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Investigation of sudden death caused by asymptomatic respiratory infections in infants

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SUMMARY

Previous studies have reported that respiratory infections can cause sudden death in infants. In one report, many infants had mild respiratory infection symptoms before their sudden death. However, we have also seen many cases of sudden death in asymptomatic infants who were diagnosed with respiratory infections based on detailed postmortem examinations. However, no study has investigated the differences between symptomatic death and asymptomatic death in infants with respiratory infections. In the present study, the risk factors for sudden death in infants with asymptomatic antemortem respiratory infections were investigated using forensic autopsy cases in our laboratory. The investigation showed that deaths associated with asymptomatic respiratory infections were relatively more common in infants younger than one year, of normal birth weight, and fed exclusively with formula milk, as well as infants who had fallen asleep within one hour of their last meal. The results reconfirmed that such small daily changes, such as expression and behavior changes, should be carefully observed when managing infants, including those with no apparent health problems.

Keywords: sudden infant death syndrome (SIDS) – sudden unexpected death in infants (SUDI) – asymptomatic sudden death – infants – respiratory infection

Náhlá úmrtí kojenců způsobená asymptomatickou respirační infekcí

SOUHRN

Z předchozích studií vyplývá, že respirační infekce mohou způsobit náhlé úmrtí kojence. Jeden z článků uvádí, že mnoho kojenců mělo před náhlým úmrtím mírné příznaky infekce respiračního traktu. Nicméně z naší zkušenosti vyplývá, že je i mnoho případů náhlých úmrtí asymptomatických kojenců, přičemž diagnóza respirační nákazy je prokázána až na základě podrobného posmrtného vyšetření. Bohužel žádná ze studií nebyla zaměřena na porovnání rozdílů mezi náhlým úmrtím kojenců s klinickými příznaky a při jejich absenci.

Autoři prezentují studii, ve které jsou zkoumány případy náhlých úmrtí asymptomatických kojenců a hodnotí rizikové faktory u těchto jedinců, jejichž pitvy byly provedeny na daném pracovišti. Studie prokazuje, že k těmto asymptomatickým úmrtím dochází častěji u dětí do 1 roku věku, normální porodní váhy, krmených výlučně náhražkami mateřského mléka, a dále u kojenců, kteří usnuli do jedné hodiny od posledního krmení. Výsledky studie potvrzují, že i nejmenší odchylky od běžných projevů dítěte by měly být pečlivě sledovány pečující osobou, a to i v případě, že kojenec nevykazuje žádné zřejmé zdravotní problémy.

Klíčová slova: syndrom náhlého úmrtí kojence (SIDS) – náhlé a neočekávané úmrtí kojence (SUDI) – asymptomatické náhlé úmrtí – kojenci – respirační infekce

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Respiratory infections have long attracted attention as potential causes of sudden death of infants, namely in cases of sudden infant death syndrome (SIDS) and sudden unexpected death in infants (SUDI) (1,2). Globally, no reports have performed detailed analyses of the causes of serious progression of the infection despite the infant being asymptomatic and the related risk factors. The present study aimed to examine cases with clear antemortem symptoms and asymptomatic cases in terms of individual factors, medical factors, and environmental factors in infants with respiratory infection who died suddenly. In addition, the risk factors that led to death despite the absence of symptoms were examined retrospectively.

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MATERIALS AND METHODS

Of the 2,453 medicolegal autopsy cases over 15 years (January 2005 to January 2020) in our department, 65 death cases were caused by respiratory infection before 2 years of age. These cases were classified into two groups: 26 cases (40 %) in the group presenting with some kind of symptom before death (symptom-positive group) and 39 cases (60 %) in the asymptomatic group (symptom-negative group). The factors evaluated in all cases included individual factors, medical factors, and environmental factors. In particular, since we hypothesized that disturbances in the rhythm of daily activities might be a risk factor for various infections, based on our experience, we focused on the time of milk intake before and during sleep, as well as the bath time and bedtime, when conducting the examination. For comparisons between groups, the nonparametric χ^2 test was used. The Games-Howell test was used for analyses involving multiple comparisons.

