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Histochemical Study of the Brain in an Atypical Case of Amaurotic Idiocy

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With 8 Figures in the Text

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The following is a description of the clinical, pathological and histochemical findings in a child suffering from an atypical form of amaurotic idiocy. The findings in this case considered together with other reports in the literature, indicate that amaurotic idiocy might not represent a nosological entity caused by a single, well defined metabolic derangement, but rather a morphological and clinical syndrome which includes a number of different though akin metabolic derangements.

Clinical Data*

The patient was the second son of healthy unrelated parents. Both parents were Ashkenazi Jews, the father's family originating in Poland, whereas the mother's ancestors lived for the last five generations in Palestine. The first born (brother to the patient described in this article) was a spontaneously delivered boy, who weighed at birth 3500 gm. Development was normal during the first six months of life, but at 7 months the mother noticed arrest and regression of development. The examining physician (Dr. H. ROETHLER) found decorticated posture and spasticity of the lower extremities. The infant could not hold its head and examination of the fundi revealed a typical finding for Tay-Sachs' disease. The physician was later informed that the child died at the approximate age of two years and that no autopsy had been performed.

The second born, also a son, was spontaneously delivered after an uneventful pregnancy. Weight at birth 3800 gm. The infant was examined by Dr. ROETHLER at the age of 5 months. Until that time his development was reported to be normal. During the last weeks prior to its examination the infant was running an undiagnosed sub-febrile temperature. Clinical examination at this stage, including ophthalmological study was not particularly contributory, except for some hyperreflexia, muscular hypotonia and slight irritability.

At the age of 7 months the infant was re-examined. No further development had occurred during these two months; the child stopped turning over in his bed, obesity developed, and the circumference of the head was 44 cm. Examination of the fundi revealed early changes of Tay-Sachs' disease, with typical findings in the maculae of both eyes, although the papillae were not yet quite pale.

At the age of two the child was amaurotic and an almost completely motionless idiot.

At the age of $2^1/_2$ years the child was admitted to the Pediatric Department of the Kaplan Hospital after a week's illness, with cyanosis, high temperature and cough. Penicillin treatment brought down the temperature, but the child continued to be subfebrile, unconscious, with repeated attacks of cyanosis and dyspnea. Clinical examination at the hospital revealed an unconscious spastic child with hyperreflexia. Diffuse râles could be heard over both lungs.

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The head was enlarged (circumference 51,5 cm). Liver and spleen were not enlarged. Ophthalmoscopic examination showed atrophy of the optic nerves and typical cherry-red spots. The child died on the 12th day of hospitalization after progressive increase in severity of the dyspnea and cyanosis.

A complete autopsy was not performed. The brain was extracted and sent to the Assaf Harofeh Hospital Department of Pathology already fixed in formalin. Pieces of the brain were kindly sent by Drs. REIF and SANDBANK to the author for further study.

Histological and Histochemical Findings

Both paraffin and frozen sections of many pieces of the brain were made. The staining methods are listed together with the findings. The pathological process in the gray matter was basically similar in all the areas examined with only slight variations in intensity. The

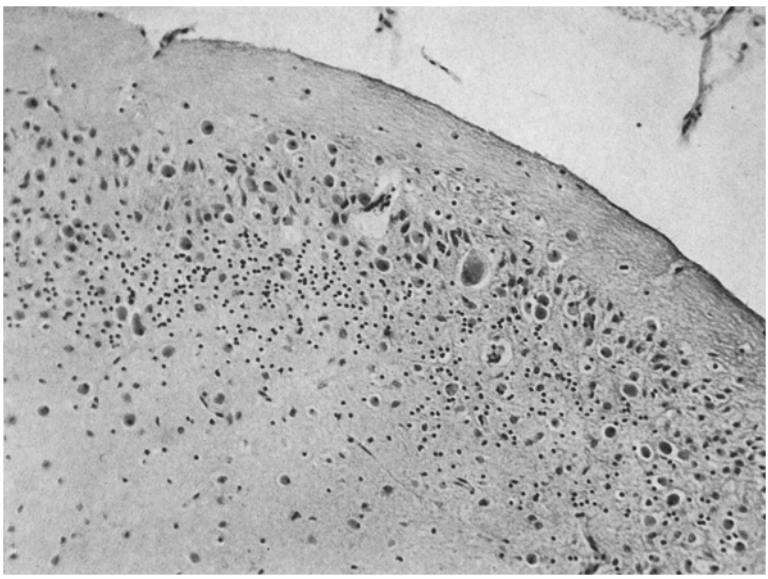

Fig. 1. Cerebellar cortex showing a single swollen Purkinje cell and numerous swollen satellites. H.&E. × 130

changes in the white matter were less homogeneous, as demyelination was not of equal intensity in the different areas. Topographical study of the demyelinating process was impossible, however, because of insufficient material.

