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Original Investigations

Dysplastic Gangliocytoma of the Cerebellum—An Ultrastructural Study

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Summary. A case of dysplastic gangliocytoma of the cerebellum, a rare disorder with unknown etiology and pathogenesis, was studied ultrastructurally. The intranuclear inclusions identified were not seen to be of viral origin. The ultrastructural characteristics of the abnormal cells support the prevailing theory that these cells represent hypertrophied granular neurons.

Key words: Dysplastic gangliocytoma – Ultrastructure.

Dysplastic gangliocytoma of the cerebellum is a rare disorder with features of a congenital malformation and a neoplasm (Lhermitte and Duclos). In this unusual disorder, enlarged cerebellar folia with abnormal neurons occupy segments of the cerebellar cortex and become manifest in adulthood, presenting clinically as a cerebellar neoplasm (Rubinstein; Russell and Rubinstein). Comprehensive reviews of the literature have been rendered by Oppenheimer, Hallervorden, Simeoni, and most recently by Ambler et al., who counted 36 reported cases. The wide variety of names applied to the disorder include Lhermitte-Duclos disease, granular cell hypertrophy, diffuse hypertrophy of the cerebellar cortex, gangliomatosis of the cerebellum, hamartoma of the cerebellum, ganglioneuroma, and Purkinjeoma.

The pathogenesis as yet remains unknown. Oppenheimer, Hallervorden, and Ambler et al. regard the lesion as a graded hypertrophy of the internal granular neurons. To date, no electron microscopic studies have been reported to our knowledge. The purpose of this report is to describe ultrastructural findings in a recently studied case, potentially casting light on the nature and origin of the abnormal cells.

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Case Report

The patient was a 24-year-old male who was referred to University Hospital with complaints of worsening occipital headaches and dizziness of 5 months' duration. Past medical history and family history were not remarkable. General physical examination was unremarkable, but neurological examination revealed bilateral papilledema, mild bilateral intention tremor greater on the left side, slight dystaxia on rapid alternating movements, inability to do tandem gait or stand on one leg alone, and unsteady Romberg position.

A vertebral arteriogram showed inferior displacement of the left posterior/inferior cerebellar artery and its vermian branches by a large avascular mass. Computerized automated tomography (C.A.T.) scan revealed a large right cerebellar hemisphere mass which extended across the midline but did not enhance with contrast media. At surgery, the right side of the occipital bone and dura were thinner than the left, and the underlying cerebellar folia were widened and pale. A transcortical incision was made, and a firm solid tumor was seen diffusely infiltrating the right cerebellar hemisphere. All of the visible tumor was removed. The patient recovered uneventfully and was discharged on the eighth post-operative day.

Materials and Methods

At the time frozen section diagnosis, tissue was fixed in 2% glutaraldehyde, post-fixed in osmium tetroxide, dehydrated and embedded in plastic. 0.5 μ thick, toluidine blue stained sections were utilized to select appropriate areas for electron microscopic study. Thin sections were stained with uranyl acetate and lead citrate, and examined with a Hitachi 11-C electron microscope. Paraffin embedded tissue was cut at 4–6 μ for hematoxylin and eosin stain, Luxol fast blue-PAS-Hematoxylin and Bodian silver impregnation.

Results

A. Pathology Findings. The specimen consisted of multiple pieces of gray-white tissue with total weight of 6.8 g. The largest piece measured 4 × 2 × 1.5 cm. Enlarged cerebellar folia were visible on gross inspection.