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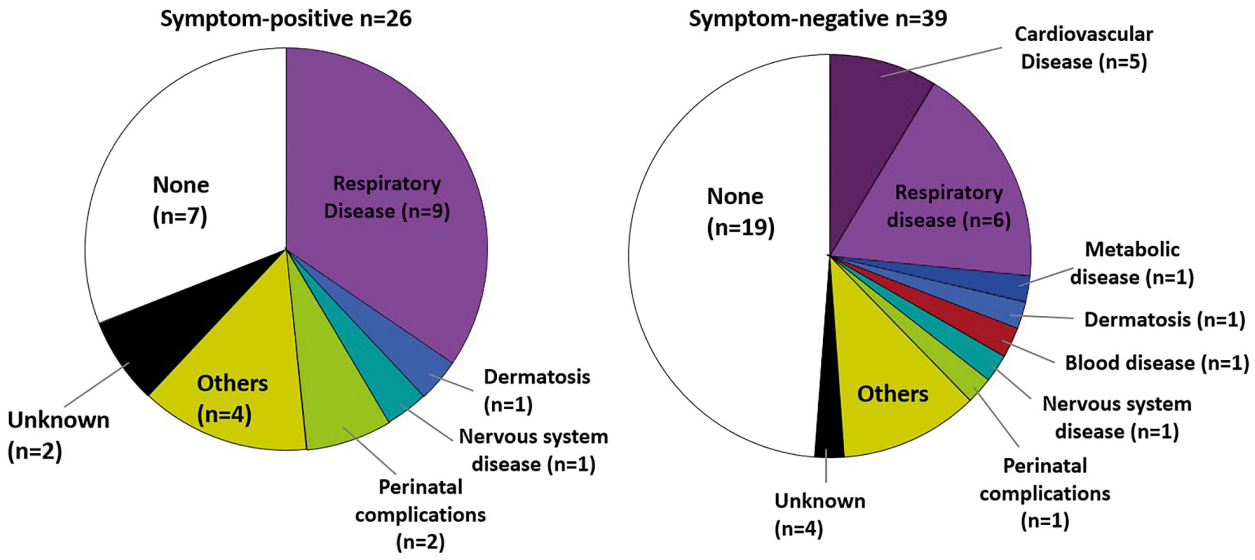


Fig. 1. Medical history of the infants.

