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Juvenile diabetes eye complications and treatment

Očne komplikacije i njihovo lečenje kod obolelih od juvenilnog dijabetes melitusa

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Abstract

Background/Aim. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. The aim of this study was to explore the prognosis of patients with juvenile DM regarding diabetic eye complications, as well as the course of the diabetic eye disease related to the treatment undertaken. **Methods.** The study series involved 33 patients with juvenile DM during the period 1992–2007. The influence of the following factors on the course of the disease was estimated: age, the age of the disease onset, time when eye complications appeared, treatment modalities. **Results.** Of the total of 33 diabetics 15 patients were followed for 10 or more years and 18 from 5 to 9 years. At the time of their first visit the mean age was 23.12 ± 6.39 and the mean duration of DM was 17.42 ± 7.42 years. On their first visit, 7 eyes were without any complication. Most of the patients already developed clinical signs of proliferative diabetic retinopathy (41.39%), the signs of nonproliferative diabetic retinopathy (13.13%) and macula involvement (10.10%). Diabetic cataract was found in 8.8% as well as tractional retinal detachment. Eleven out of 66 eyes were with vitreous hemorrhage. Two patients (5.5%) suffered neovascular glaucoma. There was 1 (2.2%) patient with developed rubeosis iridis and simplex glaucoma. Panretinal photocoagulation was performed in 65% of patients, focal photocoagulation in 15%, 12% patients underwent pars plana vitrectomy and 4% had cataract surgery with intraocular lens implantation and peripheral retinal kryopexy. **Conclusion.** Total vision loss due to eye complications of juvenile DM may be prevented if timely diagnosed with regular check ups and early treatment.

Key words:
diabetes mellitus, type I; diabetic retinopathy; therapeutics; laser coagulation; treatment outcome.

Apstrakt

Uvod/Cilj. Dijabetes melitus (DM) je metabolički poremećaj koji karakteriše hiperglikemija. Cilj studije bio je da se ispita prognoza vida bolesnika sa insulin-zavisnim juvenilnim DM, kao i efekta lečenja komplikacija dijabetičke bolesti oka. **Metode.** U studiju su bila uključena 33 bolesnika sa juvenilnim DM u periodu 1992–2007. Razmatran je uticaj sledećih faktora na tok bolesti: životno doba bolesnika, vreme početka bolesti, vreme pojave komplikacija, vrsta lečenja. **Rezultati.** Od ukupnog broja bolesnika, 15 su praćeni u periodu od 10 i više godina, a 18 od pet do devet godina. U vreme prvog oftalmološkog pregleda, srednje životno doba obolelih bilo je 23,12 ± 6,39, a srednje vreme trajanja bolesti je 17,42 ± 7,42 godine. Na prvom pregledu sedam očiju bilo je bez dijabetičkih promena. Većina drugih bolesnika imala je komplikacije u vidu proliferativne dijabetičke retinopatije (41,39% očiju), neproliferativne dijabetičke retinopatije (13,13% očiju), dok je makula bila zahvaćena kod 10,10% očiju. Dijabetička katarakta bila je prisutna kod 8,8%, kao i trakciona ablacija retine. Jedanaest od 66 očiju imalo je vitreusne hemoragije. Dva bolesnika (5,5% očiju) bolovalo je od neovaskularnog glaukoma. Jedan bolesnik (2,2% očiju) imao je rubeozu dužice i simpleks glaukom. Urađena je panretinalna fotokoagulacija 65% očiju, fokalna fotokoagulacija 15%, pars plana vitrektomija 12%, dok je 4% operisano zbog katarakte uz ugradnju intraokularnog sočiva i perifernom kriopeksijom retine. **Zaključak.** Potpuni gubitak vida kao posledica komplikacija juvenilne dijabetičke bolesti oka može se prevenirati pravovremeno postavljenom dijagnozom, urednim kontrolama i adekvatnom terapijom.

Ključne reči:
dijabetes melitus, insulin-zavisni; dijabetesna retinopatija; lečenje; koagulacija laserom; lečenje, ishod.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. In the Western World, approximately 1% of the population is diabetic, and at least another 1% is with undiagnosed high levels of serum glucose. Juvenile onset insulin-dependent DM (IDDM) accounts for approximately 10–15% of DM, the remainder being maturity onset or non insulin-dependent diabetics. Aside from acute glucose serum level abnormalities, the main risks to health are the characteristic long-term complications. These include cardiovascular diseases, chronic renal failure, retinal and nerve damages [1].

