Int J Legal Med (2003) 117 : 193–203
DOI 10.1007/s00414-003-0374-7

REVIEW ARTICLE

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Pathological changes of the heart in sudden infant death

Received: 30 August 2002 / Accepted: 8 January 2003 / Published online: 25 June 2003

Abstract There are more than 120 different theories on the possible causes of sudden infant death (SID). In particular, dysfunctions of the central nervous system, cardiorespiratory insufficiency due to infections including atypical immune reactions, and cardiac dysregulation have been discussed during the previous decade. Reports on disturbances of the cardiac rhythmogenic function due to LQTS were among the most speculative. Based on gross histological, immunohistochemical and molecular genetic investigations of SID cases, the most important and most frequent findings of the heart are shown. The significance of different types of myocarditis, hypoxia-related changes, disturbances of the rhythmogenic function, cardiomyopathy, and other changes is discussed with regard to the cause of death. In conclusion, most of the changes reported in the literature are not sufficient to explain the cause of death. Problems in the diagnosis are shown which influence the classification of these disturbances as well as the classification of SID.

Keywords Sudden infant death (SID) · Myocarditis · Hypoxia · Long QT syndrome · Cardiomyopathy

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Introduction

Sudden infant death (SID) is the most common cause of death in infancy in industrial countries with an incidence between 0.3 and 1.5 per 1,000 live births [1]. In 1999, 507 infants died suddenly and unexpectedly (SID) in Germany compared to 666 infants and children up to 15 years old who died from traffic accidents (n=329) and malignant tumors (n=337) [2].

The term sudden infant death syndrome (SIDS) has been defined in 1969 at the Second International Conference on Causes of Sudden Death in Infants, as "the sudden death of any infant or young child, which is unexplained by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death" [3].

This definition was criticised because the term is defined per exclusion and it connects the previous history and the circumstances of death with the autopsy findings (which is often not done in practice, and if it is done the results can be doubtful). Also, the standard of the autopsy is not defined. Furthermore the SID cannot be a syndrome or an entity. Later the upper age limit was defined as 1 year at the time of death and an extensive death scene investigation was included in the definition [4, 5].

SID cases are characterised by typical but not specific autopsy findings [6, 7, 8]. There can arise difficulties for the investigator to evaluate diagnostic findings. Pathological changes can be observed and their significance has to be addressed. The examiner has to decide whether the findings can be regarded as the cause of death and thus exclude the case from being classified as SID. Since the severity grades of some alterations show a continuous distribution, in a large collective further subdivision into subgroups can become necessary.

Investigation procedure

A total of 415 cases of infant death were investigated during the 8-year-period from 1990 to 1997 in the Institute of Legal Medicine in Münster. The investigation included an

examination of the scene of death (mainly carried out by the police) and a complete autopsy using a standardised autopsy protocol similar to the international standardised autopsy protocol [9]. Apart from routine histology on all relevant organs and tissues including the central nervous system, musculature, endocrine and lymphatic organs (H&E, van Gieson, alcian blue-PAS, Berlin blue, Sudan III), the myocardium was investigated using paraffin-embedded samples (cross section through both ventricles 2 cm above the apex, longitudinal sections through the left atrium and left ventricle including the mitral valve as well as the right ventricle (staining by H&E, van Gieson, Sudan III). The cardiac conduction system was dissected and systematically examined using serial sections in some selected cases only. Immunohistochemistry was carried out to detect structural changes of the myocardium (antibodies against troponin C, fibronectin, complement complex $C_{5b\text{-}9}$) and cellular infiltration by granulocytes (antibody NP57) as previously described [10, 11, 12]. The investigation has been completed by a routine toxicological screening for centrally acting drugs, illegal drugs and ethanol, microbiology and virology. Virology was performed using nested PCR methods to detect different subtypes of adenoviruses, cytomegaloviruses, influenza A and B viruses, parainfluenza 3 viruses and respiratory syncytial viruses [12, 13]. If these techniques were not available conventional methods of virus detection were used (virus culturing, electron microscopy).

Pathological changes of the heart

In a total of 70 out of 387 SID cases (18%) different pathological changes could be detected. This means that disturbances of the heart belong to the most frequent changes in SID cases after inflammatory diseases of the respiratory tract. In 28 unnatural deaths the frequency of pre-existing cardiac findings was less than half (7%, *n*=2).

A number of reports have dealt with cardiac alterations in sudden and unexplained infant death. While findings such as previously unknown malformations, cardiomyopathy [14] or expressed endocardial fibroelastosis [15, 16] could explain the sudden death, other findings can be coincidental (e.g. intimal thickening of nodal arteries [17]) or residues of the physiological development during the first year of life [18].

