THE EFFECT OF HYPERTHYROIDISM DURING PREGNANCY ON THE STRUCTURAL DEVELOPMENT OF THE FETAL SPINAL CORD

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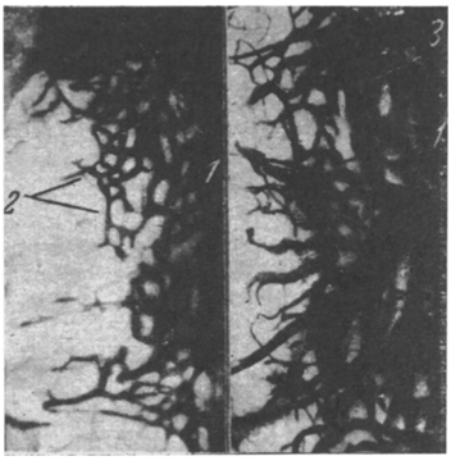
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 53, No. 4,
pp. 111-115, April, 1962
Original article submitted May 22, 1961

Clinical and experimental researches by workers at the laboratory of brain development and psychoneurological clinic of the Institute of Pediatrics of the AMN SSSR have shown that the developing brain is highly sensitive to various harmful agents, including chemical and therapeutic substances administered to pregnant women or animals in order to prevent or terminate pregnancy, fetal asphyxia during the intrauterine period or at birth, prematurity, disturbance of the activity of the thyroid gland or pancreas of the pregnant women or animal, and an increased concentration of pituitary hormones in her blood, parental alcoholism, and so on [1, 2, 5-8, 11].

During a clinical study of children and their mothers, M. F. Yankova [11] discovered that hyperthyroidism in the pregnant woman leads to the birth of children with disturbances of the nervous and endocrine systems. In some children congenital cardiac defects and retardation of physical development are also observed. M. F. Yankova confirmed these findings experimentally in pregnant rabbits in which hyperthryroidism was induced during pregnancy. The fetuses obtained from the experimental rabbits showed severe disturbances of cardiac activity and of the external respiratory functions, which were more superficial and irregular than in the control fetuses, with frequent pauses. The brain was underdeveloped in all the fetuses: changes in its size, gross disturbances of differentiation of its individual parts, and sometimes hydrocephalus were observed.



A B

Fig. 1. Venous plexus on the dorsal surface of the cervical division of the spinal cord of control (A) and experimental (B) rabbit fetuses. Accelerated differentiation of the venous plexus and dilation of the veins forming loops in the experimental fetus. 1) Dorsal venous tract; 2) venous loops; 3) veins of the subarachnoid space, situated above the venous plexus. The vessels of the spinal cord were injected with ink. Magnification 45×.

The problem of the effect of abnormal thyroid activity of the pregnant woman on the developing spinal cord has not yet been investigation. Nevertheless, we know that in children suffering from myxedema or in cretinism changes are found in the cardiac and respiratory activity, the muscle power is diminished and muscle tone lowered.

The respiratory disturbances in these children suggest that changes may have taken place in the spinal portion of the respiratory center. Great interest is therefore attached to the experimental study of the spinal cord in the offspring of hyperthyroid animals, especially because the structures of the spinal cord develop earlier than those of the brain.

In this paper we describe the results of a study of the effect of hyperfunction of the thyroid gland of the pregnant animal on the developing fetal spinal cord. The experimental material was taken from the experiments of M. F. Yankova [11].

EXPERIMENTAL METHOD

Hyperthyroidism was produced in pregnant rabbits by administration of thyroidin with the diet for 10 days before the onset of pregnancy and throughout its course, in a dose of 300 mg/kg body weight. The experimental and control animals were decapitated on the 30th day of pregnancy. The fetuses were extracted from the uterus, weighed, and their length measured. The spinal cord was fixed in 10% formalin. Before being extracted from the uterus, some fetuses received an injection of a 1.5% solution of gelatin in ink through the umbilical vein. The spinal cord of these fetuses was also immersed in 10% formalin. After fixation, an external inspection of the spinal cord was made, after which the vascular system on the surface of the cervical division of the cord was examined and its histological structure studied.

