International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Retinitis Pigmentosa: A Case Series

Jayashree S Shah[1], Niveditha RK[2], Shubham Sehgal[3], Lokesha HM[4]

[1]HOD & Professor, Department of Ophthalmology, Sri Siddhartha Academy of Higher Education (SSAHE), TUMKUR, Karnataka

[2]Assistant Professor, Department of Ophthalmology, Sri Siddhartha Academy of Higher Education (SSAHE), TUMKUR, Karnataka

[3]Post Graduate Resident, Department of Ophthalmology, Sri Siddhartha Academy of Higher Education (SSAHE), TUMKUR, Karnataka.
Corresponding Author Email: *Shubhamsehgal2527[at]gmail.com*

[4]Professor, Department of Ophthalmology, Sri Siddhartha Academy of Higher Education (SSAHE), TUMKUR, Karnataka.

Abstract: ***Background: Retinitis Pigmentosa (RP) is a group of inherited retinal dystrophies (IRDs) characterized by progressive vision loss. Worsening symptoms are associated with increased difficulty in performing daily activities and reduced autonomy. This results in difficulties staying in work, higher levels of anxiety and depression, social isolation, and an overall reduced quality of life. Bardet Biedl syndrome and Usher syndrome are ciliopathies that can manifest with retinal degeneration. Case Presentation: Here, we report four patients who presented with a variety of clinical manifestations of retinitis pigmentosa. The first two patients presented with features of Bardet - Biedl syndrome, third patient presented with features of typical retinitis pigmentosa and fourth patient presented with features of Usher syndrome. Case 1: A case of 16yr old male patient admitted in medicine ward with microcytic hypochromic anaemia, referred to department of ophthalmology for diminution of vision in both the eye more during night time diagnosed as Bardet Biedl syndrome as he fulfilled five criteria of primary features (retinitis pigmentosa, obesity, mental retardation, polydactyly and features of hypogonadism) and one secondary feature (delayed developmental milestones). Case 2: A case of 9 year old male patient presented to ophthalmology OPD with diminution of vision in both eyes, more during night time, diagnosed as Bardet Biedl syndrome as he fulfilled four criteria of primary features (retinitis pigmentosa, central obesity, mental retardation and post axial polydactyly). CASE 3: A case of 57 year old male patient presented to ophthalmology OPD with loss of vision in left eye and diminution of vision in right eyes since 1 year diagnosed as typical Retinitis pigmentosa (RP). Case 4: A 21 year old male patient presented to Ophthalmology outpatient department with complaints of diminished vision in both eyes more at night since 5 years. He also had history of difficulty in hearing for last 3 years, diagnosed as Type II usher syndrome. Conclusion: The management of patients with RP is multidisciplinary and requires a focused and structured system where all healthcare providers involved in the care of patients closely collaborate. Disease monitoring, visual prognosis and enrollment of patients in upcoming and ongoing clinical trials are all steps that can be taken to aid the patient.***

Keywords: retinitis pigmentosa, Bardet Biedl syndrome, Usher syndrome, vision loss, multidisciplinary management

1. Introduction

Retinitis pigmentosa (RP) comprises a group of inherited retinal dystrophies characterized by the degeneration of rod photoreceptors, followed by the degeneration of cone photoreceptors. As a result of photoreceptor degeneration, affected individuals experience gradual loss of visual function, with primary symptoms of progressive nyctalopia, constricted visual fields and ultimately central vision loss. The onset, severity and clinical course of RP shows great variability and unpredictability, with most patients already experiencing some degree of visual disability in childhood. [1] RP is the most common inherited retinal dystrophy (IRD), with prevalence rates reported between 1 in 3745 to 4000 [3, 4] affecting over 1.5 million patients worldwide. [2, 5]

Patients with Retinitis Pigmentosa are classified into 'syndromic RP' or 'non - syndromic RP' categories based on the distinction of whether extra - ocular features are present or absent, respectively. Additionally, most patients with syndromic RP can be further classified into either 'inborn errors of metabolism (IEM) ' or 'ciliopathies. ' IEM includes a large group of genetic disorders in which the function of a crucial enzyme in one of the metabolic pathways is lost (e. g., carbohydrate, protein, or glycogen storage pathways) eg. adult Refsum disease, Bassen - Kornzweig syndrome and PHARC syndrome (polyneuropathy, hearing loss, ataxia, RP, and cataract). [6]