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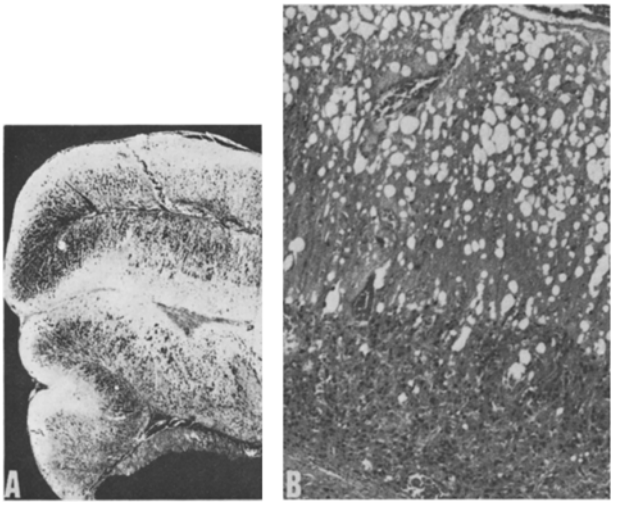

Fig. 1. A Low power magnification of cerebellum showing enlarged cerebellar folia with outer and inner zone (H.-E., × 3.3). **B** Higher magnification showing outer zone with spongiosis (above) and cellular inner zone (below). (H.-E., × 20)

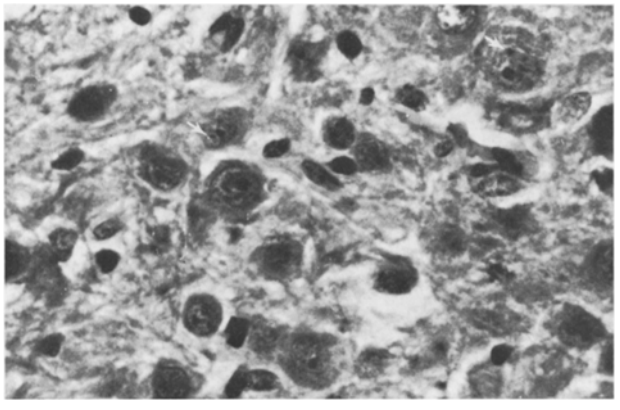

Fig. 2. High magnification of neurons. Note large nucleoli plus intranuclear inclusions at arrows. (H.-E., × 200)

Low power microscopic examination revealed an enlarged cerebellar cortex with a densely staining outer zone and a pale inner zone (Fig. 1 A). The outer zone (molecular layer) was homogeneous, acellular and spongiotic, showing focal calcific deposits, while the inner zone (granular layer) was cellular (Fig. 1 B). The central white matter was absent. The granular layer was populated by large neurons 40 – 60 μ in size with large nuclei. In addition to macronucleoli, intranuclear structures resembling inclusions were identified (Fig. 2). The Nissl substance was scant and finely granular when stained with toluidine blue. With Bodian silver impregnation and Luxol fast blue-PAS-hematoxylin stains, large myelinated axons up to 7 μ in diameter were seen to course through the molecular layer in perpendicular orientation to the pia (Fig. 3).

