THE ROLE OF FLUORESCEIN ANGIOGRAPHY IN DIAGNOSIS AND TREATMENT OF DIABETIC RETINOPATHY

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Keywords: *fluorescein angiography, diabetic retinopathy, macular edema*

Abstract: *Purpose of the paper: Assessment of retinal fluorescein angiography role in the patients with diabetic retinopathy and implicitly, the role of this method in establishing the diagnosis and the optimal therapy for these patients. Methods: Prospective interventional non-comparative study. We performed fluorescein angiography in a group of patients with diabetic retinopathy in different stages of development. In all the studied patients, eye examinations were performed prior to fluorescein angiography examination, that included determination of visual acuity, biomicroscopy of the anterior and posterior pole and retinal photography. Results and discussions: Fluorescein angiography showed with certainty the stage of the diabetic retinopathy and macular leakage in the cases associating diabetic maculopathy. Retinal and/or papillary neovessels have been showed in the patients in whom fundus examination through biomicroscopy and retinal photography did not reveal these changes (fundus visibility was reduced by the presence of changes in the transparency of the lens and vitreous). In addition, this technique had a major contribution in establishing the type of maculopathy and its severity; so in many patients with a relatively good visual acuity (VA) and discrete clinical changes, infraclinical, extremely important lesions were highlighted. Conclusions: Fluorescein angiography is an essential examination for the proper monitoring of the diabetic patients, this investigation being particularly useful in the diagnosis and classification of diabetic macular edema, with the different therapeutic approach depending on the type of macular edema.*

Cuvinte cheie: *angiofluorografie, retinopatie diabetica, edem macular*

Rezumat: *Scopul lucrării: Evaluarea aportului angiofluorografiei retiniene la pacienţii cu retinopatie diabetică şi, implicit, rolul acestei metode în stabilirea diagnosticului şi terapiei optime în cazul acestor pacienţi. Material şi metodă: Studiu prospectiv intervenţional non-comparativ. Am efectuat angiofluorografia la un lot de pacienţi cu retinopatie diabetică în diverse stadii de evoluţie. La toţi pacienţii studiaţi au fost realizate, anterior examenului angiofluorografic, examene oftalmologice care au inclus determinarea acuităţii vizuale, biomicroscopia polului anterior şi posterior şi retinofotografii. Rezultate şi discuţii: Angiofluorografia a arătat cu certitudine stadiul retinopatiei diabetice şi leakage macular în cazurile ce asociau şi maculopatie diabetică. S-au evidenţiat neovase retinene şi/sau papilare la pacienţi la care examinarea fundului de ochi prin intermediul biomicroscopiei şi al retinofotografiei nu a relevat aceste modificări (vizibilitate fundului de ochi era diminuată prin prezenţa unor modificări de transparenţă ale cristalinului şi vitrosului). În plus, această tehnică a avut un aport major în stabilirea tipului de maculopatie şi a gravităţii acesteia; astfel, la numeroşi pacienţi cu AV relativ bună şi modificări clinice discrete au fost puse în evidenţă leziuni infraclinice extrem de importante. Concluzii: angiofluorografia este o examinare indispensabilă pentru monitorizarea corectă a pacientului diabetic, această investigaţie fiind deosebit de utilă în diagnosticul şi clasificarea edemului macular diabetic, cunoscută fiind abordarea terapeutică diferită în funcţie de tipul edemului macular.*

INTRODUCTION

Fluorescein angiography (FA) has been successfully used in ophthalmology since the early 1960s. Being a dynamic method, it provides us with multiple information relatively easily reproducible; it is a method of recording vascular perfusion and retinal fluid dynamics using the fluorescein sodium as contrast agent.(1,8,11) FA provides a topographic image of the retina helping to establish the treatable lesions, to identify ischemia in diabetic retinopathy and to determine a diagnosis of certainty; it is a technique that highlights chorioretinal blood vessels, even small capillaries surrounding the foveal avascular zone.(2,5,9,10)

Diabetes mellitus (DM) has become epidemic in the XXIth century, due to lifestyle westernization, aging, urbanization, which resulted in diet changes, in adopting a sedentary lifestyle with the development of obesity.(13) Diabetic retinopathy (DR) is the most common retinal vascular disease and the most important cause of blindness in the working age population worldwide.(3,6,7,12,30) DR is an ocular microangiopathy affecting the precapillary arterioles, capillaries, venules, and to a lesser extent, the higher retinal vessels. Chronic hyperglycemia causes in time biochemical changes leading to vascular endothelial injury; these changes are correlated with the occurrence and severity of DR.(4,14)

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In diabetic retinopathy, FA is not performed routinely, because fundus biomicroscopy reveals in most cases the macular edema or the proliferative changes, which can be well visualized.(27,28)

PURPOSE

This paper aims at addressing a topic of wide interest in ophthalmology, that is fluorescein angiography, a very valuable examination for the patients with diabetic retinopathy, without which we cannot establish a proper and an effective treatment. We aimed at highlighting the large number of information that can be obtained by using the fluorescein angiography and also at emphasizing the importance of properly informing the patient about the risks and benefits alike.

