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G_{M1} — GENERALIZED GANGLIOSIDOSIS WITH UNUSUAL INVOLVEMENT OF THE WHITE MATTER *)

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Profuse, intensive demyelination of the white matter in degenerative lipid storage diseases of the central nervous system is a common feature. This is accompanied by an accumulation of various lipid substances and glial reaction varying in intensity. The pathogenic interpretation of these findings in not univocal.

There is also a group of lipid storage diseases in which the nature, intensity and distribution of white matter alterations suggest either the existence of an equiponderant leucodystrophic component of the essentially neuronal pathology or coexistence of two different pathological processes involving different structures of the central nervous system.

The case presented below represents such a group of lipid storage diseases.

CASE HISTORY

A 13 mos old boy, third child in the family was delivered normally following a full term normal pregnancy. His parents were young, healthy and non-consanguinous. Family history was negative. The early development was entirely normal. At the age of 5 months the parents noticed progressing enlargement of his head, asymmetry of the skull and distention of the superficial veins in the frontal and left parietal regions. The boy became restless and cried frequently. The arrest and later deterioration of his physical and mental ability was a leading feature.

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The child was admitted to the Bielany City Hospital in Warsaw with a preliminary diagnosis of hydrocephalus. He was small poorly developed and malnourished. He lay quietly in bed without reaction to his surroundings and did not follow objects with his eyes.

Examination: large and asymmetric head, 49.5 cm in circumference. Anterior fontanelle large (4 × 4 cm), protruding and pulsating.

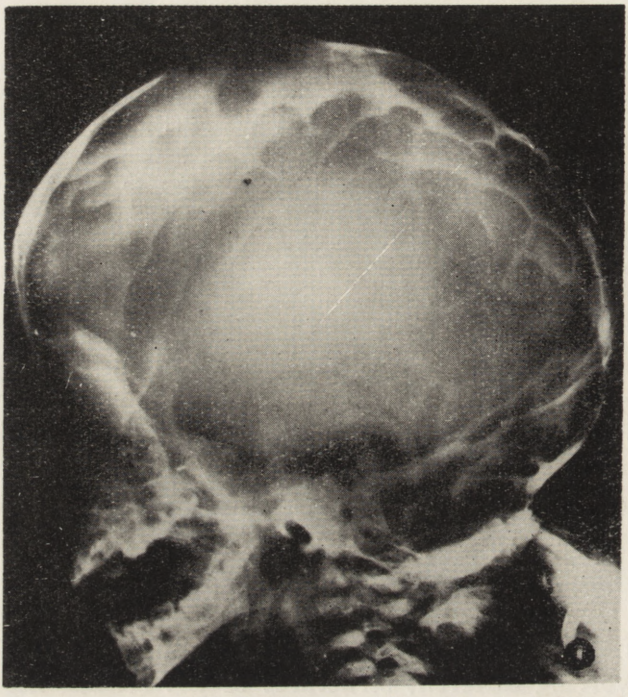

Fig. 1. Lateral projection of skull. Numerous bone tissue defects in the skull.
Ryc. 1. Boczne zdjęcie czaszki, widoczne liczne ubytki w kości ciemieniowej, czołowej i skroniowej.

Sagittal suture and lateral fontanelles not obliterated. Numerous small bone defects palpable in left frontal, temporal and parietal regions of skull. In frontal region a large subcutaneous angioma racemosum. Eyeballs pushed down and slightly exophthalmic. On ophthalmological examination the optic discs pale, white - grayish, with indistinct edges. Physiological cups filled bilaterally; optic arteries narrow, and veins congested and tortuous. Marked reduction of muscle tonus in upper extremities with no paralytic features. Tendon reflexes in the arms active and symmetrical. Paratonic muscular tonus in lower extremities, accompanied by clonic knee-jerks. Plantar responses were extensor. Tremendous enlargement of liver, which occupied the whole right side of the abdominal cavity. Spleen palpable 3.5 cm below left costal margin.

Laboratory data. Cerebro-spinal fluid examination and urinalysis normal. Moderate normochromic anemia, with slightly elevated leucocytosis. Cytological examination of bone marrow: generally reduced blastosis with normal for the age proportion of various groups of haemopoietic cells. Among reticular population lymphoid cells with severely vacuolated cytoplasm prevailed. Typical foamy cells present. Protein

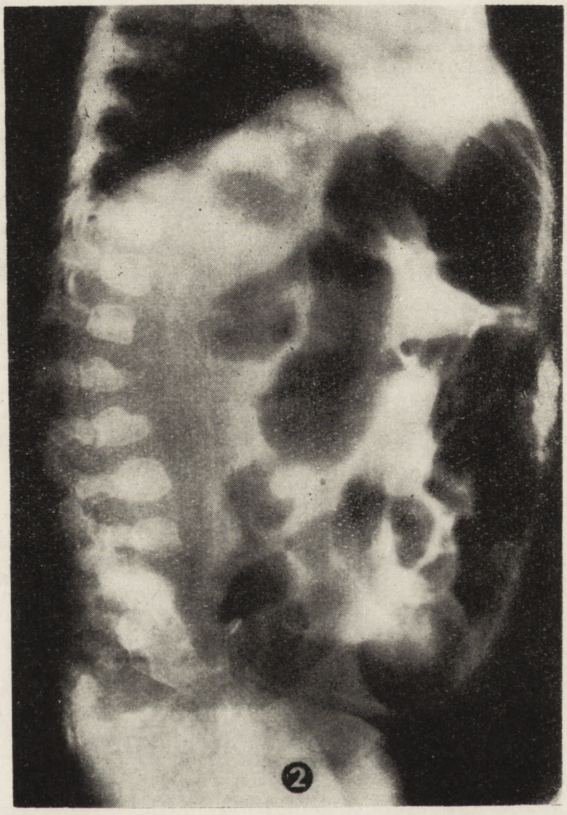

Fig. 2. Lateral projection of spine. Typical deformity of vertebral bodies at L_1—L_3 levels.
Ryc. 2. Zdjęcie boczne kręgosłupa. Chondrodystroficzne zmiany w trzonach kręgowych w odcinku L_1—L_3.

level in blood serum slightly reduced. GOT and GPT activities 40 and 26, respectively.

X-ray of skull: widening of coronal and sagittal sutures, deformity and asymmetry of skull and exensive craniolacunia of its left side (Fig. 1). Pneumoencephalography: lateral ventricles narrow, shifted to right side. X-ray of long bones and spine: moderate atrophy of tissue with marked reduction of cortical layers in long bones. Spine kyphotically deformed in lumbar region. Bodies of lumbar vertebrae showed deformities typical for chondrodystrophy (Fig. 2).

During hospitalisation the general state of the patient deteriorated. A high variability of neurological state was also noted. Periodic spasticity of lower limbs and shortlasting right-side epileptic fits were observed. The child died following 3 weeks observation of bronchopneumonia.

