Childhood Neoplasms Presenting at Autopsy; 20 year Experience

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Abbreviations key:

SUDNIC	Sudden Unexpected Death due to Neoplasia in Infancy and Childhood
CNS	Central nervous system
ALL	Acute lymphoblastic lymphoma/leukaemia
GP	General Practitioner
A&E	Accident & Emergency department
CoD	Cause of death

Abstract

Objective:

The aims of the review are to establish the number of undiagnosed neoplasms presenting at autopsy in a single centre and to determine the incidence and most common causes of Sudden Unexpected Death due to Neoplasia in Infancy and Childhood (SUDNIC).

Design:

Retrospective observational study of paediatric autopsies performed on behalf of Her Majesty's Coroner over a 20-year period (1996-2015; n=2432). Neoplasms first diagnosed at autopsy were identified from an established database and cases meeting the criteria for sudden unexpected death were further categorised.

Results:

Thirteen previously undiagnosed neoplasms were identified including five haematological malignancies, two medulloblastomas, two neuroblastomas, two cardiac tumours and two malignancies of renal origin. Eight cases met the criteria for SUDNIC (0.33% of autopsies) of which the commonest group were haematological malignancies (n=3).

Conclusions:

Neoplasms presenting as unexpected death in infancy and childhood and diagnosed at autopsy are rare. The findings suggest that haematological malignancies are the commonest cause of SUDNIC and highlight the importance of specialist autopsy in cases of sudden unexpected death.

Introduction

Neoplasms are rare in childhood, with around 1,600 new cases diagnosed annually in the UK in children under 15 years of age.[1] Despite this they are the most common cause of death from illness in children aged 1-15 years, accounting for around one quarter of such deaths in 2014.[2] Sudden unexpected death due to neoplastic disease in infancy and childhood (SUDNIC) is rare. A variety of neoplasms presenting as SUDNIC have been described, predominantly as case reports, most being cardiac neoplasms and central nervous system (CNS) tumours, accounting for a perception that these tumour types are the commonest causes of SUDNIC.[3-7] However, a retrospective series from Toronto reported haematological malignancies to be the commonest group in this setting.[3] The aims of this study are to establish the number of undiagnosed neoplasms presenting at autopsy in a specialist paediatric centre and to determine both the incidence and the most common cause of SUDNIC. The clinical presentation and autopsy findings will be examined together with a review of the literature related to SUDNIC.

Methods

At Great Ormond Street Hospital for Children, specialist paediatric pathologists perform perinatal, infant and childhood autopsies, including hospital referrals, forensic cases and those on behalf of Her Majesty's Coroner. The majority of infant and childhood autopsies for unexpected deaths are referrals from Her Majesty's Coroner with cases received mainly from the southern regions of England. Autopsies are performed according to a standard protocol, which includes a range of ancillary investigations (radiology, microbiology, virology and metabolic studies).

The Pathology Department has established a research database containing details of all autopsies performed over a 20-year period (1996-2015). The database contains fields with pre-defined criteria to ensure consistency of entries and death categorization. A computerised search identified all Coronial autopsies performed on infants and children (0-18 years) where a neoplasm, benign or malignant, was diagnosed for the first time at post-mortem examination. For these cases, clinical and autopsy findings were reviewed and the findings compared to published cases.

Cases were categorised as SUDNIC if the following criteria were met:

1. Sudden death in a seemingly healthy individual or within 24 hours of onset of acute illness.
2. Death occurring in the course of an acute illness that was not recognised as potentially life threatening by carers or healthcare professionals.

Exclusion criteria for SUDNIC included:

1. Any previous diagnosis of neoplasia.
2. Individuals with significant preceding signs and symptoms (as judged by the authors) who had sought medical opinion on multiple occasions or been admitted to hospital for investigation or treatment.

PubMed was searched for studies in English, using search terms including 'sudden death', 'unexpected death' and 'neoplasm' in all fields and filtered for age, ranging from birth to 18 years. Citations were tracked to identify any studies not retrieved in the original search. Only studies with clearly defined SUDNIC cases were included, whether from case reports, small case series or autopsy series.

