Nigerian Journal of Paediatrics 1999; 26 (2-4):47-52

Laurence-Moon-Biedl Syndrome in Nigerian Siblings: A Four-year Follow-up

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Summary

Ahmed H, Hassan RY. Laurence-Moon-Biedl Syndrome in Nigerian Siblings: a Four-year Follow-up. *Nigerian Journal of Paediatrics* **1999; 26: 47.** Two sisters with typical clinical features of Laurence-Moon-Biedl syndrome are described. The proband, an eight-year old girl and her sister aged three years, presented with gross, progressive obesity, mental retardation, digital anomalies and retinal dystrophy. Retinitis pigméntosa in the index patient had already reached an advanced stage causing severe restriction of the visual fields and diminished visual acuity, while in the three-year old sister, the retinal changes and visual defect were milder. Hypogonadism was not clinically obvious as both girls were in the latent prepubertal stage. The proband, up to the age of 12 years, remained at the prepubertal stage of sexual development and her gonadotrophin levels did not rise appreciably. The other sibling, a six-year old boy, and both parents, who were consanguineous, showed no clinical signs of the syndrome.

Introduction

THE Laurence-Moon-Biedl (LMB) syndrome, also referred to, as the Laurence-Moon-Biedl Bardet syndrome,[1] Bardet-Biedl syndrome,[1-3] Biedl-Bardet syndrome[1,4] or the Laurence-Moon-Bardet-Biedl syndrome[5] is an autosomal recessive disorder characterised by the pentad of obesity, mental deficiency, digital anomalies (postaxial polydactyly, syndactyly or both), retinal dystrophy (retinitis pigmentosa) and hypogonadism.[1-5] Nephropathy is also a significant feature and is sometimes included as one of the characteristic features of the syndrome,[1] although renal defects including a chronic glomerulonephritis-type of lesion, are generally regarded as associated anomalies in this condition.[2] Other abnormalities of lesser frequencies include cardiac defects, nystagmus, strabismus, diabetes insipidus, clinodactyly of the fifth finger, cystic dilatation of intrahepatic and common bile ducts, hirsutism, ovarian stromal hyperplasia, moderate shortness of stature and rarely, spinocerebellar degeneration.[2] The basic defect and the prevalence of the LMB syndrome are unknown.[1] It is an exceedingly rare disorder and about 300-400 cases have been described worldwide,[1,2] since the intial description of the syndrome by Bardet and Biedl in the early 1920s.[2] The LMB syndrome is now regarded as a clearly different disorder from the condition first described by Laurence and Moon in 1865 and known as Laurence-Moon syndrome (LM syndrome).[2,4] The principal features of LM syndrome resemble the LMB syndrome but do not include postaxial polydactyly.[2,4] Because of the clear differences between LMB and the LM syndromes, and to avoid confusion, some authorities prefer to call Laurence-Moon-Biedl (LMB) syndrome, simply Bardet-Biedl syndrome,[2,3] or Biedl-Bardet syndrome.[4]

To the best of our knowledge, this is the first report of the LMB syndrome in the siblings of a Nigerian family. We describe two sisters with the syndrome who have been followed-up for four years and draw attention

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to the phenotypic variation and progressive nature of the syndrome, and the diagnostic and management problems related to this condition in the current economic setting in the country.

Case Reports

Patient 1

The proband, an eight-year old girl, was referred to the Usman Danfodiyo University Teaching Hospital (UDUTH), Sokoto because of a rapid and excessive weight gain, associated with a voracious appetite, blurring of vision and poor performance in school. The parents first became aware that the child was growing rather fat from the age of four months when, in addition to breast-feeding, milk-based cereals were introduced, and the infant cried excessively for food. No action was taken until at the age of seven years when the obesity became very gross and an associated poor vision which was initially noticed one year earlier worsened, and the school teachers complained of her very poor academic performance. The voracious appetite was not associated with polydipsia or polyuria. There was no history of steroid therapy or central nervous system infection. She had developed mild ataxic gait and incoordination six months earlier, but these were not associated with headache or vomiting. At the age of seven years, the anthropometric indices measured by the referring physician were as follows: weight, 44.5kg (above the 97th percentile), height, 124cm (on the 75th percentile) and mid upper arm circumference (MUAC), 27cm (above the 95th percentile).

