OCULAR MUCOUS MEMBRANE PEMPHIGOID

(sometimes called Ocular Cicatricial Pemphigoid or OCP)

A detailed explanation of what we know about the disease

Web version 21_4_21

This leaflet is designed for patients, as well as their relatives, friends and carers, to help explain Ocular Mucous Membrane Pemphigoid (or Ocular Cicatricial Pemphigoid). This explanation is more detailed than the one on the Moorfields Eye Hospital website and the content may be too much for new patients. We hope it will be helpful to existing patients

What is Ocular Mucous Membrane Pemphigoid (OMMP)?

Mucous Membrane Pemphigoid (MMP) is an autoimmune disease (a group of diseases caused by the reaction of the person's immune system to produce antibodies - called autoantibodies - against normally healthy body substances) which affects the skin and mucous membranes (the soft wet tissue lining the body openings including eyes, mouth, throat, genitals and back passage). When the eyes are affected, it is called ocular MMP (OMMP).

What causes MMP?

The cause of MMP is not clearly understood. You can't "catch" it from someone else and it isn't due to allergies or diet. It is not an inherited disease although it is known to have a genetic predisposition; because this predisposition is common in the general population it only plays a minor role in the development of the disease. The disease is rarely associated with cancers when it is called paraneoplastic pemphigoid. Pemphigoid autoantibodies can be identified in most patients with disease at non-ocular sites but less often in patients with disease restricted to the eye. The autoantibodies are directed at the subsurface layer (basement membrane) of the mucous membranes and, in some cases, of the skin causing inflammation and ulceration or blistering which lead to scarring.

How common is MMP?

MMP is a rare disease and its manifestation in the eyes is even more unusual. This also contributes to the difficulty of obtaining a swift and accurate diagnosis. About 1 new patient will develop the disease per million population per year in Western Europe with about 25 per million living with the disease at any one time. In the UK there are about 50 new cases of ocular MMP diagnosed each year.

What age groups are affected?

It usually affects people over 40 of both sexes but it has been diagnosed in younger adults and, rarely, in children.

What are the older names for MMP?

Another older term for the disease was "Benign MMP"; so called because it rarely caused death in the past, unlike Pemphigus which was often fatal before the development of

modern treatments which started in the 1950's. When the eyes have been affected the conjunctiva (the mucous membrane lining the eyelids and the surface of the white of the eye) always scars (cicatrises); for this reason the eye component of the disease has been called Ocular Cicatricial Pemphigoid (OCP) in the past instead of the currently agreed terminology of OMMP.

Which body sites are affected?

Although MMP can affect the skin it is only diagnosed when mucous membranes are involved. The mucous membranes targeted by the disease, for reasons that are not understood, are those at our orifices; mouth, eyes, nose, throat, genitals, anus and less often the tracheal region and oesophagus. MMP rarely affects all of these sites in any one person, more often 1-3 sites are involved in 95% of individuals. The most commonly affected site is the mouth (gums and oral mucosa) followed by the eyes, then the nose and throat followed by other sites. When the eyes are affected both are usually involved. Some diseases, previously thought to be distinct from MMP, have recently been re-classified as MMP variants; these include mucosal dominated epidermolysis bullosa acquisita, linear IgA disease and anti-laminin 332 (formerly anti-epiligrin or anti-laminin 5) pemphigoid.

How would I know if I had MMP?

In the eyes the disease starts as a conjunctivitis which may be mild and intermittent or severe and persistent. The conjunctivitis (meaning any cause of red, painful and sticky eyes) does not respond to antibiotics or eye drops and can create a lot of pain and irritation. Although scarring in the conjunctiva occurs early it can be difficult to see with the naked eye until the disease is quite advanced.

As the inflammation and scarring progress, it can also cause the pocket between the eyelids and eyeball (the conjunctival fornix) to reduce in depth which may show as a droopy lid or as a smaller gap between the lids.

The eyelids may turn in and the eyelashes begin to scratch the surface of your eye. This is called trichiasis.

The tear ducts can also be affected by scarring and inflammation, causing the eyes to be dry.

