureus*<br>*Serratia rubidea* | *Staphylococcus aureus*<br>*Serratia rubidea* | sterile | sterile |
| Case 5 | *Staphylococcus aureus*<br>*Klebsiella oxytoca*<br>*Candida albicans* | *Staphylococcus aureus*<br>*Klebsiella oxytoca*<br>*Candida albicans* | sterile | sterile |
| Case 6 | *Enterobacter aerogenes* | *Enterobacter aerogenes*<br>*Enterococcus faecalis* | *Enterococcus faecalis* | sterile |
| Case 7 | *Escherichia coli*<br>*Enterobacter aerogenes* | *Escherichia coli*<br>*Enterobacter aerogenes*<br>*Parainfluenza virus* | sterile | sterile |
| Case 8 | *Escherichia coli* | *Escherichia coli* | sterile | sterile |
| Case 9 | *Staphylococcus aureus* | *Staphylococcus aureus* | sterile | sterile |
| Case 10 | *Escherichia coli* | *Pseudomonas aeruginosa*<br>*Enterococcus faecalis* | *Enterococcus faecalis* | *Enterococcus faecalis* |
| Case 11 | *E. chloaceae* | *E. chloaceae* | sterile | sterile |
| Case 12 | *S. aureus*<br>*S. pyogenes* | *S. pyogenes* | sterile | sterile |
| Case 13 | *E. coli*<br>*C. albicans* | sterile | sterile | sterile |

The screening of nasopharyngeal flora of 100 healthy infants under the age of one year showed normal microbial flora with only few number of *S. aureus* (37%). (Table III). There were only 16/100 (16%) toxin producers (Table IV). SEA, SEB, SEC, SED and/or TSST-1 toxins were detected (Table VI). Compared to the SIDS infants, the proportion of carriers and the quantity of the excreted toxins proved fewer numbers among healthy infants (Table VI). Distribution of toxigenic and non-toxigenic strains in *S. aureus* carriers were 85% pyrogen toxin producers in SIDS cases but 43% in healthy infants (Table VII).

**Table III**

*Distribution of* S. aureus *strains in the investigated cases*

| | *S. aureus* | | |
|---|---|---|---|
| | positive (%) | negative (%) | Total |
| SIDS infants | 7 (54) | 6 (46) | 13 |
| Healthy infants | 37 (37) | 63 (63 ) | 100 |
| Total | 44 | 69 | 113 |

OR=1.986 95% CI=0.55–7.33

**Table IV**

*Distribution of toxigenic* S. aureus *in the investigated cases*

| | Toxigenic *S. aureus* carriers (%) | Non-toxigenic *S. aureus* carriers and non-*S. aureus* carriers (%) | Total |
|---|---|---|---|
| SIDS infants | 6 (46) | 7 (54) | 13 |
| Healthy infants | 16 (16) | 84 (84 ) | 100 |
| Total | 22 | 91 | 113 |

OR=4.500 95% CI=1.15–17.72

Antibiotic sensitivity of SIDS isolates: 6 *S. aureus* strains were resistant to penicillin and 1 strain to oxacillin; they were sensitive to other antibiotics tested.

The III phage group was dominant among *S. aureus* strains isolated from SIDS infants (Table V).

## Discussion

During the first six months, infants undergo many physiological adaptations including the decrease of maternal antibody level and gradual induction of the infant's immune system following the influence of environmental antigens and immunization [5, 6]. In this period the normal microbial flora of epithelial and mucosal surfaces are

developed and this is a highly important factor contributing to the development of immune response [7, 8].

The microbial flora of infants who died in SIDS was studied. The role of isolates was assessed in the cases in which the same species were cultured from various organs or pathogenic bacteria and yeasts were isolated in large number. *S. aureus* and different *Enterobacteriaceae* strains were isolated alone or together most frequently from the pharynx and lungs of SIDS victims. *C. albicans* was also a frequently isolated microorganism.