In sections of paraffin-embedded material stained with haemotoxylin and eosin the neurones showed the change typical for amaurotic idiocy. All ganglion cells were swollen, often pear-shaped, and the tigroid substance and the nucleus were usually pushed to one side of the cell. The cytoplasm of these cells appeared finely vacuolated. In most areas there was clear evidence of loss of neurones. In the cerebellum, for example, very few Purkinje cells remained (Fig. 1). In addition to the swollen ganglion cells at least two other types of enlarged cells containing deposits of an abnormal material could be discerned in the gray matter (Figs. 1 and 2):

a) swollen astrocytes of the "gemaestete" type, with acidophilic homogeneous cytoplasm. In sections stained with CAJAL's gold sublimate method, slender processes could be seen expanding from the bodies of some of these "gemistocytes" (Fig. 3);

b) Gitter cells (compound granular cells) with frankly vacuolated cytoplasm and central nuclei.

In the white matter some oligodendrocytes were surrounded by a wider halo than usual, and there was marked gliosis (Fig. 4). No inflammatory infiltrate was found anywhere. The adventitial cells and periadventitial histiocytes were swollen and often foamy, especially in the white matter.

Frozen sections stained by BIELSCHOWSKY's method revealed an appearance typical for amaurotic idiocy with the neurofibrils pushed against the cell walls by the stored material

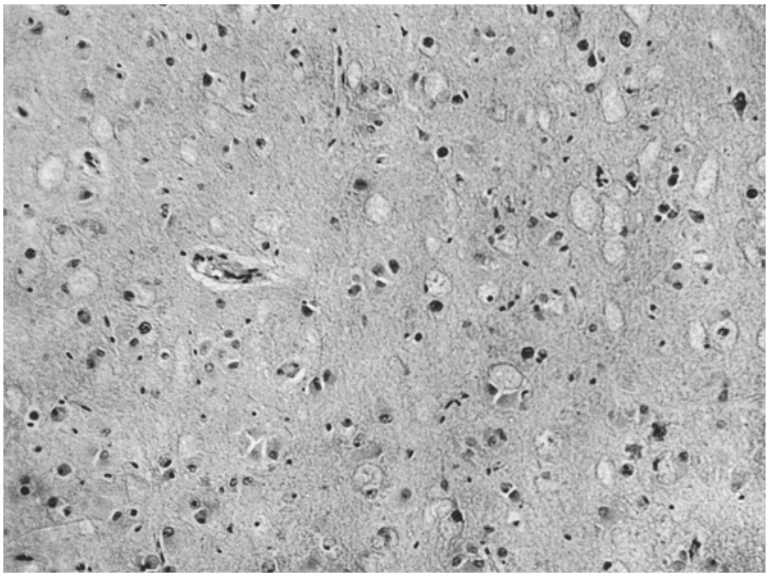

Fig. 2. Cerebral cortex showing pale swollen neurones, chromophilic gemistocytes, and vacuolated Gitter cells. H. & E. × 130

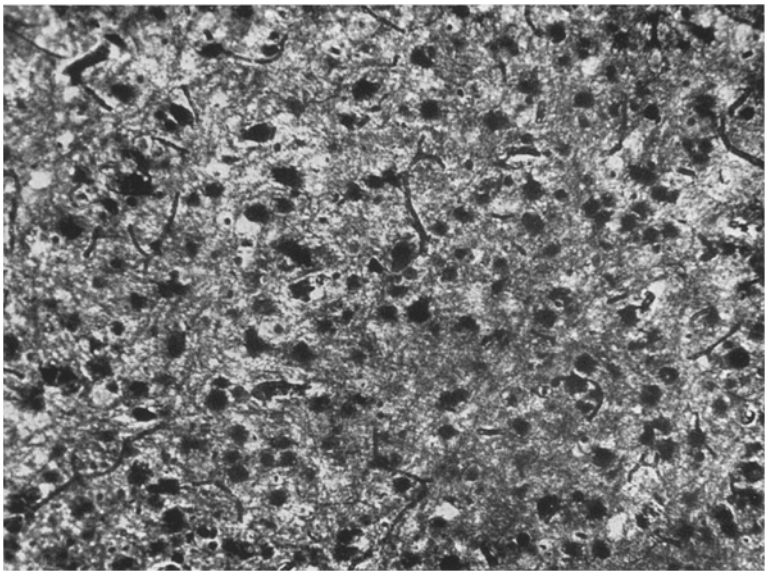

Fig. 3. Cerebral cortex showing slender processes emanating from bodies of densely stained gemistocytes. Cytoplasm of Gitter cells is almost unstained. Cajal's gold sublimate method × 135

(Fig. 5). The substance within the neurones as well as the substance accumulated in the various glial cells stained weakly with this method.

In frozen sections stained with MILLON's reagent and with the ninhydrin-Schiff technique the neurones and the pathological glial cells stained very lightly and much less than the

background. With the Einschlußfärbung of FEYRTER (using toluidine blue instead of thionin) the ganglion cells and the gemistocytes remained unstained or were faintly orthochromatic whereas the Gitter cells stained in different shades of blue and purple-blue. With the Bi-Col

