

Juvenile Batten's disease: an ophthalmological assessment of 26 patients

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SUMMARY Twenty-six children with juvenile Batten's disease are reviewed. On clinical and histological evidence they appear to represent a specific disease entity, which though rare is a substantial cause of blindness in children aged 5-15 years. Children present with rapid progressive visual loss at age 6-7 years, early mental deterioration, and fits about 2-4 years later, and this is the stage at which the diagnosis is usually made. Macular degeneration appears to be a consistent early feature, and peripheral retinal changes become more marked as the disease progresses. Phototoxicity may possibly play a part in the retinal degeneration.

In 1903 Batten described 2 siblings with progressive macular dystrophy and cerebral degeneration.¹ For many years after this there was a considerable controversy as to whether these 2 conditions were always causally related and whether a macular dystrophy represented a *forme fruste* of a far more devastating condition. It gradually became established that the 2 conditions were not invariably related, and the group of conditions in which these 2 degenerations occurred together became known as amaurotic familial idiocy. Clinical Tay-Sachs disease was later separated from this group, and the remaining diseases, being characterised by the deposition of autofluorescent pigments in neurones and other cells, became known under the generic name of Batten's disease. Today this group of conditions represents the most common cause of neurodegenerative disease seen in children at the Hospital for Sick Children in London.

Batten's disease can be divided into 4 principal

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groups (Table 1) on clinical, electrophysiological, and ultrastructural grounds,²⁻⁴ and although intermediate forms occur it is likely that these groups represent specific disease entities. In the infantile and late infantile types visual loss occurs later in the disease, usually long after the diagnosis has been established. Kuf's disease, or so-called adult Batten's disease, is very rare and certainly does not represent a single disease entity.

Juvenile Batten's disease usually presents with visual failure. It is characterised by early visual loss followed by progressive mental deterioration and fits and is invariably fatal, usually in the early 20s. No treatment has yet been shown to improve the prognosis. The condition is inherited as a recessive trait, and early diagnosis of the disease is important so that genetic counselling can avert the unwanted birth of further affected children. No method of prenatal diagnosis is available.

In the Batten disease complex autofluorescent pigments are deposited especially in neurones, but also in other cells throughout the body, and the ultrastructural examination of these has produced

Table 1 *Batten's disease: subtypes*

	<i>Old name</i>	<i>Age of onset</i>	<i>Presentation</i>	<i>Electron microscopy</i>
Infantile	Haltia-Santavouri	Infancy	} CNS and late } optic atrophy	'Snowballs'
Late infantile	Jansky-Bielschowsky	2-4 years		Curvilinear bodies
Juvenile	Spielmeyer-Sjögren	6-8 years	Eyes	Finger-print bodies
Adult	Kuf	Adult	CNS/eyes	?

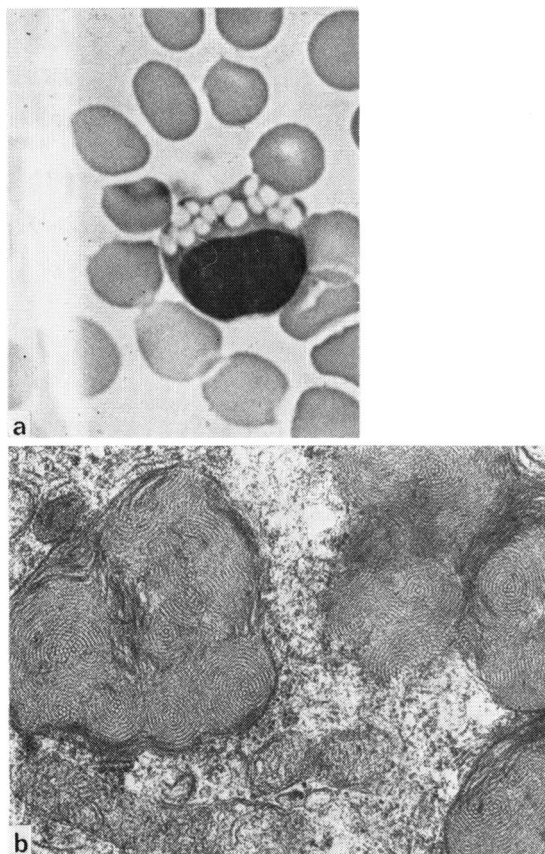


Fig. 1A Vacuolated lymphocyte. About 30% of lymphocytes in the peripheral blood are vacuolated in all children with juvenile Batten's disease. 1B Typical intracellular finger print bodies seen in a rectal neurone of a child with juvenile Batten's disease.