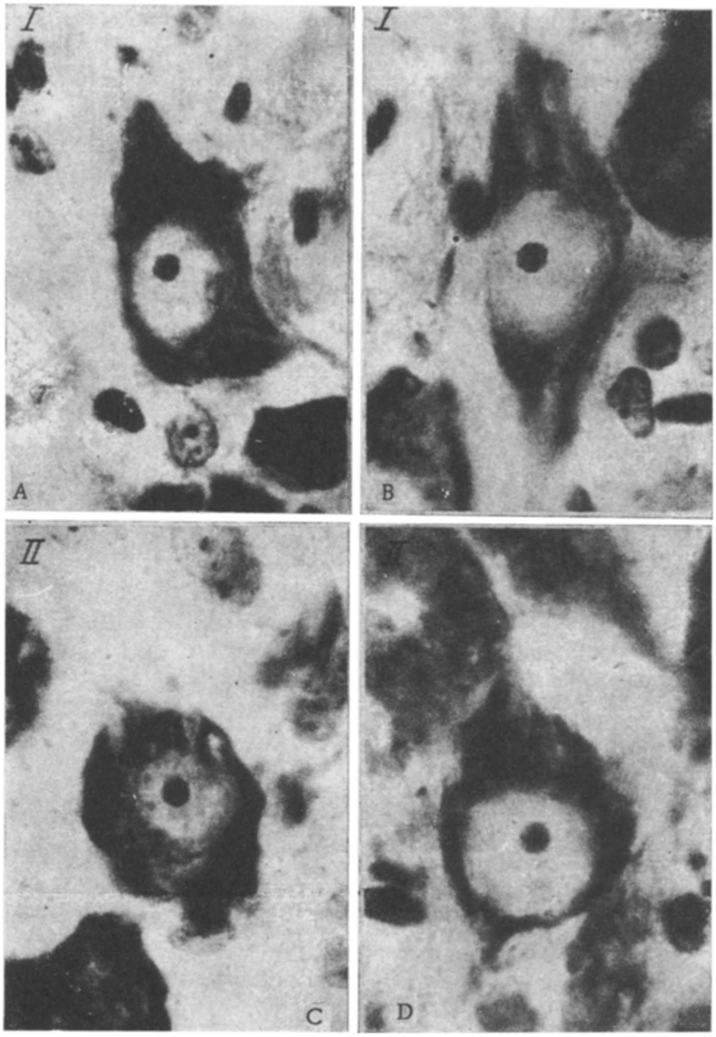


Fig. 2. Nerve cells of the phrenic nerve nucleus and the anterolateral group of the cervical division of the spinal cord. Swelling of the nerve cells in the experimental fetus. I) Phrenic nerve nucleus of the control (A) and experimental (B) fetuses; II) anterolateral group of the cervical division of the control (C) and experimental (D) fetuses. Nerve cells stained by Nissl's method. Magnification 900×.

We undertook morphological investigations of the spinal cord of 58, and histological examinations of the cord of 20 experimental and control fetuses.

EXPERIMENTAL RESULTS

The dura matter in the experimental fetuses was tightly stretched and the spinal cord appeared edematous. No changes could be seen in the external structure of the cord. As a rule the spinal cord was longer and wider, but this corresponded to the larger size of the trunk of the experimental fetuses.

Examination of the blood vascular system on the surface of the cervical division of the spinal cord of the experimental fetuses showed no changes affecting the arterial plexus, but the venous plexus was considerably modified. In contrast to the control fetuses, the venous plexus consisted of large loops and was formed by vessels of a larger diameter. The changes in the venous plexus were most obvious on the dorsal surface of the cervical division. This part of the vascular plexus was characterized by a larger number of venous trunks than in the control fetuses, partially separated from the plexuses and forming direct channels for the drainage of blood. In contrast to the control fetuses, the venous plexus in some areas consisted of two layers, i.e., the vessels forming this plexus were arranged in two tiers on the surface of the cord. Among these could be distinguished the more numerous veins lying closer to the surface of the cord, and the separate venous trunks lying over them. All these vessels were interconnected, for they were formed by the same venous loops (Fig. 1).

These features of the venous plexus on the dorsal surface of the cervical division which we have described, namely the separation of a larger number of direct drainage channels than in the control fetuses and the two-tier structure of the venous plexus, demonstrate that this plexus is more highly differentiated in the experimental rabbit fetuses [4, 9].

