

Retinitis pigmentosa in Laurence-Moon-Bardet-Biedl syndrome in India: Electronic medical records driven big data analytics: Report II

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Purpose: To describe the clinical presentation and demographic distribution of retinitis pigmentosa (RP) in Laurence–Moon–Bardet–Biedl (LMBB) syndrome patients. **Methods:** This is a cross-sectional observational hospital-based study wherein 244 patients with RP in LMBB syndrome presenting to our hospital network between March 2012 and October 2020 were included. An electronic medical record database was used for data retrieval. **Results:** There were 244 patients in total, with a hospital-based prevalence rate of 0.010% or 1000/100,000 population. The mean and median age of patients was 15.22 ± 7.56 and 14 (IQR: 10–18.5) years, respectively, with the majority being in the age group of 11–20 years (133/244 patients; 54.50%). Males were more commonly affected (164 patients; 67.21%), and the majority (182 patients; 74.59%) were students. All 244 patients (100%) complained of defective central vision at presentation. More than one-fourth of the patients had severe visual impairment to blindness at presentation. Prominent retinal feature at presentation was diffuse or widespread retinal pigment epithelial degeneration in all patients. **Conclusion:** Patients with RP in LMBB syndrome present mainly in the first to second decade of life with severe visual acuity impairment to blindness early in life. It is important to rule out LMBB syndrome in early-onset RP with central visual acuity impairment. On the contrary, all patients diagnosed or suspected with LMBB syndrome systemic features at physician clinic should also be referred for ophthalmic evaluation, low vision assessment, rehabilitation, and vice versa.

Key words: Big data analytics and clinical presentation, Laurence–Moon–Bardet–Biedl syndrome, retinitis pigmentosa

Laurence–Moon–Bardet–Biedl (LMBB) syndrome is a rare genetic disorder involving multiple organs. Laurence–Moon syndrome (LMS) and Bardet–Biedl syndrome (BBS) are separate groups of disorders with a majority of the phenotypical features overlapping.^[1,2] Features common to both LMS and BBS are pigmentary retinal degeneration, mental retardation, renal dysfunction, and hypogonadism. Progressive spastic paraplegia and distal muscle weakness are predominantly seen in LMS, whereas polydactyly and central obesity are more in favor of BBS.^[3,4] Due to the overlapping features, both are often considered a single entity as LMBB syndrome.

Prevalence of LMS and BBS have been reported to be higher in regions with consanguineous marriage.^[5-7] The inheritance pattern is autosomal recessive with nearly 21 mutations reported in the *BBS* gene (BBS1-BBS20), following an

oligogenic inheritance pattern,^[8] while mutations in the *PNPLA6* gene (Chromosome 19) are responsible for LMS.^[9] The ocular features of LMBB syndrome include retinal degeneration, nystagmus, strabismus, cataract, and astigmatism. Pigmentary retinal degeneration is the major feature among all the ocular presentations as well as a major criterion for establishing the diagnosis of LMBB syndrome. The major retinal degeneration noted has been retinitis pigmentosa (RP), a rod-cone type of progressive pigmentary retinal degeneration.^[10] Rarely, cone-rod degeneration has also been found. The rod-cone dystrophy is usually of juvenile-onset, progressive with early macular involvement. Owing to the severity and progressive nature of the disease, an individual with LMBB syndrome can become legally blind by the age of 20–30 years.^[1,3,11]

Recognition of underlying systemic LMBB syndrome is important when any child presents with RP. Renal failure is the most common cause of mortality among these patients; thus, early detection of LMBB syndrome in childhood-onset RP helps in prolonging the lifetime of the affected individual. In

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1999, Beales *et al.*^[1] laid down the criteria for LMBB syndrome through a survey of 109 patients in the UK.^[11,12] Since then, there have been multiple case reports citing new systemic features. However, there is no large dataset on the ocular features of LMBB syndrome, specifically regarding the features of retinal degeneration. We report a large series of children who had pigmentary retinal degeneration due to LMBB syndrome by using electronic medical records-driven analytics. We discuss the ocular features typical of LMBB syndrome, compare them with existing literature, and suggest specific approach for managing children with RP due to LMBB syndrome.

