THE THALAMIC PATHOLOGY OF AMAUROTIC FAMILY IDIOCY

A CONTRIBUTION TO THE CYTOLOGY OF THE THALAMUS*

LIONEL H. LEMIEUX, M.D.**

[Québec, Canada]

Most of our knowledge of the human thalamus has evolved from experimental work on animals and from the study of focal lesions in the human brain. Strangely enough, not much progress has been made in the investigation of the pathology of the thalamus. While the anatomist and the physiologist, in studying the thalamus, are aware of the fact that they are dealing with a combination of different nuclei, the pathologist seldom refers to these different structures, except in a vague manner. As a rule he deals with the thalamus as a whole, while, in describing the pathology of other organs, he will consider their subdivisions in detail.

It was felt that studies of the optic thalamus in disease, even in diseases as widespread as Amaurotic Family Idiocy, might yield interesting information. It is the object of this paper to attempt this neuropathological approach to the problem of thalamic cytology. This study is based on 2 cases of the late infantile form of Amaurotic Family Idiocy, which occurred in identical twins, aged 4 years, lasting for 5 years.

Only the pathology of the optic thalami of the 2 cases shall be considered here. Sections at various levels of the main thalamic nuclei were available for investigation. The staining methods included the following: cresyl violet, Spielmeyer's myelin stain, Holzer's neuroglial stain, Scharlach-R, Reumont's silver method, van Gieson's hematoxylin stain, and Lendrum's phloxin method for inclusion bodies.

The typical nerve cell change of Amaurotic Family Idiocy is well known. The ubiquitous marked swelling of the nerve cells, with displacement of the nucleus, with partial to complete tigrolysis, and with much abnormal lipoidal material within the cytoplasm is encountered solely in the lipoidoses. Under this term has been included, besides Amaurotic Family Idiocy, Hurler's disease and Niemann-Pick's disease. These diseases are characterized by a severe cell loss and glial overgrowth, which is most marked in the medial and lateral nuclei of the thalamus. Most authors agree that this is due to retrograde degeneration arising from severe cortical cell lesions. Selective damage to the deeper layers of the cortex was stressed by Vogt (10). A definite cell loss with astroglial reaction in the deeper part of the fourth and in the fifth cortical layers was noted in the cases to be presented. The precentral and the striate areas were more severely affected than the rest of the brain. Although the neuropathology of the twins

* Read at a meeting of the Montreal Neurological Society, in Québec, November 19, 1952.

** From Institut Bunge, Berchem-Antwerp, Belgium (Prof. Ludo van Bogaert) and the Department of Neuropathology, Hôpital St.-Michel-Archange, Québec, Canada.
was identical, it was somewhat more pronounced in the twin whose clinical symptoms had been more severe.

Besides cellular loss and glial outgrowth, a peculiar finding has been often described in the thalamus in the more complete anatomical reports on Amaurotic Family Idiocy (Hassin (4, 5), Greenfield and Holmes (3), Sjövall (9), Wildi (11)), on Niemann-Pick’s disease (Hassin (6), Ley (7), Didion (2)), and on Hurler’s disease (Ashby (1)). These changes consist of unusually large lipoidal granules or enclosures set in vacuoles formed in the endocellular meshwork of the cytoplasm. Greenfield and Holmes (3) stated that they sometimes attained or even exceeded the size of a red blood corpuscle. These large enclosures in vacuoles were a constant finding in the series of cases reported by Sjövall (9). The only attempt to establish in detail the exact localization of this distinct cell change in the thalamus was made by Wildi (11). In his monograph on Tay-Sachs’ Disease, he pointed out that, in contrast to the less affected centro-median nucleus, neurons of the anterior, the medial and the lateral nuclei were fewer in number and contained giant vacuoles with large lipoidal inclusions. Our findings are in agreement with Wildi’s observations.

Amaurotic Family Idiocy, as well as other lipoidoses, by producing different lesions in various neurons and neuronal groups of the thalamus, may contribute to further our knowledge of the detailed cytology of thalamic nuclei.

FINDINGS

Our own detailed histopathological findings are demonstrated in Figures 1 and 2. One type of nerve cell, with uniform pathology was prominent in the following nuclei: the midline nuclei, the paracentral (fig. 3a), the central lateral, the centro-median (fig. 3b and c), the parafascicular, the antero-dorsal, the reticular and the lateral geniculate body (fig. 3d and e). Moreover, there were only insignificant differences in the cellular types and in the cellular lesions in the paracentral, the central-lateral, the centro-median and the latero-dorsal nuclei. There was no cell loss and no gliosis within these nuclei. The impression was that these nuclei belonged to a single cellular system.

Cells of the same structure and pathology could be seen in other nuclei: (1) along the lateral and dorsal borders of the dorso-medial nucleus, (2) within this nucleus itself, where they were observed as quite distinct clusters (figs. 1a and 3f), (3) along the dorso-lateral surface of the posterior lateral nucleus (fig. 2a), (4) between the medial pulvinar and the posterior lateral nucleus, and (5) running in small compact groups along the medial concave surface of the reticular nucleus (fig. 3g and h).