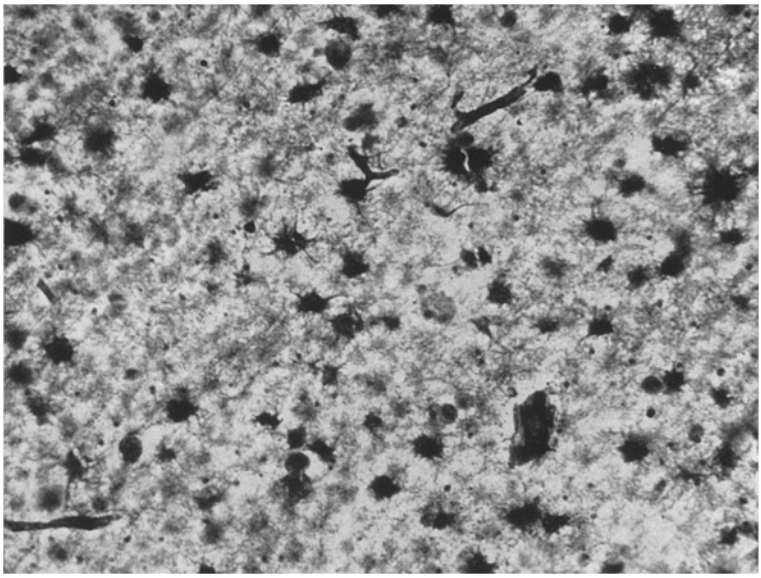

Fig. 4. Subcortical white matter showing gliosis. Cajal's gold-sublimate method. × 135

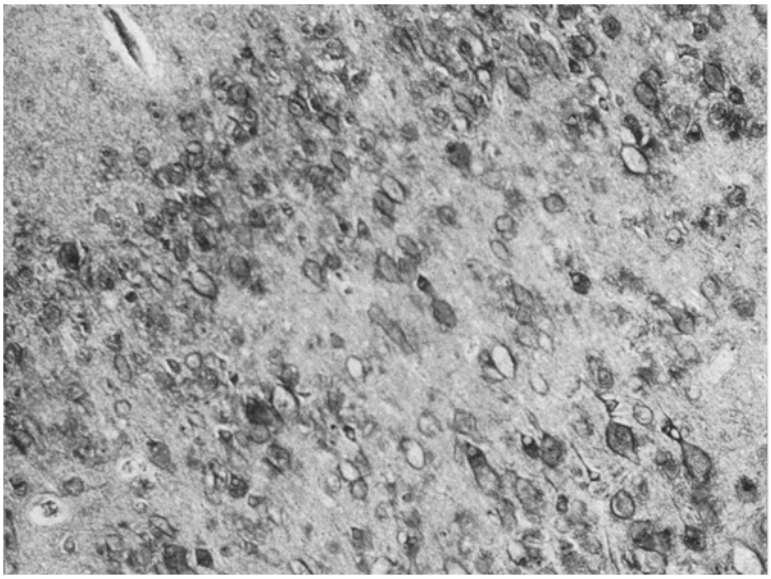

Fig. 5. Cerebral cortex showing swollen ganglion cells with neurofibrils pushed to the periphery by the stored material. Bielschowsky's neurofibril method. × 110

stain (WOLMAN 1956) similar results were obtained: the ganglion cells and the gemistocytes were practically unstained and the Gitter cells stained faintly blue.

In frozen sections stained with P.A.S. all the three types of cells in the cortex, as well as the adventitial cells and the Gitter cells of the white matter, stained intensely. Twenty four

hours immersion in 2% OsO_4 did not produce any staining in the affected neurones, whereas the Gitter cells and the gemistocytes stained pale yellow to pale brown; the staining was more intense in some adventitial cells. Similar results were obtained in sections stained

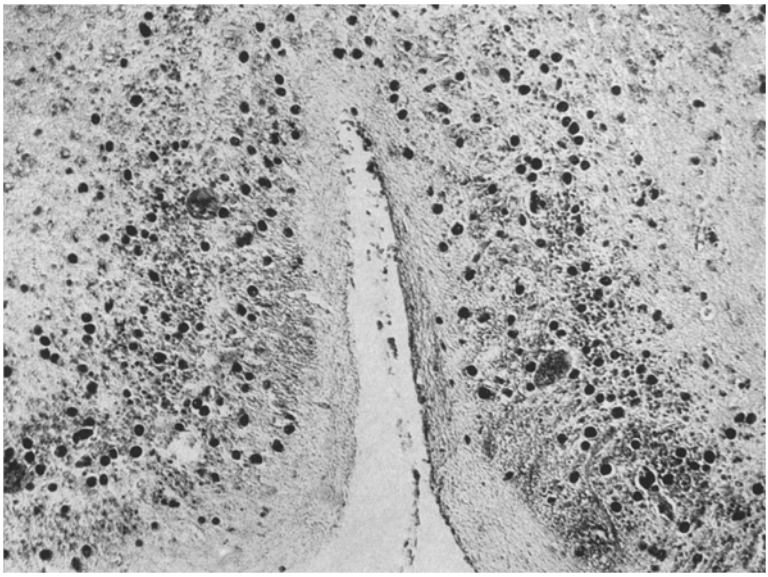

Fig. 6. Cerebellar cortex showing relatively weak sudanophilia of the three Purkinje cells and of the gemistocytes, contrasted by the intense staining of the Gitter cells. Sudan Black B staining on a frozen section. × 105