Postmortem examination: Body emaciated. Bilateral bronchopneumonia. Pronounced enlargement of the liver and spleen.

Microscopic examination: in lungs confirmed the gross diagnosis. Radiate arrangement of hepatic lobuli severely altered. Enlarged, roundish in shape hepatocytes with large vacuoles, empty in all preparations from formalin-fixed material (Fig. 3). Only small traces of PAS- and Sudan black B-positive material in the periphery of cells and around displaced nuclei. Among these cells numerous clusters of foamy cells, probably of reticulo-endothelial origin. Their weakly eosinophilic cytoplasm filled with fine granular material staining positively with Sudan black B and PAS, even in paraffin-embedded material. Identical in appearance and histochemical properties cells present in the parenchyma of spleen, mostly within Malpighian bodies (Fig. 4).

Epithelial cells of numerous renal glomeruli swollen with fine granular cytoplasm. Subcapsular spaces widened (Fig. 5). Cytoplasm of cells forming some proximal convoluted tubules pale and vacuolated. In their lumina PAS-positive hyaline deposits.

Brain large and asymmetric, left hemisphere larger than right one. Cortical convolutions wide and flattened, vascular sulci compressed. White matter of cerebral and cerebellar hemispheres on coronal sections unequally discoloured. Its consistency lowered. In many places cortico-subcortical junction outlined. Corpus callosum 1.5 mm thick. Lateral ventricles very narrow.

Two fundamental types of microscopic changes were present: a generalized storage process involving to a different degree all neurons of central nervous system and profuse leucodystrophic type demyelination of white matter. Distended, baloon neurons present in all gray formations. Their cytoplasm in paraffin embedded sections empty, or filled with fine granular material (Fig. 6). Their nuclei displaced towards cell periphery. Apart from severely changed neurons there occurred also nerve cells less altered and some proportion of normal neurons. Storage process in cerebral cortex increased in intensity towards the occipital poles and deep cortical layers. High neuronal loss, most marked in the III — VI layers, leading to complete disappearance of normal cortical striation and accompanied by strong glial reaction; numerous hypertrophied, sometimes multinuclear astrocytes present.

The great variability in the intensity of neuronal changes was also typical for the brain stem formations (Fig. 7). Dentate nucleus neurons

severely distended while Purkinje cells only moderately involved (Fig. 8). Cerebellar molecular layer contained a limited number of distended Purkinje cell dendrites. Purkinje cells loss moderate, so was rarefaction of granular layer, however Bergmann's glia proliferation was considerable.

Histochemical examination revealed that the fine granular neuronal deposits were gangliosides. They were Sudan black B- and PAS-positive (Figs. 9 and 10). They stained metachromatically red with toluidine blue and acid cresyl violet (Fig. 11) and gave a positive reaction with alcian blue. Ganglioside deposits were not bound with cellular proteins and were easily extractable with organic solvents. They disappeared after one hour incubation in absolute ethanol, methanol-chloroform and in pyridine. Besides some neurons stored small amounts of glyco- and phospholipids.

The white matter of cerebral and cerebellar hemispheres as well as that of brain stem revealed diffuse, severe demyelination, involving also axis of cerebral gyri and U-fibres. Most severe demyelination in frontal and temporal lobes, practically lacking any traces myelin (Fig. 12). The same was typical for commissural formations and long nervous pathways. Some, weakly, stained myelin in the optic chiasma, striopallidal fasciculi and in medial and lateral lemnisci. Even though preserved myelin sheaths revealed severe changes in the form of swelling, fragmentation and granular breakdown, this was accompanied by severe damage of axis cylinders and in some areas by spongy degeneration of tissue.

No sudanophilic myelin breakdown products were present both in the areas completely devoid of myelin and those fields of white matter where an active demyelination process was occurring. Neither inflammatory nor macrophagic reaction was present. Diffuse fibroglial reaction in all demyelinated areas (Fig. 13). Cellular reaction to demyelination purely astrocytic. In areas lacking myelin number of astrocytes generally reduced (Fig. 14); the cells small, their nuclei regressively shrunken. In areas with recent active demyelination astrocytes more numerous with more abundant cytoplasm and large, pale nuclei. Oligodendrocyte population greatly reduced.

Histochemical test: Cytoplasm of astrocytes filled with PAS- and Sudan black B- positive substances (Figs. 15 and 16) which stained metachromatically red with acid cresyl-violet and pale bluish-green with alcian blue.

Ultrastructural study of needle-biopsy material from frontal cortex: marked rarefaction and destruction of intracellular spaces and presence

of great variety of cytoplasmic inclusions in neurons, glial cells and cellular elements of blood vessel walls.

Intracytoplasmic deposits exhibited a great ultrastructural variability depending on cell type. As a rule, they occurred in the greatest number in neurons, and were less numerous in glial cells. In nuclei of abnormal neurons diffusely rarefied chromatin. In majority of nerve cells the number of normal cellular organelles greatly reduced. Mitochondria scanty, their matrix pale and cristae severely damaged. Endoplasmic reticulum widened in same areas in saccular fashion. Scanty ribosomes irregularly dispersed throughout the cytoplasm with a tendency to abnormal compact grouping. Majority of swollen cortical neurons filled with numerous, round or oval membraneous cytoplasmic bodies (MCB), with typically circumferentially arranged layers of lamellar outer shells (Fig. 17). Less frequently they were arranged paralelly across the long axis of the bodies. Inner cores of MCB more pleomorphis, filled with fine granular or vesicular structures. None of these organelles appeared to have any limiting membrane around them. MCBs occurred also in nerve cell processes. Besides MCBs, in some neurons there occurred irregular, aggregations of membraneous structures varying a great deal in diameter and character. Sometimes they took the form of parallelly arranged membraneous formations lying free in the cytoplasm or surrounded on their full circumference or part of it by thick, electron--dense limiting membranes (Fig. 18). In part with no limiting membranes the fibrillary structures turned into amorphous material varying remarkably in its electron density. There occured also abnormal organelles composed of circumferentially arranged huge lamellar formations, with greatly distorted membrane arrangement turning into homogenous electron-dense material.

The abnormal cytoplasmic inclusions found in damaged glial cells were very pleomorphic and varied widely from those described in neurons. The lamellar membraneous structures of various arrangement, surrounded with a single membrane or lying free in the cell cytoplasm seemed to be the most common. In some instances inclusions with a circumferential arrangement of lamellae resembled most MCBs occurring in neurons. The spaces between lamellae in such types of inclusions were usually filled with electron dense, homogenous material or contained small vesicular formations. The common ultrastructural feature consisted of intracytoplasmic inclusions which were single membrane surrounded and contained numerous varying in diameter vesicular formations (Fig. 19). Some inclusion bodies were composed of short ele-

ctron-dense, membraneous conglomerates, similar in ultrastructural patter to those described in amyloid bodies (Fig. 20).

