Diabetes — Part 3

Clinical features of diabetic maculopathy

In the final part of our series on diabetes, **Chris Steele**, **David Steel** and **Colin Waine** conclude their review of retinopathy with a discussion of maculopathy and proliferative changes.

C7208, one general CET point, suitable for optometrists and DOs

Diabetic retinopathy is well recognised as the most common cause of blindness among people of working age in the UK. It is also responsible for 12 per cent of all new cases of blindness in the US each year. One of the ways in which blindness occurs is when the central macular area of the retina is damaged, causing maculopathy. Increased permeability of retinal vessels allows leakage of plasma constituents which accumulate in the extra-cellular spaces, initially at the outer-plexiform layer and inner nuclear layer level and later extending to involve the entire retinal thickness. Such oedema at the macula is the most common cause of reduced vision in non-proliferative diabetic retinopathy.

The frequency of maculopathy varies between type 1 and type 2 diabetes and their duration. Diabetic maculopathy (DM) is more common in type 2 diabetes. In both types, however, the cumulative risk rises to about 30 per cent after 20 years. Other risk factors include pregnancy, hypertension, poor glycaemic control, renal disease and hyperlipidaemia.

The underlying changes which occur in DM are the same as in NPDR, although they are classified separately due to the special anatomy and function of the macula. The macula is defined as the central area of retina between the superior and inferior temporal arcades, from the disc and two disc diameters temporal to the fovea.

Oedema is difficult to see using direct ophthalmoscopy without binocular cues. Using an aspheric (eg Volk) lens (eg 78D or 90D) with slit-lamp biomicroscopy makes this easier to appreciate, although the best stereoscopic view is achieved using a fundal contact lens.

Classification of diabetic maculopathy

There are four main types of maculopathy according to clinical examination and fluorescein angiography. These are:

- **Focal**: Leakage from dilated segments of capillaries and microaneurysms
- **Diffuse**: Characterised by the presence of diffuse oedema
- **Ischaemic**: Capillary shut-down results in retinal non-perfusion and ischaemia. It is chararacterised by the presence of large blot haemorrhages, multiple cotton-wool spots and IRMAs
- **Mixed**: It is not uncommon to see a combination of focal, diffuse and ischaemic maculopathy.

Clinically significant macular oedema v referrable maculopathy

Diabetic macular oedema according to the ETDRS can be defined as hard exudates and retinal thickening involving the macular area. Clinically significant macular oedema (CSMO) is defined as any one of the following:

- Retinal thickening at or within 500µm of the centre of the macula
- Hard exudates at or within 500µm of the centre of the macula if associated with adjacent retinal thickening
- A zone or zones of retinal thickening one disc area in size at least part of which is within one disc diameter of the centre of the fovea.

In most English screening protocols referrable maculopathy is defined as any exudates or haemorrhages within one disc diameter of the fovea (Figure 1). This is different to the definition of CSMO.

Early non-referrable maculopathy

In mild NPDR (Figure 1) the earliest visible changes that develop are microaneurysms, usually in the area temporal to the fovea. At this early stage macular oedema with retinal thickening or hard exudate formation is rare but may be a threat to macular function (Figure 2). It is quite common for patients to develop one or two microaneurysms or an isolated dot haemorrhage at the macula but with no clinically significant macular oedema. Such patients do not

