NERVE-CELL SWELLING OF THE JUVENILE AMAUROTIC FAMILY IDIOCY TYPE

ASSOCIATED WITH TUBEROSE SCLEROSIS IN AN INFANT
AGED TWELVE MONTHS

BY

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This paper records the occurrence in the brain of an infant aged twelve months of tuberoses sclerosis together with nerve cell changes of a type which, until recently, has been considered peculiar to the juvenile or Spielmeyer-Vogt variety of amaurotic idiocy. Pathological coincidences of this sort in the nervous system are rare and with the exception of Ostertag's (1925) description of infantile amaurotic idiocy associated with pachygyria and microgyria, I have been unable to find in the literature of either tuberoses sclerosis or amaurotic idiocy a comparable example of double abnormality. Recently evidence has been brought forward suggesting that Hunter-Hurler's disease (gargoylism) is a member of the group of so-called lipoidoses (Ashby, Stewart and Watkin, 1937; Kressler and Aegerter, 1938), and it has been shown that the nervous system may be affected in a manner closely simulating juvenile amaurotic idiocy. There are reasons for believing that the condition now described differs materially from these two diseases, though the type of nerve cell change is very similar in all three. That such a pathological picture, hitherto reported only in much older individuals, should be found in fully developed form in an infant is sufficiently remarkable to deserve comment.

Case report

The patient, a male infant aged one year and ten days, was admitted to Stoke Park Colony on August 8, 1938.

Family history. Enquiry was welcomed by the parents, who were visited and a full family history obtained. This was entirely negative, but is summarized here for the sake of completeness. On the mother's side the patient's grandmother aged seventy is alive and healthy. The grandfather died aged sixty-four from 'pleurisy following influenza.' The paternal grandmother aged seventy-one is healthy. The paternal grandfather died from Bright's disease at the aged of fifty-nine. The father and mother are healthy, in comfortable circumstances and of superior mental type. They are non-Jewish and not blood relatives. The father was thirty-three and the mother thirty-one years old at the time of patient's birth. The mother has four healthy sisters living. One sister died at the age of eighteen months, the cause of death being

'gastritis.' Two are married and one has a normal child. The father has two brothers both married. One has four healthy children, the other a single child also stated to be normal. The father also had an infant sister who died from 'meningitis' aged two and a half years. He understands that the child was of normal mentality. The patient was the younger of two children, the elder sister aged four (seen) is a normal and well developed girl. There is no history of epilepsy or psychopathic traits in the pedigree and the mother knew of no relative with skin abnormalities or heart disease.

History prior to admission to colony. The pregnancy and labour were uneventful. The baby took the breast and was considered to be normal by the parents up to the age of about three months. Until this time development as judged by weight records was satisfactory. On looking back upon these early months, however, the mother now recalls that although reacting to sounds the baby did not seem to recognize her. Visual defect was not suspected until after an operation for circumcision, which was performed at four months. At that time nystagmus of the non-fixation type was first noticed. Teething started at four months. By six months physical and mental defect were obvious. At ten months the child could not sit up and the head tended to fall forwards. He did not grasp objects placed in his hands. Twitching of the side of the face was observed at eight months and generalized convulsions started two months later. These increased in frequency and at the time of the child's death at the age of twelve months averaged six a day. The blood Wassermann reaction was negative.

Examination on admission to the colony. A well-nourished baby; weight: 1 stone 8 lb. Height: 2 ft. 7 in. The upper and lower incisors were present. Apart from a rapid rate no cardiac abnormality was found. There was no enlargement of thyroid, liver or spleen. The infant was unable to hold up his head, sit up or stand. He paid no attention to visual stimuli. The head was large: length, 166 mm.; breadth, 134 mm.; height, 127 mm. The facies was not that of gargoylism.

NERVOUS SYSTEM. Muscle tone was not increased in the limbs. The tendon reflexes were equal on both sides and not exaggerated in arms and legs. The abdominal and cremasteric reflexes were not obtained. There was a variable Babinski sign on both sides. The pupils were equal and reacted to light.