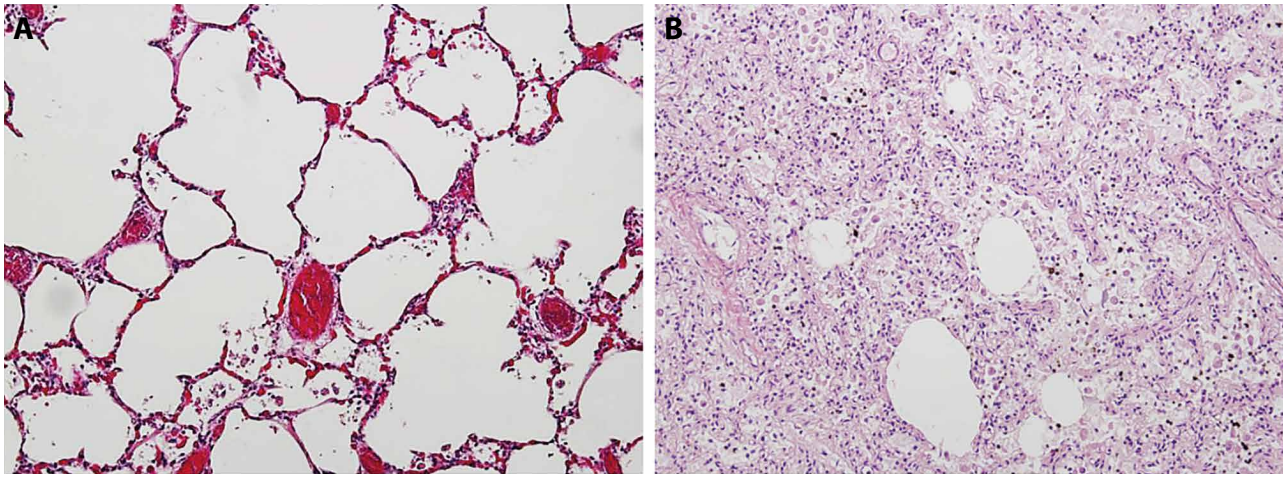


Fig. 2. Histopathological finding of lymphocytic infiltration within the alveoli and the alveolar interstitium (H.E. ×100) (**A**: asphyxia case (control), **B**: viral infection).

RESULTS

Medical history (including congenital anomalies)

Of the 65 cases, 34 had a medical history (34/65, 52.3 %), including 17 cases in the symptom-positive group (17/26, 65.4 %) and 17 cases in the symptom-negative group (17/39, 43.6 %) ($P>0.05$ by χ^2 tests). Respiratory diseases included five cases of a common cold (symptom-positive group: n = 4/26, 15.4 % and symptom-negative group: n = 1/39, 2.6 %), four cases of tachypnea (symptom-positive group: n = 2/26, 7.7 % and symptom-negative group: n = 0/39, n=0 %), and the following other respiratory conditions: bronchitis, asthma, chronic lung diseases, pneumonia, pneumothorax, and herpangina in 1-2 cases each (χ^2 $p<0.05$). All diseases reported in the medical history were stable or cured completely. Therefore, these diseases were not related to death (Fig. 1).

Medical factors

Types of causative viruses and bacteria

Of the 65 cases of respiratory-related deaths, most were viral infections (30 were viral infections, 46.1 %), excluding six cases of mycoplasma (6/65, 9.2 %) (χ^2 $p<0.05$). Adenovirus was the most common in the symptom-positive group (7/26, 26.9 %), and respiratory syncytial virus (RS virus) was the most common in the symptom-negative group (7/39, 17.9 %). The *Staphylococcus* genus was most commonly detected among primary bacterial infections in both the symptom-positive and symptom-negative groups (12/26, 46.2 %; *Staphylococcus aureus* 4/12, methicillin-susceptible *Staphylococcus aureus* (MSSA) 5/12 (χ^2 $p<0.05$). Distinct swelling of the hilar lymph nodes was observed in 16 cases (16/65, 24.6 %), including 10 in the symptom-positive group (10/26, 38.5 %) and six in the symptom-negative group (6/39, 15.4 %). Finally, histopathological examination showed lymphocytic infiltration within the alveoli and alveolar interstitium in 25 cases in the symptom-positive group (25/26, 96.2 %) and 34 cases in the symptom-negative group (34/39, 87.2 %) (Fig. 2).

Environmental factors

Time of last meal, such as milk

Milk was the main food, taken from late at night to early in the morning (12 midnight to 6 am) in 11 cases each in the symptom-positive and symptom-negative groups (11/26, 42.3 % and 11/39, 28.2 %, respectively), from early morning to midday (6 am

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to 12 noon) in three and six cases (3/26, 11.5 % and 6/39, 15.4 %, respectively); and from noon to evening (12 noon to 6 pm) in two (2/26, 7.7 %) and three (3/39, 7.7 %) cases (Grames-Hamell test $p<0.05$), respectively. To clarify the link between late-night eating and death, the last meal was taken from evening to late at night (6 pm to 12 midnight) in eight (8/26, 30.8 %) and 16 (16/39, 41.0 %) of the symptom-positive and symptom-negative cases, respectively (χ^2 $p<0.05$) (Fig. 3).