METHODS

We conducted a prospective interventional non-comparative study on 17 patients with diabetic retinopathy in different stages of evolution, with or without macular edema. Fluorescein angiography was initiated in cases where visual acuity deterioration could not be explained by the fundus picture, to differentiate the retinal neovascularization from the intraretinal microvascular abnormalities and in those patients with macular edema, in view of treatment planning. In all the patients included in the study, we have performed FA, using the Carl Zeiss fundus camera within Dr. Stanilă Medical Centre in Sibiu. No patient was known with a history of allergies to other contrast agents.

Previously to the fluorescein angiography examination, we determined the visual acuity, intraocular pressure, biomicroscopy of the anterior and posterior pole, and colour retinal photography (black, red, blue, green) in five positions (the patient was asked to look ahead, up, down, right, left), for the assessment of the central and peripheral retinal changes. The patients were informed about the technique, possible risks and the complications that may arise. They gave their consent for understanding the procedure and its accomplishment. Also, the patients were warned that they might experience transient discoloration of the skin, mucous membranes and urine in yellow-orange. Each patient was prepared 30 minutes before the mydriatics instillation examination, so that the pupils should be sufficiently dilated. In the presence of a physician experienced in intensive care, we intravenously administered 5 ml of 10% fluorescein solution for 2-3 seconds. With the patient correctly positioned at fundus camera, we did serial fundus photographs (every one second), using a camera equipped with special filters. About 45 seconds after administration, we set the other eye in order to record the middle phase images, then we took pictures every one minute in each eye for 15 minutes to capture the fluorescein circulating late times.

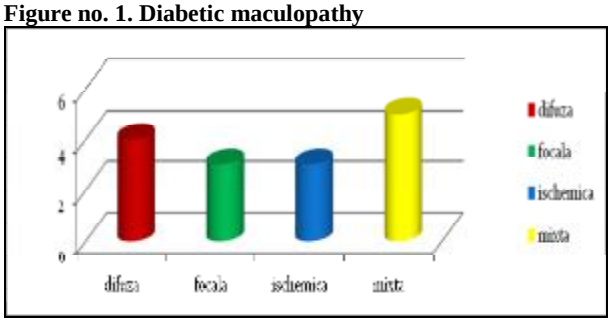
RESULTS

Between November 2009 and February 2012, we conducted FA in 17 patients with DR, aged between 45-70 years old (8 men and 9 women, 11 patients with insulin-dependent diabetes mellitus and 6 non-insulin dependent patients). We did not report any complications or major side effects. After fluorescein angiography examination, 9 patients in the study fit the specific criteria of nonproliferative diabetic retinopathy (NPRD). In 2 patients, in whom fundus biomicroscopy showed changes specific to NPRD, fluorescein angiography revealed fine neovessels, which were mistaken for intraretinal microvascular abnormalities. In all patients examined, FA emphasized micro and/or macroaneurisms in a much larger number than on ophthalmoscopy. They appear as hyperfluorescent spots with maximum intensity in the arteriovenous time with extinction or blur in late venous time.

There were few cases where a diffuse hyperfluorescence could be noticed, as a result of aneurysms rupture. Retinal hemorrhages were located on the FA due to the hypofluorescent spots, as a result of the faulty transmission of normal fluorescence, the so-called “blocking/masking effect”. We pointed the hard hypofluorescent exudates (by masking the background choroidal fluorescence) available mainly in the crown (circinate exudates). On FA, we identified the intraretinal edema as late diffuse hiperfluorescence (through diffusion from the retinal capillaries). On FA, we noticed in 4 patients, cotton-wool exudates with focal hipofluorescence by masking, associated with adjacent capillary nonperfusion. In 2 patients, we identified intraretinal microvascular abnormalities, as focal hiperfluorescence associated with adjacent capillary occlusion with no diffusion. Eight patients showed changes specific to proliferative diabetic retinopathy. Neovascularization is characterized by hyperfluorescent “leakage” areas, which grow in size and intensity, while passing the 6 times of the fluorescein circulation through the circulating tree: Retinal neurovascularization - 5 patients; Papillary neurovascularization – 3 patients (a patient also showed iris neurovascularization).