All the other thalamic nuclei contained more than one type of neuron. There were small neurons, showing only some swelling and lipoidal accumulation. These cells had a delicately honeycombed cytoplasm and a small nucleus with small nucleolus (fig. 4a and b). This may be interesting in view of McLardy’s (8) observation that “many of the thalamic nuclei appeared to contain small nerve cells of a different order of magnitude from those usually described and studied.” Whether or not these neurons are intrathalamic in their connections, as McLardy suggests, the fact remains that, in our material, small neurons of the type described here were not seen within the intralaminar nuclear system, while they were abundant in certain other nuclei, namely, the anterior, the dorso-medial and the posterior lateral nuclei. They were less numerous in the posterior ventral nuclei and scarce in the pulvinar, particularly the lateral pulvinar. They were neither seen in the midline nuclei, in the medial and lateral geniculate bodies, nor in the reticular nucleus.

The anterior nucleus contained a large number of small neurons and also medium-sized
FIG. 1. Diagram, showing the distribution of neuronal lesions in the various thalamic nuclei at two different levels. Vacuolar changes are indicated by circles, and small dots indicate the small type of neuron. Designation of nuclei: Figure 1 A: AD anterior dorsal; Ant anterior; Pc posterior central; Ret reticular; VA ventral anterior. Figure 1 B: CM centro-median; DM dorso-medial; LD lateral dorsal; LP posterior lateral; Pc posterior central; Ret reticular; VPL posterior lateral part of ventral nucleus; VPM median arcuate portion of ventral nucleus.
FIG. 2. Same as Figure 1. Figure 2 A: CL central lateral; CM centro-medial; DM dorso-medial; LGB lateral geniculate body; LP postero-lateral; PL lateral pulvinar; PM medial pulvinar; Ret reticular; VPL posterior lateral part of ventral nucleus; VPM median arcuate portion of ventral nucleus. Figure 2 B: MGB medial geniculate body; PM medial pulvinar; PL lateral pulvinar; Ret reticular.
Fig. 3. a) Paracentral nucleus; cells of the intralaminar type; cresyl violet stain. b) Centro-median nucleus; neurons of the intralaminar type; cresyl violet stain. c) Centro-median nucleus; clear cell drawing; cresyl violet stain; oil immersion. d) Reticular nucleus; cresyl violet stain. e) Reticular nucleus; clear cell drawing; cresyl violet stain; oil immersion. f) Intralaminar neurons within the dorso-medial nucleus; cresyl violet stain. g) Intralaminar neurons along medial surface of reticular nucleus; cresyl violet stain. h) Intralaminar neurons along medial surface of reticular nucleus; clear cell drawing; cresyl violet stain; oil immersion.
FIG. 4. a) Anterior nucleus; vacuolated neurons with a small type nerve cell in center; cresyl violet stain.
b) Anterior nucleus; two vacuolated neurons and one small neuron; cresyl violet stain; clear cell drawing; oil immersion.
c, 1) Anterior nucleus; vacuolated neuron; cresyl violet stain; high power. c, 2) Same cell type; Reumont silver stain; oil immersion.
d) Anterior nucleus; inclusions within a vacuolated neuron; Landrum's method for inclusion bodies; oil immersion.
e) Dorso-medial nucleus; lipoidal inclusions within vacuolated neurons; Spielmeyer's myelin stain.
f) Posterior-lateral nucleus; vacuolated neurons; cresyl violet stain.
g) Posterior-lateral nucleus; vacuolated neuron. Reumont's silver method; oil immersion.
h) Dorso-medial nucleus; vacuolated neurons; cresyl violet stain.
Fig. 5. a) Dorso-medial nucleus; vacuolated neuron; clear cell drawing; cresyl violet stain; oil immersion.
b) Dorso-medial nucleus; vacuolated neuron; Reumont’s silver method; oil immersion.
c) Anterior ventral nucleus; neurons with typical swelling; cresyl violet stain.
d) Anterior-ventral nucleus; typically swollen neuron; clear cell drawing; cresyl violet stain; oil immersion.
e) Ventral postero-medial nucleus; vacuolated neurons; cresyl violet stain.
f) Ventral postero-lateral nucleus; large, markedly swollen neurons with Nissl substance about the nucleus; cresyl violet stain.
g) Ventral postero-lateral nucleus; large neuron; clear cell drawing; cresyl violet stain; oil immersion.
h) Medial pulvinar; vacuolated neurons; cresyl violet stain.
nerve cells with large, clearly visible vacuoles, when stained with the cresyl violet method (fig. 4a, b and c). When treated with silver salts, these vacuoles appeared surrounded by a dense argentophilic network (fig. 4c); with the Scharlach-Red method, they appeared to be filled with large inclusions of a bright orange color. When stained with Lendrum’s phloxin method for inclusion bodies, the lipoidal material would appear as rounded bright red enclosures in the cytoplasm (fig. 4d). On sections stained with Spielmeyer’s myelin method, the lipoidal inclusions often appeared as large, black, rounded granules (fig. 4e). This phenomenon was not seen in cells elsewhere. These staining characteristics were found in vacuolated cells of the entire thalamus. The dorso-lateral nucleus contained many densely packed medium-sized neurons, showing small, irregular and numerous vacuoles. It also contained small neurons and medium-sized swollen cells. The latter were mostly located in the dorsal part of the nucleus (fig. 1b). There was no cellular destruction, and the neuroglial overgrowth was moderate.