the present classification of the disease.³ Vacuolated lymphocytes are found in the peripheral blood of all patients with the juvenile type, and the deposited intracellular neuronal material has a characteristic ultrastructural 'finger print' form (Figs. 1A and B). The nature of the autofluorescent material is unknown. It has been suggested that the material is ceroid and lipofuscin, pigments normally associated with aging, and the diseases have been called neuronal ceroid lipofuscinoses.⁵ It has been postulated that a defect in peroxidation of fatty acids might be responsible and treatment with antioxidants suggested. The finding of low levels of docosahexaenoic acid in the peripheral leucocytes of 4 patients with juvenile Batten's disease has been used to support this hypothesis.⁶ However, further interest in this group of conditions has been recently stimulated by the sophisticated biochemical analysis⁷

of the brain of a child who died from the late infantile form of the disease which suggested that the stored material was a retinoic acid metabolite. On these grounds a low vitamin A diet has been used to treat some children. Neither antioxidants⁸ nor low vitamin A diets have yet been shown to be convincingly successful treatments. A disease similar to Batten's disease has been found in inbred English Setters and provides a good animal model.⁹

By historical association the Hospital for Sick Children and the National Hospital for Nervous Diseases have always had a special interest in this group of conditions. We have reviewed the ocular findings by histological examination of biopsy material from a group of children diagnosed as having juvenile Batten's disease.

Materials and methods

The case records and fundus photographs of a group of children with juvenile Batten's disease were reviewed. This diagnosis had been confirmed by finding vacuolated lymphocytes in the peripheral blood of all cases and biopsy (usually rectal biopsy) studied by histochemical and electron microscopical techniques in at least 1 member of a family where more than 1 child was affected.

Results

Twenty-six children are included in this series. Five families had 2 affected children, no family had any more than 2. In only 2 families was there a possibility of consanguinity between the parents.

All children, apart from 1 who presented with fits, presented with visual failure (Fig. 2) with a peak incidence of 6 to 7 years of age. Mental symptoms were noticed about the same time or soon afterwards (Fig. 3), and by the time of our review 23 patients had developed fits. These can be accurately dated (Fig. 4), and usually occurred about 2–4 years after the onset of visual failure, though a small number of children did not develop them until much later in the illness. In spite of the presentation with visual failure there was frequently a considerable delay of several years in reaching a definitive diagnosis (Fig. 5), and this was because the diagnosis was not usually established until the onset of fits (Fig. 6). Early diagnosis and genetic counselling would not have prevented the second sibling being affected in any of the 5 families with more than 1 affected child, as in each the second child had already been born by the time the elder sibling had presented.

Nine children had adequate fundus photography and 5 of these also had fluorescein angiograms. Two

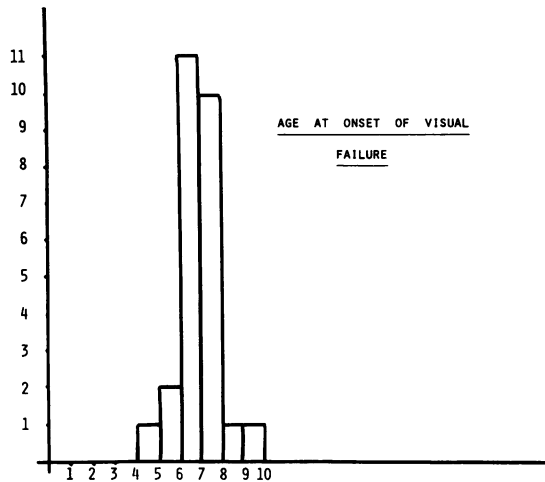


Fig. 2 Children present with visual failure at a peak incidence of 6-7 years of age.