Retinal damage is presented with diabetic retinopathy (DR) which is the most frequent complication of diabetes and a leading cause of impaired vision in the Western World. It is well-known that the age of onset and the duration of diabetes are the strongest risk factors for development and progression of retinopathy [2, 3], which can be presented in the form of nonproliferative (NPDR), preproliferative or proliferative form (PDR), depending on the presence of the new blood vessels on the surface of retina or optic disc. For juvenile onset IDDM, PDR is the most frequent finding [3].

The essence of eye complications are the mechanisms through which microvascular occlusion transforms DR into an ischemic retinopathy**,** with neovascularisation [4, 5]. The first pathologic sign seen in the retina are retinal capillary microaneurysms. They cause the development of excessive vascular permeability and therefore leakage. Further, microvascular occlusion occurs followed by the proliferation of new blood vessels and accompanying fibrous tissue on the surface of the retina and optic disk which contracts together with the vitreous. Further, bleeding that occurs from new blood vessels and contraction of the fibrous tissue compromises visual acuity (VA) through hemophthalmos or tractional retinal detachment. If the process spreads to the anterior part of the eye, neovascular glaucoma develops with painful eye and total vision loss. Aside from these severe complications, VA is more often compromised through macular edema, due to disruption and increased permeability of perifoveolar capillary network, in a form of clinically significant macular edema.

In attempt to avoid diabetic eye complications and total visual loss, laser photocoagulation (LFK) of retina is indicated. It may be performed in a form of focal or panretinal LFK (PRP). The aim of these procedures is to decrease retinal ischemia through direct destruction of the retinal tissue and reduction of angiogenic factors indirectly. There are also opinions that pigment epithelial proliferation after photocoagulation has some antiangiogenic effect [6].

New vessel proliferation is a consequence of the effect of angiogenic factors, delivered from the ischemic retinal tissue. Researchers learn more about how angiogenic agents such as vascular endothelial growth factor, as well as the isoenzyme protein kinase C beta conspire to disrupt endothelial cell function, leading to increased retinal vascular permeability. In that sense, modern investigations are trying to find an answer to the question whether pharmacological treatments might someday supplement LFK as a preferable early intervention for diabetic eye disease [7–10]. But, until new therapeutic possibilities are available, we have to perform PRP in order to save patient's vision, although there are some undesirable effects of it, such as compromised VA, visual field constriction, color vision perception disturbances, reduced contrast sensitivity and night vision.

Therefore, in order to gain a better understanding of this serious disease, the authors performed a 15-year follow up based on young patients with IDDM–related eye complications and therapy performed in order to save VA. The base for this research is general agreement that early diagnosis and treatment of DR can slow its progression and help to prevent blindness [1, 11].

Methods

A retrospective study was based on records of 33 patients (66 eyes) diagnosed with juvenile onset DM at the Department of Ophthalmology, University Hospital "Zvezdara", Belgrade, Serbia, between 1992 and 2007. All the patients came with the diagnosis of juvenile-onset IDDM.

All the patients were examined by the same ophthalmologists (authors) for at least five times and the examination included the same procedure. An incorrected best VA and best corrected VA were taken, intraocular pressure measurments with Goldmann applanational tonometry, examination on the slit lamp and finally, after pupil dilatation, optic disc and retina were evaluated. Fundoscopy was performed by direct and indirect ophthalmoscopy (included biomicroscopy).

The diagnosis of DR was established based on its characteristic presentation, either as a NPDR or PDR form. Fluorescein angiography was obtained for the small number of patients. It was done in cases in which clinical presentation was not sufficient for classification of retinopathy. It was performed also in cases with maculopathy to ease focal photocoagulation. Slit lamp presentation of rubeosis iridis, neovascular glaucoma or cataract formation were recorded, too. During the treatment, ophthalmologic evaluation was performed to determine new retinal lesions, enlargement of pre-existing lesions, and changes in their appearance.

As a complication of DR we posed a diagnosis of rubeosis iridis, neovascular glaucoma, cataract, partial or total hemophthalmos and tractional retinal detachment.

