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Infantile Neurological Gaucher's Disease in Three Siblings

An Ultrastructural Study

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Summary. The clinical, histological and histochemical aspects of infantile neurological Gaucher's disease in three siblings are described.

In one of them, electron-microscopic examination of Gaucher cells from a cervical lymph-node biopsy was carried out. We believe that the term "tubes" is inadequate to describe Gaucher bodies, since we have shown that most Gaucher bodies consist of flattened sac-like structures. A fragment of the cerebral cortex obtained from the same subject four hours after death was also studied with the electron microscope; surprisingly, Gaucher bodies were observed in some neurons.

The various factors which can favour the deposition of kerasin are discussed.

We have been able to study a family with *three children*, a male and two females, affected by infantile neurological Gaucher's disease.

Case 1 (Bueno *et al.*, 1970) was a female infant with a birth weight of 3.19 kg. She was the first daughter of healthy parents and since birth had shown signs of prematurity with generalised hypertonia, marked opisthotonos, dysphagia, weak crying, seborrhoeic dermatitis, strabismus and trismus. Death occured at age 45 days.

Case 2 was a stillborn male foetus, gestation period of 35 wk; foetal heart was still sensible two days before birth.

Case 3 was a female infant weight at birth 2.95 kg, gestation period of 32 wk. The pregnancy, birth, and neonatal period were normal. At age 18 days, the patient was brought to us because she showed hypertonia which reminded the family of the onset of the fatal disease in Case 1. The patient showed a general state of prematurity, hypertonia, opisthotonos, and eczematous yellowish skin and hepatosplenomegaly which increased with time. The infant deteriorated and neurological signs became more evident. The patient died at age three months.

Laboratory data: The serum acid phosphatase reached values of 90 mU per ml. Bone marrow study showed Gaucher cells in large numbers.

Pathological Findings

The organs from all three necropsies were available for study. Electron-microscopic studies were done on a fragment of the cerebral cortex obtained post-mortem from Case 3 four hours after death, and on a cervical lymph-node biopsied 54 days before death. The following organs were affected in Case 3: the central nervous system, lungs, thymus, bone marrow, lymph-nodes, liver, spleen, and suprarenal glands.

Active erythro-phagocytosis by the Gaucher cells in the hepatic sinusoids was a feature (Fig. 1).

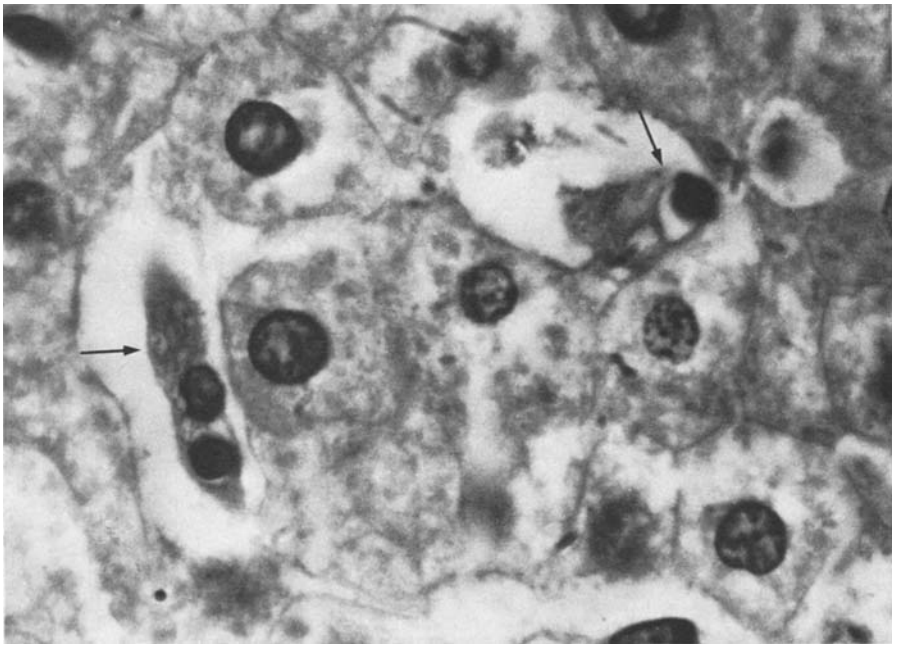
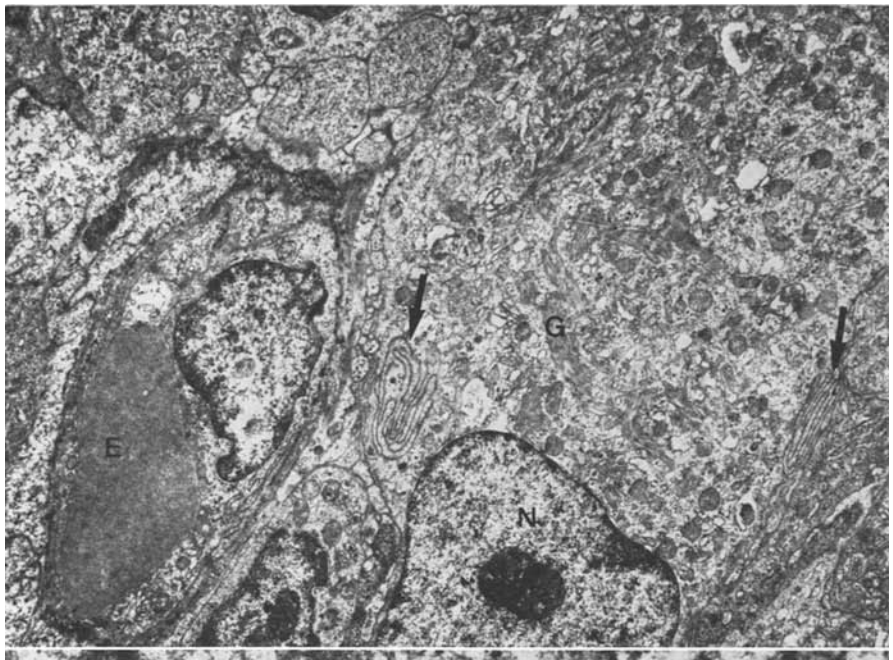


