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Visual Function and Ocular Abnormalities in CHARGE Syndrome: A Comparative Study of Ophthalmic Features and Systemic Manifestations

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ABSTRACT

Background: CHARGE syndrome is a multifaceted genetic disorder characterized by systemic as well as ocular anomalies, which include craniofacial malformations, coloboma, optic nerve hypoplasia, and congenital heart defects.

Purpose: The aim of the study is to explore the visual function and ocular anomalies with a focus on understanding the correlation between ocular and systemic features.

Methods: A prospective study was conducted in the period from May 2022 to December 2023, which includes 74 subjects who are diagnosed with CHARGE syndrome. Data was collected from specialty clinics and special schools across Gujarat, including detailed ophthalmic evaluation such as visual acuity testing with Log MAR charts. Retinal imaging and fundus examination were performed in all subjects. Systemic anomalies like craniofacial malformations and congenital heart defects were recorded.

Results: Visual acuity score ranged from 0.1 to 1.2 LogMAR with an average score of 0.48., which indicates varied degrees of visual impairment. Ocular anomalies were more predominant with coloboma in 34% of subjects, optic nerve hypoplasia in 23%, and retinal thinning in 29%. Subjects with craniofacial malformations showed significant poor visual acuity, and those with congenital heart defects showed lower visual acuity. A moderate negative correlation was found between visual acuity and retinal thickness.

Conclusions: This study highlights the strong association between systemic manifestations and ocular anomalies in CHARGE syndrome. Craniofacial malformations and congenital heart defects were substantial predictors of visual impairment, emphasizing the need for early and comprehensive monitoring of systemic and ocular features. The findings of this study contribute to better understanding of the genetic and developmental mechanisms underlying this syndrome with implications for diagnostic and therapeutic approaches.

1. Introduction

CHARGE syndrome is a rare genetic disorder that is characterized by a constellation of congenital abnormalities, including ocular anomalies, craniofacial malformations, and systemic manifestations involving multiple organ systems (Martin *et al.,* 2020). Among the defining features, visual dysfunction stands out as a critical factor persuading the quality of life and developmental outcomes in affected subjects. Despite the increasing recognition of CHARGE syndrome in medical genetics and pediatrics, there remains a limited understanding of the specific ocular features and their relationship to the broader systemic anomalies associated with the condition (Burton *et al.,* 2021). The lack of detailed investigation into the ocular aspects of CHARGE syndrome presents a significant gap in clinical knowledge (Hysi *et al.,* 2020). This gap is concerning because visual impairments in these subjects can have profound implications for cognitive and sensory development, yet it is often underdiagnosed or overdiagnosed by other systemic issues (Dell'Osso *et al.,* 2018). The absence of targeted research limits the ability of clinicians to develop complete management strategies that integrate both visual and systemic care (Van Ravenswaaij-Arts *et al.,* 2017). Addressing this deficit is essential for improving diagnostic accuracy and prognostic assessment and customized multidisciplinary interferences for subjects with this syndrome (Usman & Sur, 2023).

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The main aim of this study is to conduct a comparative analysis of the ocular features and systemic manifestations of this syndrome, with a focus on explicating the spectrum of visual dysfunction and ocular anomalies (De Geus *et al.,* 2018). By systemically examining this feature in the context of the broader scientific phenotype, this research aims to uncover patterns and correlations that can inform clinical practices and further research (Legendre *et al.,* 2012). This examination holds significant suggestions for the fields of pediatric ophthalmology, medical genetics, and developmental medicine. Better understanding of the ophthalmic aspects of CHARGE syndrome can improve early diagnostic efforts, guide therapeutic interventions, and ultimately contribute to better developmental and functional outcomes of affected subjects (George *et al.,* 2020). Additionally, the comparative approach employed in this study offers an innovative perspective, highlighting the relationship between visual and systemic features and bridging existing knowledge gaps. The findings of this study are expected to have translational value, which provides a framework for more unified care pathways and apprising policy decisions regarding the management of rare genetic disorders (Martin *et al.,* 2020). This study is focused on the analysis of visual function and ocular anomalies in subjects diagnosed with CHARGE syndrome, as defined by established clinical criteria. The scope is deliberately limited to observational and comparative analyses, without investigating therapeutic or experimental interventions (Singh *et al.,* 2020). This limitation ensures a clear focus on identifying and characterizing ocular and systemic correlations within the study group. In summary, this study aims to provide a detailed, evidence-based understanding of ocular dimensions of this syndrome, with the ultimate goal of improving clinical outcomes and improving quality of life for affected individuals.

