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MORPHOLOGY AND HISTOCHEMISTRY OF RETINAL LESIONS IN THE INFANTILE (TAY-SACHS) AND LATE-INFANTILE (BIELSCHOWSKY) FORMS OF AMAUROTIC IDIOCY

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Results of morphological and histochemical studies on the retina in cases of infantile and late infantile amaurotic idiocy are reported.

The morhological pattern of the retina in the first case corresponds to alterations of the Tay-Sachs type. The second case represents the Batten type of lesion.

On the basis of their histochemical properties, the intracellular deposits in the cytoplasm of the ganglion cells of the retina, in both cases, may be defined as acid glycolipid compounds containing neuraminic acid and combined with the structural cell protein. In both types of the disease these compounds are virtually identical.

Comparison of the histochemical character of the deposits in the ganglion cells of the retina and in the cerebral nerve cells showed that they are identical in the late-infantile form, but exhibit significant differences in the infantile form. Apparently, the retinal glycolipids become „mature" earlier than the cerebral glycolipids.

Retinal lesions are an essential element of the pathological process in amaurotic idiocy. The morphology of these lesions differs in the various forms of this disease. *Greenfield* (1958), *Hogan* and *Zimmerman* (1962) recognize two principal morphological patterns of retinal lesions in amaurotic idiocy, namely: the Tay-Sachs type, peculiar to the infantile form of the disease with the classical ophthalmoscopic sign, the „red spot", and the Batten type appearing in the juvenile and late adult variants, presenting features of *retinitis pigmentosa* under ophthalmoscopic examination. In both variants storage of lipids within the ganglion cells of the retina is found during microscopic examination. The essential difference is the limitation of the pathological process to the layer of ganglion cells only, with secondary involvement of the nerve fibers in the infantile type, while in the late types, besides lipid accumulation in the ganglion cells, degeneration of the retinal receptors is apparent along with atrophy of the retinal granular layers, especially in the outer layer and the migration of melanin pigment into the retina.

In the infantile type a most pronounced storage of lipid substances in the ganglion cells is prevalent, with marked atrophy of these cells especially near the fovea. Lipid material released from the disintegrated cells lies freely in the tissue or is swallowed up by the phagocytes.

In the Batten type the intensity of the storage process is much less pronounced and atrophy of the ganglion cells is less visible. Distinct glial reaction accompanies the atrophy of the cells in the granular layers. Rods and cones are both degenerated and atrophied. Melanin pigment in the form of free granules or present in the cytoplasm of macrophages penetrates the outer layers of the retina. *Hogan* and *Zimmerman* (1962) stress the fact that pigmentary degeneration of the retinal receptors is primary in this case in contradistinction to the primary atrophy of the ganglion cells in the infantile type.

There exist fairly numerous aberrations from the above mentioned dividing line between the two forms. Cases of the juvenile forms have been described, and even late adult ones with retinal lesions characteristic of the infantile type, e.g. the second case of *Anderson, Margolis* and *Lynn* (1958) or the third case in *Greenfield's* series (1951).

The intensity of the pathological changes and their extent are variable in cases belonging to one type. In some cases of the juvenile type lesions were present only in the external granular layer, in other cases they involved all the retinal layers (*Greenfield, Holmes* 1925, *Escola* 1961). Similarly in the infantile type the degeneration of rods and cones has been described along with storage and atrophy of the ganglion cells (*Clement, Gruner, Rameix, Bretagne* 1953). *Greenfield* (1951) stresses that the length of the disease is of primary importance for the intensity and extent of the pathological process in the retina.

The late-infantile type of Bielschowsky takes an intermediate position in relation to the characteristics of retinal pathological changes. In a considerable number of cases the only finding at ophthalmoscopy is simple atrophy of the optic nerve. No description of retinal morphology in such a case could be found in the available literature. On the other hand in most described cases either changes of the infantile type (*Greenfield, Nevin* 1933, *Anderson, Margolis, Lynn* 1958) or of the juvenile type (*Batten, Mayou* 1915, *Bielschowsky* 1921, *Torrance* 1927, *Bird* 1948, *Greenfield* 1955) were present. *Bielschowsky* (1921) stresses the finely granular appearance of the pigment accumulations as characteristic for the late-infantile type; according to *Torrance* (1927) the uneven, spotty pigmentary degeneration is characteristic. In the early stages of the disease the pigmentary changes are limited to the area near the fovea; with an increase in the intensity of the process they become generalized and occupy the more peripheral parts of the retina (*Bird* 1948).