The girl was born at term after an uneventful pregnancy and delivery in a general hospital in Yauri town, Kebbi State. Her birthweight was 3.2kg (50th percentile), but the length and head circumference at birth were not recorded; the Apgar scores were however, 8 and 10 at one and five minutes, respectively. Postaxial polydactyly was noted in both hands and right foot at birth, and at the age of two weeks, a small umbilical hernia became obvious, otherwise, no other dysmorphic features were seen. The extra digits of the fingers were excised during the neonatal period and those of the toes were amputated at the age of three months. There had been no history of seizures and hypotonia had not been noticed in infancy. The patient was the first-born of her parents, who are first-degree cousins, of the Hausa ethnic group. The family was monogamous and at the time of presentation, the proband was eight years old, there were two other siblings: a boy aged six years and a girl three years old. The boy was healthy, but the three-year old sister had started to show evidence of obesity from the age of two years (weight 17kg; above the 97th percentile; height 86cm – on the 50th percentile, and MUAC of 19cm, above the 97th percentile), but her appetite had not been as voracious as her senior sister's at comparable ages, and visual impairment had not yet become obvious to the parents. There was no history of obesity, visual impairment or postaxial polydactyly in the parents or grandparents. Both parents were accountants and belonged to the middle socio-economic class. Gross motor developmental milestones were achieved as and when due, but speech development was delayed; the first phrases were spoken at about 36 months of age.

Clinical examination at presentation in Sokoto, revealed very gross global obesity (Figs 1A & 1B), a weight of 55kg (above 97th percentile), height, 127cm (50th centile), MUAC, 29cm (above 95th centile) and triceps skin fold thickness of 28cm [far greater than 19mm (95th centile)]. There was a large, reducible umbilical hernia (Fig. 1A), otherwise, the abdominal findings were normal as were the cardiovascular and respiratory systems. The stumps from previously excised extra digits of the hands and right foot were noted (Fig 1C). Sexual development was within Tanner stage I. Neurological examination revealed a mild truncal and limb ataxia and incoordination, with sensory ataxia (positive Romberg's sign), moderate hypotonia and reduced tendon reflexes without weakness. Her hearing was normal. Formal psychological testing, using the draw-a-person test[6] placed her in the moderately mentally retarded range. Ophthalmological examination showed an alternating divergent squint of about 45° that was worse for near vision (Fig. 1A). Visual acuity was 6/18 bilaterally and the visual fields were constricted to about 30° temporally. Both eyes showed otherwise normal anterior segments. Funduscopy showed attenuation of retinal vessels in both eyes with pale discs, changes that were compatible with optic atrophy. There was bilateral retinal pigmentation resembling bone spicules most dense in the nasal fundi of both eyes; these were typical of retinitis pigmentosa.

Laboratory investigations revealed haematocrit of 34 percent, haemoglobin concentration of 116g/l and ESR of 67mm; leucocyte and platelet counts were

normal as were blood chemistry values, while urinalysis showed no abnormality. Assay of gonadotropic hormones (at *DE Laboratories*, Kaduna) revealed both hormones to be at the prepubertal levels: follicle-stimulating hormone (FSH) was 2mIU/ml (normal for her age = <1-5mUIU/ml) and the luteinizing hormone (LH) was 1.5mIU/ml (normal range for her age 1-4mIU/ml). Facilities for karyotyping were not available. The skeletal maturation was within the normal range, while skull radiographs, including a cone view of the sella were normal. A computed tomographic (CT) scan of the brain (at University College Hospital, Ibadan) showed no abnormalities; magnetic resonance imaging (MRI) was however, not available. Meanwhile, ultrasonography of the abdomen revealed no abnormality.

