FAMILY CEREBRAL DEGENERATION WITH MACULAR
CHANGE (SO-CALLED JUVENILE FORM OF FAMILY
AMAUROTIC IDIOCY)

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With Plates 35-38

Introduction.

Certain forms of progressive cerebral degeneration occurring in children
of one family are generally recognized. That described by Warren Tay and
Sachs under the title of 'Family Amaurotic Idiocy' has received careful patho-
logical investigation and is the best known. Continental observers (Vogt (24),
Bielschowsky (3), and others) recognize a late infantile and juvenile form of
amaurotic idiocy without the distinctive macular changes, and on pathological
grounds they assign all these cases to one group, namely hereditary degenerative
disease. Jendrassik and Higier have, on clinical grounds, contended that there
is no essential difference between the various forms of familial disease.

A rare form of progressive cerebral degeneration occurs in children during
the first decade of life, and these cases have been described under the title of
'Cerebral Degeneration with Symmetrical Changes in the Macula' by Mayou (2),
Batten (1), and others. Nettleship (12), in his paper 'On Cases possibly allied to
Tay's Infantile Retinitis', refers to these. Spiehleyer (19) described a form of
cerebral degeneration occurring in the children of one family associated with
blindness. The children in this family were healthy till six years of age; they
then showed mental deterioration, epileptic fits occurred, and the children died at
the age of puberty. Four of the five children were affected, only the eldest
escaping. Failure of vision, due to optic atrophy and a profuse retinal atrophy
of the type retinitis pigmentosa sine pigmento, was present. Syphilis as a factor
could not be excluded, for it is possible that the father contracted syphilis after
the birth of the first child. On pathological examination the Betz cells of the
cerebral cortex showed a destruction of the cell body, the processes remaining
more or less normal.

Müllerberger (11) describes two cases of a similar nature in a boy and girl
aged 3½ and 1½ years respectively; both children were living at the time of the
report.

(Q. J. M., July, 1914.)
H. Vogt (24), under the title ‘Über familiäre amaurotische Idiotie und verwandte Krankheitsbilder’, describes a form of family cerebral diplegia with blindness, and progressive dementia which does not commence during infancy but in the later years of childhood. The family which he records resulted from six pregnancies. The mother and father were healthy, and there was no evidence of syphilis. The following is the family tree:

![Family Tree]

The first boy, O. A., was normal till four years old, he then began to degenerate. He had learnt to walk at eleven months, and to talk at one and a half years. He gradually lost these faculties, became blind, irritable, and, lastly, apathetic. He died when fifteen years old. The autopsy showed nothing abnormal in the brain macroscopically; the convolutions were not small, and there was no dilatation of the ventricles. The brain weighed 980 grm.

The second boy was normal till five years old; learnt to walk at one year old, and to talk in his second year. Failure of sight began when he was five years old, and an attempt was made to teach him in the blind school. His intelligence, however, became more and more impaired and school had to be given up. Epileptic fits first occurred when ten years old, but he only became completely paralysed a year before his death, which took place when fifteen years old. Macroscopically the brain showed no change, but on microscopical examination a primary degeneration of the ganglion cells was found with changes similar to those found in family amaurotic idiocy. Vogt gives the following as a typical clinical picture of the disease. A hitherto healthy child (usually more than one in a family without any special race disposition) becomes ill during the school age, sometimes between the age of fourteen and fifteen. The children in the same family become affected in the same year of life. The beginning is gradual; the first symptom is usually the failure of sight, but loss of mental capacity or motor weakness may first appear. The loss of sight passes in the course of months to a complete blindness. Ophthalmoscopically there is atrophy of the papilla. The mental development stands still, or goes back. The children do not progress in the school, soon lose the acquired capacity to read and write, and, lastly, of speech. They become unsocial, dirty in eating, unclean in habits, and totally inattentive to their surroundings, no longer know their own mother or make articulate speech. Little by little they become completely demented. Hand in hand, in most cases, there is diminution of motor function, at first weakness in the limbs and back, later complete paralysis. The paralysis is some-
times flaccid, sometimes spastic, leading to complete helplessness, atrophy, and death.