Last bat,h time

A bath was taken from late at night to early morning (from 12 midnight until 6 am) in only two cases in the symptom-negative group (2/39, 5.1 %). There were no cases in which a bath was taken from early morning to midday (6 am to 12 noon). A bath was taken from noon to evening (12 noon to 6 pm) in two (2/26, 7.7 %) and one (1/39, 2.6 %) cases, respectively, and from evening to late at night (6 pm to 12 midnight) in five (5/26, 19.2 %) and 10 (10/39, 25.6 %) cases (Grames-Hamell $p<0.05$), respectively, in the symptom-positive and symptom-negative groups. For a total of 20 cases, including 11 cases in the symptom-positive group (12/26, 46.2 %) and nine cases in the symptom-negative group (9/39, 23.1 %) (χ^2 $p<0.05$), it was reported that the infants were not bathed at regular times.

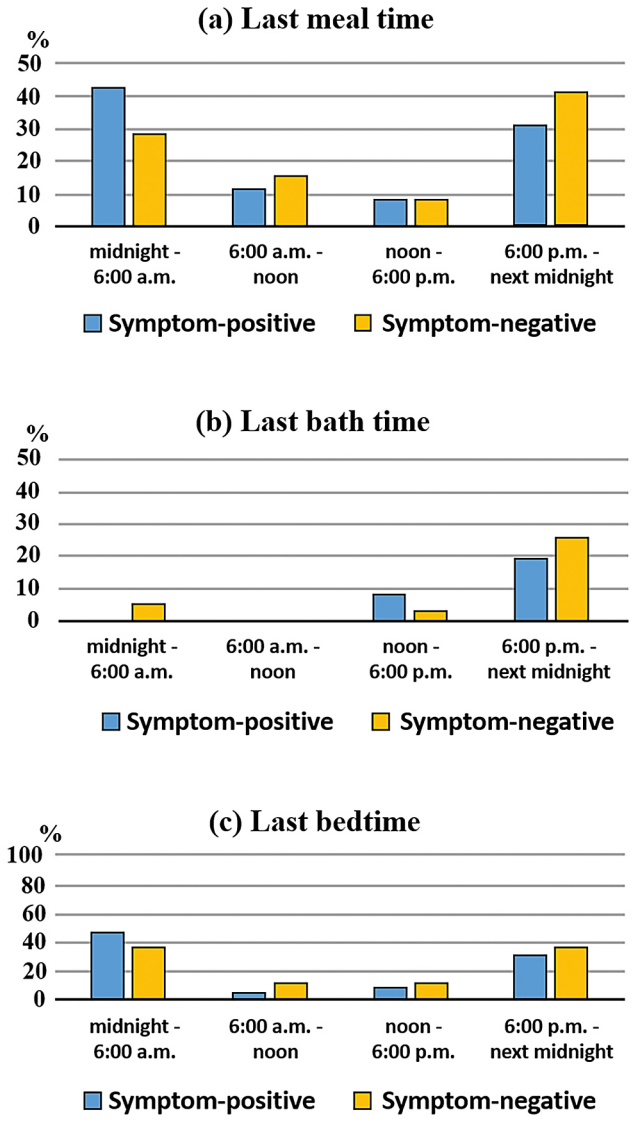


Fig. 3. A: Last meal time. In the symptom-negative group, approximately 40% of cases have their last meal before death from 6 pm to midnight. **B**: Last bath time. **C**: Last bedtime

Last bedtime

The last bedtime was from late at night to early morning (from 12 midnight to 6 am) in 12 (12/26, 46.2 %) and 14 (14/39, 35.9 %) cases, from early morning to midday (6 am to 12 noon) in one (1/26, 3.8 %) and four (4/39, 10.3 %) cases (Grames-Hamell $p<0.05$), from noon to evening (12 noon to 6 pm) in two (3/26, 11.5 %) and four (4/39, 10.3 %) cases, and from evening to late at night (6 pm to 12 midnight) in eight (7/26, 26.9 %) and 14 (14/39, 35.9 %) cases in the symptom-positive and symptom-negative groups, respectively. Furthermore, 39 (39/65, 60.0 %) of the infants went to bed within 1 h of their last meal, including 12 cases in the symptom-positive group (12/26, 46.2 %) and 27 cases in the symptom-negative group (27/39, 69.2 %); infants mainly went to bed within 1 h in symptom-negative cases (Grames-Hamell $p<0.05$ tests).