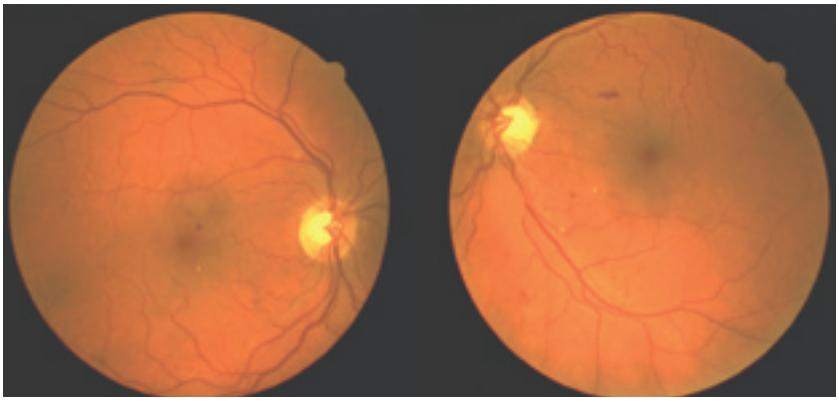

Figure 1

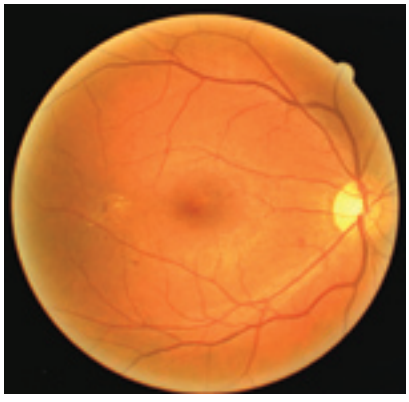

Figure 2

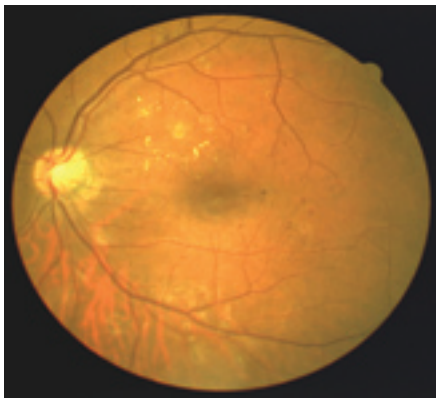

Figure 3

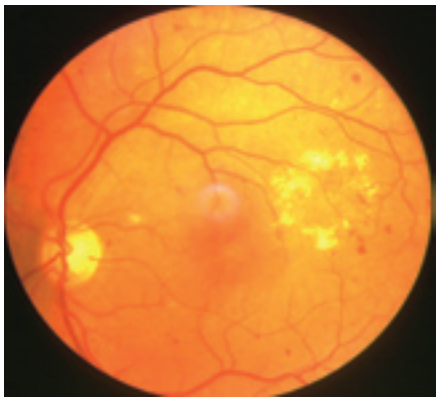

Figure 4

require referral yet, but do require follow up around every six months. If macular oedema (thickening) becomes clinically significant then laser treatment should be undertaken.

Established focal diabetic maculopathy

The features are well defined focal areas of leakage with microaneurysms, haemorrhages and retinal thickening. These areas are often surrounded by circinate hard exudates. Figure 3 shows a focal area of leakage with microaneurysms, haemorrhages and retinal thickening. This area is surrounded by circinate hard exudates. Note also the cluster of dot haemorrhages just temporal to the macula.

With focal exudative macular oedema, discrete leakage sites are a consistent feature. Leakage may occur from retinal microaneurysms or areas of dilated retinal capillaries.

The extent of the vascular changes can vary considerably. Leakage from capillaries can occur from the deep or superficial capillary network in the retina. Leakage from either micro-vascular abnormality gives rise to intra-retinal oedema with a bulk fluid flow towards competent capillaries. At these sites the fluid is reabsorbed into the relatively normal retinal capillary bed, causing the deposition and accumulation of the large molecules such as proteins and lipids which are seen as hard exudates.

The exact configuration of the exudate depends not only on the degree and sites of leakage, but also on the characteristics of fluid movement and absorption. Therefore exudates found at the macula vary considerably (Figure 4). Both these cases require referral for focal laser treatment.

In many patients with focal exudative macular oedema, the areas of leakage are well away from the fovea ▶

