

The triple classification of dry eye for practical clinical use

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ABSTRACT. *Clinicians need a practical classification to face diagnosis, prognosis, and treatment. Dry eyes have many etiologies and pathogenesis, different affection of the various dacryoglands and ocular surface epithelium, and diverse grades of severity. The specialists in xero-dacryology must know these three parameters to evaluate any case of dry eye, and to establish an adequate treatment. To facilitate this, an open session in the VIII congress of the International Society of Dacryology and Dry Eye (Madrid, April, 2005) proposed modifying the Triple Classification of Dry Eye approved in the XIV congress of the European Society of Ophthalmology (Madrid, June 2003). The following classification has been established: first, a classification of the etiopathogenesis, distributed in 10 groups: age-related, hormonal, pharmacologic, immunopathic, hyponutritional, dysgenic, infectious/inflammatory, traumatic, neurologic, and tantalic; second, a classification of the affected glands and tissues, which under the acronym of ALMEN includes the aqueo-serous deficient, lipo deficient, mucin deficient, and epitheliopathic dry eyes, and the non-dacryologic affected exocrine glands (i.e., saliva, nasal secretion, tracheo-pharyngeal secretion); third, a classification of severity, in three grades: grade 1 or mild (symptoms without slit lamp signs), grade 2 or moderate (symptoms with reversible signs), and grade 3 or severe (symptoms with permanent signs). (Eur J Ophthalmol 2005; 15: 660-7)*

KEY WORDS. *Dry eye, Tears, Triple Classification*

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INTRODUCTION

Dry eye is a lexicon in common use among scientists, patients, and the general population, which like any other word may have diverse, fluctuating, and changing meanings. The term dry eye is usually referred to a symptom, a sign, a syndrome, and many diseases. The scientific definition of the syndrome of the several diseases is that "dry eye is a disorder produced by the inadequate interrelation

between lacrimal film and ocular surface epithelium, caused by quantitative and qualitative deficits in one or both of them. It can be produced by one or combined etiologic causes, affect one or several of the secretions of the glands serving the ocular surface, and produce secondary manifestations of different grades of severity".

Dry eye is one of the most frequent ophthalmologic conditions. It can be produced by hundreds of causes. Dry eye diseases are almost always chronic, progressive,

and until the present incurable. Usually they produce mild or moderate manifestations, but in severe cases they provoke incapacitating discomfort and severe low vision. The prevalence of dry eye syndrome is not well established as it changes with sex, race, geography, epoch, socio-sanitary levels, age, and severity. By using the two last variables (severity and age) it is possible to calculate approximately that grade 1 is present in 1% of the population under 30 years, 20% between 30 and 60 years, and 100% over 60 years. Grade 2 is present in 0.1% of people under 30 years, 1% between 30 and 60 years, and 10% over 60 years. Grade 3 is present in 0.002% of persons under 30 years, 0.01% between 30 and 60 years, and 0.1% over 60 years. Women are usually more precociously affected than men.

The evolution of our knowledge on dry eye was at first slow, then it became quicker, and it is at present, vertiginous. The historical evolution can be divided into three eras: Hippocratic (from Hippocrates to the end of the 19th century), Sjögrenic (last years of the 19th century, and 20th century), and 21st century. The limits among these three periods are not precise and brusque, and the two connecting periods overlap in a progressive transition. These three periods correspond approximately with the knowledge and evidence of severe (classical xerophthalmia), moderate (keratitis punctata, keratopathia filamentosa, keratoconjunctivitis sicca), and mild dry eye (symptoms of dry eye without slit lamp signs).

During the transition years between Sjögrenic and 21st century periods many etiopathogenetic causes and combinations, glandular affectations, and severity manifestations of clinical combinations were discovered or became better known. It was evident that a classification for practical clinical use was necessary. Therefore, at the XIV Congress of the European Society of Ophthalmology, held in Madrid in June 2003, it was decided that one of the preferential tasks of xerodacryology was to make a classification for practical clinical use. It was presented, discussed, decided, and published as the Madrid Triple Classification of Dry Eye (1). Two years later the 8th Congress of the International Society of Dacryology and Dry Eye took place in Madrid, in April 2005, and it was decided to discuss and improve the previous classification. The results are reported in the present article.

When a clinician receives, examines, and determines the characteristics of any dry eye, he or she needs to know several characteristics throughout the anamnesis and examination in order to elaborate a diagnosis, prog-

nosis, and treatment. For practical clinical use, dry eye should be expressed by means of three parameters: etiopathogenesis, damaged exocrine glands and tissues, and severity.

Classification according to the etiopathogenesis

The many causes that can produce a clinical dry eye can be distributed for practical clinical use in 10 groups (Tab. I). The first five groups of this etiopathogenetic decalogue generally, but not always, affect many exocrine glands (lacrima, salivary, nasal, vaginal, etc.) because the damage is usually produced in cellular structures common to exocrine glands. The last five groups usually only affect the dacryoglands (aqueo-serous, lipid, mucinic), or even only some of them, or even only those of one eye.

Age-related. With aging, all cellular structures of the body undergo a progressive apoptotic process. This also affects all exocrine glands, and consequently there is presentation of a general dryness in the body, including the dacryoglands. The lacrimal secretion begins to diminish from the age of 30 years, but as there is an overabundance for the normal necessities, it is only noticed by people in situations of overexposure. The critical level between production and necessities is reached at about 45 years. Production decreases at about 60 years, when secretion becomes insufficient for the necessities of some normal situations. Many persons over 60 feel symptoms or signs of dry eye in circumstances such as late afternoon or at night when the circadian rhythm of tear production is lower, when working for a long time in front of a video display terminal (VDT) doing convergence in horizontality, when using contact lenses, or in drafts or dry environment, as tear evaporation leads to an increase in tear film osmolarity.

Age-related dry eye is usually multiexocrine (eye, mouth, nose, tracheo-pharynx, vagina, etc.). As to the severity, it is usually grade 1, but frequently reaches grade 2.