Myocarditis

According to the Dallas classification which has been introduced for the diagnosis of myocarditis in endomyocardial biopsies and can also be used for autopsy material, myocarditis is a non-ischemic process which is characterised by cellular infiltration, myolysis and/or degenerative changes of the myocardium [19]. For the diagnostics three main methods are recommended: 1) histological detection of cellular infiltration and necrosis of myocytes, 2) immunohistochemical investigations to demonstrate an

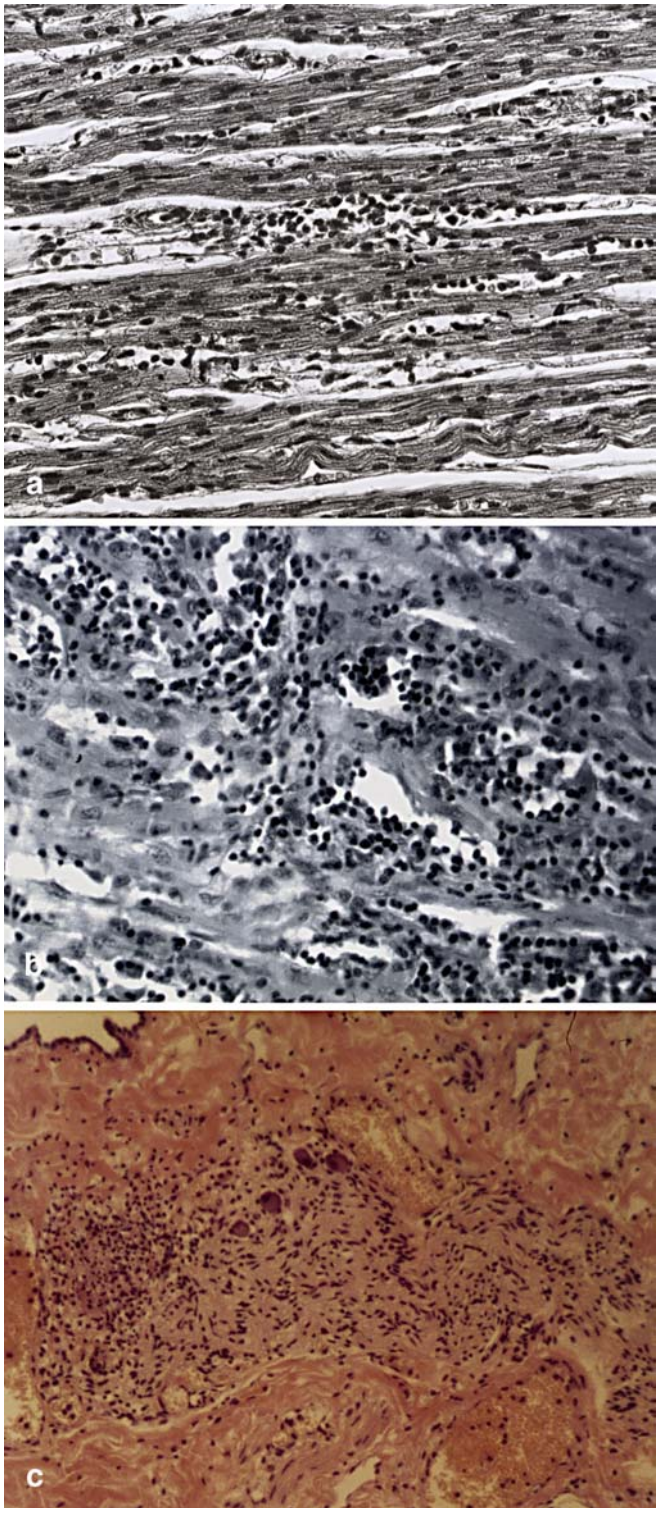

Fig. 1A–C Different types of myocarditis. **A** Borderline myocarditis showing mild focal infiltration of the myocardium by lymphocytes (HE ×100), **B** perivascular oedema, severe cellular infiltration of the interstitium by lymphocytes and some granulocytes and damage of myocytes (HE ×100), **C** ganglionitis, lymphocyte and granulocyte infiltration in the left ventricular wall around a ganglion (HE ×40)

inflammation-associated immunoreaction and 3) the detection of the responsible microorganisms.

In older references inflammatory diseases of the heart have been reported, especially interstitial myocarditis [20, 21, 22, 23], which have been held as the cause of death. Therefore these cases were excluded from the SID group. During the previous decade a severe myocarditis was diagnosed in individual cases only. A mild infiltration of the myocardium by lymphocytes without signs of myolysis can be observed especially in cases with infectious diseases of other locations and has no significance for the cause of death.

There are only two reports where myocarditis was found more frequently in SID cases [24, 25]. In particular Dettmeyer et al. [26, 27] successfully used immunohistochemistry (antibodies against HLA-DR, leukocyte common antigen, CD68, CD3, and C_{5b-9}) in combination with RT-PCR for the detection of enteroviruses (especially coxsackie B viruses) affecting the myocardium.

