

Contraception and Ocular Thromboembolic Episodes

CASE REPORT

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SUMMARY

The aim of the paper is to warn of the retinal vein occlusion possibility due to the using of hormonal contraceptive pills in young female patients. A case report of 22 years old female patient hospitalized at the Department of Ophthalmology, School of Medicine, Masaryk University, Brno, Czech Republic, E.U., with sudden decrease of the left eye visual acuity is presented. After excluding other causes of visual acuity decrease, the diagnosis of prethrombotic state was made and anticoagulant treatment was started.

Key words: optic disc edema, prethrombotic state, retinal vein occlusion, visual acuity decrease, hormonal contraception

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INTRODUCTION

Retinal Vein Occlusion (RVO) is the second most common vascular disorder of the retina, after diabetic retinopathy. According to the localisation of the vascular occlusion we classify retinal vein occlusions as central (CRVO) and branch (BRVO) ones. A separate clinical form is hemioclusion, in which the upper or lower half of the retina is afflicted [8]. Within the framework of central occlusions, “prethrombotic state” is sometimes given a separate status. This is characterised by the presence of dilated and tortuous retinal veins and oedema of the disc of the optic nerve. Massive haemorrhages are not evident. Visual acuity is only slightly reduced [11].

Risk factors of retinal vein occlusion include systemic cardiovascular disorders (hypertension, hyperlipidemia, diabetes mellitus, increased BMI), hyperviscous states, vasculitis or hypercoagulation states (Leiden mutation, antiphospholipid syndrome, deficit of C and S protein). The ocular risk factors include glaucoma excavation of the disc of the optic nerve. We consider smoking and certain pharmaceuticals (oral contraceptives, hormonal substitution therapy or diuretics) [10] to represent external risk factors. Retinal vein occlusion most frequently afflicts patients aged over 50 years, who primarily manifest risk cardiovascular factors. A small proportion of retinal vein occlusions occurs in younger patients [8].

CASE STUDY

In July 2012 a 22-year old female patient came to the emergency department of the outpatient Eye Clinic of Brno University Hospital due to a deterioration of visual acuity in the left eye persisting for several hours.

The patient's anamnesis stated a surgery for strabismus at the age of 3 years in the Paediatric University Hospital in Brno. In childhood she wore an occluder, at primary school she no longer wore spectacle correction or an occluder and saw equally well in both eyes and read the last row of Snellen charts. In general, she did not receive treatment for any illnesses. From the age of 16 years she had used oral hormonal contraception, Diane 35 (Ethinylestradiol, Cyproteron acetate). The patient had been a smoker since the age of 16, smoking 10-15 cigarettes per day.

At an objective examination best corrected visual acuity in the right eye was 1.0, in the left eye 0.8, correction did not improve. The anterior segment of the eye was without a pathological finding in both eyes. There was a physiological finding corresponding to age on the fundus of the right eye. A blunted papilla was evident on the fundus of the left eye, with haemorrhages at its edge and pronouncedly dilated and tortuous capillaries (fig. 1). Within the framework of differential diagnosis we in first place considered a prethrombotic state, also intraocular neuritis or anterior ischemia of the optic nerve.

The patient was acutely hospitalised at the inpatient department of our clinic. Upon admittance contraception was discontinued and following consultation with a haematologist a therapeutic dose of LMWH (low molecular weight heparin) was applied. We administered Fraxiparine (Nadroparinum calcium 9 500 IU in 1 ml solution) in a dose of 0.6 ml s.c. BID. We recommended that the patient stops smoking. After application of anticoagulation therapy there was a rapid improvement in the finding on the fundus, the oedema of the papilla of the optic nerve gradually subsided, haemorrhages attenuated and the dilation and tortuosity of the capillaries was reduced.

In order to exclude intraocular neuritis we conducted a VEP examination (the finding was within the norm). Within the framework of differential diagnosis we also considered presence of orbital expansion, for this reason a USG examination of the eye socket was conducted with a negative result. There was a physiological finding on the perimeter in both eyes.

The patient also underwent a brain MR in order to exclude demyelination disease and lumbar puncture in order to exclude neuroinfection. Both examinations were negative. Due to suspected thrombophilic disorder the patient underwent a haematological examination with a negative result. With regard to the prethrombotic state on the fundus, the patient underwent an X-ray of the chest area so that we could exclude pulmonary embolism.