The parallelism of the clinical symptoms with the Waren Tay cases is clear. The agreement lies in (1) the familial character and the absence of syphilis, (2) the symptoms, and (3) the course. The difference lies in (1) the absence of race proclivity, (2) the absence of characteristic macular change, and (3) the difference of age.

Bielschowsky (3), in a paper entitled 'Über spät-infantile familiäre amaurotische Idiotie mit Kleinhirnsymptomen', gives an account of a family of three children, a boy and two girls, not of Jewish race. The mother had only these three children; there had been no miscarriages and the Wassermann reaction was negative both in parents and in children. There was a marked history of epilepsy both on the mother's and father's side, but strongest on the mother's side. The parents themselves were free from epilepsy.

In all three children the illness began at the fourth year of life, up to which time the development had been normal. The eye symptoms developed relatively late, the failure in intelligence being the first and motor weakness the last symptom. In the final stage the children became completely paralysed, the arms hung flaccid by the side, and when the child was placed in a sitting position the head fell upon the chest. In the two older children the disease lasted three and a half and four years respectively. At the autopsy the dura mater appeared normal, the pia mater was thickened, and the brain weighed 670 grm., which is said to be about 230 grm. less than the normal. The frontal convolutions approached the normal, but the further posteriorly one went the more atrophic were the convolutions. Gross abnormalities of the convolutions and sulci were not present. The cerebellum was unusually small, not only in its absolute mass but also in its relation to the large brain. The microscopic examination showed some change in the pia mater, swelling of the pyramidal cells in the cortex, with changes similar to those described by Schaffer in the Tay-Sachs disease. The Nissl granules had disappeared from the cell body, but were not replaced by the usual fine granulation. The calcarine region showed the most marked degeneration, with glia cell proliferation; no changes were seen in the vessels. In the cerebellum the cells of Purkinje showed the same form of degeneration, as did also the ganglion cells of the spinal cord.

Lütge (8), in a paper entitled 'Über einen besonderen pathologischen Befund aus dem Gebiete der frühinfantilen familiären Erkrankungen des Nervensystems', describes a similar condition in two infants of a mother whose two brothers were stated to have suffered from the same disease.

Karl Schaffer (16), in a paper entitled 'Beitrag zur Nosographie und Histopathologie der amaurotisch-paralytischen Idiotieformen', describes a case in a girl, aged 19 in 1895, who died at the age of 24 with progressive mental defect, defective eyesight, in whom no gross changes were found in the brain, but extensive ganglion cell degeneration. Schaffer suggested that this case corresponded to the juvenile form of amaurotic idiocy.
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Schaffer (17), in a paper entitled 'Zur anatomischen Wesensbestimmung hereditärer Nervenkrankheiten', sums up as follows:

1. The hereditary degenerative diseases (H.D.D.) affect primarily the hyaloplasm of the neurons.

2. The so-called fibrillae play no part in the cytopathology of the H.D.D.; the Nissl granules only a secondary part. The H.D.D. may be designated as affection of the non-differentiated protoplasm of the neuron.

3. The affection of the hyaloplasm may be either a hypertrophy or an atrophy; the qualitative factor in H.D.D.

4. The affection of the hyaloplasm can be general or local, the difference producing the variations in the form of the H.D.D. This is the quantitative factor in H.D.D.

5. The affection of the hyaloplasm may be rapidly progressive, leading to death in a short time, or so slowly progressive that the length of life is little or not at all affected. This is the intensity factor in H.D.D.

Weber (23) has described a family amaurotic idiocy without characteristic ophthalmoscopic signs. Autopsy was performed in one case, but no microscopical examination is recorded.

Darier (4), in a paper entitled 'Progressive Familial Macular Degeneration', gives an account of five cases of macular degeneration occurring in two families, and refers to the published cases with and without cerebral degeneration. He says that it is probable that the more precocious the macular changes the more likely are the cerebral functions to be affected—when the eye symptoms do not appear till twelve to fourteen years the brain is not affected.