Fig. 1. Liver. Two Gaucher cells have phagocitized an erythroblast (see arrows). H and E. × 1600

The findings in the other two infants, a male and a female, were similar but electron-microscopic studies were not performed.

Histochemical studies were carried out on the three cases with post-mortem material fixed in 10 per cent formol saline which conserves in part the enzymes later described. Enzymes were qualitatively evaluated in the Gaucher cells, 4 plus (++++) being the maximum intensity. Results were as follows: esterases +, acid phosphatase +, ubiquinones ++ and alkaline phosphatase −. The PAS reaction was graded from ++ to +++, not being uniform in all of the cells.

Electron Microscopy of Biopsy Material. The Electron-microscopic examination of the cervical lymph-node showed Gaucher cells with the typical packets of tubes constituting the Gaucher bodies (Fig. 2). These packets are elongated masses which tend to bend, are of variable thickness, and show easy branching and have interconnections with each other. They are distributed at random in the cytoplasm. At times they may be surrounded by a clear sharp membrane (Fig. 3). Inside this membrane are found tubes of some 250 Å in diameter, the majority of which are probably laminated cisternae, because most of the sections are predominantly longitudinal in nature. The Gaucher bodies are masses in which obscure laminae of medium intensity alternate regularly with clear fissures which appear to have a twisted course bifurcating often at right angles (Fig. 4). Mitochondria are present in good proportions, some showing non-specific degenerative phenomena such as swelling and loss of cristae. These altered mitochondria at times show an intimate relation with the Gaucher bodies but, as we ascertained,



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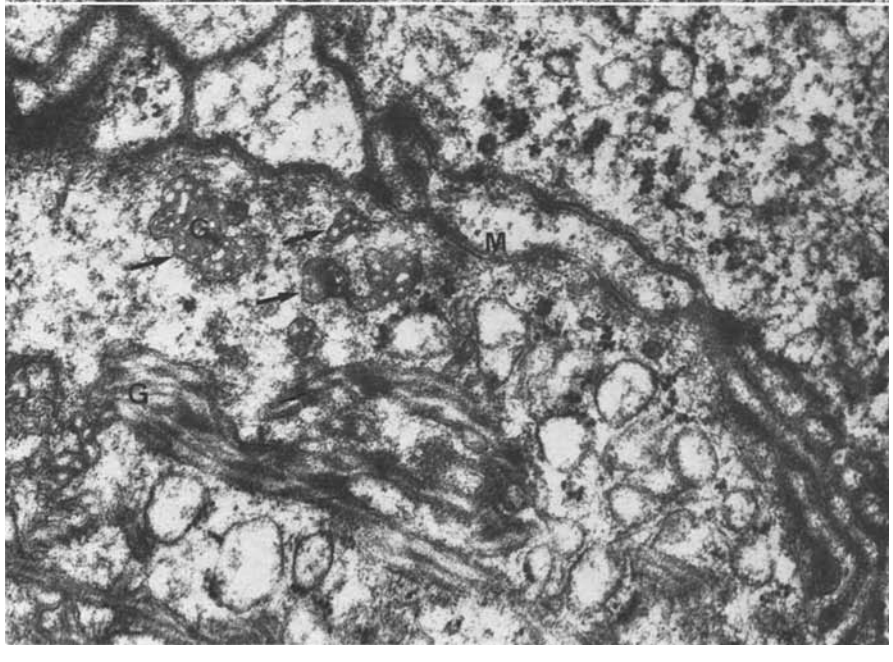

