TAY-SACHS DISEASE WITH VISCERAL INVOLVEMENT AND ITS RELATION TO GARGOYLISM

BY

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There is an accumulation of clinical, neuropathological, and chemical evidence pointing to the clear separation of Tay-Sachs disease from other forms of amaurotic family idiocy. One point of distinction is the rarity of visceral lipidosis in the infantile form of the disease. We have, in fact, only been able to find reference to five cases of Tay-Sachs disease in which the neuronal lipidosis was associated with signs of a more generalized storage disease, and in some of these the evidence is not very convincing. Davison and Jacobson (1936) reported foam cells in the spleen, and vacuoles containing sudanophil lipid in the cells of the liver and renal tubules. Brouwer (1936) also found foam cells in the spleen of his case. Marburg (1942) described vacuoles in the liver which were filled with lipid staining in the same way as that in the nerve cells. This case was unusual because of the severe atrophy and fibrosis of some of the other glandular organs. It is difficult to assess the significance of these changes as part of a primary lipidosis, and it is certainly unlikely that the lipid in the organs of these three cases was chemically identical to that stored in the neurones. The brain in Tay-Sachs disease stores large amounts of ganglioside, and an essential component of this substance is neuraminic acid. Neuraminic acid is not normally present in the spleen, liver, or kidneys, so that an accumulation of ganglioside would not be expected to occur in these sites as the result of deranged local metabolism. On the other hand, it is well known that in certain lipidoses there may be differences between the substances or mixtures of substances that are stored in the brain and in the viscera. In gargoylism the nerve cells contain an increased amount of ganglioside (though usually much less so than in Tay-Sachs disease), while the other affected organs predominantly store polysaccharides. The latter material is readily diffusible, so that the involved tissues, after ordinary fixation, are characterized histologically by the presence of empty vacuoles.

There are two recorded examples of undoubted Tay-Sachs disease, in which a similar change has been found in some of the visceral organs. Turban (1944) described a non-Jewish child who died at the age of 2 years after a progressive neurological illness. The characteristic cherry-red spot at the macula had been noted. Analysis of the cerebral cortex by Klenk showed a fivefold increase in ganglioside, and histologically the brain was typical of Tay-Sachs disease. Empty vacuoles were a conspicuous feature of the cells of the liver and renal tubules, and foam cells, also devoid of lipid, were present in the pulmonary alveoli and their walls. More extensive visceral involvement of the same type was described by Norman, Urich, Tingey, and Goodbody (1959) in their case of infantile amaurotic idiocy. This child had shown typical macular changes and also came from a non-Jewish family. There was hepatomegaly and slight enlargement of the spleen. Empty vacuoles were present in the parenchyma of the liver, kidney, pancreas, and thyroid. Empty foam cells were numerous in the liver, spleen, lymph nodes, thymus, intestines, bone-marrow, and lungs, both in the alveoli and their septa.

The case to be reported in this paper is a further example of this unusual combination of neural and visceral lesions in a chemically verified case of Tay-Sachs disease. Additional interest is given by the detailed clinical examination which was made at a time when hypotonia was the main neurological abnormality.

Case Report

Clinical Findings. This child (J.C.) was first referred under the care of Professor D. V. Hubble in December 1960, for investigation of motor and mental retardation, first suspected three months previously, at the age of 9 months. She was the first child of normal parents, with a
negative family history. Delivery was by forceps, for disproportion. Birth weight, 8 lb. 11 oz. (3,939 g.).

The neonatal period was uneventful, but she was noted to be lethargic before leaving the maternity hospital. There were no feeding difficulties. Vaccination, whooping cough, and diphtheria immunization and B.C.G. were tolerated normally.

When seen at the age of 1 year, her condition was as follows. Weight was 24 lb. 4 oz. (11 kg.), on the 90th percentile; length, 32-5 in. (82-5 cm.), above the 97th percentile; and head circumference, 19-5 in. (49-4 cm.), above the 97th percentile. The skull showed a metopic ridge. She was said to respond to her parents, and was seen to smile, chuckle, and cry. There had been no convulsions, but twitching affecting all limbs was observed once.

