

Ocular Findings in Benign Joint Hypermobility Syndrome Patients

Mohammed H.M. Al-Osami^{1*}, Najah K. Mohammad², Faiq I. Gorial³ and Enas Adnan Majeed⁴

¹Rheumatology Unit, Department of Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq; mohammed-alosami@yahoo.com

²Department of Surgery, College of Medicine, University of Baghdad, Baghdad, Iraq; njahkma@yahoo.com

³Rheumatology Unit, Department of Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq; faiqig@gmail.com

⁴Rheumatology Units, Baghdad Teaching Hospital, Baghdad, Iraq; enasmajeed@yahoo.com

Abstract

Objectives: To evaluate the prevalence and characteristics of ocular findings in a sample of Iraqi patients with (BJHS). **Patients and Methods:** This cross-sectional study included 100 patients diagnosed with BJHS according to Brieton criteria and another 200 healthy controls matched in age and sex. Demographics were collected, and full ophthalmological examination was done on both groups. **Results:** Prevalence of refractive errors was 78% of them: myopia was 49%, followed by astigmatism 20%) and hypermetropia 9%. The other identified ocular manifestation was dry eye (15%), while anterior & posterior blepharitis 5% and 4% respectively. Pigment dispersion syndrome was diagnosed in 3% of patients and the cataract was 2% of BJHS patients. All previous findings were statistically significant except cataract not reach to statistically significant level. **Conclusions:** Ocular findings in BJHS were relatively common. The most common BJHS-related ocular findings were myopia followed by astigmatism and hypermetropia. Dry eye symptoms, anterior and posterior blepharitis, pigment dispersion syndrome and cataract are rare in patients with BJHS.

Key words: Benign Joint Hypermobility Syndrome, Joint Hypermobility, Ocular Manifestations

1. Introduction

Benign Joint Hypermobility Syndrome (BJHS) is an inherited connective tissue disease, distinguished by musculoskeletal pain and an excessive range of motion in joints¹. With the absence of systemic rheumatological disease². Many ocular manifestations of BJHS have been described, some being well-known associations and others reported for the first time in case report³. In a survey of Chilean patients, qualitatively assessed blue sclerae were considered common on Benign Joint Hypermobility Syndrome/Ethlers Danols Syndrome Hypermobility Type (BJHS/EDSHT)⁴. Few ocular complications of EDS, including eyelid and conjunctiva abnormalities, keratoglobus corneal thinning and keratoconus, dry eye, pathologic myopia, angioid streaks and abnormal retinal vessels, retinal detachment, scleral atrophy, and globe perforation⁵⁻⁸.

Ocular features like blepharochalasis, antimongoloid palpebral slant, and blue sclerae are relatively common

findings in BJHS/EDSHT. A survey on 22 patients defined the BJHS/EDSHT phenotype as mostly consisting in xerophthalmia (i.e., positive BUT and Schirmer I tests), steeper corneas, pathologic myopia, and minor lens opacities and vitreal abnormalities⁹⁻¹⁰.

Because of limited reports on prevalence of ocular manifestations, this study was designed to assess ocular manifestations in a sample of Iraqi patients with benign joint hypermobility

2. Patients and Methods

2.1 Study Design

This cross-sectional study was conducted at the Rheumatology Unit, Department of Medicine in Baghdad Teaching Hospital from August 2015 to April 2016.

2.2 Sample Selection

A total of 300 subjects were enrolled in the study, 100 of them were diagnosed as benign hypermobility syndrome and 200 were controls. JHMS is diagnosed according to the Brighton criteria².

Informed consent was obtained from each participant included in this study according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Baghdad University, College of Medicine, and Medical Department.

Patients were excluded from the study if they had history of previous eye trauma, hypertension, diabetes mellitus, and overlap with other connective tissue diseases or inflammatory arthritis.

