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Brain stem lesions in the sudden infant death syndrome: variability in the hypoplasia of the arcuate nucleus

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Abstract In the present study we investigated quantitatively the incidence of hypoplasia of the arcuate nucleus (ARCn) of the medulla oblongata, reported earlier [Matturri et al. (2000) Acta Neuropathol 99:371], as well as its distribution in 62 cases of sudden infant death syndrome (SIDS; mean age 14 postnatal weeks, 39 male and 23 female) and 25 controls (mean age 16 postnatal weeks, 14 male and 11 female), using detailed histopathological and morphometric analyses performed on serial sections of medulla oblongata. The SIDS cases were divided into four subtypes: SIDS A (27 cases, 43%) with histologically well-developed ARCn; SIDS B (16 cases, 26%) with severe bilateral hypoplasia along the whole length; SIDS C (11 cases, 18%) with partial bilateral hypoplasia, located mainly in the lateral portions of the caudal two thirds of the nucleus, and SIDS D (8 cases, 13%) with right monolateral hypoplasia of the ARCn. ARCn hypoplasia was detected in 56% of cases (35 cases). Three-dimensional volume reconstruction showed that in the SIDS A victims the mean volume was analogous to controls, whereas in the SIDS group with ARCn hypoplasia, severe or partial, the mean volume was significantly different from controls on both sides of the medulla oblongata (SIDS B group: P=0.003, P=0.002; SIDS C group: P=0.007, P=0.008). The mean ARCn volume in the SIDS D group was statistically significant only on the right side (P=0.005). We also observed reduced neuron density of the ARCn, associated with a decrease in the total number of neurons over the whole length of the nucleus itself. On the basis of the morphometric results of neuronal population in the different portions of the ventrolateral medulla in SIDS cases, we hypothesized that infants without the full complement of neurons and neuropil (ARCn hypoplasia) are at risk for SIDS because they are unable to develop appropriate cardioventilatory control during this crucial developmental period.

Keywords Arcuate nucleus · Brain stem · Sudden infant death syndrome · Ventral medullary surface · Central chemoreception

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Introduction

The sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under 1 year age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history [32]. This is a major socio-medical problem for which no solution has been found, and it is the main cause of death in the first years of life in developed countries. The pathogenetic mechanisms most commonly cited are the following: cardiac (arrhythmia), respiratory (apnea), and autonomous nervous system abnormalities of the upper digestive tract. Anomalies in the cardiorespiratory autonomous nervous system play a key role in triggering reflexogenic death [4, 5, 9, 23, 24]. It is widely believed that SIDS victims carry abnormalities of the vegetative nervous system. A large number of congenital and/or acquired alterations of the central and peripheral nervous system have been reported [3, 5, 12, 13, 15, 18, 19, 25]. Hypoplasia of the arcuate nucleus (ARCn) is particularly noteworthy because, as detailed studies show, it appears to provide a plausible cause in some SIDS victims. In an earlier investigation on 36 SIDS cases and 12 controls, we showed that this developmental defect was present in 30% of the cases [15]. Histopathological observations of serial sections of the entire medulla oblongata showed significant differences in this developmental congenital anomaly in different portions of the ARCn (cranial, middle, caudal) as well as variations in the neuronal population. We therefore investigated in detail the

morphometric characteristics (volume, neuronal density, total number of neurons) of ARCn hypoplasia in a large number of cases.

Materials and methods

The morphometric analysis was carried out at the Institute of Pathology of the University of Milan, on human brain stem from 62 infants (39 males, 23 females) who had died of SIDS and 25 age-matched control infants who had died of known causes. The SIDS cases includes 14 SIDS cases supplied by the Instituto Nacional de Toxicología (Madrid, Spain). The age for SIDS victims ranged from 1 to 52 postnatal weeks (mean: 14 weeks). The control cases comprised 25 infants (14 males, 11 females), with mean age 16 postnatal weeks (range: 1–52 weeks). Control cases were healthy infants under 1 year of age who had died suddenly, and for whom an autopsy had established a cause of death that was neither cardiorespiratory nor neuropathological in origin, and included 13 malignant neoplasms, 8 acute rejections of liver transplant, 2 acquired immunodeficiency syndrome, 2 acute glomerulonephritis. Anamnesis showed that in all cases the babies were born at term (38–40°weeks) and there had been no major problems during pregnancy. The brains were fixed in toto for 2–3 weeks in 10% phosphate-buffered formalin. Subsequently the brain stem was removed, sectioning perpendicular to the main axis of the medulla through the portion of the brain stem between the caudal pole of the inferior olive and the caudal border of the pons. After embedding in paraffin, 7-μm-thick serial sections were made in the horizontal plane corresponding to the macroscopic cut surface. In each case, 600 sections of the brain stem block were cut per case proceeding rostro-caudally (53,000 sections all together). The serial sections comprised the entire length of the medulla and were stored at 37°C overnight. The sections were alternatively stained with hematoxylin-eosin, Bielschowsky and Klüver-Barrera methods.

The morphometric analysis was performed with an Image-Pro Plus Image Analyzer (Media Cybernetics, Silver Spring, Md.), evaluating the surface area of the ARCn and its neuronal density (number of neurons per unit area, expressed in mm^2). The measurements were made in a blinded fashion, without knowledge of the clinical diagnosis or postnatal age.

The histological image acquisition was made via a color video camera and displayed in the PC-monitor in RGB real color. The particular area of interest of the ARCn using this method is easily isolated, identified, edited and analyzed. The outer boundary of the ARCn was delineated on both side of medulla oblongata in the same specimen. We defined and examined three levels for comparing all sections between the cases: the high level, corresponding to the rostral medulla, below the ponto-bulbo sulcus (Plate XIV); the median level, corresponding to the midmedulla (Plate XII), and the low level, corresponding to the caudal medulla, level of area postrema (Plate X). Plates in the human brain stem atlas of Olszewski and Baxter were used as reference [17].