Although the histochemistry of the central nervous system in various forms of amaurotic idiocy has been the subject of numerous investigations (*Diezel* 1954, 1960, *Seitelberger, Vogel, Stepan* 1957, *Berard-Baillier, Paillas, Gastalet, Edgar* 1958, *Seitelberger, Nagy* 1958, *Wender, Jaworska* 1960, *Mossakowski, Mathieson, Cumings* 1961, *Gumińska, Pietrzykowa, Stefanko, Szybowska* 1961, *Wolman* 1961, *Dąmbska, Czochańska, Mossakowski* 1962, *Shanklin, Issidorides, Salam* 1962) the histochemistry of the retinal lesions has been discussed in only a few publi-

cations. Histochemical investigations on the retina in the Tay-Sachs disease is the subject of the paper of *Cogan* and *Kuwabara* (1959). *Mossakowski, Mathieson, Cumings* (1961) and *Dąmbska, Czochańska, Mossakowski* (1962) in discussions on the changes in the central nervous system describe the histochemical features of the material stored in the retinal ganglion cells in the infantile type, as well as in the case of the late-infantile type of the disease.

As the morphological and histochemical investigations on the retina have rarely been described in world literature and practically never in Poland, it seemed worth-while presenting the morphological and histochemical features of the retinal lesions in two cases of amaurotic idiocy belonging to the infantile and late-infantile forms of the disease, although both these cases have been described in the two above mentioned papers *. Both these cases represent two morphologically different types of retinal lesions. Thus a possibility is given to compare the histochemical features of the accumulations in both types of this disease and to correlate them with the changes encountered in the central nervous system.

Because our interest has been limited to the retina only, data concerning the clinical and pathological changes in these cases have not been presented in detail. The latter may be found in the two earlier publications.

CASES

Case 1. The onset of the disease in the boy J. S. occured at the age of sixth months. The parents were of Jewish origin, young, healthy and there was no history of consanguinity. The boy had a healthy normally developed elder brother. The first manifestations of the disease were: apathy, absence of psychosomatic development and irritability to sounds. At a later period marked muscular rigidity appeared and he became subject to tonic-clonic seizures. The child ceased to react to external stimuli. Death occurred in the 18th month of life with seizures and hyperthermia as final symptoms. Fundoscopic examinations made several times disclosed the typical changes of the Tay-Sachs disease. In later periods increasing signs of optic atrophy were observed.

A macroscopic examination of the brain showed that its consistency was rubbery accompanied by a moderate dilatation of the ventricles.

A microscopic examination disclosed general degeneration of the neurons of the Schaffer-Spielmayer type present in all anatomical structures of the central nervous system. The nerve cells were distended baloon-like and filled with granular lipid material. The number of disintegrated nerve cells was considerable. Numerous macrophages contained chemical substances identical with those present in the nerve cells. The glial reaction was marked and its intensity

* *M. Dąmbska* — A case of infantile form of amaurotic idiocy...

was in proportion to the intensity of the cellular changes. In the white matter of the cerebral and cerebellar hemispheres slight demyelinization was present, with associated glial proliferation. The pyramidal tracts were degenerated.

Histochemical studies showed that the chemical properties of lipid accumulations in the nerve cells were typical for the Tay-Sachs disease.

Case 2. The onset of the disease in a girl F. B. occurred at the age of 14 months. She was the second child in a family of five. The parents were young, healthy and there was consanguinity between them. The signs of the same disease were detected in two of her siblings. Her development was normal up to the 14th month of her life, when her psychic and somatic development ceased and then began to regress. At the beginning of the disease difficulty in walking appeared, then hearing and vision began to fail. The child ceased to walk and talk. Then reactions to visual and auditory stimuli disappeared. The disease ran a slowly progressive course. The girl died at the age of 5 in a state of complete decortication and cachexia. A fundoscopic examination performed several times revealed no abnormalities.

A macroscopic examination of the brain showed a markedly increased consistency of the nervous tissue, cerebral and cerebellar atrophy and dilatation of the ventricular system.