Results

In total, there were 2,432 Coronial autopsies performed during the study period, including 1,670 infants (aged <1 year) and 762 children (>1 year).

In 13 cases (0.53%), previously undiagnosed neoplasms were discovered and in 12 of these, the neoplasm was considered the cause of death (Table 1). There were five haematological malignancies including one B-cell acute lymphoblastic lymphoma/leukaemia (B-cell ALL), one anaplastic large cell lymphoma and three acute leukaemias (not otherwise specified). There were two medulloblastomas (not subtyped) and two neoplasms of renal origin, one congenital mesoblastic nephroma and one disseminated renal medullary carcinoma. Two neuroblastomas, both apparently confined to the adrenal gland were found, one of which was regarded as an incidental finding with the cause of death undetermined (case 5). The final two cases were histologically benign cardiac tumours, one fibroma (Fig. 1A) and one myxoma (Fig. 1B).

TABLE 1: Presentation and diagnosis of 13 cases with neoplasia diagnosed at autopsy

Case	Age	Sex	Clinical presentation	Autopsy findings	Diagnosis and CoD
1	0 days	F	Acute deterioration at one hour of age, severe metabolic acidosis requiring ventilation. Treated as sepsis, inflammatory markers normal; died hours later	3cm tumour in the left adrenal gland	Congenital neuroblastoma, death due to 'substances produced by tumour'
2	2.5 months	M	Previously well with suspected umbilical hernia. Sudden collapse at home, confirmed dead on arrival at hospital	Extensive intra-abdominal haemorrhage, 10cm necrotic tumour arising from the left kidney	Congenital mesoblastic nephroma
3	4 months	F	Poor feeding, irritability for three days. Presented to A&E with fever, dyspnoea, bruising, oro-nasal bleeding; deteriorated rapidly and died within minutes	Widespread lymphadenopathy and hepatosplenomegaly	Acute leukaemia
4	4.5 months	M	Previously well until suddenly stopped breathing during a feed	Enlarged heart with 5cm tumour obstructing left ventricular outflow tract	Cardiac fibroma
5	1.3 years	M	Diagnosed with tonsillitis, found dead in bed next morning	Enlarged tonsils with micro abscesses. Left adrenal gland with 2.7cm tumour	Incidental neuroblastoma. CoD: undetermined
6	1.3 years	M	Coryzal 'symptoms' for seven days, poor feeding for two days and fever the night before death; found dead in cot	Lymphadenopathy, hepatosplenomegaly. Acute leukaemic infiltrate in bone marrow and viscera. Group A streptococcus isolated	Acute leukaemia and septicaemia
7	1.8 years	F	Two-month history of pancytopenia; non-diagnostic bone marrow aspirate. Treated for sepsis one week prior to death. Reviewed in outpatient clinic and was well. Found later the same day not breathing	Acute leukaemic infiltrate in the bone marrow. Submandibular abscess - Staphylococcus aureus isolated	Acute myeloid leukaemia
8	2.3 years	M	History of 'recurrent throat infections'. Diagnosed with tonsillitis two days before death. Suddenly stopped breathing	Grossly enlarged tonsils and lymphadenopathy. Leukaemic infiltrate in bone marrow and viscera. Moraxella catarrhalis isolated	B-cell ALL and sepsis
9	4.2 years	M	Knee pain two days before death, seen in A&E with tachycardia and low-grade fever. Well next morning until sudden collapse	Dilated right ventricle with complete occlusion of the pulmonary valve by 4.7cm tumour arising from the right ventricle.	Cardiac myxoma causing acute heart failure
10	7.1 years	F	Admitted with sudden onset severe headache; CT scan: posterior fossa mass, hydrocephalus. Brainstem death confirmed within 24 hours of presentation	Yellowish tumour covering the tonsillar area and bulk of the brainstem and filling the fourth ventricle	Medulloblastoma*
11	12.3 years	F	Sickle cell trait. Four-month history of cough, malaise, weight loss. Admitted with dyspnoea, mild pyrexia and treated with antibiotics, showing improvement until unexpected respiratory arrest	Enlarged right kidney partially replaced by tumour. Numerous tumour deposits in lungs, pleura and lymph nodes	Renal medullary carcinoma
12	13 years	F	Two-week history of fever, cough, weight loss. Admitted with respiratory failure, generalised lymphadenopathy and treated for sepsis. Rapidly deteriorated requiring ECMO; developed intraventricular haemorrhage and obstructive hydrocephalus	Widespread lymphadenopathy and consolidation of both lungs	Anaplastic large cell lymphoma
13	15.6 years	F	Three-week history of headache and vomiting. Initial investigations and CT scan 'normal'; prescribed glasses for blurred vision. Admitted with cortical blindness, rapidly became unresponsive. MRI-'inflammation of cerebellum', treatment withdrawn	Bilateral necrosis of cerebellar tonsils, midline posterior fossa tumour involving the roof of the fourth ventricle and infiltrating the cerebellar peduncles and vermis	Medulloblastoma*