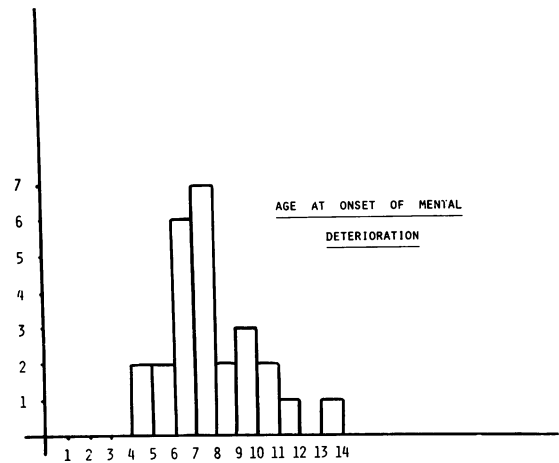


Fig. 3 Mental symptoms are usually apparent at the initial presentation but may be unnoticed.

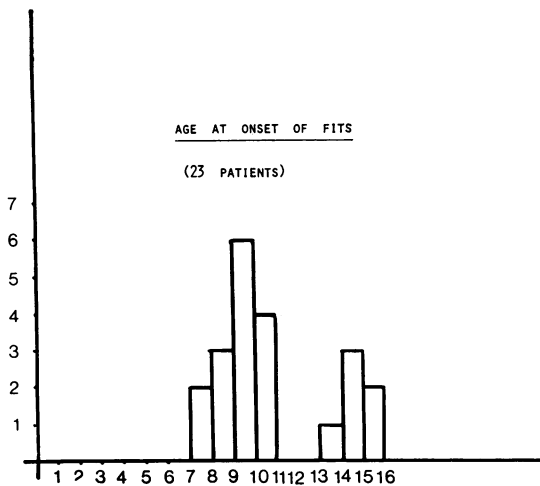


Fig. 4 Fits tend to appear 2-4 years after visual failure.

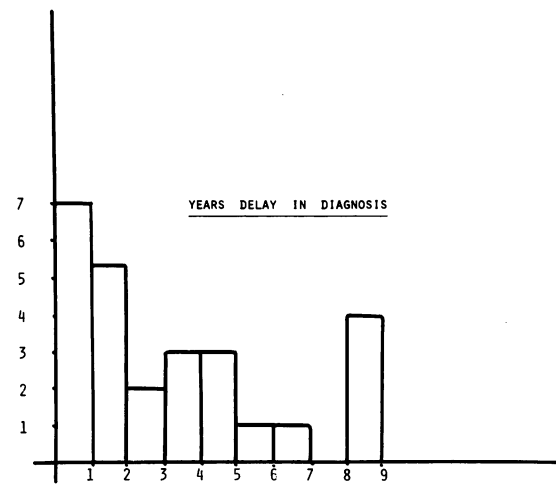


Fig. 5 Diagnosis is frequently delayed for several years.

children showed marked leakage of dye into the retina. The male:female incidence in this series was 11:17.

Discussion

Juvenile Batten's disease is rare. About 2 or 3 new patients are seen each year at the Hospital for Sick Children, and they probably represent the majority of patients seen in England. Nevertheless, in the age range 5-15 years it must be a significant cause of blindness, as approximately 10 children are

registered blind in this age group each year in England from retinitis pigmentosa, macular lesions, or other retinal disease which might be included in the differential diagnosis of juvenile Batten's disease.¹⁰

All the children presented with visual failure (apart from 1 child who developed fits a few months previously) with a peak incidence at 6-7 years of age (Fig. 2). Typically juvenile Batten's disease produces a bull's eye macular dystrophy (Figs. 7A and B), but while a review of the available fundus photographs (from 9 patients) showed pigmentary

macular changes in each case these were frequently subtle and easily missed unless the pupils were dilated and the fundus examined carefully (Fig. 8). Fluorescein angiography defined the pigmentary disturbances much more clearly (Figs. 9A and B), and in our patients, although they were not all fully documented photographically, it is unlikely that the disease occurs in the presence of a normal macula. Two patients showed leakage of fluorescein from the retinal circulation (Figs. 9B, 10A, and B) and it is probable that this is a sign of an actively degenerating retina, as it is seen in a variety of other tapetoretinal degenerations.¹¹ About half the