Progress. During the first three days after admission he averaged six fits a day. The fits started with a scream, followed by twitching of the limbs for several seconds. On the fourth day his colour became poor, the temperature rose to 100° F., and an impaired percussion note and diminished breath sounds were detected over the left base. The heart sounds were rapid and feeble. No improvement in the general condition occurred, and the next day death took place.

Post-mortem report. At the autopsy signs of early broncho-pneumonia were present in the lower lobe of the left lung, but they were not considered sufficient to have accounted for death in a normal child. Small areas of atelectasis were found in the lungs. In the heart numerous small greyish areas, lying flush with the adjacent muscle tissue, were observed in the walls of both ventricles and auricles, in the interventricular septum and in some of the papillary muscles. There was no valvular abnormality. The spleen, liver, suprarenals and other visceral organs appeared normal.

On removing the calvaria, which was of normal thickness, the dura and leptomeninges showed no abnormality, but the brain consistency was much denser than usual, suggesting a diffuse cortical sclerosis.

After fixation in formol saline the weight of the brain was 1,307 grammes. A closer inspection of the cerebral hemispheres after stripping showed that

the cerebral cortex was extensively affected by tuberosc sclerosis, for although all parts of the brain seemed tougher than usual to palpation, portions of the gyri showed the whitish, hard, discrete patches characteristic of the condition. The width of the gyri varied abnormally, those affected by tuberosc sclerosis being sometimes unusually massive; but the general impression given was that of a richly convoluted brain. Although no gross malformation of gyral pattern was present, a few minor abnormalities were seen, the left superior temporal sulcus being short and irregular, the right Rolandic sulcus being in two parts and the right angular and supramarginal gyri ill-defined.

The left cerebral hemisphere was reserved for microscopical examination. On section the lateral ventricle was found to be dilated, especially in the posterior horn. Small subependymal tumours and 'candle-gutterings' were attached to the caudate nucleus and thalamus.

Microscopical examination of the visceral organs

The LUNGS showed an early broncho-pneumonic process of limited extent and also areas of atelectasis.

The BRONCHIAL LYMPH NODES contained small deposits of neutral fat, but not in abnormal amount.

In the SPLEEN groups of endothelial cells enclosed material having the staining properties and solubility of neutral fat. After treatment with chloroform, minute granules, staining yellow with scharlach R, were found in some of the endothelial cells. Similar findings occurred in normal control material. There were no foam cells visible.

The LIVER showed an unusual degree of fatty infiltration, small closely packed droplets of fat being uniformly present in all zones of the lobules. No scharlach-staining material remained after treatment with alcohol. No foam cells were seen.

The KIDNEYS were normal.

In the HEART the small grey areas observed macroscopically proved to be rhabdomyomata consisting of primitive muscle cells showing a loose texture (fig. 1) in which with higher magnification transverse striation was frequently seen (fig. 2).

Microscopical examination of the nervous system

CEREBRAL CORTEX. Nineteen representative areas were examined from the left cerebral hemisphere.

NERVE CELLS. A varying degree of disorderly arrangement of nerve cells was present in the tuberosc parts of the gyri, but generally speaking there was no gross upset of cytoarchitectonics. A conspicuous feature of most of the sections were large nerve cells of abnormal shape contrasting sharply with the small size of their neighbours (fig. 3). Groups of these giant cells were frequently seen in the deeper cortical layers. The nerve cells for the most part stained poorly with cresyl violet owing to a poverty of Nissl bodies. With this stain it was possible to recognize, particularly in the larger pyramidal cells, a pyriform distension of the cell body with a finely granular substance, the nucleus and Nissl bodies being pushed to the apex of the cell. The swollen cell body often showed a finely reticulated appearance. These changes were much more easily recognized in Bielschowsky preparations. The condensed neurofibrillae forming a peripheral ring round the distended cyton were demonstrated by this method, the pathological picture being typical of juvenile

FIG. 1.—Rhabdomyoma of heart showing primitive muscle cells. (H. and E. ; $\times 36$.)

