Mumps Embryopathy

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After the correlation between maternal rubella and the developmental disorders of the foetus had been recognized [15, 28, 29], the search started for other viral diseases causing foetal damage [16, 24, 31, 32]. In the first step retrospective statistical methods were employed, evaluating subsequently the result of pregnancy.

The collection of data by the prospective method has yielded more reliable results [1, 2, 7, 18, 23, 25, 27]. The preconditions to its success are the compulsory reporting and control by specialists of viral diseases, then a careful follow-up of the course of pregnancy. In connection with the latter attention should be devoted to the number of abortions and stillbirths [14, 30], to the incidence of premature births, and according to some observers, also to the number of infants with low birth weight [18]. The newborns must be examined after birth and subsequently observed for at least two years by paediatricians experienced in the recognition of developmental disorders. It is emphasized [1, 23, 35] that further control examinations should be made at the age from 6 to 8 years, so as to detect disorders of the nervous system and of the sensory organs. A control group, too, should be set up, to facilitate proper evaluation of the results.

Concerning the embryopathic effects of mumps Warkany [37] and later Holowach et al. [19] could present only case histories in their survey of the literature. Analysing the history of large numbers of children suffering from congenital valvular heart disease and of backward ones, Dogramach and Green [5] then Key et al. [21] found only one case where parotitis had occurred in the mother during pregnancy. Ylinen and Järvinen [39] evaluated the up to then reported cases of mumps embryopathy by the retrospective statistical method. Later, Dumont [6] analysed 49 cases where mumps had occurred in the first trimester of pregnancy and found developmental disorders in 30 per cent and abortion in 15 per cent. Froewis [13] estimated the incidence of mumps embryopathy to be between 16 and 22 per cent. In a more critical analysis of the reported material, which by then had increased to 130 cases, Caughey took into consider-

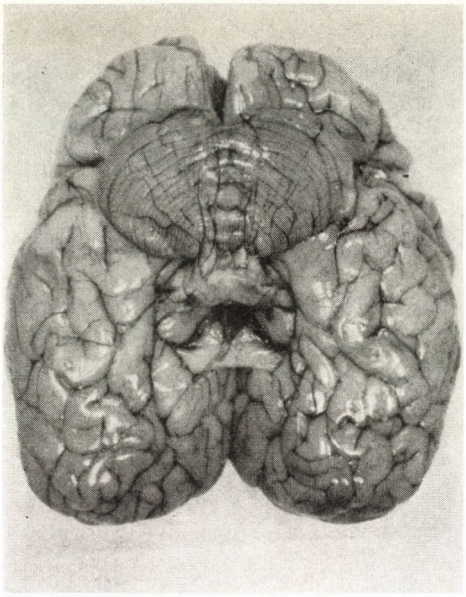

FIG. 1. After bending back the cerebellum, the defect of the corpora quadrigemina and the third ventricle is clearly visible

ation maternal parotitis in the first four months only and found developmental disorders "worth mentioning" in 6 per cent [3].

The prospective statistics made even more doubtful whether mumps produced developmental disorders [12]. According to the investigations of SIEGEL and GREENBERG in 1957 in New York, viral disease had been suffered by 89 out of 168.000 pregnant women with 24 cases of parotitis among them. Congenital developmental defects occurred in just one case, after rubella. On the other hand, the foetal mortality rate was as high as 7 per cent, as compared to the 1 per cent value for the control group of similar size [27]. In Great Britain MANSON [23] found that no matter in which stage of pregnancy it had occurred, parotitis had no effect on the incidence of malformations and did not increase the incidence of abortions and still-births, either.

In the light of these contradictory, or apparently contradictory, data even single cases seem to be of significance in the assessment of mumps embryopathy, if the correlation between the noxa and its sequelae can be proved to be real.

REPORT OF A CASE

K. T., a male infant, had been born January 16, 1961. Nervous disease, developmental malformations had not occurred in the family, two siblings of the patient are normal. The mother according to her physician had had during the 6th and 7th week of pregnancy severe epidemic parotitis, with fever, swelling of the parotids on either side, pain, difficulties on mastication and general malaise. Subsequently the pregnancy had been uneventful, delivery normal, the child weighed 3400 g at birth, cried immediately. Neonatal jaundice had been physiological.

