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CLINICAL MANIFESTATIONS OF BARDET BIEDL SYNDROME

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ABSTRACT **Background:** Bardet – Biedl syndrome is a rare autosomal recessive ciliopathic genetic disorder. It is a rare multisystem disorder characterized by rod-cone dystrophy, learning difficulties, central obesity, syndactyly and hypogonadism affecting children of consanguineous marriages. It is characterized by few major and many minor features which aid in the clinical diagnosis and management. **Materials And Methods:** case series of 8 cases studied over a period of 6 months **Results:** Out of the 65 cases diagnosed with retinitis pigmentosa, 8 cases have features of Bardet – Biedl syndrome of which 6 are males and 2 are females, all are within the age group of 8 to 15 years. All the 8 have decreased visual acuity of which 2 males had visual acuity less than 6/60 and 4 males and 2 females have best corrected visual acuity of more than 6/60. Fundus examination showed pale disc with normal size and shape of optic disc with distinct margins and 7 have arteriolar attenuation and Background retina showed bony spicules in the mid periphery in 5 cases and 3 have mottling and 1 female has tessellations in the periphery. All the 8 cases had truncal obesity and short stature with polydactyly and few have learning difficulties, speech delay, developmental delay, ataxia and hyposmia. **Conclusion:** The morbidity and mortality due to Bardet – Biedl syndrome can be avoided by increasing awareness among the physicians to promote early diagnosis and treatment.

KEYWORDS : Bardet – Biedl syndrome, ciliopathies

INTRODUCTION:

A rare genetic multisystem disorder called Bardet-Biedl syndrome (BBS) due to malfunctioning primary cilia. This ciliopathy is distinguished by rod-cone dystrophy, renal abnormalities, postaxial polydactyly, learning disabilities, central obesity, and hypogonadism. Twenty-one genes (BBS1–BBS21) have been found to cause BBS thus far.[1]

A family of four siblings with retinal degeneration, obesity, spastic paraparesis, and cognitive deficiency was reported by Laurence and Moon in 1866.[2] Laurence–Moon–Bardet–Biedl syndrome was named after Bardet [3] and Biedl [4] independently reported on other similarly affected people who also had post-axial polydactyly. Although the disease is frequently separated into two categories, Bardet-Biedl disease (BBS) and Laurence-Moon Syndrome (LMS), there is a significant amount of phenotypic overlap that raises the possibility that they are allelic. [1] BBS is currently the phrase that is most commonly used. We emphasized the significance of recognizing BBS as soon as possible in order to provide comprehensive and multidisciplinary care and minimize avoidable morbidity and mortality, as there is currently no particular treatment for the condition.

AIMS AND OBJECTIVES

To study the varied presentations in cases of Bardet – Biedl syndrome

MATERIALS AND METHODS

This is a prospective observational case series of Bardet – Biedl syndrome patients done over a period of 6 months at Ophthalmology outpatient department, Government General Hospital, Guntur. During the study period we have seen 65 cases of Retinitis Pigmentosa, of which 8 cases of Bardet – Biedl syndrome have been studied. Detailed ophthalmic and systemic examination of each patient was conducted and cases of Bardet – Biedl syndrome were noted.

REQUIREMENTS:

1. Snellen's chart and Landolt C chart
2. Slit lamp with 90 D lens
3. Indirect Ophthalmoscope with 20 D lens
4. CX-1 canon fundus camera with an imaging angle of 45 degree
5. Stadiometer and measuring tape
6. Ultrasound abdomen

RESULTS:

Of the total 65 cases of Retinitis Pigmentosa, 8 cases have features of Bardet – Biedl syndrome. Of the 8 cases, 6 are males and 2 are females, all are within the age group of 6 to 14 years. All the 8 cases presented with a chief complaint of difficulty in night vision of varied duration ranging from 3 months to 4 years which is gradually progressive in nature. Of the 8 cases, 7 cases have family history of consanguineous marriage of parents and 5 cases have siblings who are all normal.