In most of the cases the disease has to be classified as borderline myocarditis (Fig. 1A) [19] because a mild infiltration of the myocardium by lymphocytes could be observed while cardiomyolysis was not detectable. In these cases the "myocarditis" should be associated with infectious diseases of the respiratory or intestinal tract and should be classified as being caused by virus infection only if virus detection was successful. Bacterial myocarditis is characterised by granulocyte infiltration and a more or less intensive myolysis (Fig. 1B). It can be caused by e.g. ß-haemolytic B-streptococci and is a rare disease in infants.

Sudden and unexpected deaths due to myocarditis have been observed in adults as well as in children, sometimes without a typical history of illness. In our working group we classify myocarditis in infants only as the cause of death if the disease is characterised by significant damage of the myocardium or if the inflammation has affected the cardiac conduction system and/or the autonomic nervous system (Fig. 1C).

Hypoxia-related changes

Hypoxic changes of myocytes due to acute, repeated or chronic hypoxemia can be caused by internal disturbances or by external hypoxia (e.g. suffocation). The consequence is a decreased oxygen concentration of the myocardium (hypoxidosis), which can be associated with structural changes. Early changes can be observed about 10 min. after the beginning of the hypoxaemia and are characterised by perinuclear located vacuoles, hydropic swelling of myocytes (Fig. 2A) and dehydration [28]. An acidophilic cytoplasm can also be observed. In cases of longer acting hypoxaemia, fatty degeneration and myolysis can be observed [28]. These microscopical changes should be due to homogenisation and reduction of the christae of mitochondria [29] which can be seen only by electron microscopy. Besides such structural damages the activity of oxygen-dependent enzyme systems can be re-