Numerous vacuoles with sharp, folded borders, some electron empty others containing homogenous light material were present in a great number of neurons and glial cells (Fig. 21). Majority of them seemed to correspond to empty spaces, from which unknown material had been dissolved by the preparation procedure. Their relation with the endoplasmic reticulum had to be also taken into consideration. The blood vessels showed distinct ultrastructural changes both in endothelial cells and pericytes: cytoplasm in many instances swollen with single-membrane limited inclusion bodies filled with varying number of small vesicles (Fig 22). Typical MCB's and MVB's were rather rare in this localization.

The biochemical study of brain tissue fixed in formalin for 5 months carried out by Wender and his colleagues, revealed a high increase of ganglioside content both in gray and white matter. Thin-layer chromatography of ganglioside fraction from gray matter showed an increase of G_{M1}-ganglioside corresponding to 67.1% of NANA and a less pronounced rise of G_{M2}-ganglioside equal to 14.9% of NANA (Table 1). Despite the known limitations in ganglioside analysis in formalin-fixed material (Piltz, et al. 1966), we consider our results as significant, because of the relatively short time of formalin fixation. Since full biochemical analysis has not been completed, we have to limit our information to the fact that the cerebrosides content in gray matter was 2.9% of dry tissue, while that of sulphatides was 1.8%; the same data for white matter were 11.5% and 4.0% respectively.

Table 1. Gray Matter — Distribution of NANA %
Tabela 1. Istota szara — Procentowy rozkład NANA

	G_o	G_{T1}	G_{D1b}	G_{D1a}	G_{M1}	G_{M2}	G_{M3}
Case presented	1.3	3.4	2.6	7.0	67.1	14.9	3.7
G_{M1} Gangliosidosis*)	1.1	1.1	7.0	12.5	73.7	2.3	2.3
Normal controls*)	3.6	15.9	16.7	42.5	18.5	2.3	< 1

*) After Suzuki et al. 1968

DISCUSSION

The clinical, pathological, ultrastructural and biochemical observations permitted in our case the diagnosis of generalized gangliosidosis — Landing disease, described under various names by many authors

(Craig, et al. 1959; Davison, Jacobson, 1936; Farkas-Bargeton, 1966; Landing, et al. 1964; Norman, et al. 1959), identified by Gonatas et al. (1965) and O'Brien et al. (1965) and further elaborated among others by Sacrez et al. (1967), Seringe et al. (1968), Suzuki et al. (1968 a, 1968 b, 1969), Hooft et al. (1969), Roels et al. (1970) and Wolfe et al. (1970).

From the clinical point of view our case represents this type of the disease in which severe neurological symptomatology is accompanied by visceral involvement, first of all of liver and spleen, and severe damage of the skeletal system (Suzuki, et al. 1969). An additional clinical manifestation of the disease, which has not been described in Landing's disease was craniolacunia and very severe deformation and asymmetry of the head. Megalencephaly, very striking in our case, has been already described in some cases of G_{M1}-gangliosidosis (Hooft, et al. 1969; Roels, et al. 1970). Enlargement of the head, configuration of the skull, dilatation of cranial sutures and position of the eyeballs could suggest on superficial examination a preliminary diagnosis of hydrocephaly. In contrast to several cases of Landing disease, such as those described by Landing et al. (1964), Sacrez et al. (1967), Seringe et al. (1968), Hooft et al. (1969), in our case no retinal abnormalities were present. In addition to typical clinical symptoms in our case a large subcutaneous angioma racemosum in frontal area was present. Vascular changes in the skin were previously described in Suzuki's case (1968 a) and that of Hooft et al. (1969).

The pathological picture of our case was in general similar to that described in other cases. However, some minor differences, concerning the histochemical properties of the substances stored in brain or viscera were noted. In contrast to Suzuki's (1968 b) observation — the substances accumulated in white matter astrocytes were very strongly PAS-positive and stained rather weak with Sudan black B. On the other hand, substances accumulated within the cytoplasm of the liver and spleen foamy cells were both PAS- and Sudan black B-positive. These staining properties indicate the presence of a lipid component in the substances accumulated; this is in contrast with the observations of Attal et al. (1967) and in some contradiction with Suzuki's (1969) opinion according to which the visceral changes are due first of all to accumulation of keratan sulphate and its derivates. More essential differences were found at the ultrastructural level.

They consisted in a considerable disintegration of nerve tissue, similar to that described by Nelson et al. (1962) in cases of diffuse sclerosis, and in a greater variability of ultrastructure of abnormal inclusion bodies, occurring both in neurons and in glial cells. Among these found

inclusion bodies with a content similar to that seen in amyloid bodies (Field, 1967) and numerous vacuoles, occurring in neurons and glial cells. In some cases they were the only abnormality seen in those cells. They may indicate a high solubility of some stored materials.

Our biochemical data, concerning the content of G_{M1} gangliosides in brain tissue fit well with the observations of other authors (Hooft, et al. 1969; Suzuki, et al. 1968 a, 1968 b; Wolfe, et al. 1970).

In the discussion of our case special attention should be called to the pathological changes in the white matter which took the form of severe and diffuse demyelination and tissue rarefaction accompanied by diffuse fibrogliosis of moderate intensity, and by a weak or totally absent astrocytic and microglial reaction. Most of the cellular population of white matter were scanty astrocytes, regressively changed.

This stands in striking contrast with the intensive cellular astrocytic reaction in the gray matter. In the white matter only some small areas with an active demyelinating process exhibited a small number of hypertrophied reactive astrocytes. However, in all areas of white matter an accumulation of PAS-, Sudan black B-, and alcian blue-positive substances within the astrocytic cytoplasm was seen. These substances stained red with acid cresyl violet. The number of oligodendrocytes was greatly reduced. The most striking feature was a complete lack of a microglial reaction. Granular compound cells were not seen in any areas of white matter, despite the enormous accumulation of free-lying granular products of myelin breakdown; these showed a strong affinity to iron haematoxylin and stained positively with Schiff's reagent and Sudan black B, giving a red metachromatic reaction with acid cresyl violet. The myelin changes were accompanied by severe degeneration of the axon cylinder, out of any proportion to the neuronal loss.