A microscopic examination of the brain revealed the coexistence of two kinds of pathological changes. In the grey matter an advanced process of lipid storage in the nerve cells was striking.

This phenomenon was present in all the nerve cells but its intensity was different in various anatomical structures. It was most pronounced in the cerebral cortex and gradually decreased in the brain stem and spinal cord. Extensive atrophy and marked glial reaction accompanied the degenerative changes in the neurons. The atrophy of the cerebellar cortex was striking, Purkinje cells contained accumulations of lipids, their dendrites were swollen.

Histochemical studies disclosed that lipid accumulations had typical properties of the late-infantile form of retinal degeneration. The nerve cells of certain anatomical structures (dentate nucleus of the cerebellum, pallidum, motor cells of the cranial nerves and the anterior horns) presented besides that a brown metachromatic staining with the method of Hirsch and Peiffer (1955) using acid cresyl violet. In the white matter of the cerebral and cerebellar hemispheres striking demyelinization with a myelin breakdown to metachromatic prelipid products was noted. The chemical properties of these products showed that the principal lipid substance accumulated in the white matter were sulphate esters of cerebrosides.

On the basis of the morphological and histochemical features of this case the coexistence of two pathological processes could be recognized, namely: the late-infantile form of amaurotic idiocy and metachromatic leukodystrophy.

RETINAL EXAMINATION

Parafin sections stained with hematoxylin-eosin were used for general examinations.

Case 1. The pathological changes involved layers of nerve fibers and ganglion cells. The layer of nerve fibers was markedly thinned, the number of ganglion cells decreased, especially near the fovea (Fig. 1). In the peripheral parts of the retina the number of ganglion cells was unchanged. The remaining ganglion cells were balooned, rounded (Fig. 2), their dark shrunken nuclei were displaced

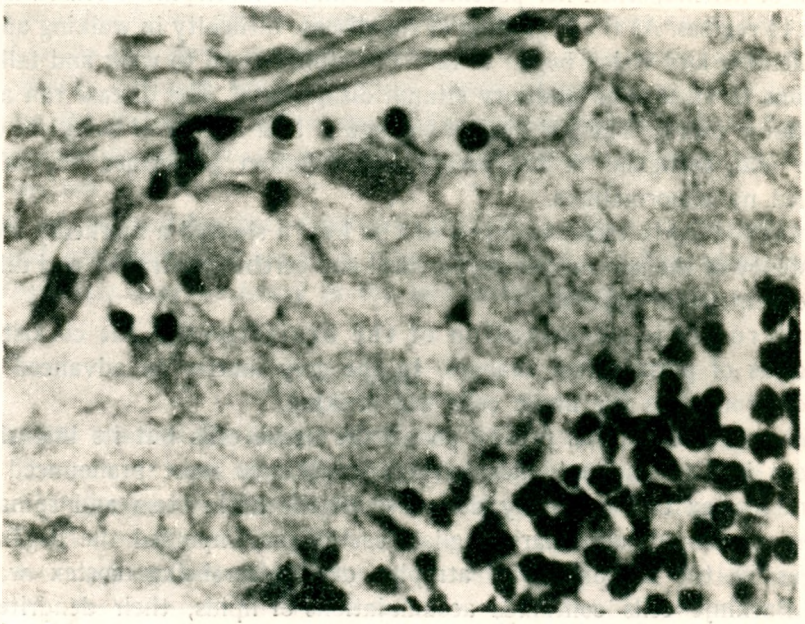

Fig. 1. Case 1. Marked loss of ganglion cells. The cytoplasm of the preserved cells is filled with granulations stained with alcyan blue. Lison. Magnif. × 300.

towards the periphery. The cytoplasm in the usual staining had a reticular-foamy structure, the cells were clear, no Nissl bodies were visible. In sections stained with Sudan black b PAS and acid cresyl violet large granular accumulations were evident filling the cytoplasm of the nerve cells (Fig. 3). Two types of granules could be detected — the coarse and the dust-like ones, present in fairly equal proportions, with a slight tendency of the coarse granules to accumulate around the nucleus of the cell. Most nerve cells had distinct contours, only a few cells were found to be disintegrated. No phagocytes were noted. The remaining retinal layers remained unchanged (Fig. 4). Some rods and cones were slightly degenerated but most of them were undamaged. No pigment