The treatment was initiated as soon as the diagnosis was confirmed. Depending on the type of changes, we performed focal LFK or PRP, cataract surgery with intraocular lens implantation, glaucoma medications, pars plana vitrectomy or peripheral retinal kryopexy.

All analyses were performed using an electronic database organized in the SPSS (version 11.5) statistical package. Descriptive methods were used for mean values of the onset of DM, age of patients, gender, etc. The effects of treatment to VA, and VA on the first and the last examination were compared by the one-way ANOVA, with the level of significans of 0.05. The Kaplan-Meier survival method was used to determine the median time complications appearing.

Results

We reviewed the charts of 33 patients with juvenile IDDM, out of which 39.39% males and 60.60% females. The youngest patient at the first visit was 12-year old and the oldest one was 37, with the mean age of 23.12±6.39 years. The minimum duration of DM was 7 years and the maximum 33 years with the mean 17.42±7.42 years. The age at which the diagnosis of DM was first established was as little as 2 and as big as 19, with the mean age of 8.61±4.27 years.

For 15 patients we reviewed the charts for more than 10 years of a regular follow-up and for 18 patients from 5 to 9 years of a regular follow-up.

In 13 eyes the first eye complication developed 6 to 10 years from the beggining of the diesease. In 30 eyes DM lasted betwen 11 and 20 and in 16 eyes over 21 years before the first signs of ophthalmological complications were noticed. After 20 years of duration there were no patients (eyes) without complications. Using the Kaplan Meier test of probability, we can see that after 10 years of duration 50% of patients would have some complications, but after 20 years of DM, almost 90% of patients would have it, and this difference is significant.

On their first visit, a diagnosis of PDR was established in 41.39% of the patients, NPDR at 13.13%, macula was involved in 10.10% of the patients. Cataract was found in 8.8% as well as tractional retinal detachment. Seven of 66 eyes were without any changes at the first visit. Eleven of 66 (16.66%) eyes had vitreous gel hemorrhage. Neovascular glaucoma suffered 5.5% of the patients. There were 2.2% with rubeosis iridis and simplex glaucoma.

Panretinal laser photocoagulation was performed in 65% of the patients, focal treatment in 15%, 12% had pars plana vitrectomy and 4% had cataract surgery and peripheral retinal kryopexy. We compared best corrected VA at the first visit with best corrected VA at the last visit according to the therapy performed, and found statistical significance (p = 0.037 and p = 0.045).

Visual acuity at the time of first visit was as follow: none of the patients were blind, light perception had 7 eyes, 14 eyes had VA less than 0.7 and 45 eyes had VA of 0.8 or better. At the last visit 7 of the eyes were blind, two had light perception, 14 eyes had VA less than 0.7 and VA of 0.8 and better had 43 eyes. The VA at the first and last visit differed significantly (p = 0.00).

Discussion

Diabetic retinopathy is the most frequent complication of diabetes and a leading cause of impaired vision in most countries. Its asymptomatic nature and its etiopathogenesis, which is still unclear due to its multifactorial complexity makes DR-related blindness a growing social problem in many countries [12]. This refers especially to the cases of juvenile-onset DM.

Physicians are aware of the fact that with the age of onset and the duration of juvenile diabetes, the development and progression of retinopathy rises [1, 11, 13]. Still, it remains unknown which is the best time to start with controls of young diabetics, having in mind that there are still some subjects who develop mild changes in spite of a long duration of disease.

Burger et al. [3] point out that compared with ophthalmoscopy, as performed by an experienced ophthalmologist, fluorescein angiography allows detection of retinal changes about 4 years earlier.

Some authors confirm that preschool-age children at the onset of diabetes stay free from even minimal retinal complications longer than adolescents. Furthermore, the "onset" of retinopathy over 15 years of age in the great majority of subjects suggests some influence of sexual maturation during puberty [3, 14]. Based on up to date studies, yearly exams are not necessarily required for juvenile-onset diabetics within the first decade of life, but should be performed after 5 years of diabetes in younger children and after 2 years in adolescents [15].

On the other hand, proliferative changes may develop in previosly "normal" fundus from one examination to another within only two years in young diabetics [3].

Most of our patients had complications on their first visit. There were no patients with DM lasting less than 7 years. The mean age of duration of DM was 17.42 ± 7.42 and the mean age at their first visit was 23.12 ± 6.39 years.

