Pathomorphology of Higher Autonomic Centers in Newborns with Congenital Heart Disease

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The incidence of congenital heart defects is high, and these defects are often responsible for lethal outcomes in the early neonatal period [1,2]. Congenital heart disease is often associated with other defects, including those of the nervous system [4,7]. Abnormalities of the autonomic centers responsible for reflex regulation of heart activity play an important role in the pathogenesis of dyscirculatory syndromes and in thanatogenesis in congenital heart disease [3]. The autonomic nervous system status of infants with congenital heart disease is particularly important in the early neonatal period, when a whole set of adaptive reactions is taking place. It is not only secondary lesions which are of importance here, but the level of morphofunctional maturity of the autonomic centers as well. The brainstem and spinal portions of the CNS, and their most significant autonomic centers have not been studied in this respect in infants with congenital heart defects. The present study aimed to follow up autonomic center development in newborns with congenital heart disease.

MATERIALS AND METHODS

Pathomorphological examination of 25 newborns in the first week of life were carried out; the majority (76%) of them were born full-term. Most congenital heart defects detected were classified among groups 2 (28%), 3 (12%), and 4 (44%) of the universally acknowledged system [2]. The hypothalamus, medulla oblongata, and superior thoracic segments of the spinal cord were fixed in formalin after Bouin and embedded in paraffin; the sections were stained by survey methods to be tested for nucleic acids and proteins, and impregnated with silver. Thirteen morphometric parameters were assessed in every portion and the relevant nuclei (supraoptic nucleus, vagus nerve posterior nucleus, lateral horn nuclei). In cases of early autopsies the material was routinely treated for electron microscopy and photographs were taken using a Tesla BS-500 electron microscope. Digital data were processed using Student's t test. Developmental parameters of 25 full-term fetuses without diseases or noticeable injuries in the supraoptic nucleus, vagus posterior nucleus, or lateral horn nuclei were used as references.

RESULTS

The full-term fetuses and newborns were characterized by identical anthropometric data, but the brain mass of newborns with congenital heart disease was reliably lower than in normal fetuses (372.3±9.5 g vs. 417±13.7 g, respectively, $p<0.05$). The groups did not differ from each other in terms of the mean metric characteristics of development of the hypothalamus, medulla oblongata, spinal cord, and their nuclei. There was no differences in neurocyte microenvironment in a radius of 50 μ. In infants with congenital heart disease the num-

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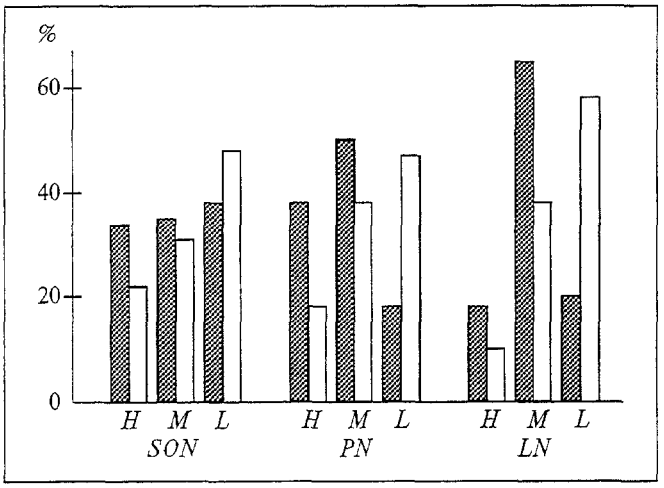

Fig. 1. Normal fetuses (dark bars) and newborns with congenital heart disease (light bars) with high (H), medium (M), and low (L) levels of development of supraoptic nuclei (SON); nerve posterior nucleus (PN), and lateral horn nuclei (LN).