The spinal cord was investigated histologically by means of horizontal sections stained by Nissl's method. Groups of nerve cells innervating the muscles of respiration were studied, i.e., the cells of the phrenic nerve nucleus, situated in the 5th and 6th segments of the cervical division, and sending their axons to the diaphragm, and also the nerve cells of the anterolateral group of the thoracic division, the axons of which pass to the intercostal muscles. The motor cells of the anterolateral group of the cervical division, innervating the skeletal muscles of the shoulder girdle, were also investigated. The dimensions of the nerve cells and of their nuclei were obtained by calculating the relative area of section (the product of the long and short axes of the cell or nucleus). Large cells were studied, in which the nucleus and nucleolus were visible, and 150 cells were measured in both the phrenic nerve nucleus and the anterolateral groups of the cervical and thoracic divisions, and the mean cross-sectional area of the cell body and nucleus was deduced.

The nerve cells in the phrenic nerve nucleus of the control 30-day old fetuses were arranged in small groups along the axis of the spinal cord. In each of these groups the cells lay close together. They were elongated, polygonal, and as a rule oriented longitudinally together with their processes. Their cross-sectional area averaged 485 μ^2. The chromatin of these cells was intensively stained in the form of granules. Their nucleus was oval in shape, and the average cross-sectional area of the nucleus was 120 μ^2. The plasmonuclear ratio was 4:1. In the experimental fetuses of the same age the nerve cells of this nucleus were barrel-shaped. The chromatin granules in these cells were arranged in a narrow band around the periphery of the cell body. The cross-sectional area of the nerve cells averaged 700 μ^2 and that of the nucleus 210 μ^2. The plasmonuclear ratio was 3.3 (Figs. 2).

In the anterolateral group of the thoracic division, supplying the intercostal muscles, the nerve cells in the control fetus were distributed uniformly throughout the nucleus. They also were elongated and polygonal in shape, and oriented together with their processes in the long axis of the spinal cord. The average cross-sectional area of these cells was 385 μ^2. The chromatin in the cytoplasm was granular and intensively stained. In most cases the nucleus was oval. The average cross sectional area of the nucleus was 110 μ^2. The plasmonuclear ratio was 3.5:1. The nerve cells in the experimental fetuses were barrel-shaped. The chromatin was arranged in granules around the periphery of the cell body. The average cross sectional area of the cells was 510 μ^2 and of the nucleus 180 μ^2. The plasmonuclear ratio was lowered to 2.8:1.

In the anterolateral group of the cervical division, giving off axons to the skeletal muscles of the shoulder girdle, the nerve cells in the control fetus had no definite orientation as in the nuclei innervating the muscles of respiration. These cells were polygonal in shape and their average cross sectional area was 743 μ^2. The chromatin in their cytoplasm was granular and brightly stained. Their nucleus was round in shape, its average cross sectional area was 212 μ^2, and the plasmonuclear ratio was 3.5. In the experimental fetuses, the nerve cells of this groups showed changes similar to those described above. The cross sectional area of the cells had increased to an average value of 946 μ^2 and the longitudinal sectional area of the nucleus was 336 μ^2. The plasmonuclear ratio was lowered to 2.7 (see Fig. 2).