For the evaluation of the neuronal density (expressed as number of neurons per mm^2) all the neurons with clearly defined edges and a distinct nucleolus were counted in transverse sections, coplanar, using an optical microscope at ×200 magnification. The analysis was performed in the same three defined histological levels of the medulla oblongata.

The volume of the ARCn and the total neuronal number were measured by three-dimensional reconstruction. A computer program developed by Voxblast (VayTek, Inc., Fairfield, Iowa) was used to digitize and display serial section reconstruction, and to obtain volumetric measurements of the selected cell populations. The outer boundaries of the ARCn in every tenth section were traced, and the tracings were digitized by computer and registered to re-establish their original positions relative to one another. The fourth ventricle and central canal served as landmarks for registration. The brain stem was reconstructed from the cervicomedullary to the pontomedullary junction [11]. The morphometric results of the measurements are expressed as mean values and SD. Statistical calculations were carried out on personal computer using the SPSS statistical software. The statistical significance of direct comparisons between SIDS cases and controls was determined using the analysis of variance (ANOVA). The selected threshold level for statistical significance was $P<0.05$.

Results

In the blinded qualitative survey, the brain stems from 87 cases (62 SIDS victims and 25 controls) were examined. Comparison of the SIDS and the control groups showed no significant differences between mean gestational age, birth weight and Apgar scores. Histopathological examination of the medulla oblongata in the 25 controls showed the area of the ARCn. Its area was greatest in the cranial portion especially at middle level, where it makes contact with the raphe pale nucleus. In the caudal portion, the width of the ARCn was reduced at the middle level; it then increased laterally, next to the anterior lateral fissure where the hypoglossal nerve originates, becoming thinner along the ventral medullary surface (Fig. 1). Histological examination of all serial sections and subsequent the three-dimensional reconstruction of the ARCn revealed hypoplasia only in the SIDS victims, with variations in length and in reduction of the neuron population. ARCn hypoplasia was detected in 56% of cases (35 cases). Severe bilateral hypoplasia was found in 16 SIDS cases (26%), homogeneously distributed along the full length of the ARCn. In 11 cases (18%) we found partial bilateral hypoplasia, located exclusively in the lateral projections of the caudal two thirds of the medulla oblongata. In the latter cases the development of the cranial portion was similar to that of controls. Furthermore, in 8 of the SIDS victims (13%) severe monolateral hypoplasia in the right portion of the ARCn was observed along its full length. We therefore divided the SIDS cases into four subsets on the basis of the ARCn development: SIDS A, cases with “normal” length and width (Fig. 2); SIDS B, cases with severe bilateral hypoplasia along the whole length (Fig. 3); SIDS C, cases with partial bilateral hypoplasia, located mainly in the caudal two thirds and more precisely in the lateral projections of the ARCn (Fig. 4) and SIDS D, cases with monolateral hypoplasia on the right side only (Fig. 5).

ARCn area

In both control and SIDS A cases, the ARCn had a bilateral median area of 1.75–1.84 mm^2 and 1.59–1.63 mm^2 at cranial level, of 1.25–1.38 mm^2 and 1.09–1.11 mm^2 at intermediate level and of 0.98–1.03 mm^2 and 0.92–1.07 mm^2 at caudal level (Table 1). There was no difference in mean values between SIDS A cases and controls. In the SIDS B group the mean area of ARCn on left and right, respectively, was 0.38 and 0.32 mm^2 at cranial level, 0.22 and 0.29 mm^2 at intermediate level and 0.03 and 0.05 mm^2 caudal level. These differences were statistically different in relation to the mean values for controls ($P=0.003$, $P=0.001$, $P=0.0009$). In the SIDS C group the median

