Causes of Sudden Unexpected Death in Childhood: Autopsy findings from a Specialist Centre

Bryant VA[1], Jacques TS[2], Sebire NJ[2]

[1] Department of Cellular Pathology, The Royal London Hospital, London, UK

[2] Histopathology Department, NIHR GOSH Biomedical Research Centre and GOS Institute of Child Health UCL, London

Correspondence
Prof NJ Sebire
Histopathology
Level 3 CBL Labs
Great Ormond Street Hospital
London WC1N 3JH
neil.sebire@gosh.nhs.uk

Abstract

Objectives: To investigate the aetiologies of sudden unexpected death from natural causes in children aged 1-18 years by retrospective examination of autopsy records from a single centre.

Materials and methods: The post-mortem findings from 548 children (1996-2015), were examined. Details were entered into an established research database and categorized according to >400 pre-defined criteria.

Results: There were 265 previously apparently healthy children and 283 with pre-existing, potentially life-limiting, conditions. There were more males than females (M:F 1.4:1), and deaths were more frequent in the winter. Infection was commonest accounting for 43% of all deaths. Non-infectious diseases were identified as cause of death in 28%, and 29% of all deaths were unexplained. There was no significant difference in the proportions of deaths in each category between the previously healthy children and those with pre-existing conditions.

Conclusion: Sudden unexpected death is a rare presentation of death in childhood and those with pre-existing conditions may be more at risk. Standardization of the post-mortem procedure in such cases may result in more ancillary investigations performed as routine and may reduce the number of cases that are ‘unexplained’.

Key words: sudden unexpected death, autopsy, post-mortem, unexplained, pre-existing conditions

Introduction

Around half of all childhood deaths in England and Wales are due to pre-existing conditions (PEC), most commonly malignant diseases and non-malignant neurological conditions.[1] Of the approximate 5,000 deaths per annum in 0-19-year olds, around half affect infants (defined as aged <1 year), with the majority of these occurring in the neonatal period (0-28 days of age).[1] In infants older than 28 days, the commonest single cause of death is 'unexplained', accounting for around 25% of all such deaths. Sudden unexpected death (SUD) in childhood is defined as the death of a child, over 1 year of age, which was not reasonably expected to occur 24 hours previously.[2] SUD is rare and may be due to natural or non-natural causes (such as accidents, trauma, suicides and non-accidental injury). It can affect both apparently previously healthy children as well as those with pre-existing conditions (which we have termed SUD-PEC), defined as life-limiting conditions for which there is no reasonable hope of cure.[3]

In the UK, investigation of SUD in childhood falls under the auspices of Her Majesty's Coroner (HMC) or Procurator Fiscal (PF) in Scotland, hence all are treated as medicolegal cases. As part of the investigation of such deaths HMC (or PF) will instruct that a post-mortem examination (autopsy) be performed usually by a registered specialist paediatric pathologist, with a review of the circumstances of death and previous medical history. In cases of suspected non-accidental injury the autopsy is performed in conjunction with a forensic pathologist. Fortunately, SUD in childhood is a rare presentation of death. However, this, coupled with the need for specialist investigation, has resulted in limited published evidence of the underlying aetiologies.

The aim of this study is to provide data from a retrospective review of the autopsy findings from a large cohort of SUD in childhood investigated in a single centre.

Materials and Methods

Great Ormond Street Children's Hospital (GOSH) is a tertiary referral centre for rare diseases of childhood. There is a team of specialist paediatric pathologists who perform post-mortem examinations on foetuses, infants, and children including consented hospital autopsies, and medicolegal autopsies at the behest of HMC.

This is a retrospective, observational study based on the autopsy records of a large series of consecutive post-mortem examinations performed in cases of SUD in childhood on behalf of HMC over a 20-year period from 1996-2015 inclusive. All autopsies were performed by or under the direct supervision of specialist paediatric pathologists.

All autopsies in children aged 1-18 years who died suddenly and unexpectedly from natural causes were included. Cases were divided into two groups: the SUD cohort included all previously apparently healthy, normally developed children in whom death occurred unexpectedly and without evidence of significant antecedent illness (i.e. the child was reported to be in good health, or with symptoms developing less than 24 hours prior to death which were not considered to be life-threatening by guardians or medical professionals). The SUD-PEC cohort included those children with pre-existing debilitating conditions who were reported to be in relatively good health prior to a sudden unexpected death. Consented autopsies, suspected non-natural deaths, second post-mortem examinations, incomplete autopsies, and deaths associated with recent invasive procedures were not included.

Data were extracted from the post-mortem report and entered into a research database containing >400 standardised pre-defined fields. This included clinical and demographic information, details of external and internal macroscopic and microscopic findings, results of ancillary investigations, and the cause of death as diagnosed by the examining pathologist. For each case the cause of death was categorised into infectious causes, non-infectious or unexplained, based on objective pre-defined criteria and definitions.[4] The database was anonymised with no personal identifiers entered, and birth dates were

reassigned to the 1st day of the birth month with linked changes to the date of death to preserve the age at death.

