

Etiopathogenesis of cataract: An appraisal

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Natural eye lens is a crystalline substance to produce a clear passage for light. Cataract is opacity within the clear lens of the eye and is the dominant cause of socio-medical problem i.e., blindness worldwide. The only available treatment of cataract is surgery. However, insufficient surgical facilities in poor and developing countries and post-operative complications inspire researchers to find out other modes of treatment for cataract. In this review, an attempt has been made to appraise various etiological factors of cataract to make their perception clear to build up counterpart treatment. Present study is an assortment of various available literatures and electronic information in view of cataract etiopathogenesis. Various risk factors have been identified in development of cataracts. They can be classified in to genetic factors, ageing (systemic diseases, nutritional and trace metals deficiencies, smoking, oxidative stress etc.), traumatic, complicated (inflammatory and degenerative diseases of eye), metabolic (diabetes, galactosemia etc.), toxic substances including drugs abuses, alcohol etc., radiation (ultraviolet, electromagnetic waves etc.) are implicated as significant risk factors in the development of cataract.

Key words: Blindness, cataract, eye lens, risk factors, treatment of cataract

Cataract is defined as opacity within the clear lens inside the eye that reduces the amount of incoming light and results in deterioration of vision. Natural lens is a crystalline substance and a precise structure of water and protein to create a clear passage for light. Cataract is often described as being similar to looking through a waterfall or waxed paper.^[1]

Blindness causes human suffering is economically devastating, and many early deaths.^[2] According to WHO, one-third of the world's 45 million blind and half of the world's 1.5 million blind children live in South-East Asia region. The blind persons are often leading a miserable life and are disenfranchised.^[2] Three national surveys in India have extrapolated the survey result to project that number of people affected with cataract will reach to 8.25 million by 2020.^[3] Currently available treatment is surgical extraction of the cataractous lens. Reports say that all cataract surgeries in India are not sight-restoring.^[4] Blindness due to cataract is terrific challenge for ophthalmologists on public health stance. It imposes great economic burden on people and surfeit to be handled by surgery alone. Alternatively, the preventive ophthalmology offers another approach to tackle the problem to identify factors, which might modify or simply delay the onset and progression of cataract by a period of 10 years, the number of cataract surgeries would drastically decrease by 45% or more.^[5] Therefore, identifying modifiable risk factors is of great importance from a public health perspective. The better understanding of causes can definitely have great impact in its management, as elimination of causes is the main key to

eradicate any disease. The present study recapitulated after reviewing various literatures, research articles, reviews, and internet data associated with etiopathogenesis of cataract.

Risk factors of cataract

Cataract develops from a variety of reasons. Human cataract formation is mostly considered to be a multifactorial disease. Most of them develop with their specific etiologies and can be diagnosed through it, e.g., posterior (classically due to steroid use) and anterior (common senile cataract).^[6] Table 1 represents the cataracts with their causes and vulnerable persons.

Congenital

Following factors are generally involved in the development of the congenital cataracts.

Genetic factors

Genetically determined cataract is due to an anomaly in the chromosomal pattern of the individual. About one third of all congenital cataracts are hereditary.^[7] It may occur with or without microphthalmia, aniridia, anterior chamber developmental anomalies, retinal degenerations, other multisystem genetic disorders such as chromosome abnormalities, Lowe syndrome or neurofibromatosis type.^[8] *PITX3* gene are reported to be responsible for some inherited cataracts in anterior segment mesenchymal dysgenesis.^[9] Hereditary Mendelian cataract is inherited autosomal-dominant and autosomal-recessive or X-linked traits. Phenotypically, identical cataracts can result from mutations at different genetic loci and may have different inheritance patterns.^[8]

Maternal and fetal factors

Malnutrition during pregnancy or in early infancy has been associated with non-familial zonular cataract. Maternal infections like rubella, toxoplasmosis, and cytomegalo-inclusion etc., are also associated with congenital cataracts.^[10] Endocrine disturbance,^[8] abuses of alcohol or drugs (thalidomide, corticosteroids etc.) as well as exposure of radiation during

Access this article online

Website:

www.ijjo.in

DOI:

10.4103/0301-4738.121141

Quick Response Code:



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Manuscript received: 07.05.12; **Revision accepted:** 06.11.12