Ciliopathies are a group of disorders that affect the assembly or function of primary cilia. Most known ciliopathies that can manifest with retinal degeneration include Usher syndrome and Bardet - Biedl syndrome (RP, intellectual disability, polydactyly, obesity, and hypogonadism) [6]

Bardet - Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy characterized by rod - cone dystrophy, learning difficulties, polydactyly, obesity, genital malformations, and renal abnormalities. From 1925, the syndrome was known as Laurence - Moon - Bardet - Biedl syndrome, but there was disagreement as to whether they were the same entity. Later, it was considered as two entities, Laurence - Moon and Bardet - Biedl syndromes, today, it is most usually known as BBS. [7]

Bardet - Biedl syndrome is a pleiotropic disorder and diagnosis is based on the presence of at least four primary features or three primary features and at least two secondary features in accordance with the diagnostic criteria published by Beales et al. (table 1) [8]

Table 1: Clinical Signs of BBS Patients

Primary Diagnostic Features	Secondary Diagnostic Features
• Retinal degeneration • Obesity • Postaxial polydactyly • Renal Anomalies • Learning Disabilities • Hypogonadism	• Strabismus, cataracts, and astigmatism • Metabolic/endocrine abnormalities • Brachydactyly/syndactyly • Anosmia/olfactory dysfunction • Neurodevelopmental abnormalities (developmental delay • speech delay epilepsy, behavioral disturbances) • Liver and other gastrointestinal diseases inflammatory bowel disease, celiac disease)

Usher Syndrome is a rare genetic disorder, autosomal recessive, involving abnormalities in the retina and hearing, where the sufferer will experience blindness and hearing loss due to mutations of the gene. Other names for Usher syndrome include Hallgren syndrome, Usher - Hallgren syndrome, retinitis pigmentosa - dysacusis syndrome, and dystrophia retinae dysacusis syndrome. [9]

Usher Syndrome is divided into three subtypes: Type I, Type II and Type III Usher Syndrome.

Usher syndrome I patients have difficulties in maintaining their balance owing to problems in the vestibular system and are born deaf. Patents with Usher I are usually slow to develop motor skills such as walking. Usher type I is caused by mutations in any of the following genes: cdh23, myo7a, pcdh15, ush1c, and ush1g. Alterations in these genes can cause an inability to maintain balance (vestibular dysfunction), hearing loss and retinitis pigmentosa.

Usher syndrome II is characterized by - Moderate to severe hearing loss and their hearing does not reduce over time with a normal vestibular system. Usher syndrome type II caused by mutations in any of three different genes: ush2a, gpr98, and dfnb31. The protein encoded by the ush2a gene, usherin, is located in the supportive tissue in the inner ear and retina.

Usher Syndrome III is characterized by 'progressive' loss of hearing and vestibular dysfunction. Mutations in only one gene, clrn1, have been found in Usher III. clrn1 encodes clarin - 1, a protein important for the development and maintenance of the inner ear and retina. But how its mutation causes hearing and vision loss, is still not clearly understood.

An overview of the epidemiology is also displayed in Table 2. [10, 11].

Table 2: Types and subtypes of Usher syndrome and distribution in the general population as estimated* by epidemiological studies. Nine confirmed causative genes are reported in grey. The gene CIB2 has recently been excluded by the extended research of Booth et al. in 2018. There is some evidence that suggest a role of gene HARS in Usher 3B; however, its role must be confirmed in further studies.

Type	Gene	Chr. (Locus)	Protein Epidemiology	% Mutations	Year of identification
Usher Type I (35 - 40%)					
IB	MYO7A	11q13.5	Myosin Vlla	50–70%	1995
IC	USH1C	11p14.3	Harmonin	6–20%	2000
ID	CDH23	10q22.1	Cadherin 23	10–20%	2001
IE	Unknown	21q21.3	Unknown	Unknown	1997
IF	PCDH15	10q21.1	Protocadherin 15	5–10%	2001
IG	USH1G (SANS)	17q25.1	Usher syndromeType 1G protein	0–5%	2003
IH	Unknown	15q22 - q23		Unknown	2009
IJ	CIB2 (?)	15q25.1	CIB2	No longer USH gene	2012
IK	Unknown	10p11.21 - q21.1	Unknown	Unknown	?
Usher type II (60–65%)					
IIA	USH2A	1q41	Usherin	50–80%	1998
IIC	ADGRV1 (GPR98)	5q14.3		5–20%	2004
IID	WHRN (DFNB31)	9q32	Whirlin	0–10%	2007
Usher type III (0–5%)					
IIIA	CLRN1	3q25.1	Clarin - 1	90–95%	2001
transcript variant					

