

Navigating the maze of ocular rare diseases



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1. Introduction

Rare ocular diseases present a significant challenge within the public health landscape. Unlike common eye disorders such as near and farsightedness, cataracts, and macular degeneration, these rare maladies are characterised by diagnostic hurdles and dearth of established protocols for treatment. However, the ophthalmologists are uniquely prepared to investigate the multifaceted impact of rare eye diseases in addressing the unmet medical need (1).

2. The burden of rarity

The designation of "rare" typically applies to diseases affecting less than 200,000 individuals within the United States. Many of these unusual ophthalmic disorders currently lack effective treatments or cures. However, advancements driven by innovative research, hold promise for unlocking solutions to some of these most challenging eye diseases. Rare ocular diseases inflict a profound detriment on patients' quality of life. Frequently it affects both the eyes (bilateral), and even if the presentation is asymmetric, it causes a significant drop in the visual acuity. Another major concern remains that the asymptomatic progression can lead to delayed diagnoses, and this can further compound the challenge.

A thorough awareness of disease pathogenesis, diagnosis, and therapy is paramount. Primary care providers recommend high-risk patients for a comprehensive ophthalmological examination and take a more active role in their care. A particular cause of concern is the limited availability of approved treatments for a significant number of these rare diseases (2). This lack of therapeutic options underscores the urgent need for further research and development efforts.

To regain a normal quality of life after a permanent vision loss, a patient requires multifaceted approach-based structure including medical care, psychological rehabilitation, and social reintegration. Patients with rare diseases frequently face a similar set of obstacles, including a lack of reliable qualitative information, delayed diagnoses, and limited access to effective treatment and specialised care. The primary concern with these diseases is that their novelty leads to misdiagnoses, under treatment, and require multiple secondary consultations and treatment trials. For these reasons, their effective management call for a two-pronged approach, viz., the healthcare system requires a robust network of specialists with expertise in these uncommon conditions and secondly sufficient resources for research initiatives for unraveling the complexities of these diseases for development of novel diagnostic tools and therapeutic interventions (3).

3. Types of ocular rare diseases

Few people are afflicted with a category of disorders known as rare diseases. Sixty-eight percent of mutations are inherited, accounting for 72% of uncommon disorders. The residual fraction is attributed to environmental causes, allergies, or illnesses (3). According to the National Institute of Health (NIH), there are about 550 uncommon eye diseases, including those that impact the retina and orbit. Cranial neural crest development plays a pivotal role in ocular health, and abnormalities in this process can manifest as a spectrum of rare eye diseases. Fate mapping studies have emerged as a powerful tool for deciphering eye development, offering crucial insights into potential pathogenic pathways. Notably, numerous rare ocular diseases have been linked to dysregulation of specific transcription factors governing cranial neural crest development. Mouse models have been successfully established for a variety of rare eye diseases affecting both the anterior and posterior segments of the eye. Some of the rare eye diseases are presented in Figure 1.