Time of death

Of the 65 cases, infants died from late at night to early morning (12 midnight to 6 am) in 11 (11/26, 42.3 %) and 17 (17/39, 43.6 %) cases, mainly late at night to early morning, respectively (Grames-Hamell $p<0.05$); from early morning to midday (6 am to 12 noon) in eight (8/26, 30.8 %) and eight (8/39, 20.5 %) cases; from noon to evening (12 noon to 6 pm) in four (4/26, 15.4 %) and seven (7/39, 17.9 %) cases; and from evening to late at night (6 pm to 12 midnight) in three (3/26, 11.5 %) and seven (7/39, 17.9 %) cases in the symptom-positive and symptom-negative groups, respectively. On investigation of the bedtime of infants who most commonly died during the period from late at night to early morning (12 midnight to 6 am), in the symptom-positive group, eight of the infants (8/11, 72.7 %) ($p<0.05$) fell asleep from late at night to early morning (12 midnight to 6 am); of the eight infants, two fell asleep (2/11, 18.2 %) from evening to late at night (6 pm to 12 midnight), and the bedtime was unknown in one case (χ^2 $p<0.05$). Meanwhile, in the symptom-negative group, nine (9/17, 52.9 %) of the infants fell asleep from late at night to early morning (12 midnight to 6 am), seven (7/17, 41.2 %) from evening to late at night (6 pm to 12 midnight), and the bedtime was unknown in one case.

DISCUSSION

In our department, 65 infants with respiratory infections identified on autopsy were evaluated. Of them, 39 cases were asymptomatic before their death, accounting for 60 % of the deceased infants with respiratory infections, despite the infection being fatal.

There was no clear difference in the male-to-female ratio between the groups with and without respiratory symptoms. In the deceased infants, over 90 % of the symptom-negative group were younger than 1 year of age. Previous reports have also demonstrated that infants are less likely to show signs of infection despite having a higher incidence of respiratory infections than adults (3,4). Furthermore, the younger the age, the easier it is for pneumonia to become serious (6,7). Reportedly, low birthweight makes infants prone to pneumonia exacerbations (5).

Regarding the living environment of the deceased infants, the time of the last meal, such as milk, was common in two time periods, i.e., from midnight to 6 am and from 6 pm to midnight. Consumption of the last meal between midnight and 6 am was seen in 42 % of cases in the symptom-positive group, where-

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as the last meal was consumed between 6 pm and midnight in 41 % of the symptom-negative group. Regarding bedtime, many cases in the symptom-positive group had a bedtime between midnight and 6 am, whereas bedtime soon after feeding between 6 pm and midnight was common in the symptom-negative group. Sleeping within 1 h of feeding is thought to be one of the risk factors for sudden death in cases of respiratory infection. In the present study as well, the proportion of cases that slept within 1 h of feeding was higher in the symptom-negative group than in the symptom-positive group.

Infants with respiratory infections are thought to have poor underlying respiratory status, and the use of soft bedding, such as an adult mattress, for such infants might enhance the risk of sudden death, and, thus, should be avoided. (6).

The most common time of death was from late at night to early morning (from 12 midnight to 6 am) in both groups. In cases of death between midnight and 6 am in the symptom-negative group, the time of the last meal was between 6 pm and midnight in over two-thirds. Examination of the relationship between the time of death and bedtime showed no bias in the bedtime in cases of death in the early morning in the symptom-negative group, whereas bedtime was from 12 midnight to 6 am in over half the cases, and the time from bedtime to death was short in the symptom-positive group.

The present study showed a tendency for asymptomatic deaths associated with respiratory infection to include a relatively high number of infants of normal birthweight, younger infants (less than 1 year of age) who were only fed formula milk, and those who fell asleep within 1 h after their last meal. Therefore, they should be considered risk factors for death associated with asymptomatic respiratory infections, although further evaluation with a larger study population is needed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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