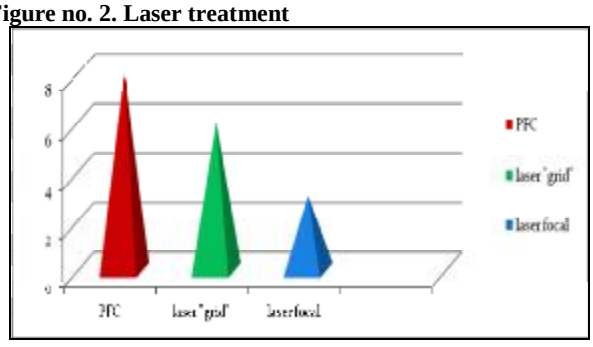
Macular edema was revealed on FA, both in the patients with non-proliferative diabetic retinopathy, and in the patients with proliferative diabetic retinopathy. 15 patients have been diagnosed with diabetic maculopathy (diffuse - 4 patients, focal - 3 patients, ischemic - 3 patients and mixed - 5 patients) – figure no. 1

Figure no. 1. Diabetic maculopathy



On FA, focal maculopathy is characterized as a circumscribed area of “leakage” with late focal hyperfluorescence in networking and good macular perfusion. Diffuse maculopathy shows a generalized “leakage” with early stained hyperfluorescence and late diffuse hyperfluorescence with macula “in flower petal” or “wheel spokes”. In ischemic maculopathy, the nonperfusion area is highlighted as broad foveal hypofluorescence. Subsequently, all the 17 patients received laser treatment - 8 patients pan photocoagulation (PPC - spot with the diameter of 300-500 μm for 0.1 sec, variable energy until getting a whitish-grey impact), 6 patients – “grid” laser (spot with the diameter of 100-150 μm for 0.1 sec, power 100mw), 3 patients – focal laser (spot with the diameter of 50-100 μm for 0.1 sec, power 100mw) – figure no. 2.

Figure no. 2. Laser treatment



DISCUSSIONS

Currently, laser represents the gold standard for the therapy of diabetic retinopathy and, especially for macular edema.(3,17). Laser impacts bring about burns that destroy the retinal ischemic territories, thus inhibiting the neurovascularization process.(18,21) In order to locate ischemia responsible for neurovascularization, FA is compulsory, being the only investigation able to identify these hypoxic retinal areas and that can properly guide the laser treatment.(12,16,24) The patient should represent one of the most important parts of the treatment itself.(22) It is important to help the patients understand that fluorescein angiography is not a treatment method, but that without it, we cannot be sure that we have applied the correct treatment.(25) FA changes in DR represent the mirror of the pre-existing systemic disease control. In terms of treatment, we have to reduce or eliminate hypoxia, as it is one of the key factors in diabetic retinopathy. During hypoxia, gene expression of vascular endothelial growth factor increases the activity of the protein, which is modulated by other factors including inflammatory cytokines, insulin growth factor, reactive oxygen species and degradation products of advanced glycosylation.(14,19,20) Increased macular edema, hard exudates and ischemia at the level of fovea form the diabetic maculopathy - the most common cause of vision loss in diabetic patients.(3,6,21,26) Ischemic diabetic retinopathy is highlighted ophtalmoscopically in the preploriferative or proliferative stage. Ischemia causes blood vessels hyperpermeability, resulting in a break in the hematoretinal barrier and therefore, retinal exposure to neurotoxic biochemical substances. Ischemic diabetic retinopathy with relatively normal fovea evolves through neovascularization or neovascular proliferation.(7,13,23) Preretinal and papilary neovascular proliferation is complicated with vitreous haemorrhage, tractional retinal detachment and secondary neovascular glaucoma.(15,29) Laser photocoagulation is the indispensable therapeutic method of choice for diabetic retinopathy through which all nonperfusion areas are confluently photocoagulated as ischemic territories are responsible for proliferation.(21)

CONCLUSIONS

Fluorescein angiography is the most important method of paraclinical investigation in diabetic retinopathy. In the initial non-proliferative stage, FA demonstrates lesions of the hemato-retinal barrier by highlighting areas of extracapillary diffusion of fluorescein or it can show ischemic territories caused by capillary occlusion. In the stage of proliferative diabetic retinopathy, intraretinal microvascular abnormalities and neovascular networks are highlighted. FA allows the differentiation between the ischemic macular edema and the exudative one; it has a major contribution in determining the type of maculopathy and its severity. FA provides details inaccessible through ophthalmoscopy or fundus biomicroscopy and the images obtained can be stored on photographic film or in digital form, allowing the study of ocular changes occurring over time through repeated examinations.