ECMO – Extra-corporeal membrane oxygenation; PM – post mortem examination

* diagnosis of medulloblastoma was made by a Neuropathologist, both cases presented prior to 2002 and no further subtyping was made available on the PM report

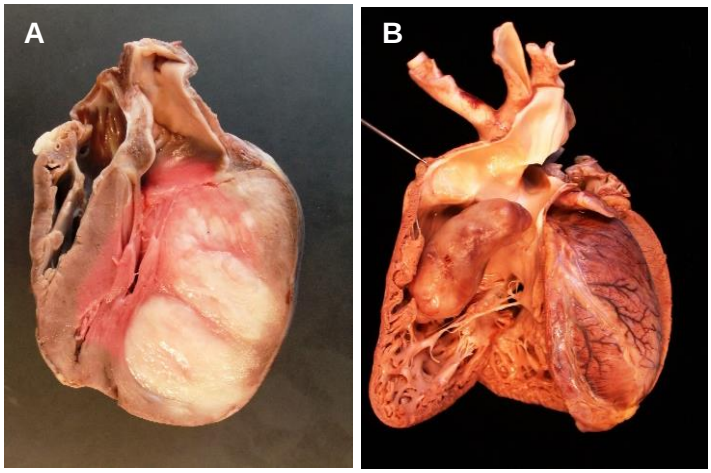

Figure 1 A. Cardiac fibroma causing obstruction of the left ventricular outflow tract (case 4). **B.** Cardiac myxoma arising within the right ventricular outflow tract, extending beyond the pulmonary valve (case 9).

Eight cases (8/2432; 0.33%) were further categorised as SUDNIC based on the previously described criteria (Table 2). Four were in children and four were infants, one of whom, a neonate, died shortly after birth. The SUDNIC cases included three acute leukaemias, two cardiac tumours, one medulloblastoma, one neuroblastoma and one renal tumour. Of these, three individuals had been seen by the family doctor (general practitioner [GP]) or in the emergency department (A&E) more than 24 hr prior to death; one child (with B-ALL) was diagnosed with tonsillitis two days prior to death and one infant (with mesoblastic nephroma) was seen almost two weeks before death and diagnosed with a probable incidental umbilical hernia.

Table 2: SUDNIC cases

Case	Age	Sex	Medical review >24 hours before death	Diagnosis
1	0 days	F	Not applicable	Neuroblastoma
2	2.5 months	M	Yes - GP with swollen abdomen 13 days before death	Mesoblastic nephroma
3	4 months	F	Not applicable - seen on day of death, died soon after arrival in A&E	Acute leukaemia
4	4.5 months	M	No	Cardiac fibroma
6	1.3 years	M	No	Acute leukaemia
8	2.3 years	M	Yes - GP diagnosed tonsillitis 2 days before death	B-cell ALL
9	4.2 years	M	Yes - A&E twice in 48 hours, mild fever and tachycardia	Cardiac myxoma
10	7.1 years	F	No – admitted <24 hours prior to death	Medulloblastoma