The patient was admitted to our Department at the age of two weeks with the complaint of poor development and respiratory difficulties.

On admission, the infant, weighing 3400 g, was covered by lanugo. There was thrush in the mouth. The heart was enlarged by a finger breadth to the right and to the left to the anterior axillary line. Praecordially a loud systolic murmur, conducted mainly toward the great blood vessels, could be heard. The liver was dense and somewhat enlarged, the spleen was palpable. Other physical findings were normal as also those of the otological and ophthalmological examinations.

Laboratory tests yielded the following results. The urine was normal; RBC, 3.9

million; WBC, 5800; differential count, normal; blood group, 0, — Rh negative; ESR, 5 mm in 1 hour, Serum protein, 4.5 g per cent.

Chest X-ray showed the heart enlarged by 1 finger's breadth to the right, to the left to reach the chest wall; in the left oblique view the arc of the left ventricle was large, with marked bulging of the right atrial arc. In the right lung increased density medially. ECG revealed sinus rhythm, rate 144/min; P_1 and P_2 positive, biphasic, high and wide; P_3, isoelectric. PQ distance 0.11", +130° deviation to the right of main axis; QRS, 0.06", nodular; $ST_{1,2,3}$ isoelectric; $T_{1,2,3}$ isoelectric; right and left atrial disturbance of conduction (P cardiale); intraventricular disturbance of conduction.

The mumps complement fixation test made on the 55th day of life showed a positive titre of 1 : 4 in the blood of the baby and a titre of 1 : 32 in the blood of the mother.

Circulation deteriorated in spite of cardiac treatment, the liver increased in size, cyanosis and oedemas developed, the lungs were congested and the baby died with bronchopneumonia on March 14, 1961 at the age of 2 months.

At autopsy (Dr. Szemenyei) the body weighed 3550 g and measured 57 cm in length. The shoulders and back were covered by fluffy hairs 2 to 3 mm long. In the abdominal cavity 50 ml, in the pericardial sac 30 ml of straw-yellow fluid was found. The size of the heart was 7 × 7 × 4 cm, the wall of the left ventricle was 4 mm thick, that of the right one 6 mm thick, the cavities were dilated. The atrial septum was merely a low crest. The circumference of the aorta was 2 cm at its origin. Botallo's duct was similar to a goose feather's stalk in diameter, anteriorly to its orifice the lumen of the aorta was narrowed down so that a probe could not be passed through it, then its circumference increased again to 2 cm. The orifice of the aorta had two valves.

The lungs were dense, glandular in

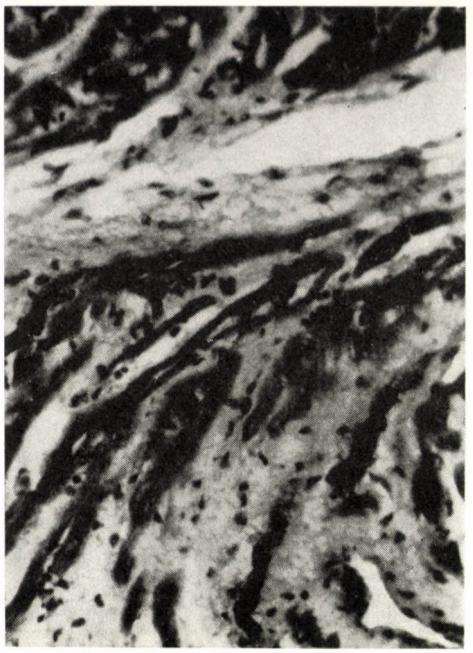

FIG. 2. Connective tissue with round cell infiltration in myocardium of the left ventricle

structure. The lobes of the thyroid were pea-sized, the structure was blurred. In the liver golden-yellow areas of pinpoint size were visible.

The brain weighed 450 g. Between the meninges an ample volume of water-clear fluid was found. Over the pons the cover of the third ventricle and the corpus quadrigeminum were absent, so that a dehiscence of about 2 cm in diameter was created *(Fig. 1)*.

Histological examination. The heart muscle fibres, especially in the subendocardial area of the left ventricle, were vacuolized, the vacuoles did not stain with Sudan. In the left ventricle at several sites diffuse scarring of the muscle fibres and round cell infiltration were visible *(Fig. 2)*.