2. Methods

This prospective, descriptive study intended to investigate the ocular features and systemic manifestations of CHARGE syndrome, with a specific focus on discovering correlations and patterns between visual dysfunction and systemic anomalies. Data were collected from May 2022 to December 2023 from varied specialized clinics in Gujarat, directing subjects who were diagnosed with CHARGE syndrome. A sample of 74 subjects was selected through purposive sampling to ensure depiction of various phenotypic presentations. Subjects who have a confirmed diagnosis of CHARGE syndrome and those whose medical records were accessible. Medical reports include both systemic and ocular health. Exclusion criteria include missing ocular or systemic data and the existence of unrelated ophthalmic conditions that could misperceive the results. All the subjects were diverse in age and gender, which reflects the heterogeneity and developmental impact of this syndrome. Data collection involves direct clinical assessment as well as analysis of retrospective records. Testing includes visual acuity testing, fundus evaluation, optical coherence tomography, refractive error evaluation, ocular alignment, and visual field evaluations. Trained eye specialists conducted all the examinations, and all standard protocols are followed to ensure consistency. For cooperative subjects, visual acuity was measured with LogMAR visual acuity charts, and for younger or non-verbal children, Lea symbols or Teller acuity cards were used. To evaluate structural anomalies like coloboma, optic nerve hypoplasia, retinal thinning, OCT, and fundoscopy were used. Ocular alignment and strabismus assessment were conducted by using Hirschberg and cover tests with alternative tests for fixation instability. Refractive error evaluation along with cycloplegic refraction was performed with retinoscopy and autorefractometers. Visual field assessment was performed with automated perimetry or confrontation tests depending on the cognitive ability of the subject. The data was analyzed using SPSS version 28.

A combination of descriptive and inferential statistics was applied to uncover significant patterns and relationships. Descriptive statistics include demographic characteristics, prevalence rates of systemic and ocular anomalies, and metrics of visual function. Inferential statistics includes chi-square tests to identify the associations between categorical variables like congenital heart defects. Independent t-tests were performed to compare mean values between 2 groups, like the score of visual acuity of subjects with and without optic nerve hypoplasia. One-way ANOVA was utilized to know age-related differences in visual function. Non-parametric tests like Mann-Whitney U tests and Kruskal-Wallis tests were employed for ordinal and non-normally distributed data. Pearson correlation coefficient assessed the relationship between continuous variables like the correlation between retinal thickness and visual acuity, which provides quantitative measures of the relationship between structural and functional ocular characteristics. The logistic regression model had analyzed whether craniofacial malformations increased the likelihood of optic nerve hypoplasia or strabismus with adjusting confounders like age and gender. For data normality assessment, Shapiro-Wilk tests were utilized, and data transformations were applied to correct skewed distributions as necessary. To examine the multi-dimensional relationship, principal component analysis was employed to identify underlying patterns within the dataset. Structural equation modeling further showed direct and indirect effects on visual outcomes facilitated through structural ocular anomalies.

3. Results

3.1. Participant Characteristics

74 participants were diagnosed with CHARGE syndrome, including 37 males and 37 females. The mean age of the patient is 15.6 years, and the standard deviation is 7.8, and the range variation of the age is between 5 and 40 years. This variation shows developmental changes in a wide age range. In this wide age range, they exhibit visual acuity in LogMAR, which is 0.1 to 1.2, and its mean value is 0.48 ($\pm$ 0.28), and it indicates visual impairment variation. Here, 34% have coloboma, 23% have optic nerve hypoplasia, and 29% show retinal thinning. Showed craniofacial malformations and congenital heart defects, which were also common and observed in 56% and 41% of participants, respectively.

3.2 Primary Outcomes

The Chi-Square test was applied to categorical variables, which showed significant associations between certain ocular and systemic abnormalities. There is a strong correlation between craniofacial malformations and coloboma of the eye ($\chi^2 = 6.89$, $p = 0.009$) and optic nerve hypoplasia ($\chi^2 = 5.67$, $p = 0.017$). The independent t-test was applied between poorer visual acuity (0.58 $\pm$ 0.31) without craniofacial malformations (0.41 $\pm$ 0.22) and poorer visual acuity with craniofacial malformations, and $p = 0.011$. Here congenital heart defects with lower mean visual acuity (0.60 $\pm$ 0.32) than those without heart defects (0.41 $\pm$ 0.25), and this difference was statistically significant $t = 2.74$, and $p = 0.008$. It shows the significant impact of systemic abnormalities on visual function in CHARGE syndrome.

3.3 Secondary Outcomes

In this study, it is shown that significant V/A deterioration is found at different age groups by the use of one-way ANOVA and age groups ($F(3, 70) = 4.22$, $p = 0.008$), with younger participants (5–12 years) having significantly lower visual acuity compared to older participants. There is a strong negative Pearson correlation analysis found between retinal thickness and visual acuity ($r = -0.56$, $p = 0.001$), indicating that greater retinal thinning was associated with poorer visual function. Strong correlation between optic nerve hypoplasia and visual acuity ($r = -0.65$, $p < 0.001$). Logistic regression analysis shows craniofacial malformations have significant ocular abnormalities such as coloboma (OR = 3.45, $p = 0.002$) and optic nerve hypoplasia (OR = 2.93, $p = 0.004$).

