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Clinicopathological features of sudden unexpected infectious death: Population-based study in children and young adults

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ABSTRACT

Introduction and objectives: Infectious diseases are one of the major causes of sudden death, but data of sudden unexpected death from infectious diseases (SUDID) are sparse in children and young people. The aim of this study is to analyse their epidemiological, clinical, pathological and microbiological characteristics.
Methods: Population observational study of all deaths due to infectious diseases in people aged 0–34 years in Biscay between 1991 and 2010. The data of Mortality Register and Forensic Pathology Service were analysed. The SUDID cases in which a forensic autopsy was performed were identified.
Results: There were 56 SUDID cases (16% of the all sudden deaths). Myocarditis ($n = 20$) and acute bacterial bronchopneumonia/pneumonia ($n = 18$) were the most frequent causes, followed by meningococcemia ($n = 5$) and viral pneumonia ($n = 4$). A chronic co-morbid condition (mainly drug abuse in young people and moderate low birth weight in infants) was recorded in one-third and prodromal symptoms in two-thirds. Seventeen young people had consumed illegal drugs and/or methadone. In 17 of the 23 autopsies where microbiological analyses were performed, the organism responsible was identified. The incidence of SUDID was 0.6/100 000 inhabitants/year, representing 5% of all deaths from infectious diseases. SUDID rate was 1.87 times higher in males than in females. The highest incidence occurred in infants (3.7).
Conclusions: SUDID is infrequent, but it represents a significant proportion of all sudden deaths in children and young people. The relationship between methadone and bronchopneumonia is noticeable. This article stresses the importance of microbiological analyses in SUDID. Investigation based on forensic pathology provides useful epidemiologic, clinico-pathological and microbiological information for prevention of infectious diseases.

1. Introduction

In high-income countries, mortality from infectious diseases in children and young people is uncommon [1]. Occasionally, the course of the infectious diseases is atypical, especially aggressive, and death occurs unexpectedly without a diagnosis in life. In these sudden deaths (SDs), a forensic autopsy is required and microbiological analyses are needed to identify the aetiology of the infection [2]. The relevance of performing microbiological investigations in sudden unexpected deaths in infancy has been pointed out in recent articles [3,4].

SD in children and young people is infrequent. Infectious diseases are one of the major causes, especially in the youngest [5–14]. Although in the past decade concern about sudden cardiac death has been growing, data addressing the issue of epidemiology and causes of sudden unexpected death from infectious diseases (SUDID) are sparse. According to a systematic review done on 30 June 2011, we did not identify any specific population based series about SUDID in children and young people. Data are limited to case reports, small descriptive series, sudden unexpected death in infancy and inclusion of SUDID cases within series of SD of all causes, where data about SUDID are neglected. Furthermore, in these studies mortality is usually evaluated together for children, adolescents and young people,

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and SUDID data are not disaggregated by age group. In addition, no previous studies have evaluated the proportion of deaths due to infectious diseases that are sudden and unexpected. As a consequence, the actual incidence and distribution of SUDID by sex and age group in well-defined populations is poorly characterised.

Prospective population studies based on forensic autopsies could be useful to improve our knowledge of these fatal infections. This population-based observational study has three main objectives:

- to assess the incidence of SUDID in a well-defined general population and its magnitude in relation to the total number of deaths due to infectious diseases in children and young people;
- to analyse the causes of SUDID and its clinical characteristics; and
- to evaluate the utility of microbiological post-mortem analysis in the identification of the aetiological agent.

2. Materials and methods

The study was conducted from 1991 to 2010 (inclusive) in Biscay, an industrial province of the Basque Country, with a population about 1 150 000 inhabitants. In accordance with the law, a forensic autopsy (judicial investigation) is necessary in all violent deaths and those where a crime is suspected. This includes natural or unexpected sudden deaths in non-hospitalised people. A medical death certificate, signed by the doctor treating the patient for a previously detected illness, is required in all other natural deaths (without judicial intervention).

The information from the medical death certificates and the forensic autopsy reports reaches the Mortality Register of the Autonomous Community of the Basque Country, where the basic cause of death is selected and codified, following the regulations established in the International Classification of Diseases: from 1991 to 1998 it was coded with ICD-9 and from 1999 with ICD-10 [15].

People aged 0–34 years who died due to an infectious disease (ICD-9 codes: 001-139, 279.5.6, 795.8, 320-324, 420.9, 421.0, 422.9, 460-466, 475, 480-487. 510, 540, 566, 567, 569.5, 574.0.1.3.4., 575.0.1, 680-686, 580, 599.0, 614, and 771; ICD-10 codes: A00-B99, G00-G07, I30.1, I33,0, I40,0, J00-J22, J36, J39,0,1, J85-J86, K35, K61, K63,0, K65, K80,0,1,3,4, K81, L00-L08, N10, N39.0; N70, P35-P39, and R75) [15] were included in the study. The incidence of mortality for the total of infectious diseases (forensic autopsy and medical death certificate data) was calculated according to data from the Mortality Register. By definition, we assumed that only those cases in which a forensic autopsy was performed were SD, and therefore, frequency and incidence of SUDID derived from data of the Forensic Pathology Service.