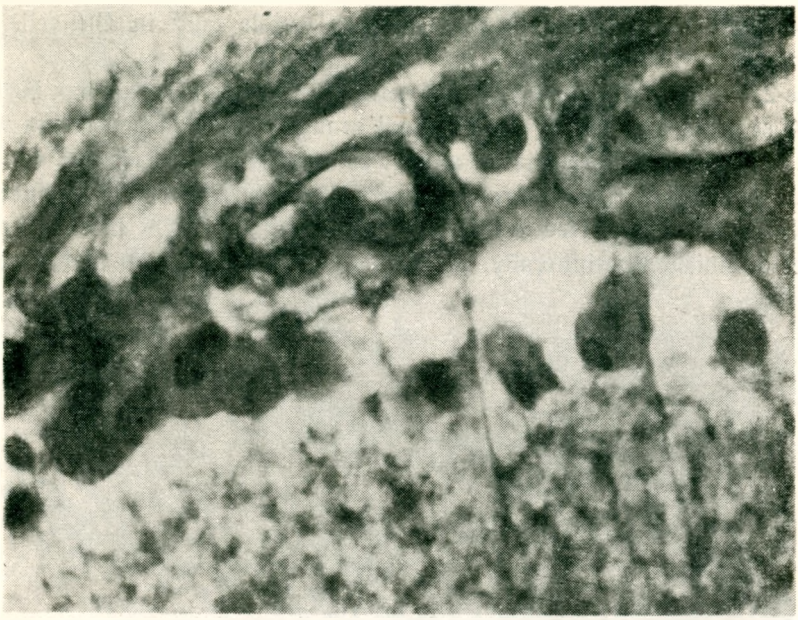

Fig. 2. Case 1. Preserved ganglion cells. The neurons are enlarged, with rounded outline and the nuclei are displaced to the cell periphery. Granulations are visible in the cytoplasm, these are stained with Danielli's method. Magnif. × 300.

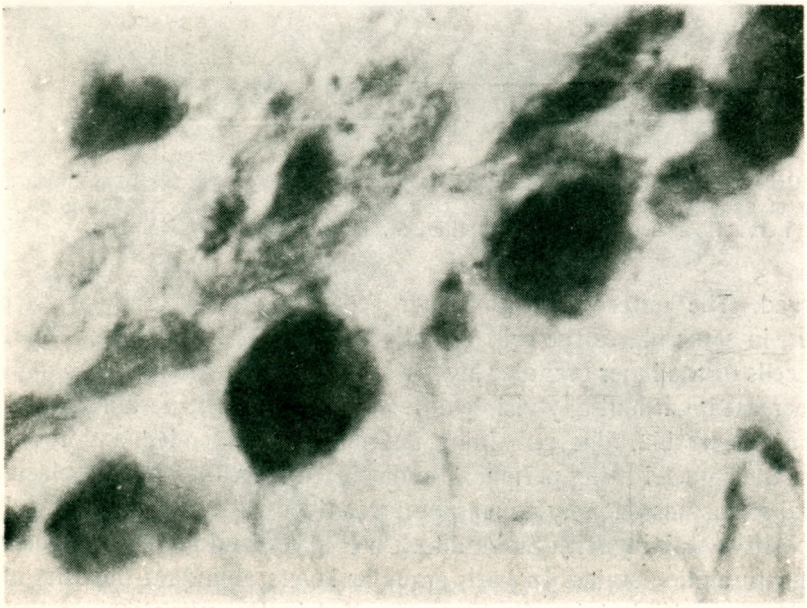

Fig. 3. Case 1. Cytoplasm of ganglion cells filled with granular deposits stained with Sudan black b; magnif. × 500.

granules were found. Melanin pigment was visible only in the cells of the pigmentary epithelium.