Table 1: Various types of cataract, their causes, and persons at risks

Type of cataract	Causes	Vulnerable people
Congenital and developmental	Heredity, gestational mal-development of lens, maternal malnutrition, infection, drugs, radiation, Fetal/infantile factors- anoxia, metabolic disorders, birth trauma, malnutrition, congenital anomalies, idiopathic	It may occur since birth or from infancy to adolescence.
Senile	Senescent changes, dehydration, systemic diseases, smoking, oxidative stress, and lack of essential dietary elements.	Elderly persons, mostly those over the age of 50 years.
Traumatic	Some physical damage to the eye lens capsule, penetration of foreign objects etc.	People working in hazardous conditions such as welders and those in glass furnaces.
Complicated	Complications of some chronic inflammatory and degenerative eye diseases.	Patients of skin diseases, allergy, uveitis, glaucoma diabetes, emphysema, asthma, etc.
Metabolic	Metabolic disorders – diabetes mellitus, galactosemia etc.	Persons deficient in certain enzymes and hormones
Toxic	Certain toxicants and drugs - steroids, NSAID's etc.	People on steroid therapy and toxic drugs.
Radiation and Electrical	Infra-red rays, X-rays, ultra violet rays, and powerful electric current etc.	Persons who come in contact with sunlight, artificial radiations, high voltage etc.

pregnancy increases the risk of cataracts in their infants.^[10] Intrauterine hypoxia in the last trimester of pregnancy, Lowe's syndrome, myotonia dystrophica, congenital ichthyosis etc., are infantile factors to cause cataract in infants.^[8,10] The Osaka variant of galactokinase with an A198V substitution was shown to be associated with bilateral cataract in adults.^[11]

Gender

Women have a higher incidence and risk for most types of cataracts than men,^[7] probably due to lack of estrogen in post-menopausal years. An experimental study suggested the protective effects of estradiol or estrone treatment against cataractous eyes up to 25%, in the MNU-treated, ovariectomized rats.^[12]

Race and ethnicity

African-Americans and Hispanic Americans seem to have nearly twice the risk of developing cataracts than Caucasians. This difference may be due to other medical illnesses, particularly diabetes, and due to lack of treatment.^[7]

Ageing

Age-related (or senile) cataract is defined as cataract occurring in people >50 years of age, unrelated to known mechanical, chemical, or radiation trauma. It becomes progressively more severe and frequent in elderly^[13] and is responsible for 48% of world blindness.^[14] Breakdown and aggregation of protein, damage to fiber cell membranes, deficiency of glutathione, oxidative damage, elevated calcium, abnormal lens epithelial cell migration etc., are some specific mechanisms responsible for senile cataract. Some of the following factors may provoke the above mechanisms for cataract.

Diarrhea/dehydrational crisis

Minassian *et al.*^[15] reported that one episode of severe diarrhea is 4.1 times more likely to cause cataract. The risk rose to 21% with two or more episodes of diarrhea and was still higher in those with history of both severe diarrhea and heatstroke. Harding^[16] summarizes that the diarrhea, malnutrition, acidosis, dehydration, high level of urea in the body, and associated osmotic imbalance lead to accumulation

of cyanate, thus adversely affect the glutathione level, which causes cataract.

Hypertension

Early clinical studies of cataract formation in diabetes mellitus noted a high prevalence of arterial hypertension.^[17] Decreased lenticular ionic transport resulting from a specific decrease in Na⁺ K⁺ Adenosine Triphosphatase (ATPase) activity in the lens epithelium leads to cataract formation in the Nakano mouse.^[18] Some *in vitro* studies with Na⁺ K⁺ ATPase inhibitors also results in lens opacification.^[18] Low Na⁺ K⁺ ATPase activity has been reported in renal microsomal preparations from hypertensive Dahl salt-sensitive rats.^[19,20]

Smoking

The role of smoking in cataractogenesis has been highlighted in various studies.^[21-23] These studies have shown 2-3 fold increased risk of cataract in smokers. The increase in smoking dose was associated with increasing severity of nuclear opacities. Aromatic compounds present in the inhaled smoke oxidatively modify lenticular components.^[24]

Oxidative stress - oxygen-free radicals (Oxidants)