Varying in degree myelin disintegration forms a fundamental element of the pathological picture of G_{M1}-gangiosidosis (Attal, et al. 1967; Farkas-Bargeton, 1966; Hooft, et al. 1969; Suzuki, et al. 1968 a, 1968 b, 1969). Suzuki et al. (1969) on the evidence of their biochemical studies consider this myelin involvement as a secondary, nonspecific type of demyelination. However, at the same time they stress the fact of abnormal accumulation of G_{M1}-gangliosides in white matter tissues. A similar increase of gangliosides within white matter formations, even those which did not reveal any histological abnormalities has been shown by Edgar (1955) and Thieffry et al. (1960) in cases of Tay-Sachs disease. Myelin damage has been encountered in numerous cases of various storage diseases, such as Tay-Sachs disease (Berard-Badier, et al. 1968; Thieffry, et al. 1960), Niemann-Pick disease (Crocker, Farber, 1958), and glycogenosis (Bargeton, 1963). There is no univocal interpretation of

these findings. The presence of sudanophilic products of myelin breakdown in demyelinated areas in Tay-Sachs disease (Benda, Melchior, 1958; Berard-Badier, et al. 1958) suggest a normal secondary demyelination. A less univocal interpretation must be taken into consideration in cases of non-sudanophilic myelin breakdown products. Thieffry et al. (1960), Fardeau and Lapresle (1963), Bargeton (1963), Attal et al. (1967) consider that the pathological process, taking the form of neuronal storage involves also to the same extent myelin sheath. Therefore in their opinion demyelination forms an integral component of the fundamental pathological process. On the evidence of 3 cases of coexistence of cerebral gangliosidosis with metachromatic leucodystrophy. Mossakowski et al. (1961) assumed that a single, genetically caused metabolic defect might affect the normal pathways of several sphingolipids which are closely related to each other but located in different structural components of the brain. Further clinical, pathological and histochemical observations of Lüthy et al. (1966), confirmed by biochemical data of Pilz and Jatzkewitz (1968) seem to support this view.

The pathological changes in the white matter in the present case vary videly from those in other cases of G_{M1}-generalized gangliosidosis. Detailed biochemical analysis of the lipid content is not yet completed, thus limiting the possibility of precising univocally whether we are dealing with a very intensive leucodystrophic process in Landing's dissease or with the true coexistence of two separate processes — G_{M1}-generalized gangliosidosis and orthochromatic type of leucodystrophy. Such a possibility could be taken into consideration in view of our previous observations (Mossakowski, et al. 1961;) and those of Lüthy et al. (1966) and Pilz and Jatzkewitz (1968). The nature intensity and distribution of myelin changes and glial insuficiency in our present case are also very suggestive of such a nature of pathological process.

We are indebted to Prof. dr med. Maria Kobuszewska-Faryna in whose Department of Pathology, Postgradual Medical School, Warsaw, the necropsy was performed and to Prof. dr med. Mieczysław Wender in whose Department of Neurochemistry the biochemical study of the case was done.