**Table V**

*Examination of staphylococcal strains isolated from SIDS cases*

| No. of patients/ Strains | *Staphylococcus* species | Enterotoxin* | | | | TSST-1* | phag group | Localisation of isolation |
|---|---|---|---|---|---|---|---|---|
| | | A | B | C | D | | | |
| 1/1 | *S. haemolyticus* | – | – | – | – | – | | nose |
| 1/2 | *S. aureus* | 1/64 | – | – | – | – | III. | throat |
| 2/3 | *S. aureus* | 1/8 | 1/8 | – | – | 1/4 | mixed | throat |
| 2/4 | *S. aureus* | 1/2 | – | – | – | 1/2 | mixed | lung |
| 2/5 | *S. aureus* | 1/2 | – | – | – | 1/2 | mixed | blood |
| 2/6 | *S. haemolyticus* | I/I | I/I | – | – | 1/2 | | lung |
| 3/7 | *S. epidermidis* | – | – | – | – | – | | nose |
| 3/8 | *S. aureus* | 1/32 | 1/32 | – | – | 1/4 | III. | lung |
| 3/9 | *S. epidermidis* | – | – | – | – | – | | nose |
| 4/10 | *S. aureus* | 1/32 | – | – | – | 1/4 | III. | lung |
| 4/11 | *S. aureus* | 1/16 | 1/4 | – | – | 1/2 | II. | throat |
| 5/12 | *S. aureus* | 1/32 | – | – | – | 1/2 | III. | throat |
| 5/13 | *S. aureus* | 1/32 | 1/4 | – | – | 1/2 | III. | lung |
| 5/14 | *S. haemolyticus* | – | – | – | – | – | | nose |
| 5/15 | *S. haemolyticus* | – | – | – | – | – | | nose |
| 9/16 | *S. aureus* | 1/32 | – | – | – | – | III. | lung |
| 13/17 | *S. aureus* | – | – | – | – | – | III. | throat |

*Dilution ratio of the culture filtrates, where the endpoint of the reaction is

Our results agree with reports on the isolation of *Enterobacteriaceae* strains and *S. aureus* from SIDS infants [9–11]. These microorganisms are transient in low number in the upper respiratory tract, though the large number of these toxin-producing strains could be a decisive factor triggering the events leading to SIDS [12].

**Table VI**

*Examination of staphylococcal strains isolated from the nasopharynx of healthy infants*

| No of patients/ strain | *Staphylococcus* species | Enterotoxin* | | | | TSST-1* | phag group |
|---|---|---|---|---|---|---|---|
| | | A | B | C | D | | |
| 101/a | *S. aureus* | 1/2 | 1/2 | – | – | 1/16 | II. |
| 109/a | *S. aureus* | 1/8 | – | – | – | – | mixed |
| 123/a | *S. aureus* | 1/2 | 1/2 | 1/2 | 1/2 | 1/2 | II. |
| 123/b | *S. aureus* | – | – | – | – | – | II. |
| 504/a | *S. aureus* | 1/8 | 1/2 | – | – | – | II. |
| 505/a | *S. aureus* | 1/2 | – | – | – | – | II. |
| 510/a | *S. aureus* | – | 1/8 | – | – | – | mixed |
| 516/a | *S. aureus* | – | 1/8 | – | – | – | II. |
| 524/a | *S. aureus* | I/I | – | – | – | – | III. |
| 526/a | *S. aureus* | – | – | – | 1/8 | 1/8 | II. |
| 601/a | *S. aureus* | – | 1/8 | – | – | – | II. |
| 606/a | *S. aureus* | – | 1/8 | – | – | – | II. |
| 704/a | *S. aureus* | – | 1/4 | – | – | – | III. |
| 710/a | *S. aureus* | 1/4 | 1/4 | – | – | – | I. |
| 714/a | *S. aureus* | 1/8 | – | – | – | – | III. |
| 714/b | *S. aureus* | – | – | – | – | – | I. |
| 717/a | *S. aureus* | 1/2 | – | – | – | – | III. |
| 725/a | *S. aureus* | 1/4 | – | – | 1/4 | 1/4 | I. |

*Dilution ratio of the culture filtrates, where the endpoint of the reaction is
a = throat isolate, b = nasal isolate

*S. aureus* strain plays a significant role in the pathomechanisms of SIDS. Many infants (40–50%) are colonized by *S. aureus* in the first few months of life [13, 14]. Pyrogenic toxins are produced only between 37–40 °C [15]. Normally the temperature of mucous membranes of respiratory tract is under 37 °C, therefore, increases in local nasal temperature as was observed in the prone position as respiratory discharge provide a favorable microenvironments for the production of toxin [16, 17]. The superantigen activity of pyrogenic toxins of *S. aureus* might trigger powerful inflammatory mediators [2, 18]. The significance of pyrogenic toxin-producing strains of *S. aureus* in the pathogenetic reactions of SIDS has been suggested by several researchers [5, 19, 20].