In our series, the risk of severe eye complications rose with the duration of diabetes, so that after 10 years of duration almost half of the patients had some complications, while after 20 years, none of the patients was without complication ($p < 0.05$).

In the series of Krolewsky et al.[16], the risk of development of severe eye complications was almost nonexistent during the first 10 years of diabetes, but rose abruptly to its maximum level, and remained at that level for the next 25 years. Other authors report that the median risk age for the development of retinopathy 17.5 years, which is consistent with our findings [5, 16, 17].

In our serie the most common DM-related complication on the first visit was PDR (41.39%). Some authors mention different percents (21.6%; 55.2%) [13, 16–18].

To avoid blindness, nowadays methods include medical management (control of blood sugar, blood pressure, and serum lipids) and ocular management (LFK and pars plana vitrectomy). Adjunctive pharmacologic therapies (intravitreal triamcinolone acetonide and antivascular endothelial growth factor agents) have shown early promise in the treatment of both diabetic macular edema and PDR [15]. Meanwhile, laser treatment is still the gold standard of treatment for focal and diffuse diabetic macular edema and PDR, although its associations with some decline in visual functions are expected [2, 15, 19– 22]. When properly treated, PRP reduces the risk of moderate and severe visual loss by 50–90% in patients with severe NPDR and PDR, and the risk of visual loss from macular edema by 50–70% [22–25]. Some other treatment possibilities are recommended in cases in which PRP is not enough, like pars plana vitrectomy, cataract surgery and peripheral retinal kryopexy [26–29].

The goal of these treatments is to obtain good VA. Yet, VA in our patients was worse at the end of the study. This is because most of the patients came when severe complica-

tions already developed, so the therapy had no beneficial effect. These values for VA were statisticaly significant ($p = 0.00$). On the other hand, patients who came with PDR and less macular involvement, kept their VA for a long period of time. In the series of some authors, VA was guarded through the study (0.5 and better) and at the end of their treatment, although they did not find any significance in a VA before and after the therapy [30].

Visual stability after PRP indicated the need for this kind of treatment in an early phase of PDR in order to preserve visual function.

Conclusion

According to our results, we would like to confirm and support the opinion that if a patient with DM refers to ophthalmologist on time, VA could be saved for a long period of time. In that sence, the most important are early detection of the disease, intensive metabolic control, patient education about asymptomatic nature of DR and the use of screening programs for the youngsters from the age of 10 years. In case of present complications the treatment should be considered as soon as possible.