In total, six autopsy series and 28 case reports and case-series were identified on literature review, revealing 47 further SUDNICs (Table 3). Of the autopsy series only one study was broadly comparable with the current series. This was a 20-year retrospective study from The Sick Children's Hospital in Toronto (1984-2003).[3] Seven cases of SUDNIC were identified including four haematological malignancies (two acute leukaemias and two mediastinal T-cell lymphoblastic lymphomas), one benign cardiac tumour (papillary fibroelastoma), one medulloblastoma and one Wilms tumour. Of the other autopsy series, one study of infant deaths identified two cases of SUDNIC from 423 medico-legal autopsies over a 15-year period,

one oligodendroglioma and one cardiac fibroma.[8] Two series were concerned only with CNS tumours[9,10] and one also included adults.[10] A study from the CRY Centre for Cardiac Pathology in London, UK, was focused on benign cardiac tumours associated with sudden cardiac death in all ages, however one case described in a neonate fitted the criteria for SUDNIC and is included in table 3.[11] One autopsy series was not included because although it reported three 'brain tumours' there was insufficient detail for this review.[12]

Table 3: SUDNIC cases (1980-2016)

Tumour type	Total	Age	Sex	References
Cardiac				
Rhabdomyoma	7	7d,2m,4m,5m,11m,11m,6y	4F, 3M	(11, 13-18)
Fibroma	6	4m,6m,6m,7m,7m,16y	4F, 2M	Current series; (8, 19-22)
Myxoma	2	2m,4y	2M	(23); current series
Myofibroblastic sarcoma	2	3m,5y,	2F	(24, 25)
Inflammatory myofibroblastic	1	8y	M	(26)
Angiomyoma	1	12m	M	(20)
Papillary fibroelastoma	1	2y	F	(3)
Benign teratoma	1	2y	F	(27)
CNS				
Medulloblastoma	4	7y,7y,12y,13y	3F, M	Current series; (3, 9, 10)
Glioblastoma	1	7y	M	(28)
Haemangiopericytoma	1	9y	M	(29)
Pineal teratoma	1	9y	M	(9)
Astrocytoma	2	5y,16y	F, M	(9, 10)
Ependymoma	1	2y	M	(9)
Ganglioglioma	2	3y,5y	F, M	(30, 31)
Oligodendroglioma	1	1m	F	(8)
Haematological				
T-cell ALL	3	4y,6y,5y	3M	(3, 4)
B-cell ALL	2	1m,2y	F, M	(3); current series
Acute Leukaemia NOS	2	4m,1y	F, M	Current series
Acute myelogenous leukaemia	1	2m	M	(3)
Renal				
Wilms tumour	2	2y,7y	F,M	(3, 32)
Congenital mesoblastic nephroma	1	2m	M	Current series
Stromal sarcoma	1	5y	F	(32)
Hepatic				
Hepatoblastoma	1	6m	F	(5)
Haemangioendothelioma	2	1m,3m	M, F	(6, 33)
Adrenal				
Neuroblastoma	2	0d,2y	F, M	current series; (7)
Other				
Paraganglioma	1	12y	M	(34)
Malignant hemangioendothelioma	1	5m	F	(35)
Disseminated adenocarcinoma	1	11y	F	(3)
Pleuropulmonary blastoma	1	1m	M	(36)

d, day; m, month; y, year

The SUDNIC cases from table 3 are presented as a stacked bar chart to demonstrate where each case was reported (Figure 2). It is apparent that cardiac tumours are the most frequently reported neoplasms in the literature but are mostly described in case reports rather than in

autopsy series, hence are not necessarily representative of the population so no inference about incidence can be made. In contrast, SUDNICs due to haematological neoplasms are rare as case reports but have a higher frequency in the two major autopsy series.