Sight examination revealed that she followed bright objects. The pupils were small, but reacted briskly to light. She blinked in reaction to a loud noise, but showed no other reaction.

Examination of the cranial nerves revealed that the optic disks appeared normal; the retinas were somewhat pale: the right macula was noted to resemble a Koppik spot, in that there was a central pale point surrounded by a zone pinker than the adjacent retina. No cranial nerve palsies were present, but there was a suggestion of ptosis. There was a marked hypotonia of neck, trunk, and limbs. The tendon jerks, however, were brisk, and there were equivocal plantar responses and positive finger jerks (thumb adduction). Abdominal reflexes could not be obtained. There was also abnormal persistence of some neonatal reactions, such as tonic neck reflexes, palmar grasp, lateral trunk incursion, and a modified Moro reflex. Voluntary movements were weak, of low amplitude, and appeared non-purposive. The muscles were flabby but not wasted. There was no fasciculation.

Painful stimuli produced a weak withdrawal response and cry.

Other findings included two café au lait spots on the trunk.

Respiration was normal, and there was no chest deformity nor other abnormality. There was no apparent enlargement of lymph nodes, liver, or spleen.

An electroencephalogram (Dr. B. D. Bower) consisted mainly of well-organized theta activity which was symmetrical and of normal amplitude. There was also low amplitude fast activity. It was thought that the record was normal.

Cerebrospinal fluid (lumbar puncture) yielded one white cell per c.mm.; protein 35 mg./100 ml.; sugar 64 mg./100 ml. Cerebrospinal fluid (ventricular puncture) yielded 2 lymphocytes, 2 red cells per c.mm.; protein 20 mg./100 ml.; sugar 57 mg./100 ml. Skull radiograph was normal in appearance, as was the air encephalogram (Dr. R. Astley). Urinalysis gave albumin 10 mg./100 ml. only; very occasional dead white cell, and numerous epithelial cells. Amino acid excretion was normal. Negative test for phenylpyruvic acid. Xanthurenic acid excretion after tryptophan load (Dr. B. D. Bower) was normal (increase of 3-8 mg. over 24 hours). Tests for toxoplasmosis were negative.

Since the investigations were negative, a provisional diagnosis of hypotonic cerebral palsy with mental retardation and possible special sense impairment was made.

The later stages of the illness were marked by a rapid deterioration in the child’s clinical condition. She became almost amental, lying motionless, and not following objects with her eyes. There were no tonic spasms. Death occurred from bronchopneumonia when she was 2 years old.

Necropsy. External examination revealed a well-nourished female child.

Internal Examination. The brain was normal in size but grossly oedematous with distended dural sinuses and marked congestion of the vessels of the arachnoid and pia matter. The mucosa of the trachea and bronchi was congested and covered by thick purulent mucus. The lung tissue showed patchy bronchopneumonic consolidation. The heart was normal. The liver, spleen, and kidneys were congested but otherwise normal and there was no lymphadenopathy.

Histology. Numerous foam cells were present both in the walls and lumina of the lung alveoli (Fig 1). Exudate and pus cells filled many of the alveoli and small bronchi, and there was inflammatory infiltration of the interstitial lung tissue. The lobular pattern of the liver was preserved.
Fig. 2.—Liver: large single vacuoles are present in many of the cells. (H. and E. × 405.)

Fig. 3.—Kidney: vacuolation of the collecting tubules. (H. and E. × 240.)

Fig. 4.—Pons: nucleus centralis: ballooning of the nerve cells. (Carbol azure. × 240.)

Fig. 5.—Cerebral cortex: the nerve cells are filled with haematoxyphil lipid. (Kultschitsky-Pal. × 31.)
and there was marked congestion. Many of the liver cells showed a large central vacuole (Fig. 2). There was marked vacuolation of the epithelial cells of the collecting tubules and of many of the convoluted tubules of the kidney (Fig. 3). The normal splenic structure was maintained.

**Examination of the Brain**

Blocks of tissue were available from parts of the cerebral cortex, the anterior part of the corpus striatum including the internal capsule and corpus callosum, and from the pons. Frozen sections were stained by standard methods for nerve cells, axis cylinders, myelin, fibrous neuroglia, and lipid.

