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THE PROBLEM OF COEXISTENCE OF NEURONAL LIPID STORAGE DISEASES AND VARIOUS FORMS OF LEUCODYSTROPHIES

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The sharp delimitation between leucodystrophies, characterized by primary degeneration of myelin sheath and neurolipidoses in which storage of lipid substances in the ganglion cells is the fundamental feature, has been gradually obliterated in view of the new, mostly biochemical observations.

In the early fifties of this century it was noticed that one of the typical feature of the pathological picture in metachromatic leucodystrophy was cellular deposition of abnormal glycolipids in certain neuronal groups.

Later biochemical studies mostly those of Austin (1960, 1967), Jatzkewitz (1960), Sourander and Svennerholm (1962) and others proved that metachromatic leucodystrophy fulfills all cryteria of neurolipidosis. The same being true for Krabbe's leucodystrophy.

On the other hand damage to the myelin sheath varying in degree and character is a common feature in the morphological picture of those diseases in which neuronal storage of lipids, lipoproteins or even polysaccharides is an essential process.

Severe and extensive white matter damage was described in cases of Tay-Sachs disease (Ostertag 1925, Bérard-Badier et al. 1958, Thieffry et al. 1960, Fardeau and Lapresle 1963), Niemann-Pick disease (Crocker and Farber 1958), glycogenosis, (Bargeton 1963) and generalized gangliosidosis (Farkas-Bargeton 1966, Attal et al. 1967, Suzuki et al. 1968a, Hooft et al. 1969).

These changes were sometimes accompanied by deposition of abnormal amounts of lipids characteristic for fundamental metabolic disorder. Suzuki et al. (1968a, 1968b, 1969) for instance found in generalized gangliosidosis increased amount of G_{M1}-ganglioside; Thieffry et al. (1960), Nor-

man et al. (1964) in cases of infantile amaurotic idiocy an increase of G_{M2}-ganglioside both in damaged and morphologically unchanged white matter.

Interpretation of myelin damage in those cases is not univocal. The presence of myelin breakdown products in demyelinated areas in Tay-Sachs disease as observed in the cases of Bérard-Badier et al. (1958) or Benda and Melchior (1958) suggests secondary degeneration.

But more controversial are cases in which sudanophilic myelin breakdown products were not observed. Suzuki et al. (1969) consider these changes in generalized gangliosidosis as ordinary secondary degeneration despite of biochemically stated increase of G_{M1}-ganglioside in the white matter.

Thieffry et al. (1960), Fardeau and Lapresle (1963), Bargeton (1963), Attal et al. (1967) consider that the pathologic process taking the form of neuronal storage disease involves to some extent myelin sheath. Thus, in their opinion, demyelination constitutes an integral component of the fundamental pathological process.

Certainly one must take into consideration the delay in the myelination process, especially in cases in which normal or abnormal myelin breakdown products are lacking.

There exist however sporadical cases, in which the character, intensity and topography of white matter damage suggest either the existence of equiponderant leucodystrophic component in the primarily neuronal storage disease or coexistence of two different processes affecting various structures of the central nervous system.

A series of such cases was described by one of us with Mathieson and Cumings (1961).

There were three sibs coming from a sibship of five in the family. Their parents were healthy and not consanguineous. All three children were delivered normally folloving a fullterm, uncomplicated pregnancy and all developed normally until the age of 15—24 months. At that time in each of them neurological disorder became apparent; this was characterized by arrest and progressive retreat of somatic and mental ability, blindness, deafness, muscular rigidity and terminal marantic state. Death occurred after 11, 20 and 45 months of illness at the age of 3.5 and 5 years.

Histopathological examination of the brain revealed in all cases two fundamental features — one was generalized neuronal storage process in all gray formations (Fig. 1), the second — profuse, severe demyelination of the cerebral and cerebellar white matter. The PAS-, Sudan black B-, Alcian blue- and Bial-positive reactions permitted identification of the stored substance as glycolipids, probably gangliosides. These

substances shoved striking beta-metachromasia when stained by Feyrter's method, but only in some neuronal groups brown metachromasia in acid cresyl violet staining was noted.