R E F E R E N C E S

1. *Rubio Cabezas O, Argente Oliver J.* Diabetes mellitus in children and adolescents: chronic complications and associated diseases. An Pediatr 2007; 66(3): 282–9. (Spanish)
2. *Mohamed Q, Gillies MC, Wong TY.* Management of diabetic retinopathy: a systematic review. JAMA 2007; 298(8): 902–16.
3. *Burger W, Hövener G, Düsterhus R, Hartmann R, Weber B.* Prevalence and development of retinopathy in children and adolescents with type 1 (insulin-dependent) diabetes mellitus. A longitudinal study. Diabetologia 1986; 29(1): 17–22.
4. *Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW, Jefferson LS,* et al; JDRF Diabetic Retinopathy Center Group. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes 2006; 55(9): 2401–11.
5. *Hykin PG.* Diabetic Retinopathy: Clinical Features and Management. J Comm Eye Health 1996; 9: 58–62.
6. *Glaser BM, Campochiaro PA, Davis JL Jr, Jerdan JA.* Retinal pigment epithelial cells release inhibitors of neovascularization. Ophthalmology 1987; 94(7): 780–4.
7. *Ryan GJ.* New pharmacologic approaches to treating diabetic retinopathy. Am J Health Syst Pharm 2007; 64(17 Suppl 12): S15–21.
8. *Das Evcimen N, King GL.* The role of protein kinase C activation and the vascular complications of diabetes. Pharmacol Res 2007; 55(6): 498–510.
9. *Dieudonné SC, La Heij EC, Diederen RM, Kessels AG, Liem AT, Kijlstra A,* et al. Balance of vascular endothelial growth factor and pigment epithelial growth factor prior to development of proliferative vitreoretinopathy. Ophthalmic Res 2007; 39(3): 148–54.
10. *Damico FM.* Angiogenesis and retinal diseases. Arq Bras Oftalmol 2007; 70(3): 547–53. (Portuguese)
11. *Massin P, Erginay A, Mercat-Caudal I, Vol S, Robert N, Reach G,* et al. Prevalence of diabetic retinopathy in children and adolescents with type-1 diabetes attending summer camps in France. Diabetes Metab 2007; 33(4): 284–9.
12. *Morello CM.* Etiology and natural history of diabetic retinopathy: an overview. Am J Health Syst Pharm 2007; 64(17 Suppl 12): S3–7.
13. *Chetthakul T, Likitmaskul S, Plengvidhya N, Suwanwalaikorn S, Kosachunhanun N, Deerochanawong C,* et al. Thailand diabetes registry project: prevalence of diabetic retinopathy and associated factors in type 1 diabetes mellitus. J Med Assoc Thai 2006; 89(Suppl 1): S17–26.
14. *Frank RN, Hoffman WH, Podgor MJ, Joondeph HC, Lewis RA, Margherio RR,* et al. Retinopathy in juvenile-onset type I diabetes of short duration. Diabetes 1982; 31(10): 874–82.
15. *Bloomgarden ZT.* Screening for and managing diabetic retinopathy: current approaches. Am J Health Syst Pharm 2007; 64(17 Suppl 12): S8–14.
16. *Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR.* Risk of proliferative diabetic retinopathy in juvenile-onset type I diabetes: a 40-yr follow-up study. Diabetes Care 1986; 9(5): 443–52.
17. *Palmberg P, Smith M, Waltman S, Krupin T, Singer P, Burgess D,* et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. Ophthalmology 1981; 88(7): 613–8.
18. *Maia OO Jr, Takahashi WY, Bonanomi MT, Marback RF, Kara-José N.* Visual stability in diabetic retinopathy treated by panretinal laser photocoagulation. Arq Bras Endocrinol Metabol 2007; 1(4): 75–80.
19. *Fong DS, Girach A, Boney A.* Visual side effects of successful scatter laser photocoagulation surgery for proliferative diabetic retinopathy: a literature review. Retina 2007; 7(7): 16–24.
20. *Sánchez MC, Luna JD, Barcelona PF, Gramajo AL, Juarez PC, Riera CM,* et al. Effect of retinal laser photocoagulation on the activity of metalloproteinases and the alpha(2)-macroglobulin proteolytic state in the vitreous of eyes with proliferative diabetic retinopathy. Exp Eye Res 2007; 85(5): 644–50.
21. *Schwartz SG, Flynn HW Jr.* Pharmacotherapies for diabetic retinopathy: present and future. Exp Diabetes Res 2007; 2007: 524–87.
22. *Lang GE.* Laser treatment of diabetic retinopathy. Dev Ophthalmol 2007; 39: 48–68.
23. *Mohamed Q, Gillies MC, Wong TY.* Management of diabetic retinopathy: a systematic review. JAMA 2007; 298(8): 902–16.
24. *Boyer DS, Ron P.* Gallemore, Changing Approaches to Diabetic Retinopathy Despite a variety of treatments, diabetic retinopathy is a common couse of blindness in adults. Review of Ophthalmology 2007; 14(3): ID 13269.
25. *Giusti C.* Retinopathy in juvenile diabetes: a 10-year (1990–2000) review. Pediatr Diabetes 2001; 2(2): 83–93.
26. *Korda V.* Surgical treatment of diabetic retinopathy. Vnitr Lek 2007; 53(5): 509–11.
27. *Kleinmann G, Hauser D, Schechtman E, Landa G, Bukelman A, Pollack A.* Vitreous hemorrhage in diabetic eyes previously treated with panretinal photocoagulation. Int Ophthalmol 2008; 28(1): 29–34.
28. *Meyer CH.* Current treatment approaches in diabetic macular edema. Ophthalmologica 2007; 221(2): 118–31.
29. *Wilson ME Jr, Levin AV, Trivedi RH, Kruger SJ, Elliott LA, Ainsworth JR,* et al. Cataract associated with type-1 diabetes mellitus in the pediatric population. J AAPOS 2007; 11(2): 162–5.
30. *Hitani K, Yamamoto T, Sato Y.* Long-term results of grid pattern photocoagulation for diffuse diabetic macular edema. Nippon Ganka Gakkai Zasshi 2007; 111(5): 401–6.

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