2. Case Presentation

Case 1: A case of 16yr old male patient admitted in medicine ward with microcytic hypochromic anaemia, referred to dept. of ophthalmology for diminution of vision in both the eyes more during night. Mother gives h/o consanguineous marriage and delayed developmental milestones. On general physical examination, he had truncal obesity, mental retardation, polydactyly and features of hypogonadism (figure 1). His Weight was 49 kg and his height was 145 cm with BMI of 33.7.

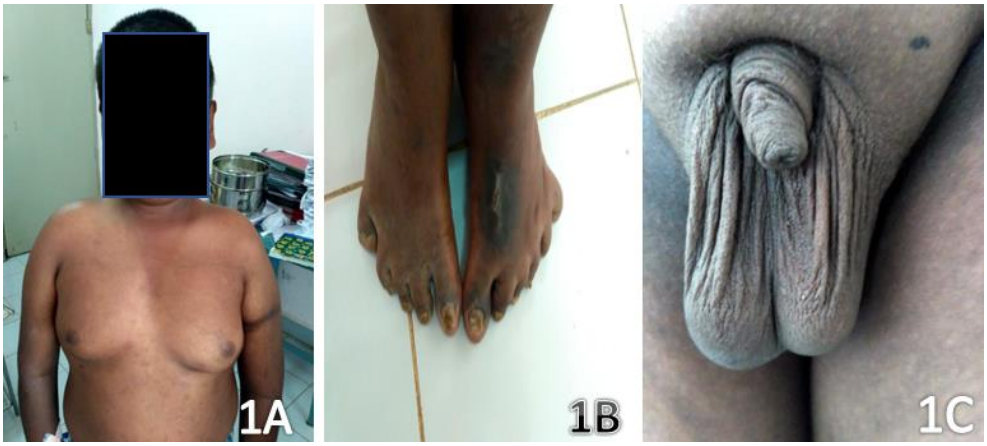

Figure 1A Truncal obesity, **1B** Polydactyly, **1C** Hypogonadism

On Ophthalmic examination of both eyes: Visual acuity was counting fingers at 3 meters, Colour vision was found to be normal. Anterior chamber appears to be normal in depth and content. Pupils of both eyes were round, regular and reactive. Fundus examination showed the features of retinitis pigmentosa i. e., waxy pallor disc, arteriolar attenuation and bony spicule pigmentation (VOLK In view fundus camera) as shown in figure 2.

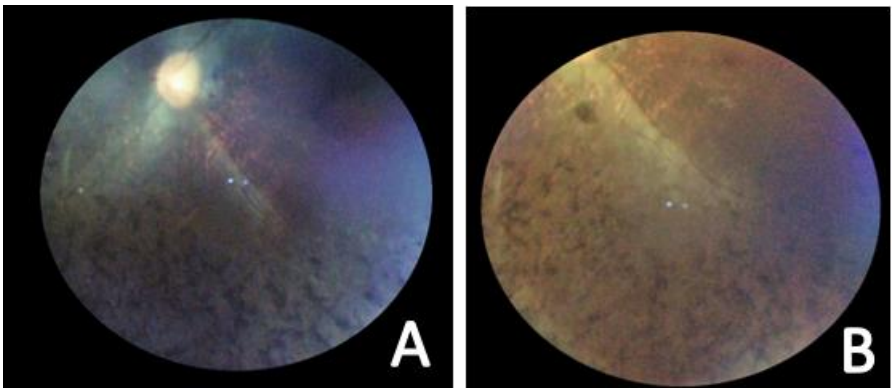

Figure 2A & 2B showing features of retinitis pigmentosa i. e., waxy pallor disc, arteriolar attenuation and bony spicule pigmentation

Investigations

- CBC: Hb – 4gm%
- Bone marrow aspiration report: Hypocellular marrow (megaloblastic anaemia)
- Liver function test: T Bilirubin – 2.5mg% (↑)

Direct Bilirubin – 1.6mg%
Indirect Bilirubin – 0.9%

- Thyroid Function Test: Normal
- Renal Function Test: Normal

Case 2: A case of 9 - year - old male patient presented to ophthalmology OPD with diminution of vision in both eyes, more during night time. Mother gives h/o consanguineous marriage and delayed developmental milestones. On general physical examination, he had central obesity, mental retardation and polydactyly (figure 3). His Weight was 31 kg, height was 129 cm with BMI of 18.63.