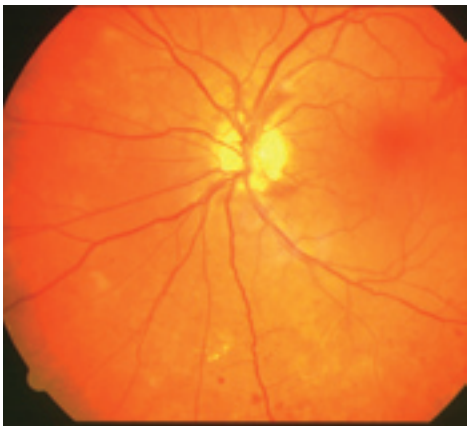

Figure 5

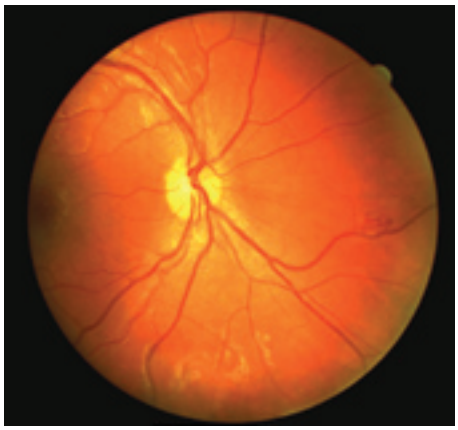

Figure 6

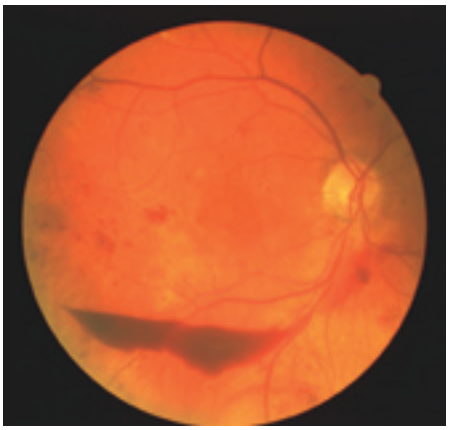

Figure 7

and central vision is preserved. This is where macular oedema is not clinically significant. Most patients in this group are asymptomatic, although some may suddenly notice fluctuations in their vision or even paracentral scotoma. In patients who do suffer with disturbed central vision, the degree of visual loss is usually related to the extent of retinal oedema and hard exudate formation. Once retinal thickening or hard exudates are coming as close as 500µm to the centre of the fovea, focal laser treatment is advised, even in patients with perfect vision.

Effects of statins on diabetic exudative maculopathy

When serum lipids, particularly triglycerides, increase substantially in a diabetic patient, the prevalence of hard exudates increase. There is now mounting evidence that lipid-lowering drugs such as the statins can reduce the extent of macular hard exudates in patients with diabetic retinopathy (DR). However reducing hard exudates does not necessarily induce improved vision.

Proliferative diabetic retinopathy

Proliferative diabetic retinopathy (PDR) is characterised by development of new vessels from the surface of the retina or optic disc as a result of retinal ischaemia. New vessels represent a serious threat to vision because they can bleed, causing pre-retinal and vitreous haemorrhages. Fibrous tissue accompanies the development of the new vessels and can lead to tractional retinal detachment.

Optic disc neovascularisation (NVD) in a diabetic subject generally indicates advanced diabetic retinopathy with retinal ischaemia and is an indication for pan-retinal photocoagulation (PRP). It is uncommon to see NVD when the area of capillary non-perfusion is less than a quarter of the whole retina.

NVD may extend over the surface of the disc and across the disc margin in one or more quadrants (Figure 5). Often NVD follow the retinal vessels, especially along the temporal arcades. At the advancing edge of each vessel is a loop, the tip of which serves as a focus for new growth and extension of the vessel. The fact that the advancing edges of the NVD in Figure 5 are blurred is an indication that the NVDs are not all in the plane of the retina but actually also growing forwards. The vessels usually grow between the internal limiting membrane of the retina and posterior vitreous face to which they eventually become adherent. Fibrous tissue accompanies the development of the new vessels and becomes progressively more clinically obvious as seen here, superiorly to the disc.

NVD may be derived from the retinal or choroidal circulation, although it is more likely to be from the choroidal circulation if the new vessels originate from the deeper part of the cup. It is, however, difficult to be absolutely sure of the exact origin of the vessels and in any case makes no difference to the clinical management.

In the early stages it is easy to confuse NVD with fine, slightly dilated disc capillaries or even small disc collaterals. NVD does not, however, develop in the absence of signs of retinal ischaemia. On fluorescein angiography, NVDs show leakage, whereas IRMA, collaterals and dilated disc capillaries do not.

New vessels elsewhere

New vessels elsewhere (NVE) nearly always develop from the venous sides of the capillary network adjacent to an area of retinal ischaemia. Note that the isolated NVEs in Figure 6 are located on the nasal fundus with very little other evidence of retinopathy present. This is quite a common presentation in type 1 diabetics with retinopathy. In certain camera-based diabetic screening programmes, only one fundus picture is recorded, usually including the disc, macula and temporal arcades. This case highlights the importance of always checking the nasal fundus. Had this not been the case, this relatively young patient would have been graded as mild NPDR when in fact they have proliferative disease requiring treatment.