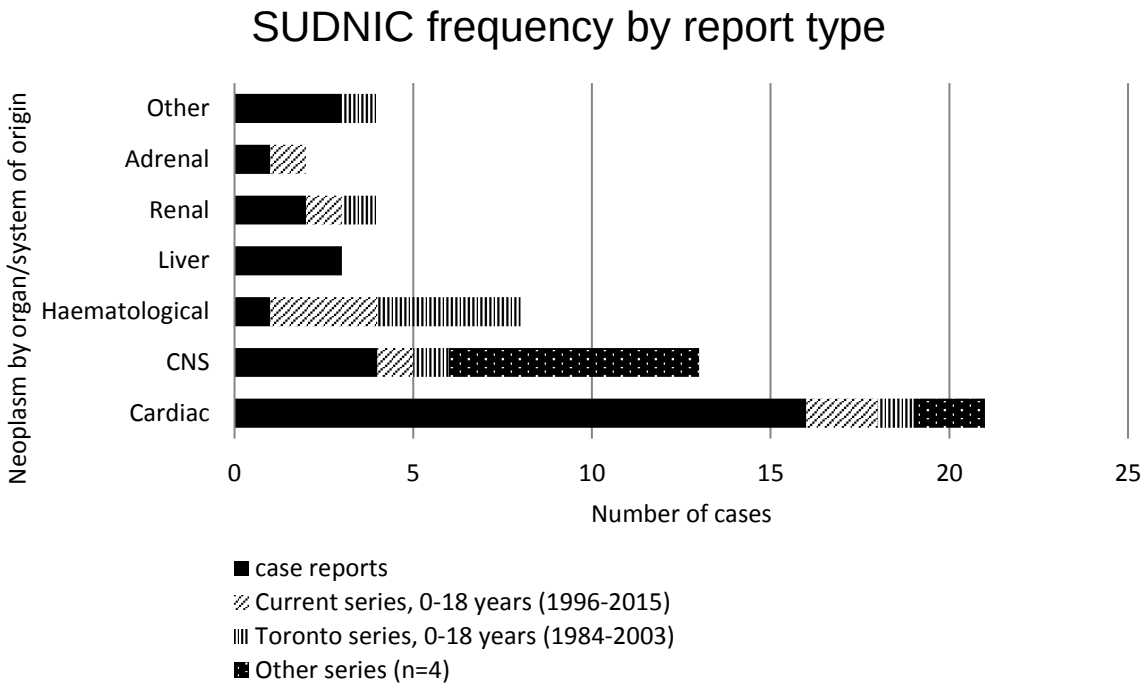

Figure 2 A stacked bar chart shows SUDNIC frequencies by report type; "other series" refers to the cases described in the two CNS series, the cardiac series and the infant series as described above

Discussion

The findings of this study have demonstrated that undiagnosed neoplasms presenting at autopsy are rare, being found in 0.53% of paediatric Coronial cases. SUDNIC cases account for 0.33% of all such autopsies with haematological malignancies representing the commonest subtype, which is similar to the findings of the only previous similar study.[3] The two cardiac cases (fibroma and myxoma) serve as a reminder of the potential lethality of histologically benign neoplasms.

Of all childhood neoplasms diagnosed in Great Britain, the acute leukaemias are the commonest and represent around 31% of cases.[37] CNS tumours are second, accounting for approximately 26% followed by lymphoma at 10%.[37] In this series, although the numbers of SUDNIC are small, haematological malignancies overall are the commonest (3/8, 37.5%) occurring in a similar proportion to their relative frequency overall (41% - combined acute leukaemias and lymphomas). This is not entirely unexpected given that the natural history of haematological malignancies is often short; patients present with signs and symptoms related to acute bone marrow failure (infection and/or bleeding diatheses) as is apparent in cases 3, 6 and 8. This was also the finding in the Toronto series, where four out of seven cases of SUDNIC were haematological malignancies (two acute leukaemias and two T-cell lymphoblastic lymphomas).[3]In the Toronto series the incidence of SUDNIC was 0.14%, less than in the present series (0.33%). However, it is not clear whether the denominator data

were Coronial autopsies; a separate study from the same group investigating undiagnosed heart disease over the same period, states that only around half of the cases (2,422) were Coronial which would indicate a more comparable relative incidence of SUDNIC of 0.29%.[38]