Initial treatment consisted of dietary management of obesity and visual aid in the form of optical lenses. To ensure adequate supervision and restriction of food, the patient was initially admitted in hospital for six weeks. The energy intake was adjusted to encourage weight reduction using the guidelines established recently, for the management of morbid obesity in Prader Willi syndrome.[7] For the weight reduction, the energy intake was restricted to 29.3 – 33.4 KJ/cm height (ie 7-8 Kcal/cm height) with 20 percent of energy from protein, 20-25 percent from fat and the remaining 55-60 percent from carbohydrate. A weight reduction of 1.2kg in six weeks was achieved on this regime. The child was discharged home after the parents had been educated on the need for continued supervision on restriction of food. The patient was subsequently reviewed every six months for the next four years. At the age of eight and a half years, the weight had dropped to 50kg, a loss of 5kg in six months, but still remained on the 95th centile. The height was 127cm (25th – 50th centile). For weight maintenance, the energy intake was adjusted to 41.8 – 58.5 KJ/cm height (10-14 Kcal/cm height) and the ratios of protein, fat and carbohydrates maintained as before. The weight and triceps skinfold thickness (TST) continued to be above the 95th percentile throughout the four-year follow-up period and the height oscillated between the 25th and 50th percentiles. At age 12 years, the weight was 63.5kg (above 95th centile), height, 142cm (25th centile) and the TST, 33mm (above 95th centile). Appetite suppressants were not used.

Ophthalmological review of the patient at nine years of age revealed further constriction of the visual fields to about 20° and the visual acuity had diminished to 6/36 bilaterally. At the age of 12 years, the visual acuity had diminished to 4/60 in both eyes. Cataract formation or glaucoma had not been observed during the four-year follow-up period. However, a slow progression of the ataxia and incoordination continued.

Patient 2

This was the three-year old sister of the proband in whom extra digits in both hands were excised during the neonatal period and obesity became obvious at the age of two years. The patient was born

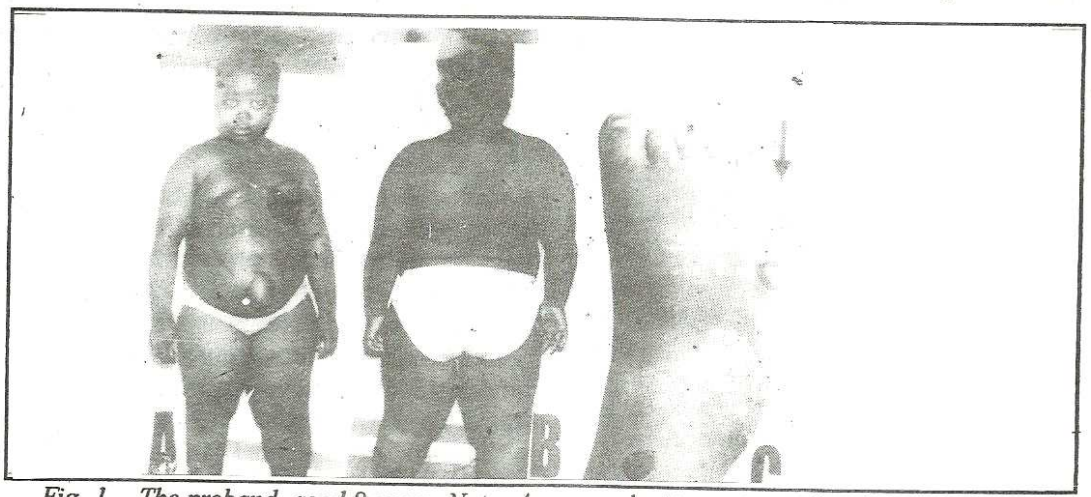

Fig. 1. The proband, aged 8 years. Note: A: gross obesity, squint and umbilical hernia. B: Posterior view of the patient showing gross truncal obesity. C: Right foot of the patient; the arrow indicates the remnant of an amputated extra digit.