Abundant myelin breakdown products lying free in demyelinated white matter or accumulated within numerous macrophages (Fig. 2) were also PAS- and Sudan black B-positive, but they gave strong brown metachromasia in Hirsch-Peiffer staining (Fig. 3).

Biochemical analysis of lipids content in the brains of two autopsied cases revealed an increase of hexosamine both in gray and white matter, particulary noticeable in one case and fourfold increase of sulphatides in the white matter.

We considered these cases as an example of coincidence of two neurolipidoses, namely family amaurotic idiocy of late infantile type and metachromatic leucodystrophy. On the evidence of our observations we suggested that a single genetically induced factor might affect the normal pathways of several sphingolipids, closely related to each other, but located differently with regard to the structural components of the brain.

In later years Lüthy et al (1966) published a case similar to ours in its clinical, pathological and histochemical aspects. Biochemical analysis of the brain lipids carried out by Pilz and Jatzkewitz (1968) revealed an increase of sulphatides accompanied by reduction of galactocerebrosides in the white matter and raised amount of gangliosides in the gray one. Pilz and Jatzkewitz consider that the only adequate explanation of this findings might be the simultaneous defect of two different enzymes concerning the metabolism of sphingolipids.

Recently we examined another case in which the white matter damage suggest the existence of leucodystrophic component in the neuronal storage process, although in concerned different type of neurolipidosis and leucodystrophy (Mossakowski et al. 1971).

This case was a boy delivered after uncomplicated pregnancy and developing normally until 5th months of age. At that time progressive enlargement of the head accompanied by arrest and deterioration of physical and mental ability developed. The boy died in the decerebrate state at the age of 13 months after 8 months of steadily progressing neurological illness. In addition to neurological disorders, remarkable enlargement of liver and spleen, extensive craniolacunia, chondrodystrophic changes of lumbar spine and lumbar kyphosis were noticed.

Histological examination of body organs disclosed severe vacuolation of hepatocytes and presence of foamy cells filled with glycolipids, in liver and spleen; swelling and vacuolation of endothelial cells of renal glomeruli with widening of subcapsular space.

Histopathological examination of the brain revealed a generalized neuronal storage process (Fig. 4) accompanied by adequate glial reaction, and severe and widespread demyelination of cerebral and cerebellar white matter (Fig. 5).

The histochemical properties of the stored substances premitted to identify them as gangliosides. The myelin breakdown products in the white matter stained positively with iron hematoxylin, were PAS- and Sudan blakc B-positive and gave beta-metachromasia in Feyrter's and Hirsch-Peiffer staining. These reaction were also positive in the scanty astrocytes of actively demyelinating white matter (Fig. 6). The poverty of glia reaction to demyelination was striking. Fibrogliosis was moderate, a number of oligodendrocytes and astrocytes was reduced. There were no compound granular cells. Scanty astrocytes showed evident regressive changes (Fig. 7).

Electron microscopic examination of brain biopsy revealed considerable amount of abnormal inclusion bodies in the cytoplasm of neurons (Fig. 8), glia (Fig. 9) and cellular elements of vascular walls.

In neuronal cytoplasm typical and atypical membranous cytoplasmic bodies (Fig. 8) and huge aggregations of membranous structures varying a great deal in diameter prevailed. The latter being entirely or partially surrounded by an electron dense single membrane. The abnormal cytoplasm organelles in damaged glia were also pleomorphic (Fig. 9) and varied widely from those observed in neurons. Atypical membranous cytoplasmic bodies and typical membrane-vesicular bodies were very common. Besides, lamellar membranous structures of various arrangement, totally or partially bounded by a single limiting membrane and inclusions showing properties of amyloid bodies were present. In many neurons, glial and endothelial cells light vacuoles with sharp, folded borders were observed.