Cardiac tumours are identified in 0.02-0.04% of the paediatric population and 50% are diagnosed in the first year of life.[39] Rhabdomyomas are the commonest (45%) followed by cardiac fibromas (25-30%) with other tumours such as myxomas, lipomas and teratomas being far less common. The vast majority are histologically benign, have minimal growth potential and many spontaneously regress. Whether there are symptoms or signs depends entirely on the position within the heart as demonstrated in cases 4 and 9. Cardiac fibromas (case 4) rarely regress and their infiltrative nature renders many unresectable. More than one third are diagnosed in infancy, presenting with congestive heart failure or cyanosis; sudden death is reported in 10-30%.[39] In contrast, cardiac myxomas (case 9) are exceedingly rare in childhood. The diagnosis raises the possibility of Carney complex, an autosomal dominant multiple neoplasia syndrome characterised by multiple skin lentigines, endocrine and neural myxomatous tumours and multiple cardiac myxomas,[40].

Case 1 is an unusual cause of SUDNIC because, although neuroblastoma is the commonest malignancy in infants, the prognosis in this age group is usually good since tumours may spontaneously regress.[41] Survival of patients with neuroblastoma diagnosed in the neonatal period reaches almost 100%.[42] The death in case 1 was attributed to substances released by the tumour; clinically the neonate was thought to be septic, although inflammatory markers were normal. This phenomenon has been reported previously in a new-born who survived - signs of severe sepsis and metabolic acidosis developed three hours after the birth together with systemic hypertension, unusual in sepsis. Subsequently, a 7cm retroperitoneal neuroblastoma with intraspinal extension was identified and successfully treated.[43] It was postulated that compression of the neuroblastoma during delivery might have induced the release of catecholamines mimicking sepsis. Case 1, however, was a much smaller tumour confined to the adrenal gland. No information regarding the neonate's blood pressure was supplied to the Pathologist at the time of autopsy and the placenta was not submitted for examination, which may have provided further information. Whether congenital neuroblastoma was the true cause of death in this case remains uncertain. Conversely, incidental neuroblastomas are well described at autopsy (as in case 5).[44,45]

Congenital mesoblastic nephroma (case 2) is a rare tumour of infancy and accounts for 50% of renal masses in neonates.[46] Generally regarded as benign, this tumour has a good prognosis if diagnosed before 3 months of age, with surgical excision the mainstay of treatment. Case 2 is unusual for both its extensive intra-abdominal spread and presentation as SUDNIC.

Of the non-SUDNIC cases, case 11 was renal medullary carcinoma; an entity described in 1995, almost exclusively occurring in young individuals with sickle cell trait or disease. A recent review of 64 articles plus four new cases described a total of 217 cases with 50% occurring in children; 88.6% had sickle cell trait and 8% had sickle cell disease; 94% presented with metastatic disease and mortality was 95%; none of these cases presented at autopsy.[47]

Literature review revealed an apparently greater proportion of cardiac tumours presenting as SUDNIC but most of these are case reports (Figure 2) which are not necessarily representative of the true population. CNS tumours were the second most common with just over half (7/13) reported in autopsy series. A number of articles have also stated that the majority of SUDNICs involve neoplasms arising in the brain or heart but without references to support this view.[3-

[7] A further complication is the inclusion of cases of "oncocytic cardiomyopathy" as cardiac "tumours".[48] It is now accepted that "oncocytic cardiomyopathy", a synonym for histiocytoid cardiomyopathy, is not a neoplasm but rather a mitochondrial cardiomyopathy.[49]

The pooled data from this and the Toronto series suggest that haematological malignancies are the most common causes of SUDNIC which is not unexpected given their overall relative frequency and natural history. Neoplastic disease represents a rare cause of sudden unexpected death in childhood but it should always be considered. These findings illustrate the value of specialist autopsy examination in all cases of sudden and unexpected death.

Contributorship
VAB conceived the study. VAB and JB collated and analysed the data. VAB drafted the initial manuscript. All authors contributed to the writing and reviewed the final manuscript.

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Competing interests
None.

Ethical approval Local research ethics committee approval has been granted, Bloomsbury LREC

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