It is widely accepted that oxidative stress is a significant factor in the genesis of cataract, both in experimental animals^[25,26] and in cultured lens models.^[27,28] The oxidative processes rise with age in the human lens, and concentration of proteins found significantly higher in cataractous lenses.^[29] The overproduction of oxidants is very harmful that they can even affect genetic material.^[30] One theory postulated that in the aging eye, barriers develop that prevent glutathione and other protective antioxidants from reaching the nucleus in the lens, thus making it vulnerable to oxidation.^[7]

Lipid content and cholesterol

The composition and metabolism of membrane lipids may affect the formation of various types of cataracts.^[31] Lens membrane contains the highest cholesterol content of any known membrane.^[32] The development of cataract is associated with increased accumulation and re-distribution of cholesterol inside these cells. The Smith-Lemli-Opitz syndrome, mevalonic

aciduria, and cerebrotendinous xanthomatosis all involve mutations in enzymes of cholesterol metabolism, and affected patients can develop cataracts. Hypocholesterolemic drugs like statins can block cholesterol accumulation by these lenses and can produce cataracts.^[31,33]

Traumatic

A cataract can form after blunt or penetrating injuries to the eye and entry of a difficult-to-remove foreign object, leads to physical damage and discontinuation of the eye lens capsule. When the outer lens capsule breaks, the inner lens swells with water and turns white due to denaturation of lens proteins. Concussion of the lens without rupture of the capsule may result in a cataract that is initially sub-capsular and commonly has a star-shaped appearance.^[34] These injuries typically occur in young men, and the lenses are very soft and easy to suck out. People working in hazardous conditions such as welders and those in glass furnaces are more susceptible to this kind of injury-induced cataract.

Complicated

This term refers to cataracts that are secondary to local eye as well as systematic inflammatory and degenerative diseases.

Skin diseases and allergy

Lens opacities associated with cutaneous diseases are termed syndromatotic cataracts, occur at young age and are bilateral.^[10] Atopic cataract is most common condition associated with atopic dermatitis (AD), especially in children.^[35] The mechanism is not known; however, habitual tapping and rubbing of the face in pruritic conditions may play a role.^[36] Patients with AD have been found to have higher levels of protein flare in the aqueous humor.^[37] Other skin disorders associated with cataract include poikiloderma, vascular atrophicus, scleroderma, and keratosis follicularis.^[10]

Eye conditions

Glaucoma and its treatments, including certain drugs (notably miotics *viz*; demecarium, isoflurophate, and echothiophate) and filtering surgery, posing a high risk for cataracts.^[7] Inflammatory conditions of eye *viz*. uveitis caused by an autoimmune disease or response, including Fuch's heterochromic cyclitis and Still's disease, hypopyon corneal ulcer, endophthalmitis, myopic chorioretinal degeneration, retinitis pigmentosa and other pigmentary retinal dystrophies, retinoblastoma or melanoma (complicated last stages) are the other factors.^[10] The myopic change also precedes the development of cataract.^[38] Nuclear cataract is associated with presumed acquired myopia.^[39,40] Posterior sub-capsular cataract reported as significantly associated with myopic refraction.^[41,42]

Metabolic

These cataracts occur due to endocrine disorders and biochemical abnormalities. Galactosemic and diabetic cataracts are common example of this kind of cataract.

Galactosemia

Galactosemia is associated with inborn error of galactose metabolism, which can occur due to deficiency of galactose-1 phosphate uridyl-transferase (GPUT) and due to deficiency of galactokinase (GK). Development of bilateral cataract in

the form of oil droplet central lens opacities is characteristic feature of galactosemia.^[10]

Diabetes

Poor control of diabetes mellitus (DM) is linked to the formation of several systemic and ocular complications included vision loss.^[43,44] Evidently, direct *in vivo* and *in vitro* experimental studies suggest that diabetes is a cause of cataract. Uncontrolled DM results in hyperglycemia, which is associated in ocular tissues with non-enzymatic protein glycation,^[45] osmotic stress,^[46] and oxidative stress.^[47]

Insulin therapy, strict control of blood glucose levels, exercise, anorexia as well as ischemia-induced hypoglycemia leads to unfolded protein response (UPR),^[48,49] lens epithelial cell (LEC) death^[50] through activation of specific death pathways, and apoptosis.^[51]

Hypocalcemia

Cataractous changes may be associated with parathyroid tetany, which may occur due to atrophy or inadvertent removal (during thyroidectomy) of parathyroid glands. Multicolored crystals or small discreet white flacks of punctate opacities are formed in the sub-capsular region of lens, which seldom matures.^[37]

Hypothyroidism

Cataract is not a common feature of hypothyroidism or cretinism; however, an association has been claimed,^[52] and the described opacities resemble those seen in hypoparathyroidism. Thyroidectomy without interference with the parathyroids has also been stated to cause cataract, usually a blue dot type.