Methods

Study design, period, location, and approval

This retrospective cross-sectional observational hospital-based study included patients presenting between March 2012 and October 2020 to our institute and its ophthalmology network. Records of hospitals located in 200 locations spread across four Indian states (Telangana, Andhra Pradesh, Odisha, and Karnataka) were analyzed.^[13] These 200 hospitals contain tertiary referral centers, secondary centers, and cases from primary care centers. All the cases included in the study are confirmed with diagnosis of LMBB and RP by a trained ophthalmologist in secondary and tertiary centers.

The patient or the parents or guardians of the patient filled out a standard consent form for electronic data privacy at the time of registration. None of the identifiable parameters of the patient information were used for the analysis of the data. The study adhered to the tenets of the Declaration of Helsinki and its later amendments, and was approved by the institute's ethics committee (Ethics Reference No. LEC-BHR-R-09-20-505). The clinical data of each patient who underwent a comprehensive ophthalmic examination was entered into a browser-based electronic medical records system (eyeSmart EMR) by uniformly trained ophthalmic personnel and supervised by an ophthalmologist using a standardized template.^[14]

Cases

A total of 2,541,810 patients of all ages presented to the tertiary and secondary centers of the network during the study period. The eyeSmart EMR was initially screened for patients with the final diagnosis of RP in one or both eyes with LMBB syndrome. The diagnosis was based on clinical examination by a trained ophthalmologist. The diagnostic criteria used for rod-cone dystrophy/RP were diffuse and/or widespread retinal pigment epithelial degeneration, arterial narrowing, disc pallor, and commensurate visual field loss. Whenever available, reduced amplitudes on electroretinogram (ERG) with evidence of rods and cones were recorded.^[15] Clinical and demographic information from the database of electronic medical records (EMR) was extracted into excel for the analysis. The volume of the unique patient base is large and the disease of interest is mined from this database with respect to the disease of interest.^[14] The use of Big Data is for the 2.5 million patient database that was analysed to extract the patients of retinitis pigmentosa (RP) and further as RP with LMBB syndrome. The clinical criteria used for LMBB syndrome included primary features of rod-cone dystrophy, polydactyly or dystrophic extremities (brachydactyly and syndactyly), obesity, reduced intelligence, features of mental retardation, progressive spastic paraplegia, distal muscle weakness, renal dysfunction, and

male hypogonadism that manifests in the first decade of life with polydactyly as a congenital feature. All the cases of LMBB syndrome were diagnosed by either a physician or pediatrician or endocrinologist and/or by a trained ophthalmologist with referral to a pediatrician.^[1,4] Any cases not fitting the criteria were excluded from the study.

Data retrieval and processing

In total, 244 patients with RP in LMBB syndrome were included in this study. The data were retrieved from the electronic medical record database and segregated in a single excel sheet. The columns included data on demographics, clinical presentation, and ocular diagnosis and were exported for analysis. The excel sheet with the required data was then used for analysis by using the appropriate statistical software. Standardized definitions were used for geographic locations, occupations, pedigree-based family history, and socioeconomic status.^[16] The visual acuity was classified according to the guidelines of the WHO.^[17]

Statistical analysis

Descriptive statistics using mean \pm standard deviation and median with interquartile range (IQR) were used to elucidate the demographic data. Chi-square test (Stata software, Stata Corp. 2015. College Station, TX: Stata Corp LP) was used for univariate analysis to detect significant differences in the distribution of demographics features between patients with RP and the overall population.

Results

Prevalence

Of the 2,541,810 patients who presented across the network during the study period, 244 patients were diagnosed with LMBB syndrome and RP in at least one eye, translating into a hospital-based prevalence rate of 0.010% or 1000/100,000 population.

Age

The mean and median age of patients with retinitis pigmentosa with LMBB syndrome was 15.22 ± 7.56 and 14 (IQR: 10–18.5) years, respectively. The majority among them were in the age group of 11–20 years (133/244, i.e., 54.50%). Sixty four (26.22%) were in the age group of 0–10 years; 45 (18.44%) were in the age group of 20–40 years. Only two (0.82%) patients were in the age group of 40–50 years. The decade-wise distribution of age is described in Fig. 1.