Hormonal. Lacrimal secretion is influenced by some endocrine gland activity, the most important of which are androgens, estrogens, and prolactin. Dry eye is frequently a hormone-related condition in cases of aging, castration, antiandrogenic treatment, hypoovarism, ovariectomy, climacteric, menopause, estrogenic contraceptives, and lactation. Other hormones, such as insulin and thyroxin/thyroxamine, have no consensus in the interpretation of their action on dry eye.

Hormonal dry eye is generally multiexocrinic. Aqueous and lipid secretions are the most affected. Severity usually reaches grades 1 or 2.

Pharmacologic. Some systemic medicines have a collateral exocrinic hyposecretory effect. Among them are antidepressants (fluoxetine, imipramine), anxiolytics (bromazepam, diazepam, clorazepate), sleeping pills (brotizolam, chloral hydrate, chlormethiazole), antiparkinsonians (biperiden, benztropine), diuretics (chlorthalidone, furosemide), vascular antihypertensives (chlorothiazide, clonidine), anticholinergics (atropine, metoclopramide), antihistaminics (dexchlorpheniramine, cetirizine), and antiarrhythmics (disopyramide, mexiletine). Some of these drugs are mainly taken by elderly or menopausal people, or at night, when they can aggravate the multiexocrinic dryness. Systemic pharmacologic dry eye is generally multiexocrinic, and is usually grade 1 or 2 severity.

Some topical collyria and ointments produce damage of the corneal epithelium, conjunctiva, or lid margin. Among these are some preservatives (benzalkonium chloride, thiomersal, chlorobutanol, EDTA), anesthetics (cocaine, tetracaine, proparacaine, lidocaine), and vitamin A derivatives (topical or systemic isotretinoin). The damage is usually restricted to the ocular surface and related structures when the application is local. Drug-induced adverse effects are far from being restricted to only allergic reactions and the long-term use of eye drops has consistently been reported to induce inflammatory ocular surface changes, causing progressive ocular discomfort upon instillation, tear film instability, corneal surface impairment, and subconjunctival fibrosis.

Immunopathic. Some autoimmune diseases can produce eye dryness by damaging the dacryoglands and/or ocular surface. There are several main groups of immunologic dry eyes: 1) those preferentially affecting the glands, as occurs with what were known until recently as primary Sjögren syndromes, in which vasculitis by immunocomplex deposits and pseudolymphomas and lymphomas are

sometimes associated; 2) those affecting the exocrine glands and the connective tissue as in rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma, etc., as occurs with what were also known until recently as secondary Sjögren's syndromes. Today it is preferable to use the expression "Sjögren syndrome associated with ...," in order not to confuse the many different varieties of Sjögren syndromes; 3) those where there is an autoimmune attack of the ectodermal and mesodermal tissues and the secondary destruction of non-attacked glands, as occurs in the mucus membrane pemphigoids, Lyell syndromes, Stevens-Johnson syndromes, and CREST syndrome; 4) those affecting other tissues, which secondarily can affect the exocrinic glands and ocular surface, such as the pluriglandular endocrine deficiencies or Schmidt's syndrome (thyroid and adrenal insufficiency).

Immunopathic dryness is usually multiexocrinic. It affects about 1% of the population. Sjögren's syndromes frequently reach grades 1 and 2, and occasionally, grade 3. But immunopathic dry eyes of group 3 frequently reach grade 3, with permanent ocular surface damage and sometimes definitive decreased visual acuity.

Hyponutritional. Hypovitaminosis A was the most frequent cause of severe xerophthalmia for millennia. It produces multiexocrinic dryness and other ophthalmic manifestations such as Bitot's spots in the conjunctival exposed trigoni, keratomalacia, blepharitis, and bad scotopic adaptation. It can be produced by severe hyponutrition or by a selective fat-free diet. It may also be due to the intestinal malabsorption associated with Crohn's disease, chronic alcoholism, and intestinal resection.

Lack of omega-3 essential polyunsaturated fatty acids (alpha-linolenic acid, EPA, and DHA) available from dark oily fish such as salmon, sardine, and tuna produces dry eye through mechanisms that are currently being explored.

Other controversial deficiencies with respect to their influence in dry eye are vitamins B₂, B₁₂, and C.

Xerophthalmia by hypovitaminosis A when treated in time retrogrades without producing sequelae, but if not treated in time, it may produce corneal blindness or even corneal melting.

Dysgenetic. In the evolution of the medical language genetic and congenital (from Greek *γενετικός*, birth) were applied for centuries to conditions presented at birth. They were due to hereditary parenteral transmission, or to intrauterine exposure to infections, toxins, traumas,

TABLE I - ETIOPATHOGENETIC CLASSIFICATION OF DRY EYE

Pan-exocrinic	Dacryo-exocrinic
1. Age related	6. Dysgenetic
2. Hormonal	7. Infectious/inflammatory
3. Pharmacologic	8. Traumatic
4. Immunopathic	9. Neurologic
5. Hyponutritional	10. Tantallic

mechanical factors, or unknown causes. When genes were discovered and understood in the 20th century, genetic also took a second meaning: expressed by anomalous genes (even when developed in the phenotype not at birth but in childhood, puberty, or later). In the future terminology it seems that genetic and genic will be reserved for hereditary diseases (expressed at birth or later on), and that congenital and connatal will be the ones appearing at birth (by gene diseases or by accidental occasional damage to the embryo or fetus). As the future terminology is not yet precise, in this classification we consider dysgenetic to include all genetic and congenital diseases.

Dysgenetic dry eye can affect one or several types of dacryoglands: aqueo-serous (alacrima, dysplasia ectodermica anhydrotica), lipid (epicanthus-blepharophimosis syndrome, keratopathy-ichthyosis-deafness syndrome, first branchial arc syndromes, dysplasia ectodermica anhydrotica), and mucinic (aniridia, Bietti syndrome), or the ocular surface epithelium (Meesmann dystrophy, Fleischer cornea verticillata, Franceschetti-Cogan microcystic dystrophy).

Infectious/inflammatory. Infection (from Latin *inficere*, filled with noxious corruption or germs) is today applied to the contamination of the body by harmful organisms. Inflammation (from Latin *flamma*, flame) had a classical definition recorded by Celsus in the 1st century: *tumor, rubor, calor, et dolor* (swelling, redness, heat, and pain). Usually inflammation was due to infection. For the last two centuries the term inflammation has been applied to mild conditions without some of those signs. As it has recently been discovered that proinflammatory mediators promoting reaction and healing are present in any corporal tissue damage, the name of inflammation may be applied to new meanings, which can result in confusion.