bers of adjacent neuroglial complexes for the supraoptic nuclei, vagus posterior nucleus, and lateral horn nuclei were 3.05±0.31, 1.81±0.2, and 1.97±±0.17, and of free gliocytes 6.13±0.29, 8.09±0.71, and 6.85±0.27, respectively. Supraoptic nuclei are characterized by the highest concentration (37.8±1.1) of evenly distributed neurocytes. This parameter is much lower (17.1±0.63) for the posterior nucleus of the vagus, the neurocytes also being evenly arranged. Neurocyte concentration in the lateral horn nuclei is minimal (14.2±0.43), but the cells more frequently form compact accumulations. In the group with congenital heart disease the share of neurocytes with perisomatic gliocytes in the supraoptic nuclei, vagus posterior nucleus, and lateral horn nuclei is virtually the same as in normal fetuses, varying from 20% in the supraoptic nucleus to 30% in the lateral horn nuclei. Similar cells with large, light nuclei, with medium-sized nuclei of moderate density, and with high-density small nuclei are identified among perisomatic gliocytes in the supraoptic nuclei, vagus posterior nucleus, and lateral horn nuclei. The mean area of a nucleus section of high-, medium-, and low-density perisomatic gliocytes in the supraoptic nuclei, vagus posterior nucleus, and lateral horn nuclei was identical in the two groups, being, respectively, 15.1±0.6, 22.7±0.97, and 29.3±1.44 μ^2, in infants with congenital heart diseases.

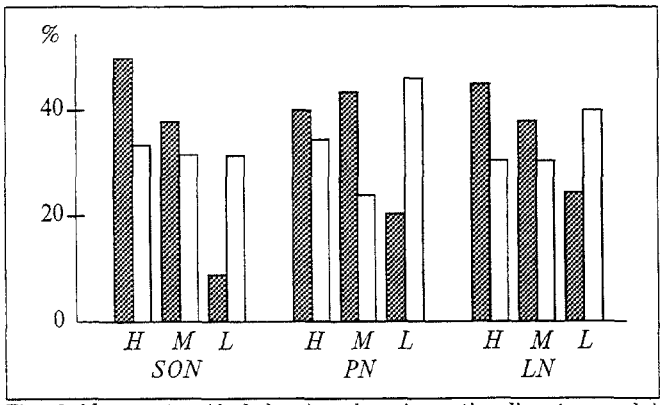

Fig. 2. Neurocytes (dark bars) and perisomatic gliocytes nuclei (light bars) with a low (L), medium (M), and high (H) density of nucleic acid in SON, PN, and LN of infants with congenital heart disease.

The principal criteria in assessment of the development of autonomic nuclei were their size and the metric and cytochemical parameters of the neuroglial complexes. Neurocyte metric characteristics were integral. Supraoptic nuclei, vagus posterior nucleus, and lateral horn nuclei of infants with congenital heart disease were characterized by a markedly lower level of development (Fig. 1), but with mean density parameters of nucleic acids and proteins similar to those of normal fetuses. In the majority of infants with congenital heart disease no matter what the nucleoprotein content in the neurocytes, the content of perisomatic gliocytes with a high density of nuclear nucleoproteins was markedly increased in all the nuclei examined (Fig. 2). Perisomatic gliocytes of normal fetuses, in contrast to neurocytes of supraoptic, vagus posterior, and lateral horn nuclei, were characterized by the same mean ratios of low-, medium, and high-density nuclei in the proportion 2:2:1. In the infants the number of cases with high (30.7%) and low (30.7%) neurosecretion volumes in supraoptic nuclei neurocytes increases proportionally, this frequently correlating with high and low nucleoprotein concentrations, respectively.

Both groups compared were characterized by similar anamnestic data and pregnancy conditions. In 32% other defects were detected besides congenital heart disease. The neonatal age was in proportion to the gestation age, and the number of disorders increased with the increase of life duration, pneumonia and circulatory disorders predominating in full-term newborns.