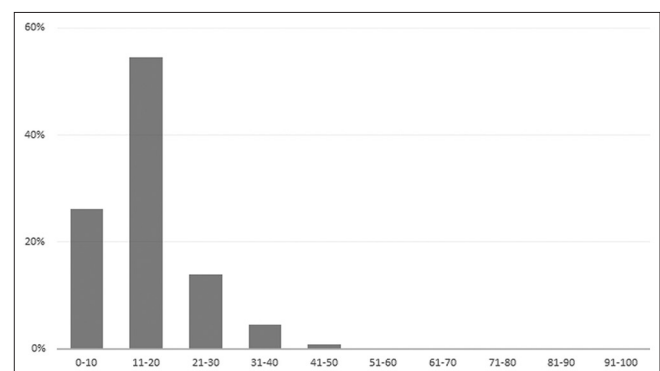


Figure 1: Bar graph showing the decade-wise distribution of Laurence-Moon-Bardet-Biedl (LMBB) syndrome patients

Sex

There were 164 (67.21%) male and 80 (32.78%) female patients. The overall prevalence of retinitis pigmentosa was significantly greater ($P < 0.0001$) in males (0.67%; 164/1,371,479) as compared to females (0.32%; 80/1,170,331).

Rural-urban-metropolitan distribution

There were 110 (45.08%) patients of retinitis pigmentosa with LMBB syndrome from rural districts, 100 (40.98%) from urban districts, and 34 (13.93%) from metropolitan regions. The prevalence of retinitis pigmentosa was higher ($P < 0.00001$) in the rural community.

Occupation

Of the 244 patients with retinitis pigmentosa and LMBB syndrome, a majority (182; 74.59%) were students, nine (3.69%) were professionals, four (1.64%) were homemakers; three (1.23%) were manual laborers, and in the remaining 46 (18.86%), the occupational category was not available/applicable. The overall prevalence of retinitis pigmentosa and LMBB syndrome in students (0.042%; 182/434,713) was significantly higher ($P < 0.00001$) in comparison to other professions.

Presenting complaints & family history

Of the 244 patients with retinitis pigmentosa and LMBB syndrome, 76 (31.15%) complained of defective night vision, 10 (4.10%) had a defective peripheral vision, six (2.46%) had photophobia/photopsia, and all 244 (100%) patients complained of defective central vision. In 23 (9.43%) patients, there was a family history of retinitis pigmentosa with LMBB syndrome, and 28 (11.48%) patients had a history of a parental consanguineous marriage.

Laterality and ocular co-morbidities

The retinitis pigmentosa in LMBB syndrome was bilateral in 243 (99.59%) cases and unilateral in one case. This case had retinochoroidal coloboma and retinal detachment in the fellow eye. In the 487 eyes affected with retinitis pigmentosa in LMBB syndrome, associated cataract was found in 68 (14.17%) eyes, and one eye had retinal detachment (0.21%). None of the eyes had associated glaucoma or coats disease at presentation.

Best-corrected visual acuity (BCVA)

In the 487 eyes, mild or no visual acuity impairment (20/20–20/70) was seen in 73 (14.99%) eyes, moderate visual impairment (>20/70–20/200) in 89 (18.28%) eyes, severe visual impairment (>20/200–20/400) in 39 (8.01%) eyes, blindness grade 3 (>20/400–20/1200) in 127 (26.08%) eyes, and blindness grade 4 (>20/1200–PL) in 42 (8.62%) eyes at presentation. The visual acuity was undetermined or unspecified in 117 (24.02%) eyes. More than one-fourth of the patients had severe visual impairment to blindness at presentation. Further, 74.18% (181/244) of the patients with RP and LMBB syndrome had visited our visual rehabilitation and low-vision aids center for services.