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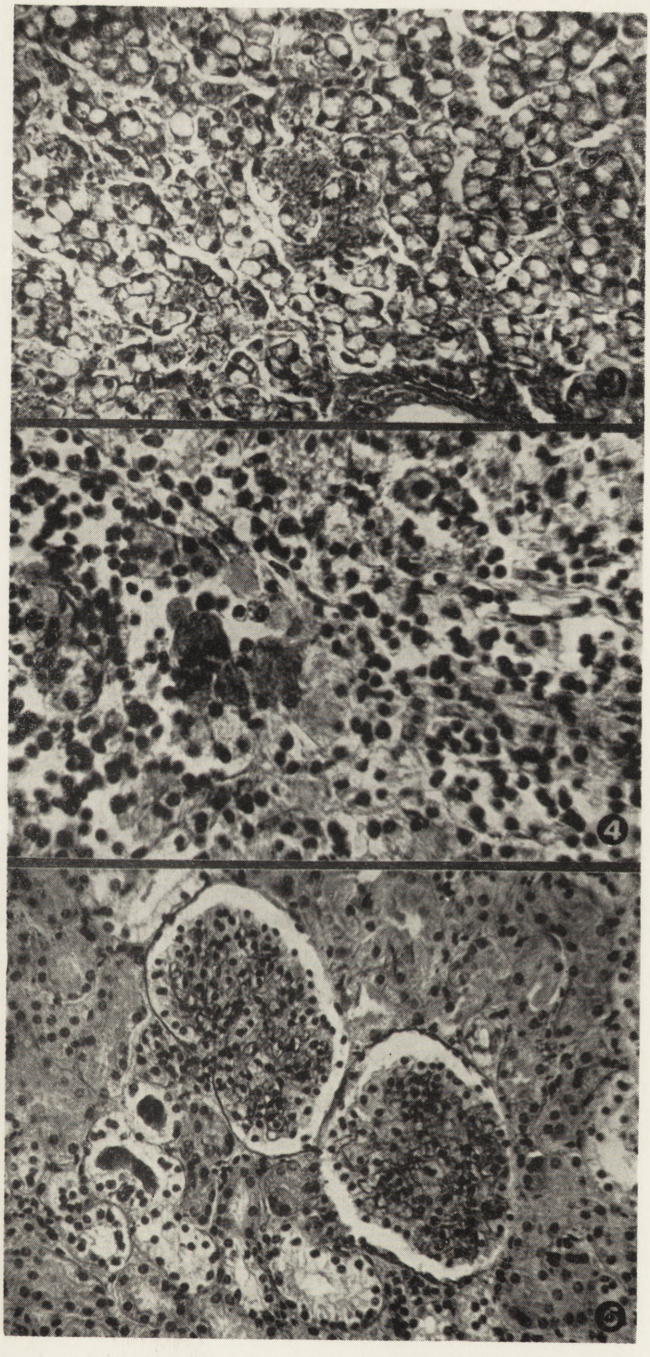
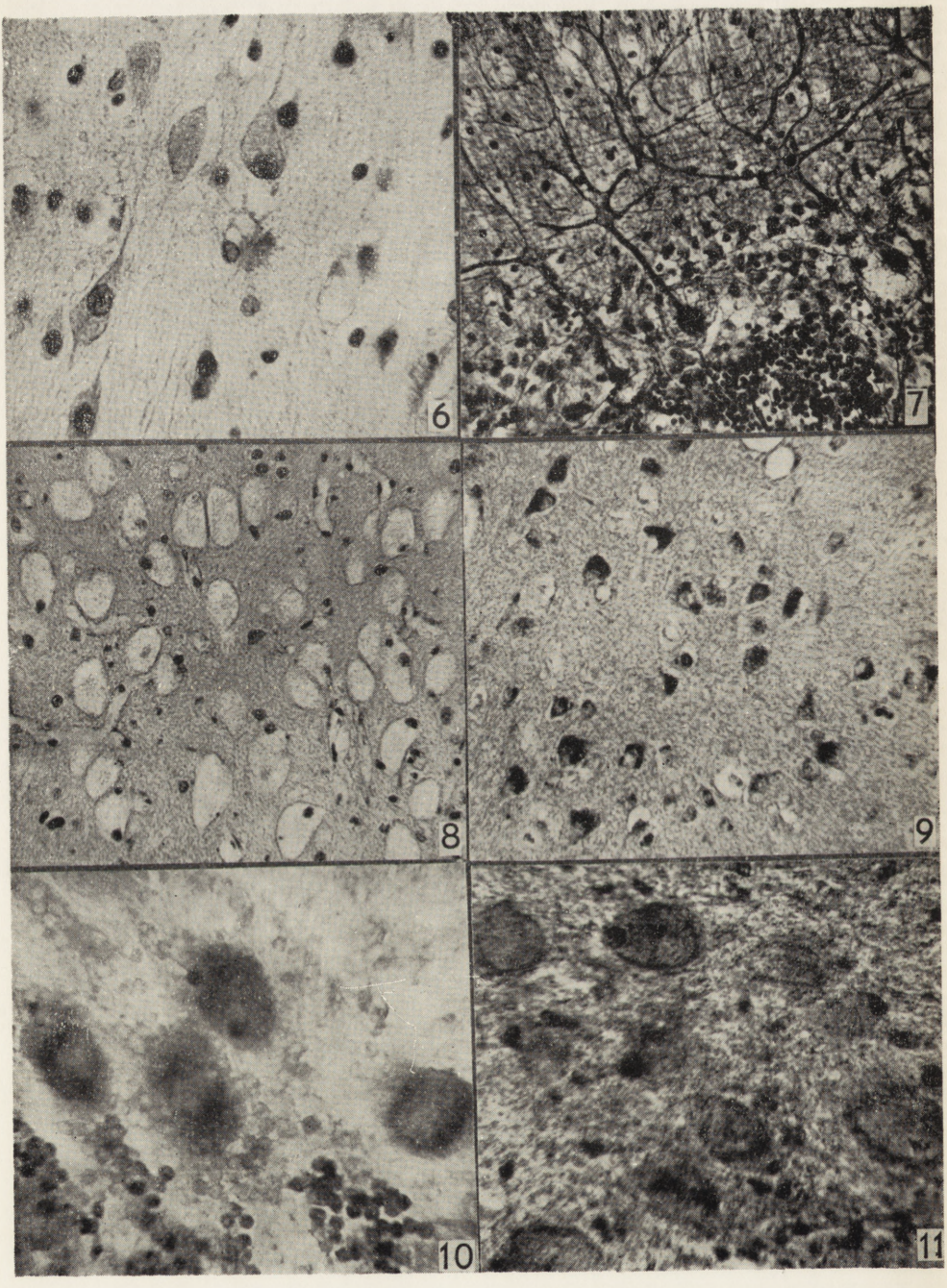
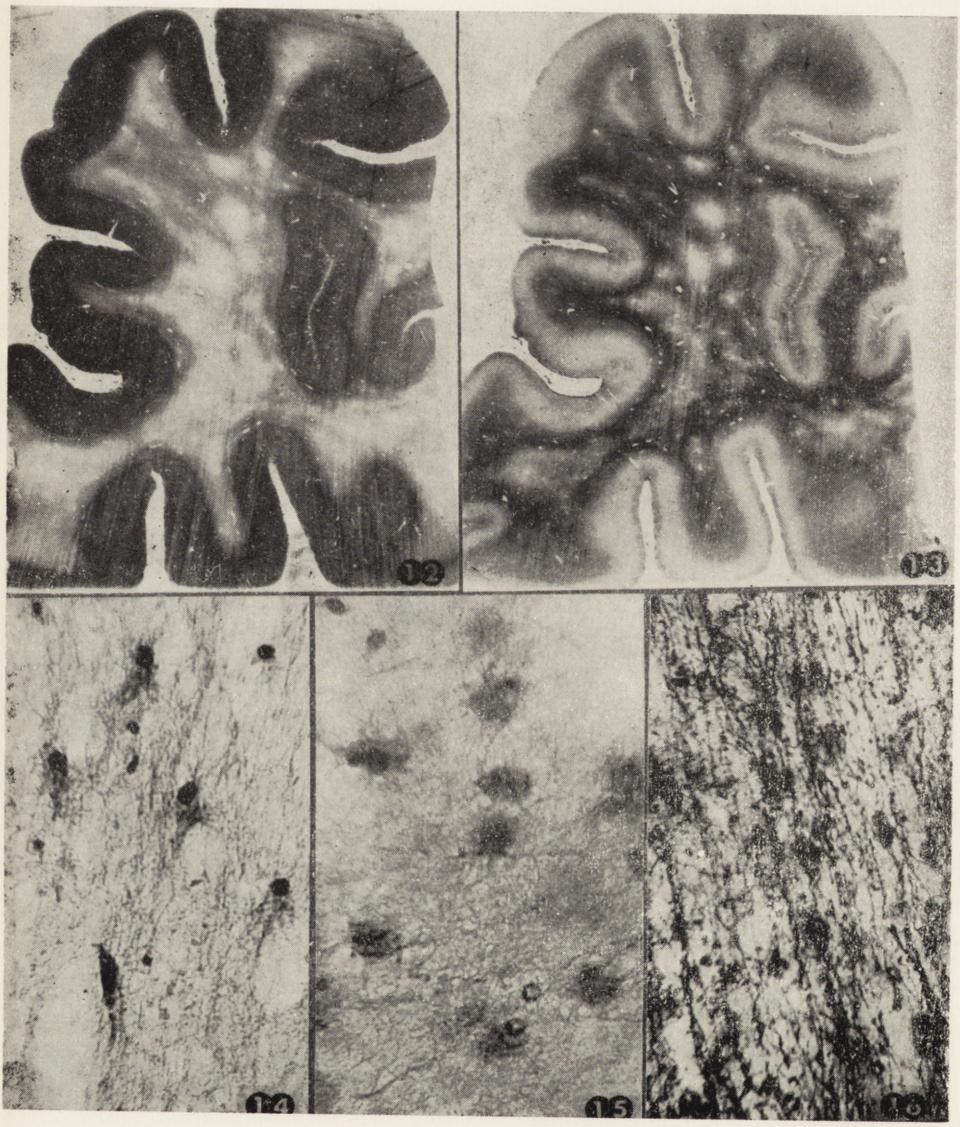
UOGÓLNIONA GANGLIOZYDOZA G_{M1} Z NIEZWYKŁYM ZAJĘCIEM ISTOTY BIAŁEJ