In the lungs the alveolar walls were thickened, the interlobular septa were wide, but no inflammatory infiltration was

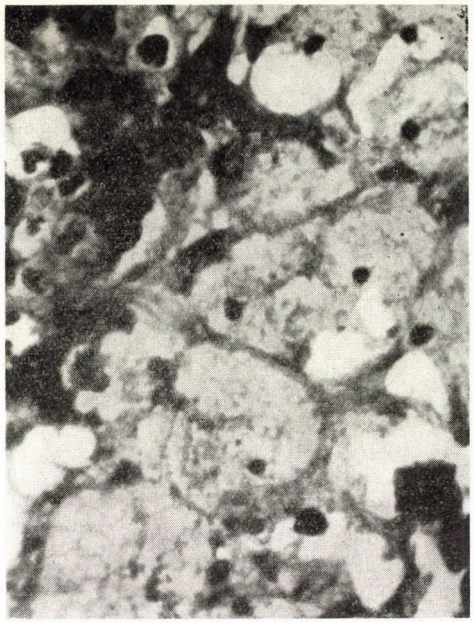

FIG. 3. Group of liver cells storing glycogen

detectable. The wall of both the small and medium-sized blood vessels was thickened.

In the liver groups of cells with broad, foamy cytoplasm and small, dark-staining nucleus occurred in haphazard distribution. Best's carmine demonstrated glycogen in their cytoplasm *(Fig. 3)*.

The pancreas contained wide fascicles of connective tissue, with round cell infiltration in them. Interacinarly diffuse lymphocytic infiltration was visible. The Langerhans' isles showed no changes *(Fig. 4)*.

In the salivary gland conspicuously large quantities of interlobular connective tissue, with sparse lymphocytic infiltration, were found. Lymphocytes occurred also interacinarly

The thyroid gland was of the embryonic type. In some areas thick bundles of connective tissue were found. The pituitary was markedly hyperaemic, the chromophobic cells dominated the pattern; eosinophile and basophile cells were scarcely seen.

No other pathological changes have been detected.

DISCUSSION

The mother had doubtlessly suffered from epidemic parotitis during the 6th week of pregnancy. The disease was observed by a physician and its severity was such that the woman had to be confined to bed. Similar disease had occurred in several persons in her environment. The mumps complement fixation test was positive up to a titre of 1 : 32, which proves that the mother had in fact suffered from the disease at some previous date.

There was no evidence whatever of the occurrence during pregnancy of any other embryopathic or foetopathic condition.

Embryopathy means a noxa occurring during the first trimester of pregnancy, at the time the organ systems are developing. TÖNDURY goes even further [33] and restricts the period of embryopathy to that between the second and the sixth weeks. The correlation between noxa and developmental disorder is significantly supported by the coincidence in time of the noxa and the period of evolution of the affected organs. In our case the following data from the development schedule of PLIESS [26] are relevant.

Onset of development of aorta, 6th week;

development (complete) of septum primum, 7th week;

onset of development of midbrain

with hypothalamus, 6th—7th week; closure of neural tube, 6th week.

Thus in our case the onset and course of mumps coincided with the arisal of changes of undoubtedly intrauterine origin, i. e. the malformations of the heart and large blood vessels and the dysraphic phenomenon observed in the brain.

The results of the serological tests also merit further consideration. According to the investigations of FLORMAN, SCHICK and SCALETTAR [10], as well as by VIVELL [36], the complement fixing and virus haemagglutination inhibiting antibodies pass through the placenta with a small loss of titre, and thus their maternal blood and umbilical blood levels are closely similar. FLORMAN and KARELITZ [11] have found in 31 out of 34 newborns titres of 1 : 4 to 1 : 32 with the mumps complement fixation test. However, after the 44th day of life the titre was but in one case always lower than 1 : 4. From this it was concluded that the newborn's antibodies disappear in about 45 days, when the antibodies inhibiting virus haemagglutination also disappear. Thus the 1 : 4 titre of the mumps complement fixation test on the 55th day of life, as found in our case, cannot be considered usual and suggests that both mother and child had had epidemic parotitis.

Prior to evaluating the pathological findings, certain important data from the literature will be reviewed.