Error of copper metabolism

Inborn error of copper metabolism results in Wilson's disease (hepatolenticular degeneration) may develop a characteristic opacity in the anterior capsular region brightly-colored sunflower pattern, green-colored, and has negligible effect on vision. The more commonly observed feature is 'Kayser-Fleischer ring' in the cornea.^[10,53]

Nutritional

Animal studies and *in vitro* investigations have shown that nutritional deficiencies of micronutrients are associated with cataract.

Aldose reductase (for reduction of sugars) is the basis for the formation of cataracts related to abnormalities in sugar metabolism.^[54,55] Studies suggested that poor nutritional status of cataract patients accelerates protein insolubilization in the lens of most types of human and experimentally induced animal cataracts.^[56] Tryptophan deficiency-induced cataract has consistently been documented.^[57] Cataracts have also been produced in experimental animals on a diet low in folic acid.^[58] Study published recently shows that regular intake of multivitamin supplement decreases the risk for all types of cataracts.^[59-61]

There are many evidences suggesting that the trace elements, especially zinc and copper in nutrition, may play a role in the formation of human cataract. Animal and human studies have reported the involvement of various inorganic

minerals linked to cataract formation.^[60,62] These elements have recently attracted much attention as possible causative factors in development of cataract.^[63-65]

Neonatal hypoglycemia, aminoaciduria, homocystinuria, Fabry's disease, Hurler's disease, Lowe's syndrome are other metabolic conditions, which lead to cataract development.

Toxic cataracts

Drug abuses

Many drugs can contribute to cataracts, including corticosteroids (such as prednisolone and cortisone),^[66] tranquilizers, radiomimetic drugs,^[67] quinoline, methotrexate, oral contraceptives, miotics, ergot, sulfanilamide, streptozotocin, methoxsalen, accutane, epinephrine psoralen, thiazide etc.^[68]

Steroid use is the fourth leading risk factor for secondary cataract and accounts for 4.7% of all cataract extractions.^[69] In addition to systemic steroids, cataracts have also been associated with ocular topical steroids, inhaled steroids, and topical steroid creams.^[70,71] Steroids, such as prednisone, block normal metabolism of connective tissue, of which the lens is composed. Even low potency steroid creams applied to the eyelids may result in increased intra-ocular pressure and cataract.^[72] The mechanism of corticosteroid-induced cataract is not known but may be due to osmotic imbalance, oxidative damage, or disrupted lens growth factors.^[70]

Thiazolidinediones is major new therapy for non-insulin-dependent diabetes.^[73,74] On oral administration, it was associated with the formation of lenticular opacities during non-clinical safety assessment studies conducted in rats.^[75]

An asymptomatic anterior sub-capsular lens opacities and keratopathy characterized by sub-epithelial corneal whorls similar to those noted in Fabry's disease are well documented as ophthalmic side-effects of Amiodorone (anti-arrhythmic drug).^[76]

Neuroleptic drugs are used in the treatment of various psychiatric disorders.^[77] Chlorpromazine (CPZ) therapy is associated with anterior capsular lens pigmentation, followed by corneal endothelial pigmentary changes.^[78,79] During carbamazepine therapy, blurred vision, transient diplopia, and conjunctivitis, in addition to lens opacities, have been reported.^[80,81] Such visual disturbances are reversible and respond to decrease in dose.