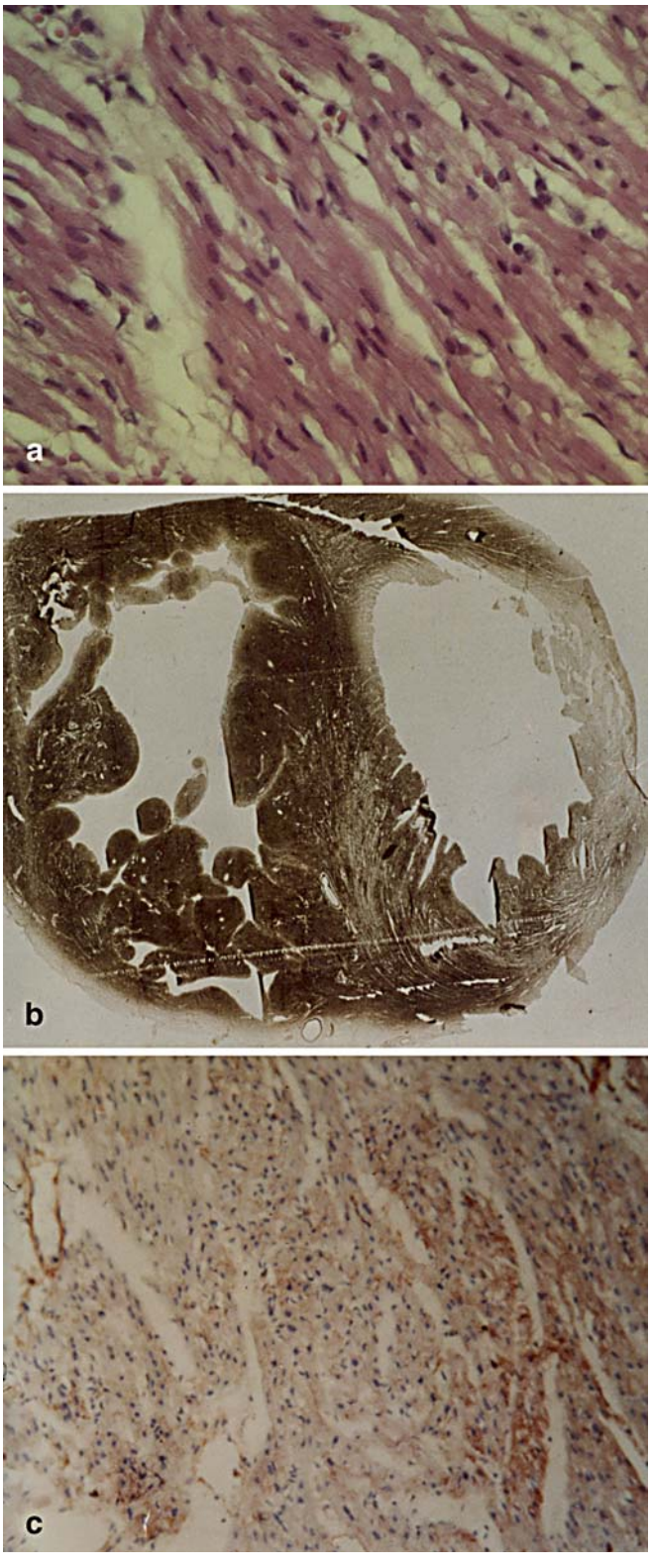

Fig. 2A–C Hypoxia-related changes. **A** Hydropic swelling and perinuclear vacuoles, and mild interstitial oedema (HE ×100), **B** histochemical detection of reduced ATPase activity in the right ventricular wall (reduced staining intensity) indicating hypoxia. ATPase staining, incubation at pH 7.4, ×4. **C** Mild accumulation of fibronectin in the same case **B** indicating an early stage of myolysis (immunohistochemistry anti-fibronectin ×40)

duced (Fig. 2B) [28]. In current studies [30, 31] the terminal deoxynucleotidyl transferase-mediated desoxyuridinetriphosphate nick end-labeled method (TUNEL) is recommended for the detection of cardiomyocyte apoptosis as well as sudden cardiac death due to ischaemia, but studies in cases of SID have not been performed yet.

Hypertrophy of the right ventricular wall was first described by Naeye et al. [32] who suggested that this could be due to sleep apnea with repeated episodes of hypoxia. This observation was evaluated by others using the same method for morphometry but could not be confirmed [33, 34].

The quantitative analysis of myocardial mast cells in 25 SID and 15 non-SID cases [35] resulted in an age-dependent increase during the first months of life up to the value of about 200 cells/cm^2 at the age of 6 months which was defined to be "normal". Significant differences between both groups could not be observed indicating no specific process of chronic inflammation, fibrosis, or repeated hypoxemia.

Even immunohistochemical investigations using an antibody to detect the C5b-9$_{(m)}$ complement complex, which is an early and sensitive marker for hypoxic cell damage, were completely negative in a series of 136 SID cases [36].

But immunohistochemistry using antibodies against the structural protein troponin C and plasma proteins such as fibronectin (Fig. 2C) are suitable for the detection of early hypoxic changes of the myocardium [10, 11] especially in cases of external suffocation which have to be differentiated from SID. Of course a diagnosis can only be made if typical equivalents of the suffocation could be found in the lungs.

Contraction band necrosis (CBN)

Different types of CBN (Fig. 3) can be observed in many different diseases and conditions leading to death as well as sometimes in SID. CBN can especially indicate adrenergic stress but does not belong to certain types of hypoxia-related changes. Fineshi et al. [37] could not find CBN in cases of fatal CO intoxication and postulated an anti-adrenergic effect of this type of hypoxia despite a longer survival period. In cases of reoxygenation contraction bands without interstitial haemorrhages were described [37]. Baroldi et al. [38] found a few contraction bands in accidental deaths depending on the survival time and suggested an "agonal adrenergic stimulation to promote the cardiac pump" which is usually carried out during resuscitation. The authors emphasised that the differentiation between agonal and "pathological" CBN (due to noradrenalin) can be made by morphometry only. As a morphological threshold of adrenergic stress in the history of some diseases thus explaining malignant arrhythmia/ventricular fibrillation, they defined >37±7 foci of CBN and >322± 99 myocells/100 mm^2 showing CBN.

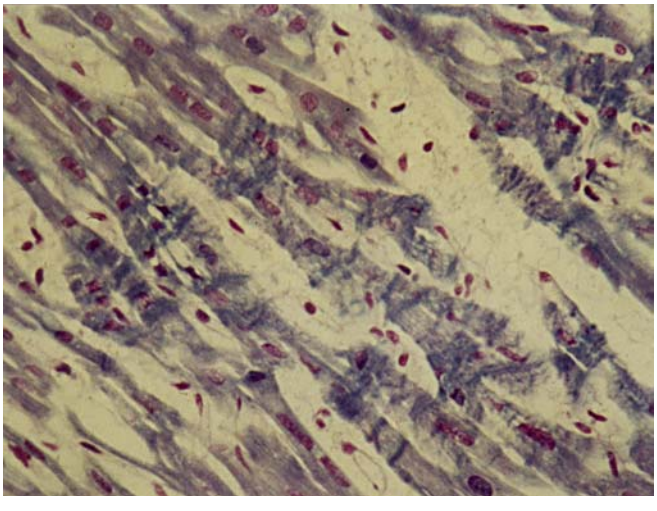

Fig. 3 Contraction band necrosis in myocytes (Luxol fast blue ×100)