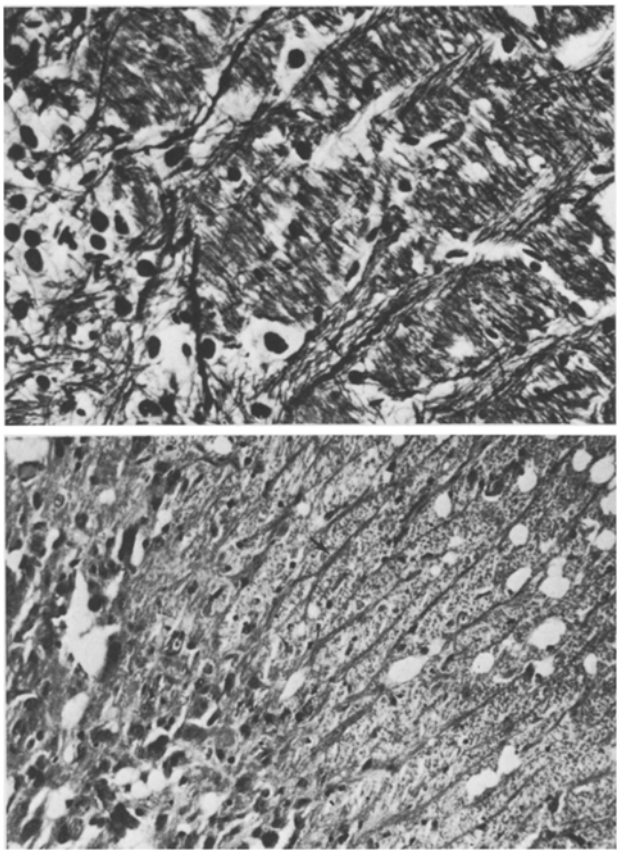

Fig. 3. Large myelinated axons (arrows) course perpendicularly to pia through molecular layer (Bodian silver impregnation × 200, above) (Luxol fast blue × 80 below)

Bundles of smaller myelinated fibers comprised the remainder of the molecular layer, coursing parallel to the pia.

B. Ultrastructural Findings. The granular layer was populated almost exclusively, except for rare neuroglial cells, bylarge neurons corresponding to those seen on light microscopy (Fig. 4). Cell shape was irregular and cell size was variable. The cytoplasm contained large numbers of mitochondria, a few electron-dense lipid bodies and occasional membrane-limited multivesicular bodies. Golgi complex was moderate in size while Nissl substance was characteristically small. Winding between the mitochondria were seen neurofilaments, microtubules, small segments of smooth endoplasmic reticulum and branches of rough endoplasmic reticulum. Free ribosomes and polyribosomes were present in small numbers. The rough endoplasmic reticulum and polyribosomes were condensed in small areas corresponding to Nissl bodies (Fig. 5). Non-membrane bound cytoplasmic vacuoles containing a small amount of fibrillar material were presumed to be degenerative in nature. Near the periphery of the

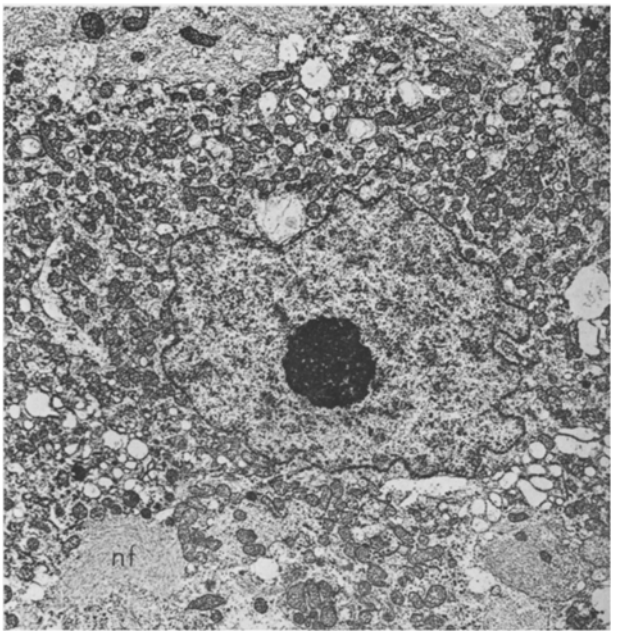

Fig. 4. Electron micrograph of dysplastic neuron. Note macronucleolus, abundant mitochondria and coarse bundles of neurofilaments (*hf*). (×3769)

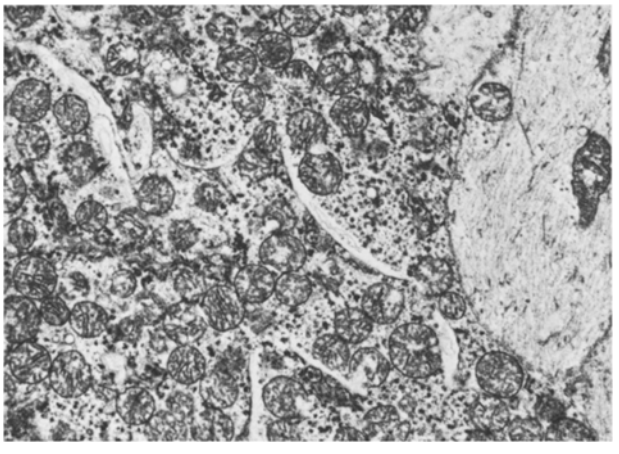

Fig. 5. Detail of organelles. Mitochondria are numerous, but Nissl substance (arrows) is not prominent. Note cell process at right with small neurofilaments and larger microtubules. (×4977)

