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THE LAURENCE - MOON - BIEDL SYNDROME A PATHOLOGICAL REPORT

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REFERENCES to the Laurence-Moon-Biedl syndrome have appeared in the literature of recent years with increasing frequency.

In 1931 I published a case showing the typical characters in a girl of five years of age. She was big, obese, dull mentally, had symmetrical polydactyly and syndactyly of the feet, and retinitis pigmentosa with a squint and nystagmus. There was a family history of polydactyly and syndactyly, and a brother, who died soon after birth, probably exhibited the same syndrome.

The child made satisfactory progress for two years, growing brighter and less torpid, and becoming much more interested in things. She grew about four inches, and her weight remained stationary while under treatment with whole gland pituitary tablets. Unfortunately she fell a victim to an epidemic of measles, developed intestinal and pulmonary symptoms, and died on the fourteenth day of her illness with a sudden rise of temperature to 106° F.

An autopsy was performed within twenty-four hours of death. The skull was symmetrical, broad at the parietal eminences and very thin, the thickness of the bone being from 1 to 2 mm. The greatest transverse diameter was 13.3 cm., and the anteroposterior diameter 18 cm. There were no bosses or indentations, and the base of the skull appeared normal. The brain had been fixed in situ by formalin introduced by cisternal puncture soon after death; it weighed on removal 1,300 gm.

Of the other organs, the lungs were very congested; the heart appeared normal; the liver was congested and showed early nutmeg change; the spleen was congested but normal in appearance. The uterus, ovaries and tubes were unusually small, even for a child of seven; their microscopical structure was normal, but primordial follicles were very few. Both kidneys were markedly abnormal, with irregular deep lobulation and some capsular adhesions. They were congested. Sections showed a foetal appearance, with thick bands of fibrous tissue forming the lobulations. The thyroid was normal in size and appearance; it had well-formed vesicles full of colloid. The thymus was normal in size, but microscopically it consisted of small islets of thymic tissue separated by thick, fibrous bands, with

much fat; Hassall's corpuscles were small and very few in number. The adrenals were normal in appearance; they gave no fuchsinophil reaction with the Ponceau-fuchsin stain. The pituitary body was very small; serial sections were made through it in the sagittal plane. The posterior lobe was small but normal in appearance; the anterior lobe showed great vascularity; the sinuses were unusually obvious and dilated, and seemed more numerous than normal. In every section there appeared to be a high proportion of basophil cells throughout the lobe, but there was no adenoma formation. There was a relative paucity of eosinophil cells. No colloid was seen. There was no extension of pars tuberalis up the stalk.

External examination of the brain showed marked and universal congestion of the membranes and vessels. Small thrombi appeared in some of the smaller vessels. At the base of the brain was evidence of some hæmorrhage, and on the vertex were two small subarachnoid hæmorrhages, each about the size of a penny. The convolitional pattern was normal, but the frontal poles were shrunken. Vertical section of the brain gave a normal picture, with no evidence of internal hydrocephalus.

For microscopical examination, serial sections were made of the base of the brain from the anterior part of the chiasma to the midbrain. Sections were stained by hæmatoxylin and eosin, and intermediate sections by Nissl, Loyez, Mallory's phosphotungstic acid hæmatoxylin, and by the Gross-Bielschowsky methods. Comparable series were made of several other brains.

Sections of the hypothalamic region showed the central grey matter with an abundance of small nerve cells, which stained rather faintly. Towards the pituitary stalk these cells were more numerous and closely packed, without showing any other characteristics.

The paraventricular nuclei, lying roughly parallel to the walls of the third ventricle, were well marked with their rather large, closely packed cells. The nuclei were not sharply defined, the cells tending to scatter at the periphery. In this plane the cells appeared mostly multipolar, with a few bipolar cells, having eccentric nuclei which is normal, and rather faintly staining cytoplasm, except that in two or three cells in each section it was very deeply stained.

The supraoptic nuclei were well defined as two groups, lateral and mesial, joined by a narrow band of cells. In size, shape, and staining qualities the cells resembled those of the paraventricular nuclei. A few cells showed the same deep staining, which was not seen in any of the other brains examined, and may be due to the fixing method.

The tuberal nuclei in this plane appeared in two groups, a lateral reniform and a mesial smaller round nucleus, rather difficult to demonstrate, but showing clearly with some staining methods. They formed paler, emptier areas, relatively avascular, with few cells. These were small, with well-stained nuclei, the cytoplasm forming a faint halo, sometimes being filled with a pale yellowish substance. In the periphery of the nuclei were a few larger pale cells, easily distinguished from the well-stained cells of the adjoining premamillary group. In this brain the tuberal nuclei seemed emptier than normal, with fewer of the large cells, but there was no evidence of cell degeneration or destruction.

Scattered in the central grey matter between the paraventricular and supraoptic nuclei were some clusters of 6-8 large, well-stained cells, usually closely related to a blood vessel, but apparently not connected with the main cell groups, or with each other. They were present in all cases examined, the cells resembling those of the well-marked premamillary group.

The mamillary body was well marked and showed no abnormality. Similarly, other cell groups, the well-marked basal nucleus of Meynert and the nucleus substantia innominata, which are considered by many as identical, the corpus Luysii, substantia Nigra, and the midbrain, appeared quite normal.

In sections stained by the Loyez method, the myelinated nerve fibres appeared

to be normal in distribution and quantity. The optic tracts appeared to be well myelinated and normal in size. In the central grey region there were a few rare myelinated fibres, apart from the commissure of Meynert, and constantly two small fibre groups were seen in the lateral part of the supraoptic nucleus.