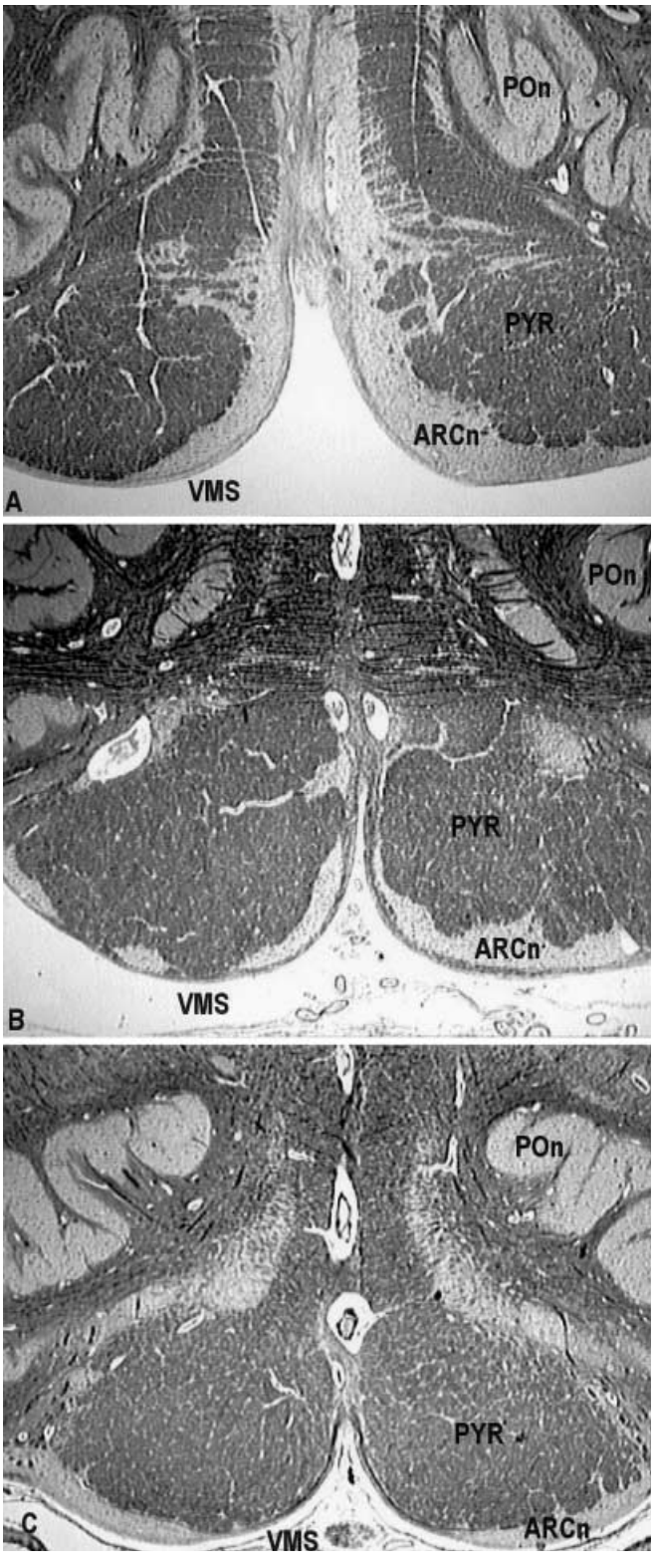

Fig. 1A–C Control case: normal area of the ARCn at each of the three standard sections of the medulla oblongata: cranial portion (A), middle portion (B) and caudal portion (C) (*ARCn* arcuate nucleus, *POn* principal inferior olive nucleus, *PYR* pyramid, *VMS* ventral medullary surface). Klüver-Barrera stain, original magnification ×20

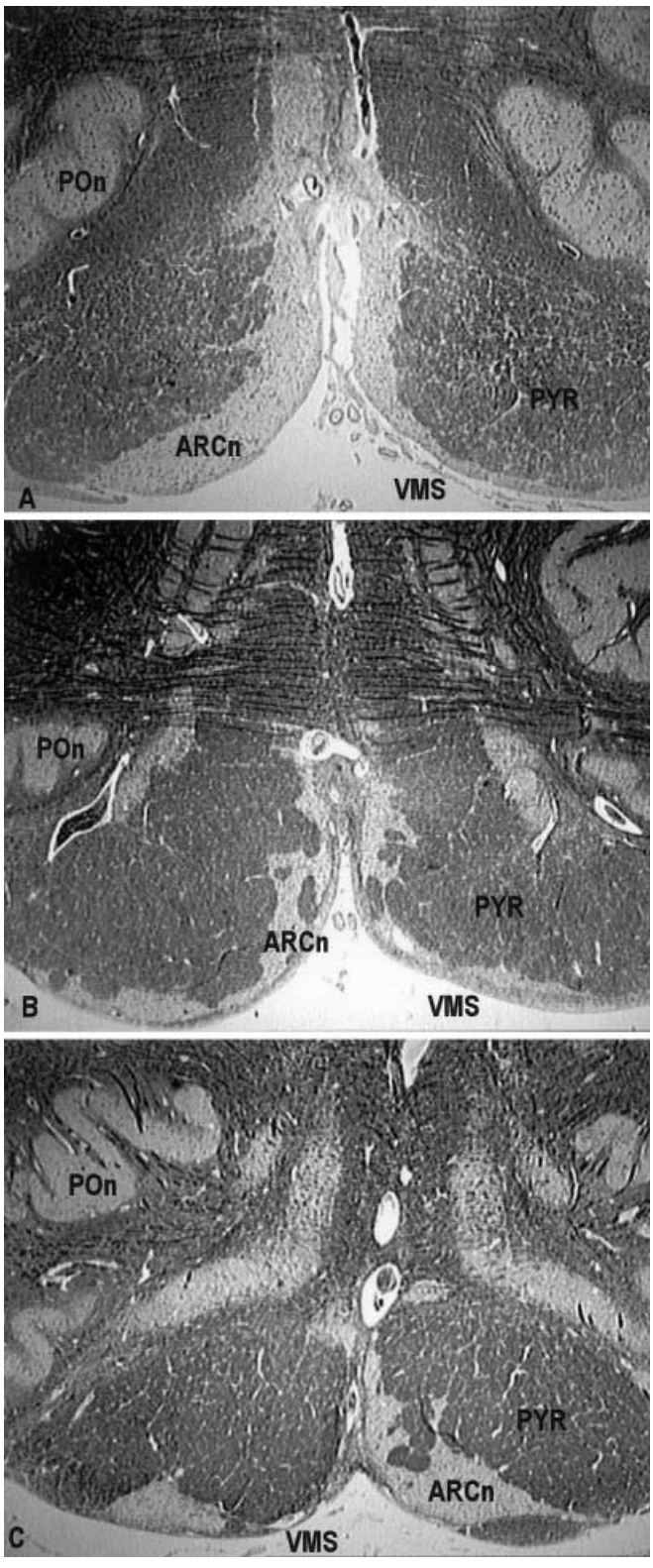

Fig. 2A–C SIDS A: normal area of the ARCn, analogous to control cases. Cranial portion (**A**), middle portion (**B**) and caudal portion (**C**) of the medulla oblongata (*SIDS* sudden infant death syndrome). Klüver-Barrera stain, original magnification ×20