On ocular examination, all the 8 have decreased visual acuity of which 2 males had visual acuity less than 6/60 and 4 males and 2 females have best corrected visual acuity of more than 6/60. One female has left eye exotropia with a Hirshberg test of 15 degree. Anterior segment is within the normal range in all cases, 7 cases have brisk pupillary reactions and 1 female has sluggishly reacting pupils and all 8 have clear lens. Upon fundus examination using 90D lens under slit lamp and indirect ophthalmoscopy along with fundus photographs taken, media is clear in all pale disc with normal size and shape of optic disc with distinct margins and all 8 have arteriolar attenuation and macula is normal in all the cases and foveal reflex is present in 6 cases and dull in one male and one female. Background retina showed bony spicules (figure 1) in the mid periphery in 5 cases and 3 have mottling and 1 female has tessellations in the periphery.

On systemic examination, all the 8 cases had truncal obesity and short stature. All the 6 male cases had penile hypoplasia and one male and one female had renal parenchymal cysts diagnosed in ultrasound abdomen. 5 males and 2 females had learning difficulties of which 3 have labile behavior, 2 had delayed milestones and 2 had autism with speech delay. 1 male had hypodontia and 6 have post-axial polydactyly (figure 2), of which 1 has brachydatyly and 2 have pre- axial polydactyly. 3 cases have ataxia with poor coordination and 2 have hyposmia.

FEATURES	FREQUENCY (PERCENTAGE)
PRIMARY FEATURES	
Rod-cone dystrophy	8 (100%)
Polydactyly	8 (100%)
Obesity	8 (100%)
Genital abnormalities	6 (75%)
Renal anomalies	2 (25%)
Learning difficulties	7 (87.5%)
SECONDARY FEATURES	
Speech delay	2 (25%)
Developmental delay	2 (25%)
Diabetes mellitus	0 (0%)
Dental anomalies	1 (12.5%)
Congenital heart disease	0 (0%)

Brachydactyly/ syndactyly	8 (100%)
Ataxia/ poor coordination	3 (37.5%)
Anosmia/ hyposmia	2 (25%)

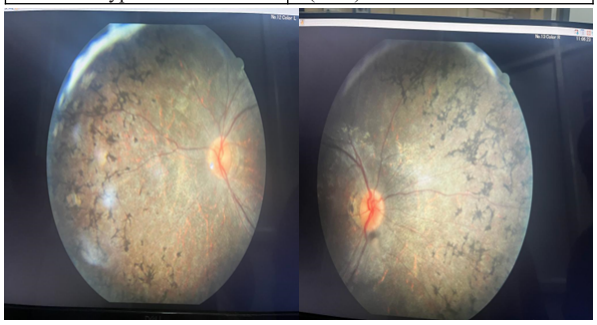

Figure 1 showing clear media with pale optic disc and arteriolar attenuation and the background shows bony spicules in the mid periphery

Figure 2 showing post-axial polydactyly of hands and feet along with central obesity

DISCUSSION:

Bardet- Biedl syndrome is a rare autosomal recessive multisystem disorder. Twenty-one BBS genes (NPHP1 and BBS1–BBS20) are known to exist. The two main genes associated with BBS are BBS1 and BBS10, and these gene changes were found in over 20% of patients. [5] Genetic analysis is only used for complicated situations and experimentation because it is expensive and time-consuming. Due to its high cost, genetic testing was not conducted in our cases.

Consanguinity has played a significant role in this disease's prevalence. Of the 8 cases, 7 cases had history of their parents' consanguineous marriage.

Presence of 4 primary features or 3 primary and 2 secondary features are diagnostic of BBS. All our 8 cases are fulfilling the diagnostic criteria.