**Nerve Cells.** In all parts of the brain that were available for examination, the nerve cells were greatly distended with a granular material, the nuclei in pyramidal cells usually being displaced towards the apical dendrite (Fig. 4). Neurofibrils could not be demonstrated in the majority of the cortical nerve cells but in some of the less swollen ones they were present as a thin marginal ring. Large fusiform dendritic expansions containing similar granular material were occasionally seen. The material stored in the neurones stained crimson with the periodic acid-Schiff (PAS) method, black with the Kultschitsky-Pal method for myelin (Fig. 5), and the same colour as the myelin with Luxol fast blue. With Sudan IV, Sudan black, and Nile blue sulphate, there was only a very feeble coloration. Most neurones contained scanty sudanophil granules. The PAS staining was negative or greatly reduced in intensity after sections had been kept overnight in cold ethyl alcohol, only a light pink colour remaining in some of the larger cells.

**Microglia.** Phagocytes filled with closely packed granules which stained brightly with PAS, Sudan, and Nile blue were scattered diffusely through the grey matter. They were numerous in areas in which nerve cell loss had occurred, as in parts of the cerebral cortex, and, particularly, the griseum pontis. In contrast to the nerve cells, the PAS staining remained strongly positive after treatment with alcohol. Small collections of fat granule cells were seen around vessels in the white matter.

**Neuroglia.** Fibrous gliosis was a marked feature of the whole of the grey matter (Fig. 6). In the white matter gliosis was dense in the poorly myelinated areas, particularly the internal capsule (Fig. 8), and in the pes pontis.

**Myelin.** The cores of the cerebral gyri and the deeper white matter showed a diffuse reduction in myelinated fibres. A more severe loss of fibres was found in the internal capsule (Fig. 7), transverse fibres of the pons, and the descending cortical tracts. The corpus callosum and the tracts in the tegument of the brain-stem stained normally.

**Chemistry**

The analytical methods used were those described in previous papers (Tingey, 1959; Tingey and Edgar, 1963). The brain had been fixed in 10% formal saline for 14 months. Comparison has been made with a normal control (16 month-old child; brain 12 months in formalin), and with our previous case of Tay-Sachs’ disease in which
visceral involvement had also been found (17 months at death; brain 18 hours in formalin, Norman et al., 1959).

The results of chemical analysis of the cerebral cortex and white matter are shown in the Table. The very high levels of lipid hexosamine and neuraminic acid are the most striking finding and strongly suggest Tay-Sachs disease. The level of ganglioside may be calculated from either of these substances. The chromatogram (Fig. 9) shows that the excessive ganglioside fraction in Case J.C. occupies the position of the monosialo-ganglioside G.M.2 described in Tay-Sachs disease by Svennerholm (1963). In normal brains this particular fraction constitutes only 3-6% of the total ganglioside. The greatly increased total lipid hexose reflects the accumulation of this component. The main differences between Case J.C. and our previously reported case of Tay-Sachs disease lie in the considerably increased cortical cholesterol and in the much smaller amount of non-lipid hexosamine.

**Discussion**

When this child was examined at the age of 12 months there was little to suggest Tay-Sachs disease except for the marked hypotonia which is a characteristic early sign (van Bogaert, 1962). Macular changes of the sort seen in this patient's right eye

**Table**

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<thead>
<tr>
<th></th>
<th>Cerebral Cortex</th>
<th>Cerebral White Matter</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Case J.C.</td>
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<tr>
<td>Total lipid</td>
<td>30.6</td>
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<tr>
<td>Cholesterol free</td>
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<td>Cholesterol ester</td>
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<tr>
<td>Total phospholipid</td>
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<tr>
<td>Lecithin</td>
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<tr>
<td>Sphingomyelin</td>
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<tr>
<td>Total lipid hexose</td>
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<td>4.50</td>
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<tr>
<td>Neutral hexose</td>
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<tr>
<td>Lipid hexosamine</td>
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</tr>
<tr>
<td>Non-lipid hexosamine</td>
<td>0.466</td>
<td>0.320</td>
</tr>
<tr>
<td>Water</td>
<td>86.6</td>
<td>81.9</td>
</tr>
</tbody>
</table>

