INFANTILISM, OBESITY AND RETINAL DYSTROPHY

A 'Forme Fruste' of the Laurence-Moon-Biedl Syndrome

BY

RICHARD W. B. ELLIS, M.A., M.D., F.R.C.P., and
FRANK W. LAW, M.A., M.D., F.R.C.S.

(From the Children's and Eye Departments, Guy's Hospital, London)

In 1866 Laurence and Moon reported 'Four cases of "retinitis pigmentosa" occurring in the same family and accompanied by general imperfections of development.' These imperfections included small stature, hypogenitalism, obesity and mental defect, although little emphasis was placed on the two last. Over fifty years later, Bardet (1920) added polydactyly to the syndrome, and in 1922 Biedl, reporting three new cases, emphasized the familial character of the syndrome, the occurrence of mental defect and the occasional association of other abnormalities.

Comprehensive reviews of the literature have been made by Raab (1924), Reilly and Lissner (1932), Cockayne, Krestin and Sorsby (1935), Streiff and Zeltner (1938), and Sorsby, Avery and Cockayne (1939). Reilly and Lissner found seventy-seven cases, of which they regarded twenty-five as complete examples of the syndrome, ten as questionably complete, twenty-seven incomplete and fifteen doubtful. Sorsby et al. discussed a number of allied conditions, including Biemond's (1934) syndrome (familial infantilism, coloboma of the iris and skeletal abnormalities) and Cockayne's (1936) syndrome (familial dwarfism, mental deficiency, deafness and retinal atrophy), but regarded the Laurence-Moon-Biedl syndrome as clear-cut and distinct. Warkany, Frauenberger and Mitchell (1937), however, put forward the view that the syndrome is not a disease entity but 'a rare combination of more or less frequent heredo-familial symptoms.'

According to Marmor and Lambert (1938) the six cardinal signs of the syndrome, in order of their frequency, are obesity, retinitis pigmentosa, mental deficiency, genital dystrophy, familial incidence and polydactyly, the last occurring in approximately 60 per cent. of cases. Less common signs are dwarfism, syndactyly, deafness, atresia ani, oxycephaly and congenital morbus cordis.

Although the term 'retinitis pigmentosa' has generally been used to describe the retinal changes, in only 15 per cent. of cases (Clay, 1933) do these conform with the classical picture of retinitis pigmentosa. In the great majority of instances they have been 'atypical' or have even differed profoundly in essential features. Sorsby (1940) considers that 'the significance of the affection in the elucidation of the pathology of retinitis pigmentosa has been overrated, for the fundus lesion is not generally a typical pigmentary degeneration of the retina. 'Atypical' retinitis pigmentosa is the rule, and occasionally the lesion is essentially a macular dystrophy with optic atrophy.'

In the case reported below, the fundus lesion differed essentially from that of retinitis pigmentosa, but we have little hesitation in classifying the case as a 'forme fruste' of the Laurence-Moon-Biedl syndrome, in view of the infantilism and obesity and of the occurrence of mental defect and polydactyly in members of the immediate family.

Case report

Monica M., a girl aged thirteen years and three months, attended the Royal London Ophthalmic Hospital in April, 1940, on account of defective vision, and because of her small size was subsequently transferred to Guy's Hospital (later to the Kent and Sussex Hospital) for further investigation.

FAMILY HISTORY. Both parents are of normal stature and are unrelated. The father is alive and well, and the paternal grandparents were normal: a younger brother of the father, who was drowned, had very defective vision, but was otherwise normal.

Of the maternal forebears, the patient's grandmother died from pulmonary tuberculosis and the grandfather from angina pectoris. The patient's mother has suffered from open tuberculosis and had artificial pneumothorax treatment. Ophthalmic examination of the mother showed: vision, right 6/6, left 6/6. No nystagmus present: fundi normal.

The mother's two brothers and one sister all died from pulmonary tuberculosis. The younger of the two brothers had a sixth digit on the radial side of the right hand.

The patient has two elder sisters, and a brother who died at birth. One sister, aged twenty-five, is normal. The second sister (Kathleen M.), aged twenty-three, is mentally defective and has suffered from chronic fibroid phthisis for the past eight years. She is at present in a sanatorium, where she was examined by one of us (R. W. B. E.). During infancy she suffered from spasmus nutans. She was late in walking and talking, and did not learn the alphabet until twelve years old. She began to menstruate at sixteen: menses are now regular. Her eyesight has been defective for at least ten years. On examination, she is below the average height, being 5 feet (152 cm.) tall: she weighs 102½ lb. The circumference of head is 19¾ inches. The fingers are clubbed, and there are signs of extensive fibrosis at both apices. Secondary sexual characters and genitalia are normal. She is of defective mentality, but understands simple requests and is cheerful and co-operative. She can read, but holds print very close to her eyes. She does not appear to suffer from night blindness. There is no nystagmus. The optic discs are a deeper colour than normal, but are well defined. The vessels are normal. There is no abnormal pigmentation of the retinae.