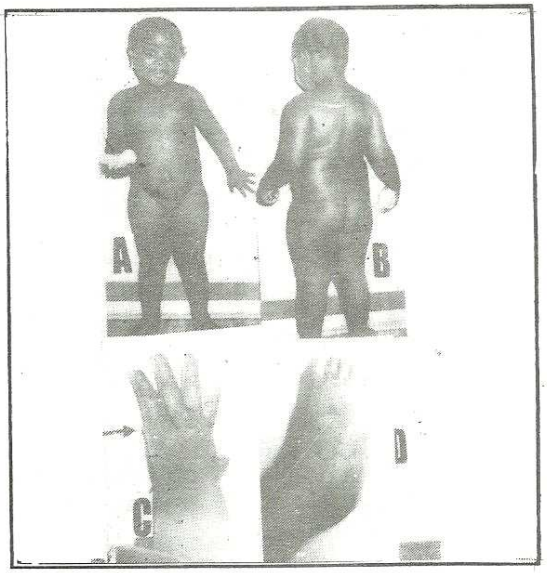

Fig. 2. The three-year old sister of the proband, also with LMB syndrome. A & B show the anterior and posterior views of the patient demonstrating moderate obesity. C shows the remnant of an excised digit (arrow), and D: mild syndactyly of the 4th and 5th toes.

full term, normal delivery. Apgar score was not known but the baby cried immediately after birth. The birth weight was 3.3kg (50th percentile). Length and head circumference at birth were not recorded. Developmental milestones for gross motor activities were achieved at the normal periods. Language development was delayed; first phrases were uttered just after 24 months of age. Physical examination at age three years revealed a very jovial girl. The weight was 18.5kg (above the 95th percentile), height 94cm (25th percentile), and TST was 19mm (above 95th percentile). The child was moderately obese (Figs 2A and 2B). Small projections were noted on the ulna border of both hands; these were residual stumps from the previously excised digits (Fig 2C). In addition, mild syndactyly of the 4th and 5th toes of both feet was noted (Fig 2D). She had no obvious neurological deficits. Ophthalmological examination showed a normal visual acuity of 6/6 bilaterally, minimal retinal dystrophic changes, and retinitis pigmentosa limited to the superior temporal region of the retina of both eyes, with a pink optic disc. Other systems were normal. Her haemogram, ESR, blood chemistry and gonadotrophins were within the normal ranges. Bone age was normal as were ultrasonography of the abdomen and an electrocardiogram; karyotyping was not available. Initial treatment consisted of measures to prevent morbid obesity. Constant supervision by parents on restriction of access to food was emphasized, and the need for cooperation on the part of other care givers including the extended family, was stressed.

The patient was also reviewed every six months. At ages four, five, six and seven years, she weighed 23, 28, 34 and 38kg respectively (above the 95th percentile) and the corresponding heights were 98, 105, 110 and 115cm, respectively (25th percentile). The TST values at these ages were 20, 21, 22 and 23mm, respectively (above 95th centile). The weight and especially the TST measurements indicated that although her obesity was not as severe as that of her sister, it continued to be progressive. Psychometric assessment[6] at age five years placed the child in the mildly retarded range. Her visual acuity had only slightly reduced to 6/9 between the ages of five and seven years. Further follow-up on both patients and the whole family has continued.

Discussion

The association of gross obesity with visual loss, retinitis pigmentosa, mental retardation and postaxial polydactyly and the history of obesity and postaxial polydactyly in a first degree relation as were found in our cases, are classical features of Laurence-Moon-Biedl syndrome. The diagnosis of the syndrome is not in doubt if a combination of the above clinical manifestations in addition to hypogonadism is found among siblings.[1-5] There is however, considerable phenotypic variation among reported cases, but since no specific diagnostic test is known at the present time, the diagnosis must still be established clinically.[1,2] The extent of the abnormality may vary considerably between affected siblings, and it may be impossible to make the diagnosis in an isolated case demonstrating only part of the syndrome, especially if the only manifestations are mental retardation, obesity and genital hypoplasia.[2]