Biochemical analysis of brain tissue revealed a high increase of gangliosides both in gray and white matter. TLC of gangliosides fraction showed increase of G_{M1}-ganglioside corresponding to 67.1% of NANA and rise of G_{M2}-ganglioside equal to 14.7% of NANA. Cerebrosides content in gray matter was 2.9% of dry tissue weight, while that of sulphatides was 1.8%. The corresponding data for white matter were 11.5% and 4.0% respectively.

The above mentioned results led in our case to diagnosis of generalized gangliosidosis.

The white matter changes, exceeding those in usual cases of Landing's disease, peculiar insufficiency of astroglia and differences in EM-picture indicate a remarkable leucodystrohic component in the primary neuronal storage process. These peculiarities permitt in our opinion even the

assumption of coexistence of generalized G_{M1}-gangliosidosis with an ortochromatic type of leucodystrophy.

We would like to add to the group of cases presented one more case of neurolipidosis, observed recently by Dąmbska et al. (1970) although the leucodystrophic nature of the process involving the white matter is up till now a matter of discussion and controversion.

The case concerned a boy of Polish-Jewish provenience, who was the first child of young, healthy and nonconsanguineous parents. At the age of three months in the apparently normally developing child progressive enlargement of head and liver was noticed. In later months severe neurological illness developed which was characterized at the beginning by apathy and inability to control his head and then by feature of motor and mental development, blindness, epileptic fits, involuntary movements and generalized spasticity. Optic atrophy, chondrodystrophic changes in lumbar spine and generalized skin edema completed the clinical picture. The child died at the age of 16 months in marantic state. The histopathological findings in liver, spleen and kidneys were identical with those described in the previous case.

The brain weighed 1300 g. On the coronal sections the white matter of cerebral and cerebellar hemisphere was gray, soft and honeycomb in appearance.

Neuropathological examination revealed a generalized storage process (Fig. 10), this was accompanied by considerable neuronal loss and tremendous gemistocytic reaction in the cerebral cortex. The substances accumulated in neuronal cytoplasm were histochemically identical with those observed in previous case.

The white matter of brain (Fig. 11) and cerebellum was the most stricking feature; this resulted in some areas in cavitation of large fields of centrum semiovale. In less involved areas the prevalence of spongiosis in subcortical white matter was obvious (Fig. 12). Spongy changes involves also gray matter, especially in deep cortical layers and to a lesser degree cerebellar cortex. Cellular astrocytic reaction in white matter was very poor, so was fibrogliosis. Oligodendrocytes seemed to be unchanged in number and appearance. In cerebral cortex among the rich gemistocytic population numerous pale, large astrocytic nuclei, similar to those described as Alzheimer cells, type II were present. The same cells were seen in great number in basal nuclei and pons (Figs 13, 14). They were less common in the white matter.

On the evidence of histopathological and histochemical analysis we feel authorized to diagnose Landings disease, despite the fact that brain lipid analysis has not yet been performed.

The character of white matter changes, generalized spongiosis and peculiar glial abnormalities suggest spongy degeneration of neuraxis in infancy described originally by van Bogaert and Bertrand (1949).

The modifications of the pathological picture in our case as compared with typical cases of both diseases seem to be due to interference of two different pathological processes.

Our three first cases together with that of Lüthy et al. (1966) indicate the possibility of coexistence of two different neurolipidoses due to two different enzymatic blocks in the same case.

The fourth case is more suggestive of neurolipidosis with very intensive leucodystrophic component, but the coexistence of neurolipidosis with a leucodystrophy can not be difinitively excluded.

The last case of our series showed a possibility of coexistence of neurolipidosis with other degenerative process of the central nervous system, the leucodystrophic nature of which is still uncertain (van Bogaert, Bertrand 1967; Adachi, Aronson 1967).

The genetically induced metabolic errors underlie all of the processes discussed. Therefore it seems to be justified to assume that various pathological disorders of this nature can occur simultaneously as the result of combined genetic defect.