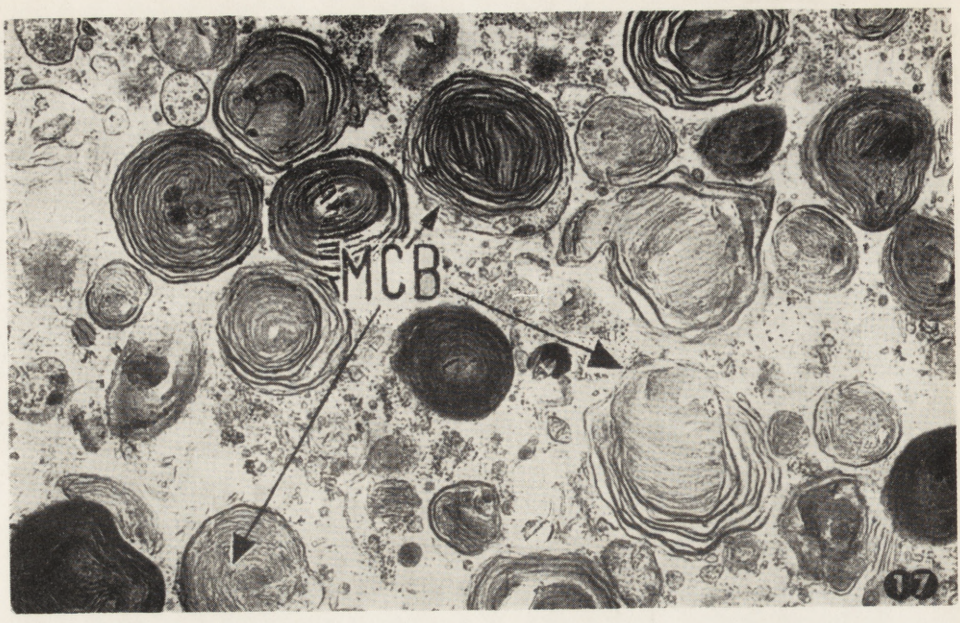
Streszczenie

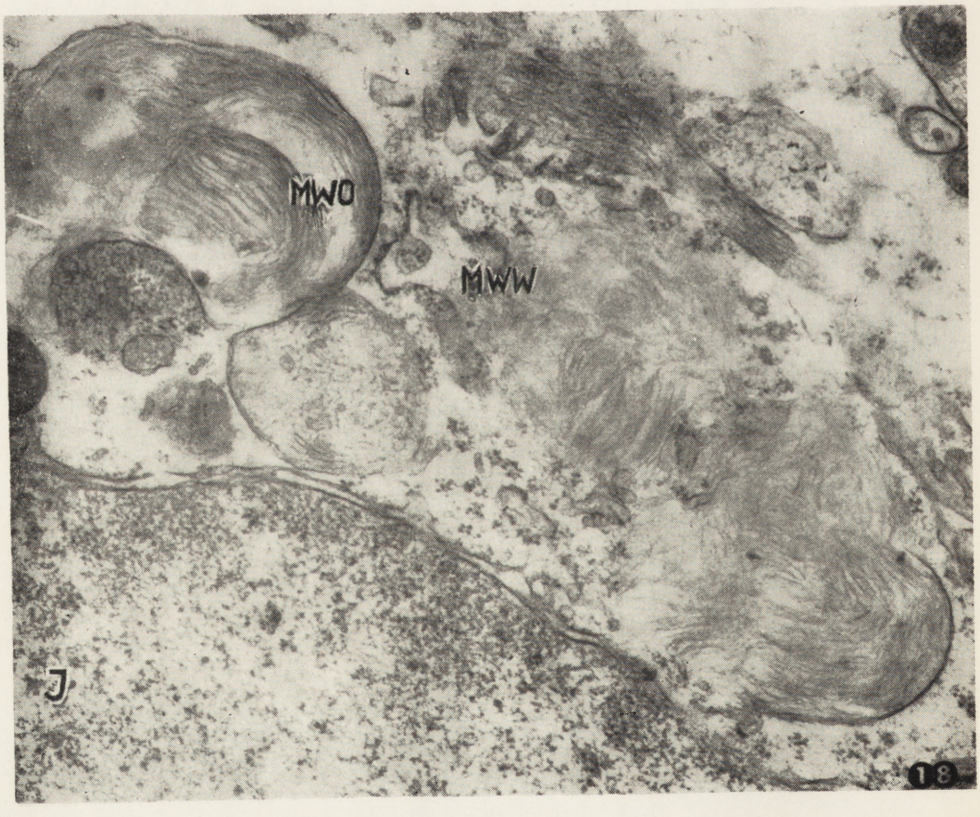
Przedstawiono opracowanie morfologiczne, histochemiczne i mikroskopowo-elektronowe przypadku dziecięcej uogólnionej gangliozydozy. Przypadek dotyczy chłopca, u którego choroba rozpoczęła się w 5 m-cu życia powiększaniem się obwodu

