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Case Report

Myocardial Hyperplasia in Sudden Infant Death Syndrome

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Introduction

Sudden infant death syndrome (SIDS), also known as cot death or crib death, is the sudden unexplained death of a child of less than one year of age. Diagnosis requires that the death remain unexplained even after a thorough autopsy [1].

Environmental factors have been implied and may include sleeping on the stomach or side, overheating, and exposure to cigarette smoke. Accidental suffocation as is birth before 39 weeks' gestation. SIDS makes up about 80% of sudden and unexpected infant deaths (SUIDs). The other 20% of cases are often caused by infections, genetic disorders, and heart problems.

Rates of SIDS vary nearly tenfold in developed countries from one in a thousand to one in ten thousand. Globally it resulted in about 19,000 deaths in 2017 down from 22,000 deaths in 1990. SIDS was the third leading cause of death in children less than one year old in the United States in 2011. It is the most common cause of death between one month and one year of age [2].

About 90% of cases happen before six months of age, with it being most frequent between two months and four months of age. It is more common in boys than girls.

By definition, SIDS deaths occur under the age of one year, with the peak incidence occurring when the infant is at 2 to 4 months of age. This is considered a critical period because the infant's ability to rouse from sleep is not yet mature.

Chronic hypoxia has been implicated in some cases of the Sudden Infant Death Syndrome. We sought to investigate the occurrence of myocardial hyperplasia in children who had died with a clinical diagnosis of sudden infant death syndrome, comparing their hearts to a cohort of infants with known causes of death.

Ventricular tissue was examined by computer aided morphometry to determine any nuclear abnormalities in this important cause of infant mortality in the United Kingdom and elsewhere [3].

Methods

Left and right cardiac ventricular tissue was investigated in a total of 56 infants. Of these, 28 cases (14 male, 14 female) were diagnosed as having died of Sudden Infant Death Syndrome (SIDS). 28 infants (15 male, 13 female) had died of other known natural causes and were used as controls. The subjects varied in age from 37 weeks gestation (but who died after delivery) to 56 weeks post-natal age.

All relevant Departmental ethical committee permissions were obtained to examine the tissue specimens for this research project. Blocks of tissue from each ventricle were taken at random and 5um thickness transverse sections cut for Haematoxylin and Eosin staining. The specimens were then assessed by computer aided morphometry to determine nuclear profile density and morphology. 10 fields per ventricle were analyzed having been selected at random by computer. Throughout the study period the observer was blinded to the nature of the case.

A Kontron MOP Video plan image analysis computer system was used for the analysis. The system was linked to a Leitz Dialux 20EB microscope, operating at a magnification of X860. The image of the slide field was projected onto a monitor allowing the number of nuclear profiles per unit cross sectional area to be determined for myocytic and non-myocytic tissue components. By tracing the outline of each myocytic nucleus with a stylus and digitized tablet, computer generated measurements of nuclear morphology could be derived. The Kontron computer system was able to calculate the geometric characteristics of the myocytic nuclei displayed. Thus, nuclear cross sectional area and mean diameter in the long axis, were obtained. Every nucleus in each of the 10 fields per ventricle was analyzed in this way.

Results

The mean values derived from the measurements taken in left and right ventricles in control and SIDS subjects are shown in Table 1.

Parameter	Control LV Mean	Control SD	Control RV Mean	Control SD	SIDS LV Mean	SIDS SD	SIDS RV Mean	SIDS SD
Myocytic Nuclear Density	852.91	7.39	902.98	4.93	846.62	4.45	1124.57	9.48
Non Myocytic Nuclear Density	715.30	5.70	751.47	4.13	782.10	7.48	887.75	8.35
Nuclear Long Axis Diameter (um)	8.02	0.54	8.26	0.48	9.09	0.67	9.34	0.51
Nuclear Profile Area (um2)	35.25	1.16	34.05	0.53	35.74	0.79	30.80	0.82
Nuclear Shape Coefficient	3.45	0.32	3.17	0.52	3.51	0.29	2.51	0.29

Table 1: Mean Values of Study Parameters.