Morphological changes in the cardiac conduction system

Since 1968 [39] histological investigations of the cardiac conduction system have been performed in SID cases. Due to the time and labour-intensive techniques these investigations are not included in routine SID diagnostics. The dissection technique of the different morphological structures has been described again in detail [40]. Besides a number of case reports dealing with morphological variations of the conduction system there exist only very few systematic investigations (Table 1) where the results in SID cases are compared to those obtained in a much smaller number of controls (cases of explained death). The results obtained are not consistent and the interpretation of the results is partially contradictory. James [39] and Ferris [41], for example described a uniform process of "resorptive degeneration of the His bundle and AV-node". They described this degeneration as characterised by "a slowly destructive process in which neighboring fibroblasts were replacing scattered necrotic fibres of the His bundle". The authors could not find an associated inflammation, massive necrosis or haemorrhages. This process was felt to be responsible in general for fatal cardiac arrhythmia. Other authors [42, 43] discussed the findings of James and Ferris to be age-related physiologically and refuted the existence of an active process of necrosis in the myocardium of infants. Bharati et al. [44] described a "left-sided His bundle" and postulated that this morphological variant of the cardiac conduction system could be more affected by left ventricular pressure than the normal variant leading to a higher vulnerability for cardiac arrhythmia. This interpretation is in contrast to others [45] who described His bundle dispersion (Fig. 3) and left-sided His bundle as normal anatomical variants of the cardiac conduction system in infants with no functional significance. Suarez-Mier and Aguilera [45] observed accessory fasciculoventricular tracts in only 7 out of 55 SID cases (Fig. 4) and discussed a possible pathological significance for pre-excitation syndromes. A systematic investigation of the cardiac conduction system in 69 SID cases and 24 age-

Table 1 Histological findings in the cardiac conduction system in SID cases

Author	Year	SID cases (*n*)	Controls (*n*)	Important findings
James [39]	1968	40	16	Resorptive degeneration of the His bundle and the AV node without inflammation
Anderson et al. [109]	1970	18	12	Focal hyperplasia of the AV node artery in 35% of the SID cases and in 10% of the controls
Ferris [41]	1972	47	0	Resorptive degeneration (James) confirmed
Ferris [110]	1973	50	0	11 SID cases showing haemorrhages in the SA node and in internodal tracts
Valdes-Dapena et al. [42]	1973	31	16	Findings like James [39] but other interpretation: normal anatomical variant
Anderson et al. [111]	1974	15	15	Accessory atrioventricular tract in one SID case, haemorrhages and specific myocytes in both groups
Kendeel and Ferris [112]	1974	38	28	Increased amount of connective tissue in the atrioventricular complex in SID cases
Lie et al. [113]	1976	26	24	Resorptive degeneration in all cases, haemorrhages in 27% of the SID cases and in 29% of the controls
Anderson and Hill [114]	1982	40	0	Fibromuscular hyperplasia of the AV node artery (5×) and of the SA node artery (1×)
Marino and Kane [115]	1985	7	0	Accessory tracts (2×) and dispersion of the AV node and His bundle (4×)
Bharati et al. [44]	1985	15	8	Left-sided His bundle in 8 SID cases and in 2 controls
Ho and Anderson [48]	1988	30	19	Wide variety of pathomorphological changes in both groups (e.g. hyperplasia of the AV node artery, dispersion of the AV node and the His bundle, accessory tracts, haemorrhages)
Dudorkinova and Bouska [43]	1993	21	6	No signs of resorptive degeneration
Suarez-Mier and Aguilera [45]	1998	55	15	Fasciculoventricular tracts in 7 out of 55 SID cases and in none of the controls

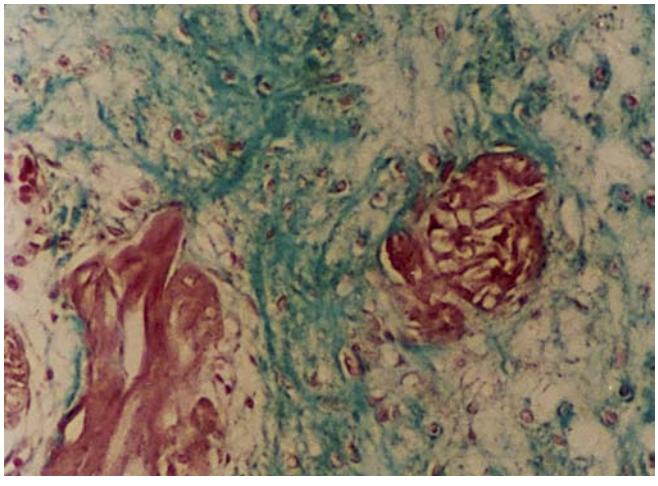

Fig. 4 Accessory fasciculoventricular tract (*arrow*) in the central fibrous body. In contrast to the well known Mahaim fibres it has no anatomical relationship to the AV node (Masson-Goldner ×200)

matched explained deaths was carried out by Matturri et al. [46]. The authors compared the frequency of resorptive degeneration, His bundle dispersion, Mahaim fibres, cartilaginous metahyperplasia, intramural right bundle, left-sided His bundle, atrio-ventricular node dispersion, His bundle hypoplasia and other anatomical abnormalities in both groups and found no significant differences except for the presence of resorptive degeneration (in 97% of SID cases compared to 75% of the controls).