PERSONAL HISTORY (Monica M.). The patient was born at term, weighing 8 lb.; delivery was normal. At birth she is said to have had a thick growth of hair on the head which extended posteriorly on to the dorsal region 'like a pigtail.' She gained poorly in weight during the first year, and has always been small for her age since then. She walked and talked early, and cut her first tooth at six months old. Obesity has developed gradually over a period of several years and more rapidly recently. Her general health has been good, and measles and influenza are the only illnesses she has had.

During the past twelve months her eyesight has rapidly deteriorated. She frequently trips over the curb and cannot see the markings on a ruler. There have been no headaches, and she has not suffered from polyuria, excessive thirst or frequency.

At school she is slightly above the average, consistently being placed amongst the first four in a large class of girls of her own age.

Examination (June, 1940). A bright, co-operative little girl, who, whilst normally intelligent for her age, tends to have the emotional reactions and interests of a considerably younger child. She measures $45\frac{1}{2}$ inches (115.5 cm.) in height, i.e. the same as a normal child of seven years, and weighs $61\frac{1}{2}$ lb. (The average figures for a normal girl of thirteen-and-a-quarter years are $59\frac{1}{2}$ inches and 92 lb.) Other measurements are: sitting height $23\frac{1}{2}$ inches, circumference of head 20 inches (normal 21 inches), chest (nipple level) 26 inches, abdomen (umbilical level) $26\frac{1}{2}$ inches, around midgluteal region 28 inches, length of arm (acromion to radial styloid) $13\frac{1}{2}$ inches, hand (radial styloid to tip of middle finger) $4\frac{1}{2}$ inches, leg (anterior superior iliac spine to internal malleolus) $24\frac{1}{2}$ inches, from umbilicus to ground (standing) $26\frac{3}{8}$ inches.

THE FACIES is that of early childhood, the nose and maxilla showing no sign of the development normally associated with the onset of puberty.

THE SKIN is fine and smooth over the face and greater part of the trunk, but there is some hypertrichosis over the back, particularly in the mid-line, and over the extensor surfaces of the forearms. There are no striae atrophicae. The colour is normal. The hair is moderately abundant, silky, and brown; the eyebrows and eyelashes are black, and of normal distribution.

OBESITY. The distribution of fat is principally of 'girdle' type, though the whole of the trunk is involved. The extremities are affected less in the proximal than the distal segments; the hands and feet are small, and the fingers tapering (figs. 1, a and b).

DENTITION. Teeth present:

$$\begin{array}{r} 6E4C21 \quad 12C4E6 \\ 6EDC21 \quad 12CDE67 \end{array}$$

Radiological examination shows that the unerupted teeth are normally present.

SEXUAL CHARACTERS. There is no axillary or pubic hair, and no mammary development. The nipples are retracted, owing to the deposition of fat in the

FIG. 1, a and b.—Monica M. with normal control, aged $13\frac{1}{4}$ years. Anterior and posterior views showing brevilinear proportions, infantilism, and distribution of obesity.

mammary region, and there is no pigmentation of the areolae. The genitalia are infantile.

Ophthalmic examination. **VISUAL ACUITY.** The patient was first seen in April, 1940, complaining of defective vision. Visual acuity was found to be: right, 6/24; left, counts fingers at 2 feet. Refraction under atropine was carried out and the following results obtained:

Right -1.5 D.S.— 2.0 D.C.— $150^\circ = 6/12$ partly.
 Left -1.0 D.S.— 1.0 D.C.— $45^\circ = 6/18$.

Two weeks later a postmydriatic test was carried out, when the same glasses produced only 6/18 in the right eye and again less than 6/60 in the left. On re-examination in July, on which occasion she had failed to bring her glasses, it was found to be, unaided, right 6/24, left 6/36. Such a variable subjective result is not uncommon in patients, especially children, suffering from nystagmus, and is probably dependent on the frequency and amplitude of the oscillations, these in turn possibly being influenced by psychological and nervous factors.

As regards the child's description of her own vision, she stated in April that she suffered from defective vision in the dusk. This she now denies; indeed, when evacuated ten months ago she wrote to her mother and volunteered the information that her vision was improved in a dim light. Whatever her subjective sensation, there is no discoverable clinical evidence of abnormal variation of visual acuity in varying illumination.

EXTERNAL EXAMINATION. There is (July, 1940) a constant fine nystagmus of the type usually associated with defective macular vision, perhaps better termed defective fixation than true nystagmus. The movements are in the vertical meridian and consist of a quick rising phase and slower regular fall. In addition to this there is a coarse horizontal nystagmus on deviation to right or left, the phases being approximately equal. Pupillary movements are normal and there is no external abnormality.