Infection/inflammation of the aqueo-serous dacryoglands (tuberculous, fungic) are at present very rare. Infection/inflammation of the lipid dacryoglands (blepharitis), both posterior (meibomitis) or anterior, usually have a causal or secondary infectious component. The abundance of cholesterol esters in normal meibomian secretion makes a good culture medium for microorganisms such as *Staphylococcus aureus* that produces lipases that denature the meibomian secretion and increase the evaporation of the aqueo-serous phase of the tears. About 10% of the tear of the lacrimal basin evaporates, and this rate increases in patients with blepharitis due to the lipid layer insufficiency of their lacrimal film.

Mucoadenitis of the conjunctiva (conjunctivitis) is highlighted by trachoma, herpes zoster, herpes simplex, and adenoviruses.

At present, aqueo-serous dacryoadenitis is very infrequent, conjunctivitis is in decreasing prevalence, but blepharitis is very frequent.

Traumatic. The traumatic damage of dacryoglands and ocular surface may be mechanical (surgical or accidental), chemical, or radiation induced. This damage to dacryoglands is produced accidentally or with therapeutic aims, and may affect the aqueo-serous glands (surgical ablation, tumor radiation), the lipid glands (lid wound, Mustardé lid reconstruction, Webster operation for distichiasis), the mucinic glands (chemical caustication, thermic destruction, conjunctivectomy), and the corneal epithelium (abrasion, caustication, limbal destruction).

Severity of traumatic dry eyes varies, depending on the causes, the affected tissues, and the intensity of the destruction.

Neurologic. Lacrimal secretion is very dependent on nervous stimulation. Its influence may be separated into three types: hypothalamic and limbic influences, afferent neurodeprivation, and efferent neurodeprivation.

Hypothalamic and limbic influences. Hypothalamus determines a circadian production of tear secretion that is at its maximum at morning and noon, diminishes at sunset, and reaches its minimum at night and when sleeping.

Limbic influences such as anxiety, tiredness, psychic influences, and somnolence diminish the basal tear secretion.

Afferent neurodeprivation. The afferent means of the reflex stimulation of tear secretion is due to lid and eye friction, environmental temperature, and intermittent changes of corneal thermometry when blinking, retinal light activation, trigeminal activity, etc. Therefore, ocular surface anesthesia due to herpetic keratitis, topical anesthetics abuse, corneal refractive surgery, corneal transplantation, and pre- and post-semilunar trigeminal damage diminishes lacrimal secretion.

Contact lenses, mainly hydrophilic and semipermeables, restrict the external stimuli. Lamellar refractive surgeries (mechanical keratotomy, femtosecond laser-assisted *in situ* keratomileusis, etc.) produce a moderate dry eye that is partially recoverable. The discomfort of eye dryness in persons with altered rapid eye movement (REM) sleep becomes worse, maybe because the objective of REM sleep is to stimulate tear secretion during prolonged sleep.

Efferent neurodeprivation. The efferent means of the reflex stimulation of tear secretion may be damaged in the pontobulbar nuclei (nucleus salivalis superior and lacrimalis) and their connections, nervus intermediarius and nervus facialis pregeniculi, nervus intermedius Wrisbergi, ganglion geniculi, nervus petrosus superficialis major, nervus canalis pterygoidei sive vidianus, ganglion pterygopalatinum Meckeli, nervus zygomaticus, ramus communicans cum nervo lacrimale, and nervus lacrimalis. This can be produced by different causes, such as trauma, tumors, and botulinic toxin infiltration, and may have various collateral manifestations such as neurotrophic keratitis, pregeniculate facial palsy, neuralgia, and crocodile tears.

Tantalic. Tantalos, son of Zeus and Pluto, offended the Olympic gods, and therefore was condemned to live in the Tartarus lake, but when he tried to drink, the water drew back. So, despite living in water, he suffered from thirst and dryness. Therefore, tantalic dry eyes are those that, despite having enough tears, have a dry ocular surface. There are three types of tantalic dry eyes: lid-eye incongruency, epitheliopathic, and evaporation.

Lid-eye incongruency. Lids cannot create, maintain, and reshape the lacrimal film onto the ocular surface because of lid palsy, ectropion, lagophthalmos, lid coloboma, exophthalmos, local protrusion by pterygium or dermoid cyst, blepharochalasis, conjunctivochalasis, antimongoloid lid fissure, or half-opened eye sleep.

Epitheliopathic. Corneal and conjunctival epithelium is hydrophobic. They need to increase their critical surface tension with a healthy surface covered with the appropriate mucins to make them dacryophilic, so that tear spreads over them forming a lacrimal film. Therefore, epithelial dystrophies, limbal deficiency, corneal conjunctivalization, keratitis-ichthyosis-deafness syndrome, rare cases of diabetic or hypoparathyroid endocrine keratitis, corneal caustications, corneal thesaurismosis, endothelial decompensation, and many other causes can produce a tantalic dry eye.

Evaporation due to environmental circumstances (and not to the patient's condition). Among these are excessive air conditioning, fans, electric fans, open car window, wind, running without spectacles, polluted air, or dry air.

The "Stingy taxi driver syndrome" includes dry eye and scurfy hair; it is caused by the taxi driver lowering his window for coolness, and the back passenger receives the draft on his/her head.

As an addendum to the decalogue of etiologic groups,

it must be explained that most of the dry eye conditions are multicausal, and sometimes the aggressiveness of one of them puts it in a prevalent position in diagnosis, clinical severity, and treatment. Each cause has its own evolutive characteristics: self-limited, permanent, progressive. Most causes will last for life. Only some of them are reversible in the present state of medicine, such as most pharmacologic causes, and incipient hyponutritional ones.

When the underlying etiopathogenesis is identified, it can sometimes be classified in different decalogic groups if etiology and pathogenesis are applied; for instance, traumatic damage of the pregeniculate nervus facialis is a traumatic and a neurodeprivative dry eye. Therefore, for descriptive purposes they may be classified in both groups.