Moreover, the Mann-Whitney U test and Kruskal-Wallis test were applied to know the distribution of visual acuity and retinal thickness data. By the use of the Mann-Whitney U test, it is revealed that V/A deterioration is found between those with and without coloboma ($U = 526.0$, $p = 0.019$), and by the use of the Kruskal-Wallis test, it is revealed that V/A deterioration is found between those with and without coloboma ($U = 526.0$, $p = 0.019$), and craniofacial malformations and congenital heart defects have significantly poorer V/A compared to those who don't have systemic abnormalities ($H = 9.34$, $p = 0.025$).

In the tables, the results are summarized, highlighting the participant's demographic characteristics and the correlation between ocular and systemic abnormalities at different age groups. V/A deterioration and ocular and systemic features correlation.

Table 1: Demographic Characteristics of the Study Participants, including their Age, Gender Distribution, and the Presence of Ocular and Systemic Abnormalities Meticulously

Characteristic	N (%)	Mean (SD)	Range
Age (Years)	-	15.6 (7.8)	5–40
Gender	-	-	-
Male	37 (50%)	-	-
Female	37 (50%)	-	-
Visual Acuity (LogMAR)	-	0.48 (0.28)	0.1 – 1.2
Ocular Abnormalities	-	-	-
Coloboma	25 (34%)	-	-
Optic Nerve Hypoplasia	17 (23%)	-	-
Retinal Thinning	21 (29%)	-	-
Systemic Abnormalities	-	-	-
Craniofacial Malformations	42 (56%)	-	-
Congenital Heart Defects	30 (41%)	-	-

Table 2: Correlation between Ocular Abnormality and Systemic Abnormality with Application of Chi-Square Test (X^2) with P-Value

Ocular Abnormality	Systemic Abnormality	χ^2 Value	p-value
Coloboma	Craniofacial Malformations	6.89	0.009
Coloboma	Congenital Heart Defects	3.21	0.073
Optic Nerve Hypoplasia	Craniofacial Malformations	5.67	0.017
Optic Nerve Hypoplasia	Congenital Heart Defects	2.84	0.092
Retinal Thinning	Craniofacial Malformations	4.58	0.033

Table 3: Comparison of Visual Acuity between Craniofacial Malformations & Congenital Heart Defects by the Use of Independent t test with P value

Systemic Abnormality	Group Size (n)	Mean Visual Acuity (LogMAR)	Standard Deviation (SD)	t-value	p-value
Craniofacial Malformations (Yes)	42	0.58	0.31	2.62	0.011
Craniofacial Malformations (No)	32	0.41	0.22		
Congenital Heart Defects (Yes)	30	0.60	0.32	2.74	0.008
Congenital Heart Defects (No)	44	0.41	0.25		

Table 3 shows the Pearson r correlation between visual acuity and retinal thickness, visual acuity and optic nerve hypoplasia, retinal thickness and craniofacial malformations, and visual acuity and congenital heart defects, and the data value is on that table accordingly.

4. Discussion

The findings of the present study were interpreted and compared with existing data. The correlation was shown between ocular abnormalities and systemic manifestations in individuals with CHARGE syndrome (Onesimo *et al.,* 2021). In this study, 34% were coloboma, 23% were optic nerve hypoplasia, and 29% were retinal thinning, with visual acuity scores varying (mean = 0.48, ±0.28 LogMAR). Here correlation is held between craniofacial malformations (56%) and congenital heart defects (41%), and it is strongly correlated with ocular anomalies (*Singh et al., 2020*). Here these all-statistical analyses were included to see the significant interrelationships between visual function and systemic abnormalities; these are chi-square tests, independent t-tests, ANOVA, and regression models. Poor visual outcomes ($t(72) = 2.62$, $p = 0.011$) were seen in craniofacial malformations, and those with congenital heart defects have significantly lower visual acuity ($t(72) = 2.74$, $p = 0.008$). It indicates comprehensive ocular investigation during diagnosed Charge Syndrome (Martin *et al.,* 2020). These findings are correlated with existing studies and strongly positively correlated in individuals with CHARGE syndrome. The same correlations between craniofacial malformations and visual defects were reported by Smith *et al*. (2019). However, in our study, participants were 74 and included advanced statistical techniques. Here, a correlation between retinal thinning and visual acuity ($r = -0.56$, $p = 0.001$) is found. There is a considerable limitation in this study, and that is the limitation of the findings of the generalizability (Hysi *et al.,* 2020). Due to its cross-sectional nature, the study could not continue with its long-term progression.

5. Conclusion

In conclusion, this study shows the correlation between ocular abnormalities and systemic manifestations in CHARGE syndrome. These findings indicate the benefits of early diagnosis and multidisciplinary management for patients who were affected by this syndrome. Finally, this research is helpful for indicating further progress for enhanced clinical outcomes and quality of life for individuals.

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Authorship Contribution

Partha Haradhan Chowdhury: Conceptualization, data interpretation, and methodology; Brinda Shah: Data analysis, manuscript writing, and review, etc.

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Conflict of Interest

Authors declare that there is no conflict of interest.

Ethical Approvals

Ethical clearance was obtained from Shree Satchandi Jankalyan Samiti.

Declaration

It is an original article and has been neither sent elsewhere nor published anywhere.

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