Spherical equivalent

In the 487 eyes, emmetropia (–0.50 to +0.50D) was seen in 13 (2.67%) eyes, >–0.50 to –3.00D (mild myopia) in 52 (10.68%) eyes, >–3.00 to –6.00D (moderate myopia) in 48 (9.86%) eyes, >–6.00D (high myopia) in 61 (12.53%) eyes, >+0.50 to +3.00D (mild hyperopia) in 14 (2.87%) eyes, and >+3.00D

to +6.00D (moderate hyperopia) in 14 (2.87%) eyes where refraction was performed at presentation. Overall, myopia was the predominant refractive error; 122 eyes (25.05%) had astigmatism of more than –2D cylinder, and the mean astigmatism was -2.94 ± 0.79 DC.

Lens

In the 487 eyes, the lens findings included nuclear cataract in 53 (10.88%) eyes, sub-capsular cataract in eight eyes (1.64%), cortical cataract in two (0.41%) eyes, and complicated cataract in three (0.62%) eyes. A clear lens was noted in 135/487 eyes (27.7%) at presentation.

Vitreous

Vitreous analysis was performed by indirect ophthalmoscopy examination. Not all patients had documented vitreous data in the files. In the 487 eyes, the available vitreous findings included posterior vitreous detachment in four (0.82%) eyes and vitreous opacities in six eyes (1.23%).

Macula

In the 487 eyes, the optical coherence tomography-confirmed macular findings included central foveal thinning (<150um) in 58 (11.91%) eyes, epi-retinal membrane in three (0.62%), and macular edema in only two eyes (0.41%).

Retina and vitreous

In the 487 eyes, the retinal signs included waxy disc pallor in 391 (80.29%) eyes, attenuated vessels in 447 (91.79%), and all eyes had had diffuse or widespread retinal pigment epithelial degeneration signs. None of the patients had atypical RP features. Further, 8/487 (2.05%) eyes vitreous abnormalities (vitreous opacities and posterior vitreous detachment).

Full field electroretinogram (ERG) and Humphrey visual field (HVF) analysis

Fifty-six eyes had reliable full-field ERG available for analysis. The majority of the eyes (54%, 30/56) had extinguished photopic and scotopic responses [Fig. 2], 25% of the eyes (14/56) had extinguished photopic, scotopic and oscillatory potentials, 14% of the eyes (8/56) had extinguished scotopic responses and reduced photopic responses, and 7% of the eyes had (4/56) had reduced photopic and scotopic responses. Fifty-seven eyes had reliable HVF analysis for review. Among 57, 85% of the eyes (49/57) had affection of central as well peripheral visual fields with only less than central 10 degree of functioning visual field, and the rest of the eyes (15%, 8/57) had affection of only peripheral visual fields in 30-2 HVF analysis [Fig. 3].

Surgical management

A minor proportion of four (0.82%) eyes required surgical intervention. The most common procedures performed were cataract surgery in two (0.41%) eyes and vitreoretinal surgery in two (0.41%) eyes for retinal detachment. Only one eye had RD, as mentioned before.

Discussion

Our study covers a large cross-section of patients with retinitis pigmentosa in LMBB syndrome. The prevalence of BBS has been reported to be from 1:125,000 to 1:18,500 in population-based studies, and the prevalence of LMS varies from 1 in 160,000 to 1 in 13,500 depending on the geographic location.^[1,18,19] Both are