VISUAL FIELDS. Response to this test was very willing and co-operative, but the results must be read in the light of the defective fixation present. There is no peripheral field loss to a 1° object at 330 cm.; the blind spots, however,

appear to be enlarged (fig. 2, a and b). It is obvious that delicate scotometry was impossible.

FUNDUS EXAMINATION. Gross atrophic changes are evident, of which an indication is given in the two monochrome drawings here reproduced (fig. 3,

R.E. Monica M. 1st white, artl. light, July 11, 1940. L.E. Monica M. 1st white, artl. light, July 11, 1940.

FIG. 2, a and b.—Right and left visual fields.

FIG. 3, a and b.—Right and left fundi.

a and b). These, however, were made under difficult conditions, and must not be taken to represent a completely accurate picture. The discrepancies may be deduced by comparing the description of the fundi with the drawings.

The two most obvious features on ophthalmoscopic examination are the

easy visibility of the choroidal vessels and the presence of plaques or 'veils' of pigment scattered over the fundi. The retinae appear 'thin' and there is evident general deficiency of pigment throughout. The choroid itself is not heavily pigmented either, and, as already mentioned, the choroidal vascular system is plainly seen. The macular regions are atrophic and 'moth-eaten' in appearance; there is fine scattered peppery pigmentation at the left, but the right area is the actual site of one of the plaques in addition. (This point is not brought out in the drawing).

The plaques or 'veils' of pigment which are unevenly scattered over both fundi vary in size, some being nearly as large as two discs. Their depth is difficult to assess, but is estimated as being about that of the retinal vessels. Their outlines are quite irregular; their density is fairly constant, underlying structures not being entirely obscured.

There is no definite change in the appearance of the vessels or optic discs. The fundus picture may be summed up as showing retinal atrophy with pigment migration and macular degeneration; there is not the slightest ophthalmoscopic or clinical resemblance to retinitis pigmentosa.

Radiological examination. SKULL. There is no evidence of raised intracranial pressure or other abnormality. The pituitary fossa is normal, and there is no erosion of the clinoid processes.

OSSIFICATION. The ossification centres of the carpus are normal for age, except that the pisiform is not visible. At the elbow, the centre of ossification of the olecranon process of the ulna is just visible. Those of the trochlear and of the internal epicondyle of the humerus are well developed, but that of the external epicondyle has not appeared. Ossification, therefore, appears to be slightly delayed for age (i.e. that of a child of eleven or twelve), but not to the extent that the size of the patient might suggest.

CHEST. The hilar shadows are enlarged, but there is no evidence of active pulmonary disease.

Other investigations. WASSERMANN and KAHN reactions negative.

MANTOUX TEST (1 in 10,000 dilution) strongly positive.

BLOOD UREA. 34 mgm. per cent.

UREA CONCENTRATION TEST (15 gm. urea):

TIME	URINE, C.C.	UREA, PER CENT.
7 a.m.	73	2.12
8 a.m.	43	2.38
9 a.m.	94	2.87

FLUID INTAKE averaged 18 oz. (540 c.c.) daily over a three-day period.

URINARY OUTPUT averaged 24 oz. (720 c.c.) daily over a three-day period.

URINE contained faint trace of albumin, but no other abnormality. Specific gravity 1012.

STOOL examination showed no excess of faecal fat.

Discussion

In discussing the etiology of the condition, Sorsby et al. drew attention to 'the frequent occurrence of one or more components of the Laurence-Biedl syndrome in the ascendants of patients showing the full syndrome,' and suggested that the syndrome is 'determined by two recessive genes in the same chromosome, or that it is dependent on some chromosome error such as a dislocation or translocation.' In so far as information is available with regard

to the presence or absence of consanguinity, the complete sibships published indicate the recessive character of the condition; thus, in the fifty sibships in which a definite statement is made, 20.4 per cent. were the result of marriages between first cousins and 38.7 per cent. the result of consanguineous marriages.

The present case, an incomplete example of the full syndrome, was the offspring of unrelated parents, but the features of the syndrome which were lacking in the one individual, viz. mental defect and polydactyly, were found in a sister and uncle respectively. The patient herself was a singularly perfect example of infantilism associated with obesity, and though her intelligence was normal for age her emotional development was commensurate with her physical state. An unusual feature of the polydactyly present in the uncle was that the extra digit appears to have been situated in the preaxial position, whereas in previously reported cases it has been postaxial. As, however, the affected patient is dead, and no photograph is available, this point cannot be confirmed from personal observation.