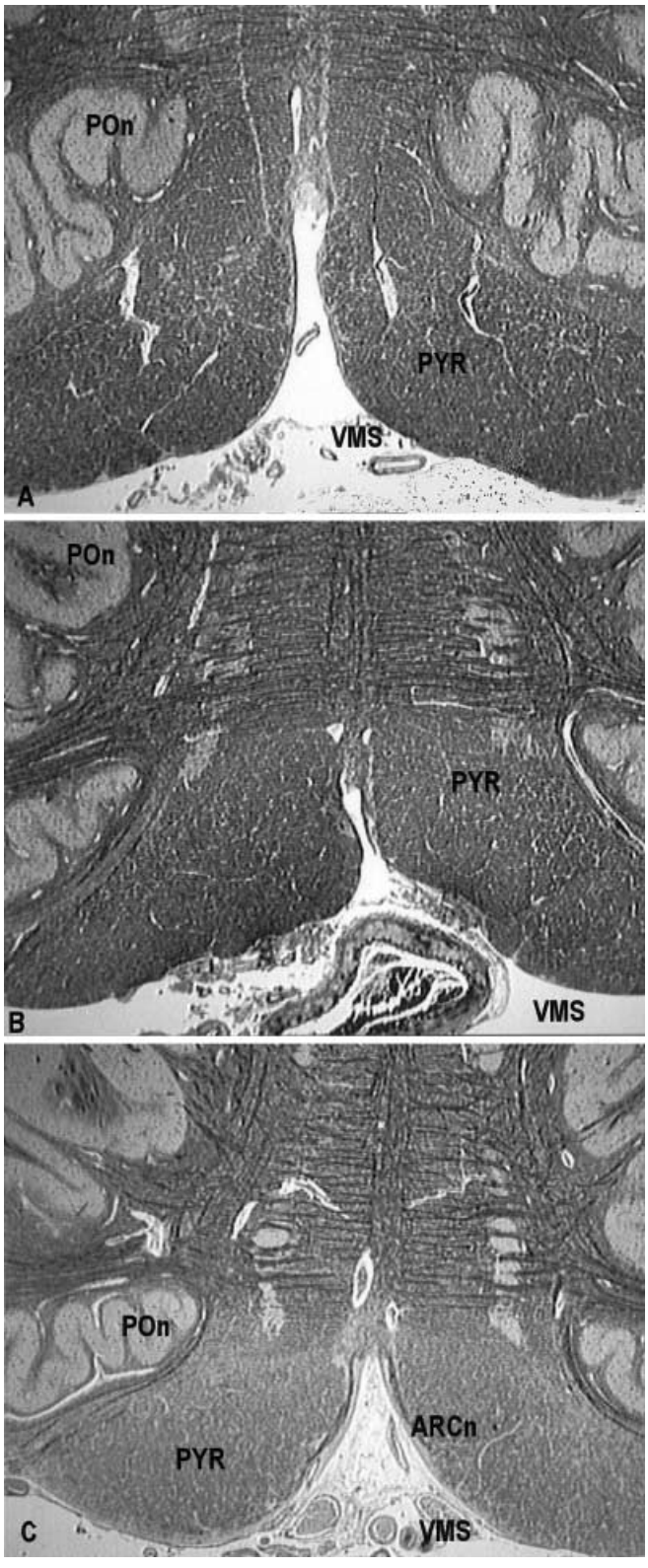

Fig. 3A–C SIDS B: ARCn severe bilateral hypoplasia expressed in all three levels of the medulla oblongata. Cranial portion (**A**), middle portion (**B**) and caudal portion (**C**) of the medulla oblongata. Klüver-Barrera stain, original magnification ×20

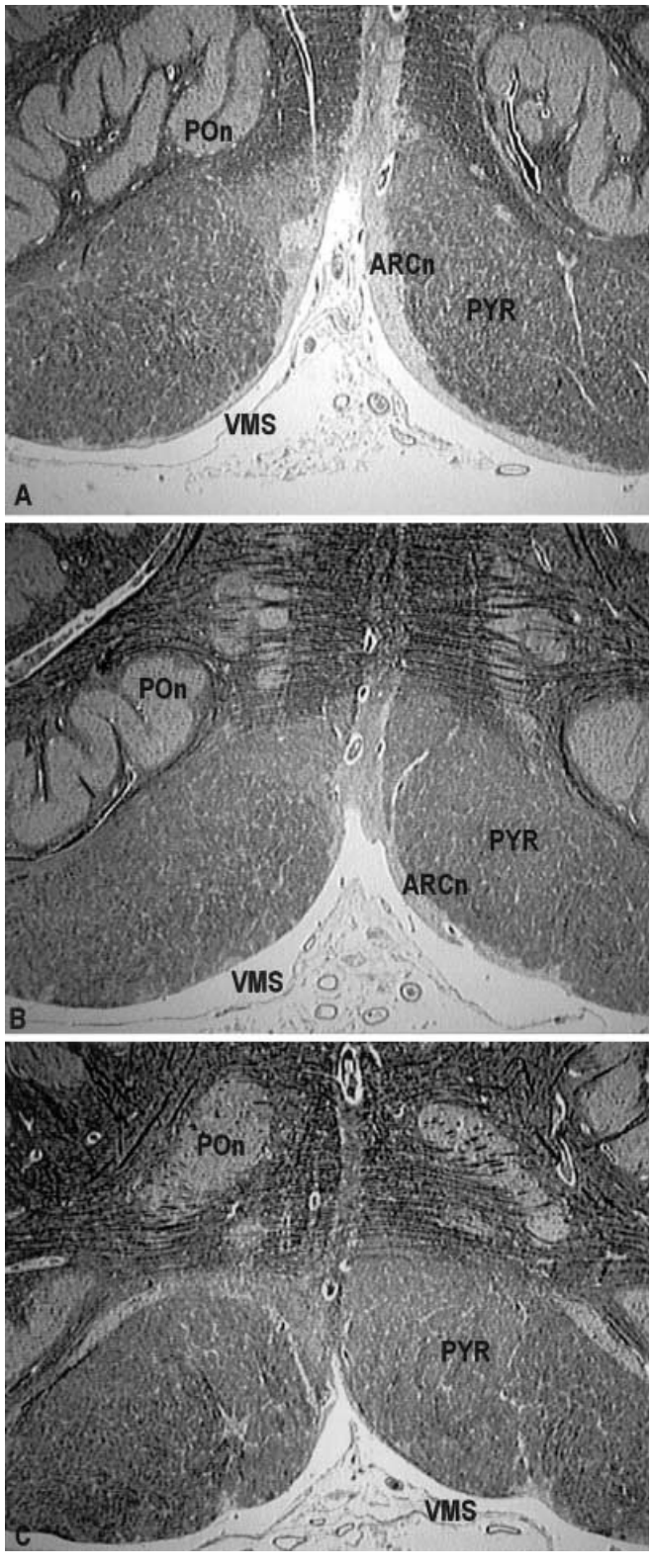

Fig. 4A–C SIDS C: ARCn partial hypoplasia, located mainly in the portions of caudal two thirds of the medulla oblongata. Cranial portion (**A**), middle portion (**B**) and caudal portion (**C**) of the medulla oblongata. Klüver-Barrera stain, original magnification ×20