2.1. Data from the forensic pathology service

SD was defined as that which occurs naturally (non-violent), unexpectedly and within a period of few hours from the beginning of the warning symptoms in a person in an apparently good state of health who has not been admitted to hospital and who is performing everyday activities at the time of the beginning of the symptoms [4,13,16]. In the unwitnessed deaths or those occurring during sleep, data were included when these people had been seen in a good state of health in the 24 h before their death. Healthy people with prodromal symptoms – defined as apparently mild or moderate health changes in the days or hours before death – were included.

In Biscay, an autopsy – following a standardised protocol – is performed in cases of SD in children and young adults. All autopsies are carried out in the province's only pathology service, which is also in charge of supervising medical death certificates. This procedure allows for optimal capture of SD cases in this age.

In 1991, we began a project for the study of sudden death in Biscay. Since then a prospective assessment of the cases with uniform registration of relevant data has been performed. In each case, a complete autopsy was carried out, as well as toxicological and histopathological studies. Medical information and circumstances surrounding death were also reviewed. This information was obtained from medical reports, police statements and usually from interviews with relatives of the deceased. In some autopsies, principally along the last 10 years, microbiological studies were also performed. A specific microbiological procedure was not implemented until 2001 [17]. Before then, microbiological analyses were only performed when there was a high suspicion of infection. The cause of death was established according to medical, histopathological and microbiological criteria. For the diagnosis of bronchopneumonia, diffuse involvement of the majority of lung fields by the inflammatory process, or abscess formation was required [16].

2.2. Statistical analysis

Age was classified into four groups: <1 year, 1–14 years, 15–24 years and 25–34 years. The chi-square test was used to assess the possible existence of differences in the distribution of the absolute frequencies in the groups of causes of SD (SUDID and other causes of SD) according to sex and age groups. For this analysis, the Fisher exact test was used to compare qualitative variables with expected counts <5. The significance level chosen was $p < 0.05$. All the analyses were performed using the SPSS programme (Statistical Package for Social Sciences).

2.3. Epidemiological analysis

The population of Biscay by age and sex was obtained by linear inter- and extrapolation between the censuses provided by the Basque Institute of Statistics/EUSTAT. The population aged 0–34 years in 1991 was 576 151; in 1996 it was 515 530; in 2001 it was 454 150; in 2006 it was 425 288; and in 2010 402 202.

The following were calculated for each sex:

- adjusted rates for age by means of direct standardisation with a confidence interval of 95%, using the standard European population as the reference population for the population between 0 and 34 years of age;
- ratio of standardised rates with a confidence interval of 95% to calculate the relative risk between sexes; and
- specific rates for age groups [18].

3. Results

3.1. General data of sudden unexpected infectious death

According to the data from the Forensic Pathology Service during the 20 years of the study, there were 339 SDs in Biscay in people aged 0–34 years (Table 1). Of them, 56 were SUDID (16.5%). This percentage was higher among children aged 1–14 years (32%) than in other age groups, but did not reach statistically significant differences.

The main pathologies responsible for SUDID by organ system were respiratory and cardiac diseases. The percentage of SUDID in relation to the total SD was the highest for respiratory pathology (Table 1). Myocarditis and acute bronchopneumonia/pneumonia were the most frequent causes, followed by meningococcaemia and viral pneumonia (Table 2). In people aged 15–24 years, the main cause of SUDID was myocarditis (60%) and in people aged 25–34 years, it was bronchopneumonia (39%).

The circumstances surrounding SUDID are shown in Table 3. Most deaths occurred out of hospital. Approximately one-third of the subjects were found dead in bed. In 53% of those with a known period of time since the onset of symptoms (excluding also the deaths in bed), it was higher than 1 h. Eighty-two percent of deaths with an interval of less than 15 min were due to myocarditis.

A history of chronic co-morbid conditions predisposing for fatal infectious disease was recorded in one-third of the subjects and prodromal symptoms in the hours and/or days prior to death in two-thirds (Table 3).

Table 1
Distribution of cases of sudden deaths (SD) and sudden unexpected death from infectious diseases (SUDID) according to sex and age groups.

	SD cases	SUDID cases (% file)
Sex		
Male	231	37 (16)
Female	108	19 (17.6)
Age-group (years)		
<1	67	7 (10.4)
1–14	25	8 (32)
15–24	72	10 (13.9)
25–34	175	31 (17.7)
Causes of death (by organ system)		
Cardiac	123	21 (17.1%)
Sudden unexplained death[a]	97	0
Respiratory/pulmonary	53	24 (45.3%)
Neurologic	44	2 (4.5)
Others	22	9 (40.9)
Total	339	56 (16.5)

[a] Sudden unexplained death includes sudden infant death syndrome of infants under 1 year of age.