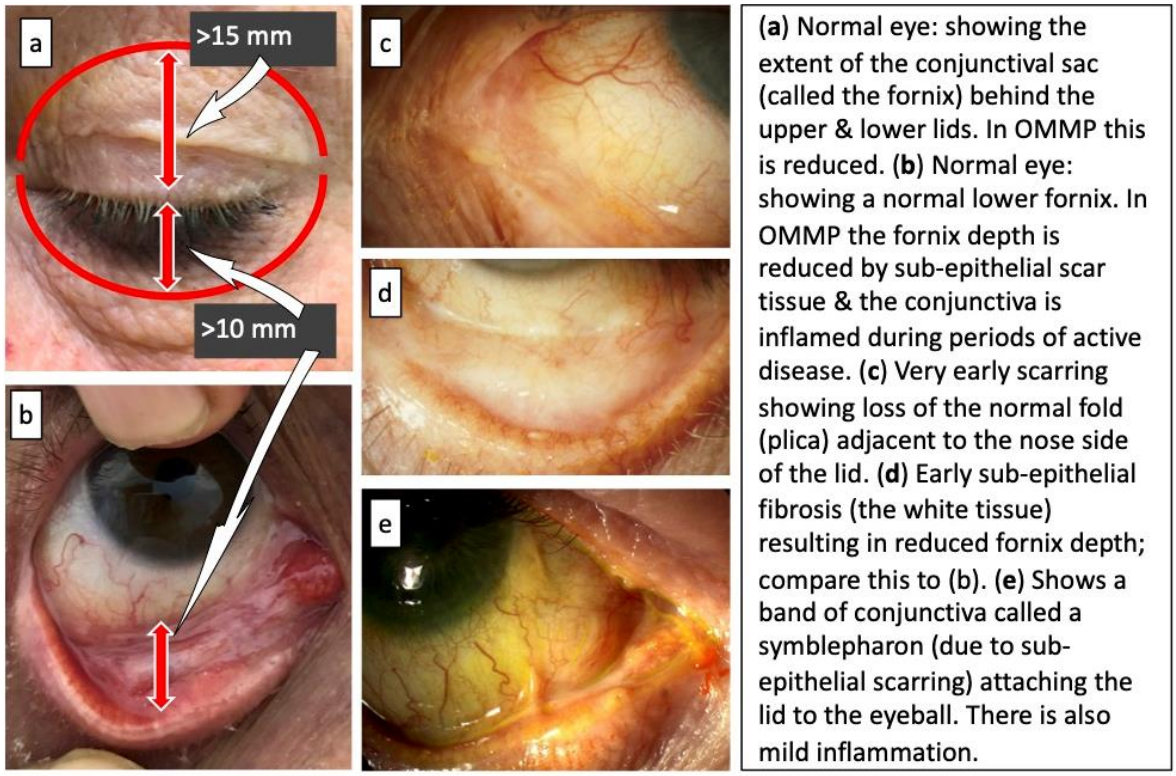
What is know about the effects and mechanisms of this disease?

Currently there is reasonable evidence for the role of pemphigoid autoantibodies in the precipitation of the inflammation which underlies the effects of the disease resulting, at some sites, in ulceration and or scarring. The autoantibodies are directed at the epithelial basement membrane of the mucous membrane(s) and sometimes skin. The epithelial basement membrane is a very thin (measured in microns) structure made of proteins which has the function of attaching the thin surface layer of epithelium to the underlying support tissues which include blood and lymph vessels. When the antibodies attach to the basement membrane proteins this attachment triggers the inflammatory process. The latter is designed to protect the body against foreign proteins, such as those of bacteria, but which in the case of autoantibodies results in a misdirected "attack" against one's own tissues. Given that autoantibodies can be difficult or impossible to detect in MMP and that even when present only limited sites are affected It is also probable that cellular immune

responses are important in the both the modulation of the disease process and its cause although the evidence for this is limited at present. Inflammation is usual at all sites affected by MMP and causes pain, as does ulceration, although the development of ulceration and scarring varies from site to site. For example, ulceration is common in the mouth but infrequent in the eyes whereas scarring is infrequent in the mouth but a hallmark of eye disease. Scarring in itself does not cause pain but the effects of scarring may result in loss of function such as difficulty swallowing and speaking, or lead to ingrowing eyelashes and loss of tear production.

How does this disease process affect the eyes?

In the eyes the disease results in inflammation (conjunctivitis) and scarring of the conjunctiva. The illustration shows the conjunctiva which is the thin membrane (0.25 mm which equals 250 microns) that covers both the white of the eyeball and which extends into the sacs (fornices) behind the lids (a) and (b) and which lines the back surface of the eyelids to the lash margin (b). Conjunctival scarring occurs in the thin layer (basement membrane) behind the surface epithelium and is called sub-epithelial fibrosis resulting in contraction (shortening) of this large area of thin lining tissue. This scarring and contraction causes loss of the fold of conjunctiva adjacent to the nose (c) and shortening of the fornices (d) followed by the formation of bands of tissue between the eyeball and eyelid called symblepharon (e). In more advanced cases this process results in the loss of all of the conjunctival tissue between the eyeball and eyelid, so that the two appear to have stuck together.