Each classification of the Triple Classification of Dry Eye for a patient must be written in the patient's chart or the sheet for the Triple Classification of Dry Eye for the Clinical Record, which can be attached to the patient's chart, as seen in Table II.

Classification according to the damaged glands and tissues ("ALMEN" classification)

From a clinical point of view, and in order to establish a treatment, the etiologic classification must be completed with the evaluation of the participation of the different parts that form the lacrimal basin, i.e., the anatomic space between the ocular surface, posterior surface of the lids, and lid rim, where the mixture of the lacrimal sea is poured. These components of the tear may be simplified as produced by three basic types of dacryoglands — aqueo-serous, lipid, and mucinic — with an important component of the epithelium, mainly the corneal one. The affected parts of the lacrimal basin may be summarized in this histopathologic classification expressed with the acronym ALMEN, in which the A indicates the aqueo-serous deficiency; L, the lipid deficiency; M, the mucin deficiency; E, the epithelial deficiency; and N, the non-dacryologic exocrine deficiencies.

The **aqueo-serous deficiency** is basically produced by the damage of the main and accessory lacrimal glands. The aqueo-serous production may be measured by the Schirmer test, tear clearance, volumetry of the lacrimal menisci (cisterna and rivi lacrimales), lactoferrin, and other tests of controversial value but increasing efficacy. Some of these tests such as BUT (breakup time) or osmolarime-

darone thesaurismosis, stromal mucopolysaccharide deposits, Fuchs endo-epitheliopathy, and corneal endothelium decompensation. Secondary epitheliopathies produced by dry eye are those in which an aquo-serous, lipid, or mucinic deficiency due to any dysfunction of the dacryoglands damages the normal corneal epithelium, increasing the problem of the eye dryness.

The affected dacryogland may be initially of one, two, or of all types. It depends on the type of etiology. In any case, all dacryoglands and the lacrimal basin are usually finally implicated in a vicious circle that with different intensities affects all of them. For instance, an age-related dry eye produces directly and with a certain synchrony a general affection of all dacryoglands. But the extirpation or radiation of the main lacrimal gland initially only affects the aqueo-serous secretion, and little by little secondarily affects all other ocular surface dacryoglands and the epithelium of the ocular surface.

Ocular surface epitheliopathy is diagnosed by slit lamp-biomicroscopic signs, short BUT, punctate vital staining, cellular or secretory filaments, laboratory histopathologic tests such as impression cytology, or biochemical tests such as low mucins MUC1, MUC4, MUC16, or aquaporin AQP5. There is a steady advance in examination techniques.

The **non-ocular exocrine glands deficiencies** are an important orientation about etiology because they can indicate if it belongs to one of the multiexocrine conditions, such as age-related, hormonal, pharmacologic, or autoimmune. The more bothersome organs because of their objective or subjective dryness manifestation are as follows:

Mouth: oral cavity and lip dryness sensation, thirst, frequent linguo-labial humidification movements, dense saliva, bad breath (halitosis), taste dysfunction (dysgeusia), expulsion of saliva drops when speaking (sialo-lalopalassia), fungal stomatitis.

Nose: dryness sensation, dry nasal mucus, itching, impairment of the sense of smell (dysosmia, anosmia).

Throat: dryness sensation, thirst, need to clear the throat when talking, dense phlegm, dense sputum, hoarseness, change of voice or raucousness (dysphonia).

Skin: cutaneous dryness, axillary itching.

Vagina: pruritus, itching, painful coitus (dyspareunia), vaginitis sicca.

Seminal glands: dense ejaculation.

Ear: itching of the outer ear, earwax plugs.

These pluri-exocrine manifestations are not usually of synchronic presentation, and do not all reach the same clinical level. Frequently, the dryness of an exocrine sys-

tem does not usually correspond with the subjective sensation of the patient. So, a similar dryness in several exocrine body glands is usually first noticed in the eyes and mouth. Throat, nose, and vagina occupy an intermediate position, followed by skin and tracheo-bronchial tract. Dryness of ear, seminal glands, and intestinal tract are not usually noticed.

Classification according to the severity

The clinical symptoms and signs of the many millions of patients with dry eye can present with thousands of combinations related to etiologies, affected types of dacryoglands and ocular surface, and severity of the damage. In order to do a practical classification of severity capable of satisfying the clinician it has been decided to classify them into only three grades, attending the bases of the clinical examination, i.e., symptoms and signs: grade 1 or mild (symptoms without slit lamp signs); grade 2 or moderate (symptoms with reversible signs); or grade 3 or severe (symptoms with permanent signs).

Grade 1 or mild. Patients in this grade frequently have symptoms of ocular surface dryness in normal environmental circumstances: dryness sensation, itching, ocular tiredness, photophobia, photoinduced cough, momentarily blurry vision that improves with repeated blinking (BIVA: blinking-improved visual acuity), and fissural clonic blepharospasm.

No signs related to these symptoms can be seen when fentobiomicroscopically examined at the slit lamp. Fentobiomicroscopy is the basic or gold standard ocular surface examination used and interpreted by ophthalmologists. With any symptom there is always a sign that sometimes in present day medicine could be inferred or detected with analytical, electrophysiologic, or invasive tests, such as hyperosmolarity, hypolysozyme, or inflammatory cytokines. These non-slit lamp signs are excluded from grade 1 of this classification, which is done for practical clinical use.

In this grade 1 or mild dry eye, a previous initial period can be introduced with the name of grade 1-minus when these symptoms appear only under overexposure that in the same conditions do not produce symptoms in normal persons, i.e., wind, fan, open car window, air conditioning, polluted air, low environmental humidity, contact lens wear, or physical corporal tiredness. Usually, in this stage of grade 1-minus the patient is not aware that he or she has an incipient dry eye.

Grade 2 or moderate. The patient, besides more or less evident symptoms, has reversible slit lamp signs, such as epithelial erosion, keratopathia punctata, keratopathia filamentosa, short BUT, hyperemia of the exposed conjunctival trigoni, secretion sleep of the ocular surface, or marginal blepharitis.