cell membrane, coarse bundles of neurofilaments and microtubules were seen near the origin of cell processes. Cell processes consisted of numerous dendrites and less frequent axons.

Nuclei were large, with macronucleoli spanning one-third or more of the nuclear diameter. Intranuclear inclusions $1-2\,\mu$ in size were rarely seen. On high magnification these were fibrillogranular in nature and no viral bodies were identified (Fig. 6).

The neuropil between somas of the large neurons consisted of tangled cell processes (Fig. 7). Axo-den-

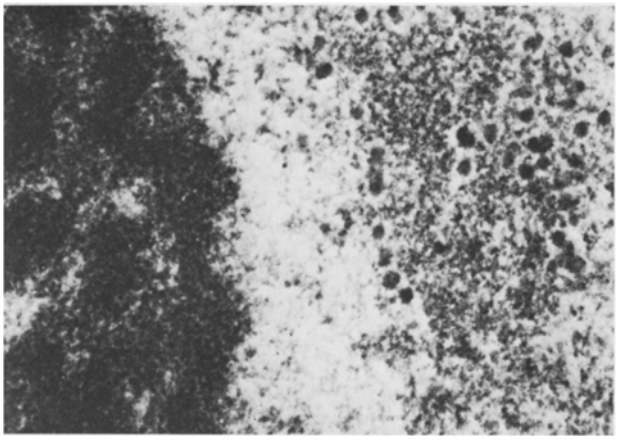

Fig. 6. Fibrillogranular intranuclear inclusion at right. Contrast with nucleolus, left. (×35289)

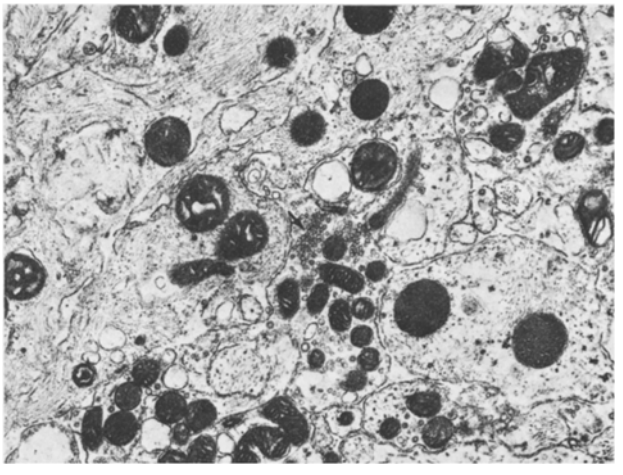

Fig. 7. Electron micrograph of neuropil showing tangled cell processes. Note synaptic vesicles (arrow). (×4974)

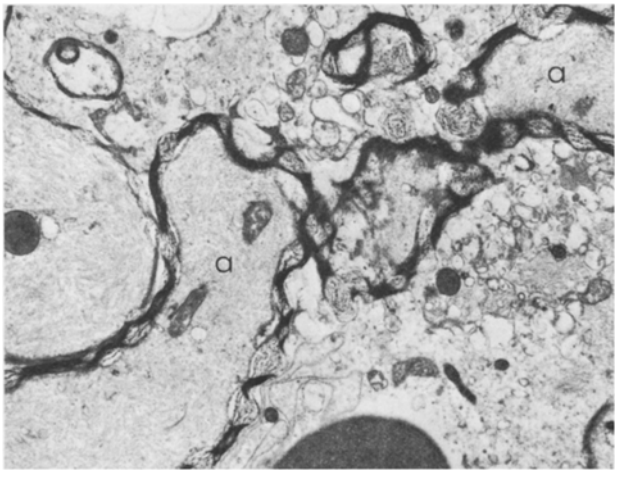

Fig. 8. Electron micrograph of molecular layer showing large myelinated axons (*a*). (×7360)