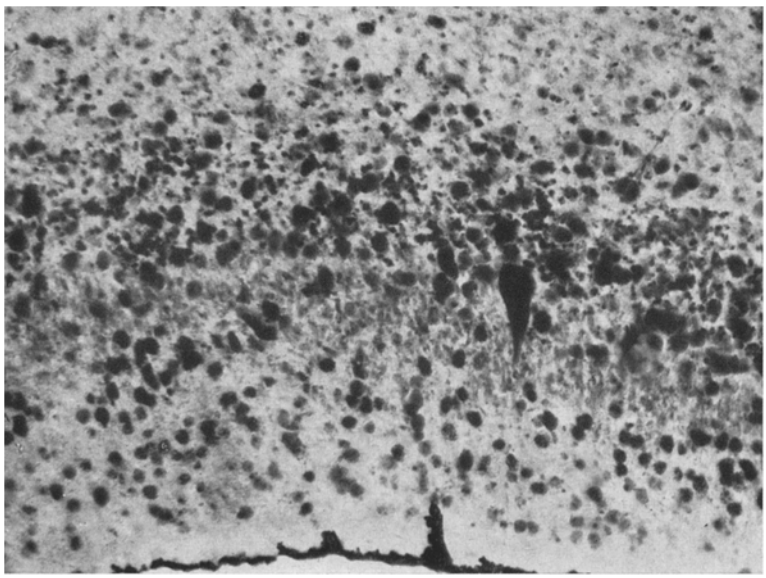

Fig. 7. Cerebellar cortex showing intense staining of the cytoplasm of Purkinje cells and of satellites. Fischler's stain on a frozen section. × 105

by SWANK and DAVENPORT's (1934) method for degenerating myelin. Staining with Sudan III resulted in a clear differentiation between the neurones and the gemistocytes which stained pale yellow on the one hand, and of the Gitter and adventitial cells which stained

red on the other. Staining with Sudan Black showed similar relations, but all the cells stained more intensely than with Sudan III. Fig. 6 shows the weak staining with Sudan Black of the affected Purkinje cells and the intense staining of the satellites. There were few anisotropic crystals in some Gitter cells and practically none in the neurones. With Nile blue the substances stored in all types of cells stained pale blue. With SPIELMEYER's method for myelin and with BAKER's method for phospholipids marked variation in the staining intensity of the affected neurones was found. Most nerve cells stained weakly or did not stain at all. In most Gitter cells the stored material remained unstained, whereas most of the material within the gemistocytes stained intensely with both methods. With the performic acid Schiff procedure of LILLIE (1954) the neurones and the various storing glial and adventitial cells stained pale

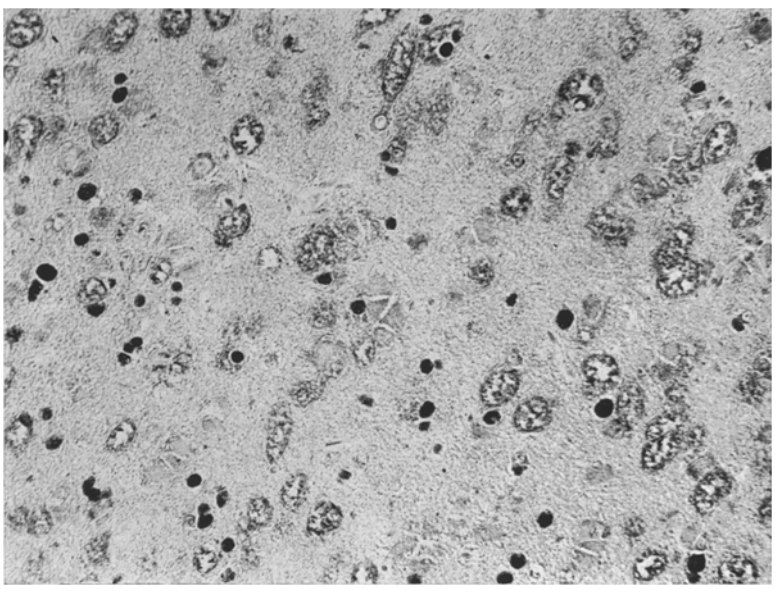

Fig. 8. Cerebral cortex showing intense and lipid-solvent resistant sudanophilia of the cytoplasm of the gemistocytes. Scattered sudanophilic droplets in cytoplasm of neurones and Gitter cells. Sudan Black B staining on a paraffin section. × 150

pink, much paler than the myelin sheaths and in a slightly stronger hue than the background of the gray matter. With FISCHLER's method the ganglion cells and most satellites stained intensely (Fig. 7).

SCHULTZ's method for cholesterol revealed unexpected findings: The ganglion cells, as well as the Gitter and the adventitial cells stained very intensely. The gemistocytes appeared to be unstained.

In paraffin embedded sections stained with Sudan black or with P.A.S. it was found (Fig. 8) that the gemistocytes retained most of the staining materials. In the neurones there were scattered intensely stained droplets; similar droplets but in somewhat smaller amounts were found in the Gitter cells.

From the histochemical findings summarized in Table, it can be concluded that the material stored in the affected neurones was mainly a mixture of lipids. The mixture contained abundant cholesterol, neutral glycolipids and fatty acids and small but variable amounts of phospholipids. The lipid in the mixture did not contain, or contained very few, strongly acidic groups. The amount of protein within the cytoplasm of these neurones was very small.