Immunohistochemical and morphometrical investigations of the cardiac conduction system are also rare. Fu et al. [47] demonstrated a relative lack of nerve fibres in the AV node and His bundle using S100 antibody. Ho and Anderson [48] reported three cases of infants showing cardiac arrhythmia prior to sudden unexpected death where hypoplasia of the SA or AV nodes could be found as a possible cause for the disturbances of cardiac rhythmogenic function. Because normal values for the size of the various structures of the cardiac conduction system are not available at present in this age group, these results have no objective background.

In our opinion the isolated detection of anatomical variants in the cardiac conduction system is not sufficient to explain a sudden and unexpected death of a healthy infant. In cases showing a special vulnerability, e.g. caused by infection or typical disturbances of cardiac rhythmic function in the history, these findings could be judged to be the cause of death, but per exclusion only.

Disturbances of rhythmogenic function

Changes in cardiac control centres of the brainstem and autonomic imbalance leading to cardiac arrhythmia have also been discussed to be possible causes of sudden and unexpected infant death [49, 50, 51]. Therefore some in-

Table 2 Studies on QTc measurements of infants who subsequently died from SID

Authors	Year	Number of infants investigated	Number of SID cases significant	Number of SID cases with QTc prolongation
Schwartz et al. [68]	1982	4,205	3	3
Southall et al. [69]	1983	6,914 full-term+ 2,337 pre-term	29	0
Weinstein and Steinschneider [72]	1985	1,000	8	0
Southall et al. [71]	1986	7,254	15	1
Schwartz et al. [83]	1998	34,442	24	12

vestigators [52, 53, 54] included the brainstem in the morphological investigations and indicated the possibility of a fatal reflexogenic mechanism [55, 56, 57] including an inappropriate activation of the diving reflex producing severe bradycardia with apnea [58, 59].

In the 1970s it was proposed that the long QT syndrome (LQTS) could be responsible for some cases of sudden infant death [60, 61] due to ventricular tachycardia leading to ventricular fibrillation [62, 63, 64, 65]. As the underlying mechanism is inhomogeneity of repolarisation, relevant genetic mutations leading to changes in protein structure seem to affect proteins controlling the myocardial ion channels [53, 66, 67].

In 1982 Schwartz et al. [68] reported 3 cases of SID which occurred among 4,205 prospectively investigated infants and showed a significant prolongation of QTc and the authors speculated that LQTS could be the main cause of SID. However, these results could not be confirmed by other investigators [69, 70, 71, 72] (Table 2) and therefore considerable discussion arose. In 1998 the working group of Schwartz [73] published a new investigation of more than 34,000 infants where an ECG was performed during the first week of life. A prolonged QTc was found in 50% of 24 SID cases which occurred in the investigation group. The authors evaluated this result as being confirmation of their previous hypothesis with regard to the causes of SID, but the assumption that 50% of all SID cases could be caused by LQTS does not seem to be justifiable.

New molecular genetic investigations enabled further light to be brought into this field since mutations on 5 different genes (KCNQ1, HERG, SCN5A, KCNE1, KCNE2) on chromosomes 3, 4, 7 and 11 have been described in the 1990s and an association with defects in cardiac sodium and potassium channels leading to LQTS [74, 75, 76, 77, 78] could be shown.

Up to now mainly case reports dealing with the diagnosis of LQTS in SID cases have been published [79, 80]. Bajanowski et al. [79] reported an investigation of two SID victims who were suspected of having died due to LQTS using polymerase chain reaction (PCR) combined with single stranded confirmation polymorphism analysis (SSCP) and sequencing. None of the known mutations responsible for LQTS could be detected, but a number of polymorphisms (frequency in the population >1%) could be found which either do not lead to amino acid substitution or the amino acid substitution is of no detectable significance. It needs to be stressed that results of these molecular genetic investigations do not totally exclude the existence of this syndrome. The mutation analysis using fluorescence SSCP is a screening method and the sensitivity is about 90% [81]. Furthermore LQTS is a multi-gene disease which can be divided into different types with regard to the genes involved. Other still unknown genes or gene loci could be involved in the pathogenesis and the significance of some of the molecular genetic changes defined to be polymorphisms is still unknown. Theoretically it has to be taken into consideration that the presence of two or more polymorphic sites can lead to functional disturbances if they are combined. In another suspected case of LQTS, the same working group found a mutation in the SCN5A gene and was able to demonstrate a new biophysical mechanism for the development of ventricular arrhythmias by a positive shift in voltage dependence of inactivation, a slowing of the time course of inactivation, and a faster recovery [80].