dritic synapses were identified. No axo-somatic synapses were seen, and axonal processes and perikarya showed no ensheathment by neuroglial processes. Capillaries were few in number and lacked association with the neuronal cell processes. The molecular layer contained numerous large myelinated axonal processes 5–7 μ in diameter (Fig. 8).

Discussion

In 1920 Lhermitte and Duclos reported the first case of an unusual disorder of the cerebellum chracterized by enlargement of cerebellar folia which were populated by dysplastic ganglion cells. Subsequently, accounts of dysplastic gangliocytoma or Lhermitte-Duclos disease have been reported under a variety of names.

Ambler et al. reported the most comprehensive review of published cases to date (including one verbal communication) and added two familial cases, the first so published. Their listing consisted of 36 cases which met criteria of: 1. abnormal ganglion cells, and 2. excessive numbers of large axons in the cerebellar cortex. Associated congenital anomalies were seen in a minority of cases. The most frequently reported associated anomaly encountered was enlargement of skull and/or brain seen in 19 cases. While the etiology remains unknown, congenital and viral causes were proposed as possibilities. The pathogenesis was regarded as a graded hypertrophy of the internal granular neurons in concurrence with the majority of previous investigators.

In our study, the enlarged cells populating the granular layer have ultrastructural characteristics of neurons. In consideration of the prevailing theory of origin of these cells, a most pertinent question is – are the ultrastructural findings consistent with granule cell origin?

Nonpathologic granule cells are small with scant cytoplasm, scant organelles, small Nissl bodies and small nucleoli. They lack both axo-somatic synapses and ensheathment of the perikaryon by astrocytic process (Peters et al.). The abnormal neurons as studied ultrastructurally have several features in common with granule cells. They have small Nissl bodies, lack axo-somatic synapses and show no ensheathment of the perikaryon by astrocytic processes. On light microscopy the perpendicular orientation of their large axons in relation to pia is a characteristic peculiar to granule cells in the cerebellum (Ramon y Cajal). This orientation of axons has been noted in previously studied cases and has been regarded as important supporting evidence at the light microscopic level for granule cell origin (Duncan and Snodgrass; Ambler et al.).

Purkinje cells also have small Nissl bodies but show ensheatment of the perikaryon by astrocytic processes and have bulbous dendritic spines (Peters et al.). The absence of the last two features would be against a Purkinje cell origin as some have suggested (Foerster and Gagel; Christensen; Courville).

Electron microscopic features that were not characteristic of granule cells include large cell size, large number of mitochondria, and macronucleoli. These characteristics, however, could well be secondary to cellular hypertrophy. Increased numbers of mitochondria suggest increased cellular utilization of oxygen and glucose whose pathways are ATP-dependent. The enlarged nucleoli also suggest increased cellular activity, perhaps in relation to protein synthesis. The light and electron microscopic findings in this case, then, would support the theory that the abnormal neurons are hypertrophied granule cells.

Intranuclear inclusions were identified in this case as well as in one of the cases studied by Ambler et al. Ultrastructurally these were seen to be fibrillogranular in character, similar to those described in nonpathologic neurons (Peters et al.). No viral bodies were seen and no evidence was uncovered in support of a viral etiology for the disease. The frequent association of megalencephaly and the reporting of two familial cases add weight to the theory of a congenital etiology. Genetic studies of future cases is indicated in the hope of further elucidating the cause of this unusual disease.

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