A further point of interest in connexion with the patient, Monica M., arises from a consideration of the actual type of retinal atrophy present, and its ophthalmoscopic appearance. The term 'retinitis pigmentosa' is pathologically and descriptively unfortunate for any known ophthalmoscopic condition; when it is applied to the retinal changes found in conditions such as the one under consideration it is unjustifiable, since there is no evidence that the retinal condition bears any fundamental relationship to that usually referred to by this name, and the case provides good ophthalmoscopic evidence of a lack of relationship. The recurring use of the term 'atypical' in the writings quoted is significant.

The original description by Laurence and Moon reads as follows: 'Scattered over the fundus oculi, but especially aggregated towards its periphery, were several irregular figures of deep black colour. None was visible either in the situation of the macula lutea or its immediate neighbourhood. Their forms were exceedingly various, some being flakes or streaks of pigment, whilst others appeared as black oblong or oval spots, with fine dark lines extending from them, very closely resembling bone corpuscles in shape.

The pigment spots were apparently situated in the substance of the retina, on a level with its vessels, in some places interrupting these in their course and at others running for a short distance closely by their sides. They were distinctly on a plane anterior to the choroid. The vessels of this latter structure could everywhere be most beautifully seen, even to the minutest ramifications, excepting at those parts where the pigment obscured them from view. The spaces between these vessels were of a paler colour than the vessels themselves.

Each optic papilla was of a reddish-pink colour, with a rather brightly stippled centre; its margin softly defined, surrounded by a pale zone.'

Cockayne et al. summarized the ophthalmoscopic appearance thus: 'Typical retinitis pigmentosa is recorded . . . Atypical retinitis pigmentosa is noted . . . The atypical forms range from small chorioretinal lesions . . . from peripheral pigmentary lesions . . . sparing the macula to a lesion involving the macula . . . from retinitis pigmentosa sine pigmento to atypical retinitis punctata albescens . . . Typical retinitis pigmentosa would appear to be the exception.'

The paper by Laurence and Moon is a careful and very valuable piece of work, but was written over seventy years ago, and an improved terminology might to-day be justifiably substituted; anticipatory permission for this is indeed then given by the authors: 'In calling these cases by the name of Retinitis Pigmentosa, we have been guided rather by usage than by the intimate nature of the cases.'

As has been already stated, there is no resemblance between the fundus appearances in the present case and those of 'typical retinitis pigmentosa,' nor is the subjective disturbance of vision compatible. The more obvious differences in appearance may be summed up as follows:

1. The pigment disturbance and distribution is atypical.
2. The vessels are not constricted.
3. The discs are not of the pale yellowish colour found in typical cases.
4. The choroidal vessels are rarely seen in a typical case as clearly as in ours, at least in the early stages.

It is interesting to note that, whereas there are such wide variations in ophthalmoscopic appearances in cases of this syndrome, the description in the original paper of the first case might well be applied to the present one. Amongst other points of resemblance, the clear visibility of the choroidal vessels is emphasized, and Laurence and Moon's term 'flakes' and the use here of the term 'veils' in describing the pigment patches suggest similar pictures.

In considering the ophthalmoscopic picture, no less than the general clinical one and family history, we have no hesitation in placing our case in the Laurence-Moon-Biedl category.

REFERENCES

- Bardet, G. (1920). Sur un syndrome d'obésité congénitale avec polydactylie et rétinite pigmentaire. *Thèse de Paris*, No. 470.
- Biedl, A. (1922). *Dtsch. med. Wschr.*, **48**, 1630.
- Biernond, A. (1934). *Ned. Tijdschr. Geneesk.*, **78**, 1801.
- Clay, G. E. (1933). *Trans. Amer. ophthal. Soc.*, **31**, 274.
- Cockayne, E. A. (1936). *Arch. Dis. Childh.*, **11**, 1.
- , Krestin, D., and Sorsby, A. (1935). *Quart. J. Med.*, **4**, 93.
- Cooperstock, M. (1937). *Amer. J. Dis. Child.*, **54**, 334.
- Laurence, J. Z., and Moon, R. C. (1866). *Ophthal. Rev.*, **2**, 32.
- Marmor, J., and Lambert, R. K. (1938). *Arch. intern. Med.*, **61**, 523.
- Raab, O. (1924). *Wien. Arch. inn. Med.*, **7**, 443.
- Reilly, W. A., and Lissner, H. (1932). *Endocrinology*, **16**, 336.
- Sorsby, A., Avery, H., and Cockayne, E. A. (1939). *Quart. J. Med.*, **8**, 51.
- (1940). *Modern Trends in Ophthalmology*, London, 148.
- Streiff, E. B., and Zeltner, C. (1938). *Arch. Ophthal., Paris*, **2**, 289.
- Warkany, J., Frauenberger, G. S., and Mitchell, A. G. (1937). *Amer. J. Dis. Child.*, **53**, 455.