Spontaneous regression of new vessels

There have been a few reports describing unusual spontaneous regression of new vessels. When this occurs it is often associated with improving metabolic control or the end of a pregnancy. In other very rare cases these have been reported in type 1 diabetes in non-pregnant females with no notable improvement in their overall control of their diabetes. Such improvements are associated with a marked improvement in blood retinal barrier breakdown and remarkably, re-perfusion of areas of capillary drop out observed on fluorescein angiography.

Pre-retinal haemorrhage

The dark mass of blood in this characteristic (boat) shape (Figure 7) is a pre-retinal haemorrhage, with the blood settling in the space between the retina and vitreo-retinal membrane. The haemorrhage has a flat top due the blood settling under the force of gravity. Although not discernible in the photograph, there must be leaking NVEs to produce this pre-retinal haemorrhage. In Figure 8 extensive pre-retinal haemorrhages can be seen.

Subsequent development of untreated NVD

Signs of activity in new vessels include neovascular buds and paucity of fibrous tissue. Signs of inactive new vessels include general reduction in vascular calibre in both the new vessels and the neighbouring retinal vessels with increase in the fibrous component in the new vessels.

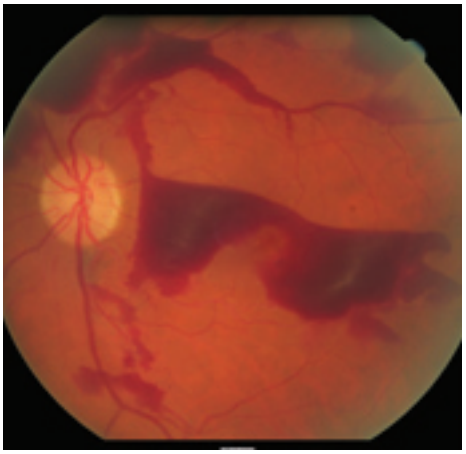

Figure 8

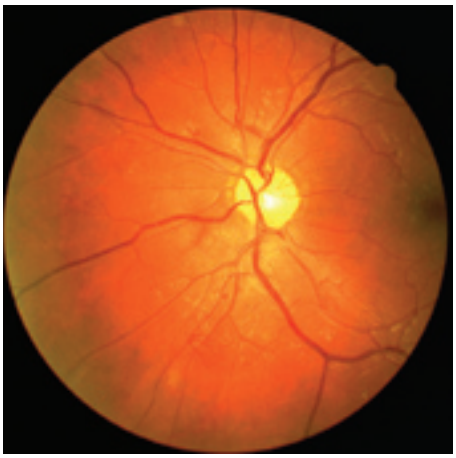

Figure 9

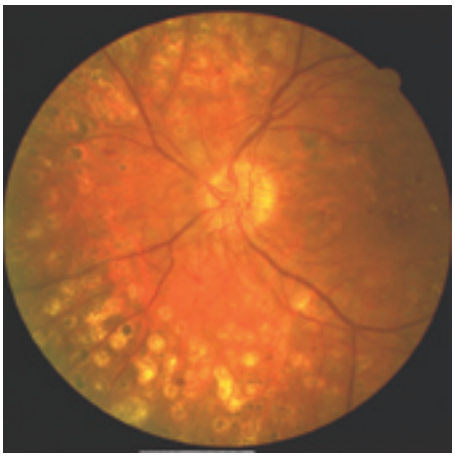

Figure 10

Potential consequences of untreated PDR

Vitreous haemorrhage occurs as a result of vitreous traction on any pre-retinal neovascular proliferation. This may result in obscuration of the fundus view in severe cases. Where the fundus cannot be visualised, a B scan ultrasound can be performed to exclude any other significant pathology such as retinal detachment.

Fibrovascular tissue may shrink, causing contraction and distortion of the normal retinal tissue. Combined with the process of vitreous detachment, this may progress to a tractional retinal detachment normally affecting the temporal arcades first. Temporal tractional detachments may remain more localised and do not significantly affect vision.