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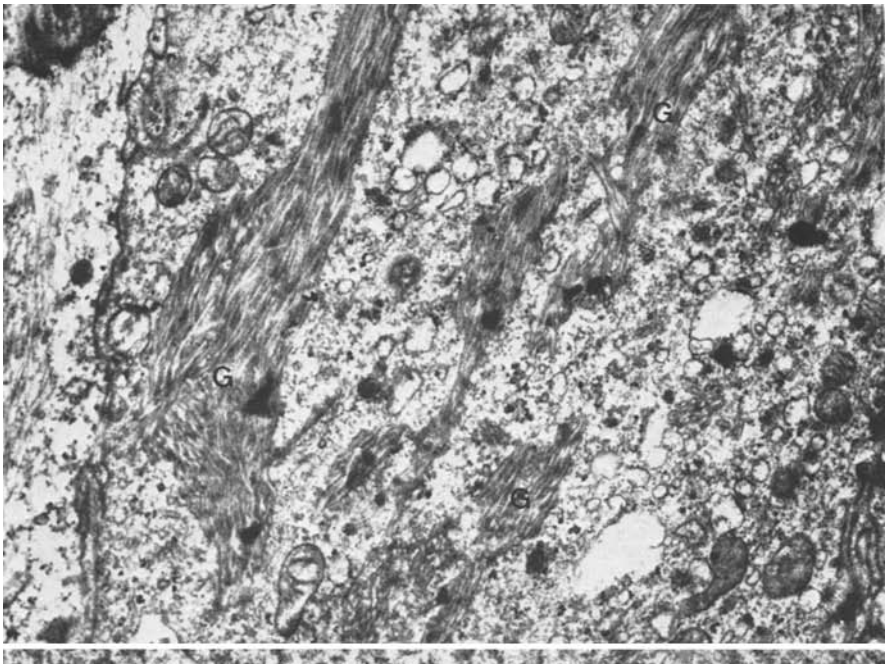
Fig. 2. Biopsy material. Gaucher bodies (*G*), nucleus (*N*), folds in the plasmatic membrane (arrows) and to the left is a capillary containing an erythrocyte (*E*). ×7800

Fig. 3. Biopsy material. Next to the plasmatic membrane (*M*) Gaucher bodies (*G*) are seen; in the transverse cuts emphasis is on the sharp membrane (arrows) ×46400



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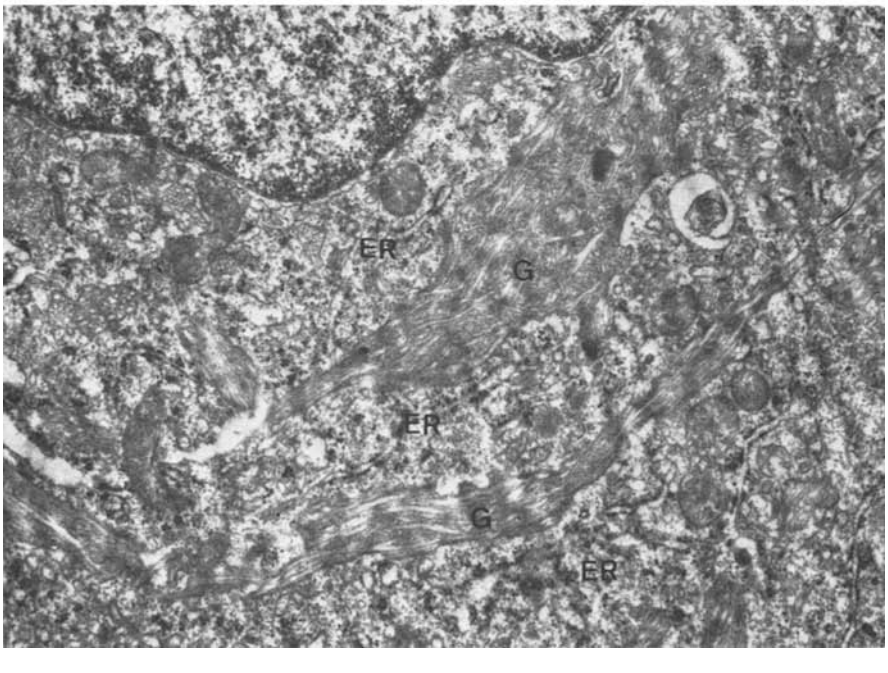

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Fig. 4. Biopsy material. Gaucher bodies (*G*), clearly manifest a longitudinal striation. ×17400

Fig. 5. Biopsy material. Gaucher bodies (*G*) alternating with zones of the rough endoplasmic reticulum (*ER*). ×26000