All values (except water) in g./100 g. of dry tissue.
TAY-SACHS DISEASE AND GARGOYLISM

have never been described in the infantile form of amaurotic idiocy (Danis, Bégaux, and Decock, 1957), but there is a single observation by Holmes and Paton (1925) of an apparently similar phenomenon occurring as the earliest manifestation of the macular degeneration of Batten’s juvenile type of the disease. The fundi in this case were normal except that ‘at both maculae there had appeared a tiny white area surrounded by an areola of redness, fading off into the normal retina’. As will be seen, however, our patient was certainly not an example of precocious Batten’s disease.

The neuropathological features were similar to those described in previous cases of infantile amaurotic family idiocy, particularly as regards the different staining and solubility of the lipids in the neurones and microglia. Histological distinctions from Niemann-Pick’s disease are undoubtedly difficult to draw in the brain, but apart from the chemical findings, the absence of foam cells in the spleen and liver makes this diagnosis untenable. The neuronal changes were unlike those of Batten’s disease or of gargoylism in which the intracellular lipid is strongly resistant to solvents and is much less haematoxyphilic (Bishton, Norman, and Tinge, 1956). Nor were the meningeal fibrosis or the perivascular lacunae and networks of gargoylism seen in this brain.

The most convincing evidence of a visceral storage disease was provided by the changes in the lung, though the vacuolation in the liver and kidney may well be significant in this respect when viewed in the light of Turban’s and our own previous case. Foam cells confined to the alveolar air spaces may be found in a variety of conditions, but to our knowledge these cells are widely distributed in the alveolar septa only as part of a storage disease. They are commonly seen, for example, in Niemann-Pick’s disease, and have been noted in infantile Gaucher’s disease (Bérard-Badier, Payan, and Edgar, 1962), in lipogranulomatosis (Farber, Cohen, and Uzman, 1957), and in gargoylism (Henderson, MacGregor, Thannhauser, and Holder, 1952).

The chemical analysis of the brain yielded the large increment of ganglioside appropriate to Tay-Sachs disease. This substance, however, is also increased in gargoylism, and Klenk (1955) has reported levels as high as four to five times the normal. This is about the same increase as was found in the cortex of Turban’s case and is higher than in our two cases. Tinge (1959), however, has analysed two gargyle brains using the same methods as in the present case and found only a small increase of ganglioside in the grey and white matter. In our opinion, a decisive difference from gargoylism lies in the tenfold increase of ganglioside in the white matter of our case, since levels of this magnitude have never been reported in the brains of gargoyles. It is necessary to emphasize this point because in our previous case of Tay-Sachs disease there were clinical features suggestive of gargoylism, namely, the corneal clouding, the depressed bridge of the nose, the protruding tongue, and the swollen abdomen. The conclusion may be drawn that the syndrome of Tay-Sachs disease may occasionally include visceral changes that resemble those of gargoylism more closely than any other storage disease. This apparent relation may reflect a similarity in the metabolic upset present in these two nosologically distinct diseases. Klenk (1955) has stated that both conditions ‘could probably be caused by the same disturbance in the metabolism of the brain’, while Diezel (1960), in discussing the chemical pathogenesis of the neural and visceral changes in gargoylism, sees a common factor in the hexosamine component, which is shared by ganglioside and polysaccharides. Future chemical examination of unfixed tissues in Tay-Sachs disease may be expected to provide the solution to this problem.

Summary

A female non-Jewish child died at the age of 2 years after a progressive neurological illness beginning with severe hypotonia. Ophthalmoscopic examination showed a white spot surrounded by a red halo at the right macula. Neuropathologically the changes were typical of infantile amaurotic family idiocy. Chemical analysis showed that ganglioside (as estimated from the neuraminic acid content) was increased three and a half times the normal in the cerebral cortex and ten times in the white matter, the latter finding being regarded as typical of Tay-Sachs disease. Examination of the visceral organs showed foam cells in the alveolar septa and vacuolation of the cells of the liver and renal tubes. Comparison is made with two previously recorded cases in which there has been an association between Tay-Sachs disease and a visceral storage disease suggesting in some respects that of gargoylism.

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