Grade 3 or severe. The patient, besides the symptoms of ocular dryness, has signs that have evolved to permanent sequelae, such as corneal ulcers, nephelions and leukomas of the cornea, corneal neovascularization, squamous epithelial metaplasia, or retraction of the conjunctival folds of the lower cul-de-sac or of the lacunar sulci (the first between the nasal conjunctival trigonus and the plica semilunari, and the second between the plica semilunaris and the caruncula).

In this grade 3 or severe dry eye a grade 3-plus may be introduced when the keratinization, scarring, and lesions of the central cornea permanently reduce the visual acuity. The present one is a clinical classification, and the clinical situation and incapacity of the patient is very different from when the lesions are in the periphery or do not diminish the visual acuity than when they are in the center and do diminish visual acuity. For this reason grade 3 has been enriched with this more incapacitating grade 3-plus.

COMMENTS

To find a consensus in a medicine that is continuously changing and progressing is not easy. This classification has been made not only by collecting many opinions, but also by producing a classification of dry eye conditions for practical clinical use that allows diagnosis, prognosis, and treatment of patients with dry eye.

The authors have no commercial or proprietary interest in any aspect of the article.

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and until the present incurable. Usually they produce mild or moderate manifestations, but in severe cases they provoke incapacitating discomfort and severe low vision. The prevalence of dry eye syndrome is not well established as it changes with sex, race, geography, epoch, socio-sanitary levels, age, and severity. By using the two last variables (severity and age) it is possible to calculate approximately that grade 1 is present in 1% of the population under 30 years, 20% between 30 and 60 years, and 100% over 60 years. Grade 2 is present in 0.1% of people under 30 years, 1% between 30 and 60 years, and 10% over 60 years. Grade 3 is present in 0.002% of persons under 30 years, 0.01% between 30 and 60 years, and 0.1% over 60 years. Women are usually more precociously affected than men.

The evolution of our knowledge on dry eye was at first slow, then it became quicker, and it is at present, vertiginous. The historical evolution can be divided into three eras: Hippocratic (from Hippocrates to the end of the 19th century), Sjögrenic (last years of the 19th century, and 20th century), and 21st century. The limits among these three periods are not precise and brusque, and the two connecting periods overlap in a progressive transition. These three periods correspond approximately with the knowledge and evidence of severe (classical xerophthalmia), moderate (keratitis punctata, keratopathia filamentosa, keratoconjunctivitis sicca), and mild dry eye (symptoms of dry eye without slit lamp signs).

During the transition years between Sjögrenic and 21st century periods many etiopathogenetic causes and combinations, glandular affectations, and severity manifestations of clinical combinations were discovered or became better known. It was evident that a classification for practical clinical use was necessary. Therefore, at the XIV Congress of the European Society of Ophthalmology, held in Madrid in June 2003, it was decided that one of the preferential tasks of xerodacryology was to make a classification for practical clinical use. It was presented, discussed, decided, and published as the Madrid Triple Classification of Dry Eye (1). Two years later the 8th Congress of the International Society of Dacryology and Dry Eye took place in Madrid, in April 2005, and it was decided to discuss and improve the previous classification. The results are reported in the present article.

When a clinician receives, examines, and determines the characteristics of any dry eye, he or she needs to know several characteristics throughout the anamnesis and examination in order to elaborate a diagnosis, prog-

nosis, and treatment. For practical clinical use, dry eye should be expressed by means of three parameters: etiopathogenesis, damaged exocrine glands and tissues, and severity.

Classification according to the etiopathogenesis

The many causes that can produce a clinical dry eye can be distributed for practical clinical use in 10 groups (Tab. I). The first five groups of this etiopathogenetic decalogue generally, but not always, affect many exocrine glands (lacrima, salivary, nasal, vaginal, etc.) because the damage is usually produced in cellular structures common to exocrine glands. The last five groups usually only affect the dacryoglands (aqueo-serous, lipid, mucinic), or even only some of them, or even only those of one eye.

Age-related. With aging, all cellular structures of the body undergo a progressive apoptotic process. This also affects all exocrine glands, and consequently there is presentation of a general dryness in the body, including the dacryoglands. The lacrimal secretion begins to diminish from the age of 30 years, but as there is an overabundance for the normal necessities, it is only noticed by people in situations of overexposure. The critical level between production and necessities is reached at about 45 years. Production decreases at about 60 years, when secretion becomes insufficient for the necessities of some normal situations. Many persons over 60 feel symptoms or signs of dry eye in circumstances such as late afternoon or at night when the circadian rhythm of tear production is lower, when working for a long time in front of a video display terminal (VDT) doing convergence in horizontality, when using contact lenses, or in drafts or dry environment, as tear evaporation leads to an increase in tear film osmolarity.

Age-related dry eye is usually multiexocrine (eye, mouth, nose, tracheo-pharynx, vagina, etc.). As to the severity, it is usually grade 1, but frequently reaches grade 2.

Hormonal. Lacrimal secretion is influenced by some endocrine gland activity, the most important of which are androgens, estrogens, and prolactin. Dry eye is frequently a hormone-related condition in cases of aging, castration, antiandrogenic treatment, hypoovarism, ovariectomy, climacteric, menopause, estrogenic contraceptives, and lactation. Other hormones, such as insulin and thyroxin/thyroxamine, have no consensus in the interpretation of their action on dry eye.

Hormonal dry eye is generally multiexocrinic. Aqueous and lipid secretions are the most affected. Severity usually reaches grades 1 or 2.

Pharmacologic. Some systemic medicines have a collateral exocrinic hyposecretory effect. Among them are antidepressants (fluoxetine, imipramine), anxiolytics (bromazepam, diazepam, clorazepate), sleeping pills (brotizolam, chloral hydrate, chlormethiazole), antiparkinsonians (biperiden, benztropine), diuretics (chlorthalidone, furosemide), vascular antihypertensives (chlorothiazide, clonidine), anticholinergics (atropine, metoclopramide), antihistaminics (dexchlorpheniramine, cetirizine), and antiarrhythmics (disopyramide, mexiletine). Some of these drugs are mainly taken by elderly or menopausal people, or at night, when they can aggravate the multiexocrinic dryness. Systemic pharmacologic dry eye is generally multiexocrinic, and is usually grade 1 or 2 severity.