(**a**) Normal eye: showing the extent of the conjunctival sac (called the fornix) behind the upper & lower lids. In OMMP this is reduced. (**b**) Normal eye: showing a normal lower fornix. In OMMP the fornix depth is reduced by sub-epithelial scar tissue & the conjunctiva is inflamed during periods of active disease. (**c**) Very early scarring showing loss of the normal fold (plica) adjacent to the nose side of the lid. (**d**) Early sub-epithelial fibrosis (the white tissue) resulting in reduced fornix depth; compare this to (b). (**e**) Shows a band of conjunctiva called a symblepharon (due to sub-epithelial scarring) attaching the lid to the eyeball. There is also mild inflammation.

The shortening of the conjunctiva on the back surface of the lid may also cause the eyelid(s) to turn inward (called entropion) which often results in the lashes rubbing on the surface of the eye (called trichiasis). The conjunctival scarring may also cause damage to the accessory lacrimal (tear) glands in the conjunctiva, the mucous producing cells, and the very fine ducts

that bring the tears from the lacrimal gland (situated under the outer end of the upper eyelid and eye socket) causing a dry eye.

Ocular MMP progresses at different rates in different patients, a small proportion get a rapid onset of severe inflammation and scarring which can lead to blindness in months whereas in most patients the inflammation is initially mild and/or intermittent resulting in a slower onset over years. In both groups the lack of appropriate treatment can cause severe visual debility or even blindness. Diagnosis and appropriate treatment at this stage can largely prevent or greatly slow down disease progression. Correct diagnosis, as early as possible, is important for the reasons outlined below.

How is OMMP Diagnosed?

MMP is a rare disease, and its manifestation in the eyes even more unusual it is often not the first consideration when a physician is trying to find a diagnosis.

For patients with MMP already diagnosed at other sites: when MMP is already diagnosed at other sites, such as the mouth or nose, then disease is relatively easy to confirm or exclude in the eyes. This is because the disease at the non-ocular sites more often tests positive (in biopsies and blood) than when MMP is limited to the eyes. In patients, with known MMP at non ocular sites, any eye inflammation (conjunctivitis) or any of the early signs of scarring (as in the illustration) must be assumed to be caused by ocular MMP. All patients with MMP at other sites should be referred to an ophthalmologist, whether or not they have these symptoms and signs of eye disease, for an eye examination because early signs of ocular MMP may be present without symptoms. If there are signs of inflammation or scarring needing treatment there is no requirement for further tests on the eyes to make the diagnosis of ocular MMP, providing the tests at any other sites have confirmed that MMP is present and that the eye signs are typical. However, the ophthalmologist may want the results of additional eye biopsies, or other investigations, to exclude other diseases that can co-exist with MMP or be confused with it.

For those patients with possible ocular MMP and no involvement of other sites the path to diagnosis may be more difficult. There are over 20 causes of conjunctival inflammation and scarring although, in the UK, MMP is the most common of these. In addition, the majority of the other causes are associated with easily identified diseases with the exception of surface tumours (usually affecting only one eye whereas MMP usually affects both), sarcoidosis and other autoimmune bullous diseases; the latter may very rarely show up in the eye before developing at other sites. Diagnosis requires one or two small (2-3 mm) biopsies taken from conjunctiva, often from the loose conjunctival tissue on the ball of the eye under the upper lid, using local anaesthetic eye drops, together with blood tests. It is optimal to take an additional biopsy from another site, even though there are no symptoms at that site, usually the mouth mucosa or the skin because these sites may test positive when the ocular samples test false negative. The eye biopsies are processed for both the direct immunofluorescence test (as are the biopsies from the apparently uninvolved sites) and for routine histopathology to exclude other potential causes of the inflammation and scarring. Blood is taken to detect pemphigoid antibodies using a variety of tests.

Why may it be difficult to make a diagnosis?

When MMP affects the eye, with no other sites of involvement, the tests described above, that have been considered necessary for diagnosis, are negative in about 50% of cases. This has caused a lot of problems for ocular MMP patients because effective treatment for ocular MMP requires quite different treatment than that for the other causes of scarring conjunctivitis for which the standard of care is local treatment, often with steroid eyedrops. Unfortunately, local steroid eyedrops are not very effective at controlling the inflammation in ocular MMP and do not prevent the progression of the conjunctival scarring, both of which usually require oral, or intravenous, anti-inflammatory medication.

What should I do if my tests are negative?

