

Contents

I	Introduction and Aims	1
I.1	Sudden Infant Death Syndrome	2
I.1.1	Definition and History of SIDS	2
I.1.2	Epidemiology and Risk Factors	5
I.1.3	Etiopathogenesis of SIDS	8
I.1.3.1	Reflexogenic SIDS	9
I.1.3.2	SIDS due to Metabolic Impairment	10
I.1.4	“Near Miss” and “ALTE” Episodes	10
I.1.5	SIDS Prevention	11
I.2	Sudden Intrauterine Unexplained Death	12
I.3	Cardiac Conduction System	13
I.3.1	Sinoatrial Node	13
I.3.1.1	Histology	15
I.3.1.2	Vascular Supply	16
I.3.1.3	Collagen Framework	16
I.3.1.4	Innervation	17
I.3.2	Internodal and Interatrial Pathways	17
I.3.3	Atrioventricular Node	18
I.3.3.1	Histology	18
I.3.3.2	Vascular Supply	19
I.3.3.3	Lymphatic Drainage	20
I.3.3.4	Innervation	20
I.3.4	Morphological Concept of the Atrioventricular Junction	20
I.3.4.1	Central Fibrous Body	20
I.3.4.2	Tendon of Todaro	21
I.3.5	Bundle of His	21
I.3.5.1	Histology	22
I.3.5.2	Vascular Supply	22
I.3.5.3	Innervation	23
I.3.6	Bifurcating Bundle of His or Bifurcation	23
I.3.7	Right Bundle Branch	23
I.3.7.1	Histology	24
I.3.7.2	Vascular Supply	24
I.3.7.3	Innervation	25

I.3.8	Left Bundle Branch	25
I.3.8.1	Histology	25
I.3.8.2	Vascular Supply	25
I.3.8.3	Innervation	25
I.3.9	Fetal and Postnatal Development of the Conduction System	25
I.3.9.1	The Sinoatrial Node: Fetal and Postnatal Development	26
I.3.9.2	Internodal Pathways: Fetal and Postnatal Development	27
I.3.9.3	Atrioventricular Node Development	27
I.3.9.4	Bundle of His and Bundle Branches Development	28
I.3.9.5	AVN and Bundle of His Postnatal Molding	28
I.3.10	Accessory Cardiac Conduction Pathways	30
I.3.10.1	Kent Fibers	31
I.3.10.2	James and Mahaim Fibers	32
I.4	Central, Peripheral and Autonomic Nervous Systems	32
I.4.1	Brainstem	32
I.4.1.1	Arcuate Nucleus	32
I.4.1.2	Parabrachial/Kölliker-Fuse Complex	33
I.4.1.3	Dorsal Motor Vagal Nucleus	33
I.4.1.4	Ambiguous Nucleus	33
I.4.1.5	Solitary Tract Nucleus	33
I.4.1.6	Locus Coeruleus	34
I.4.1.7	Hypoglossal Nucleus	34
I.4.2	Spinal Cord	34
I.4.3	Extrinsic Cardiac Innervation	34
I.4.3.1	Right Side of the Heart	34
I.4.3.2	Left Side of the Heart	35
I.4.4	Intrinsic Cardiac Innervation	35
I.4.5	Nervous Structures Regulating Cardiac Activity	36
I.4.5.1	Juxtacardiac and Mediastinal Ganglia and Paraganglia	37
II	Materials and Methods	39
II.1	Clinical and Pathological Information	39
II.2	Post-Mortem Regulation on SIDS and Unexpected Fetal Death ..	44
II.3	Necropsy Procedure	44
II.4	Cardiac Sampling and Study of the Conduction System	48
II.4.1	Cardiac Sampling	48
II.4.2	Removal of the Cardiac Conduction System Blocks	48
II.4.3	Treatment of the Cardiac Conduction Blocks	53
II.5	Brainstem Sampling	57

II.5.1	Complete Examination of the Brainstem	58
II.5.2	Simplified Examination of the Brainstem	59
II.5.3	Treatment of the Brainstem Blocks	59
II.5.4	Morphometric Analysis	61
II.6	Study of the Carotid Bifurcation, Ganglia and Paraganglia	61
II.6.1	Carotid Bifurcation	61
II.6.2	Mediastinal Ganglionic and Paraganglionated Plexuses	62
II.6.3	Cervical Sympathetic Ganglia	62
II.7	Lung: Evaluation of the Stage of Development	63
II.8	Immunohistochemistry and Other Techniques	63
II.8.1	Apoptosis	63
II.8.2	Proliferating Cell Nuclear Antigen (PCNA)	63
II.8.3	c-Fos	64
II.8.4	Fluorescence In Situ Hybridization (FISH)	64
II.8.5	α -Actin Immunohistochemistry	65
II.9	Cases Analyzed	65
II.9.1	SIDS Cases	65
II.9.2	"Gray Zone" SIDS Cases	66
II.9.3	SIUD Cases	66
II.9.4	Explained Death Cases	66
II.10	Statistical Analysis	67
III	Results	69
III.1	Epidemiological Results	69
III.1.1	Age	69
III.1.2	Sex	69
III.1.3	Season	70
III.1.4	Time	70
III.1.5	Death Scene: Place of Death	70
III.1.6	Death Scene: Position in the Crib	70
III.1.7	Feeding	71
III.1.8	Cigarette Smoke Exposure	73
III.2	Cardiac Conduction Findings	73
III.2.1	Resorptive Degeneration	73
III.2.2	Atrioventricular Node and Bundle of His Dispersion/Septation ..	73
III.2.3	Persistent Fetal Dispersion	75
III.2.4	Accessory Pathways	75
III.2.5	Cartilaginous Metahyperplasia/Hypermetaplasia	75