Discussion

Most authors (cf. GLOBUS 1942) distinguish five variants of amaurotic idiocy: the congenital, the infantile, the late infantile, the juvenile, and the adult forms. A sharp demarcation of these variants does not seem justified, as:

Table. *Main Histochemical Findings in the Neurones and Glial Cells*
++ intense staining; + medium staining; ± weak staining; 0 no staining

Staining Method	Molecular Groups Demonstrated	Classes of Compounds which are mainly stained	Neurones	Gemistocytes	Compound Granular Corpuscles and Adventitial Cells
Millon	Peptide linkages	Proteins	±	±	±
Ninhydrin-Schiff	Alpha amino	Proteins	±	±	±
Metachromasia (Einschlußfärbung) 1. Metachromatic	Acidic groups	Acidic polysaccharides and lipids	0	0	+
2. Orthochromatic			± — 0	± — 0	+
Bi — Col 1. Red	Weakly acidic groups	Acidic polysaccharides	0	0	0
2. Blue	Strongly acidic groups	and lipids	± — 0	± — 0	+
P.A.S.	1—2 glycols and 1 glycol — 2 amino groups	Neutral polysaccharides	++	++	++
Os O_4	Active ethylenic links; strongly reducing groups (SH etc.)	Unsaturated lipids	0	±	±
Swank and Davenport's solution	Same as Os O_4 and also hexosamine	Unsaturated lipids and some polysaccharides	0	±	±
Sudan III	Non polar groups	Lipids	±	±	++
Sudan Black B	Non polar groups	Lipids (wide range)	+	+	++
Nile Blue Sulphate 1. Red	Non polar groups	Neutral fats	0	0	0
2. Blue	Acidic groups	Fatty acids and acidic lipids	±	±	±
Baker's method	Phosphate (?)	Phospholipids	0 — +	++	0 — +
Spielmeyer's method	Probably phosphate	Probably phospholipids	0 — +	++	0 — +
Performic acid Schiff	Ethylenic bonds	Unsaturated lipids	±	±	±
Fischler's method	Acidic groups	Fatty acids	++	+ — ++	++
Schultz's method	Unsaturated sterols	Cholesterol	++	0 — ±	++
Sudan Black in paraffin sections	Non polar groups	Hardly soluble lipids	+	+	±
P.A.S. in paraffin sections	1—2 glycols and 1 glycol-2 amino groups	Glycolipids or polysaccharides hardly soluble in lipid solvents	+	++	+

a) there is considerable over-lapping between the variants in the age at onset of symptoms and in the age at death;

b) cases which were included in one variant in accordance with clinical data or age, belonged to another variant by pathological and histochemical criteria, and vice-versa.

From a clinical standpoint the first symptoms of amaurotic idiocy may appear at any age, although most commonly in early infancy. When the first symptoms appear late in life, the disease process may continue for many years, whereas in the infants the course is almost invariably short. Still, in some cases, as for example in the case of TUTHILL (1934) the first symptoms appeared early in life (three months) and the histochemical characteristics were of the infantile variant, whereas death occurred at the age of seven years, because of pulmonary tuberculosis. Such cases may be considered as protracted infantile.

From a histochemical viewpoint, when comparing most published cases there is a difference in the staining characteristics of the stored material which roughly corresponds to the age of onset of symptoms and the age at death. As has been pointed out already by SACHS (1887) the material stored within the affected neurones stains heavily by the haematoxylin-lake methods used for demonstrating myelin. This finding has been confirmed by numerous workers (e.g. VOGT 1909; BIELSCHOWSKY 1921; HASSIN 1924; SCHAFFER 1930; SCHEIDEGGER 1941; GIAMPALMO 1951). The stored material stains faintly or not at all with Sudan III or IV and is hard to extract with cold fat solvents. In the later forms of amaurotic idiocy the stored material stains progressively less intensely by the iron-haematoxylin and the myelin techniques and more intensely by the Sudan dyes (cf. GLOBUS 1923; SCHAFFER 1925; SCHOB 1930). This observation, although generally accepted, does not fit all observations. VOGT (1909) described a juvenile case of a boy who attended school at the age of six (but learned with difficulty) and died at the age of eleven. In the neurones of the brain the stored material stained with HEIDENHAIN's iron-haematoxylin and with SPIELMEYER's myelin method, and was not sudanophilic.

DIEZEL (1957) who made a thorough histochemical study of numerous cases found that cholesterol esters were present in the cells of the infantile cases (as first reported by HURST 1925) and not in the juvenile, and that metachromasia was less pronounced in cases of higher age groups. According to SEITELBERGER, VOGEL and STEPAN (1957) and SEITELBERGER and NAGY (1958) metachromasia is present in the forms occurring at lower age and is almost absent in the more adult variants. The isoelectric point of the stored material is also lower in the infantile variants.

Quantitative *chemical studies* (KLENK 1940, 1941; SVENNERHOLM and ZETTERGREN 1957) have shown there is a marked increase in gangliosides in infantile amaurotic idiocy. KLENK could not detect any definite chemical abnormality in the brains of juvenile cases. According to CUMINGS (1957) the increase in neuraminic acid (and therefore in gangliosides) is present in the cortex of cases of all ages. Other workers could not find an increase in gangliosides in late infantile or in the more adult forms of amaurotic idiocy (JERVIS 1952; TINGEY et al. 1958; TINGEY 1959).