It is now increasingly accepted by specialists in MMP that in ocular MMP, particularly when no other sites are involved by MMP, that a diagnosis does not require positive test results but can be made both after the tests have been used to exclude the other potential causes and using clinical findings. This information is in the latest publications and has been incorporated into a European Academy of Dermatology and Venereology Guideline that is to be published in 2021. Your specialist should be told about this if you think you may have MMP affecting the eyes.

Why are my eyes so painful?

The inflammation of the conjunctiva itself can be very painful and irritating. In turned eyelashes (trichiasis) can also scratch the surface of the eye and damage the cornea, and dry eyes compound the discomfort.

Can other parts of my body be affected?

About 60-70% of MMP patients have some level of eye involvement in their condition. Half of these have ocular MMP without involvement of other sites and the remainder have MMP involving other mucous membranes such as mouth, nose, larynx, oesophagus and the genital and anus areas affected. It can also cause blistering on the skin. You will probably be referred to a variety of medical specialists (typically oral medicine, dermatology and ear nose throat) to monitor the extent of your disease.

How am I going to be treated?

About 20% of patients with MMP and ocular involvement have minimal inflammation with slowly progressive scarring and will need no treatment or simple topical therapies. However, topical treatments - those that you put directly in your eye - haven't been found to be effective in controlling inflammation or the progression of scarring in the other 80% of cases and for these the current standard of care is treatment using with oral or intravenous therapy with immunosuppressive drugs designed to reduce the overactivity of the immune system that is causing the disease, whilst maintaining it enough to perform its normal activity such as fighting infection. This is quite specialised treatment, very similar to what is used for diseases like rheumatoid arthritis.

The immunosuppressive drugs most often used for OMMP are:

- azathioprine (oral)
- cyclophosphamide (oral or intravenous)
- dapsone (oral)

- methotrexate (oral)
- mycophenolate (oral)
- sulfasalazine or sulfamethoxypyridazine (oral)
- steroids usually prednisolone (oral) or methylprednisolone or (intravenous)
- CD 20 inhibitors (intravenous Rituximab or Truxima)
- Intravenous immunoglobulin

All of these drugs can have serious side effects and you will need to be monitored while you are on them. Since this disease is chronic - which means it might last for a very long time and may require you to take medication indefinitely - you will need regular check-ups.

The ophthalmologist, or another specialist working with the ophthalmologist, will usually start treating milder cases with the least risky drugs - those with the least side effects - such as dapsone and sulfasalazine. But in cases where the disease progresses quickly the more potent treatments will be deployed. These treatments may involve drugs such as steroids to get short term control of severe inflammation but which, to avoid steroid side effects, must be used with non-steroidal "immunosuppressive" drugs. Steroids are generally only needed for a few months while the immunosuppressive drugs take effect. These will reduce your immune system response and therefore the autoimmune activity which is causing the damage to your eyes. Commonly used drugs for moderately severe disease are:

- azathioprine
- mycophenolate

If your eye disease is particular severe, or unresponsive to other therapies, cyclophosphamide and steroids, or steroids before courses of intravenous "biological" treatment with Rituximab, Truxima or intravenous immunoglobulin (IVIG) may be used.

Where the disease has also caused entropion (the eyelids turning in) and the eyelashes are scratching the cornea, then you may be recommended to have the eyelashes removed (epilation) either in the clinic or by self-removal. For occasional individual lashes electrolysis may be useful. For large numbers of lashes, for which epilation has proved difficult to manage, both electrolysis and freezing therapy (cryotherapy) have been used in the past. However as these may cause increased lid scarring and disease flare ups respectively, they have been superseded by surgery to turn the eyelids out to reposition the lashes away from the eye or by surgery to totally remove all the lashes.

Treatments to control the other side effects of OMMP may also be prescribed such as lubricating gels, drops or ointments for dry eyes and treatment for blocked eyelid margin glands (blepharitis) that can be treated with hot compresses and lid margin cleaning as well as keeping your eyelids clean.

What can I do to manage my disease?

In addition to managing your medications as instructed (and reporting any worrying side effects) you can minimise some of the effects that OMMP has by:

1. If you can, remove any eyelashes or ask someone else to do it; partners, your Hospital clinic, your optometrist and occasionally a GP practice nurse may be able to help.
2. Regular treatment of blepharitis for those affected (see the Moorfields blepharitis guideline)
3. Do not let your eyes dry out. Ask for gels or ointments that you can use regularly to keep them moist.

Can I be cured?

MMP and, specifically OMMP, are not curable. But with the right treatment at the right level, it is possible to halt the progress of the disease and "remission" can be achieved. It is vital that there is an early diagnosis and effective treatment is given to control inflammation and slow the progress of scarring. At the moment, there is no reversing the blindness that very bad or untreated OMMP can cause.