Figure 3A Truncal obesity, 3B Polydactyly.

On Ophthalmic examination of both eyes: Visual acuity was counting fingers at 3 meters, Colour vision was found to be normal. Anterior chamber appears to be normal in depth and content. Pupils of both eyes were round, regular and reactive. Fundus examination: showed the features of retinitis pigmentosa i. e., waxy pallor disc, arteriolar attenuation and bony spicule pigmentation as shown in figure 4. (Zeiss fundus camera)

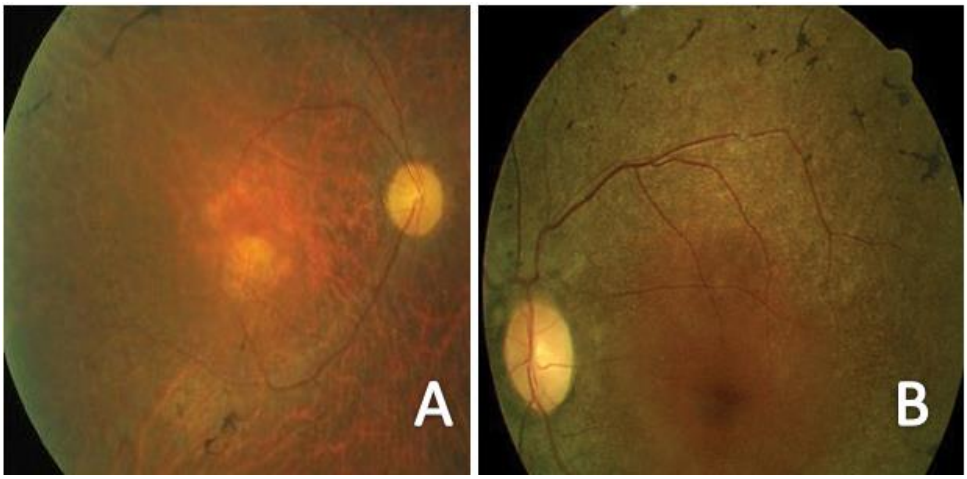

Figure 4A & 4B showing features of retinitis pigmentosa i. e., waxy pallor disc, arteriolar attenuation and bony spicule pigmentation.

Investigations:

- Renal Function Test

Serum urea: 13 mg/dl
Serum creatinine: 0.5 mg/dl

- Lipid Profile:

Total cholesterol - 161 mg/dl
HDL cholesterol - 22 mg/dl
LDL cholesterol - 125 mg / dl
VLDL cholesterol– 25 mg / dl
Triglycerides– 126 mg / dl

- Trans Thoracic Echo: normal
- USG Abdomen: normal

Case 3: A case of 57 - year - old male patient presented to ophthalmology OPD with loss of vision in left eye and diminution of vision in right eyes for 1 year. Medical history showed no systemic disorders. Family history was negative for hereditary ocular diseases.

On Ophthalmic examination of both eyes: Visual acuity of Right eye is PL positive, PR accurate and of Left eye is PL denied. Pupils of both eyes are sluggishly reactive and convergence is insufficient. Anterior chamber appears to be normal in depth and content, without any pathological findings.

On fundus examination a pale optic disc, attenuated arterioles and extensive proliferations of the pigment epithelium in form of bone spicules suggestive of typical retinitis pigmentosa and features of high myopia could be seen as shown in figure 5 (Zeiss fundus camera).