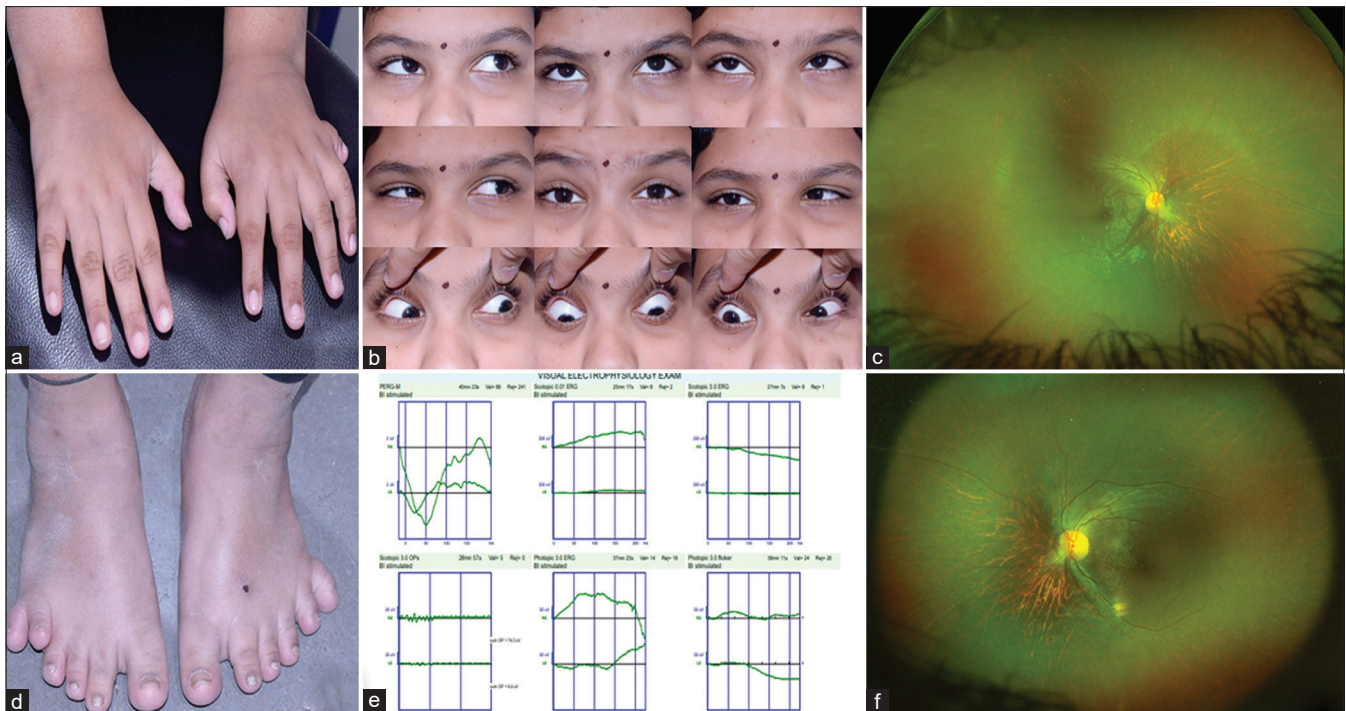


Figure 2: A 13-year-old female with LMBB syndrome and pathogenic mutation in the *BBS9* gene showing features of obesity, polydactyly in the left hand (a), left eye type 1 Duane's retraction syndrome (b), retinitis pigmentosa fundus right eye (c), polydactyly in both feet (d), extinguished photopic as well as scotopic responses in full-field electroretinogram (e) and retinitis pigmentosa fundus left eye (f)

rare entities, with few case series reporting the characteristics of RP in LMBB syndrome. We aim to highlight the clinical presentation and demographic distribution of RP patients with LMBB syndrome in 244 patients. The hospital-based prevalence rate of retinitis pigmentosa with LMBB syndrome in our study was high at 0.010% or 1000/100,000 population. The majority of them were in the age group of 11–20 years with a mean age at presentation of 15.22 ± 7.56 years. Early severe vision loss might be one of the reasons for early presentation to hospital. None of the patients were above 50 years in our study, which may be due to early mortality from renal dysfunction in these patients.^[19] It also highlights possibly the lifetime of LMBB syndrome patients with poor survival beyond 50 years due to systemic associations. However, we do not have any follow-up systemic data to support this. Males were more commonly affected than females. The majority of them were students (74.59%), indicating affection at early ages. Retinitis pigmentosa in LMBB syndrome is known to present early in the life and affecting males similar to our study.^[11,20,21] Affection of males predominantly in an autosomal recessive pattern of inheritance is to be studied further; the male and female number may also vary due to more male child presenting to the hospital.