Where no cause of death was identified from the post-mortem examination, the death was classified as 'unexplained'. Unexplained SUD-PEC required that there be no evidence of an acute event to account for the death, and for the circumstances and severity of the pre-existing condition considered by the examining pathologist to be insufficient to explain the death.

Statistical analysis was performed using R in R-studio version 3.2.0. Non-parametric tests were used for non-normally distributed data, continuous variables were presented as median and range, or mean and standard deviations if normally distributed. Differences between groups were analysed using chi-squared test, Fisher's exact test, Wilcoxon test and Kruskal-Wallis rank sum tests as appropriate.
The level of statistical significance was set at $p \leq .05$.

The study was approved by the local NHS Research Ethics Committee (BloomsburyREC16/LO/0910).

Results

During the 20-year period, 762 coronial post-mortem examinations were performed in children 1-18 years old at GOSH. Of these, 548 met the inclusion criteria, including 265 SUD and 283 SUD-PEC. The remaining 214 included 75 non-sudden or expected deaths, 70 non-natural deaths, 48 deaths related to invasive procedures, and 21 cases with incomplete data.

Of the 548 cases included, there was a male predominance with a male-to-female ratio of 1.4:1. There was no significant difference between SUD and SUD-PEC cohorts in sex

distribution, median age at death, or post-mortem interval (PMI) – defined as the time between death and post-mortem examination (Table 1).

Pre-existing neurological conditions were reported in 53% of SUD-PEC, of which one fifth were associated with prematurity. Of note, gestational age at birth was not available in all cases. Cardiovascular disease accounted for 17% of all pre-existing conditions. Non-cardiac, non-neurological syndromes affected 11%, and the others were a mix of conditions including two children under investigation for ongoing debilitating symptoms without a diagnosis made in life (Figure 1).

Infection was the commonest cause of death (43% overall) with similar proportions in each cohort: 46% of SUD versus 40% of SUD-PEC (p=.18). Post-mortem diagnosis of infection was dependant on a combination of macroscopic, histological and/or microbiological investigations. If there was evidence of a primary focus of infection, for example pneumonia which required histological evidence of acute neutrophilic inflammation within alveoli, then this was determined to be the cause of death. Septicaemia was diagnosed on the basis of pure growth of a known pathogen in blood cultures in the absence of an identified primary focus of infection. Sepsis was determined to be cause of death in the absence of definitive microbiology or histology, based on a combination of features including the clinical history and circumstances of death with supportive macroscopic and microscopic findings.

Respiratory tract infection accounted for 50% of infection related deaths, with significantly more in the SUD-PEC cohort compared to SUD, 67% versus 35% respectively ($p<0.0001$). Diagnoses of septicaemia and sepsis accounted for almost 23% of all infection related deaths and were diagnosed more frequently in SUD compared to SUD-PEC, 30% versus 20% respectively. Acute myocarditis was responsible for 15% of infection related deaths with significantly more in the SUD cohort compared to SUD-PEC, 22% versus 8% respectively (p=.002). Less than 4% of all deaths were from

meningitis, and the remainder were from various conditions including a single case of tuberculosis, and a case of Falciparum malaria.

Non-infectious diseases accounted for 28% of all deaths with the same proportion in both cohorts. Non-infectious respiratory causes of death were commonest accounting for 36% of these with no significant difference between cohorts, 29% of SUD versus 41% of SUD-PEC (p=.2). Of these, acute asthma was the single most common diagnosis, accounting for 16% overall. Cardiovascular diseases were responsible for 26%, followed by gastro-intestinal, 18%, and central nervous system diseases, 9% - all with similar proportions in each cohort.

Thirty percent of deaths remained unexplained following post-mortem examination and there were similar proportions in each cohort: 26% SUD versus 33% SUD-PEC (p=.117; Table 3).

Significantly more deaths occurred in winter compared to other seasons (p=.005, Figure 2), but deaths per season did not differ significantly different between cohorts (p>.05). The main differences in numbers of deaths occurred in summer versus winter (p=.005) and autumn versus winter (p=.002), and were due to infectious causes (p=.0002, Table 4). There was no statistically significant seasonal variation in deaths from non-infectious diseases or unexplained deaths (p>.05).

Discussion

This study is the largest single centre series of sudden unexpected death in childhood. The findings have demonstrated that the single commonest identifiable cause of death is infection accounting for more than 40% of cases. However, 30% of deaths remained unexplained following specialist post-mortem examination. The proportion of deaths in each major category is similar between previously apparently healthy children and those who died suddenly and expectedly on a background of pre-existing conditions.