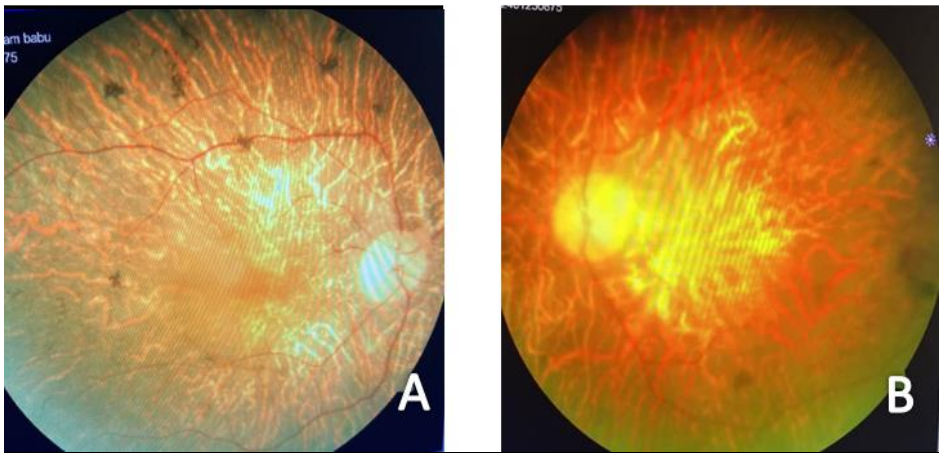

Figure 5A & 5B showing pale optic disc, attenuated arterioles and bone spicules suggestive of typical retinitis pigmentosa and features of high myopia.

Case 4: A 21 - year - old male patient presented to Ophthalmology outpatient department with complaints of diminished vision in both eyes more at night for 5 years. Diminution of vision was insidious in onset, gradually progressive and painless. He also had history of difficulty in hearing for last 3 years. There was no history of use of

spectacles or hearing aids. No history of difficulty in walking.

On Ophthalmic examination: UCVA in both eyes was 6/60, N6. BCVA in both eyes was 6/12, N6. Colour vision was found to be normal. Anterior segment appears to be normal in depth and content. Pupils of both eyes were round, regular and reactive.

On fundus examination, both eyes showed clear media, waxy pallor optic disc, severe thread like arteriolar attenuation and bone spicule retinal pigmentation, characteristic of Retinitis pigmentosa (figure 6) (Zeiss fundus camera).

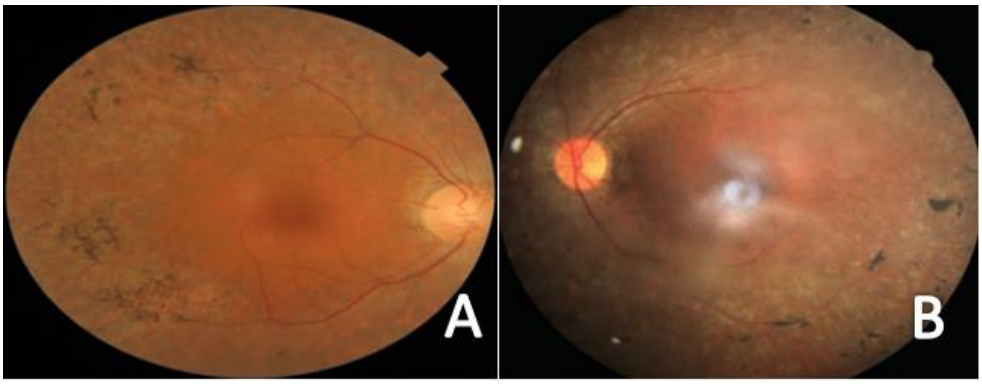

Figure 6A & 6B: Showing waxy pallor optic disc, severe thread like arteriolar attenuation and bone spicule retinal pigmentation, characteristic of Retinitis pigmentosa.

ENT consultation was done and pure tone audiometry showed moderate to severe sensorineural deafness in both ears (figure 7).