In our study, all patients with RP and LMBB syndrome had complaints of defective central vision, indicating affection of central vision early in patients of RP with LMBB syndrome when compared to RP alone. The retinitis pigmentosa in LMBB syndrome was bilateral in 99% of the eyes in our study with early vision loss. Among 487 eyes, blindness 3 (>20/400–20/1200) was seen in 127 (26.08%) eyes, which constituted the majority among other visual impairment categories, indicating severe affection of central visual acuity in RP with LMBB syndrome. The affection of central vision is accounted for predominantly by foveal thinning, and a very small contribution of epiretinal

membrane and macular edema in our study. The affection of central vision in our study was also supported by 85% of the eyes (49/57 eyes with HVF analysis) having affection of central as well peripheral visual fields with only less than central 10° of functioning visual field. Spaggiari *et al.*^[21] in their case series with 13 pediatric patients with BBS had shown that severe and progressive affection of vision started early in the first decade, with pigmentary retinopathy being predominate form with significant electrophysiological abnormalities. In our study, the majority (54%, 30/56 eyes with reliable ERG) showed severe affection of both photopic and scotopic responses. This may be one of the factor leading to early affection of central vision due to affection of cones as well in early life. Katsumi *et al.*^[22] had correlated the electrophysiological abnormalities with functional and structural changes in the retina. In their case series too, they noted diffuse involvement of macula as well as peripheral retinal involvement and severe affection of photoreceptors (both rods and cones) responsible for central vision loss and profound affection in ERG. Berezovasky *et al.*^[11] had shown in their case series of 23 patients with BBS, affection of younger cohort with only 21% having 20/40 or better vision, with predominant affection of scotopic responses.

The most common refractive error was myopia (33%) in our study. Myopic astigmatism was seen in 1/4th of the total subjects (25%). Myopia and astigmatism have been reported to be occurring as a common ocular association in previous case reports and case series as well.^[11,23,24] Nuclear cataract was more common than posterior subcapsular cataract in our study, while in eyes without LMBB syndrome, RP is usually associated classically with stellate posterior subcapsular cataract.^[25,26] Another rare ocular association was retinal detachment. None of the eyes had associated glaucoma or coats disease at presentation.