Some topical collyria and ointments produce damage of the corneal epithelium, conjunctiva, or lid margin. Among these are some preservatives (benzalkonium chloride, thiomersal, chlorobutanol, EDTA), anesthetics (cocaine, tetracaine, proparacaine, lidocaine), and vitamin A derivatives (topical or systemic isotretinoin). The damage is usually restricted to the ocular surface and related structures when the application is local. Drug-induced adverse effects are far from being restricted to only allergic reactions and the long-term use of eye drops has consistently been reported to induce inflammatory ocular surface changes, causing progressive ocular discomfort upon instillation, tear film instability, corneal surface impairment, and subconjunctival fibrosis.

Immunopathic. Some autoimmune diseases can produce eye dryness by damaging the dacryoglands and/or ocular surface. There are several main groups of immunologic dry eyes: 1) those preferentially affecting the glands, as occurs with what were known until recently as primary Sjögren syndromes, in which vasculitis by immunocomplex deposits and pseudolymphomas and lymphomas are

sometimes associated; 2) those affecting the exocrine glands and the connective tissue as in rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma, etc., as occurs with what were also known until recently as secondary Sjögren's syndromes. Today it is preferable to use the expression "Sjögren syndrome associated with ...," in order not to confuse the many different varieties of Sjögren syndromes; 3) those where there is an autoimmune attack of the ectodermal and mesodermal tissues and the secondary destruction of non-attacked glands, as occurs in the mucus membrane pemphigoids, Lyell syndromes, Stevens-Johnson syndromes, and CREST syndrome; 4) those affecting other tissues, which secondarily can affect the exocrinic glands and ocular surface, such as the pluriglandular endocrine deficiencies or Schmidt's syndrome (thyroid and adrenal insufficiency).

Immunopathic dryness is usually multiexocrinic. It affects about 1% of the population. Sjögren's syndromes frequently reach grades 1 and 2, and occasionally, grade 3. But immunopathic dry eyes of group 3 frequently reach grade 3, with permanent ocular surface damage and sometimes definitive decreased visual acuity.

Hyponutritional. Hypovitaminosis A was the most frequent cause of severe xerophthalmia for millennia. It produces multiexocrinic dryness and other ophthalmic manifestations such as Bitot's spots in the conjunctival exposed trigoni, keratomalacia, blepharitis, and bad scotopic adaptation. It can be produced by severe hyponutrition or by a selective fat-free diet. It may also be due to the intestinal malabsorption associated with Crohn's disease, chronic alcoholism, and intestinal resection.

Lack of omega-3 essential polyunsaturated fatty acids (alpha-linolenic acid, EPA, and DHA) available from dark oily fish such as salmon, sardine, and tuna produces dry eye through mechanisms that are currently being explored.

Other controversial deficiencies with respect to their influence in dry eye are vitamins B₂, B₁₂, and C.

Xerophthalmia by hypovitaminosis A when treated in time retrogrades without producing sequelae, but if not treated in time, it may produce corneal blindness or even corneal melting.

Dysgenetic. In the evolution of the medical language genetic and congenital (from Greek *γενετικός*, birth) were applied for centuries to conditions presented at birth. They were due to hereditary parenteral transmission, or to intrauterine exposure to infections, toxins, traumas,

TABLE I - ETIOPATHOGENETIC CLASSIFICATION OF DRY EYE

Pan-exocrinic	Dacryo-exocrinic
1. Age related	6. Dysgenetic
2. Hormonal	7. Infectious/inflammatory
3. Pharmacologic	8. Traumatic
4. Immunopathic	9. Neurologic
5. Hyponutritional	10. Tantallic

mechanical factors, or unknown causes. When genes were discovered and understood in the 20th century, genetic also took a second meaning: expressed by anomalous genes (even when developed in the phenotype not at birth but in childhood, puberty, or later). In the future terminology it seems that genetic and genic will be reserved for hereditary diseases (expressed at birth or later on), and that congenital and connatal will be the ones appearing at birth (by gene diseases or by accidental occasional damage to the embryo or fetus). As the future terminology is not yet precise, in this classification we consider dysgenetic to include all genetic and congenital diseases.

Dysgenetic dry eye can affect one or several types of dacryoglands: aqueo-serous (alacrima, dysplasia ectodermica anhydrotica), lipid (epicanthus-blepharophimosis syndrome, keratopathy-ichthyosis-deafness syndrome, first branchial arc syndromes, dysplasia ectodermica anhydrotica), and mucinic (aniridia, Bietti syndrome), or the ocular surface epithelium (Meesmann dystrophy, Fleischer cornea verticillata, Franceschetti-Cogan microcystic dystrophy).

Infectious/inflammatory. Infection (from Latin *inficere*, filled with noxious corruption or germs) is today applied to the contamination of the body by harmful organisms. Inflammation (from Latin *flamma*, flame) had a classical definition recorded by Celsus in the 1st century: *tumor, rubor, calor, et dolor* (swelling, redness, heat, and pain). Usually inflammation was due to infection. For the last two centuries the term inflammation has been applied to mild conditions without some of those signs. As it has recently been discovered that proinflammatory mediators promoting reaction and healing are present in any corporal tissue damage, the name of inflammation may be applied to new meanings, which can result in confusion.

Infection/inflammation of the aqueo-serous dacryoglands (tuberculous, fungic) are at present very rare. Infection/inflammation of the lipid dacryoglands (blepharitis), both posterior (meibomitis) or anterior, usually have a causal or secondary infectious component. The abundance of cholesterol esters in normal meibomian secretion makes a good culture medium for microorganisms such as *Staphylococcus aureus* that produces lipases that denature the meibomian secretion and increase the evaporation of the aqueo-serous phase of the tears. About 10% of the tear of the lacrimal basin evaporates, and this rate increases in patients with blepharitis due to the lipid layer insufficiency of their lacrimal film.

Mucoadenitis of the conjunctiva (conjunctivitis) is highlighted by trachoma, herpes zoster, herpes simplex, and adenoviruses.