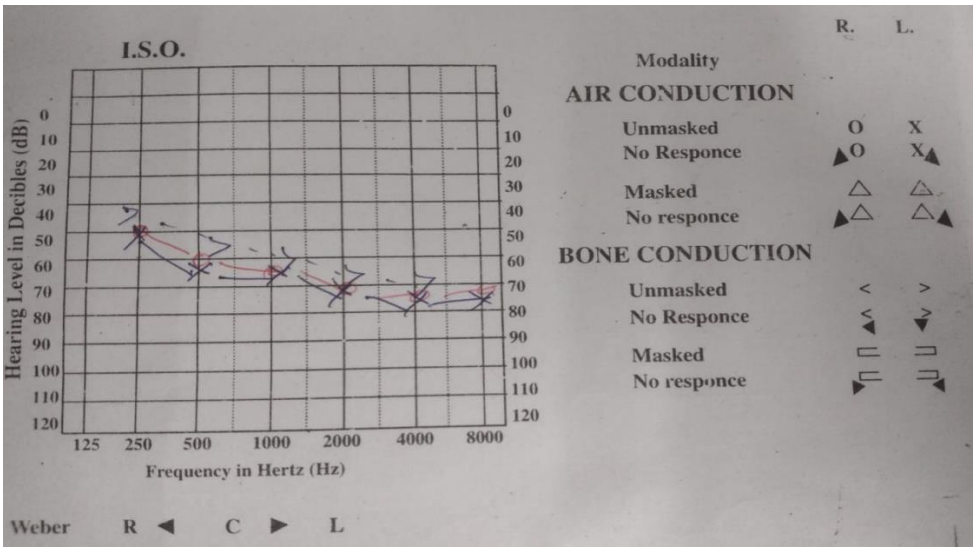

Figure 7: moderate to severe sensorineural deafness in both ears

3. Discussion

The visual impairment caused by RP and the progressive nature of this disease have detrimental effects on patients' general health, self - sufficiency and independence, which can profoundly impact their own quality of life and that of their caretakers. The impact of RP is diverse and may result in physical, mental, emotional and social disabilities. The extent to which the lives of patients are affected by RP varies greatly between individuals and relies on several factors, including their functional ability, age, daily activities, work, education, family, support networks and coping mechanisms. [14] Healthcare providers should screen patients for rehabilitation needs and, if desired, refer them to the appropriate services, such as low - vision rehabilitation, psychological counseling and mobility training services, which are commonly present in visual rehabilitation centers which help patients manage the consequences of their disease and to lead a lifestyle as autonomous as possible, optimizing their quality of life. [15]

Mutations in BBS1 and BBS10 account for most genotypes (~51 and ~20%, respectively) in Northern Europe and North America. [12] The most frequent clinical presentation Is Nyctalopia, around the age of 4 to 8, followed by progressive peripheral vision loss and lastly decline of color vision and visual acuity. One of the earliest signs is polydactyly, post axial polydactyly is common in 63 - 81% cases. BBS patients commonly manifests with obesity in 72 - 92% cases. Patients typically shows normal body weight at birth, but in 90% of cases they gain weight in first year of life and obesity becomes evident during first 3 years of life. Isolated polydactyly or obesity seen from infancy do not usually prompt referral but those presenting with renal anomalies/renal failure may be diagnosed earlier than without. [16]

Usher's syndrome is one of the most common autosomal recessive syndromes associated with double - sense impairment, hearing, and vision. The hearing test results using pure tone audiometry show a graph of air delivery and bone conduct which are both decreased and coincide with each other; this is in accordance with sensorineural deaf symptoms. The results of sensorineural deafness examination are in accordance with the pathophysiology of deafness in patients with Usher Syndrome, which is generally caused by damage and degeneration of hair cells in organ of corti. [9]

Genetics has enabled significant advances, accurate diagnosis, and improved understanding of the pathology and is expected to provide innovative treatments for gene therapy. Even if bioengineering provides continuous progression in retinal support, the best possible treatment is early identification so that educational and counseling programs can be done. Other Treatment options include hearing aids, assistive listening devices, cochlear implants. Bilateral devices can partially restore spatial orientation and support residual visual function. [13]

4. Conclusion

To date, there is no specific therapy for Retinitis Pigmentosa, but it provides a robust model disease for future opportunities in genetic and non - genetic therapeutic management of rare diseases. Our increased understanding of the underlying disease mechanisms in RP have resulted in the development of novel treatment modalities. This case series exemplifies that multidisciplinary approach is mandatory in Retinitis Pigmentosa and Supportive treatment is the milestone of patient's care. Personalized follow up is required. The treatment landscape in RP continues to evolve, and more research is needed to assess which treatment approaches are most beneficial to specific subgroups of patients with RP.

Confirming the clinical and genetic diagnosis of patients with RP should be the first step in management. Disease monitoring, visual prognosis and enrollment of patients in upcoming and ongoing clinical trials are all steps that can be taken to further aid the patient. Coordination of visual rehabilitation between clinicians and low - vision rehabilitation centers optimizing patient outcomes and also assists patients in performing daily life activities in order to maintain independence. Patients should be informed not only about new treatment developments, but also about currently available clinical management possibilities outside curative treatment, as they may provide relief of physical, psychological and social burden until early therapeutic intervention and prevention are possible.