The type, severity, and extent of dyscirculation, as well as the severity of damage to the autonomic centers in full-term newborns were unrelated to congenital heart disease group appurtenance or the presence of a concomitant disease. Total congestive plethora was detected in just a few cases. In cases with massive hemorrhagic syndrome the intraorgan hemocirculatory systems were anemic. Conflicting general (outside the CNS), systemic (in the CNS), and local (in the hypothalamus, medulla oblongata, and spinal cord) dyscirculation occurs most frequently. Types of dyscirculation may be variously directed in zones of the supraop-

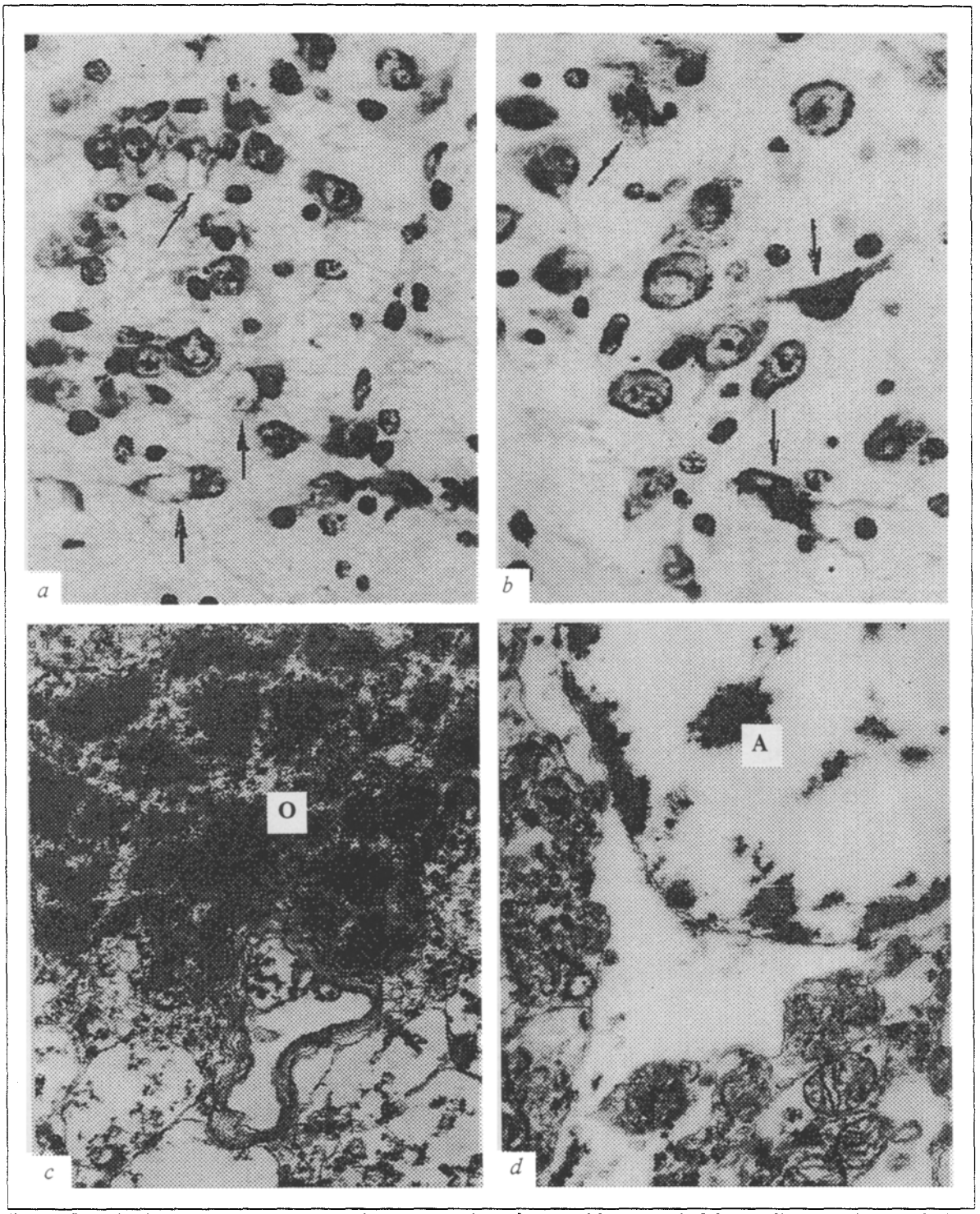

Fig. 3. Pathological changes in autonomic centers of newborns with congenital heart disease. *a*) vacuolation and lysis of SON neurocytes (shown by arrows); *b*) pyknosis and rhexis of LN neurocytes (shown by arrows); *c*) marked condensation and shrinking of nucleus, diminution of perikaryon volume with oligogliocyte (O) organoid reduction in SON; d) marked swelling of nucleus and astrocyte (A) organoid reduction in SON; *a,b*) stained with gallocyanin, ɜ620; *c,d*) Reynolds contrast – stained, ×16,000.

tic, vagus posterior, and lateral horn nuclei with respect to the corresponding brain segments. One of the common variants of dissociated dyscirculation is a combination of membranous plethora with anemia of the tissue microcirculatory bed. Brain tissue edema does not completely conform to dyscirculation type but more frequently and markedly is associated with anemia. The zone of supraoptic nuclei is characterized plethora of various degrees, less frequently by anemic microcirculation, focal

hemorrhages, and insignificant edemas. For zones of the vagus posterior nuclei and, more so, of lateral horn nuclei anemia is characteristic, associated with a marked or moderate edema.

Autonomic nuclei of the hypothalamus and medulla oblongata are frequently damaged, though not severely. A low level of injuries to the supraoptic nuclei, vagus posterior nucleus, and lateral horn nuclei was found in a few cases. Impaired "light" type neurocytes (chromatolysis, swelling, vacuolation, lysis) predominated in the supraoptic nuclei, whereas in the vagus posterior nucleus and in the lateral horn nuclei the "dark" type of neurocyte injuries predominated (pyknosis, atrophy, rhexis) (Fig. 3, *a, b*). In none of the nuclei was the severity of damage definitely connected with the direction of shifts in the total content of nucleic acids and proteins in various observations. Gliocytes