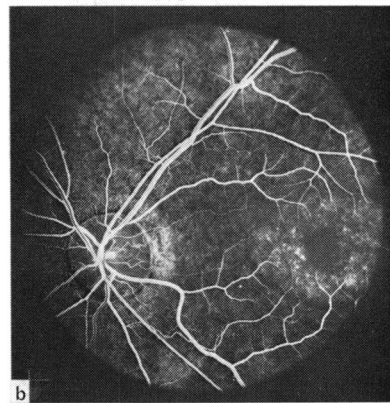


Fig. 7A The posterior poles of an 8-year-old girl. There is a typical bull's eye maculopathy, thinning of the retinal arterioles, and optic disc pallor. 7B The fluorescein angiogram of the left eye showing the pigment epithelial disturbances.

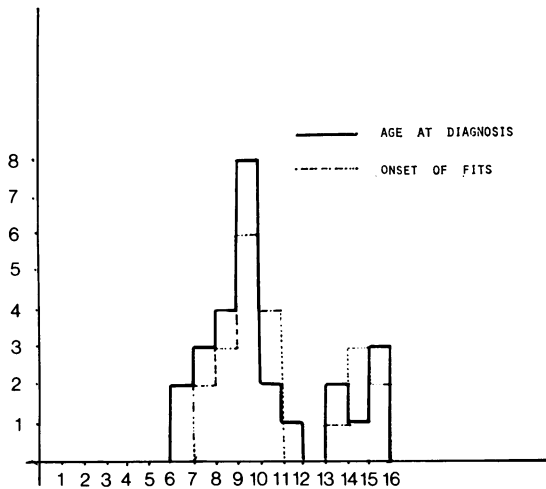


Fig. 6 Definitive diagnosis is usually made at the onset of fits.

Fig. 8 Subtle macular pigmentation in each eye of a 7-year-old girl.



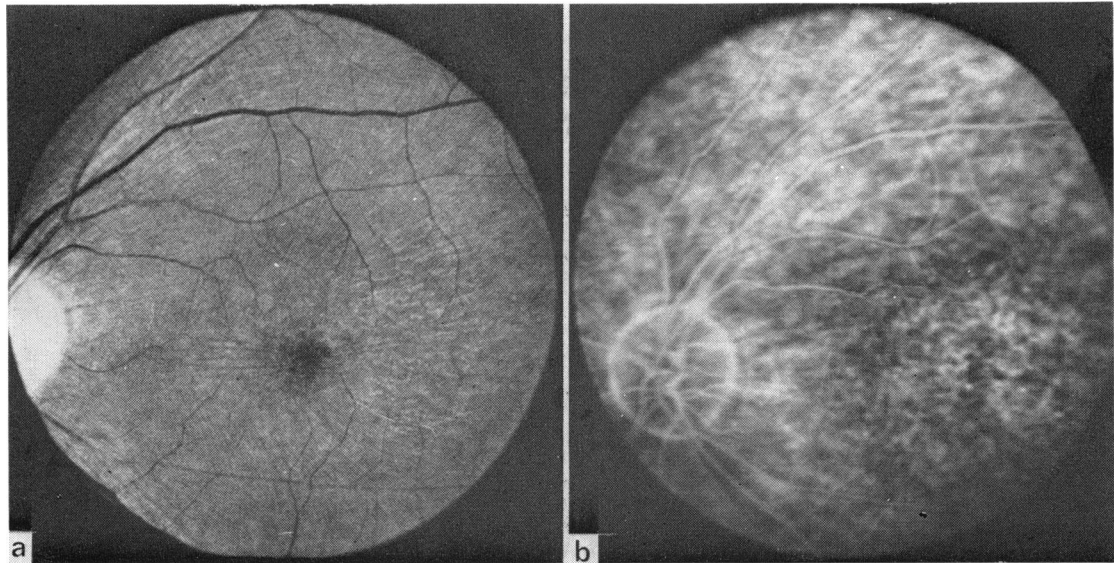


Fig. 9A The posterior pole of a 9-year-old child. 9B Fluorescein angiography emphasises the pigmentary disturbance and shows leakage of dye from intraretinal vessels.

patients were initially diagnosed as tapetoretinal degeneration. The peripheral retina in our patients varied from a normal appearance to pigment epithelial atrophy or peripheral pigmentation (Fig. 11), and this is probably related to the age of the patient and the clinical stage of the degeneration. Bone corpuscular pigment occurred very late in the course of the disease (Fig. 12).