Other forms of progressive cerebral degeneration occurring in children may be mentioned, but no advantage is gained by associating them with the above cases.

Progressive lenticular degeneration affects several members of a family, but it rarely occurs in children, and the earliest case on record is that of a child aged 10.

Pfaundler and Schlossmann (15) refer to a diffuse 'brain sclerosis' which is not congenital but develops in a child in the best of health and leads to complete dementia. They do not refer to this as a familial affection.

Pelizaesus and Merzbacher (14 and 10) describe a scattered degeneration of medullated fibres of the brain as a family affection, but the condition is essentially congenital and rarely progressive.

H. Vogt (25), in a paper entitled 'Tuberöse Sklerose', describes progressive dementia with epilepsy in children, and Paul Schuster (18), under the title 'Beiträge zur Klinik der tuberösen Sklerose des Gehirns', recognizes this as a familial disease.
Classification.

From the above digest it is clear that there is a group of cases showing progressive cerebral degeneration which do not correspond to the clinical features as originally described in the family amaurotic idiocy of Waren Tay and Sachs. It is these cases which it is proposed to discuss in this paper, and for this purpose the following division is suggested:

1) Family amaurotic idiocy—Waren Tay-Sachs.

2) Juvenile progressive cerebral degeneration, with amaurosis with or without macular and retinal changes—Spielmeyer (19), Mülberger (11), Vogt (24), Bielschowsky (3), Mayou (9), Batten (1, 9), and cases described in this paper.

It is well recognized, as Jendrassik (7) and Higier (5) have pointed out, that there is in all probability no hard and fast line between the various types of hereditary degeneration; unless, however, some form of classification based on a clinical foundation is adopted it is very difficult to form a clinical picture of the various cases which arise, and a classification should assist in a more accurate investigation, both clinical and pathological, of cases of this nature as they come under observation.

It has been shown that the pathology of some of these cases of hereditary degeneration, which present different clinical features, is similar, and it seems probable that they may be due to the same toxin, either endogenous or exogenous, and that the variation of symptoms is dependent on variations in age, race, &c. The exact nature of the toxin has yet to be proved.

Clinical Features.

The family about to be described presents symptoms of cerebral degeneration which correspond to the second division, namely, juvenile progressive cerebral degeneration with amaurosis and with macular changes.

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Fig. 2. Chart of the B. Family.

The family consisted of five members, one male and four females. The mother and father were perfectly healthy and normal individuals; they were not related, not Jews, and no history of mental defect existed in any of the collaterals.
The mother had four brothers and four sisters, five of whom were married and had children who were perfectly healthy; the father had one sister married but without children. The father had two brothers: one died of pneumonia, the other by accident, at the ages of 18 and 22 respectively. The eldest child, a boy, James B., 3 years 10 months, was in May, 1903, admitted to the Hospital for Sick Children under the care of Mr. Waugh, suffering from epilepsy. It was stated that three months previously he had been run over and suffered from a scalp wound on the vertex. He was unconscious, and was kept in the district hospital for three weeks after the accident. Since that time he had on various occasions suddenly fallen down and had convulsive movements of all his limbs. He had become irritable and constantly dirty in his habits since the accident; previously he was occasionally dirty. On August 10, 1909, Mr. Waugh trephined the boy and turned down an osteoplastic flap and exposed the whole area of the scar. The skull and dura mater appeared perfectly normal, and after opening the dura there appeared to be a slight excess of the subdural fluid, and the cortical veins were congested; otherwise nothing abnormal was noticeable. The boy recovered from the operation, but still continued to scream loudly and was in much the same condition as before the operation. No examination of the cerebrospinal fluid was made. He was discharged from the Hospital, and died in February, 1913, when 8 years old, having slowly passed into a demented condition. No autopsy was made.

The second member of the family, Bertha B., aged 7 in 1914, was physically and mentally a normal child, and on examination nothing abnormal could be discovered. She was said, however, to have had nocturnal incontinence.