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ZAGADNIENIE WSPÓŁISTNIENIA NEUROLIPIDOZ Z RÓŻNYMI POSTACIAMI LEUKODYSTROFII

Streszczenie

Ostre rozgraniczenie pomiędzy grupą neurolipidoz i leukodystrofii uległo w ostatnich latach zatarciu. Przyczyniły się do tego w dużej mierze wyniki badań biochemicznych, które wykazały zaburzenia składu i ilości lipidów w strukturach nie objętych przez podstawowy proces patologiczny.

Uszkodzenie istoty białej w neurolipidozach, szczególnie w dziecięcych gangliozydozach, należy prawie do reguły, jednak patomechanizm tych zmian wciąż nie jest ostatecznie wyjaśniony. Opierając się na własnym przebadanym materiale (rodzinny przypadek leukodystrofii metachromatycznej z późnodziecięcą postacią *idiotia amaurotica*, przypadek gangliozydozy G_{M1} ze zmianami w istocie białej, sugerującymi współistniejący proces leukodystroficzny, oraz przypadek G_{M1}-gangliozydozy z gąbczastym zwyrodnieniem istoty białej), autorzy dyskutują możliwość współistnienia dwóch różnych typów procesów uwarunkowanych genetycznie: występowania podwójnego bloku metabolicznego i skojarzenia neurolipidozy z innym procesem zwyrodnieniowym.

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ВОПРОС СОСУЩЕСТВОВАНИЯ НЕЙРОЛИПИДОЗОВ С РАЗНЫМИ ВИДАМИ ЛЕЙКОДИСТРОФИИ

Резюме

Острое разграничение между группой нейролипидозов и лейкодистрофией за последние годы стерлось. Это было вызвано, главным образом, результатами биохимических исследований, которые обнаружили нарушение состава и количества липидов в структурах, не охваченных основным патологическим процессом.

Повреждение белого вещества в нейролипидозах, особенно в детских ганглиозидозах, выступает как правило, однако патомеханизм этих изменени все еще окончательно не выяснен. Опираясь на исследованном собственном материале (семейный случай метахроматической лейкодистрофии с поздне-детской формой idiotia amaurotica, случай ганглиозидоза G_{M_1} с изменениями в белом веществе, что позволяло полагать сосуществующий лейкодистрофический процесс, и случай G_{M_1} — ганглиозидоза с губчастой дегенерацией белого вещества) авторы обсуждают возможность сосуществования двух разных типов процессов, генетически обусловленных: наличие двойной метаболической блокады и сопряжение нейролипидоза с другим дегенерационным процессом.