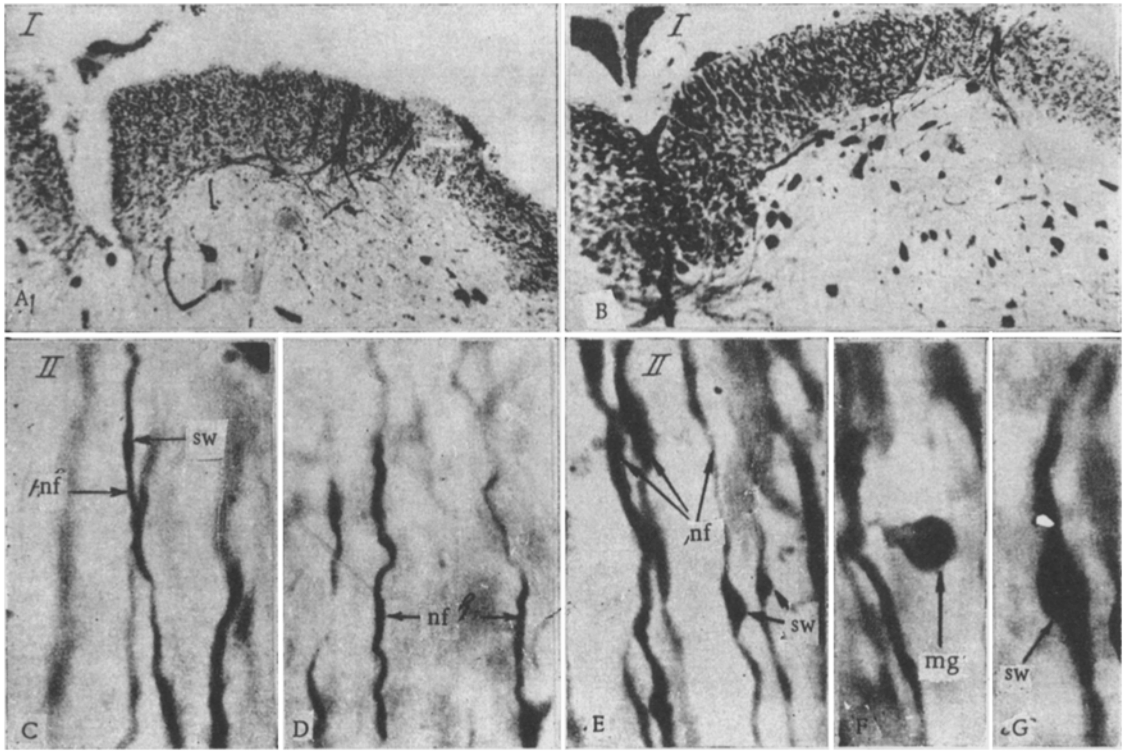


Fig. 3. Myelination of nerve fibers in the cervical division of the spinal cord of control and experimental fetuses. Accelerated myelination of the nerve fibers and pathological changes in the myelin sheath in the experimental fetus. I) Anterior columns, transverse section through the spinal cord of the control (A) and experimental (B) fetuses; II) anterior and posterior columns, longitudinal section through the spinal cord of control (C, D) and experimental (E, F, G) fetuses. nf) Nerve fiber; sw) swelling on nerve fiber; mg) myelin granules. Nerve fibers stained by Kultschitzky-Walters method. Magnification: A, B) 40×; C, D, E, F, G) 1800×.

These distinctive features of the nerve cells in the nuclei of the spinal cord of the experimental fetus, namely the change in the shape of the cells, the enlargement of the longitudinal sectional area of the cell body and nucleus, and the decrease in the plasmonuclear ratio indicate that these cells are swollen.

The study of preparations of the cervical division of the spinal cord stained by the Kultschitzky-Walters method showed that in the rabbit fetus at the 30th day of development, the anterior columns contained on the average 10, and the posterior columns 4 medullated fibers in a cross sectional area of 150 μ^2. In longitudinal sections of the spinal cord these fibers were seen to be sharply outlined, and they appeared uniformly stained a greyish-blue color. Their diameter varied from 0.5 to 1 μ. Isolated fusiform swellings, measuring 5× 2 μ and also uniformly stained a greyish-blue color, could be seen on certain fibers (Fig. 3).

In the anterior columns of the experimental fetuses there were on the average 18 medullated fibers in the same cross sectional area, and 8 in the posterior columns. Hence it may be concluded that the myelinating activity was greater in the spinal cord of the experimental fetuses than in that of the controls.

A more detailed investigation, however, shows that in addition to the outwardly unchanged fibers, differing from the controls in their more intensive staining and their larger diameter (1.5-2 μ), the anterior and posterior columns contained many fibers with a modified myelin sheath. Some of these fibers were of different diameters. In this case it could be seen that narrow, uniformly stained areas alternated with small dilations, filled with myelin granules. These granules were separated or gathered into masses, between which vacuoles could be seen. Sometimes these granules were arranged singly or in the form of a chain along the outer surface of the fiber. In some cases they were connected with the fiber by means of a thin, palely stained pedicle, while others were lying freely. These granules were stained a pale grey color, and some had a dark rim at the periphery. The fusiform swellings seen in normal conditions were slightly larger and more numerous in the experimental fetus. Sometimes the swellings were spherical or polygonal in shape and attained a giant size – 20 μ long and 7 μ wide. Some were stained a uniform pale grey color, while in others the myelin was arranged in granules (see Fig. 3).