The third member of the family, Hilda B., was well until the age of 3½ years. She was born at full term, in normal labour without instruments, cut her first tooth at five months, walked at twenty months, and began to talk about the same time. She had her first fit when 3½ years, and since that age had had frequent fits, had gradually lost power in the limbs, had become mentally defective, had become dirty in her habits, and took but little notice of her surroundings. On examination in June, 1913, she lay in bed with her legs extended; when placed in the erect position she stood on tiptoe, but could not walk. She failed to grasp objects with her hands, but could move her arms in all directions; she was unable to talk, and had attacks in which she screamed loudly. The pupils reacted well to light, the optic disks were pale, the vessels were normal and no change could be seen in the fundus. The knee-jerks were active, the plantars both gave extensor responses. Abdominal reflexes were present. The cerebrospinal fluid was quite clear and normal in character. The Wassermann reaction was negative both in the blood and in the cerebrospinal fluid. The child remained in hospital for about four weeks, but practically showed no change during that time. The fits were controlled by small doses of hyoscine. The child was discharged from the Hospital in June 1913, and readmitted to Hospital in February 1914. She was then emaciated, had rigidity of arms and legs, took no notice, did not see, but the pupils still reacted to light. The optic atrophy was more marked, and at the macula there was a fine pigmentary degeneration with considerable disturbance of the pigment in the periphery of the fundus (Fig. 3). The knee-jerks were brisk, ankle clonus was present, and both plantars gave an extensor response. The child died on March 7, 1914, and a post-mortem was made which showed a normally convoluted brain with shrunken convolutions. The microscopical appearance of the brain and eyes in this case will be dealt with in a subsequent paper.

The fourth member of the family, Jessie B., aged 3 years and 10 months, was said to be quite well up to six months previously. She was apparently a normal child in every respect till three; she learnt to walk and talk and was clean in her habits. Fits occurred about the age of three years and recurred with increasing frequency, and she had passed into a condition
showing marked mental defect. She, like her sister, had frequent attacks of screaming, could just support her weight on her legs, but could not stand or walk. The pupils reacted quite well to light, the disk and fundus of the eye were quite normal. The limbs could be moved in all directions, the knee-jerks were active, there was no ankle clonus, both plantars showed an extensor response, and the abdominal reflexes were active. The cerebrospinal fluid was perfectly normal and the Wassermann was negative in both blood and cerebrospinal fluid. This child contracted chicken-pox and died in September, 1913, aged 4 years.

A post-mortem was performed by my house physician, Dr. Moodie, and it is the changes in the brain of this child which are about to be described.

The fifth member of the family, Lily B., aged 2 years and 6 months, is alive and perfectly healthy. She talks and walks quite well for a child of her age. The knee-jerks are present, and the optic disks and fundus are normal. The grandmother believes that this child is going to be affected because of a slight turning out of the left foot.

Pathological Examination of J. B., the fourth member of the above family.

Nothing abnormal was observed in regard to the membrane or the surface of the brain. The thoracic and abdominal viscera were normal. After hardening in formalin the pia mater was removed and the brain examined. The convolutions were well formed (Fig. 4) and nothing abnormal could be detected either on the surface, base, or in cut sections of the brain or cerebellum. The liver and spleen also appeared normal, both macroscopically and microscopically.

Microscopical examination of the nervous system was carried out by the Weigert-Pal, Marchi, Nissl, van Gieson, and Bielschowsky methods.

Marchi method. Section of the cerebral cortex from the upper portion of the precentral gyrus showed a considerable amount of degeneration in the fibres of the white matter streaming down from the cells of the cortex, but very little degeneration could be seen in the grey matter (Fig. 5). The degeneration from the precentral gyrus could be traced into the medulla and spinal cord. Sections taken from the frontal, post-central, and occipital region of the cortex show comparatively little degeneration by this method.

In the cerebellum similar degeneration could be seen in the fibres of the white matter passing from the grey matter of the cortex (Fig. 6). The cells of Purkinje appeared to be diminished in number and those present stain rather darkly with the Marchi method.