FIG. 2.—Rhabdomyoma of heart showing striped muscle fibres. (H. and E. ; $\times 450$.)

FIG. 3.—Large abnormal nerve cells in a tuberosc portion of the second frontal gyrus. (Bielschowsky's stain ; $\times 80$.)

FIG. 4.—Abnormal astrocytes in tuberosc portion of second temporal gyrus. (Hortega's method for astrocytes ; $\times 80$.)

amaurotic idiocy (fig. 5). Swelling of the cell processes was not seen save in one or two doubtful instances. The ubiquitous distribution of these granular inclusions was obvious in sections stained by scharlach R, a varying amount of pinkish-orange substance, usually in the form of fine granules, being present in almost every cell. The large abnormal cells shared in this change (fig. 6). This distension of the nerve cells with scharlach-staining material was a feature of every cortical area examined and no layer was exempt. There was much variability in the degree of affection of the finer pyramids, some appearing grossly swollen, others containing but few granules. This intracellular granular substance had the following staining reactions: cresyl violet usually failed to colour the granules, but sometimes the larger deposits stained pink. There was no metachromatic staining with toluidin blue. Scharlach R gave a light pink or orange colour. There was no blackening with osmic acid, either with or without chromication. Nile blue stained the deposit deep blue. Using the Kultschitsky-Pal method greyish granules appeared in the nerve cells after two days and were well defined and darker in colour after three days in the mordant. The solubility of the deposit was tested and it was unaffected by ethyl alcohol, methyl alcohol, acetone, ether, benzine, or hot and cold chloroform. Immersion in these solvents overnight seemed rather to improve the penetration of the scharlach, the granules staining a brilliant orange. The substance was present in undiminished amount in celloidin sections. Prolonged immersion at 40° C., or boiling for five minutes in 20 per cent. trichloroacetic acid did not affect the solubility. The reaction to polarized light was also tested. The granules were not doubly refractile. No extra-cellular doubly refractile deposits were seen in frozen or celloidin sections of cortex or thalamus.

MYELIN. The cortex was poor in myelin, the radial bundles being thin. The stria of Gennari could not be identified in myelin preparations. In the tuberoso parts of the cortex myelin was often almost absent in the grey, and sometimes grossly reduced in the central core of white matter, only a few fine fibres being visible in each microscopic field. Generally speaking, however, the subcortical white matter appeared well myelinated.

NEUROGLIA. In all sections examined there was a heavy, uniform fibrillary gliosis in grey and white matter, denser in the tuberoso areas, but present also in the macroscopically less sclerosed areas. Metallic impregnation methods demonstrated several sorts of abnormal astrocytes, big fibrillary types with fleshy cell bodies and numerous coarse wavy processes predominating (fig. 4). Here and there astroblastic types were seen. Giant cells of round or oval shape with peripheral nucleus and usually without processes were scattered throughout the different cortical layers and were especially numerous round blood vessels in the white matter of the gyri. Occasional giant cells or more obviously astrocytic type having short flesh processes could be identified. More rarely, a larger type of elongated giant cell with a leash of long processes at either end of the cell body was seen. No lipid granules were found in the astrocytes, and the giant cells of glial type did not share in the granular change of their neuronal prototypes.

MICROGLIA. Compound granular corpuscles were not numerous in the cortex, but most sections showed some, usually near the vessel walls. At this site the compound granular corpuscles contained neutral fat, but elsewhere gitter cells filled with a substance having staining properties and insolubility identical with those of the granular deposit in the nerve cells were commonly found.

BLOOD VESSELS. Heavy neutral fat deposits in the vessel walls were common, especially in those of the subcortical white matter. The vessels in the sclerotic parts of the cortex showed proliferation of mesenchymal fibrils.