A literature search identified 14 autopsy studies (Figure 3), which included cases of sudden unexpected death in childhood and the results of these were compared with the current series (Table 5, Figure 4).[5-18] Several studies also included data from adults.[5-8,8,10,12] In some studies, various age ranges were grouped: for example, 1-10 year-olds and 11-20 year-olds,[8] 1-14 year- olds and 15-25 year-olds.[10,12] Several focused on the very young, often pre-school age children (< 5 years-old)[11] and the majority of their cases were infants <1 year-old.[14-18] Only three published studies separately identified those dying with pre-existing conditions.[5-7]

Several studies were concerned only with particular autopsy diagnoses; one focussed on infection and the others on non-infectious diseases, not further defined.[12] Some were most concerned with unexplained deaths, and it was not always possible to determine accurate numbers of infection and non-infectious disease-related deaths.[9,10,12,14,16,17] In six studies the sex distribution was reported or could be calculated from the published data.[6-9,11,14] All demonstrated a male predominance which is also consistent with the current series. An increased rate of deaths in males is also reported in sudden unexpected deaths in infancy (SUDI) and 60% of sudden infant death syndrome (SIDS) deaths affect males.[19]

In nine studies, infection was reported as the cause of SUD in childhood in 12-66% of cases. The two studies with very low proportions of infection-related deaths, reported as

12%[15] and 16%[6], included only small numbers of children, and also reported relatively high proportions of unexplained deaths, 76% and 44% respectively. A crude comparison with our SUD cohort (previously apparently healthy children) revealed some interesting results: overall, infection related deaths reported in the nine studies accounted for 42% (100/241) of the total SUD in childhood, which is similar to our finding of 46% ($p>.05$). SUD in childhood from non-infectious disease was reported in 12-57% of deaths in eight studies, in total amounting to 28% (63/223) of all SUD in childhood in these series , which is identical to our findings. Unexplained deaths were reported in twelve studies accounting for 14-76% of SUD in childhood, overall, this amounted to 32% (131/409) from the studies which is comparable to the 26% of unexplained SUD in our series ($p>0.5$).

Comparison of our SUD-PEC cohort, however, was very different. Only one death was reported to be from infection out of a total of 107 SUD-PEC cases in the literature. This was in the largest published study which included 92 SUD-PEC with 89% of deaths being from non-infectious causes.[5] This is totally at odds with the findings of our series and suggests that the autopsy protocols may have differed between SUD presenting in previously healthy children compared to those with pre-existing conditions. In that study the extent of microbiological investigations is not discussed, and although 'all available' histological sections were reported to be examined by the authors - the extent of histology sampling in the children with pre-existing conditions is not elaborated. Furthermore, only one death was unexplained which also does not concur with our findings. We wonder how many SUD in children with pre-existing conditions have been attributed to that condition in the absence of other findings?

This is the largest autopsy series of SUD in childhood to date including 548 cases over a 20-year period which provides more data than the other published studies combined. In our series, absolute numbers of SUD and SUD-PEC were similar. However, given that pre-existing conditions affect less than 10% of children >1 year-old [3] this must surely

reflect a greater relative frequency of sudden unexpected death in those children with pre-existing conditions. Broadly speaking the causes of death were similar in both cohorts with infection being the commonest cause overall. However, the frequency of respiratory tract infections was significantly higher in SUD-PEC versus SUD from infectious cause, 67% versus 35% respectively (p=.0001). We suspect that this may be related to the high proportion of pre-existing neurological conditions in this cohort, and further investigation is warranted. Conversely acute myocarditis and septicaemia/sepsis were more frequently observed in our SUD cohort compared to SUD-PEC. The reasons for this may be multifactorial and extend to social and environmental considerations which are beyond the scope of this study.

We recognise that the post-mortem diagnosis of sepsis as cause of death is a grey area with no specific markers for such a diagnosis. In this series only 9 (1.6%) cases were given sepsis as cause of death – whether a comprehensive review of the cases including histology would have resulted in a different outcome was beyond the scope of the current study.

The proportions of unexplained deaths are high which may, in part, be explained by the lack of a standardised protocol for the post-mortem investigation during the time period under investigation (1996-2015). In addition, autopsies were performed by ten different pathologists whose interpretation of findings could be variable, which could be a reflection on an individual's training and experience. Detailed analysis of the autopsy procedure revealed that in many cases there were further investigations which may have provided more information had they been utilized. his is particularly pertinent for metabolic investigations which historically were seldom performed in the investigation of unexpected deaths in children > 1 year-old. Today we know that metabolic diseases can manifest themselves at any age and may present as sudden unexpected death. [20-25] Toxicology was not routinely performed with only 21% of all unexplained deaths having toxicology investigations.

However, the proportion of unexplained childhood deaths in this series is significantly lower than that reported in a study of SUDI from the same centre, in which unexplained SUDI accounted for around 60%.[4]

We recognise the limitations of this retrospective observational study which was performed in a finite time period. The study did not involve a review of histology, rather relying on individual's descriptions and interpretations of findings as documented in the post-mortem report. As such subjectivity and observer bias was inevitable; this was mitigated by using predefined objective criteria for all entries into the database to standardise interpretation.

Lack of standardised post-mortem protocol was an unavoidable limiting factor. However, in 2016, the Royal Colleges of Pathologists, and Paediatrics and Child Health (RCPath and RCPCH) collaborated to produce multi-agency guidelines for the investigation of sudden unexpected death in infancy and childhood. [2] This is an update on the previous Kennedy guideline from 2004 which focussed on infant deaths. [26] The updated guidelines may help to standardise the post-mortem procedure and may result in more comprehensive use of ancillary investigations in the investigation of sudden unexpected death in childhood. This could potentially result in fewer deaths remaining unexplained.

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