It is known for a long time that the presence of balooned neurones caused by storage of lipidic material cannot be considered specific for amaurotic idiocy. In many cases of Niemann-Pick's disease the appearance of nerve cells is similar, although the substance stored is different. Furthermore, there is enough evidence to show that the stored materials in various cases of amaurotic idiocy are not always the same.

In some cases of amaurotic idiocy the material stored within the neurones or that found either in glial cells or extracellularly, is pigmented. STRÄUSSLER (1906) was probably the first to describe a form of idiocy in which the balooned neurones were pigmented. SPIELMEYER (1906) observed some pigment granules within the material stored in the cells of late infantile amaurotic idiocy. SCHOB (1912) described pigment granules in some affected cells in an early juvenile case. KUFS (1925) in his first description of the adult form of amaurotic idiocy described pigment in the affected neurones. The material stored in the neurones of the first described case of „late infantile" amaurotic idiocy (BIELSCHOWSKY 1936) also had an intrinsic pale yellow colour. Cases in which the material stored within the cells had the characteristics of chromolipoid (lipofuscin) were described by GRINKER (1927), LUBIN and MARBURG (1934), BROWN, CORNER, DODGSON (1954), and ALLEGRANZA (1956). In the cases of JERVIS (1952) and MOSCHEL (1954) there was an extensive deposition of a chromolipoid pigment in the affected areas, but outside the neurones.

It should be noted that the fact that in many cases of amaurotic idiocy the stored material belongs wholly or partly to the chromolipoid pigments, may be considered as an indication for heterogeneity of the syndrome, but cannot be considered as a positive proof of it. As has been shown by CIACCIO (1915) and confirmed by numerous workers (cf. GRANADOS and DAM 1950; LILLIE 1954) chromolipoids are formed by progressive oxidation and polymerization of unsaturated lipids. The formation of lipid pigments in some cases of amaurotic idiocy could therefore also be due to the protracted course of the disease, or to a higher content of unsaturated fatty acids within the deposited lipids, or even to the presence within the tissues of conditions enhancing oxidation (for example presence of oxidants as haemoglobin, or absence of anti-oxidants as vitamin E).

Positive proof of the heterogeneity of the amaurotic idiocy syndrome is derived from other considerations:

1. Whereas some authors (HURST 1925; BROWN, CORNER and DODGSON 1954; DIEZEL 1957) have found histochemical or chemical evidence of storage of cholesterol within the affected cells, in most cases no evidence of such storage has been found (KLENK, 1939; KLENK 1942; CUMINGS 1953; ARONSON, VOLK and EPSTEIN 1955; TINGEY et al. 1958).

2. From what have been mentioned above it is obvious that in some cases of post-infantile amaurotic idiocy, storage of gangliosides occurred, whereas in the majority of cases no such storage could be detected.

3. A number of cases has been described in the literature which could not be fitted into any of the variants of amaurotic idiocy. In the second case reported in the article of GLOBUS (1923) the stored material stained only with the Marchi method, and very faintly with the Sudan and myelin stains. In SEITELBERGER's case (1952) part of the stored material did not react with iron-haematoxylin, and

contained ionic iron. In the cases described by WILDI (1950) and by FAVARGER and WILDI (1957) there was a very marked increase in the cerebroside content of the brain.

The case described in the present paper considered without the histochemical findings, would fit clinically and pathologically the infantile variant of amaurotic idiocy. According to the histochemical findings, however, its inclusion in any of the accepted variants is not possible. The stored lipid within the neurones did not react strongly with either the myelin stains (as in the infantile cases), or the Sudans (as in the later cases). There was no evidence of the presence of appreciable amounts of acidic polysaccharides with the Bi-Col stain or with the Einschlußfärbung (metachromasia). Since it is known that gangliosides are strongly acidic, these findings do not correspond to a marked storage of gangliosides. The intense staining with P.A.S. in conjunction with the evidence for paucity of acidic compounds, indicates storage of neutral glycolipids, probably cerebrosides. Besides, the cells contained large amounts of cholesterol (or some other unsaturated sterol).

The described case is therefore similar in some respects to the cases of WILDI and FAVARGER and WILDI (l. c.) and in other respects to the case of BROWN, CORNER and DODGSON (l. c.).

In the opinion of the writer, the study of lipidoses in general suffers from overclassification. Most authors classify their cases of lipidoses in accordance with the predominant abnormal metabolite stored within the affected cells. UZMAN (1958) called attention to the fact that beside the change in the amount of the lipid which is considered to be specifically deranged in lipidoses, the amounts of other lipidic constituents are often also abnormal within the affected cells. The question, therefore, arises whether classification of amaurotic idiocy cases (and of other lipidoses) in accordance with the nature and the amount of the product mainly deposited is justified. If this is done, at least 8 variants of amaurotic idiocy will have to be recognized, and more will probably appear when more cases will be studied by modern chemical and histochemical methods. In the writer's opinion, therefore, amaurotic idiocy should be considered for the time being as a clinical and morphological syndrome, which might represent different metabolic derangements. The question of the homogeneity or heterogeneity of amaurotic idiocy will be answered satisfactorily only after further pathogenetic studies will elucidate the nature of the responsible enzymatic derangements.