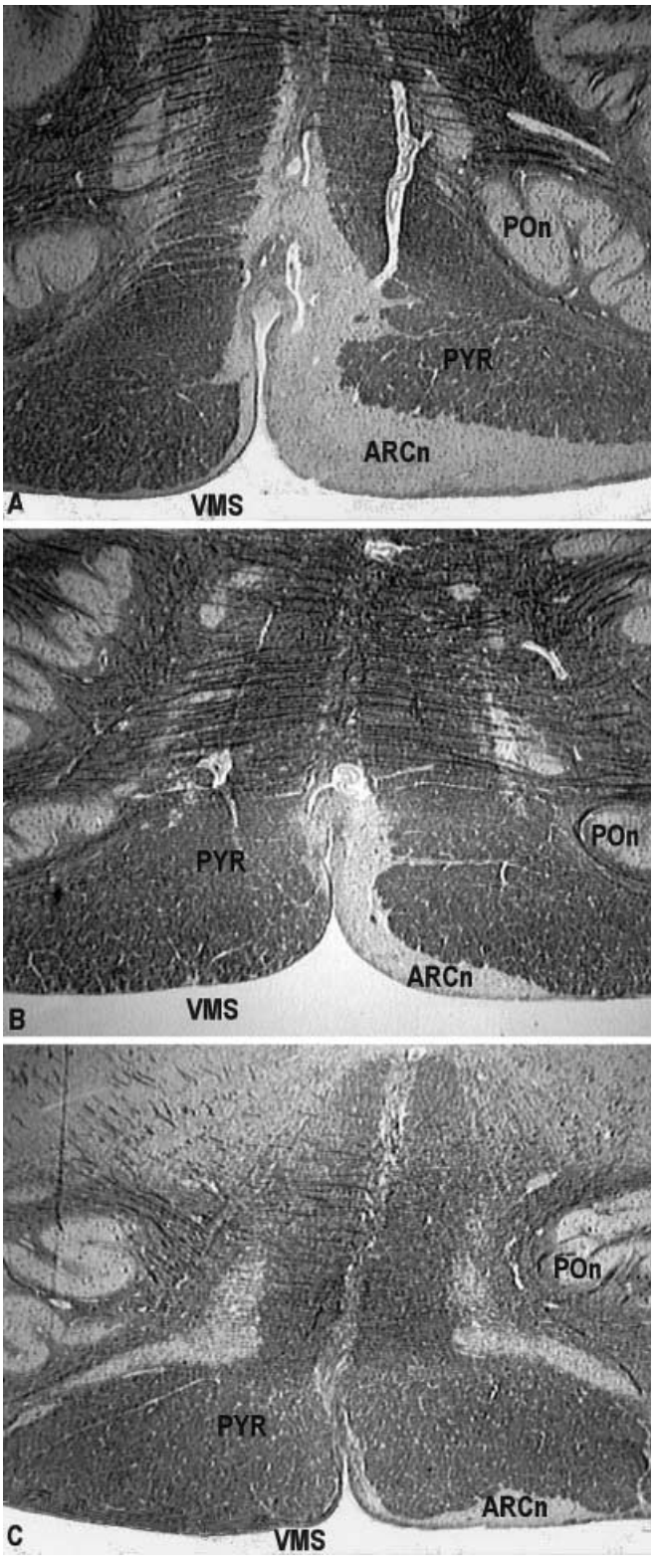

Fig. 5A–C SIDS D: ARCn right monolateral hypoplasia. Cranial portion (**A**), middle portion (**B**) and caudal portion (**C**) of the medulla oblongata. Klüver-Barrera stain, original magnification ×20

area of ARCn on left and right, respectively, was 1.52 and 1.48 mm^2 in the cranial portion, 0.26 and 0.34 mm^2 in the middle portion and 0.07 and 0.09 mm^2 in the caudal portion of the medulla oblongata. These differences were statistically significant in the middle and lower portions compared with controls (P=0.002, P=0.001). There was no difference in mean values between SIDS C cases and controls for the cranial portion. In the SIDS D group the mean area of the ARCn was significantly different on left and right. On the right it was 0.47 mm^2 in the cranial portion, 0.35 mm^2 in the middle portion and 0.07 mm^2 in the caudal portion of the medulla oblongata. Whereas on the left was 1.55 mm^2 in the cranial portion, 1.13 mm^2 in middle portion and 0.55 mm^2 in the cranial portion of the medulla oblongata. These differences were statistically significant for the whole length of the ARCn, exclusively on the right side (P=0.003, P=0.001, P=0.0008).

ARCn neuronal density

The morphometric results of the ARCn neuronal density evaluated at the three standard levels of the medulla oblongata are shown in Table 2. In control and SIDS A cases, the ARCn had a bilateral median neuronal density of 165–173 neurons/mm^2 and 162–145 neurons/mm^2 at cranial level, of 144–162 neurons/mm^2 and 133–146 neurons/mm^2 at intermediate level and of 147–142 neurons/mm^2 and 158–154 neurons/mm^2 at caudal level. There was no difference in mean values between SIDS A cases and controls. In the SIDS B group the mean neuronal density of ARCn on left and right, respectively, was 67 and 73 neurons/mm^2 at cranial level, 48 and 51 neurons/mm^2 at intermediate level and 54 and 56 neurons/mm^2 at caudal level. These differences were statistically different in relation to the mean values for controls (P=0.004, P=0.001, P=0.002). In the SIDS C group the mean neuronal density of ARCn on left and right, respectively, was 132 and 144 neurons/mm^2 in the cranial portion, 45 and 44 neurons/mm^2 in the median portion and 43 and 37 neurons/mm^2 in the caudal portion of the medulla oblongata. These differences were statistically significant in all portions compared with controls (P=0.005, P=0.003, P=0.003). In the SIDS D group the mean neuronal density was significantly different compared with control. On the left it was 135 neurons/mm^2 in the cranial portion, 101 neurons/mm^2 in the middle portion and 96 neurons/mm^2 in the caudal portion of the medulla oblongata (P=0.006, P=0.026, P=0.002). Whereas on the right was 41 neurons/mm^2 in the cranial portion, 44 neurons/mm^2 in middle portion and 51 neurons/mm^2 in the caudal portion of the medulla oblongata (P=0.001, P=0.002, P=0.002).