Young children with visual loss of whatever cause do not tend to complain of this until it is severe, and the children in this series were no exception, often being referred for ophthalmic opinion only when their visual loss was so severe that they bumped into things or were having visual difficulties at school. The visual failure tended to have a fairly rapid course, with the child being registered blind within 1 to 2 years of developing symptoms. By the time the children present it is likely that there has already been considerable structural retinal damage, and at this stage it is unlikely that any treatment would restore vision.

It is always difficult to gauge the onset of loss of skills or mental retardation, but frequently these were apparent, though perhaps not recognised, when the child presented with visual loss (Fig. 3), and this correlates with the animal model.⁹ Many children seem never to have been really bright, lagging behind their unaffected siblings in their achievement of early milestones and several had already been labelled dull or educationally sub-normal before their visual loss. One child also had

Down's syndrome. Retrospectively more easily recognisable symptoms occurring at the time of visual loss were loss of recent memory, tantrums, speech disturbances or poor learning ability at school, but these symptoms were often overlooked in the turmoil of visual failure.

The onset of fits can be accurately documented (Fig. 4). They tend to occur 2–4 years after presentation, with a small group of children developing them later in their teens. Although it is possible that they represent a subgroup in the disease, this is unlikely, as 1 of these children who developed fits when aged 15 had a brother who developed fits at the age of 9. The severity of fits varied; sometimes they presented a major therapeutic problem but occasionally were not troublesome until late in the illness.

Visual loss in dull children is a major diagnostic problem and it was sometimes many years before the final diagnosis was made (Fig. 5). Most children were referred with a diagnosis of tapetoretinal degeneration, retinitis pigmentosa, or macular dystrophy, but a few unfortunate children were inevitably thought to be hysterical and subjected to prolonged investigation through the social services before the development of more overtly organic symptoms stimulated reappraisal. In the absence of another affected sibling the diagnosis was usually made at the onset of fits (Fig. 6). In young children presenting with a tapetoretinal problem the ophthalmologist must take a careful history, and if there is

any suggestion of mental deterioration further investigations are necessary. The electroencephalograph provides good evidence of underlying cerebral dysfunction,⁴ and suspicious abnormalities indicate the need to search for vacuolated lymphocytes in the peripheral blood and the confirmation of the diagnosis by suction rectal biopsy. Although it is possible to diagnose the condition by blood examination in apparently normal younger siblings, many parents do not wish this, preferring to await the course of events.

Seven of the 26 children were noted to hold their eyes in a raised position, apparently 'overlooking' the target (Figs. 13A and B). The reason for this is

unknown, but it might be explained by increased phototoxicity of their retinæ. Phototoxicity has been well established in animals reared under constant illumination¹² and light has been shown to be detrimental to the retina of the RCS rat.¹³ Most of the natural retinal illumination comes from above and, if the retina was especially sensitive to light,

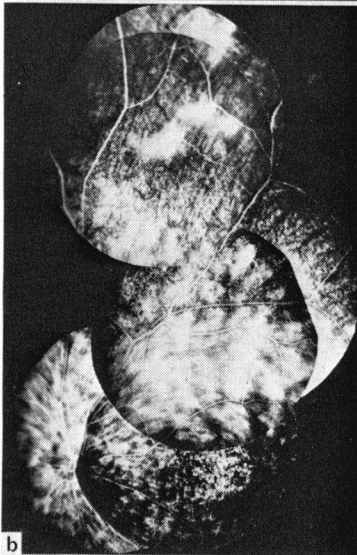
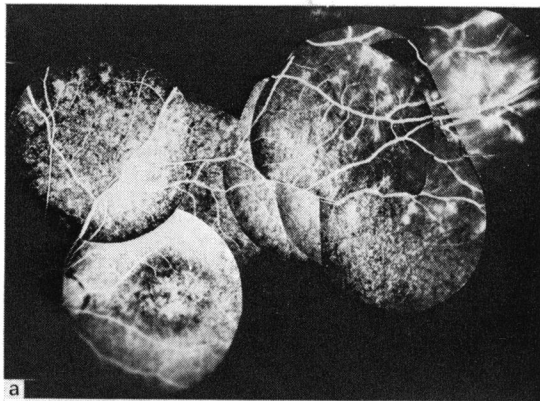