At present, aqueo-serous dacryoadenitis is very infrequent, conjunctivitis is in decreasing prevalence, but blepharitis is very frequent.

Traumatic. The traumatic damage of dacryoglands and ocular surface may be mechanical (surgical or accidental), chemical, or radiation induced. This damage to dacryoglands is produced accidentally or with therapeutic aims, and may affect the aqueo-serous glands (surgical ablation, tumor radiation), the lipid glands (lid wound, Mustardé lid reconstruction, Webster operation for distichiasis), the mucinic glands (chemical caustication, thermic destruction, conjunctivectomy), and the corneal epithelium (abrasion, caustication, limbal destruction).

Severity of traumatic dry eyes varies, depending on the causes, the affected tissues, and the intensity of the destruction.

Neurologic. Lacrimal secretion is very dependent on nervous stimulation. Its influence may be separated into three types: hypothalamic and limbic influences, afferent neurodeprivation, and efferent neurodeprivation.

Hypothalamic and limbic influences. Hypothalamus determines a circadian production of tear secretion that is at its maximum at morning and noon, diminishes at sunset, and reaches its minimum at night and when sleeping.

Limbic influences such as anxiety, tiredness, psychic influences, and somnolence diminish the basal tear secretion.

Afferent neurodeprivation. The afferent means of the reflex stimulation of tear secretion is due to lid and eye friction, environmental temperature, and intermittent changes of corneal thermometry when blinking, retinal light activation, trigeminal activity, etc. Therefore, ocular surface anesthesia due to herpetic keratitis, topical anesthetics abuse, corneal refractive surgery, corneal transplantation, and pre- and post-semilunar trigeminal damage diminishes lacrimal secretion.

Contact lenses, mainly hydrophilic and semipermeables, restrict the external stimuli. Lamellar refractive surgeries (mechanical keratotomy, femtosecond laser-assisted *in situ* keratomileusis, etc.) produce a moderate dry eye that is partially recoverable. The discomfort of eye dryness in persons with altered rapid eye movement (REM) sleep becomes worse, maybe because the objective of REM sleep is to stimulate tear secretion during prolonged sleep.

Efferent neurodeprivation. The efferent means of the reflex stimulation of tear secretion may be damaged in the pontobulbar nuclei (nucleus salivialis superior and lacrimalis) and their connections, nervus intermediarius and nervus facialis pregeniculi, nervus intermedius Wrisbergi, ganglion geniculi, nervus petrosus superficialis major, nervus canalis pterygoidei sive vidianus, ganglion pterygopalatinum Meckeli, nervus zygomaticus, ramus communicans cum nervo lacrimale, and nervus lacrimalis. This can be produced by different causes, such as trauma, tumors, and botulinic toxin infiltration, and may have various collateral manifestations such as neurotrophic keratitis, pregeniculate facial palsy, neuralgia, and crocodile tears.

Tantalic. Tantalos, son of Zeus and Pluto, offended the Olympic gods, and therefore was condemned to live in the Tartarus lake, but when he tried to drink, the water drew back. So, despite living in water, he suffered from thirst and dryness. Therefore, tantalic dry eyes are those that, despite having enough tears, have a dry ocular surface. There are three types of tantalic dry eyes: lid-eye incongruency, epitheliopathic, and evaporation.

Lid-eye incongruency. Lids cannot create, maintain, and reshape the lacrimal film onto the ocular surface because of lid palsy, ectropion, lagophthalmos, lid coloboma, exophthalmos, local protrusion by pterygium or dermoid cyst, blepharochalasis, conjunctivochalasis, antimongoloid lid fissure, or half-opened eye sleep.

Epitheliopathic. Corneal and conjunctival epithelium is hydrophobic. They need to increase their critical surface tension with a healthy surface covered with the appropriate mucins to make them dacryophilic, so that tear spreads over them forming a lacrimal film. Therefore, epithelial dystrophies, limbal deficiency, corneal conjunctivalization, keratitis-ichthyosis-deafness syndrome, rare cases of diabetic or hypoparathyroid endocrine keratitis, corneal caustications, corneal thesaurismosis, endothelial decompensation, and many other causes can produce a tantalic dry eye.

Evaporation due to environmental circumstances (and not to the patient's condition). Among these are excessive air conditioning, fans, electric fans, open car window, wind, running without spectacles, polluted air, or dry air.

The "Stingy taxi driver syndrome" includes dry eye and scurfy hair; it is caused by the taxi driver lowering his window for coolness, and the back passenger receives the draft on his/her head.

As an addendum to the decalogue of etiologic groups,

it must be explained that most of the dry eye conditions are multicausal, and sometimes the aggressiveness of one of them puts it in a prevalent position in diagnosis, clinical severity, and treatment. Each cause has its own evolutive characteristics: self-limited, permanent, progressive. Most causes will last for life. Only some of them are reversible in the present state of medicine, such as most pharmacologic causes, and incipient hyponutritional ones.

When the underlying etiopathogenesis is identified, it can sometimes be classified in different decalogic groups if etiology and pathogenesis are applied; for instance, traumatic damage of the pregeniculate nervus facialis is a traumatic and a neurodeprivative dry eye. Therefore, for descriptive purposes they may be classified in both groups.

Each classification of the Triple Classification of Dry Eye for a patient must be written in the patient's chart or the sheet for the Triple Classification of Dry Eye for the Clinical Record, which can be attached to the patient's chart, as seen in Table II.

Classification according to the damaged glands and tissues ("ALMEN" classification)

From a clinical point of view, and in order to establish a treatment, the etiologic classification must be completed with the evaluation of the participation of the different parts that form the lacrimal basin, i.e., the anatomic space between the ocular surface, posterior surface of the lids, and lid rim, where the mixture of the lacrimal sea is poured. These components of the tear may be simplified as produced by three basic types of dacryoglands — aqueo-serous, lipid, and mucinic — with an important component of the epithelium, mainly the corneal one. The affected parts of the lacrimal basin may be summarized in this histopathologic classification expressed with the acronym ALMEN, in which the A indicates the aqueo-serous deficiency; L, the lipid deficiency; M, the mucin deficiency; E, the epithelial deficiency; and N, the non-dacryologic exocrine deficiencies.