ARCn volume

The mean ARCn volume in the 27 cases defined as SIDS A was 8.70±1.56 mm^3 on the left and 9.01±1.81 mm^3 on the right, whereas in the controls the mean values were

Table 1 Morphometric analysis in the area of the ARCn of 62 SIDS and 25 control cases at three standard levels of the brain stem: cranial portion, median portion (obex), caudal portion. The area is expressed in mm^2 (mean ± SD) (SIDS sudden infant death syndrome, ARCn arcuate nucleus, *SIDS A* cases with histologically well developed ARCn, *SIDS B* cases with severe hypoplasia, SIDS C cases with partial hypoplasia, *SIDS D* cases with right monolateral hypoplasia

Level	SIDS A (*n*=27)		SIDS B (*n*=16)		SIDS C (*n*=11)		SIDS D (*n*=8)		Controls (*n*=25)	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Cranial	1.59±0.82	1.63±0.91	0.38±0.16*	0.32±0.19*	1.52±0.88	1.48±0.91	1.55±0.76	0.47±0.21*	1.75±0.77	1.84±0.84
Median	1.09±0.51	1.11±0.39	0.22±0.15*	0.29±0.18*	0.26±0.11*	0.34±0.12*	1.13±0.61	0.35±0.12*	1.25±0.54	1.38±0.46
Caudal	0.92±0.31	1.07±0.43	0.03±0.01*	0.05±0.03*	0.07±0.04*	0.09±0.06*	0.55±0.24**	0.07±0.05*	0.98±0.45	1.03±0.38

Significance related to control are expressed for *P<0.01 and **P<0.05

Table 2 Morphometric analysis of the neuronal density in the ARCn of 62 SIDS and 25 control cases at cranial portion, median portion (obex), caudal levels, expressed in neuron/mm^2 (mean ± SD)

Level	SIDS A: (*n*=27)		SIDS B: (*n*=16)		SIDS C: (*n*=11)		SIDS D: (*n*=8)		Controls (*n*=25)	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Cranial	162±34	145±48	67±28*	73±31*	132±20*	144±23*	135±37*	41±15*	165±20	173±36
Median	133±37	146±29	48±37*	51±28*	45±16*	44±19*	101±23**	44±14*	144±50	162±49
Caudal	158±28	154±34	54±34*	56±27*	43±20*	37±11*	96±22*	51±13*	147±40	142±35

Significance related to control are expressed for *P<0.01 and **P<0.05

Table 3 Morphometric analysis of the volume and the total number of neurons in the ARCn of 62 SIDS and 25 control cases, expressed as mean ± SD

Case	*n*	Volume (mm^3)		Total no. of neurons	
		Left	Right	Left	Right
SIDS cases	62				
SIDS A: normal area	27 (43%)	8.70±1.56	9.01±1.81	1508±306	1473±373
SIDS B: severe hypoplasia	16 (26%)	0.43±0.15*	0.37±0.10*	93± 25*	99± 28*
SIDS C: partial hypoplasia (caudal 2/3)	11 (18%)	3.58±0.81*	3.66±0.85*	317± 45*	328± 46*
SIDS D: monolateral hypoplasia (right side)	8 (13%)	8.35±1.17	1.51±0.47*	1562±206	295± 89*
Controls	25	9.54±2.32	9.79±1.82	1619±283	1653±282

Significance related to control are expressed for *P<0.01

9.54±2.32 mm^3 and 9.79±1.82 mm^3 on the left and the right of the medulla oblongata, respectively. There were no significant statistical differences between these two groups (Table 3). The mean ARCn volume in the 16 cases defined as SIDS B was 0.43±0.15 mm^3 on the left and 0.37±0.10 mm^3 on the right. The differences between the SIDS B group and controls were significant (P=0.003, P=0.002). In the 11 cases where the ARCn showed hypoplasia in its caudal two third region (SIDS C), mean volume values were significantly reduced compared with controls. The mean ARCn volume on the left was 3.58± 0.81 mm^3 and 3.66±0.85 mm^3 on the right (P=0.007, P=0.008). In the eight SIDS D cases the mean right ARCn volume was 1.51±0.47 mm^3, statistically lower than the controls values (P=0.005), whereas in the left portion it was 8.35±1.17 mm^3, not significantly different from controls. Figure 6 shows the correlation between ARCn volumetric results and age, expressed in postnatal weeks of the four SIDS groups and controls. There no significant statistical differences.

Total number of arcuate neurons

The evaluation of the total number of neurons along the whole length of the ARCn showed significant differences between the SIDS groups and the controls (Table 3).