The variability in clinical expression of the syndrome as it occurred in the two first degree females was obvious. Obesity, which is found in over 80 percent of the patients with LMB syndrome typically begins in early infancy and increases in severity with advancing age.[1,2,5] This pattern was demonstrated in both patients, although there was variation in the onset

of the obesity. Retinal dystrophy occurs in over 90 percent of the patients even though pigmentary changes in the retina may be minimal,[1] and retinitis pigmentosa is found in about 68 percent of cases.[1] The retinal degeneration is progressive and by the age of 20 years, more than 70 percent of the patients are blind, and by the third to fourth decades, it usually results in total blindness.[1-3] Our index patient showed progressive visual loss, while in the second patient, retinal pigmentary changes were minimal and the progress of the visual disturbance was slower. The LMB syndrome is often associated with hypothalamic hypogonadism. The gonadotrophins in both patients were within the normal prepubertal range. Hypogonadism, although present in about 75 percent of males is said to be rare in females.[1] Primary gonadal failure may occur later in life and virilism may also be a late manifestation of this syndrome.[1,2,5]

Digital anomalies are noted in about 75-80 percent of cases of the LMB syndrome.[1,2] The most frequent finding is postaxial polydactyly of one or more extremities, but some patients have only syndactyly or brachydactyly.[1,2] Our patients demonstrated variability in the manifestation of digital anomalies. While the index patient had postaxial polydactyly in three extremities, the second patient had postaxial polydactyly in the two upper extremities and mild syndactyly in the feet. The mental deficiency, which occurs in about 80 percent of patients, usually in the form of mild to moderate intellectual impairment, was milder in the younger of the two sisters. It has been reported that about 20 percent of the patients with the syndrome have severe mental retardation and another 10 percent have normal intelligence.[1]

Other important abnormalities associated with this syndrome include renal defects and hypertension, cardiac and urological anomalies. Nephropathy is a significant feature in many patients and some workers consider it as one of the cardinal features of the syndrome.[1] The renal lesions vary from mesangial proliferative glomerulonephritis to medullary cystic disease and there may also be focal areas of dysplasia.[1] There was no clinical, laboratory or ultrasonographic evidence of renal lesion in our patients, but renal biopsy was not done. Occasional defects associated with LMB syndrome include nystagmus and cystic dilatation of the intrahepatic and common bile; these were absent in our patients.

Ataxia, incoordination and hypotonia without weakness of the limbs manifested in the proband, but not in her sister. The neurological signs should be interpreted with caution. Ataxia and other cerebellar signs are not commonly associated with LMB syndrome, but may occur in long standing cases due to slowly progressive spinocerebellar degeneration.[2] On the other hand, rather than being cerebellar signs, they could in fact, be early signs of spastic paraplegia[8] which is a major feature of classical Laurence-Moon (LM) syndrome.[3-5] However, the LMB syndrome is now regarded as a clearly different disorder from the condition first described by Laurence and Moon in 1865 and known as Laurence-Moon (LM) syndrome.[2,4] The principal features of LM syndrome resemble the LMB syndrome, but postaxial polydactyly is not included in the symptomatology of LM syndrome.[2,4] Brain CT scan done in one of our patients was normal, but it is known that CT scan is not as good as MRI in demonstrating certain posterior fossa abnormalities, spinal lesions and spinocerebellar degenerative process;[9,10] unfortunately, MRI was not available during the period the siblings were being seen.

The assessment of our patients involved costly ancillary investigations some of which were not available in our centre then, e.g. brain CT scans and hormonal assays. This lack necessitated the parents and patients having to travel long distances to have such investigations carried out at great cost. The investigations therefore, placed an enormous financial burden on the family and financial assistance had to be solicited from the government and richer relations. The psychological burden of the disorder on the proband was also enormous. She was ostracized by the pupils who laughed at her on account of the severe obesity, and coupled with her poor school performance, necessitated her withdrawal from school. The dietary restriction also imposed considerable stress on both patients and parents. The most distressing problem was the progressive visual loss. Unfortunately, no effective treatment is currently known for the inherited pigmentary retinopathies.[4]

Acknowledgements

We are grateful to the parents for their cooperation, the Kebbi State Government for financial assistance to the patients, our resident staff for their support, and Umar S Maikulki for secretarial assistance.

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A PAEDIATRICIAN'S PRAYER

Like the sheer wonder of thriving children,
May the tribe of good paediatricians grow
in number, wisdom and skill;
May they prosper, for the better care of children,
within and beyond our borders!
Amen.

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