Summary

A case of familial amaurotic idiocy in a child which died at the age of two and one half years is described. The pathological findings in the brain were typical for the disease. Histochemical examination revealed that the substance stored in the neurones was a mixture containing mainly a neutral glycolipid and cholesterol. The findings in this case, taken together with other reports in the literature indicate that the composition of the substance stored in various cases of amaurotic idiocy may vary to a great extent.

The possibility is envisaged that amaurotic idiocy might be a syndrome which is due to different metabolic derangements in the various cases.

Zusammenfassung

Es wird ein Fall von amaurotischer Idiotie bei einem im Alter von $2^1/_2$ Jahren verstorbenen Kinde beschrieben. Der pathologische Hirnbefund ist für diese Krankheit charakteristisch. Histochemische Untersuchungen zeigen, daß die in den Neuronen gespeicherte Substanz aus einem Gemisch von hauptsächlich neutralen Glykolipiden und von Cholesterin besteht. Der Befund des beschriebenen Falles, sowie die Befunde von einigen Fällen der Literatur weisen darauf hin, daß die Zusammensetzung des gespeicherten Materials in den einzelnen Fällen dieser Erkrankung nicht gleichartig sein muß.

Die Möglichkeit wird erwogen, daß die amaurotische Idiotie ein Syndrom ist, das in der Vielfalt der Fälle durch verschiedene metabolische Störungen hervorgerufen wird.

References

ALLEGRANZA, A.: Studio istologico ed istochimico di un caso di idiozia amaurotica dell' adulto (tipo Kufs). Acta neurol. (Napoli) **11**, 596—620 (1956).

ARONSON, S. M., B. W. VOLK and N. EPSTEIN: Morphologic evolution of amaurotic family idiocy. The protracted phase of the disease. Amer. J. Path. **31**, 609—631 (1955).

BIELSCHOWSKY, M.: Zur Histopathologie und Pathogenese der amaurotischen Idiotie mit besonderer Berücksichtigung der zerebellaren Veränderungen. J. Psychol. Neurol. (Lpz.) **26**, 123—199 (1921).

—, Neuropathologische Mitteilungen II. Über eine bisher unbekannte Form von infantiler amaurotischer Idiotie. Z. ges. Neurol. Psychiat. **155**, 321—329 (1936).

BROWN, N. J., B. D. CORNER and M. C. H. DODGSON: A second case in the same family of congenital familial cerebral lipoidosis resembling amaurotic family idiocy. Arch. Dis. Childh. **29**, 48—54 (1954).

CIACCIO, C.: Untersuchungen über die Autooxydation der Lipoidstoffe und Beitrag zur Kenntnis einiger Pigmente (Chromolipoide) und Pigmentkomplexe. Biochem. Z. **69**, 313—333 (1915).

CUMINGS, J. N.: The cerebral lipids in disseminated sclerosis and in amaurotic family idiocy. Brain **76**, 551—562 (1953).

—, The diagnostic value of lipid estimations in the cerebral lipidoses. In: Cerebral lipidoses, a symposium. Ed.: J. N. CUMINGS. Oxford: Blackwell 1957.

DIEZEL, P. B.: Die Stoffwechselstörungen der Sphingolipoide. Berlin, Göttingen, Heidelberg: Springer 1957.

FAVARGER, P., and E. WILDI: Chemical analysis and histochemical examination of an atypical case of Tay-Sachs' disease. In: Cerebral lipidoses, a symposium. Ed.: J. N. CUMINGS. Oxford: Blackwell 1957.

GIAMPALMO, A.: Le Tesaurosi Lipidiche. Atti. Soc. ital. Patol. **2**, 33—225 (1951).

GLOBUS, J. H.: Ein Beitrag zur Histopathologie der amaurotischen Idiotie (Mit besonderer Berücksichtigung der Beziehungen zu den hereditären Kleinhirnerkrankungen und zur Merzbacher-Pelizaeusschen Krankheit.). Z. ges. Neurol. Psychiat. **85**, 424—466 (1923).

—, Amaurotic family idiocy. J. Mt. Sinai Hosp. **9**, 451—503 (1942).

GRANADOS, H., and H. DAM: On the histochemical relationship between peroxidation and the yellow-brown pigment in the adipose tissue of vitamin E-deficient rats. Acta. path. microbiol. scand. **27**, 591—596 (1950).

GRINKER, R. R.: The microscopic anatomy of infantile amaurotic idiocy, with special reference to the early cell changes and the intracellular lipoids. Arch. Path. Lab. Med. **3**, 768—784 (1927).

HASSIN, G. B.: A study of the histopathology of amaurotic family idiocy (Infantile type of Tay-Sachs). Arch. Neurol. Psychiat. (Chicago) **12**, 640—662 (1924).

HURST, E. W.: A study of the lipoids in neuronic degeneration and in amaurotic family idiocy. Brain **48**, 1—42 (1925).

JERVIS, G. A.: Familial mental deficiency akin to amaurotic idiocy and gargoylism. An apparently new type. Arch. Neurol. Psychiat. (Chicago) **47**, 943—961 (1942).

—, Hallervorden-Spatz disease associated with atypical amaurotic idiocy. J. Neuropath. exp. Neurol. **11**, 4—18 (1952).