In the SIDS A group the total number of ARCn neurons was 1,508±306 neurons in the left and 1,473±373 neurons in the right portion. These values did not differ significantly from those of the control, where the total number of ARCn neurons was 1,619±283 in the left and 1,653±282 in the right portion. In the SIDS B group the total number of ARCn neurons was 93±25 neurons in the left and 99±28 in the right portion. These values were significantly lower than those of controls in both histological sites of the ARCn (P=0.0008, P=0.0009). The total number of ARCn neurons in the SIDS C group was 317±45 neurons in the left and 328±46 in the right portion. Compared with controls these values were significantly different (P= 0.002, P=0.002). In the SIDS D group the total number of ARCn neurons was considerably lower on the right than

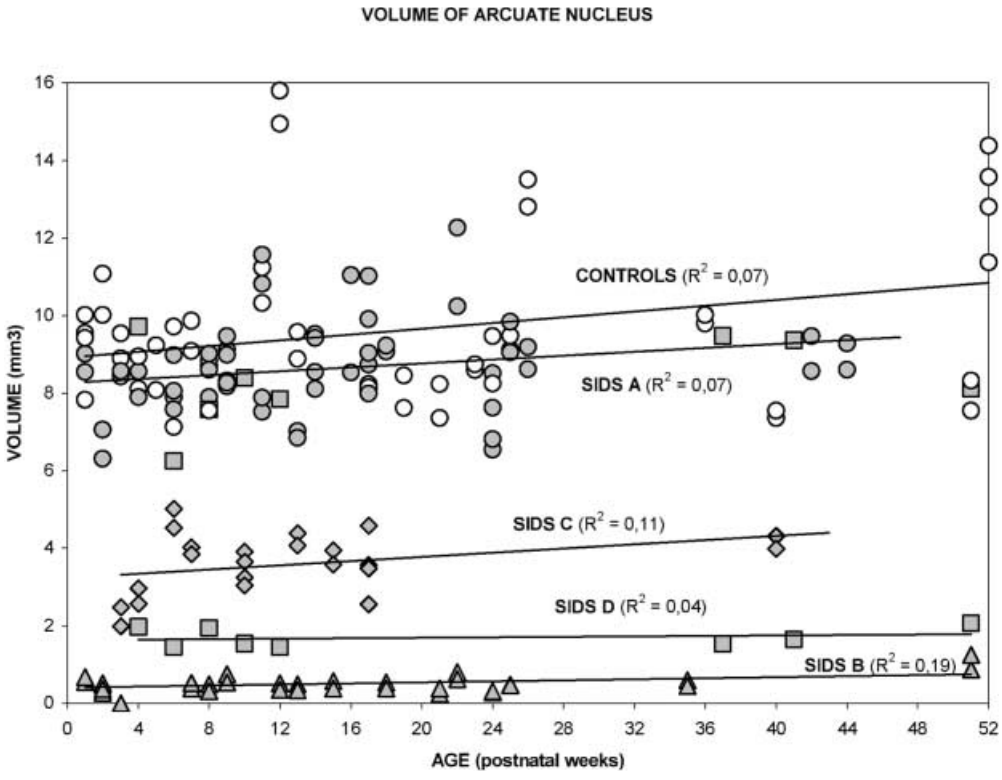

Fig. 6 Scatterplot of raw data and estimated regression lines of mean volume of the ARCn for SIDS cases [SIDS A (*gray circles*), SIDS B (*gray triangles*), SIDS C (*gray* diamonds), SIDS D (*gray squares*)] and control cases (*white circles*) by postconceptional age. Each symbol represents one medullary side of each case

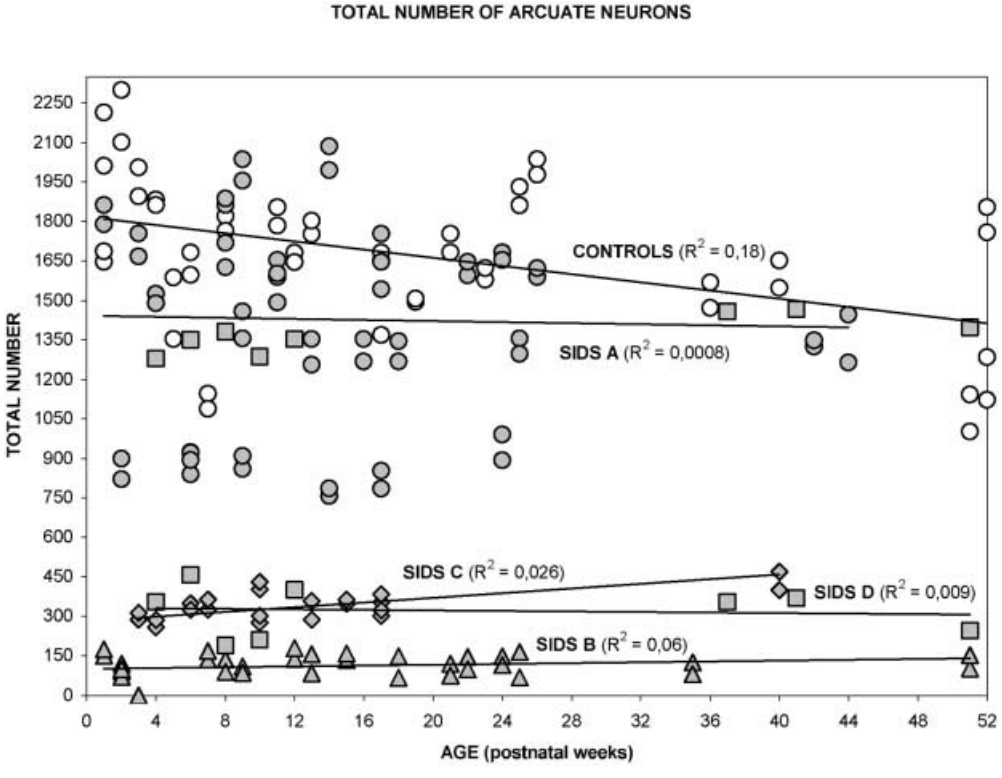

Fig. 7 Scatterplot of raw data and estimated regression lines of mean of the total number of neurons of the ARCn for SIDS and control cases (see legend to Fig. 6)

on the left: 1,562±206 on the left and 295±89 on the right. These results are only significantly different from the controls value for the right side of the ARCn (P=0.0002). Statistical evaluation of postnatal ages of the cases examined in relation to the total number of ARCn neurons showed no significant difference between SIDS cases and controls. However, in some cases (7/27) defined as belonging to the SIDS A group, the total number of neurons was found to be greatly reduced, similar to that found for ARCn in the hypoplasia cases (Fig. 7).