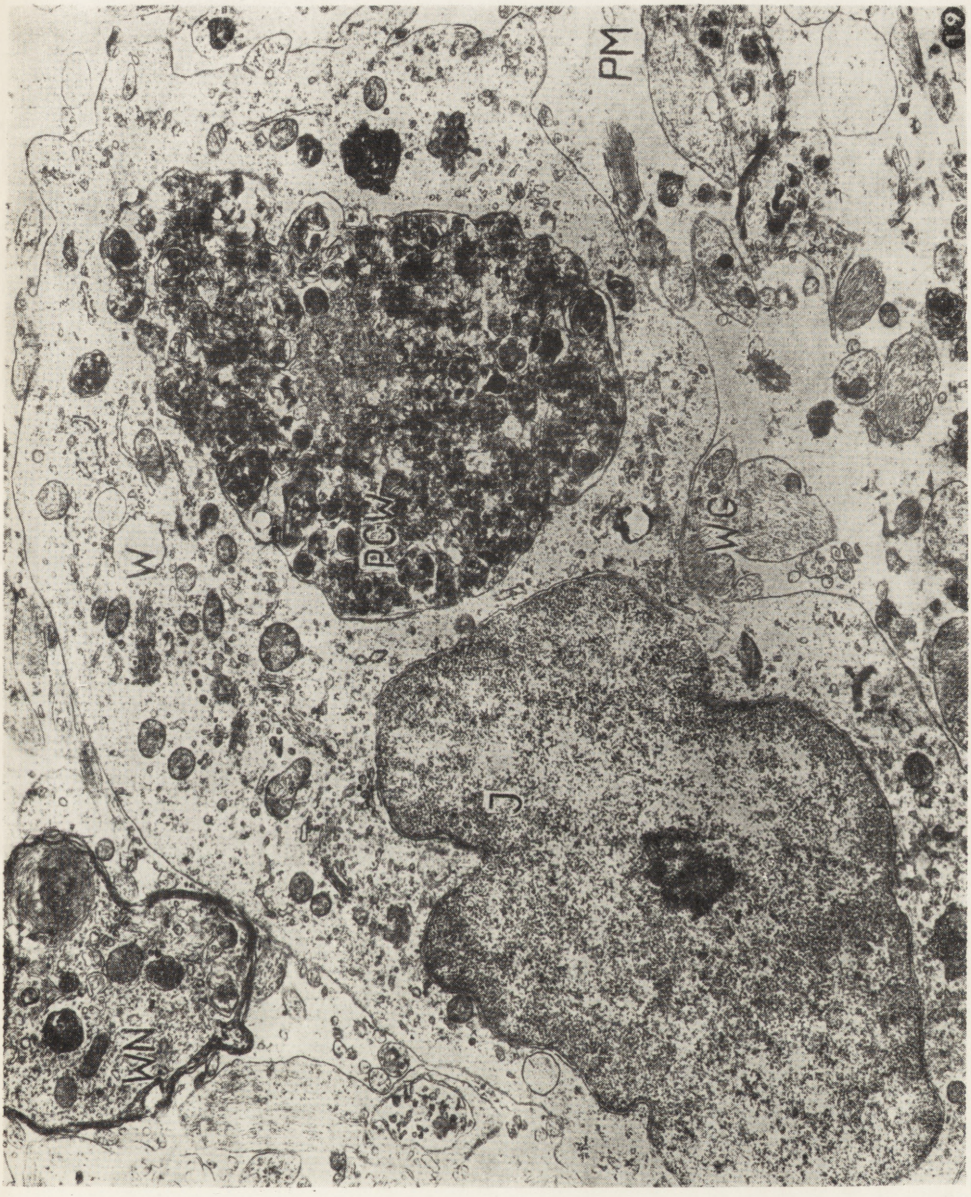


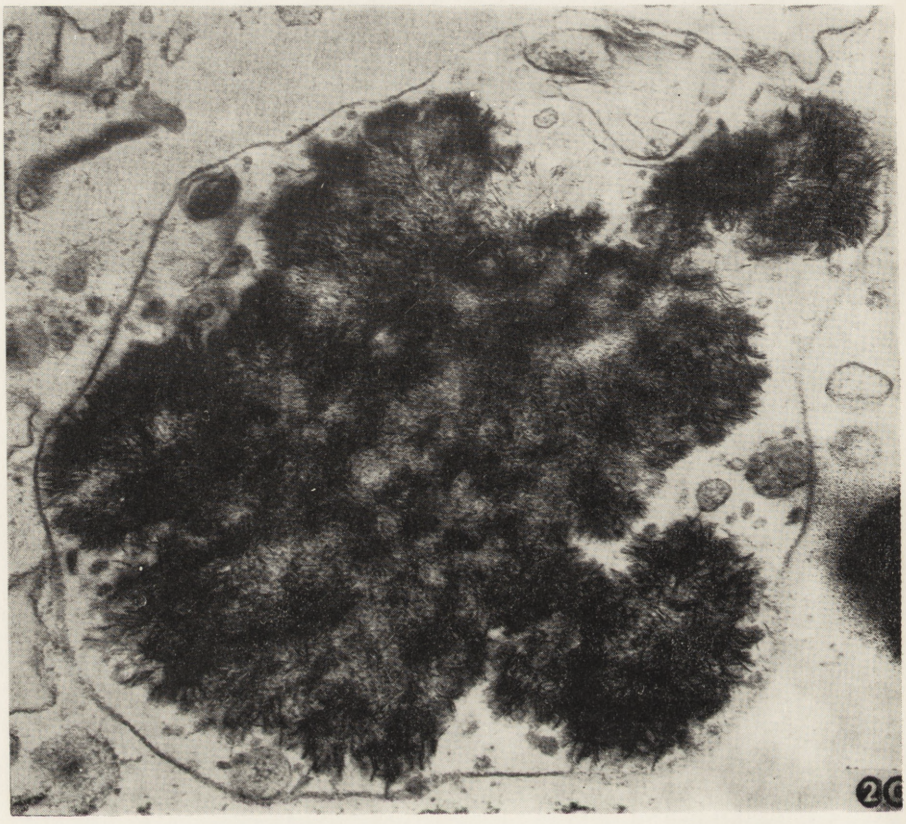


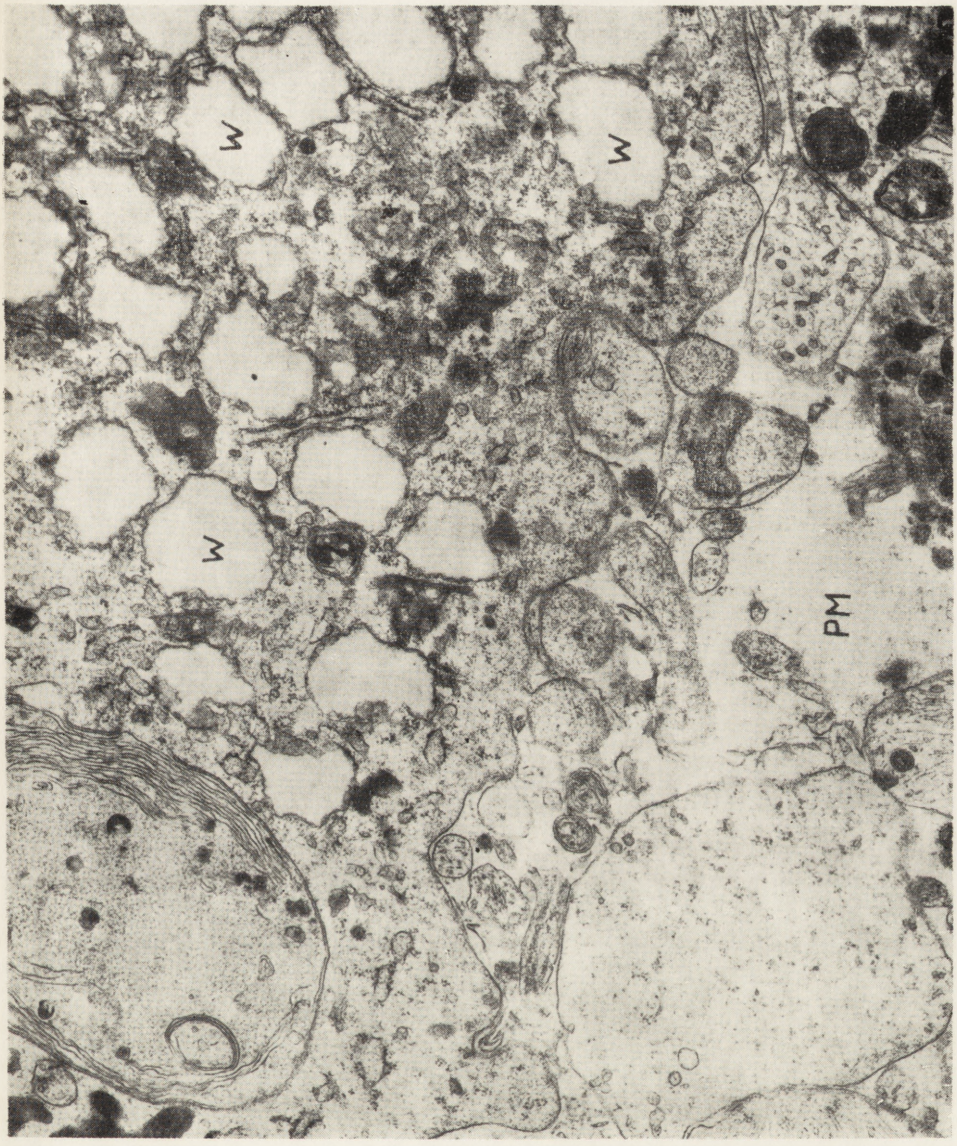


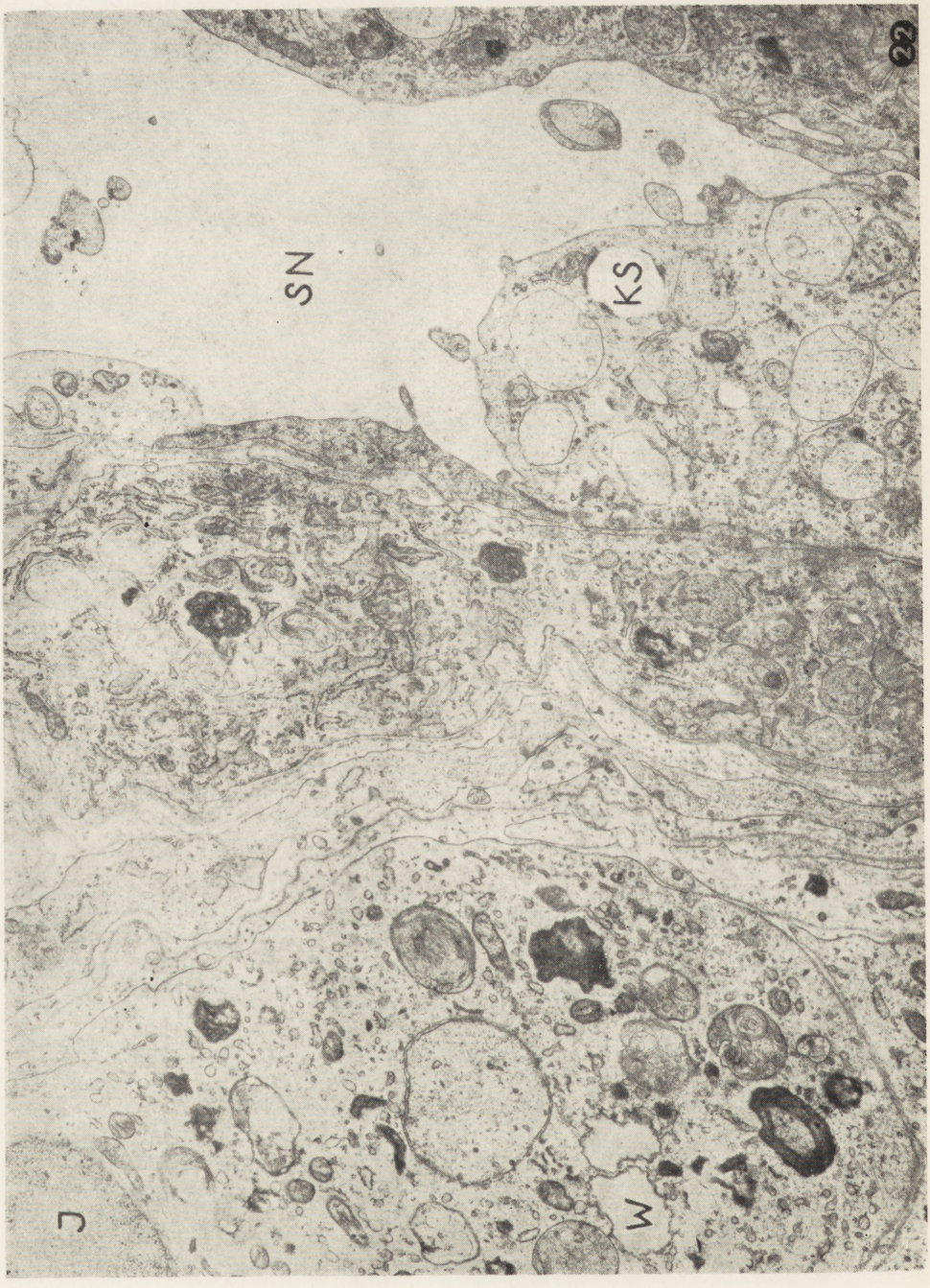












główki i postępującą regresją psychoruchową. Ponadto występowało znaczne powiększenie wątroby i śledziony, kraniolakunia oraz chondrodystroficzne zmiany w kościach długich i kręgosłupie. Dno oczu było normalne. W szpiku stwierdzono obecność komórek piankowatych i liczne zwakuolizowane limfocyty. Dziecko zmarło w 15 m-cu życia w stanie odmóżdżeniowym.

Badanie patologiczne wykazało: 1. uogólnione spichrzanie w neuronach wszystkich formacji szarych z gromadzeniem w komórkach nerwowych glikolipidu zidentyfikowanego jako gangliozyd, 2. rozlaną, symetryczną demielinizację istoty białej bez obecności sudanofilnych produktów rozpadu, ale z gromadzeniem glikolipidów w astrogleju, 3. spichrzanie w wątrobie, śledzionie i nerkach — zarówno w komórkach miąższowych jak i elementach układu siateczkowo-śródbłonkowego.

Badanie mikroskopowo-elektronowe biopsji mózgowej wykazało obecność polymorficznych inkluzji śródplazmatycznych w neuronach i gleju, z przewagą cytoplazmatycznych ciał błoniastych w neuronach. Badanie biochemiczne lipidów tkanki mózgowej wykazało wybitny wzrost G_{M1}-gangliozydu, typowy dla uogólnionej gangliozydozy. W oparciu o otrzymane wyniki autorzy poświęcają specjalną uwagę zmianom w istocie białej i dyskutują możliwość koegzystencji lipidozy z procesem leukodystroficznym.

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ОБОБЩЕННЫЙ ГАНГЛИОЗИДОЗ $Г_{M1}$ С НЕОБЫКНОВЕННЫМ ПОВРЕЖДЕНИЕМ БЕЛОГО ВЕЩЕСТВА

Резюме