Case 2. Pathological changes in the retina were more general than in the first case. A striking atrophy of the external granular layer of the retina was apparent (Fig. 5) and there was an almost complete lack of rods and cones. The atrophic changes in the external granular layer were most pronounced near the fovea, where only a few cells of this layer remained. The intensity of these changes diminished peripherally, the contours of both granular layers were well

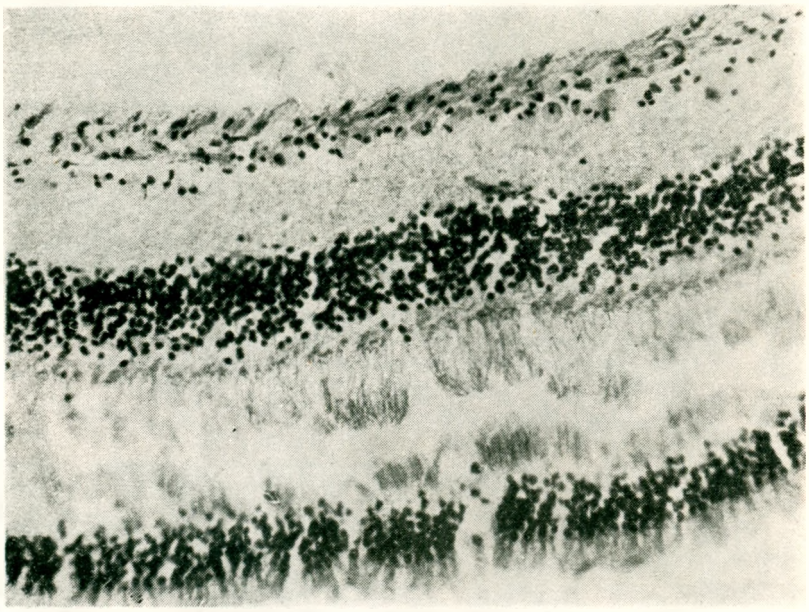

Fig. 4. Case 1. General view of the retina. Both granular layers have normal appearance. The number of ganglion cells is diminished. Balloon distension of preserved ganglion cells. The nerve fiber layer is markedly thinned. Hematoxylin-eosin. Magnif. × 175.

preserved. The outer plexiform layer separating both granular layers was thinner, in some places the cells of both these layers intermingled. Rarefaction of the cells of the inner granular layer was present. The number of ganglion cells was decreased, without any visible difference between the peripheral and central parts of the retina. The remaining neurons had distended and rounded cell bodies, their nuclei being peripherally displaced (Fig. 6). The cytoplasm, which in usual stains has a foamy appearance, was filled with finely granular deposits, PAS-positive staining with Sudan black b (Fig. 7), and giving a metachromatic reaction to aniline stains. In both granular layers abundant deposits of brown pigment were visible lying freely or engulfed in the cytoplasm of the macrophages (Fig. 8).

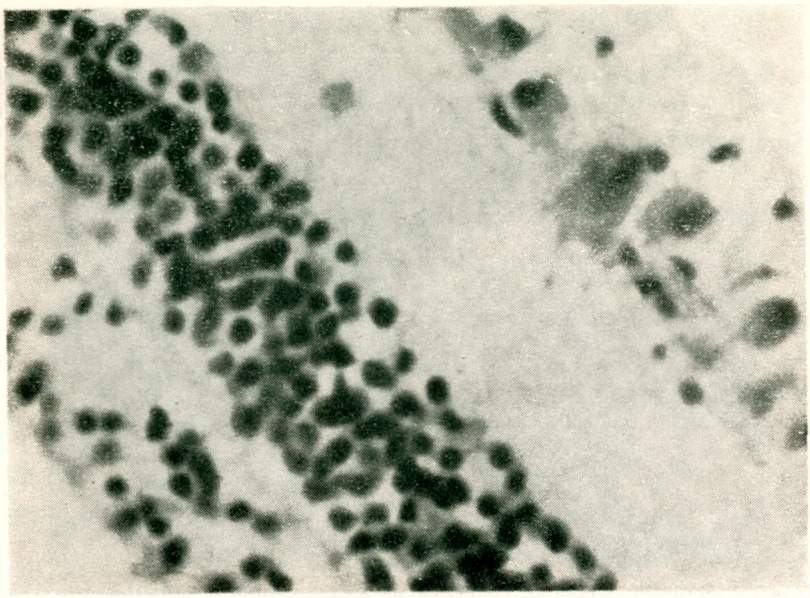

Fig. 5. Case 2. Marked atrophy of the outer granular layer of the retina, only isolated cells being preserved. The inner granular layer is well preserved. Ganglion cells are swollen with foamy cytoplasm. Hematoxylin-eosin. Magnif. × 325.