HAMBURGER and HABEL [17] have studied the effect of mumps virus in chick embryos. During the first 5 days infection was lethal. Later, the incidence of developmental defects increased, but the changes were not characteristic. WILLIAMSON, BLATTNER and SIMONSON [38] inoculated 48-hour chick embryos with mumps virus and found in the crystal lens necroses and vacuolization, depending on the concentration of virus. KITCHELL et al. [22] produced malformations, cerebral asymmetry, among others, in pig embryos, by infecting them with hog cholera virus. Of particular interest is the observation made by KAPPERS [20], who found multiple developmental anomalies in the brain of a 6-week human embryo, following rubella during the 5th week. The changes occurred first of all in the wall separating the hemispheres and con-

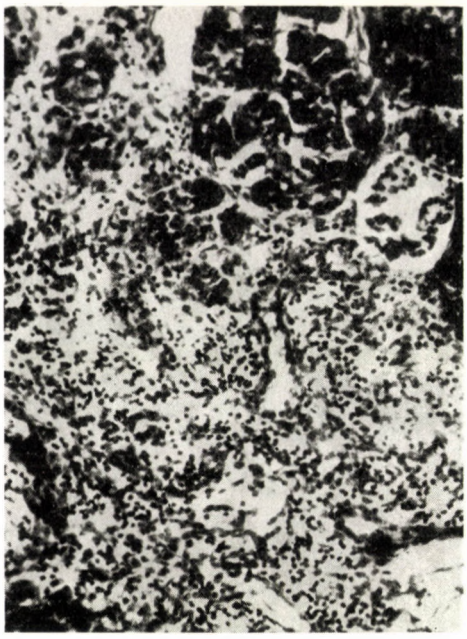

FIG. 4. Connective tissue with round cell infiltration in the pancreas

sisted mainly of necroses and lysis. On its dorsal aspect the diencephalon was split and there was rachischisis in the rhombencephalic area.

TÖNDURY [32] found changes in the crystal lens in a 60-day old human foetus whose mother had parotitis in the early phase of pregnancy. In another embryo, 94 days old, ocular changes, as well as diffuse haemorrhages, pyknosis and the appearance of giant cells in endothelial tissues were demonstrable 40 days after the onset of maternal mumps; this case has been considered to be an example of the haematogenic dissemination of transplacental viral injury [34]. The same author [33, 34] found haemorrhages and disintegration without inflammatory reaction in the foetal nervous system after poliomyelitis early in the pregnancy. FLAMM [8, 9] has emphasized that viral conditions leave behind defects in the tissues, because the changes taking place are reaction-free.

In our case the cardiac malformation and the dysraphic process of the brain were obviously developmental disorders; the wide pulmonary septa were indicative of a developmental deficiency. The changes of the pulmonary blood vessels have been interpreted as being secondary to the cardiac defect. The marked connective tissue septa and the diffuse round cell infiltration in the pancreas and salivary glands may have resulted from intrauterine inflammation and eventually of a developmental disorder. (No inclusion bodies could be detected by careful examination.) The scars containing round cells in the heart muscle must have also been due to intrauterine damage.

Considering the age and the atrophic condition of the infant, it is difficult to assess the character of the pituitary and adrenal histological pattern similar to that seen during the final months of intrauterine life [4]. The diffuse increase of connective tissue in the thyroid was another sign of embryonic inferiority.

The focal storage of glycogen in the liver cells was difficult to interpret. Such a picture, with a diffuse character, is seen in glycogen thesaurosis. However, in other organs there was no evidence of glycogen storage. No sign of an eventual latent maternal diabetes could be detected either. The foci showed no characteristic distribution or arrangement, and no inflammatory or connective tissue elements occurred among the cells storing glycogen. No such change occurs in association with infantile atrophy. For this reason the hepatic change, as well as the inflammation and scar formation in the pancreas, salivary glands and heart should be interpreted as indicative of an intrauterine viral infection of the foetus.

SUMMARY

After reviewing the pertaining literature, a case of mumps embryopathy has been described. The mother had epidemic parotitis during the 6th week of pregnancy. The infant born with a cerebral and cardiac malformation died at the age of 2 months. In addi-

tion to the defects such changes occurred in the pancreas, salivary glands, heart and liver as may be brought into correlation with an intrauterine viral infection. This contention has been supported by both the teratologic calendar and the serological evidence.

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