Results of a first systematic investigation of 93 SID cases for defects of the gene SCN5A were reported by Ackerman et al. [82] who detected 2 mutations in highly conserved regions encoding for the sodium channel.

Brugada syndrome [83] which was first described in 1992 is characterised by a right bundle branch block and ST elevation on electrocardiogram may lead to idiopathic ventricular fibrillation and is associated with sudden cardiac death. As a molecular genetic basis, mutations of the SCN5A gene were reported [84, 85, 86] to influence the function of the cardiac sodium channel. Priori et al. [87] reported five children from the same family who died after cardiac arrest and a mutation in the cardiac sodium channel could be detected confirming the diagnosis. It can be assumed that this disease which should be more frequent in the population than LQTS [88], could also be responsible for some SID cases [87].

We accept disturbances of cardiac rhythmogenic function due to congenital anomalies as the cause of death if the underlying mutation could be demonstrated, and again, per exclusion only.

Other pathological findings and functional disturbances

Cardiomyopathy (CM) has been observed as the cause of death in single cases of sudden infant death only. While dilated and hypertrophic forms and CM in storage diseases are well known in infants [89, 90, 91, 92], the histi-

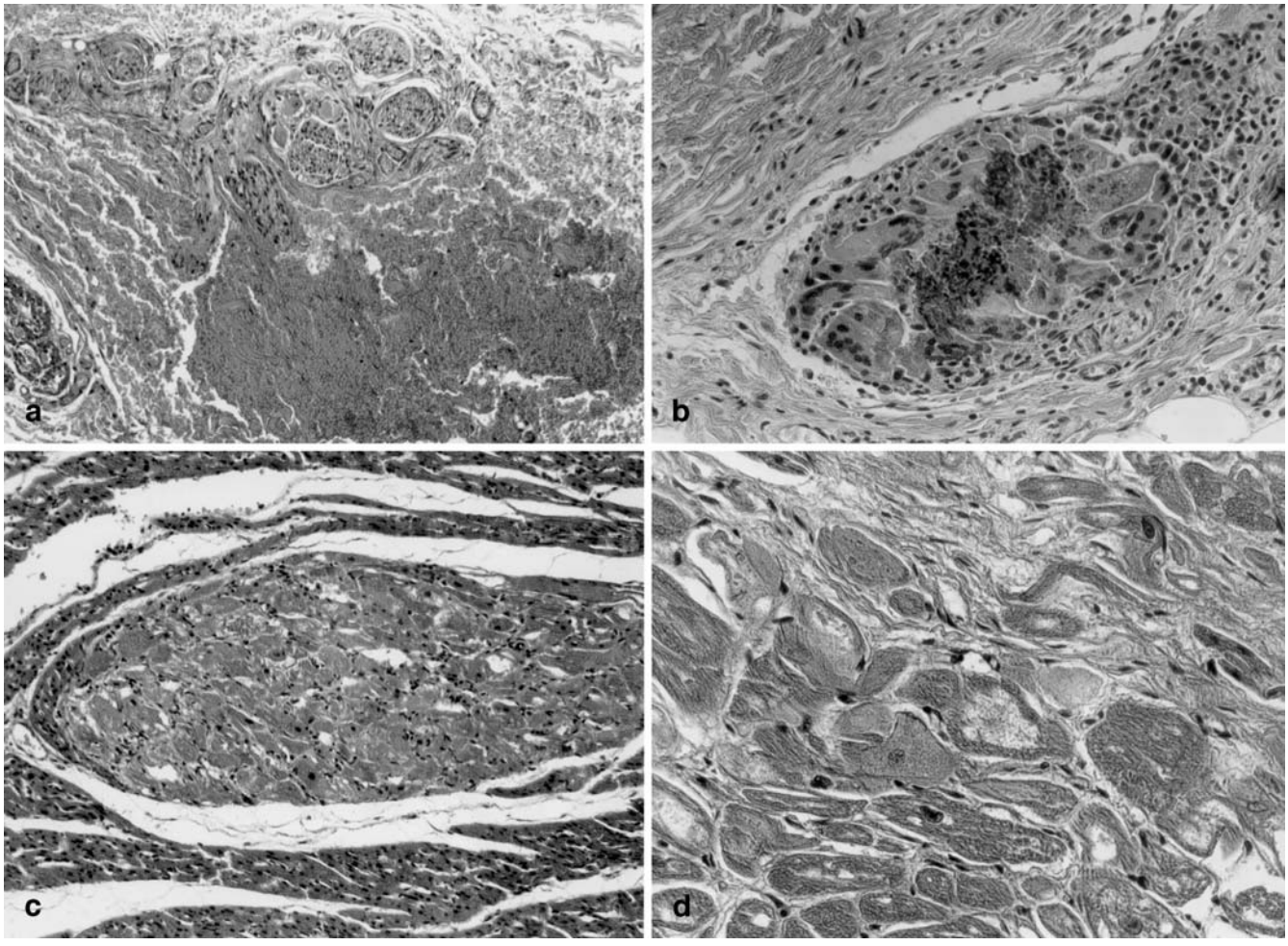

Fig. 5 **A** Haemorrhage near the SA node. Resuscitation attempts had not been carried out in this case (HE ×40). **B** Granuloma caused by inclusion of foreign bodies with typical giant cell formation located in the left ventricular wall near the Ramus interventricularis anterior of the left coronary artery, the etiology is unknown (HE ×100). **C** Circumscribed, not encapsulated rhabdomyoma of the left ventricular wall (HE×40). **D** Same tumour at higher magnification with irregular vacuolisation of the cytoplasm. The vacuoles vary in size and are separated by strands of cytoplasm. Typical spider cells are not present (HE ×200)

Table 3 Cardiac changes due to cardio-pulmonary resuscitation [116, 117]

Myocardial haemorrhages
Hypereosinophilia on the epicardial surface or just below
Epicardial damage of myocytes
Disruption of intercalated discs
Subjacent contraction bands
Coagulative necrosis without inflammatory infiltrates

ocytoid CM is rare [89] and only a few cases leading to sudden death without clinical symptoms are described in the literature [89, 93, 94, 95]. Histologically CM is characterised by myofibre disarray, nodoventricular fibres on both sides of the ventricular septum, and fibrosis of the left bundle branch [91]. In the histiocytic form multiple scattered clusters of histocytic myocytes could be found which are filled with abnormal mitochondria, as well as scattered lipid droplets and scanty myofibrils [89, 95]. It has been proposed that this form is X-linked dominant with the associated gene located in the region of Xp22 [95] while other forms of CM are also caused by different mutations [92, 96, 97].

Haemorrhages (Fig. 5A) are often the result of resuscitation and in cases where resuscitation attempts were not carried out (Table 3) they may be contributory to death if they affect main structures of the cardiac conduction system [89, 98]. In these cases the question of the origin of the haemorrhages has to be answered.