2.3 Data Collection and Measurements

Interview questionnaire included ages, gender, and joint pain. Ocular manifestations in all subject-IOS were evaluated by an ophthalmologist blinded to the diagnosis. at Ophthalmology Unit in Ghazi-Alharery Teaching Hospital. Ophthalmological examination included visual acuity assessment with Snellen charts, examination of anterior and posterior eye segments with the slit lamp, Schirmer test and corneal fluorescein staining, and assessment of intraocular pressure with Goldman applanation tonometer. Indirect ophthalmoscopy was performed with an indirect ophthalmoscope and a 20-diopter lens after both pupils were dilated with 1% tropicamide for some patients need diltation, the posterior pole was further evaluated by slit-lamp bio microscopy using a 78-D Volk lens.

2.4 Statistical Analysis

Statistical analyses were done using SPSS version 21. Normal distribution for continuous variables was done first. Independent samples t-test was used to measure the difference between means of 2 groups of normally distributed variables. Chi-square test was used to assess the statistical significant difference between 2 categorical variables or Fisher's exact was used when Chi-square test was inappropriate.

The 95% CI: the 95% confidence interval is a statistical procedure to anticipate or predict the expected range of possible values of the calculated sample estimate

of any statistic in the reference population with 95% confidence. To measure the strength of association between 2 categorical variables, such as the presence of certain risk factor and disease status the Odds Ratio (OR) was measured using binary logistic regression analysis. Differences with P value <0.05 were considered statistically significant.

3. Results

Three hundred subjects were involved in this study, BJHS were 100 and healthy controls were 200. The mean age, gender, and body mass index of patients were not statistically significantly different from that of controls ($p>0.05$) as in Table 1.

(Table 2) myopia, stigmatism, dry eye, anterior blepharitis, posterior blepharitis, and pigment dispersion syndrome, were significantly more frequent among patients with hypermobility syndrome than the control group ($P<0.05$). Cataract and hypermetropia were slightly more frequent in patients group, but the differences observed were too small to be of statistical significance ($p>0.05$).

The risk of having Dry eye is increased by 72.7 times in cases with hypermobility syndrome, while that of anterior blepharitis is increased by 23.1 times and that of posterior blepharitis is increased by 18.7 times compared to controls. In addition, the risk of having pigment dispersion syndrome, myopia and Astigmatism is significantly increased by 14.4, 11.1 and 3.9 times respectively among cases with hypermobility (Table 2).

Table 1. Demographic Features in Joint Hypermobility Syndrome and Controls

Variables	Patients = 100	Controls = 200	P value
Age, mean ±SD in years	25.72 ± 5.32	26.38 ± 4.60	0.27
Gender n (%)			
Females	94(94%)	192(96%)	0.56
Males	6(6%)	8(4%)	
BMI ,mean ±SD in kg/m2,	24.27 ± 3.70	24.58 ± 2.31	0.45

Table 2. Prevalence of Ophthalmic Features in Cases with Hypermobility Syndrome Compared to Controls

Positive ophthalmic features	Healthy controls (total N = 200)		Patients with hypermobility syndrome (total N = 100)		P value	OR	95% CI OR
	N	%	N	%			
Myopia	16	8.0	49	49.0	<0.001	11.1	(5.8 – 21.06)
Astigmatism	12	6.0	20	20.0	<0.001	3.9	(1.83 – 8.39)
Dry eye	0	0.0	15	15.0	<0.001	72.7	(9.49 – 556.84)
Hypermetropia	12	6.0	9	9.0	0.34[NS]	1.55	(0.63 – 3.81)
Anterior blepharitis	0	0.0	5	5.0	0.004	23.1	(2.74 – 194.53)
Posterior blepharitis	0	0.0	4	4.0	0.012	18.7	(2.16 – 162.15)
Pigment dispersion syndrome	0	0.0	3	3.0	0.036	14.4	(1.59 – 130.57)
Cataract	0	0.0	2	2.0	0.11[NS]	10.2	(1.05 – 99.11)

[NS] = not significant statistically

N = Frequency (count)

4. Discussion

Few reports are present on ocular complications in BJHS. Up to our knowledge, this is the first study that evaluated the prevalence and characteristics of ocular manifestations in Iraqi patients with BJHS.

Interestingly, refractive was the most frequent finding and detected in 78% patients, while myopia was detected in (49%), followed by astigmatism (20%) and hypermetropia (9%) & these results were statistically significant in this study.