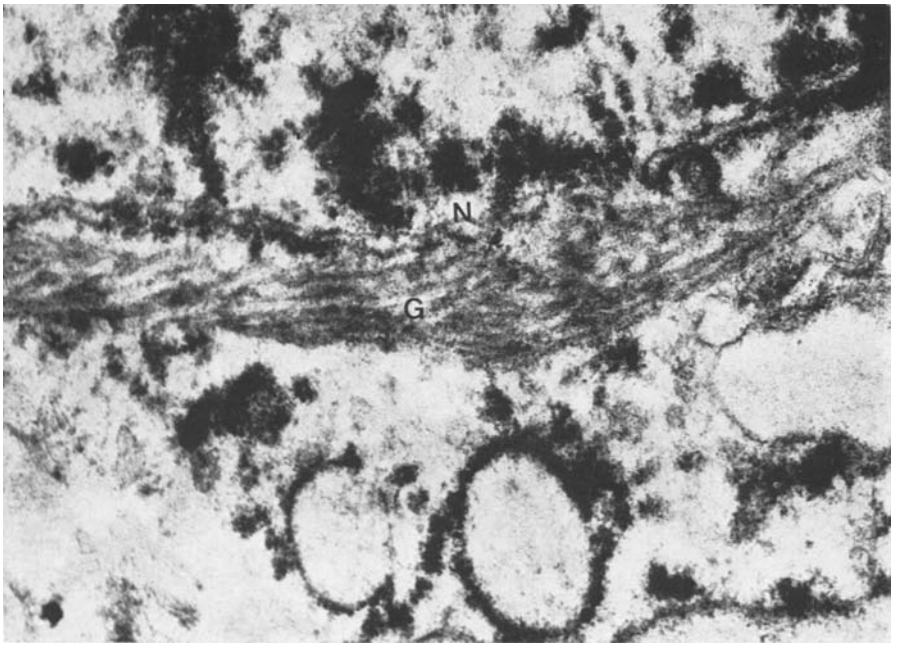

Fig. 6. A neuron containing a Gaucher body (*G*) next to the nuclear membrane (*N*). × 65000

without any continuity between the two structures at anytime. The Golgi zones appear evident, at times with two or three flattened sac-like complexes. There are abundant vesicles of the rough endoplasmic reticulum (Fig. 5). The plasmatic membrane is quite folded in some zones (Fig. 2). The nucleus (Fig. 2) is usually eccentrically located.

Electron Microscopy of Central Nervous System. Before us, only Adachi *et al.* (1967) reported Gaucher bodies in neurons.

Our observations are similar. Among the cells examined from the frontal region, only two neurons were found (Fig. 6) containing Gaucher bodies which resembled those earlier described in the cervical lymph-node.

Discussion

It has frequently been reported that Gaucher bodies are constituted fundamentally by tubes, but we believe that this view should be modified. If the structure was fundamentally tubular the predominant image seen would be circular or somewhat elongated according to the plane of section. However, these images are very infrequent (Fig. 3) and predominating are longitudinal striations with waves and bifurcations at right angles (Figs. 4 and 5). Therefore, we believe that the basic structure of the Gaucher bodies consists of saccules or flattened cisternae. Possibly the groups of tubes found next to the plasmatic membrane are the initiating zones which rapidly lose their circular form to continue in flattened plates which bifurcate and interweave.

We believe that various factors can influence the deposition of the Gaucher material, kerasin. In the first place the deficiency of glucocerebrosidase may not be of the same magnitude in all cases of Gaucher's disease (Patrick, 1965; Brady *et al.*, 1966). Also, the deposition of the material depends on the amount of cerebrosides transported. If there is an excessive destruction of cells which possess an abundance of cerebrosides such as erythrocytes (Blicharski *et al.*, 1967) (Fig. 1) or leukocytes (Albrecht, 1969), the deficit in glucocerebrosidase will be more rapidly manifested.

Another factor which might influence the deposition of kerasin is the facility of the cell to absorb cerebrosides and to react to their presence; the variation in enzymatic activity found in different organs by Öckerman and Köhlin (1968), could influence the deposition of Gaucher material.

With regard to the origin of Gaucher material we agree with Hibbs *et al.* (1970), that the major part is exogenous. The cerebrosides penetrate the plasmatic membrane possibly through "cup-like bodies" as described by Holtzman and Dominitz (1968). The cerebrosides consist of glucose, sphingosine and a fatty acid; they are not visible as such by the electron microscope. We believe that the cell elaborates a protein to form glucoproteins which could be the visible lamellar structure of the initial tubes and later of the flattened sac-like structures; the sphingosine and the fatty acid could be the structural components of the white fissure described previously. We believe that the distinct membrane which usually surrounds the Gaucher body (Fig. 3) is a lipoprotein and is elaborated by the cell due to the presence of the foreign material.

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