Discussion

SIDS is a complex pathology whose pathogenetic mechanism might, perhaps, be found in the triggering of predominantly vagal reflexes, which are manifested as lethal bradyarrhythmias and/or apnea, possibly accompanied by dyskinetic alterations of the upper digestive tract. These mechanisms may involve the autonomous nervous system, which modulates vital cardiac, respiratory and digestive functions [7, 13, 23, 24, 25]. Studies of the nervous system show mainly aspecific and/or secondary alterations such as variations in brain size, gliosis, myelinization disturbances and neurotransmitter anomalies, and defects in receptor binding [1, 13, 14, 18, 19, 29, 31]. Recently, a structure involved in the central cardio-respiratory hypothesis in SIDS was detected in the ventral surface of medulla oblongata (VMS) [3, 15]. The VMS has been regarded as an integrative site for vital autonomic functions, such as respiration and breathing arousal and reflex regulation of blood pressure, cardiac rate and rhythm [16]. Although the exact role of each neuronal and glial population is controversial, in some SIDS victims, the ARCn, a component of the VMS putatively related to central chemoreception may be selectively vulnerable [5, 22, 26, 28, 30, 33]. The role of the ARCn in human ventilatory control is supported by magnetic resonance imaging in adults exposed to a hypercapnic challenge, in which carbon dioxide responsiveness was localized to the region of the ARCn [8], and by the absence of the ARCn in an infant who died of a congenital central hypoventilation syndrome [6]. We hypothesize that SIDS cases, or at least a subgroup of SIDS cases, may be associated with developmental abnormalities of the VMS, which interfere with cardiorespiratory responses [3, 4, 9, 12, 14, 15, 21, 24, 25]. ARCn hypoplasia is notable both for its frequency and for its variability. In the present study, ARCn bilateral hypoplasia was detected in 43% of cases (27/62 cases), of which 26% (16/62 cases) represented cases with severe bilateral hypoplasia (SIDS B group) and 18% (11/62 cases) with partial hypoplasia (SIDS C group); hypoplasia was not seen in the cranial portion of the ARCn in these latter cases. In addition, 13% (8/62) of the cases had monolateral hypoplasia (right side) (SIDS D). The mean volume of the ARCn in the 27 SIDS A cases was not significantly different from the control value. The mean volumes of the ARCn in SIDS B and SIDS C cases were significantly reduced compared with controls. In the SIDS D group the ARCn volume on the right side was found to be statistically reduced, whereas on the left it was similar to that of controls. All together (total bilateral, partial, and monolateral), 57% of the cases studies displayed ARCn hypoplasia. The higher incidence detected, as compared to the earlier finding of 30% [8] is due not only to the larger number of cases examined but also to the more detailed histopathological and morphometric examination performed on the serial sections over the full length of the ARCn. The analysis of neuronal density showed that ARCn hypoplasia is characterized by a reduction of the neuron population, which, however, is not proportional to the reduction of the length of the ARCn. In fact in seven SIDS A cases, where the ARCn was easily recognizable and morphometrically similar in size to that of controls, neuron density was considerably reduced. In the cases of bilateral hypoplasia from the SIDS B group (ARCn with homogeneous hypoplasia) and SIDS C group (ARCn with hypoplasia in the lateral projection) mean neuron density was significantly different from controls. In the SIDS D group (ARCn with right hypoplasia) the density of neurons was particularly evident where hypoplasia was present, whereas in the left portion of the ARCn it was only slightly lower that that of controls. Our neuron density results do not correspond with those of another study [7] on SIDS victims in which an increase in ARCn neurons was reported. The discrepancy could reflect the variability between cases, which we also observed, or it could depend on the number of cases investigated and above all on the total serial sections observed. We consider that the evaluation of the development of the ARCn should involve the examination both of its area and of the number of the neurons. The reduced number of ARCn neurons in SIDS victims compared with controls, expressed both as density and as total neural number suggests a congenital lesion. This may occur during the development of the ARCn, possibly due to a primitive deficit in cell proliferation, migration and/or differentiation, rather than being due to a secondary pre- and/or postnatal neuron loss [1, 29, 31]. This hypothesis is also supported by a recent study on receptors, which describes the decrease of serotonergic receptor binding located in the ARCn of SIDS victims [19]. The same study shows a simultaneous reduction of serotonergic receptor binding in other medullary structures, such as the nucleus paragigantocellularis lateralis and the nucleus raphé obscurus, which contain serotonergic cell bodies. This neurotransmitter receptor binding deficit has been interpreted as being the result of an anomaly in prenatal development, rather than a degenerative disorders, because these structures have the same embryonic anlage as ARCn (the rhombic lip at the pontomedullary junction of the embryo) [2, 10, 20, 27]. We suggest that the maturational regulation of the ARCn is abnormal in the brain stem in SIDS cases, resulting in a developmental deficiency of neurons and/or neuropil (hypoplasia), with an associated deficiency of neurotransmitter binding [18, 19]. This could render an infant vulnerable to SIDS, due to modulation defects in the reflex respiratory responses to asphyxia or hypercapnia, especially coincidental with the prone or face-covered supine sleeping position. These data suggest that a larger neuronal network, than the ARCn alone, would be involved in the pathogenesis of SIDS. In conclusion, ARCn hypoplasia is noteworthy both for its frequency and for its variability, and is, according to our experience, a most frequent congenital anomaly that could be considered a plausible morphological cause for one subset of SIDS victims. Babies who die of SIDS may be born with such a congenital vulnerability that probably results from abnormalities in fetal growth. The infant's vulnerability lies latent until the critical developmental period, when

even slight alterations in cardioventilatory function and/or arousal may disturb a precarious balance [3, 4].

Infants with ARCn hypoplasia are at risk for SIDS because, without the full maturation of neurons and neuropil in the medulla oblongata, they are unable to make appropriate transitions into cardioventilatory control during this critical developmental period [21]. Further studies of the exact functional role of each distinct neuronal circuitry in the different portions of the ventrolateral medulla will lead to a better understanding of complex interactions involved in the pathophysiology of SIDS.

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