Refractive errors may be explained by that, alterations in any sclera, vitreous extracellular matrix components, or both are likely to change scleral shape, vitreous structure, or both, which in turn could affect the axial length of the eye¹¹, another explanation suggested that alterations of the fibrillar components of the connective tissue (collagen types I, III, and V) are involved in EDS variants that are clinically distinct from BJHS⁹.

The molecular defect underlying BJHS may reside in genes encoding non-fibrillar components of the extracellular matrix or enzymes involved in their posttranslational maturation. In particular, mutations in various small leucine rich proteoglycans were associated with both EDS-like phenotypes and myopia in mice⁹⁻¹⁰. Therefore, they all may be possible candidates for BJHS in humans. In Wegener et al study¹² prevalence of myopia combined with astigmatism was 33% and that of hyperopia combined with astigmatism 28%, this was statistically significant.

On other hand in study¹³, conventional ophthalmologic and special somatic examination was carried out on patients with myopia and control group showed that, all the patients with high myopia showed 12 various additional features of connective tissue hyperelasticity, on the average, with no more than 4 such features in the control group.

The other identified ocular manifestation in this study was dry eye symptoms (15%). and this finding is in agreement with previous observation³.

The cause of xerophthalmia in BJHS is unknown, but some research ESR suggest that tear production is strongly influenced by the autonomic nervous system, a possible autonomic dysfunction underlying tear production deficiency may be put forward. This hypothesis is in line with the repeated observation of cardiovascular dysautonomia signs and symptoms, including palpitations, arrhythmias, postural orthostatic tachycardia, and syncope¹⁴.

Tear secretion impairment may be result from developmental alterations of the lacrimal gland extracellular matrix, because it may play a role in regulating lacrimal gland secretion, this abnormal extracellular matrix production may be linked to an inherited defect of a non-fibrillar component of the connective tissue¹⁵.

The other identified ocular manifestation in this study was anterior & posterior blepharitis (5% and 4%) respectively and these results are statistically significant. blepharitis is a common, chronic, and potentially sight-threatening eyelid and ocular surface disease,

characterised by inflammation and obstruction of the meibomian glands¹⁶⁻¹⁷. To the best of our knowledge no other study reported these findings in BJHS, the cause of this finding in BJHS may be related to different genetic and environmental factors.

Another observed ocular finding in this study was pigment dispersion syndrome which presented in (3%) of patients with BJHS, and this finding reached a statistically significant level. Pigment dispersion Syndrome (PDS) is an ocular condition characterized by a dispersion of iris pigment throughout the eye due to idiopathic atrophy of the pigment layers of the iris¹⁸. The molecular mechanism causing PDS and the pathway by which it progresses to pigmentary glaucoma is not known. Up to our knowledge no other study reported that finding, and its presence in patients with BJHS can be explained by various genetic and environmental factors.

Finally, in this study cataract was present (2%) of BJHS patients, but this finding did not reach a statistically significant level, and it is in disagreement with another study⁶ which showed that minor lens opacities present in a statistically significant number of patients and this disagreement between the two studies may be due to sample size and differences in genetic and environmental factors between the two populations.

The current study is limited by small sample size that can be solved by a larger and longer prospective study to validate our findings. Furthermore, we reported a selected group of patients referred to tertiary care, so our findings cannot be generalized to patients in primary care so selection bias might be present. Nevertheless, it is accepted that the investigators may have introduced selection bias in those patients with more severe symptoms. In spite of these limitations, the current study revealed a significant clinical application of the association between BJHS & ocular findings that ignited a considerable clinical interest which may help physicians to early recognition of these findings and subsequently to ensure correct diagnosis and treatment, although small number of studies were similar to the current study but the discordant results suggests the need to conduct more studies with a larger population in different parts of the world with various races.

5. Conclusions

In ocular findings of BJHS were relatively common. Refractive errors symptoms were the most common BJHS related ocular findings followed by myopia, astigmatism

and hypermetropia. Dry eye symptoms, anterior and posterior blepharitis, pigment dispersion syndrome and cataract were rare in patients with BJHS. These results suggest that Early and frequent eye monitoring for patients with BJHS to early diagnose and treat the ocular findings and to recognize patients with milder phenotypes on the basis of minor ocular changes (e.g., increased corneal refractive power and lens opacities). Therefore, ophthalmologic consultation should be scheduled not only in BJHS patients, but all individuals with suspected heritable connective tissue disorder to define the diagnosis better.