Externally similar changes in the medullated fibers of the central nervous system have been reported in the literature. Gross lesions of the myelin sheath are described in Tay-Sachs' disease [12] and in association with various pathological changes in the nerve fibers [10]. These distinctive features of the nerve fibers which we have noted (inequality of diameter, distribution of myelin in the form of granules in the myelin sheath or externally, along the fiber, swellings of giant size) are evidence of pathological changes undergone by the developing nerve fibers in the spinal cord of the experimental fetuses.

We may thus conclude from the foregoing facts that in the experimental rabbit fetuses considerable changes took place in the blood vessels, the nerve cells innervating the respiratory and skeletal muscles, and the conducting pathways of the anterior and posterior columns of the spinal cord. On the one hand, as a result of the noxious action of hyperthyroidism of the pregnant animal on the developing fetus swelling of the structures of the spinal cord took place. This is shown by the dilatation of the veins and swelling of the nerve cells. It may be supposed that the phenomena described are associated with interference with the drainage of venous blood from the spinal cord and with the consequent disturbance of the circulation of the blood in the spinal cord. This hypothesis is supported by the fact that in the rabbit fetuses in this series of experiments gross histological changes were demonstrated in the myocardium, incompatible with the normal activity of the fetal heart [3]. On the other hand, the accelerating action of hyperthyroidism of the pregnant animal on the structural development of the fetal spinal cord cannot be ruled out. In the vascular system, for instance, differentiation of the venous plexus is accelerated, especially on the dorsal surface; a larger number of medullated fibers is observed in the conducting pathways, and they are more intensively stained and larger in diameter.

Further research is required, however, in order to ascertain which processes ultimately determine the changes we have observed in the spinal cord of the experimental rabbit fetuses.

SUMMARY

A study was made of the effect of thyroidin in the pregnant rabbit on the developing spinal cord of the fetus. The blood system was studied on the surface of the cervical portion of the spinal cord. Groups of cells of the cervical and thoracic portions, innervating the respiratory and skeletal muscles, and myelin fibers of the anterior and posterior stems of the cervical portion were investigated as well.

The following features were detected: accelerated differentiation of the venous network and dilatation of the vessels forming the vascular network; enlargement of the profile field of the cells and their nuclei and reduction of

the plasmonuclear ratio; an increase of the number of myelin fibers both in the anterior and in the posterior stems; increased intensity of staining of the myelin fibers; pathological changes in the myelin sheath, similar to those, for instance, in Tei-Sax disease.

LITERATURE CITED

1. Yu. I. Barashnev, In: Brain Development and the Effect of Harmful Factors [in Russian], Moscow (1960), p. 161.
2. A. P. Belkina, The Effect of Harmful Factors Acting During Pregnancy on the Development of the Brain of the Fetus and Child. Candidate Dissertation [in Russian], Moscow (1958).
3. V. A. Ermakova, In: Brain Development and the Effect of Harmful Factors [in Russian], Moscow (1960), p. 193.
4. E. V. Kapustina, Pediatriya (1952), No. 5, p. 30.
5. Z. N. Kiseleva, Byull. Éksper. Biol. (1955), No. 12, p. 32.
6. B. N. Klosovskii, Vestn. AMN SSSR (1956), No. 5, p. 47.
7. E. N. Kosmarskaya, Arkh. Pat. (1957), No. 4, p. 32.
8. B. V. Lebedev, Intracranial Birth Trauma and the Development of the Child's Brain. Candidate dissertation [in Russian], Moscow (1958).
9. N. G. Palenova, In: Brain Development and the Effect of Harmful Factors [in Russian], Moscow (1960), p. 49.
10. P. E. Snesarev, The Theoretical Basis of the Pathological Anatomy of Mental Diseases [in Russian], Moscow (1950).
11. M. F. Yankova, In: Brain Development and the Effect of Harmful Factors [in Russian], Moscow (1960), p. 152.
12. E. Wenderowic, G. Sokolansky, and B. Klossowsky, Mschr. Psychiat. Neurol. (1931), Bd. 78, S. 305.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.