Tractional retinal detachments may also develop retinal tears and breaks which often result in a rapidly progressing combined tractional-rhegmatogenous retinal detachment. Tractional retinal detachments are typically concave compared with rhegmatogenous retinal detachments that are usually convex. Also, tractional retinal detachments tend not to extend beyond the orra serrata.

Vision is significantly affected if there is foveal involvement following detachment. The vision may also be affected in other situations such as when fibrovascular tissue grows over the foveal area but with the fovea still attached. In other situations, extrafoveal fibrovascular tissue may cause tangential tractional forces, giving rise to displacement of the fovea horizontally.

Rubeosis iridis is a complication of PDR in response to significant ischaemia. New vessels grow over the surface of the iris. It is therefore important to check the iris pupil margin carefully for any signs of rubeosis in diabetics. If the new vessels obstruct the anterior chamber angles, this may lead to neovascular glaucoma.

Ocular conditions affecting diabetic retinopathy

Diabetic retinopathy seems to show less progression in myopic eyes. Myopia of -2.00D or less is thought to be protective against development of PDR in type 1 diabetics. Proposed mechanisms of protection have included posterior vitreous detachment (PVD), decreased ocular blood flow, thinning of the retina, thereby increasing oxygen diffusion and improved pressure dissipation by the arteriolar tree. Eyes with DR probably have shorter axial lengths than eyes without retinopathy, even in non-myopic patients with the disease.

Glaucoma and DR

Glaucoma has long been suspected to reduce the prevalence and severity of DR. This may be explained by reduced retinal metabolic activity in the retina due to decreasing viable ganglion cells and/or due to reduced vascular perfusion due to increased intraocular pressure. Similarly optic atrophy may have a protective effect against development of DR because of the reduced metabolic demand of the retina in this condition.

Posterior vitreous detachment

The role of vitreoretinal traction in the evolution of DR is well established. Where total posterior vitreous detachment (PVD) occurs in an eye with early non-proliferative DR, this may prevent the progression of the DR. There may well be other mechanisms present in myopic eyes?

Retinitis pigmentosa and DR

Rods have the highest metabolic rate of any cell in the body using up significant amounts of oxygen from the inner retina, rendering it almost pathologically anoxic in dark adaptation. In retinitis pigmentosa, the rods degenerate and therefore reduce the demands for oxygen in the inner retina, in turn reducing the risk of vasogenic cytokine release which has an important role in the pathogenesis of DR.

Atypical features of DR

'Featureless retina'

Occasionally, retinal neovascularisation appears in patients with DR who show no other signs of intra-retinal microvascular abnormalities usually associated with pre-proliferative retinopathy (Figure 9). This can be explained by the fact that cotton-wool spots are transient anyway and/or the fact that microaneurysms, dot and blot haemorrhages and other microvascular abnormalities tend to disappear in areas of extensive capillary closure. When featureless retinae are scrutinised, they appear to be atrophic and fluorosecein angiography often reveals extensive areas of capillary non-perfusion, often with previously undetected areas of neovascularisation.

Asymmetric diabetic retinopathy

Asymmetric DR occurs in approximately 5 to 10 per cent of diabetics. It has been defined as PDR in one eye and NPDR in the other eye, persisting for more than two years. However, it is important not to mistake featureless retina for non-proliferative DR. There are many factors which may contribute to asymmetric DR.

These include previous cataract surgery and presence of branch retinal vein occlusion. Conversely, chorioretinal scarring, optic atrophy, posterior vitreous detachment, myopia and glaucoma tend to reduce the disease progression.

Carotid occlusive disease

Severe carotid artery stenosis can also be associated with worsening of the DR on the occluded side. It is thought that the carotid stenosis in effect has a ▶

macroangiopathy which exacerbates the DR microangiopathy.

When severe enough to result in ocular ischaemic syndrome, this may be indistinguishable from PDR. It is important to recognise ocular ischaemic syndrome in DR because of the poor visual prognosis if rubeosis becomes established. Where there is only mild carotid insufficiency the effect on progression of DR is less clear.

Peripheral abnormalities in diabetic retinopathy

In a small number of cases there is a relative sparing of the posterior pole and new vessels may develop only in the far periphery where they can be easily missed. NVD may also occur even when macular and peripheral retina are well perfused. Neovascular glaucoma and anterior hyaloid fibrovascular proliferation are most likely caused by peripheral retinal ischaemia. Peripheral new vessels have certainly been reported growing from the choroid in an eye enucleated for PDR with neovascular glaucoma.