6. References

1. Grahame R. Hypermobility and hypermobility syndrome. Keer R, Grahame R. (Editors). Hypermobility Syndrome: Recognition and Management for Physiotherapists. Edinburgh, UK: Butterworth-Heinemann. 2003; p. 1-14. Crossref 1, 2.
2. Grahame R. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *Journal of Rheumatology*. 2000; 27(7):1777-9. PMID:10914867
3. Bravo JF, Wolff C. Clinical study of hereditary disorders of connective tissues in a Chilean population: joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. *Arthritis and Rheumatology*. 2006; 54(2):515-23. Crossref. PMID:16447226
4. Segev F, Heon E, Cole WG. Structural abnormalities of the cornea and lid resulting from collagen V mutations. *Investigative Ophthalmology & Visual Science*. 2006; 47(2):565-73. Crossref. PMID:16431952
5. Whitaker JK, Alexander P, Chau DY. Severe conjunctivochalasis in association with classic type Ehlers-Danlos syndrome. *BMC Ophthalmology*. 2012; 12(1):47. Crossref. PMID:22943506 PMCID:PMC3504533
6. Gharbiya M, Moramarco A, Castori M. Ocular features in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: a clinical and in vivo confocal microscopy study. *American Journal of Ophthalmology*. 2012; 154(3):593-600. Crossref. PMID:22633352
7. Chikamoto N, Teranishi S, Chikama T. Abnormal retinal blood vessels in Ehlers-Danlos syndrome type VI. *Japanese Journal of Ophthalmology*. 2007; 51(6):453-5. Crossref. PMID:18158597
8. Puri P, Gupta M, Chan J. Spontaneous perforation of the globe in Ehlers Danlos syndrome. *Eye (Lond)*. 2001; 15(4):553-4. Crossref. PMID:11767041

9. Malfait F, Hakim AJ, De Paepe A. The genetic basis of the joint hypermobility syndromes. *Rheumatology*. 2006; 45(5):502-07. Crossref. PMID:16418200
10. Chakravarti S, Paul J, Roberts L. Ocular and scleral alterations in gene-targeted lumican-fibromodulin double-null mice. *Investigative Ophthalmology and Visual Science*. 2003; 44(6):2422-32. Crossref. PMID:12766039
11. Halfter W, Winzen U, Bishop PN. Regulation of eye size by the retinal basement membrane and vitreous body. *Investigative Ophthalmology & Visual Science*. 2006; 47(8):3586-94. Crossref. PMID:16877433
12. Wegener A, Holtz FG, Finger R. Characteristics of the anterior eye segment in patients affected by Ehlers-Danlos-syndrome. *Acta Ophthalmologica*. 2011; 89(248):1755-3768. Crossref.
13. Lutsevich EE, Plekhova LIU, Borodina NV. Hyperplastic connective tissue syndrome in patients with high myopia. *Vestn Oftalmol*. 2002; 118(6):33-35. PMID:12506656
14. Gazit Y, Nahir AM, Grahame R. Dysautonomia in the joint hypermobility syndrome. *American Journal of Medicine*. 2003; 115(1):33-40. Crossref.
15. Schenke-Layland K, Xie J, Angelis E. Increased degradation of extracellular matrix structures of lacrimal glands implicated in the pathogenesis of Sjogren's syndrome. *Matrix Biology*. 2008; 27(1):53-66. Crossref. PMID:17689946 PMCID:PMC2394184
16. Jackson WB. Blepharitis: current strategies for diagnosis and management. *Canadian journal of ophthalmology*. 2008; 43(2):170-79. Crossref. PMID:18347619
17. Bernardes TF, Bonfioli AA. Blepharitis. *Seminars in ophthalmology* 2010; 25(3):79-83. Crossref. PMID:20590417
18. Veerwal V, Goyal JL, Jain P, Arora R. Pigment dispersion syndrome associated with spontaneous subluxation of crystalline lens. *Oman Journal of Ophthalmology*. 2017; 10(1):52-53. Crossref. PMID:28298869 PMCID:PMC5338057