REFERENCES

1. Arevalo JF. Retinal Angiography and Optical Coherence Tomography, Ed. Springer 2009, part I, 1, 2: 3 – 42;5:105-110.
2. Spitznas M. Understanding Fluorescein Angiography, Springer-Verlag Berlin Heidelberg; 2006.
3. American Diabetes Association – Standards of Medical Care in Diabetes Care. 2005;28,suppl 1, 4-36.
4. Joussen AM, Huang S, Poulaki V. In vivo retinal gene expression in early diabetes. Invest Ophthalmol Vis Sci. 2001;42:3047-57.
5. Dithmar S, Holz FG. Fluorescence Angiography in Ophthalmology, Springer Medizin Verlag Heidelberg; 2008. p. 1-54,132-135.
6. Kanski JJ. Clinical Ophthalmology, 5-th Edition; 2003.
7. Yanoff M, Fine B. Ocular pathology: A Color Atlas. Lippincott- Raven; 1988.
8. http://www.seeca.com/medical/ivfa.php.
9. http://en.wikipedia.org/wiki/Fluorescein_angiography.
10. http://bmb.oxfordjournals.org/cgi/pdf_extract/26/2/161.
11. Stănilă A. Oftalmologie, Ghid practic, Ed Imago Sibiu; 2000.
12. Dumitrache M. Tratat de Oftalmologie, Ed. Carol Davila; 2012. p. 984-1000.
13. Cernea P. Tratat de oftalmologie, Ed. Medicala; 2002. p. 157-161.
14. Broekhuizen LN. Effect of sulodexide on endothelial glicocalyx and vascular permeability in patients with type 2 diabetes mellitus. Diabetologia. 2010;53:2646-2655.
15. Balta F, Merticariu A, Musat Banu Panait Oana – practica patologiei maculare in imagini, Editura Medicala Antaeus, Bucuresti; 2009.
16. Stangu C, Cristescu A, Daraban C, Serghiescu S. Aspecte AFG in Retinopatia Diabetică; 2003.
17. Davidescu L. Retinopatia diabetica prezentata in imagini-Editura Medicala Universitara, Craiova; 2006.
18. Davidescu L, Balta F, Damian C, Preda M. Diabetic retinopathy- -retinophotographic album, Editura Medicala Universitara, Craiova; 2008.
19. Chern K, Zegans ME. Ophthalmology review, Lippincott Wilkins; 2000.
20. Duane's Ophthalmology on CD-ROM; 2006.
21. Fong DS, et al. Retinopathy in diabetes, Diabetes Care. 2004;27:84-87.
22. Cunha-Vaz J, Midena E, Carvalheiro M, Boyer D, Gonzales VH. Diabetic Retinopathy, 9-th EURETINA CONGRESS, Nice, France; 2009. p. 1-9.
23. American Academy of Ophthalmology Basic and Clinical Science Course, Sectuon 12, Retina and Vitreous; 2006.
24. Cohen S, Quentel G. Diagnostique angiographique des maladies retiniennes.
25. Walker J, Creuzot-Garcher C. Eurotimes – Multiple screening strategies aim to reduce burden of diabetic retinopathy. 2009;14(1).
26. Davidescu L, Ignat F. Maculopatia diabetic edematoasa-rezultate terapeutice si cause de esec – Oftalmologia. 2007;1:68-79.
27. Pavan-Langston D. Manual of Ocular Diagnosis and Therapy, 6th Edition, Copyright Â©2008 Lippincott Williams & Wilkins. 2008;8:177-205.
28. Ehlers JP, Shah CP. Wills Eye Manual, the: Office and Emergency Room Diagnosis and Treatment of Eye Disease, 5th Edition, Copyright ©2008 Lippincott Williams & Wilkins. 2008;11:275-333.
29. Rizzo SF, Patelli DR. Chow. Essentials in Ophthalmology - Vitreo-retinal Surgery, 10:89-110.
30. James B, Chew C, Bron A. Lecture notes on Ophthalmology, Ninth Edition, 12:135-142.