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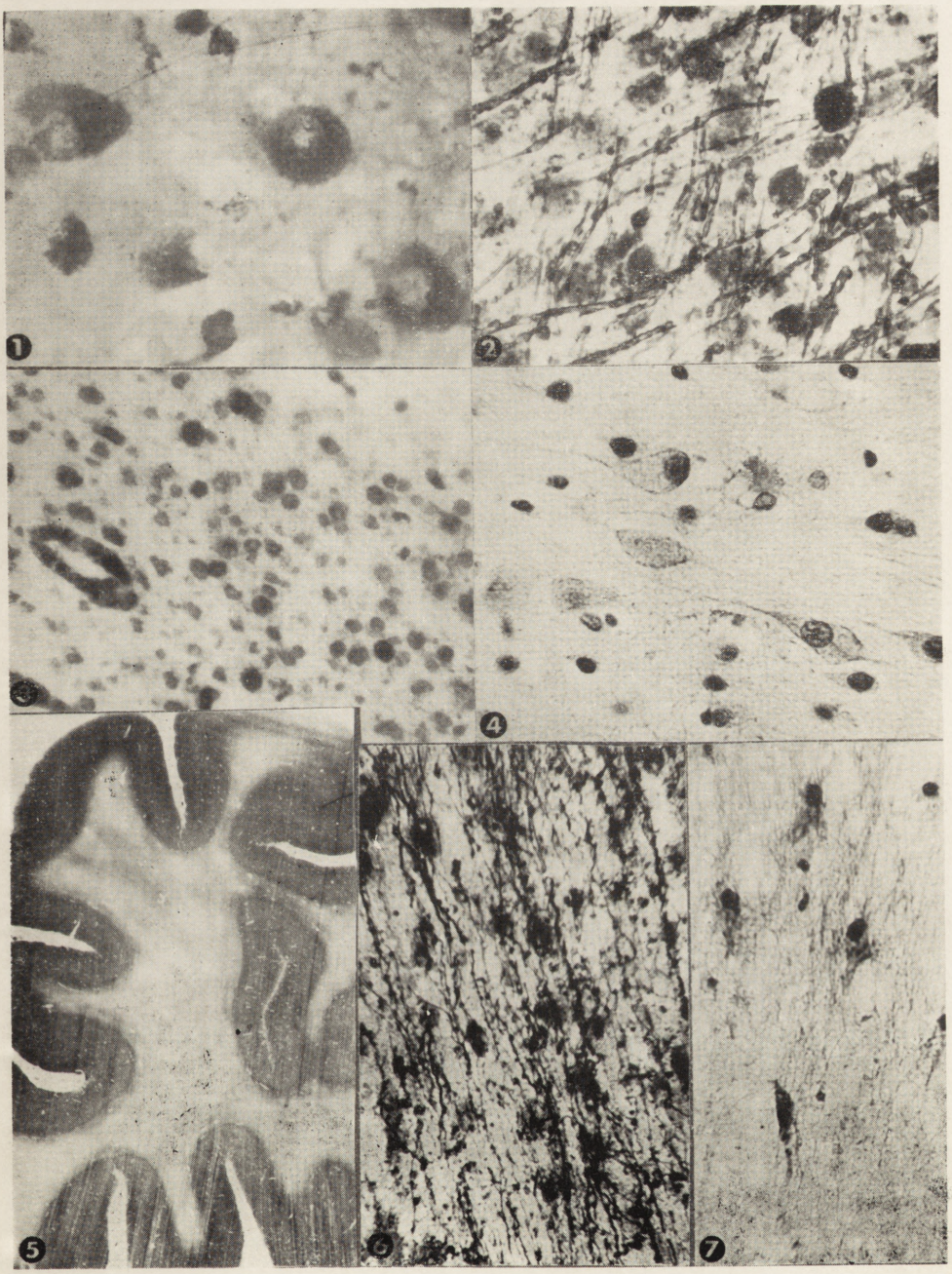