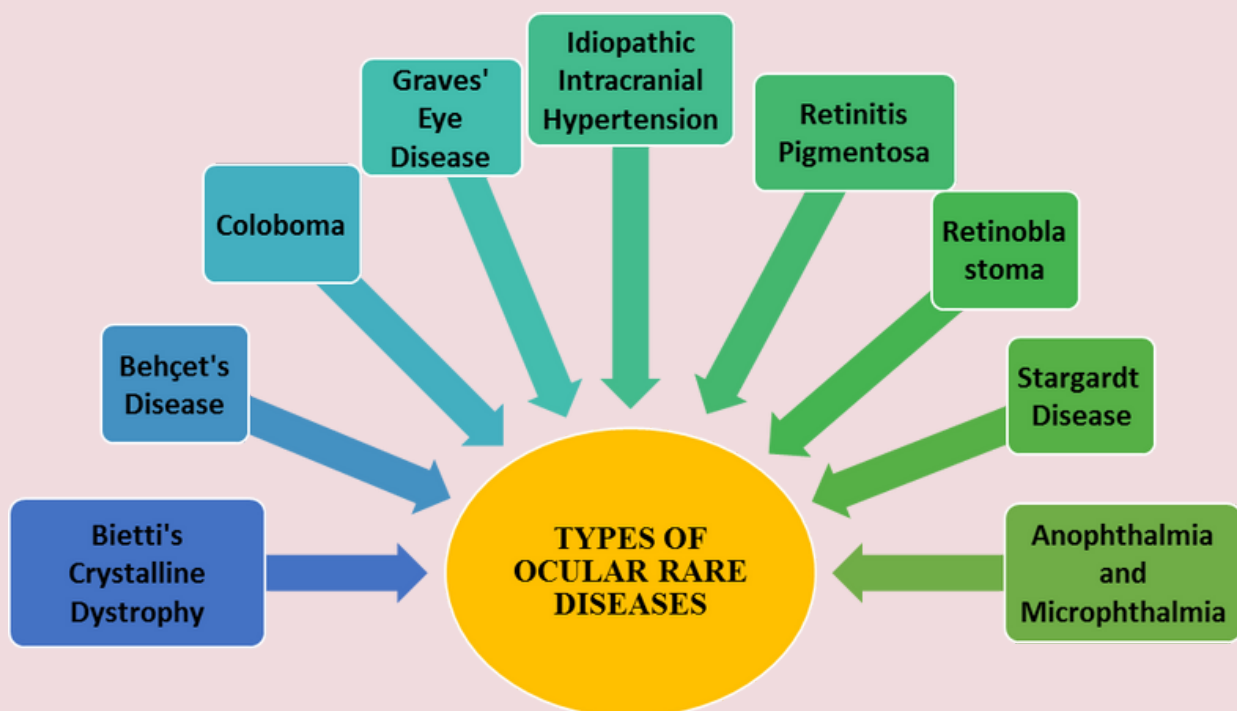


Figure 1. Types of ocular rare diseases

4. Symptoms, diagnosis and treatment of ocular rare diseases

Ocular rare diseases are those that primarily affect the eyes, are rarely seen in the general population, and frequently have little in the way of research or available treatments. Depending on the exact condition, symptoms might vary greatly, however, common indications include vision loss, blurred or clouded vision, eye pain, redness, light sensitivity, and abnormalities in the appearance of the eye or surrounding tissues. Some of the ocular rare diseases with their symptoms, diagnosis and treatment are presented in Table 1.

Table 1. Symptoms, diagnosis and treatment of ocular rare diseases

S. No.	Diseases	Description	Symptoms	Diagnosis	Treatment	Ref
1.	Bietti's Crystalline Dystrophy (BCD)	Fatty acid crystals accumulate in the retina, the light sensitive layer of tissue in the back of the eye, and the cornea, the clear outer layer of the eye	Loss of vision, especially night vision, peripheral (side) vision	Dilated eye exam, genetic testing	Contact lenses, medicine, or surgery	(4)
2.	Behçet's Disease	Causes damage to blood vessels	Genital sores, red eyes, blurry vision, eye pain	Medical history	Steroids	(5)
3.	Coloboma	Occurs when a portion of the eye's tissue is absent. It could impact one or both the eyes	Loss of vision, light sensitivity, missing tissue in a portion of eye	Visual examination	early intervention, vision aids, contact lenses, spectacles, and surgery	(6)
4.	Graves' Eye Disease	The eyes expand and protrude. Also known as Graves' ophthalmopathy, or thyroid eye disease (TED), and it is brought on by Graves' illness	Dry, puffy and bulging eyes, double vision	Eye examination	Eye drops, medicine, surgery	(7)
5.	Idiopathic Intracranial Hypertension	Headaches and altered vision are brought on by elevated blood pressure surrounding the brain	Headaches, blind patches, loss of peripheral vision	Vision test, dilated eye exam, and other tests	Medication, surgery, and weight loss	(8)
6.	Retinitis Pigmentosa	Retina is affected. Slowly deteriorating retinal cells over time results in loss of vision	Loss of peripheral (side) vision and night vision	Dilated eye examination, genetic test, electroretinography	rehabilitation and low vision aids	(9)