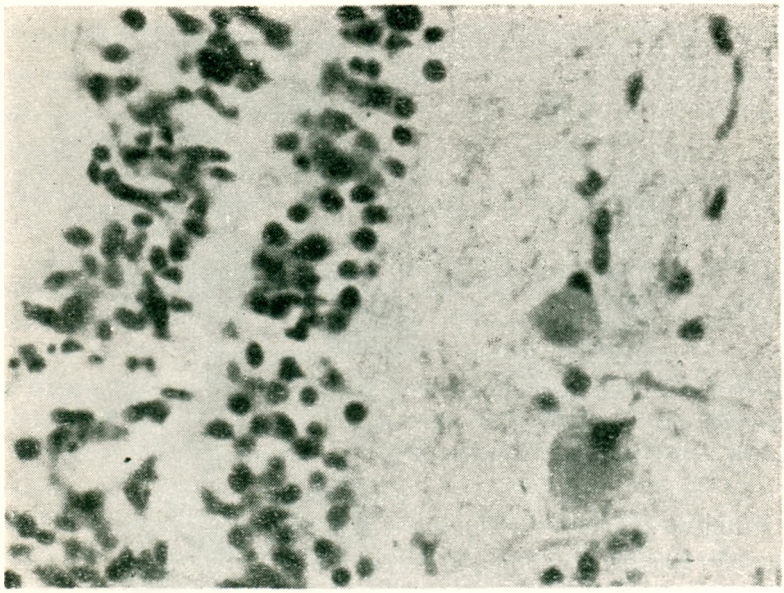

Fig. 6. Case 2. Marked rarefaction of both granular layers of the retina. The outer plexiform layer is thinned. Ganglion cells with large lobate cytoplasm and peripherally displaced nucle. Hematoxylin-eosin. Magnif. × 300.

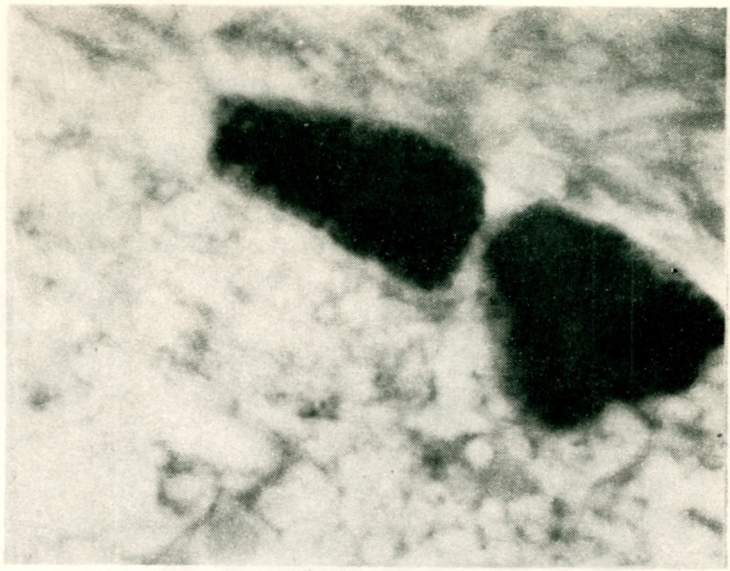

Fig. 7. Case 2. Cytoplasm of ganglion cells filled with sudanophilic granulations. Sudan black b. Magnif. × 1000.