The eye's lens consists of serotonin receptors and has shown that excess serotonin lead to cataract formation in animal studies.^[82]

Long-term use of miotics, particularly long acting cholinesterase inhibitors such as echothiophate, demecarium bromide, disopropyl fluorophosphate (DFP) etc., may induce reversible anterior sub-capsular granular type of cataract.^[10]

Many others drugs are weakly associated with cataracts including busulfan, gold, allopurinol, potassium-sparing diuretics, thyroid hormone, tetracyclines, sulfamidase, tomoxifen, naphthalene, simvastatin etc. A significant interaction between simultaneous statin and erythromycin use is reported with the development of cataract.^[32,83-85]

Toxins

Many toxins, including synthetic chemicals and

pharmaceuticals, are known to trigger cataract. They include: acetone, dinitrophenol, cresol, and paradichlorobenzol as well as numerous chemicals and solvents. Heavy metals like mercury are found at increasing levels in the lens with aging and cataractogenesis. Cadmium, bromine, cobalt, iridium, and nickel are one of the important co-factors of lipid peroxidation process and potentially deactivating antioxidant functions.^[86-88] Additional minerals thallium, zinc sulfate, cobalt chloride, sodium selenite etc., in certain forms and dosages can become toxic and cause cataract.^[89,90]

Hormonal replacement therapy

Cataract is more prevalent in post-menopausal women than in men at similar ages; this implies that hormonal differences are involved and suggests a possible role for estrogen. Estrogen receptors have been detected in the cataractous eye's lens. Naturally occurring (endogenous) estrogen appears to protect the eye from cataract, along with cardiovascular and other body systems before menopause. A prospective study on post-menopausal Swedish women found that HRT may also raise risk.^[91]

Alcohol consumption

Alcohol increases the risk of nuclear, cortical, and posterior sub-capsular cataracts (PSC). The lens is sensitive to oxidative stress and directs toxic effects of alcohol.^[92,93] The lowest level that showed an effect in the studies was 91 g pure ethanol per week, (seven-nine) standard drinks were 4.6 times more likely to suffer from PSC when compared with non-drinkers.^[94]

Radiation and electromagnetic waves

The radiation may be of any kind *viz*; ultra-violet rays, infrared, or electromagnetic waves. Ultra-violet-radiation has been linked with senile cataract in many studies. Duke-Elder had opined that the fundamental cause of cataract in all its forms may be traced to the incidence of radiant energy directly on the lens itself.^[10,95] Data from the HANES survey have shown higher ratio of cataract to non-cataractous diseases in areas with high numbers of annual sunlight hours.^[96] In Australia, areas of higher UV irradiation were shown with higher prevalence and early onset of cataract.^[97] Cataract prevalence reported 3.8 times higher in areas with an average of 12 hours of daily sunlight exposure compared to areas with only 7 hours of exposure in Nepal.^[98] Interestingly, cataract was reported more common in cloudier areas of India.^[99] Both epidemiological and experimental evidence indicates maximum lens sensitivity to UVR-B with wavelengths around 300 nm.^[100-102] Until today, little is known how the genome modulates the lens sensitivity to oxidative stress from UVR. Electromagnetic radiation with longer wavelengths, e.g., UVR-A also contributes to adverse biological effects, but as in DNA damage, the contribution is small, even though UVR-A in sunlight is nearly a thousand-fold more intense than UVR-B.^[103,104] Several epidemiological studies have consistently demonstrated the correlation between cortical cataract and exposure to solar UVR.^[105-107] Widmark (1901) described^[108] lens epithelial damage, swollen lens fibers, but no damage on the lens equator in rabbit lenses following controlled exposure to UVR. Small fraction of high energetic UVR-B 300 nm passing cornea is absorbed by lens epithelium, which is, therefore, the primary target for damage.^[109,110]

Prolonged exposure to infrared rays may cause discoid posterior sub-capsular opacities and true exfoliation of the anterior capsule (Exfoliation syndrome) as typically seen in workers of glass industries. Exposure to microwave radiation can cause cataracts.^[10] Exposure to X-rays, gamma rays or neutrons may be associated with irradiation cataract. There is usually a latent period ranging from 6 months to a few years to the development of cataract. Inadequately protected technicians, patients treated for malignant tumors, and workers of atomic energy plants are prone to this.^[10]

Discussion

Clinically, cataract patients can be classified into morphological groups *viz.* nuclear, sub-capsular or cortical for studying the risk factors. Most case-control studies have been on pooled cataracts. This approach has been strongly criticized by some authors on the basis that different morphological types have different risk factors.^[16] Since cataract is a major cause of avoidable blindness in the developing countries, the key to the success of the Global Vision 2020: The right to sight initiative is a special effort to tackle cataract blindness by finding out precise cause. Even though effective surgical procedures are available for treatment, the problem of post-operative complications, cost of surgery, and high number of people requiring surgery pose a substantial economic burden. It has been estimated that delaying cataract onset by 10 years could reduce the need for surgery by as much as half.^[111] The respective causes of different type of cataracts must be known in order to understand the patho-physiology of disease and its management. However, risk factors for cataracts summarized above cannot be comprehended this way, but they may help to confer the matter with new approaches.