Comparison of Groups

Control and SIDS groups were compared using an unpaired Student s t-test at 54 degrees of freedom and a 95% confidence interval. The mean age of control subjects was 29.3 weeks (SD=17 .8), and 34.1 weeks for SIDS subjects (SD=13. 2). There was no statistically significant difference in the ages of the two groups (p= 0.26).

Left Ventricle

The myocytic nuclear profile density per unit cross sectional area of the left ventricle was significant ly greater (p=0.003) in SIDS cases, compared with controls. A stronger difference existed regarding the non-myocytic nuclear profile density (p<0.001) and the nuclear long axis diameter (p <0.001) which was larger in SIDS subjects (8.02um versus 9.09um) The mean nuclear area was not significantly different between the two groups (p=0.07 and 0.498 respectively).

Right Ventricle

A stronger difference in myocytic nuclear profile density existed between the groups in the right ventricle (p <0.001), the nuclear profile density being greater in SIDS ventricles compared with control cases (902.98 versus 1124.57 nuclear profiles per mm2). A similar difference was demonstrated regarding non-myocytic nuclear profile density (p<0.00 1). Both nuclear morphology variables gave a p value of <0.001 when comparing SIDS and control right ventricles, unlike the left ventricle in which only the nuclear long axis diameter was significantly different.

Errors in the measurements may have resulted from parallex errors in the use of the digitised tablet due to the stylus being non-vertical when tracing the outline of nuclei. Errors were minimized by regular accuracy checking to ensure reduced variability and consistency during measurements. Reproducibility testing showed no significant degradation during the study period. We therefore concluded that the measurements obtained were indeed accurate and reliable.

Discussion

In SIDS subjects, the right ventricle in particular shows a significant increase in the nuclear profile density of myocytic and non-myocytic tissue elements when compared with control right ventricular tissue. The myocytic nuclear profile density may be used as an index of hyperplasia especially as the proportion of binucleated cells in the paediatric age group is very small [4]. The heart grows in fetal life by hyperplasia of myocardial cells. By 4 days after birth myocardial cells lose the ability to divide and further growth is by myocardial ll hypertrophy and connective tissue cell hyperplasia, after a short transitional phase [4,5]. Thus the response of the heart to increased demand depends upon the stage of growth of the heart when the stress is imposed.

The myocardial cell hyperplasia demonstrated by this study would suggest some imposition on cardiac workload in fetal or very early neonatal life. Furthermore the presence of increased non-myocytic nuclear profile density suggests this may persist in the postnatal period, as connective tissue hyperplasia occurs. The increased demand inducing the change may be chronic hypoxia.

Many SIDS victims have anatomical markers of chronic alveolar hypoxia such as increased pulmonary artery smooth muscle and increased adrenal medullary chromaffin tissue. Additionally, an abnormally heavy right ventricle is a variable finding [6-8]. Naeye [9] demonstrated a less marked increase in left ventricular weight accompanying the hypertrophied right ventricle in sudden infant death cases. This may be a consequence of the increased workload of the right side initiating similar histological changes in the left side. Our findings would suggest a similar hypothesis relating to myocardial hyperplasia. Nuclear size was significantly different between control and SIDS subjects which may be a manifestation of the immaturity of the nuclei as a result of some developmental impairment, indeed fetal myocardial cells are spindle shaped with single, small oval shaped nuclei unlike those in full term infants [3,4].

Whether the finding of these ventricular abnormalities are merely another associated finding in unexplained cot deaths or whether they are a predisposing factor in some infants is difficult to quantify. Many workers in the field have beleived that cardiac abnormalities are at least partly responsible for a number of deaths in this notoriously heterogenous group [10]. Clearly studies in a larger number of infants are required.

The potential for arrythmia and cardiomyopathy in those surviving into childhood and adolescence is also important if these hyperplastic abnormalities are present as cardiac morphologic abnormality is a recognized contributor to mortality in this later age group [11].

Conclusions

In sudden infant death victims, both cardiac ventricles display marked cellular atypia. In the right ventricle especially, myocytic and non-myocytic hyperplasia together with nuclear size differences have been shown compared with control cases. This may be a manifestation of cardiac adaptation to chronic hypoxia, but its significance is difficult to fully assess without studies on larger numbers of cases.

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