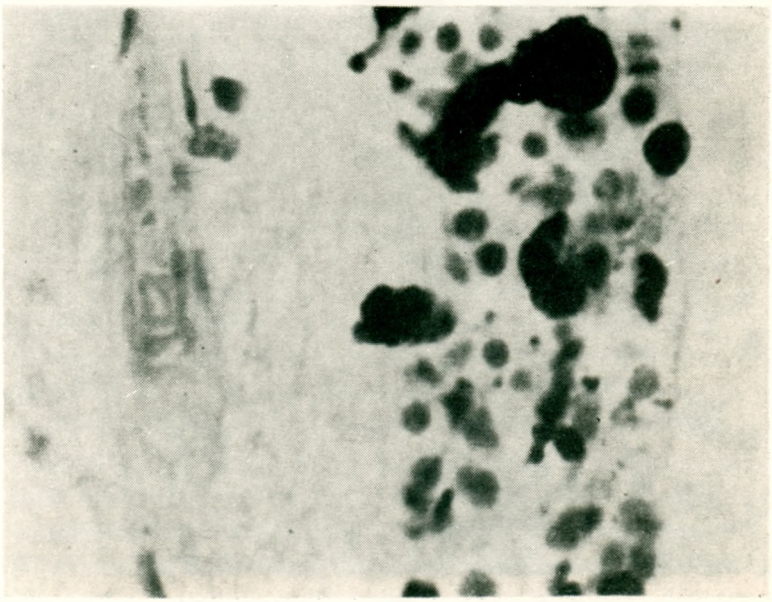

Fig. 8. Case 2. Abundant, variously shaped deposits of melanin pigment in the atrophied granular layers of the retina. Hematoxylin-eosin. Magnif. × 325.

HISTOCHEMICAL EXAMINATION OF THE RETINA

To determine the content of lipid deposits present in the cytoplasm of ganglion cells the following histochemical reactions were performed: Sudan IV, Sudan Black B, PAS with an acetylating test and reduction, PfAS and staining with the methods of Peiffer-Hirsch, Feyrter, Biala, Lison, Klüver, Danielli and Millon. The use of identical methods of investigation permits a comparison

Table I

Histochemical properties of substances accumulated in ganglion cells of the retina

Method	Infantile form	Late infantile form
Sudan IV	0 (0)	— (—)
Sudan Black B	+++ (++)	+++ (+++)
PAS	+++ (+++)	+++ (+++)
PAS after acetylation	— (—)	— (—)
PAS after reduction	+ (+)	+ (++)
PfAS	0 (0)	— (—)
Hirsch-Peiffer meth. *	++ (+)	++ (+)
Feyrter's „Mounting" meth.	++ (++)	+ (+)
Orcin-hydrochloric acid *(Bial)* meth.	± (—)	± (—)
Alcian-blue meth. *(Lison)*	+ (++)	± (+)
Copper-phthalocyanin meth. *(Klüver)*	+++ (++)	++ (++)
Coupled Tetrazonium reac. *(Danielli)*	+ (—)	++ (++)
Millon's reaction	0 (0)	+ (+)

+++ very strongly positive reaction, ++ strongly positive reaction, + positive reaction, ± faintly positive reaction, — negative reaction, 0 test not done.
* β-metachromasia.

between deposits in both types of amaurotic idiocy, and the histochemical investigations of the central nervous system performed simultaneously render possible a comparison between the characteristics of both the retinal and cerebral deposits.

The results of histochemical investigations of the retina are shown in Table I. The results of investigations on the central nervous system are given in parentheses.

The effects of different solvents were studied simultaneously using the following lipid solvents: acetone, ether, ethanol 70% and absolute alcohol,

pyridine and a mixture of methanol with chloroform 2: 1. The results of the tests with solvents with control staining using the: Schiff reagent, Sudan black b and acid cresyl violet are presented in Table II.

Table II

Effect of different solvents on staining properties of lipid deposits

Solvent	Sudan Black B		PAS		Metachromasia	
	Infantile form	Late infantile form	Infantile form	Late infantile form	Infantile form	Late infantile form
Water	++	++	++	++	++	++
Acetone	++	++	++	++	++	++
Ether	+	++	+	++	++	++
Ethanol 70%	+	0	+	0	—	0
Absolute alcohol	±	+	±	+	—	—
Pyridine	±	+	—	+	—	—
Chloroform-methanol . . .	—	+	—	+	—	—

++ Staining of substances unimpaired. + Staining of substances reduced. ± Staining of substances strongly reduced. — Staining of substances abolished. 0 Test not done.

DISCUSSION

The morphological picture of the retina in our material is essentially consistent with the typical pathological changes described in the infantile form and in most cases of late-infantile form of amaurotic idiocy. In case 1 no phagocytes loaded with lipid deposits were observed, in contrast to cases described by *Greenfield* (1951), *Shapira, Leight* (1955) and *Cogan, Kuwabara* (1959). The second case, analogous with the cases of *Torrance* (1927) and of *Bird* (1948) differed from them in that the pigment changes were evenly distributed in the whole retina with no clear-cut prevalence near the fovea.