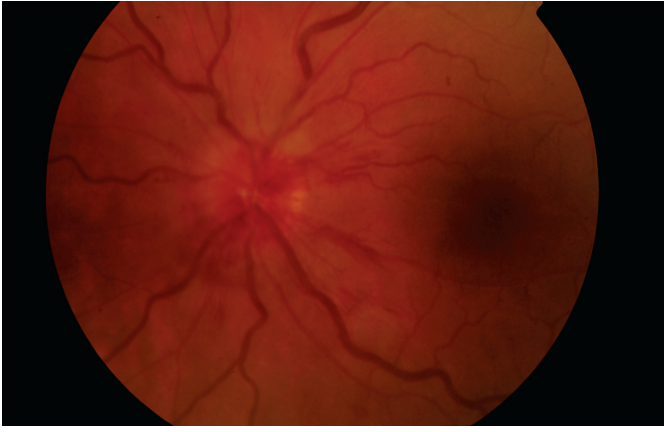


Fig. 1. Fundus of left eye upon initiation of treatment



Fig. 2. Fundus of left eye upon discharge

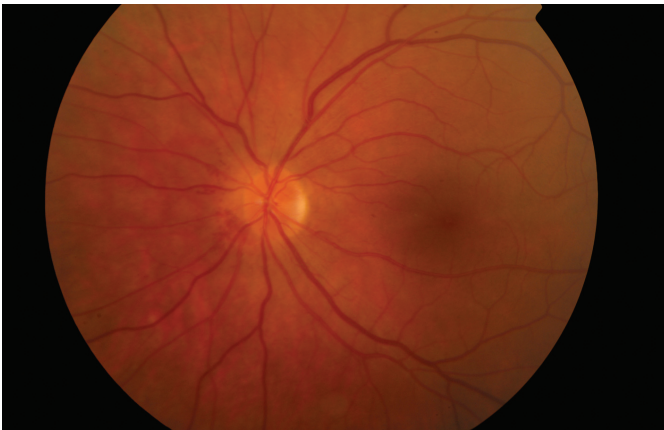


Fig. 3. Fundus of left eye after occurrence of the prethrombotic state

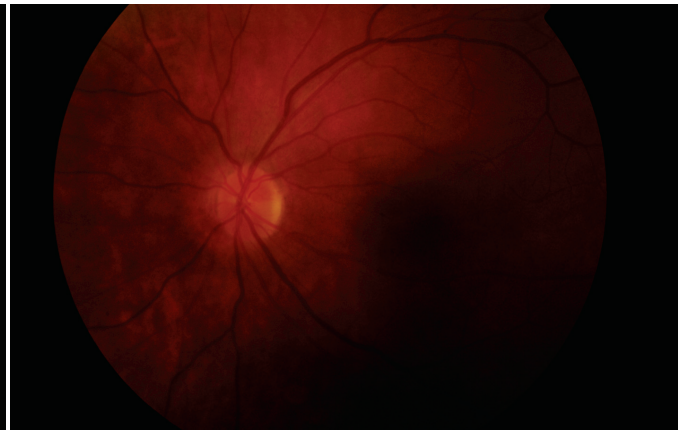


Fig. 4. Fundus of left eye 2 months after occurrence of the prethrombotic state

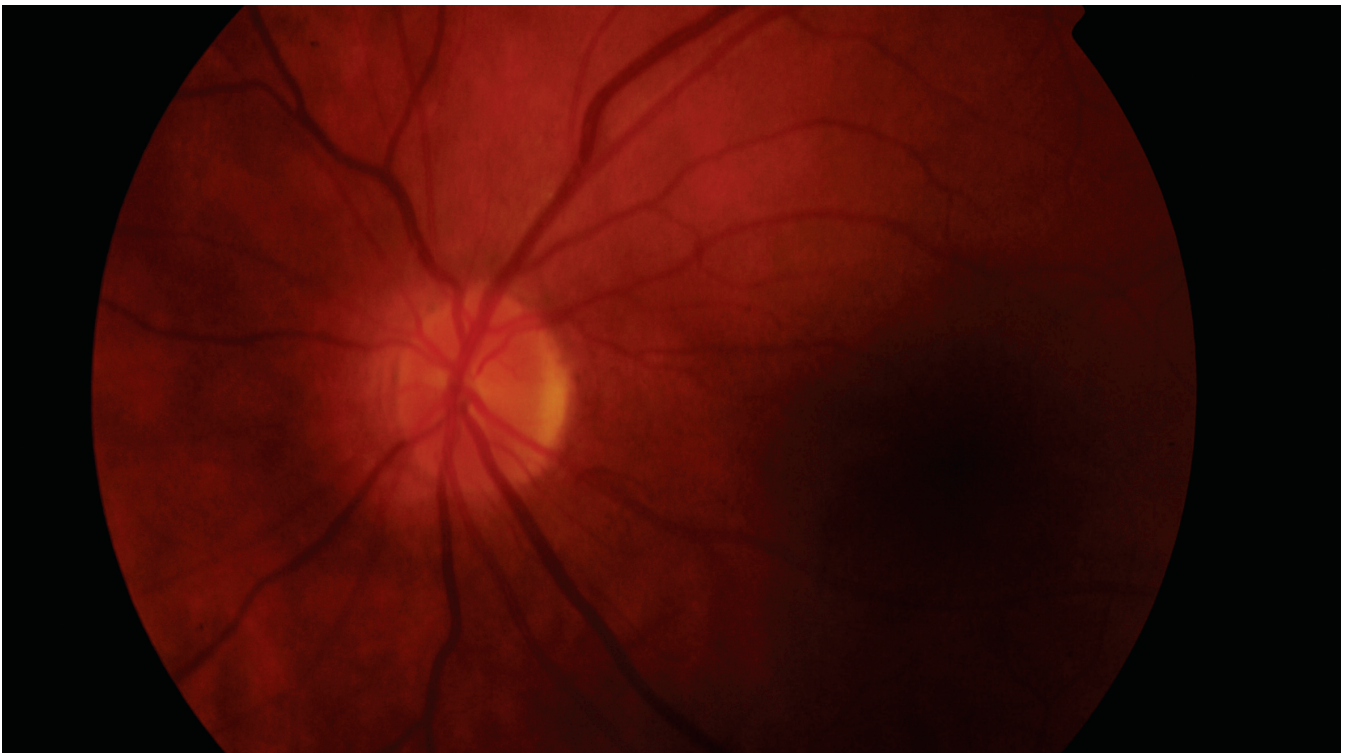


Fig. 5. Fundus of left eye 5 months after occurrence of the prethrombotic state

On the basis of the conducted examinations and with regard to the markedly improved finding following anticoagulation therapy, we concluded that the finding on the fundus of the left eye was a prethrombotic state. Upon discharge (after 7 days of anticoagulation treatment), VA in the left eye was 1.0, we observed a smaller oedema of the papilla on the fundus than upon admission, haemorrhages had subsided and dilation and tortuosity of veins had been reduced (fig. 2). The patient was further left on a therapeutic dose of LMWH (Fraxiparine 0.6 ml s.c. BID per day). The patient was further observed at our outpatient clinic, a further improvement of the finding on the fundus was evident (fig. 3). The dose of Fraxiparine 0.6 ml s.c. BID was continued for a further 20 days after discharge, then reduced to Fraxiparine 0.6 ml s.c. QD day for 10 days and subsequently the patient applied Fraxiparine 0.6 ml s.c. every other day for one month. At a check-up 2 months after the occurrence of the prethrombotic state, visual acuity of the left eye was 1.0 and there was a physiological finding on the fundus (fig. 4). This finding persisted also 5 months after the occurrence of the non-thrombotic state (fig. 5).

DISCUSSION

At present almost 40% of women in fertile age [3] use one of the available hormonal contraceptive preparations (HCP). A large quantity of oral contraceptives is used in clinical practice. Two types of preparations appear in practice: a combination of oestrogen and gestagen or only gestagens [3, 5]. Individual gestagens differ in various preparations, the oestrogenic component is ethinylestradiol or more recently, estradiol valerate [3, 13]. The contraceptive effect is induced by selective inhibition of the function of hypophysis, which leads to a suppression of ovulation. Combined preparations at the same time induce changes in the cervical mucus, the endometrium and in the motility and secretion of the oviducts. The latter changes play the main role in the action of the gestagens [5].

According to the dose of the oestrogen component, we classify HCP as preparations with a high dose (40 µg of ethinylestradiol), with a low dose (30-37.5 µg) and a very low dose (15-20 µg of ethinylestradiol). Preparations with 15 µg are sometimes classi-

fied as preparations with an extremely low dose [3].