Abbreviations
RP: Retinitis pigmentosa; BBS: Bardet–Biedl syndrome; BMI: Body mass index; CBC: complete blood count;

Acknowledgement
This work is dedicated to our faculty members.

Declarations

Ethics approval and consent to participate
The Research Ethics Committee, accepted the article.

Consent for publication Written consent has been obtained from the patients for the publication of this case series and any accompanying images. A copy of the written consent is available for review by the Editor - in - Chief of this journal.

Competing interests
The authors declare that there is no competing interest.

Corresponding Author: Dr. Shubham Sehgal, Sri Siddhartha academy of higher education (SSAHE), TUMKUR, Karnataka.
Email: Shubhamsehgal2527[at]gmail.com

References

[1] Nguyen X - T - A, Moekotte L, Plomp AS, Bergen AA, van Genderen MM, Boon CJF. Retinitis Pigmentosa: Current Clinical Management and Emerging Therapies. *International Journal of Molecular Sciences*.2023; 24 (8): 7481.
[2] O'Neal TB, Luther EE. Retinitis Pigmentosa. StatPearls Publishing; 2021.
[3] Narayan DS, Wood JPM, Chidlow G, Casson RJ. A review of the mechanisms of cone degeneration in retinitis pigmentosa. Acta Ophthalmol.2016; 94 (8): 748–754. doi: 10.1111/aos.13141.
[4] Orphanet. Prevalence and incidence of rare diseases: bibliographic data. Available from: https: //www.orpha. net/orphacom/cahiers/docs/GB/ Prevalence_of_rare_diseases_by_decreasing_prevale nce_or_cases. pdf. Accessed July, 2021.
[5] Verbakel SK, van Huet RAC, Boon CJF, et al. Non - syndromic retinitis pigmentosa. Prog Retin Eye Res.2018; 66: 157–186.
[6] Tatour, Y.; Ben - Yosef, T. Syndromic Inherited Retinal Diseases: Genetic, Clinical and Diagnostic Aspects. Diagnostics 2020, 10, 779.
[7] Forsythe E, Kenny J, Bacchelli C, Beales PL. Managing Bardet - Biedl Syndrome - Now and in the Future. Front Pediatr.2018 Feb 13; 6: 23.
[8] 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; 36 (6): 437–446. doi: 10.1136/jmg.36.6.437.
[9] DEWI, Nadia Artha; KRISTIYAN, Teddy; REFA, Safaruddin. Usher Syndrome in Two Siblings, A Case Report. International Journal of Retina, [S. l.], v.2, n.1, feb.2019. ISSN 2614 - 8536.
[10] Koenekoop, R.; Arriaga, M.; Trzupek, K. M.; Lentz, J. Usher Syndrome Type I. In GeneReviews®; Adam, M. P., Ardinger, H. H., Pagon, R. A., Wallace, S. E., Bean, L. J. H., Mirzaa, G., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1999.
[11] Koenekoop, R. K.; Arriaga, M. A.; Trzupek, K. M.; Lentz, J. Usher Syndrome Type II. In GeneReviews®; Adam, M. P., Ardinger, H. H., Pagon, R. A., Wallace, S. E., Bean, L. J. H., Mirzaa, G., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1999.
[12] Forsythe E, Beales PL. Bardet - Biedl syndrome. Eur J Hum Genet (2013) 21 (1): 8–13. doi: 10.1038/ejhg.2012.115

[13] Castiglione, A.; Möller, C. Usher Syndrome. Audiol. Res.2022, 12, 42–65. https: //doi. org/10.3390/ audiolres12010005.
[14] Slade, A.; Isa, F.; Kyte, D.; Pankhurst, T.; Kerecuk, L.; Ferguson, J.; Lipkin, G.; Calvert, M. Patient reported outcome measures in rare diseases: A narrative review. Orphanet J. Rare Dis.2018, 13, 61.
[15] Wilkinson, M. E.; Shahid, K. S. Low vision rehabilitation: An update. Saudi J. Ophthalmol.2018, 32, 134–138.
[16] Melluso A, Secondulfo F, Capolongo G, Capasso G, Zacchia M. Bardet - Biedl Syndrome: Current Perspectives and Clinical Outlook. Ther Clin Risk Manag.2023 Jan 30; 19: 115 - 132.