Fig. 10A Fluorescein angiography at age 5 shows leakage from peripheral retinal vessels. 10B One year later there is extensive leakage of dye throughout the retina. This is probably a sign of active retinal degeneration (patient of Professor A. C. Bird).

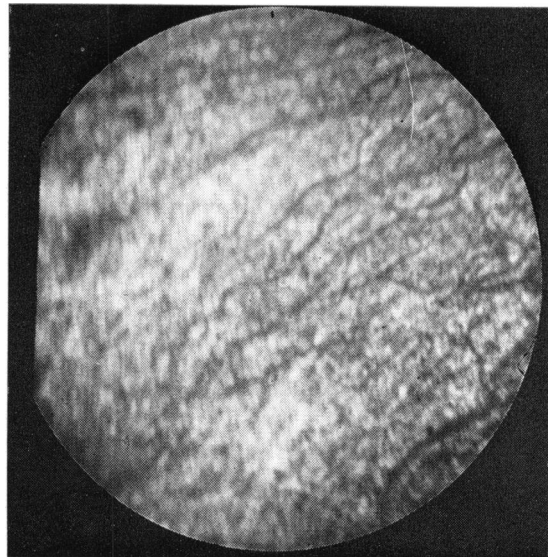


Fig. 11 Pigment epithelial atrophy in the peripheral retina of a 7-year-old boy.

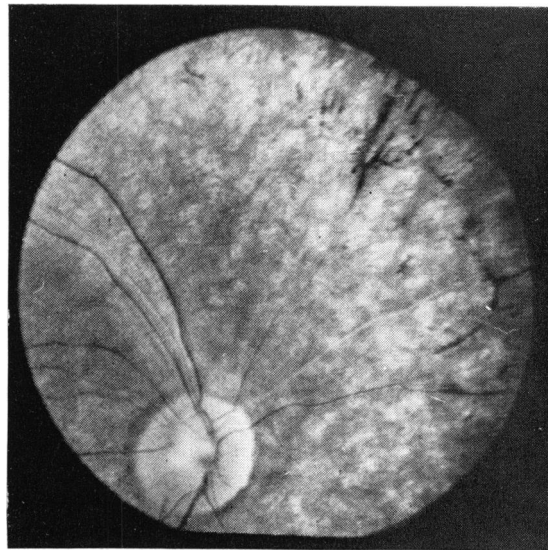


Fig. 12 Peripheral intraretinal bone corpuscular pigmentation in the retina of a 15-year-old girl. This occurs late in the disease.



Figs. 13A, 13B 'Overlooking' in 2 children. These 2 children were both asked to look straight at the camera and to fixate appeared to have to 'overlook' the target. This sign was seen in 7 of the 26 children.

might be expected to destroy preferentially the inferior retina, leading the child to fixate with the relatively unaffected superior retina and overlook the target. Experimentally phototoxicity affects the outer retina initially,¹⁴ and this has similarities with the retinal histology of juvenile Batten's disease, in which the outer retina is affected earliest.¹⁵ It is interesting to speculate whether phototoxicity might be a factor in determining the fundus appearances. Studies of albino rats reared in constant illumination showed that the posterior pole was more susceptible and that rods were more affected than cones,¹⁶ although experiments with pigeons under rather different conditions suggested that cones were the more susceptible to light.¹⁷ If this hypothesis is true visual deterioration might be simply delayed by giving the child dark glasses to wear or occluding the eye.

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Miss Josephine Lace typed the manuscript and Mr Rolf Sennhenn produced the photographs.

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