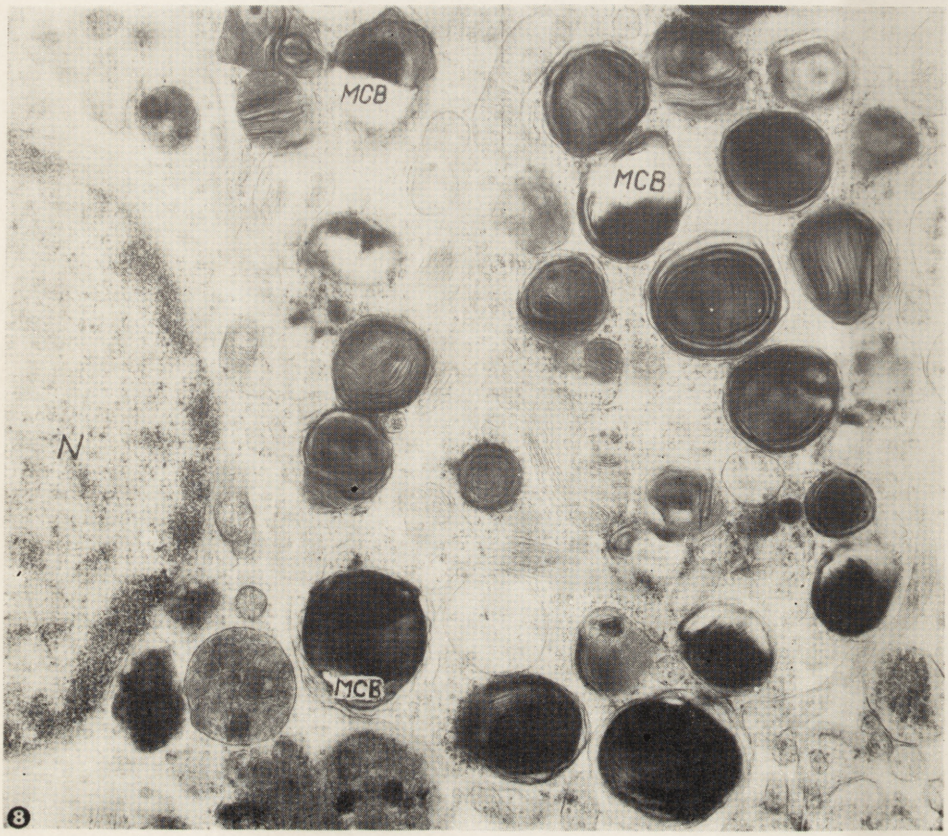

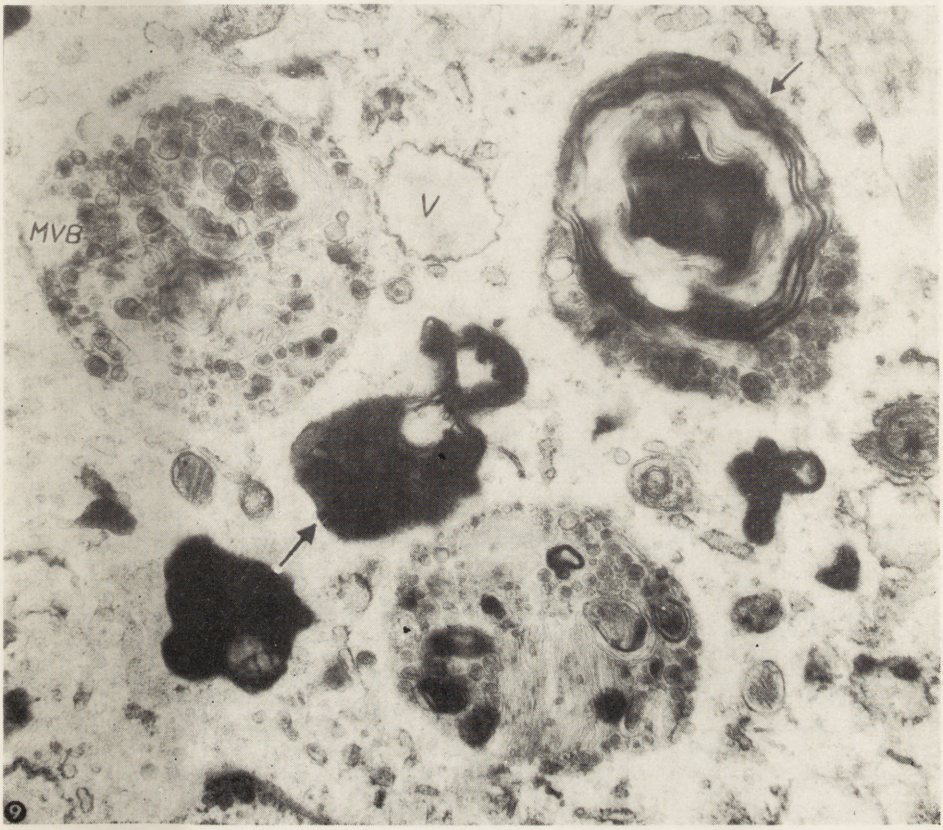

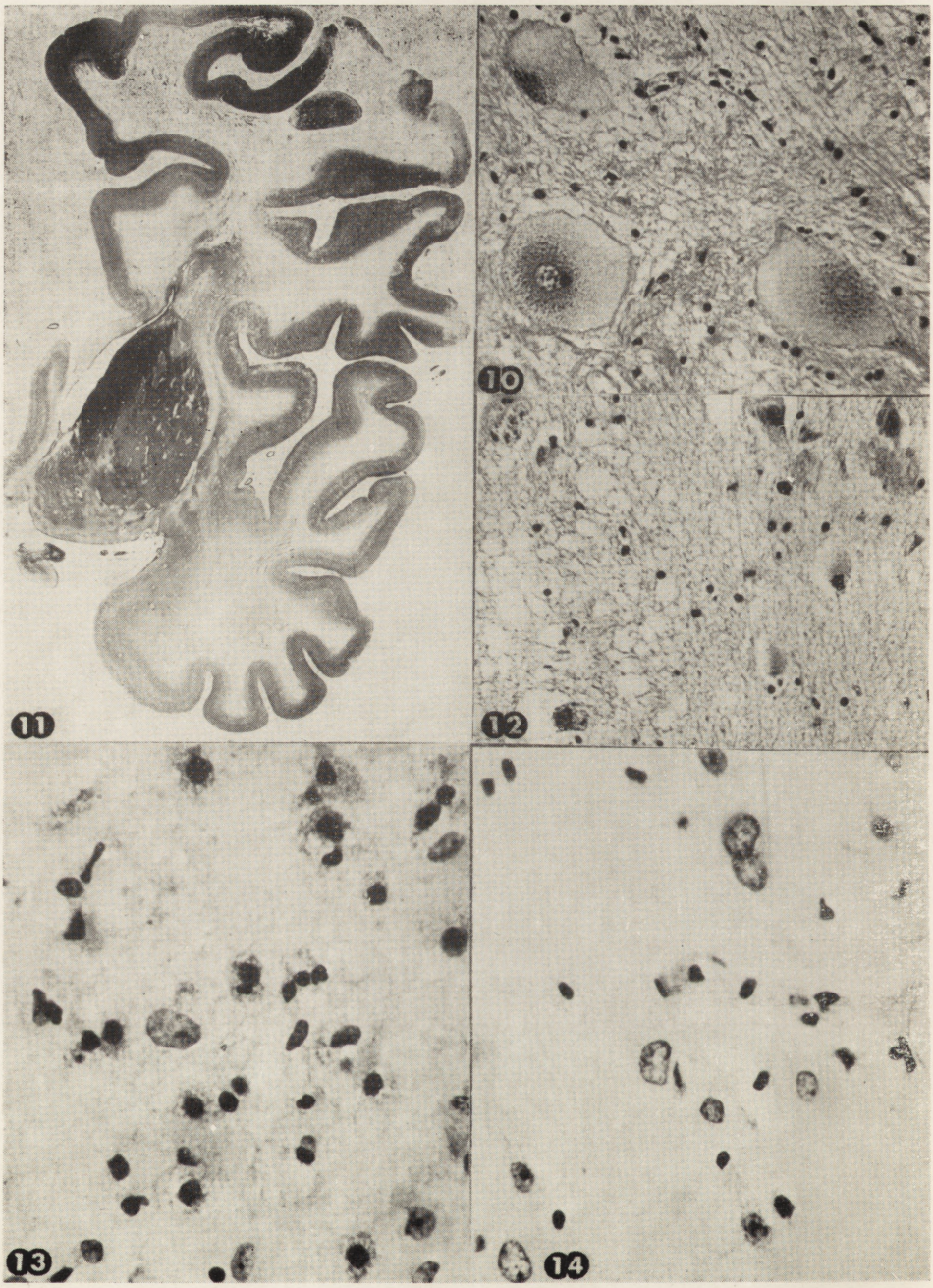

LEGENDS OF FIGURES

Fig. 1. Case 2. Frontal cortex showing lipid accumulation in neuronal cytoplasm. Frozen section. Sudan black B. × 400.

Ryc. 1. Przypadek 2. Kora czołowa. Złogi lipidowe w cytoplazmie neuronów. Skrawek mrożony, Sudan czarny B. Pow. 400 ×.

Fig. 2. Case 3. White matter showing myelin damage and lipid containing macrophages. Paraffin. Sudan black B. × 200.

Ryc. 2. Przypadek 3. Uszkodzenie mieliny w istocie białej. Widoczne liczne makrofagi zawierające złogi lipidowe. Parafina, Sudan czarny B. Pow. 200 ×.