Unknown cardiac malformations may cause single cases of sudden unexpected death, but of course these cases have to be excluded from SID. Other diseases and changes, for example tumours of the myocardium (rhabdomyoma, Fig. 5C,D [89, 99, 100, 101] or granulomas caused by inclusion of foreign bodies (Fig. 5B) [99] have been reported and the significance for the cause of death depends on various conditions such as the kind of the tumour, the localisation of the changes and their size.

Endocardial fibroelastosis (diffuse thickening of the mural endocardium due to collagenous and elastic fibres) is also known to be associated with sudden infant death

[102, 103, 104]. Williams and Emery [104] found frequencies of 3.4% for abnormal thickening and of 20% "significant" thickening of the endocardium in 262 cases of home as well as hospital deaths of infants and concluded that this finding could be a contributory factor in some cases of SID.

An elevation of the mean heart rate [105, 106] and a reduced heart rate variability during the waking state [107] have also been reported in SID cases, as well as isolated cases of Wolff-Parkinson-White syndrome in infants [108].

Conclusions

Although the extent of cardiac lesions vary from case to case and from minimal to severe, and although the cardiac findings in SID are sometimes contradictory, disturbances of cardiac function could be one pathophysiological mechanism leading to sudden death in a subgroup of SID victims. Problems in the diagnosis of these disturbances are caused by different factors, such as:

- Lack of information on the history of illness
- Morphological variations of unknown significance, e.g. in the cardiac conduction system, which are not demonstrable by routine autopsy
- A lack of standardised investigation techniques
- Lack of a suitable definition of control cases
- The necessity to use time and cost-intensive, highly specialised molecular genetic techniques
- Problems in the classification of SID cases.

In order to diagnose the cardiac lesions described, the case history including clinical reports about the pregnancy, the birth and the further infant development should be analysed. After the autopsy an extensive histological examination of all parts of the heart (including the cardiac conductive system) is necessary using different staining methods (H&E, van Gieson, Sudan III). Immunohistochemistry can be helpful to diagnose different types of myocarditis (LCA, CD68, CD3, NP57) and to show hypoxia-related changes (troponin C, fibronectin, $C_{5b\text{-}9}$). The diagnostic procedure should be completed by bacteriology and virus detection. A detailed family history and an investigation of the death scene can indicate a death due to disturbances of the rhythmogenic function as well as the detection of CBN in a high quantity by histology. This suggestion should be clarified by broad molecular genetic screening whenever possible.

Finally, the question of the significance of the finding has to be answered in each single case considering that an acute event like SID needs an acute phenomenon to explain it.

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