BASAL GANGLIA. Distension of nerve cells with insoluble granules was a conspicuous feature, the caudate nucleus and putamen being less grossly affected

- FIG. 5.—Nerve-cell swelling resembling that of juvenile amaurotic idiocy. Supramarginal gyrus layer V. (Bielschowsky's stain ; $\times 450$.)
- FIG. 6.—Giant cell of neural type affected by granular swelling. First frontal gyrus. (Bielschowsky's stain ; $\times 270$.)
- FIG. 7.—Granular swelling in nerve cells of dentate nucleus. Compound granular corpuscles. (Scharlach R. and Haematoxylin ; $\times 270$.)
- FIG. 8.—Giant cells of glial origin in thalamus subjacent to subependymal tumour. (Cajal's gold sublimate method ; $\times 180$.)
- FIG. 9.—External geniculate body. Section has been treated with boiling chloroform and shows compound granular corpuscles filled with insoluble substance. The granules in the nerve cells are visible as larger and less dense aggregations. (Scharlach R. and haematoxylin ; $\times 180$.)

than the thalamus and globus pallidus, where swelling of cells to two or three times their usual size was seen. These large cells stained a pink colour with scharlach and pink staining with cresyl violet was usual. In Bielschowsky preparations the thalamic cells often showed a reticulated appearance. Giant cells of the rounded form seen in the cerebral cortex were present in the thalamus, caudate nucleus and putamen. In all these areas there was a well-marked fibrillary gliosis, most intense in the thalamus and affecting both white and grey matter. The larger fibre tracts were well myelinated, but the finer fibres in the grey matter seemed reduced in number, particularly in the putamen. Gitter cells containing neutral fat and insoluble substance were numerous in the thalamus, and the walls of the blood vessels contained much neutral fat.

The EXTERNAL GENICULATE BODY showed changes similar to those in the thalamus, but in accentuated form (fig. 9). There appeared to be considerable cell loss and compound granular corpuscles were numerous.

SUBEPENDYMAL TUMOURS. A tumour the size of a large pea was attached to the thalamus and caudate nucleus. It was composed of leashes of coarse glial fibres in the interstices of which were seen groups of giant cells resembling those found elsewhere, but usually having processes at both poles. The central part of the tumour was highly vascular, many of the vessels being calcified. Large calcium deposits were present. The junction of this tumour with the basal ganglia was marked by a broad layer of fine neuroglial fibres, and the transition zone between this band and the parenchyma of the thalamus was particularly rich in giant cells (fig. 8). As in the cortex, these giant cells did not share in the granular change of the neurones. Similar round circumscribed tumours of coarse glial fibres and giant cells were found at the junction of putamen and globus pallidus and in the pons subjacent to the fourth ventricle.

CEREBELLUM. The Purkinje cells of the vermis and lateral lobes all showed moderate swelling of the cell body with insoluble material staining orange-pink with scharlach. Their dendrites often appeared thickened and frequently definite distension with scharlach staining material was observed (fig. 12). Axonal torpedoes were common (fig. 11 and 12). An occasional Purkinje cell of abnormally large proportions was seen (fig. 13). No gross atrophy of Purkinje or granular cells was observed and the latter seemed unaffected by the granular deposit. The basket and the tangential fibres were well preserved. There was a marked fibrillary gliosis in the white matter and the Bergmann fibres of the molecular layer were thickened and proliferated (see fig. 10). Myelinization was normal. Gitter cells containing fat or insoluble material were present in small numbers in the molecular and granular layers and the vessels in the granular layers contained excess of neutral fat.

The DENTATE NUCLEUS showed no atrophy, but all nerve cells were grossly swollen (see fig. 7). There was a heavy fibrillary gliosis around the cells and in the hilum. Compound granular corpuscles were numerous.

MIDBRAIN, PONS, MEDULLA. All nerve cells were affected by the granular change, the inferior olives and pontine nuclei particularly so (fig. 14). The larger fibre bundles, including the pyramidal tracts, were well myelinated, but the nuclear masses showed some poverty of finer fibres. There was a well-marked gliosis of fibrillary type around the affected nerve cells. Gitter cells were present in the inferior olives.