Fig. 3. Case 2. Frontal lobe. The white matter contains numerous macrophages with brown metachromatic material. Frozen section. Acid cresyl. × 130.

Ryc. 3. Przypadek 2. Płat czołowy. W istocie białej widoczne liczne makrofagi barwiące się metachromatycznie brązowo. Skrawek mrożony. Kwaśny fiolet krezylu. Pow. 130 ×.

Fig. 4. Case 4. Neuronal storage process in frontal cortex. Paraffin. Cresyl violet. × 400.

Ryc. 4. Przypadek 4. Spichrzające neurony w korze czołowej. Parafina, fiolet krezylu. Pow. 400 ×.

Fig. 5. Case 4. Frontal lobe. White matter completely devoid of myelin. Paraffin. Heidenhain. Magn. glass.

Ryc. 5. Przypadek 4. Istota biała płata czołowego całkowicie pozbawiona mieliny. Parafina. Heidenhain. Pow. lupowe.

Fig. 6. Case 4. White matter of centrum semiovale with residual myelin sheaths and lipid containing astrocytes. Frozen section. Sudan black B. × 400.

Ryc. 6. Przypadek 4. Istota biała *centrum semiovale*. Widoczne zachowane włókna mielinowe i astrocyty zawierające złogi lipidowe. Skrawek mrożony, Sudan czarny B. Pow. 400 ×.

Fig. 7. Case 4. Frontal lobe. Regressively changed astrocytes in demyelinated white mater. Paraffin. H—E. × 400.

Ryc. 7. Przypadek 4. Zmiany wsteczne astrocytów w zdemielinizowanej istocie białej płata czołowego. Parafina, H—E. Pow. 400 ×.

Fig. 8. Case 4. Electron micrograph of cerebral cortex. Cytoplasm of the nerven cell contains characteristic membranous cytoplasmic bodies *(MCB)*. × 20 800.

Ryc. 8. Przypadek 4. Komórka nerwowa zawierająca liczne cytoplazmatyczne ciała błoniaste *(MCB)*. Pow. 20.800 ×.

Fig. 9. Case 5. Electron micrograph. Glia cell with pleomorphic inclusion bodies (arrows). *MVB* — microvesicular body; *V* — vacuole × 21 700.

Ryc. 9. Przypadek 5. Komórka glejowa z polimorficznymi ciałami wtrętowymi (strzałki). *MVB* — ciała wielopęcherzykowe; *V* — wodniczka. Pow. 21.700 ×.

Fig. 10. Case 5. Neurons of brain stem showing distended, finely granular cytoplasm. Paraffin. H—E. × 400.

Ryc. 10. Przypadek 5. Neurony pnia z rozdętą, drobnoziarnistą cytoplazmą. Parafina, H—E. Pow. 400 ×.

Fig. 11. White matter completely devoid of myelin fibers. Spongiosis and cavitation in frontal and temporal lobe is seen. Normal size.

Ryc. 11. Przypadek 5. Demielinizacja w istocie białej. W płacie czołowym i skroniowym widoczne zgąbczenie tkanki i zmiany jamiste. Parafina, H—E. Wielkość naturalna.

Fig. 12. Case 5. Spongiosis in the subcortical white matter. Paraffin. H—E. × 200.

Ryc. 12. Przypadek 5. Zmiany gąbczaste na pograniczu kory i istoty białej. Parafina, H—E. Pow. 200 ×.

Fig. 13. Case 5. Glia changes in the globus pallidus. Paraffin. Cresyl violet. × 400.

Ryc. 13. Przypadek 5. Uszkodzenie gleju w gałce bladej. Parafina, fiolet krezylu. Pow. 400 ×.

Fig. 14. Case 5. Glial cells of Alzheimer, type II are present in the pons. Paraffin. H—E. × 400.

Ryc. 14. Przypadek 5. Komórki glejowe typu Alzheimera II w moście. Parafina, H—E. 400 ×.