In the medulla there was considerable degeneration in the pyramidal tract, in the transverse fibres, and also in the intramedullary portion of the cranial nerves.

In the cervical, dorsal, and lumbar region of the spinal cord there was a diffuse degeneration not only in the pyramidal tract, but also in the anterolateral tract and posterior column.

There was some degeneration in the ventral roots and a few degenerated fibres could be traced to the cells of the anterior horn. The dorsal roots show but little change.

Weigert-Pal method. The medullated fibres of the cortex were well stained, and the tangential fibres of the cortex appeared to be about normal. No abnormality was to be seen in the spinal cord stained by this method. The cerebellum showed some diminution of the medullated fibres. Sections of the optic chiasma showed but little change, as did also sections of the optic nerve. The eyes of this case were unfortunately not preserved.

Van Gieson method. No change could be detected in the vessels, either in the brain or spinal cord, by this method and no inflammatory reaction was present. The membranes of the brain and cord appeared normal.
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Nissl and v. Gieson methods. Sections of the cortex taken from the upper portion of the precentral gyrus stained by the Nissl and v. Gieson methods showed very marked changes in the pyramidal and Betz cells (Fig. 7). The cells were few in number; some were small in size, others swollen, and many of them showed an eccentric nucleus and vacuolation and diffuse staining of the chromatophilic substance, which tended to arrange itself around the nucleus.

Cerebellum. The Purkinje cells were diminished in number, had lost their dendritic process, were swollen and vacuolated. Some had central nuclei, but the cell body was poorly and diffusely stained (Fig. 8). Compare this with Fig. 9, normal cerebellum prepared and stained in a similar manner. A layer of large granular cells was very marked in the region of the Purkinje cells. The deeper granular layer was very poor in cells. Stained by the Bielschowsky method similar changes were shown (Fig. 10). Compare this with Fig. 11, normal cerebellum cortex.

Spinal cord. The cells of the ventral horn of the spinal cord were numerous and showed changes similar to those above described, but compared to the cells of the cerebrum and cerebellum were well preserved.

Summary.

An account is given of a family of five children, three of whom were affected with a progressive disease leading to dementia, blindness, and paralysis, one of whom showed changes in the macular region of the eyes. The children were healthy at birth and developed in a normal manner till the age of 3½ years. Epileptic fits then occurred and they began to degenerate. They became noisy, dirty in habits, and developed a spastic condition of the limbs. Death ensued in the one child at the age of eight, in the other at four, and in the third child at six years. All three of these children have died, and in two a post-mortem has been performed. In one case no change was visible in the nervous system macroscopically, in the other only slight atrophy, but on microscopic examination diffuse degenerative changes affecting the ganglion cells were visible in the cerebrum, cerebellum, and spinal cord. The Wassermann reaction of the blood and cerebrospinal fluid was negative in both cases, and no change in the brain or membrane was found suggesting congenital syphilis.

Another family of progressive cerebral degeneration was seen in 1905, but it has not been possible to trace the subsequent history of these two cases.

Fred B., seven years old in 1905, was the first of two children, and was, according to his mother's statement, well till three and a half years old, when he began to lose the power of walking. He gradually lost the power of talking, and since six years old has not been able to talk at all. He lost the power of sitting up, became dirty in his habits and blind.

Instruments were used at birth: he walked when eleven months old, but never talked well. He had one fit when one and a half years old.

At seven years old he was demented, took no notice; was blind, dribbled, had a general tremor of head and limbs and lay in bed with arms and legs rigid in the flexed position.

The knee-jerks were active, there were double ankle clonus and extensor responses.
Ophthalmoscopic examination showed optic atrophy and a curious pigmented condition of the whole fundus with irregular white patches. No definite change at the macula. (Mr. Herbert Parsons's report.)

Henry B., 4½. Henry, like his brother Fred, was apparently normal till about three and a half years old, when he had an epileptic fit. These fits recurred about one a week, and the boy passed into a condition of mental defect. He was noisy, lost the power of talking, and became unsteady in his gait.