The majority of Bardet-Biedl syndrome (BBS) characteristics do not become apparent in the early years of life and instead appear after many years of growth. Because clinical features of BBS develop gradually in young children, diagnosis is still difficult. The average age at diagnosis was nine years old in a significant population-based survey carried out in the United Kingdom.[1] All the 8 cases were within the age group of 6 to 14 years of which 6 were males of age 6yrs,7yrs,9yrs,10yrs,13yrs,14yrs and 2 females of age 7 yrs and 12 yrs. Rod-cone dystrophy development is the most prevalent diagnostic sign initiating examination for BBS where cone photoreceptor death occurs after the loss of rod photoreceptors. The clinical presentation includes night blindness, progressive loss of peripheral vision which finally involves the central vision, color vision, photophobia. There are numerous variations of the ophthalmological phenotype associated with BBS, and certain patients have the opposite progression of pathological events, losing rod photoreceptors first and cone photoreceptors.1 First symptoms often appear in the first ten years of life. All the 8 cases had pale disc with arteriolar attenuation and 2 patients – 1 male had dull foveal reflex and 1 female had dull foveal reflex with tessellations in the background and 5 cases – 3 males and 2 females had bony spicules in the mid periphery and 3 males presented with mottling.

This can also be associated with other abnormalities such as refractive error, cataract, squint.1 female presented with left eye exotropia with a Hirschberg reflex of 15 degree nasally. 6 out of 8 had visual acuity improving to > 6/12 with spectacles and 1 male and 1 female had vision of counting fingers 5 meters and 6/60 not improving further respectively.

Central obesity is one of the most prevalent symptoms of BBS, and it usually manifests in the first year of life. All our cases had central obesity where 3 males and 2 female had BMI >25kg/m^2, considered as overweight, 2 males had BMI >30kg/m^2, considered obese and 1 male had 42kg/m^2 BMI considered severely obese. In a study conducted by Beales and Elcioglu, 72% of post-pubertal individuals met the WHO's criteria for overweight (BMI > 25 kg/m^2), while 16% met the criteria for severely obese (BMI > 40 kg/m^2). [1]

Limb abnormalities have been observed in a variety of forms and frequency. The most prevalent anomalies in the upper and lower limbs are brachydactyly (6-100%) and polydactyly (63-81%). The signs of the disease include partial syndactyly, clinodactyly in the fifth finger, and a noticeable gap between the first and second toes.[1]In our cases 2 males and 1 female had polydactyly and syndactyly in the upper limbs, 1 male and 1 female had polydactyly and syndactyly in lower limbs and 1 male had polydactyly and syndactyly in both upper and lower limbs and 2 males had polydactyly and brachydactyly in upper limbs.
In males, hypogenitalism or delayed puberty may be the symptom of hypogonadism; in females, genital abnormalities may be the result. [1,6] This can happen on its own or in combination with hypogonadism in the biological sense. The low rates of fertility in BBS are partly due to the large range of genital abnormalities that have been seen in females. Almost always, men are infertile.5 males presented with hypogonadism and 1 female had underdeveloped ovaries on examination using ultrasound.

In BBS, renal problems may be a significant contributor to morbidity with varied presentation and death.[7] 2 males presented with renal calyces. Most of the etiology of renal disease is unknown. Although diabetes, obesity, and hypertension—all of which are commonly seen in these patients—are recognized risk factors for the advancement of kidney disease, it is necessary to examine their role in this context in further detail. According to Forsythe et al., hypertension and abnormalities of the urinary tract are associated with kidney disease stage 2–5.[8]

Learning deficit is a crucial diagnostic criterion for BBS. Various vision difficulties and low IQ have been observed in relation to this disorder. These days, objective IQ tests are used to determine just a small percentage of mentally handicapped patients. An IQ of 79 or lower has been identified in about 44% of BBS cases. A relationship has been shown between visual impairment and a lower IQ.[1] Many of the affected people are somewhat clumsy, and 40% of one cohort reports having poor coordination and ataxia.[1] Along with difficulties with tandem walking and the Fogg test, dysdiadochokinesia and past pointing are frequent (79%) in the population.[1] 7 of our patients had leaning difficulty of which 3 had poor coordination.