were less injured than neurocytes, the damage manifesting itself most frequently in oligogliocyte nuclei pyknosis and marked swelling of astrocytes (Fig. 3, *c, d*). Low neurosecretion content was observed in injuries of various severity, whereas a high content correlated with insignificant damage of the supraoptic nuclei. Dyscirculation variants found in preterm and full-term newborns were similar, but injury to the supraoptic, vagus posterior, and lateral horn nuclei was the more severe, the shorter the gestation period was.

Hence, a complex of etiological and risk factors contributing to the development of congenital heart disease causes a delay in brain development and autonomic center maturation even in a full-term pregnancy. The conformity of the metric characteristics of stem and spinal morphosystems and their nuclei to the gestational "norm" is indicative of the relative independence of their formation of the endbrain. The lower level of autonomic nuclei maturity in congenital heart disease is associated with a more serious disproportion in their maturity levels in each case. The detected morphogenetic disorders appear to persist in the postnatal development of the CNS: the detection of such disorders in other brain segments long after birth is evidence of such a possibility [5]. The variety of circulatory disorders is due to the combination in their pathogenesis of primary (cardiac) and secondary (hypoxia, infectious intoxication, autonomic dysfunctions) mechanisms realized mainly during the postnatal period. Besides the general mechanisms, specificities of local hemodynamics and its low resistance and compensatory potential contribute to the origin of variously directed circulatory disorders. Impairment of the autonomic centers is caused by different mechanisms and is compatible with injury to other CNS sections occurring in congenital heart disease [6]. In contrast to morphogenetic disorders, dyscirculatory processes and autonomic center injury are closely related to each other. Local tissue damage and neurocyte death are not paralleled by substantial cellular (macrophagal, separating) reactions because of a fulminant course of the disease and the immaturity of the reactive mechanisms. At the same time, a longer (several years) life of infants with congenital heart disease is characterized both by more serious injury to the autonomic centers (particularly of the brainstem and spinal cord) and a higher level of compensatory adaptive proces [3].

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