SIDS victims had a higher carriage rate of toxin producing staphylococci and coliforms in the nasopharynx than healthy infants in England [14, 21]. *S. aureus*, *Streptococcus* spp., *Enterococcus* spp., toxigenic *E. coli* in the nasopharyngeal flora and *C. perfringens* in faecal samples were present in higher numbers in SIDS infants

compared with infants who died of other causes and live infants in Australia [22]. *S. aureus* was found in 86% of Scottish SIDS but only in 56% of healthy infants [14].

*S. aureus* was isolated in high numbers of 2–4 month old infants. In this age group the peak of SIDS incidence was probably due to expression of the Lewis antigen, an epithelial receptor of *S. aureus*, found in nearly 90% of the infants. It has been suggested that the colonization of infants by *S. aureus* was growing in this age range [23].

**Table VII**

*Distribution of toxigenic and non-toxigenic strains in* S. aureus *carriers*

| | Toxigenic *S. aureus* (%) | Non-toxigenic *S. aureus* (%) | Total |
|---|---|---|---|
| SIDS infants | 6 (86) | 1 (14) | 7 |
| Healthy infants | 16 (43) | 21 (57 ) | 37 |
| Total | 22 | 22 | 44 |

OR=7.875 95% CI=0.78–191.89

In Hungary *S. aureus* was the predominant isolate from the SIDS cases. *S. aureus* was isolated from 54% of SIDS cases and only 37% from healthy infants /OR=1.986 (95% CI=0.55–7.33), p=0.423/. According to our study toxigenic *S. aureus* was detected in 46% of SIDS cases and only 16% in healthy infants /OR=4.500 (95% CI=1.15–17.72), p=0.010/. Considering all cases, the prevalence of *S. aureus* was twice higher and the toxin production activity of these strains was four and half times higher in SIDS cases than among healthy infants.

Distribution of toxigenic and non-toxigenic isolates showed a significant difference between SIDS (86%), and healthy infants (43%) /OR=7.875 (95% CI=0.78–191.89), p=0.041/. This result shows higher possibility for carrying of toxigenic *S. aureus* in SIDS cases than in controls.

There was also a great difference in the characteristics of the toxin producing activity of our isolates. Two or three different types of pyrogenic toxins were detected in larger amounts in the isolates from SIDS cases than in the isolates from healthy infants. The superantigenic properties of these pyrogen toxins exert a markable effect on the immune system and formation of larger amount of cytokines.

In summary: We could detect significantly larger number of toxigenic *S. aureus* strains, larger amount of toxins, different types of pyrogenic toxin producing isolates in the SIDS cases than in the control group.

SEA and SEB producing isolates were predominant. Similar results were reported by a Hungarian pediatric study dealing with urticaria like toxic allergic exanthema in early childhood and upper respiratory tract infections caused by toxin producing *S. aureus* [24]. In our study 46% of SIDS victims carried toxigenic *S. aureus* strains. These results were similar to the ELISA and/or flow cytometry data of tissue and serum of SIDS cases reported by Zorgani et al [25]. They detected pyrogenic toxins in samples from SIDS infants in Scotland (56%), France (55%) and Australia (53%) [25]. Detection of pyrogen toxins in half of SIDS cases in these three countries and isolation of toxigenic *S. aureus* in nearly 50% of Hungarian SIDS cases suggest that these findings are not local phenomena.

Results of autopsy and histological examinations did not show any special features. The circulatory failure or inflammatory mediators, pyrogen endotoxins directly could cause petechial haemorrhages in the region above the diaphragma. Howat's pulmonary immunopathological examinations of SIDS cases have indicated similar results [7].

Superantigenic toxins of *S. aureus* and LPS of Gram-negative bacteria may be linked to antigens CD14 of alveolar macrophages and monocytes. Through TNFα induction they can cause fever and release of various inflammatory mediators, including IL1, interferon-χ and thrombocyte activating factors [26, 27]. The cytokines may cause heat or vascular shocks, hypoglycemia, deep sleep and apnoe leading to sudden death during the period of adaptation to life [14, 28].

*S. aureus* strains appear to play a significant role in the pathogenesis of SIDS. Therefore, microbiological screening for the newborns at SIDS risk is considered to be highly useful to find a factor of the multicausal SIDS.

Abbreviations: **SIDS** = Sudden Infant Death Syndrome, ***S. aureus*** = Staphylococcus aureus, **SEA** = Staphylococcus Enterotoxin A, **SEB** = Staphylococcus Enterotoxin B, **SEC** = Staphylococcus Enterotoxin C, **SED** = Staphylococcus Enterotoxin D, **TSST-1**=Toxic Shock Syndrome Toxin – 1, **OR** = Odds ratio, **CI** = confidence interval

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