SPINAL CORD. Most of the nerve cells in the cervical cord showed granular distension but a few of the anterior horn cells appeared unaffected. A mild gliosis was present in the grey matter. There was no sclerosis or demyelination in the fibre tracts. The lateral columns, however, stained less intensely with the Kultschitsky-Pal method than the rest of the cord.

FIG. 10.—Lateral lobe of cerebellum. Thickening and proliferation of Bergmann's fibres. A few swollen dendrites of the Purkinje cells are visible in the molecular layer. (Hortega's method for astrocytes; $\times 60$.)

FIG. 11.—Cerebellum. Axonal torpedoes. Purkinje cells show slight granular swelling. (Bielschowsky's stain; $\times 180$.)

FIG. 12.—Cerebellum. Swelling of dendrite of Purkinje cell. (Bielschowsky's stain; $\times 180$.)

FIG. 13.—Giant Purkinje cell. (Bielschowsky's stain; $\times 180$.)

FIG. 14.—Swelling of nerve cells of pontine nuclei with surrounding fibrillary gliosis. (Hortega's method for astrocytes; $\times 180$.)

Discussion

Many of the pathological features described above are those of tuberose sclerosis and this aspect of the case requires little comment. The macroscopically sclerosed areas in the cortex, the subependymal nodules, widespread glial abnormalities, disturbed architectonics and giant cells of neural and glial type leave no doubt as to the nature of the condition, and confirmatory evidence is furnished by the association of cardiac rhabdomyomata, a not uncommon feature of the syndrome of epiloia. Clinically, as in the present case, the diagnosis of tuberose sclerosis may be impossible in an infant suffering only from epilepsy and mental defect. Adenoma sebaceum is seldom present in early life and the other skin abnormalities found in the fully developed form of the disease may be absent. Blindness has been mentioned as a suggestive sign by Globus and Selinsky (1935), but it does not appear to be common in the recorded cases. Since tuberose sclerosis is inherited in all probability as a single dominant gene (Gunther and Penrose, 1935; Penrose, 1936) it is not unusual to find other affected relatives, but in sporadic cases such as this one, in which the disease presumably arises by mutation in a parent, the family history gives no diagnostic clue. Unfortunately in the present instance the infant died before an ophthalmoscopic examination had been made, so that it is impossible to say whether the rare phakomata were present in the retina. Moreover, an examination of the fundus might have helped considerably in the interpretation of the other pathological aspect of this case, namely, the granular swelling of the nerve cells, for, as is well known, the infantile type of amaurotic idiocy does occur, though less frequently, in non-Jewish families.

From the histological point of view it is improbable that in this case the nerve-cell swelling was due to infantile amaurotic idiocy, although the possibility exists that the coincidental tuberose sclerosis may have modified the expression of the disease in a radical manner. In general, the degree of affection of the nerve cells was more akin to that seen in the juvenile type. Ballooning of the cell processes usual in the infantile form was not seen save in one or two doubtful instances. The colouring of the granular inclusions by scharlach and haematoxylin was orange rather than the rosy-red of Tay-Sachs' disease. The gross myelin defects and status spongiosus commonly seen in Tay-Sachs' disease were not present, such myelin defects as were noted being no more than are usual in tuberose sclerosis. The most important distinction of all, however, lies in the insolubility of the granular deposit. The pre-lipoids of infantile amaurotic idiocy are soluble in the more powerful lipid solvents, whereas the granules of the present case resisted boiling chloroform and celloidin embedding. A corollary of this insolubility of the nerve-cell inclusions is probably seen in the absence of scharlach-staining granules in the astrocytes. In the infantile form of amaurotic idiocy lipid granules in the cell bodies of the macroglia are conspicuous and regressive changes are common. In the juvenile type, in which the nerve-cell lipid is only soluble in hot solvents or after prolonged treatment in the cold, the lipid content of the astrocytes is often inconspicuous. The absence of lipid in the astrocytes of the present case would thus appear to