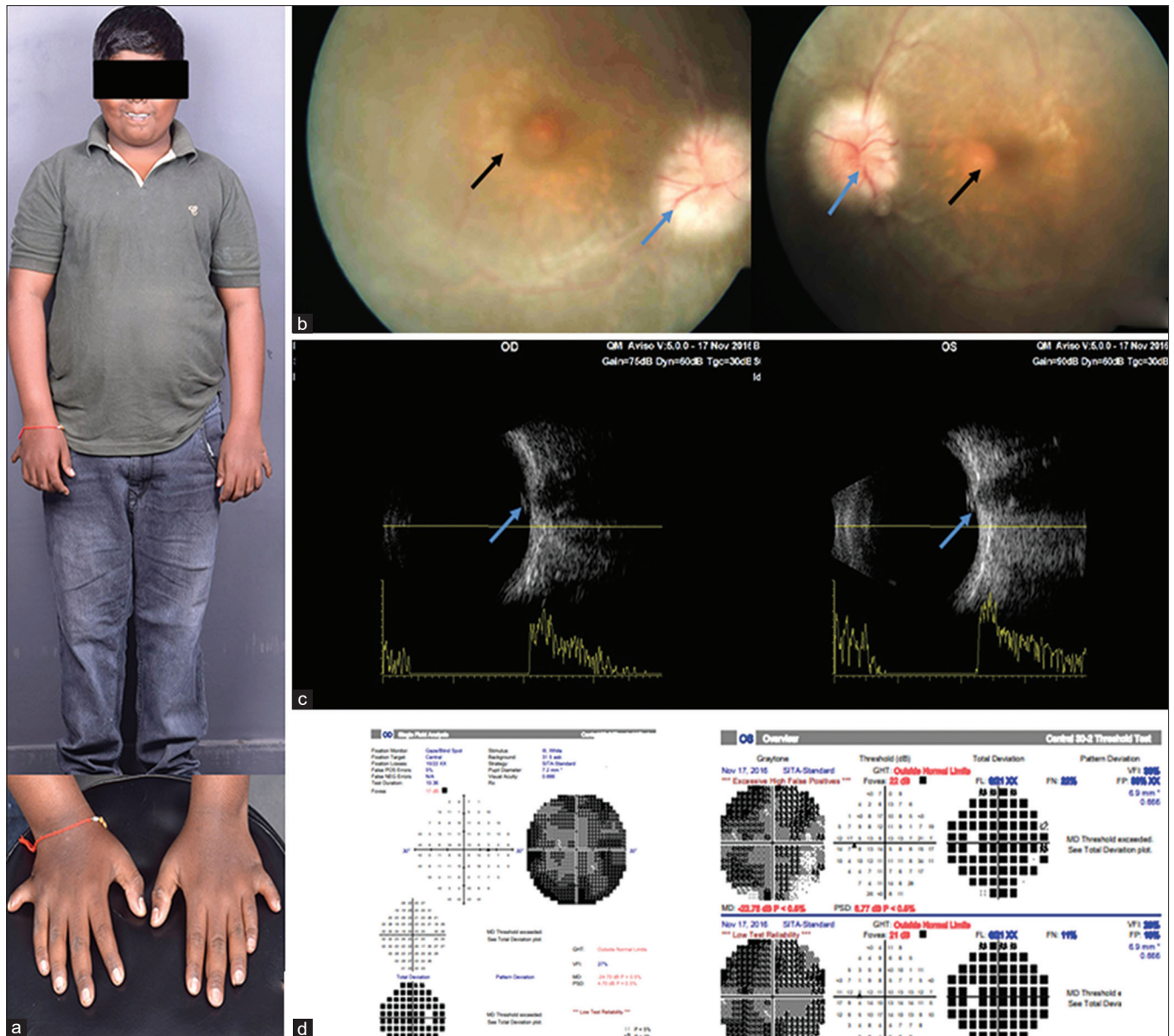


Figure 3: A 17-year-old male with LMBB syndrome showing features of obesity, polydactyly (a), fundus of both eyes (b) showing pigmentary alteration in the macula (black arrow), pseudo-optic disc edema secondary to associated drusen (blue arrow), confirmed on ultrasound B-scan (c) (blue arrow) and Humphrey visual field examination of both eyes showing affection of peripheral visual (d)

Severe and early affection with RP in LMBB syndrome patients points toward the need for early visual rehabilitation and supportive therapy. Genetic counseling is important as the disease has an autosomal recessive inheritance. The role of ophthalmologists is vital in early and prompt referral to a physician for supportive treatment of systemic associations such as renal anomalies, spasticity, gonadal hypogenesis, intellectual disability, and paralysis.

The greatest strength of this study was the large sample size of clinically detected LMBB syndrome with RP so far. The limitation of this study was its hospital-based method of data collection, which would have resulted in recruitment bias. Lack of optical coherence tomography, visual fields, and electrophysiological assessment of retinal functions in all patients is one of the limitations to justify the central

vision affection in LMBB syndrome with RP. Genetic testing or counseling could not be performed in all the cases due to lack of patient awareness, acceptability, and accessibility to the services.

Conclusion

Retinitis pigmentosa in LMBB syndrome is almost always bilateral and predominantly affects males. Patients present in the first to second decade of life with severe visual acuity impairment to blindness early in life. Data from our study shows an early onset of retinitis pigmentosa in LMBB syndrome patients affecting central visual acuity with macular involvement and optic atrophy. Myopia is the predominant refractive error, and nuclear cataract is the common form of cataract seen. It is important to rule out LMBB syndrome in early-onset RP with central visual acuity impairment. LMBB

syndrome patients diagnosed at the ophthalmology clinic should be referred to an endocrinologist. On the contrary, all patients diagnosed or suspected with LMBB syndrome systemic features at physician clinic should also be referred for ophthalmic evaluation, low-vision assessment, and rehabilitation. Early visual as well as systemic rehabilitation with supportive therapy on detection of RP in LMBB syndrome is crucial.

Author contributions

The corresponding author states that authorship credit of this manuscript was based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content, and 3) final approval of the version to be published. All listed authors met conditions 1, 2, and 3. All persons designated as authors qualify for authorship, and all those who qualify are listed. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Conflicts of interest

There are no conflicts of interest.

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