7.	Retinoblastoma	A rare kind of eye cancer develops in the retina. It is most common in children under the age of five. One eye or both eyes may be impacted	Poor vision, eye pain, swelling, watery eyes	Dilated eye examination and ocular ultrasound	chemotherapy, phototherapy, radiation therapy, cryotherapy and ocular excision surgery enucleation	(10)
8.	Stargardt Disease	An uncommon hereditary eye condition caused by the accumulation of fatty material on the macula, the small portion of the retina required for center, crisp vision	Loss of central vision and photosensitivity	Dilated eye examination, retinal images or scans, genetic testing	Vision rehabilitation and vision aids	(11)
9.	Anophthalmia and Microphthalmia	A newborn with anophthalmia is born without one or both eyes. Microphthalmia is a condition where a baby is born with either one or both of their eyes abnormally small	These disorders have the potential to result in blindness or vision loss	Physical examination and prenatal testing	Prosthetic devices, surgery and medicine	(12)

5. Rare disease registries

Rare disease registries are a significant method for accumulating vital epidemiological information and relevant samples for clinical research, as well as for feasibility studies, particularly for clinical trial enrolment and treatment protocol development (13). By systematically collecting information on patient demographics, disease prevalence, and natural history, these registries shed light on the true scope and impact of rare diseases. This streamlined approach allows researchers to identify potential participants more efficiently and design studies with greater statistical power. Once these rare disease databases are established, a collaborative environment where all stakeholders may constantly optimise and modify them for research and clinical practice become possible. Researchers leverage these registries to formulate new hypotheses and test potential interventions. Pharmaceutical and biotechnological companies utilize the data for drug development strategies. The physicians gain access to the latest insights on the disease, which ultimately translates into improved patient care. The patients and patient advocacy groups play a vital role in shaping the content and direction of these registries, ensuring that it remains patient-centric throughout the research continuum. The European Union exemplifies the global commitment to rare disease research through its comprehensive database encompassing over 651 registries. In this vast repository, 454 are national, 77 are regional, 45 are European, 71 are worldwide, and 4 are undefined (13). It can be underscored that the rare disease registries are a powerful tool and a collective effort to advance knowledge and improve outcomes for patients with rare diseases. The list of rare eye disease registries is presented in Table 2.

Table 2. List of current rare eye disease registries (13)

S.No.	Registry	Coverage	Country
1.	Bone Cone Monochromatism- Patient Registry	International	Germany
2.	National Registry for Mycotic Keratitis	National	Germany
3.	Patient Registry for Retinal Degeneration Proretina	National	Germany
4.	Neuromyelitis Optica	National	Germany
5.	Myasthenia Gravis Registry	National	Spain
6.	Spanish Patient Registry of Hereditary Retinal Dystrophy	National	Spain
7.	Behcet's Disease Registry	National	Spain
8.	Myasthenia Gravis Registry	National	Spain
9.	Cohort of Patients with Hereditary Dystrophies of Retina	National	France
10.	Registry: An Interoperable Sustainable European Rare Eye Disease Registry	Europe	France
11.	Establishment of Children and Adolescent Cohort in Behcet's Disease in France	National	France
12.	French Cohort Creation in Retinitis Pigmentosa	National	France
13.	French Patient Registry in Chorioretinopathy, Birdshot Type	National	France
14.	French Registry of Patients Affect by Leber Amaurosis and Retinitis Pigmentosa to Assess the Clinical Trial in Gene Therapy	National	France

15.	A Cohort of Patients with Hereditary Dystrophies of Retina	National	France
16.	Curing Retinal Blindness Foundation	International	Africa
17.	Fighting Blindness Canada Patient Registry	National	Canada
18.	Retinoblastoma Registry	National	Malasia

6. Conclusion

Vision, is the preeminent sense that underpins our interaction with the world, and its impairment can have a significant impact on the quality of life and poses a public health challenge. By addressing the crucial aspects pertaining to the rare conditions, we can usher in a new era of hope for patients grappling with the sight-threatening realities of rare ocular diseases. Research efforts directed towards rare eye disorders extend far beyond isolated investigations. These studies hold immense potential for yielding insights that can be translated to benefit more prevalent ophthalmic conditions. And this assumes great importance given the high costs associated with developing treatments for rare diseases. The financial hurdles may slow down the pace of studies in rare diseases. But, the future of research in this domain brims with possibilities as we are reminded of the inspirational words of Helen Keller that “Although the world is full of suffering, it is also full of the overcoming of it”.

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