Представлена морфологическая, гистохимическая и электронномикроскопическая разработка случая детского обобщенного ганглиозидоза. Случай касается мальчика, у которого болезнь началась в 5 месяце жизни увеличением периметра головки и прогрессирующей психо-моторической регрессией. Кроме того имело место значительное увеличение печени и селезенки, краниолакуния, а также хондродистрофические изменения в длинных костях и позвоночнике. Дно глаз было нормальным. В костном мозгу обнаружено наличие пенкообразных клеток и многочисленных вакуолизированных лимфоцитов. Ребенок умер в 15 месяце жизни в состоянии децеребрации.

Патологическое исследование обнаружило: 1. обобщенное скапливание в нейронах всех серых формаций с нагромаждением в нервных клетках гликолипида, идентифицированного как ганглиозид; 2. разлитую симметрическую и остро выраженную демиэлинизацию белого вещества без наличия суданофильных продуктов распада, но с нагромаждением гликолипидов в астроглии; 3. скапливание в печени, селезенке и почках как в паренхимных клетках, так и в элементах ретикуло-эндотельяльной системы.

Электронно-микроскопическое исследование мозговой биопсии обнаружило наличие полиморфических внутриплазматических включений в нейронах и в глии с проимуществом цитоплазматических мембранных образований в нейронах. Биохимическое исследование липидов мозговой ткани обнаружило резкий рост G_{M1}-ганглиозида, типичный для обобщенного ганглиозидоза. На основании полученных результатов авторы посвящают особенное внимание изменениям в белом веществе и обсуждают возможность сосуществования липидоза с лейкодистрофическим процессом.

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