On examination he was restless and irritable, he could walk unsteadily. He seemed to see; the pupils reacted to light; no atrophy or change could be seen in the fundus similar to that found in the case of the elder child. The knee- and ankle-jerks were present and the plantars were flexor.

The boy was too noisy to be kept in the hospital. The cerebrospinal fluid was not examined and no Wassermann test was made (1904).

Conclusions.

It is clear from a consideration of the cases just recorded and of those which have been described by Vogt, Bielschowsky, and others, that there is a form of familial cerebral degeneration which occurs at a later age, has no race proclivity, and somewhat different clinical manifestations from that described by Warren Tay and Sachs under the title of 'Family Amaurotic Idiocy'. The typical features in these cases are loss of intellectual faculties, loss of vision, loss of motor power.

In some cases all three defects seem to start together and run an equal and concomitant course. In other cases the mental symptoms first appear, the visual and the motor symptoms remaining long in abeyance.

In other cases, again, the visual symptoms appear first, motor and mental symptoms following later or not at all.

In some cases the degeneration begins in early life, in others in later infancy, in others, again, in early youth.

Some cases pass rapidly to a fatal termination, others are slow in their progress.

Some cases show very distinct changes in the macula, others pigmentary changes in the retina, which are not limited to the macula. Others, again, show no fundus change, or do so only in the later stages of the disease.

Clinically there is a great variation in the symptoms, and this, together with their time of appearance, forms a basis for classification. Pathologically these cases are essentially the same, and the changes in the cells are strikingly similar in all cases which have come to autopsy.

The clinical division suggested in the body of the paper is tentative, but it seems well to have some such division for the purpose of describing the various forms of familial progressive degenerations which occur in children.

It is proposed to deal with the macular and retinal changes in a subsequent paper, and especially in regard to their relation to the cases described by R. D. Batten, Stargardt, Darier, and others.
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LITERATURE.

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2. Batten, R. D., ibid., 1897, xvii. 48.
4. Darier, The Ophthalmoscope, 1914, xii. 149.
12. Nettleship, Ophthalmological Transactions, 1908, xxviii. 76.
21. Tay, Wareu, Ophthalmological Transactions, 1881, i. 56.
22. Trengolt, Mental Deficiences, 1914.

[Q. J. M., July, 1914.]
DESCRIPTION OF FIGURES.

PLATE 35, Fig. 3. Hilda H., 5½ years. Fundus of right eye to show the pigmentary degeneration which occurs at the macular region; a similar appearance was present in the left eye.

Fig. 4. Lateral view of the brain of Jessie B., aged 4 years, showing the normal appearance of the convolutions.

PLATE 36, Fig. 5. Cerebral cortex, precentral gyrus, of Jessie B. stained by Marchi’s method, showing degeneration of the medullated fibres passing from the cells of the cortex.

Fig. 6. Cerebellum of Jessie B. stained by Marchi’s method, showing degeneration of the medullated fibres passing from the cells of the cortex.

Fig. 7. Cerebral cortex, precentral gyrus, of Jessie B. stained by Nissl’s method, showing the chromatolytic changes in the Betz and pyramidal cells. The drawing is a composite one in that all the cells figured do not occur in the single field of the microscope. Magnified 800 diameters.

PLATE 37, Fig. 8. Cerebellum of Jessie B. stained by the Nissl method, showing chromatolytic changes in the cells of Purkinje and loss of the dendritic processes. Note the increase of compound granular corpuscles around the cells of Purkinje and the diminution of the cells of the granular layer. Compare with the normal cells of Purkinje and granular layer seen in Fig. 9.

Fig. 9. Normal cerebellum stained by Nissl’s method, showing cells of Purkinje, dendritic processes, and granular layer; for comparison with Fig. 8.

PLATE 38, Fig. 10. Cerebellar cortex of Jessie B. stained by Bielschowsky’s method, showing the degenerate condition of the Purkinje cells, the absence of dendrites, and the layer of large granular cells in the region of the Purkinje cells.

Fig. 11. Normal cerebellar cortex stained by Bielschowsky’s method for comparison with Fig. 10.