Cognitive impairment and developmental delays are prevalent in BBS. 62% of the 109 patients in the cohort had cognitive disability, and half of them went to special school.[1] Children typically do not acquire understandable speech until they are four years old, and their speech is primarily high-pitched nasal. [1]2 males had developmental delay with associated speech delay.

On the basis of observations made in a mouse model, anosmia has been described in majority of the cases although a few cases presented with hyposmia.[9] 2 males were diagnosed with anosmia at the age of 6 and 8 years and 1 male presented with malocclusion of molars.

Among patients, type 2 diabetes develops often. It frequently coexists with other metabolic syndrome symptoms and could be connected to the degree of obesity. None of our cases had diabetes mellitus.

Other organ systems like the heart and gastrointestinal system are also seen to be involved. There is a wide range in the kinds of cardiac anomalies seen in BBS patients. Beales et al [1] in a study with 109 patients discovered a frequency of just 7%. Valvular stenoses, cardiomyopathies, and patent ductus arteriosus are examples of cardiac abnormalities.[1]

CONCLUSION:

Bardet – Biedl syndrome is a rare autosomal recessive clinical

syndrome where the most leading cause of morbidity and mortality is renal failure. Hence early detection is required to delay the progression of the renal impairment. The possibility for Bardet – Biedl syndrome should be suspected if a person presents with post-axial polydactyly, learning difficulties, blindness, obesity and renal abnormalities.

REFERENCES:

1) Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999 Jun;36(6):437-46. PMID: 10874630; PMCID: PMC1734378.
2) Laurence JZ, Moon RC. Four cases of "retinitis pigmentosa" occurring in the same family, and accompanied by general imperfections of development. 1866. Obes Res. 1995 Jul;3(4):400-3. doi: 10.1002/j.1550-8528.1995.tb00166.x. PMID: 8521157.
3) Bardet G. On congenital obesity syndrome with polydactyly and retinitis pigmentosa (a contribution to the study of clinical forms of hypophyseal obesity). 1920. Obes Res. 1995 Jul;3(4):387-99. doi: 10.1002/j.1550-8528.1995.tb00165.x. PMID: 8521156.
4) Biedl A. A pair of siblings with adiposo-genital dystrophy. 1922. Obes Res. 1995 Jul;3(4):404. doi: 10.1002/j.1550-8528.1995.tb00167.x. PMID: 8521158.
5) Mandal, R. K., Pande, R., Kc, R. S., & Acharya, B. (2021). Bardet-Biedl syndrome: a case report from Nepal. *Asian Journal of Medical Sciences*, *12*(8), 158-163.
6) Moore, S. J., Green, J. S., Fan, Y., Bhogal, A. K., Dicks, E., Fernandez, B. A., ... & Parfrey, P. S. (2005). Clinical and genetic epidemiology of Bardet–Biedl syndrome in Newfoundland: A 22-year prospective, population-based, cohort study. *American journal of medical genetics Part A*, *132*(4), 352-360.
7) O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. Am J Kidney Dis. 1996 Jun;27(6):776-83. doi: 10.1016/s0272-6386(96)90513-2. PMID: 8651240.
8) Forsythe E, Sparks K, Best S, Borrows S, Hoskins B, Sabir A, Barrett T, Williams D, Mohammed S, Goldsmith D, Milford DV, Bockenhauer D, Foggensteiner L, Beales PL. Risk Factors for Severe Renal Disease in Bardet-Biedl Syndrome. J Am Soc Nephrol. 2017 Mar;28(3):963-970. doi: 10.1681/ASN.2015091029. Epub 2016 Sep 22. PMID: 27659767; PMCID: PMC5328148.
9) Kulaga HM, Leitch CC, Eichers ER, Badano JL, Lesemann A, Hoskins BE, Lupski JR, Beales PL, Reed RR, Katsanis N. Loss of BBS proteins causes anosmia in humans and defects in olfactory cilia structure and function in the mouse. Nat Genet. 2004 Sep;36(9):994-8. doi: 10.1038/ng1418. Epub 2004 Aug 22. PMID: 15322545.