This stain showed the distribution of capillaries very clearly in this congested brain. The paraventricular and supraoptic nuclei showed a thick network of capillaries among the cells, and the massa intermedia (nucleus reuniens) was considerably congested. The tuberal nuclei were almost free of capillaries, which were scattered throughout the central grey matter. The pituitary stalk showed much capillary congestion. In the other parts of the region the congestion was not so marked.

In sections stained by silver the unmyelinated fibres of the region were shown. Fine fibres were found running erratically throughout the hypothalamus, but there were certain well-marked tracts. A tract appearing to arise in the paraventricular nucleus curved towards the lateral part of the infundibulum; here it intermingled with fibres appearing to come from the lateral part of the supraoptic nucleus. From this mingling some fibres appeared to pass down into the pituitary stalk, and others to cross to the opposite side. The direction and connections of these fibres with cells could not be confirmed with any certainty. Fibres appeared to link up the paraventricular and lateral supraoptic nuclei, and some fibres lying parallel to the ventricular wall could be traced to the vicinity of the anterior commissure. The tuberal nuclei were outlined by fibres most marked on the lateral aspect, but their connections could not be followed in this plane. No fibres could be seen in association with the mesial part of the supraoptic nucleus, or the odd cell groups. The staining of these fibres is difficult as they are very slow to take up the silver, but the quantity and distribution of fibres in this case was comparable to that of the control brains.

The neuroglia showed no abnormal development. The subependymal glia of the third ventricle was somewhat thickened near the lower pole of the paraventricular nucleus, corresponding to an area where the ependyma itself is deeper than elsewhere. There was also a framework of neuroglia fibres in the more superficial parts of the supraoptic nuclei; these findings were constant in all cases. The tuberal nuclei were free of neuroglia, and in the Mallory stain appeared to have a light pink, rather foamy ground substance, making the nuclei particularly easy to define.

Sections were also taken from the cortex (frontal, Rolandic and occipital), the basal ganglia, pons and medulla. The outer parts of the cortex in all areas was congested, with small extravasations. The cells were for the most part normal in size and number, and the arrangement showed no gross distortion, though there were small irregularities in places. In the frontal region the shrinkage seemed to affect the white matter rather than the grey, but no disturbance of myelination was seen. All other regions were normal in appearance, except for the excessive presence of globules of free fat throughout the globus pallidus.

The pineal body appeared normal in size. The eyes, unfortunately, were not preserved.

In the case here described it is apparent that there are widespread abnormalities; developmental defects of the skeleton, kidneys and probably eyes, and abnormalities in the pituitary body, thymus and gonads. The findings in the brain are slight, a diminution of volume of the gyri of the frontal lobe, and a paucity of cells in the tuberal nuclei. Our knowledge of the histopathology of the hypothalamic nuclei is still scanty, and the peculiarities of shape and staining reactions demand caution in interpretation; while as the connections of the nuclear masses are by unmyelinated fibres, it is difficult to demonstrate with certainty the integrity of the fibre-tracts.

The syndrome called generally by the names of Laurence and Biedl has been

described fully by several authors, who have given various theories of its causation in the absence of pathological investigation. In this country Cockayne, Krestin and Soresby (1935) have discussed the genetic aspect, and compared the condition with juvenile amaurotic idiocy; the pathological findings do not suggest any relationship. The theory suggested by Raab (1924) and others that some foetal occurrence causes an internal hydrocephalus affecting the hypothalamic nuclei is manifestly incorrect. Van Bogaert and Borremans (1936) in a recent paper give the autopsy findings in a case they include in this group. Their case had the characteristics of family incidence, mental defect, obesity, genital dystrophy and retinitis pigmentosa, but the skeletal defect was a hyperostosis of the inner table of the frontal bone, a condition which has been previously associated with obesity without the other symptoms. They found the brain normal, but the pituitary body showed stasis of the vessels with no change of cell structure. They found a necrotic area in the pituitary stalk. They do not mention any other organs.

The multiplicity of anomalies in the absence of gross cerebral deformity seems to confirm the view of L'Hermitte and Bollack (1936), that it is a germinal affection "totus substantiæ." The distinction between cerebral and pituitary adiposity seems one rather of function than of anatomical change, so slight a change in the tuberal nuclei can scarcely be credited with so gross a metabolic disorder. There seems, however, to be some analogy with the syndrome of pituitary basophilism in the distribution of the fat, the colour of the cheeks, a tendency to raised blood pressure, perhaps albuminuria, and the defect of genital function. This is possibly emphasised by the large proportion of basophil cells in the anterior lobe of the pituitary body. The genetic aspect of the syndrome has obvious importance in any discussion of its causation. The stasis found throughout was probably the result of the terminal condition and not associated with the syndrome under discussion.

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Fig. 1.—Frontal poles showing shrinkage.

Fig. 2.—Part of the wall of the third ventricle, Mallory stain, showing subependymal gliosis near the paraventricular nucleus.

Fig. 3.—Supraoptic nucleus showing capillary distribution, Loyez stain.

Fig. 4.—Hypothalamic region, stained by Gross-Bielschowsky method, showing the paraventricular and supraoptic nuclei and the unmyelinated fibre tracts A.—Paraventricular nucleus. B.—Supraoptic nucleus. C.—Infundibulum.

Fig. 5.—Anterior pituitary, showing basophilia, stained by methylene blue and eosin.

Fig. 6.—Thymus, showing fibrosis.