A comparison of the histochemical reactions of the lipid products stored in the ganglion cells of the retina in both cases proved nearly identical. They differed one from another only in the intensity of their staining in the three reactions, that is in staining with the methods of Feyrter, Lison and Danielli. The differences in two former methods seem to suggest a different pH of lipid deposits. In case 2 the stronger reaction of Danielli shows a stronger binding of the stored chemical compounds to the proteins forming the structure of the cells in the late-infantile type. The results of the tests with solvents lead to

similar conclusions. The deposits in the infantile type show a greater sensitivity to the action of certain lipid solvents than in the late-infantile type. In the latter, incubation with all solvents used did not cause a complete loss of ability to stain with Sudan Black B and with PAS, while in the infantile type incubation with absolute ethyl alcohol and with pyridine caused a distinct decrease of the stainability of the deposits and the results after incubation in the mixture of methanol chloroform were already completely negative. These data confirm earlier observations on the solubility of lipids in the Tay-Sachs disease (*Greenfield, Nevin* 1933).

The properties of lipid deposits filling the ganglion cells of the retina in both cases show that they are acid glycolipid compounds. In a more detailed characteristic of the deposits two acid glycolipids must be taken into account: cerebrosides and gangliosides. Their histochemical differentiation consists in the detection of the presence of neuraminic acid, which is possible with the reaction of Biala (*Klenk* 1959, *Diezel* 1954). In both cases a weak but positive reaction of Biala was obtained. This might be an evidence that acid glycolipid is bound to neuraminic acid and thus its chemical properties resemble those of gangliosides.

A comparison of the histochemical reactions in the retina and brain shows, that in the late-infantile type the deposits in the ganglion cells of the retina are identical with the intracellular deposits in the central nervous system, but in the infantile type there exist, perhaps most important differences. In contradistinction to the cerebral deposits the products stored in the retina possess the features of acid glycolipids containing neuraminic acid and bound to the proteins of the cellular structures. These properties, peculiar to the cerebral deposits in the late-infantile type of amaurotic idiocy, distinguish them, on histochemical grounds, from the infantile type of the disease (*Diezel* 1960). A typical feature in the infantile form is the absence of neuraminic acid in the complex compound of the stored glycolipid which is present as a free compound, easily soluble, not bound to cellular proteins. It might result from these observations, that the glycolipids of the retinal cells in the infantile form of the disease closely resemble the basic substance stored in the late-infantile form of cerebro-retinal degeneration. The „maturation" of the glycolipid observed in the transition from the infantile to late-infantile form occurs therefore more rapidly in the retina than in the central nervous system.

Besides, the coexistence of metachromatic leukodystrophy in the second case should be taken into account in the discussion. The problem arises thus, how far this coexistence has modified the morphological and histochemical features of the retinal changes. It is known from these few studies, in which the retina in cases of metachromatic leukodystrophy has been studied histochemically (*Cogan, Kubawara, Richardson, Lyon* 1958) that storage of PAS-positive lipid compounds in the ganglion cells also takes place here. However, in the morphological picture a clear-cut increase in the size of the cells is absent though it

was doubtlessly present in this case. No changes in the remaining layers of the retina apart from the ganglion cells have been observed there, particularly there were no changes visible in the type of *retinitis pigmentosa*. The stored material presented on the other hand the characteristic features of brown metachromasia of Hirsch-Peiffer, while the material in this case had the appearance of red β metachromasia. It appears that it can be supposed that in this case the morphological and histochemical changes were associated mainly with amaurotic idiocy.

The fact that ophthalmoscopic examinations in second case have never shown any pathological signs also deserves attention. It seems that the existence of retinal changes could not be overlooked, because fundoscopy had been repeated several times. It can thus be assumed, that in certain cases, perhaps with a small intensity of changes, those in the form of *retinitis pigmentosa* may not be recognizable in fundoscopic examinations. This supposition might be confirmed or denied, if a larger series of cases of the late-infantile type of amaurotic idiocy without intravitally recognized retinal changes could be examined.

I wish to express my thanks to Dr *G. Mathieson* for his permission to publish the material on case 2, which belonged to him.

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