The **aqueo-serous deficiency** is basically produced by the damage of the main and accessory lacrimal glands. The aqueo-serous production may be measured by the Schirmer test, tear clearance, volumetry of the lacrimal menisci (cisterna and rivi lacrimales), lactoferrin, and other tests of controversial value but increasing efficacy. Some of these tests such as BUT (breakup time) or osmolarime-

darone thesaurismosis, stromal mucopolysaccharide deposits, Fuchs endo-epitheliopathy, and corneal endothelium decompensation. Secondary epitheliopathies produced by dry eye are those in which an aquo-serous, lipid, or mucinic deficiency due to any dysfunction of the dacryoglands damages the normal corneal epithelium, increasing the problem of the eye dryness.

The affected dacryogland may be initially of one, two, or of all types. It depends on the type of etiology. In any case, all dacryoglands and the lacrimal basin are usually finally implicated in a vicious circle that with different intensities affects all of them. For instance, an age-related dry eye produces directly and with a certain synchrony a general affection of all dacryoglands. But the extirpation or radiation of the main lacrimal gland initially only affects the aqueo-serous secretion, and little by little secondarily affects all other ocular surface dacryoglands and the epithelium of the ocular surface.

Ocular surface epitheliopathy is diagnosed by slit lamp-biomicroscopic signs, short BUT, punctate vital staining, cellular or secretory filaments, laboratory histopathologic tests such as impression cytology, or biochemical tests such as low mucins MUC1, MUC4, MUC16, or aquaporin AQP5. There is a steady advance in examination techniques.

The **non-ocular exocrine glands deficiencies** are an important orientation about etiology because they can indicate if it belongs to one of the multiexocrine conditions, such as age-related, hormonal, pharmacologic, or autoimmune. The more bothersome organs because of their objective or subjective dryness manifestation are as follows:

Mouth: oral cavity and lip dryness sensation, thirst, frequent linguo-labial humidification movements, dense saliva, bad breath (halitosis), taste dysfunction (dysgeusia), expulsion of saliva drops when speaking (sialo-lalopalassia), fungal stomatitis.

Nose: dryness sensation, dry nasal mucus, itching, impairment of the sense of smell (dysosmia, anosmia).

Throat: dryness sensation, thirst, need to clear the throat when talking, dense phlegm, dense sputum, hoarseness, change of voice or raucousness (dysphonia).

Skin: cutaneous dryness, axillary itching.

Vagina: pruritus, itching, painful coitus (dyspareunia), vaginitis sicca.

Seminal glands: dense ejaculation.

Ear: itching of the outer ear, earwax plugs.

These pluri-exocrine manifestations are not usually of synchronic presentation, and do not all reach the same clinical level. Frequently, the dryness of an exocrine sys-

tem does not usually correspond with the subjective sensation of the patient. So, a similar dryness in several exocrine body glands is usually first noticed in the eyes and mouth. Throat, nose, and vagina occupy an intermediate position, followed by skin and tracheo-bronchial tract. Dryness of ear, seminal glands, and intestinal tract are not usually noticed.

Classification according to the severity

The clinical symptoms and signs of the many millions of patients with dry eye can present with thousands of combinations related to etiologies, affected types of dacryoglands and ocular surface, and severity of the damage. In order to do a practical classification of severity capable of satisfying the clinician it has been decided to classify them into only three grades, attending the bases of the clinical examination, i.e., symptoms and signs: grade 1 or mild (symptoms without slit lamp signs); grade 2 or moderate (symptoms with reversible signs); or grade 3 or severe (symptoms with permanent signs).

Grade 1 or mild. Patients in this grade frequently have symptoms of ocular surface dryness in normal environmental circumstances: dryness sensation, itching, ocular tiredness, photophobia, photoinduced cough, momentarily blurry vision that improves with repeated blinking (BIVA: blinking-improved visual acuity), and fissural clonic blepharospasm.

No signs related to these symptoms can be seen when fentobiomicroscopically examined at the slit lamp. Fentobiomicroscopy is the basic or gold standard ocular surface examination used and interpreted by ophthalmologists. With any symptom there is always a sign that sometimes in present day medicine could be inferred or detected with analytical, electrophysiologic, or invasive tests, such as hyperosmolarity, hypolysozyme, or inflammatory cytokines. These non-slit lamp signs are excluded from grade 1 of this classification, which is done for practical clinical use.

In this grade 1 or mild dry eye, a previous initial period can be introduced with the name of grade 1-minus when these symptoms appear only under overexposure that in the same conditions do not produce symptoms in normal persons, i.e., wind, fan, open car window, air conditioning, polluted air, low environmental humidity, contact lens wear, or physical corporal tiredness. Usually, in this stage of grade 1-minus the patient is not aware that he or she has an incipient dry eye.

Grade 2 or moderate. The patient, besides more or less evident symptoms, has reversible slit lamp signs, such as epithelial erosion, keratopathia punctata, keratopathia filamentosa, short BUT, hyperemia of the exposed conjunctival trigoni, secretion sleep of the ocular surface, or marginal blepharitis.

Grade 3 or severe. The patient, besides the symptoms of ocular dryness, has signs that have evolved to permanent sequelae, such as corneal ulcers, nephelions and leukomas of the cornea, corneal neovascularization, squamous epithelial metaplasia, or retraction of the conjunctival folds of the lower cul-de-sac or of the lacunar sulci (the first between the nasal conjunctival trigonus and the plica semilunari, and the second between the plica semilunaris and the caruncula).

In this grade 3 or severe dry eye a grade 3-plus may be introduced when the keratinization, scarring, and lesions of the central cornea permanently reduce the visual acuity. The present one is a clinical classification, and the clinical situation and incapacity of the patient is very different from when the lesions are in the periphery or do not diminish the visual acuity than when they are in the center and do diminish visual acuity. For this reason grade 3 has been enriched with this more incapacitating grade 3-plus.

COMMENTS

To find a consensus in a medicine that is continuously changing and progressing is not easy. This classification has been made not only by collecting many opinions, but also by producing a classification of dry eye conditions for practical clinical use that allows diagnosis, prognosis, and treatment of patients with dry eye.

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