reflect the difficulty of assimilating a yet more insoluble substance. In this connexion it is of interest to note that the compound granular corpuscles in this brain contained both insoluble material (as in the nerve cells) and neutral fat. It is thus probable that a reduction into simpler forms may have been effected in the microglial cells themselves. Apart from this extreme degree of insolubility of the granular inclusions the pathological findings closely resemble those of the juvenile or Spielmeyer-Vogt variety of amaurotic idiocy. The cerebellar changes in particular are characteristic of that type of the juvenile form in which gross atrophy is absent. Yet, as is well known, this form of the disease manifests itself only after several years of normal development and unless once more the hypothesis is to be evoked that the coincidental tuberose sclerosis has modified the customary course of the disease it is inconceivable that an infant of one year should be suffering from a condition genetically identical to juvenile amaurotic family idiocy.

It is more difficult to rule out the possibility that this case is an early form of Hunter-Hurler's disease, for although seventeen cases have been reviewed from the clinical standpoint by Ellis, Sheldon and Capon (1936), only four examples of the disorder have been examined histologically (Tuthill, 1934, one case; Stewart and co-workers, two cases; Kressler and Aegerter, one case). It is true that in the present case there was nothing clinically to suggest gargoylism, but the characteristic osseous abnormalities are not necessarily visible at so early an age. Enlargement of liver or spleen, absent in this case, is not a constant feature of the disorder. A point of greater diagnostic significance is the congenital or early infantile clouding of the cornea often present in the Hunter-Hurler syndrome; this also was absent in the present case. From the histological point of view there are differences between the findings in this brain and those of Tuthill and Stewart.* Extracellular deposits of doubly refractile lipid were not found as in Stewart's first case. The intensity of the pathological process in the cerebellum appears to be greater in the present case than in the recorded examples of gargoylism. Also the degree of general fibrillary gliosis was much more pronounced. Although this last observation loses some of its significance owing to the presence of tuberose sclerosis it may be said that whereas in tuberose sclerosis abnormal glial cells are usually present in non-tuberose areas, a generalized fibrillary gliosis of the intensity encountered here is distinctly unusual. From this comparison it would appear that there is little or no positive evidence in favour of this case being an early example of gargoylism. The one feature the two disorders have in common is the ubiquitous distension of the nerve cells with insoluble granules, but this seems hardly sufficient support for the view that the conditions are identical, particularly since it is uncertain whether in Hunter-Hurler's disease a degree of nerve-cell affection comparable with that of the present case occurs as a congenital or early infantile phenomenon.

* The nervous changes in the case described by Kressler and Aegerter are not reported in detail. Apart from the failure of the infiltrating substance to stain, the authors considered their findings identical with those in Stewart's first patient.

The extreme insolubility of the nerve-cell deposits raises a difficulty in nomenclature, for the name 'lipoid' seems under the circumstances inappropriate. To account for the relative insolubility of the granules in juvenile amaurotic idiocy it has been suggested that a combination of lipoid and protein has taken place, but if this is so in the present case the union must have been singularly stable, since it resisted the action of hydrolysis. In view of the non-involvement of the reticulo-endothelial system in liver, spleen and lymph nodes it would also appear unjustifiable to attempt to force this case by analogy into the group of 'lipoidoses.' Certain features of this case appear to be unique and cannot readily be brought into line with previously described disorders.

Summary

The post-mortem examination of an infant of twelve months showed tuberosc sclerosis of the brain, rhabdomyomata of the heart and nerve-cell swelling resembling in the main that of juvenile amaurotic family idiocy. The granular inclusions in the nerve cells were insoluble in lipoid solvents. No evidence of a general disturbance of lipoid metabolism was found. A comparison between the clinical and pathological features of this case with those of amaurotic idiocy and Hunter-Hurler's disease suggested that the condition is distinct from these previously described disorders, but its etiology remains obscure.

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