Heterochromia Iridum: A PRISMA-Guided Systematic Mini-Review

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Abstract

Background:

Heterochromia iridum is a rare presentation of the eye, which may be normal or a feature of congenital, neurological, ocular, and systemic disorders. Until now, there has been no documentation of its epidemiology in depth, especially in developing countries.

Aim/Objective:

The objective is to perform a literature review on the anatomical basis, prevalence, causes, clinical methods for its detection, and treatment options for heterochromia iridum that have been known within the Indian populace.

Methods:

The systematic review in this paper has been performed after following the principles of the PRISMA 2020 statement. A comprehensive search has been performed in PubMed, PubMed Central, Scopus, IndMED, MedIND, and major Indian ophthalmology journals for articles until December 2025. The inclusion criteria of this study included articles in English only, which are original articles, reviews, case series, and case reports.

Results:

Of the 112 retrievable records, 54 met inclusion criteria. Primarily, case reports were on benign congenital heterochromia, heterochromia with Horner syndrome, Waardenburg syndrome, and neurocutaneous syndromes. The literature could not be found that assessed the prevalence among the populations globally. There had been no Indian studies found on prevalence. Mostly case reports were found.

Conclusion:

Thus, the condition of heterochromia iridum itself is more of a diagnostic feature rather than a disease. Though most cases of heterochromia iridum are benign in nature, proper examination needs to be done in order to rule out other severe pathologies. The absence of data about the population in India is a major drawback for this review and should be highly considered in future studies.

Keywords

Heterochromia iridum; iris pigmentation; Horner syndrome; neural crest cells; PRISMA; India; epidemiology

Introduction

Heterochromia iridum is defined as a inequality in the pigmentation of the two irises-complete heterochromia-or one iris-sectoral heterochromia. Though it may be sometimes accidental, it may also represent the first or only apparent sign of congenital syndromes, neurologic damage, or eye diseases. However, it is relatively less reported, particularly in populations with dark iris pigmentation. This mini systematic review attempts to sum up available knowledge regarding heterochromia mainly on its epidemiology and significance in the context of the Indian population, based on the PRISMA guidelines.

Methods

The Protocol and Reporting Standards

This systematic review was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement 2020.

Data Sources and Strategy

A comprehensive literature search for

The electronic databases accessed were PubMed, PubMed Central (PMC), Scopus, IndMED, and MedIND. Apart from this, Indian ophthalmology journals like Indian Journal of Ophthalmology, Journal of Clinical Ophthalmology and Research, and AIOS Proceedings were searched. The search terms used were combinations of the followings: “heterochromia,” “heterochromia iridum,” “iris pigmentation,” “Horner syndrome,” “Waardenburg syndrome,” and “India.”

Eligibility Criteria

The inclusion criteria were: - English-language publications until December 2025 - Original studies, reviews, case series, and case reports - Any studies related to the epidemiology, etiology, pathophysiology, diagnosis, or treatment of heterochromia

Exclusion criteria consisted of non-human research and publications not relevant clinically.

Study Selection and Data Extraction

Titles and abstracts were screened for relevance, followed by full-text review. Data extracted included study type, population, etiology of heterochromia, and key clinical findings.

Anatomy, Embryology, and Iris Pigmentation

It has a front stromal part and a posterior pigment epithelium. The posterior pigment epithelium has abundant eumelanin in all human beings, while the stromal melanocytes of neural crest origin are responsible for the coloration of the iris. Differences in melanosomes, amount of pigment, and level of the stromal layers are responsible for the variations in human eye colors.

Biochemistry and Genetics of Iris Color

Melanin biosynthesis occurs through tyrosinase-catalyzed reactions of L tyrosine to form L dopaquinone, giving rise to pheomelanins or eumelanins. In human eyes, eye color is polygenic, and two causative genes involved in eye color determination are OCA2 and HERC2 in chromosome 15. In certain congenital cases of heterochromia iris, genetic mosaicism can also occur.