KLENK, E.: Lipoidosen. Physiologisch-chemisches Referat. Verh. dtsch. Ges. Verdau.- u. Stoffwechselkr. 14 Tag., 6—12 (1939).
—, Beiträge zur Chemie der Lipoidosen. 3. Mitteilung. Niemann-Picksche Krankheit und amaurotische Idiotie. Hoppe Seyler's Z. physiol. Chem. **262**, 128—143 (1940).
—, Neuraminsäure, das Spaltprodukt eines neuen Gehirnlipoids. Hoppe-Seyler's Z. physiol. Chem. **268**, 50—58 (1941).
—, Über die Ganglioside des Gehirns bei der infantilen amaurotischen Idiotie von Typ Tay-Sachs. Ber. dtsch. chem. Ges. **75**, 1632—1636 (1942).
KUFS, H.: Über eine Spätform der amaurotischen Idiotie und ihre heredofamiliären Grundlagen. Z. ges. Neurol. Psychiat. **95**, 169—188 (1925).
LILLIE, R. D.: Histopathologic technic and practical histochemistry. New York, Toronto: Blakiston 1954.
LUBIN, A. J., and O. MARBURG: Juvenile amaurotic idiocy. A clinicopathologic study. Arch. Neurol. Psychiat. (Chicago) **49**, 559—573 (1943).
MOSCHEL, R.: Amaurotische Idiotie mit einer besonderen Form von Pigmentablagerung. Dtsch. Z. Nervenheilk. **172**, 102—110 (1954).
SACHS, B.: On arrested cerebral development, with special reference to its cortical pathology. J. nerv. ment. Dis. **14**, 541—553 (1887).
SCHAFFER, C.: General significance of Tay-Sachs disease. Arch. Neurol. Psychiat. (Chicago) **14**, 731—741 (1925).
—, Pathogenesis of amaurotic idiocy. Arch. Neurol. Psychiat. (Chicago) **24**, 765—775 (1930).
SCHEIDEGGER, S.: Amaurotische Idiotie. Ihre Stellung zu den Lipoidosen und die Beziehung zu der Niemann-Pickschen Krankheit. Schweiz. Z. Path. **4**, 27—120 (1941).
SCHOB, F.: Zur pathologischen Anatomie der juvenilen Form der amaurotischen Idiotie. Z. ges. Neurol. Psychiat. **10**, 303—324 (1912).
—, Die Amaurotische Idiotie. In: Handbuch der Geisteskrankheiten. Hrsg.: O. BUMKE. Bd. 11. Berlin: Springer 1930.
SEITELBERGER, F.: Eine unbekannte Form von infantiler Lipoid-Speicherkrankheit des Gehirns. Proc. 1st Int. Congress Neuropath., Rome **3**, 323—333 (1952).
SEITELBERGER, F., G. VOGEL u. H. STEPAN: Spätinfantile amaurotische Idiotie. Arch. Psychiat. Nervenkr. **196**, 154—190 (1957).
—, u. K. NAGY: Zur Histopathologie und Klinik der Spätform von amaurotischer Idiotie. Dtsch. Z. Nervenheilk. **177**, 577—596 (1958).
SPIELMEYER, W.: Über eine besondere Form familiärer amaurotischer Idiotie. Neurol. Zbl. **25**, 51—55 (1906).
STRÄUSSLER, E.: Über eigenartige Veränderungen der Ganglienzellen und ihrer Fortsätze im Centralnervensystem eines Falles von kongenitaler Kleinhirnatrophie. Neurol. Zbl. **25**, 194—205 (1906).
SVENNERHOLM, L., and L. ZETTERGREN: Infantile amaurotic idiocy. Microscopical and chemical investigation of one case. Acta path. microbiol. scand. **41**, 127—134 (1957).
SWANK, R. L., and H. A. DAVENPORT: Marchi's staining method: studies of some of the underlying mechanisms involved. Stain Technol. **9**, 11—19 (1934).
TINGEY, A. H., R. M. NORMAN, H. URICH and W. H. BEASLEY: Chemical and pathological findings in a case of late infantile amaurotic idiocy of the Batten type. J. ment. Sci. **104**, 91—102 (1958).
TINGEY, A.: The results of glycolipid analysis in certain types of lipidosis and leucodystrophy. J. Neurochem. **3**, 230—237 (1959).
TUTHILL, C. R.: Juvenile amaurotic idiocy. Marked adventitial growth associated with skeletal malformations and tuberculomas. Arch. Neurol. Psychiat. (Chicago) **32**, 198—209 (1934).
UZMAN, L. L.: The significance of the increase of nonspecific lipid components in primary lipoid-storage diseases. A.M.A. Arch. Path. **65**, 331—339 (1958).
VOGT, H.: Familiäre amaurotische Idiotie, histologische und histopathologische Studien. Arch. Kinderheilk. **51**, 1—35 (1909).
WILDI, E.: Contribution à l'étude anatomo-pathologique et chimique de la maladie de Tay-Sachs. Thèse No. 1978, Faculté de Médecine, Genève 1950.
WOLMAN, M.: A histochemical method for the differential staining of acidic tissue components (particularly ground-substance polysaccharides). Bull. Res. Council Israel **6 E**, 27—35 (1956).

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