III.2.6	Hemorrhage of the Cardiac Conduction System	75
III.2.7	Intramural Right Bundle Branch	75
III.2.8	Left-Sided Bundle of His	78
III.2.9	Intramural Left Bundle Branch	78
III.2.10	Septation of the Bifurcation	78
III.2.11	Hypoplasia of the Cardiac Conduction System	78
III.2.12	Atrioventricular Node/Bundle of His Dualism	78
III.2.13	Zahn Node	78
III.2.14	Fibromuscular Hyperplasia of the Conduction System Arteries ..	78
III.2.15	Apoptosis Expression in the Conducting Tissue	80
III.2.16	PCNA Expression in the Conducting Tissue	81
III.2.17	ECG Findings	81
III.2.18	Coronary Artery Findings	84
III.2.18.1	Infants	84
III.2.18.2	Fetuses	84
III.2.19	"Gray Zone" or Borderline Cases	85
III.2.19.1	Cardiac Purkinje Cell Tumor	85
III.2.19.2	Myocardial Infarction and Mahaim Fibers	87
III.2.20	Not SIDS/Sudden Explained Death	88
III.2.20.1	Cardiac Fibroma	88
III.2.20.2	Hypertrophic Cardiomyopathy	90
III.3	Central and Autonomic Nervous System Findings	90
III.3.1	Hypoplasia and Agenesis of the Arcuate Nucleus	90
III.3.2	Combined Pulmonary and Arcuate Nucleus Hypoplasia	93
III.3.3	Parabrachial/Kölliker-Fuse Complex Findings	93
III.3.3.1	Morphological Analysis of the Parabrachial/Kölliker-Fuse Complex	94
III.3.3.2	Lateral Parabrachial Nucleus	94
III.3.3.3	Medial Parabrachial Nucleus	94
III.3.3.4	Kölliker-Fuse Nucleus	95
III.3.3.5	Morphometric Analysis of the Parabrachial/Kölliker-Fuse Complex	95
III.3.4	Brainstem Neurons Responding to Hypoxia (c-fos-Positive)	96
III.3.5	Combined Cardiac Conduction and Brainstem Study	96
III.3.6	Gray-Zone/Borderline SIDS	96
III.4	Peripheral Autonomic Nervous System Findings	97
III.4.1	Paraganglionic Hyperplasia	97
III.4.2	Stellate Ganglion Alterations	98
IV	Discussion	99
IV.1	Cardiac Conduction Pathology	99

IV.1.1	Resorptive Degeneration	100
IV.1.2	Atrioventricular Node and Bundle of His Dispersion/Septation	101
IV.1.3	Persistent Fetal Dispersion	102
IV.1.4	Accessory Pathways	102
IV.1.4.1	Mahaim Fibers	102
IV.1.4.2	Kent Fibers	103
IV.1.4.3	James Fibers	103
IV.1.5	Cartilaginous Metahyperplasia	104
IV.1.6	Hemorrhage of the Cardiac Conduction System	104
IV.1.7	Intramural Right Bundle Branch	105
IV.1.8	Left-Sided Bundle of His	105
IV.1.9	Intramural Left Bundle Branch	105
IV.1.10	Septation of the Bifurcation	105
IV.1.11	Hypoplasia of the Cardiac Conduction System	105
IV.1.12	Atrioventricular Node/Bundle of His Dualism	106
IV.1.13	Zahn Node	106
IV.1.14	Fibromuscular Hyperplasia of the Conduction System Arteries	106
IV.1.15	Apoptosis Expression in the Conducting Tissue	107
IV.1.16	PCNA Expression in the Conducting Tissue	108
IV.1.17	ECG Findings	109
IV.1.18	Coronary Artery Findings	109
IV.1.18.1	Infants	109
IV.1.18.2	Fetuses	110
IV.1.19	"Gray Zone" or Borderline Cases	111
IV.1.20	Other Cardiac Findings	111
IV.2	Neuropathology	112
IV.2.1	Hypoplasia and Agenesis of the Arcuate Nucleus	112
IV.2.2	Combined Pulmonary and Arcuate Nucleus Hypoplasia	112
IV.2.3	Parabrachial/Kölliker-Fuse Complex Findings	113
IV.2.4	Brainstem Neurons Responding to Hypoxia (c-Fos-Positive)	114
IV.2.5	Gray Zone/Borderline SIDS	115
IV.2.6	Paraganglia Hyperplasia	115
IV.2.7	Long QT Syndrome	116
V	Concluding Remarks	119
VI	Summary	123
	References	127
	Subject Index	141