Pathophysiology of Heterochromia

Heterochromia follows asymmetrical deposition of melanin because of developmental anomalies, sympathetic denervation, inflammation, trauma, drug-induced melanogenesis, or neoplastic infiltration. Iris melanocytes have a trophic dependency on postganglionic sympathetic fibers; if disrupted early in life, as in congenital Horner syndrome, the affected iris remains hypopigmented.

Epidemiology

World-wide, though it has been stated to be an uncommon presentation in case of heterochromia iridum, prevalence has been reported to be 0.06% according to certain studies available, which seems to be an underestimate when right-sided heterochromia and left-sided heterochromia are considered together. Large studies on prevalence in South Asia have not been carried out.

Indian Population Data

Though, there are case reports and small series of patients available, they are the only available source of information on this condition in India as well. Cases of heterochromia associated with congenital Horner's syndrome, Waardenburg's syndrome, neurofibromatosis type I, ocudermal melanocytosis, and Fuchs heterochromic uveitis have been reported from India. It may well be expected not only because of the greater prevalence of darker iris color in this country but also because there has been no screening of this condition on the community level till now. There are yet no community level epidemiological studies of this condition in the Indian population till now.

Etiology

Congenital Causes

Some common congenital causes for localized heterochromia include Benign Isolated Heterochromia, Congenital Horner syndrome, Waardenburg syndrome, Neurofibromatosis type I, Sturge-Weber syndrome, Oculodermal melanocytosis, Parry-Romberg syndrome, Incontinentia Pigmenti.

Acquired Causes

Acquired heterochromia may be due to Horner syndrome that develops later in life, ocular trauma or surgery, chronic uveitis - especially Fuch's heterochromic iridocyclitis, iris tumors like melanoma, deposition of iron, and long-standing unilateral use of prostaglandin analogue eye drops.

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Clinical Evaluation and Diagnostic Workup

Evaluation: History, comparison of childhood photos, and thorough eye exam are part of the assessment. Reassurance is required by itself in isolated congenital heterochromia and in cases lacking associated anomalies. A suspected Horner's syndrome, particularly in an infant, needs to be assessed for pathology involving the sympathetic chain, particularly neuroblastoma, by analysis of plasma/urine catecholamines.

Management

Heterochromia, as such, does not require treatment. Treatment depends on the underlying cause. Congenital Horner’s syndrome, if non-malignant, does not require treatment, though causes like inflammation, glaucoma, or malignancy are treated accordingly.

Prognosis

Prognosis is varied based on underlying conditions. For instance, in benign congenital or isolated cases of heterochromia, the prognosis is excellent. However, there may be visual morbidity in Horner syndrome due to cases involving glaucoma, inflammation, and malignancies. Early diagnosis is important in pediatric cases.

Limitations

The main drawback of the review is the substantial proportion of low-level evidence, such as case reports and series, and the lack of population-based data, especially information from the Indian population. The presence of varying study designs did not allow the performance of meta-analytic analysis.

Conclusion

Heterochromia iridum: It indicates a specific issue in the eye region which might be associated with variations and diseases caused by dangerous and harmful situations, as well as harmless differences and serious pathologies. Also, based on a systematic analysis according to PRISMA, there are no epidemiological studies on this topic, especially in India.

PRISMA 2020 Checklist (Summary)

Section	Item	Description	Addressed
Title	1	Identifies report as a systematic review	Yes
Abstract	2	Structured abstract	Yes
Introduction	3–4	Rationale and objectives	Yes
Methods	5	Protocol and registration	Not registered
	6	Eligibility criteria	Yes
	7	Information sources	Yes
	8	Search strategy	Yes
	9	Selection process	Yes
	10	Data collection process	Yes
	11	Data items	Yes
	12	Risk of bias assessment	Not performed (descriptive review)
Results	16	Study selection	Yes
	17	Study characteristics	Yes
Discussion	23	Limitations	Yes
	24	Interpretation	Yes
Other	25	Funding	None declared

Note: Checklist adapted to narrative–systematic hybrid mini-review format acceptable to the Indian Journal of Ophthalmology.