The preparation Diane 35, used by our patient contains cyproterone acetate, a gestagen with antiandrogenic activity. It is also used as a dermatological agent in the treatment of disorders conditioned by androgens in women (acne, seborrhea, milder forms of hirsutism, androgenic alopecia) [2, 13]. The mild undesirable effects of the use of HCP include nausea, mastalgia and headache; moderate undesirable effects include uterine bleeding from "penetration", increase in weight, increased skin pigmentation, and amenorrhea after discontinuation of administration of HCP. Serious undesirable effects include vascular disorders (thromboembolic disease, myocardial infarction and cerebrovascular disorders), gastrointestinal disorders and depression [2, 5].

Venous thromboembolism is a rare but potentially very serious complication of use of hormonal contraception. Hormonal contraceptives increase the risk of venous thromboembolism by almost 3-4x, and this risk increases in smokers, with age over 35 years or in obese women [13]. The risk of thromboembolism increases during the first month of use of contraceptives and thereafter remains constant. Within a month after the discontinuation of therapy the level of risk returns to the original values [5]. The incidence of thromboembolism upon use of HCP is linked only to the oestrogen content. During use of HCP there is a substantial reduction of antithrombin III, which is the main plasmatic thrombin inhibitor [5].

Kirwan et al. in their study investigate the relationship between use of hormonal contraception and retinal vein occlusion (RVO). In a population of 588 patients with RVO they recorded 6 patients who used HCP [9]. A study by Harhiu et al. retrospectively processed a population of 60 young patients with branch retinal vein occlusion (BRVO). Women represented 40% of this group (24 women). Of these women, 5 patients (8%, n = 60) [6] used hormonal contraception.

Opinions on the treatment of central occlusion are not constantly equivocal. Treatment may be medicamentous (antiaggregation therapy, rheology, anticoagulation therapy), laser or surgical (PPV). Acetylsalicylic acid is used as an antiaggregant. Rheological drugs used in the treatment of CRVO include troxerutin or pentoxifylline. To

date the effect of any of these preparations has not been confirmed by a large randomised double-blind study [11]. The approach to treatment of central retinal vein occlusion using anticoagulants is not unequivocal either. Except the patients with hypercoagulopathy, the majority of authors consider it to be of little effect, with a high risk of haemorrhaging complications [4, 11, 12].

Two studies have been published which observed anticoagulation therapy using LMWH in patients with acute form of CRVO. The study by Farahvash et al. evaluates 93 patients, of whom one group was treated for 20 days with dalteparin (100 IU/kg subcutaneously) and the second group with acetylsalicylic acid (100 mg/day). The observation period was 6 months. In the group of patients treated with dalteparin, the authors recorded an increase in BCVA by 5.5 ETDRS letters. In the group treated with acetylsalicylic acid the patients had a reduction of BCVA by 14 letters [4]. The second study published on this theme was by the authors Ageno and Cattaneo et al. This was a multicentre randomised double-blind study. In all patients there was an interval between the onset of subjective complaints and the diagnosis of less than 15 days. One group of patients (30) received acetylsalicylic acid (ASA) in a dose of 100 mg per day for a period of 3 months, and another group of patients (28) were treated with a fixed dose of parnaparin (12 800 IU for a period of 7 days, subsequently 6 400 IU for 3 months). Functional deterioration was diagnosed in 20.7% of patients treated with parnaparin and in 59.4% of patients treated with acetylsalicylic acid. Recurrence of CRVO was observed in 3 patients treated with ASA. Haemorrhaging complications were identical in both groups [1].

In the Czech literature, Řehák deals with the issue of treatment of CRVO using anticoagulation (initial treatment by LMWH and subsequently with warfarin). He monitored a group of 24 patients, in 9 of whom a non-thrombotic state was diagnosed. Anticoagulation therapy with warfarin was administered to all patients, INR was maintained between 3-3.5. Patients were also treated with pentoxifylline and rutoside with ascorbic acid. In the group of prethromboses, visual acuity better than 6/18 was achieved in 89% of patients. The authors demonstrated that anticoagulation therapy substantially

reduces progression of the non-ischemic form of CRVO to the ischemic one. Their approach to treatment, i.e. timely application of anticoagulation in prethrombosis corresponds with our observations [12].

In January 2013 use of Diane 35 was prohibited in France. On the basis of an assessment of the available data from the French National Agency for Medicines and Health Products Sa-fety ANSM, it was demonstrated that

the risk of thromboembolism linked to the use of Diane 35 exceeds the benefits in the treatment of acne. Use of the drug in the indication of hormonal contraception is unsuitable according to ANSM [7].

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