Florid diabetic retinopathy

Florid diabetic retinopathy (Figure 10) is a rare complication of severe DM typically occurring in type 1 diabetics with long-standing poor control, affecting women more than men. Other systemic complications are common. This condition is encountered in less than 1 per cent of cases with PDR. Florid DR is characterised by bilateral, rapidly progressive, severe ischaemic retinopathy associated with loss of vision and a very high risk of subsequent blindness. Therefore early detection is crucial and retinal photocoagulation is required with early vitrectomy when indicated to improve prognosis.

Diabetic retinal pigment epitheliopathy

Although diabetic macular oedema is mainly associated with a vascular origin, the retinal pigment epithelium may also play an important role. A disruption of the blood retinal barrier may contribute to the development of diabetic maculopathy. This is through diffuse late-phase leakage from the macular retinal pigment epithelium in the absence of many microaneurysms and no signs of clinically significant macular oedema.

Cilioretinal artery and diabetic maculopathy

It is often stated that the presence of a cilio-retinal has certain advantages regarding vascular perfusion. However, where DR is concerned there may be distinct disadvantages, particularly where asymmetric retinopathy is present. This is where these vessels may be the cause of an increased prevalence of dot and blot haemorrhages, hard exudates and maculopathy with CSMO in certain patients.

Conclusion

It was the initial observation that eyes with extensive chorioretinal scarring from any cause were much less likely to develop DR, or if they did for it to be less severe, which led to the iatrogenic induction of chorioretinal scarring that paved the way for the development of pan retinal photocoagulation treatment.

The identification and better understanding of some the less common features of DR may similarly open new as yet undiscovered treatment options for such retinal disease. ●

MULTIPLE-CHOICE QUESTIONS

1 Which of the following statements about maculopathy is true?
A It is more common in type 1 diabetes
B Pregnancy is a risk factor
C The cumulative risk is 50 per cent after 20 years' disease duration
D Macular oedema is the commonest cause of sight loss in proliferative diabetic retinopathy

2 Which of the following would give the best stereoscopic view of an oedematous macula?
A 78D lens with slit lamp
B 90D lens with slit lamp
C Contact fundus viewing lens
D 20D with headset BIO

3 Maculopathy showing large blot haemorrhages, multiple cotton-wool spots and IRMAs would be best categorised as what?
A Focal
B Diffuse
C Ischaemic
D Mixed

4 Which of the following would represent clinically significant macular oedema?
A Retinal thickening half a disc diameter in size and two disc diameters from the fovea
B Retinal thickening one disc diameter in size and within one disc diameter of the disc
C Retinal thickening half a disc diameter in size and within one disc diameter of the fovea
D Retinal thickening one disc diameter in size and within one disc diameter of the fovea

5 What treatment might be promted by NVD?
A Laser of the disc
B Laser of the peripapillary area
C Panretinal photocoagulation
D Monitoring without intervention

6 In what percentage of diabetics is the retinopathy asymmetric?
A 5-10 per cent
B 10-20 per cent
C 30-40 per cent
D 50 per cent

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Further reading

1 Akduman L and Olk RJ. The early treatment of diabetic retinopathy study. Chapter 2 in *Clinical trials in ophthalmology* – a summary and practice guide. Eds Kertes PJ and Conway MD 1995.
2 Benson W. Diabetic retinopathy Chapter 20.8.4 In *Ophthalmology*. Editors Myron Yanoff and Jay S Duker. Mosby 2000.
3 Harvey W. Background diabetic retinopathy (Parts 1&2). Diabetes module parts 1-12 Continuing professional development series. Published by Association of Optometrists and City University 1997.
4 Hamilton AMP, Ulbig MW, Polkinghorne P. *Management of diabetic retinopathy*. In chapter 3: Lesions of diabetic retinopathy pp 96-156. Published by BMJ Publishing Group 1996.
5 Kanski J. *Clinical Ophthalmology: A systematic approach*. Fifth Edition. Published by Butterworth Heinmann 2003.

This article is based on Diabetes and the Eye, *a forthcoming volume in the Eye Essentials series published by Butterworth-Heinemann.*

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