The cell composition of the posterior-lateral nucleus was similar to that of the anterior
nucleus, but its vacuolated neurons were slightly smaller (figs. 4f and g). There was severe cell loss, especially in the caudal part of the nucleus, and dense fibrillary gliosis was present throughout. The dorso-medial nucleus also exhibited the same cellular composition as the anterior nucleus, with small neurons and vacuolated medium-sized nerve cells (figs. 4h, 5a and b). The nucleus was divided into two parts by an area practically free of nerve cells except for clusters of neurons of the 'intralaminar' type (fig. 5f). There was obvious cell loss, especially in the medial part of the nucleus, and glial overgrowth was very marked in both parts, with only a small area within the nucleus being relatively free of gliosis. The anterior ventral nucleus was made up of the usual clusters of neurons. These were mostly of medium to large size, and exhibited globular swelling of the cell body with honeycombed structure of the cytoplasm and with some Nissl substance about the nucleus (fig. 5c and d). There were also small neurons and only a few vacuolated nerve cells in the most lateral parts of the nucleus. The number of cells was normal and there was no gliosis. It was not possible to map out the latero-ventral nucleus as a separate unit, although the thalamus was sectioned at different levels.

The posterior-ventral nuclei contained 3 types of nerve cells. There were only a few small neurons, and a fair number of vacuolated, medium-sized nerve cells (fig. 5e). These were more numerous in the oral part of the nucleus and in the median arcuate portion (figs. 1B and 2A, VPM). The ventral postero-lateral nucleus contained only sparse vacuolated neurons. The third type of neuron was obviously different, being rather large, with marked globular swelling, and contained a considerable amount of Nissl substance (fig. 5f and g). Cells of this type were especially numerous in the ventral posterolateral nucleus. There was no cell loss, and gliosis was absent.

The medial pulvinar contained markedly vacuolated nerve cells (fig. 5h), with few small neurons. Cell loss and gliosis were severe. Most of the neurons of the lateral pulvinar were swollen, pale cells which frequently contained a few small vacuoles (fig. 6a and b); the small type of neuron was uncommon. There was neither cell loss nor gliosis. The medial geniculate body did not contain small neurons; most of the cells were moderately swollen, honeycombed, with some Nissl substance about the nucleus (fig. 6c). The dorso-medial part of the nucleus, however, contained many typically vacuolated neurons (fig. 6d). The lateral geniculate body contained mainly a single type of medium-sized neuron, moderately swollen and devoid of Nissl substance (fig. 6e). Neither the medial nor the lateral geniculate bodies showed cell loss or gliosis.

**COMMENT**

The histopathological findings demonstrated in our material may not warrant valid conclusions as to the histology of the normal thalamus. However, bearing in mind that, in these cases, the neuronal swelling was ubiquitous, both in the thalamus and the cerebral cortex, and that cell loss in the cortex affected the same layers throughout its whole extent, it would appear that the systematization of the cellular lesions in the thalamus and in its various nuclei is more than a chance occurrence, and that it may throw some new light on the cytological arrangement of the normal thalamus.

**SUMMARY**

From a cytological investigation of the thalami of 2 cases of Amaurotic Family Idiocy, the following conclusions may be drawn:

1. The intralaminar nuclear system appears, in this material, to be much more diffuse than is generally stated.
2. All the nuclei, usually classified as nuclei with subcortical connections, are
352 LIONEL H. LEMIEUX

composed of a single type of neuron, and none of these neurons show vacuolar changes.

3. Within the group of the so-called cortical relay nuclei, the anterior nucleus contains only vacuolated neurons and small nerve cells. The ventral nuclei, however, exclusive of the antero-ventral nucleus, contain 3 types of nerve cells, with few vacuolated neurons. The number of vacuolated nerve cells was still smaller in the medial geniculate body, and they were absent in the lateral geniculate body.

4. All the nuclei, comprising the group of "association nuclei", show vacuolar changes and some loss of nerve cells.

5. Many of the thalamic nuclei contain a distinct type of small neuron which is not found in: the intralaminar system, the midline nuclei, the reticular nucleus, and the medial and lateral geniculate bodies.

Acknowledgment. I wish to express my sincere gratitude to Professor Ludo van Bogaert, who provided this valuable pathological material and made this study possible through constant guidance. I also wish to thank Miss Snieders and Mrs. Suzanne Lemieux, for their excellent technical assistance, Sister Celine, for the preparation of the photomicrographs, and Mr. Jean-J. Cuvelier, for the clear-cell drawings.

REFERENCES