Inherited disorders are often involved in the development of congenital cataracts in children with ratio of 1:10,000 births.^[7] Such cataracts are most often due to inborn abnormalities in the structure or shape of the lens capsule. *PITX3* gene has been reported as responsible for some inherited cataracts. The role of Osaka variant is new interest of point at present. Infantile cataracts, those developing within the first year of life, are frequently associated with a metabolic or systemic disease.^[112] The role of gender and race or community could not be made clear in the development of cataract. Age-related cataracts are mostly developed due to increase in oxidative stress in lens due to various systemic diseases or imbalance in pro and anti-oxidants in body particularly eyes. Trauma has direct impact to induce denaturation processes in eye lenses. Removal and implant placement can be complicated in these cases though, as the blunt force often tears the zonular support.^[113] Complications of untreated systemic as well as local conditions are well-elaborated in development of cataract, though their mechanism is still unclear. Cataracts, those precede by metabolic abnormalities, are mostly associated with congenital aberrations. Most of them are having peculiar diagnostic characters like oil droplet type of opacity appearance in galactosemia,^[10] multicolored crystals-like opacities can be seen in hypocalcemia,^[10] and sunflower-like appearance in copper metabolic error.^[53] The deficiencies of micronutrients directly affect the antioxidant systems in eyes lens.^[114,115] The role of nutrition in cataract formation in developing countries is perhaps closely linked with diarrhea and poverty, all of which are closely interrelated.^[116] Many drug abuses as well

as various toxins may cause oxidative damage and interrupt the lens growth. They bind to sulfhydryl groups, including glutathione peroxidase and Na⁺ K⁺ ATPase, along with superoxide dismutase and catalase, which are responsible for the maintenance of clarity of the lens during oxidative stress.^[69] Most of them are reversible in nature. Radiation stimulates the senile changes in eye lenses. Radiation or electromagnetic waves can rouse the exfoliation process in lens that leads to disturbance in protein arrangement and oxidative systems. Experimental evidence indicates maximum lens sensitivity to UVR-B in the wavelength region around 300 nm.^[101,102] ROS are mediators of damage induced by UVR^[117] and can trigger alteration in growth factors- and cytokine-mediated signal transduction pathways, leading to aberrant gene expression.^[118]

Elimination of causes of cataract which were described above may reverse the cataractous changes in the initial stage. Nutritional supplements and balancing antioxidants during old age and malnutrition and in condition of diarrhea are reported in preventing senile cataract.^[119] Correction of transient metabolic defects e.g., treatment of galactosemia, copper metabolism etc., are also found useful in the prevention of cataract. Eluding factors affecting congenital defects like consanguineous marriage, galactosemic diet, medication and radiation during pregnancy can be helpful in preventing development of congenital cataract.^[120-122] Prescription of alternate medications for steroid and other drugs prone to cataract formation can be used to prevent cataractous changes.^[123] Many studies reported that antioxidants (Vit E, Vit C, thiamine, riboflavin, lutein, flavonoids, carotenoids etc.)^[28,124,125] can effectively prevent and cure UVB-induced protein oxidation and photo-peroxidation of lipids in lens. Local protective measures like use of UV-protected sun glasses as well as use of UV-absorbing hydrogel polymers also can be useful in this way.^[126] Though many of the factors identified are responsible for the development of cataract, but their mechanism of action is still unclear. There is much space to work in this direction.

Conclusion

Present review summarizes the various etiopathogenesis of cataract. Senile cataract due to aging is more common than other types of cataract. Apart from aging, various risk factors of cataract like: Nutritional inadequacy, metabolic and inherited defects, ultraviolet radiation, and smoking have been implicated as significant risk factors in development of cataract. Most of the risk factors are mingled with other factors and leads to unavoidable progression of the disease. It is today's need to categorize the causative factors according to the nature of cataract appropriately and incorporate with the diagnosis, which may be helpful in the treatment of cataract.

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Cite this article as: Gupta VB, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: An appraisal. *Indian J Ophthalmol* 2014;62:103-10.

Source of Support: Nil. **Conflict of Interest:** None declared.