ASSESSMENT OF OCULAR MANIFESTATION FREQUENCY AND QUALITY OF LIFE IN CHRONIC MYELOPROLIFERATIVE DISORDERS

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Chronic myeloproliferative disorders (CMPD) include hemoblastoses with abnormal proliferation of myeloid lineages and concomitant alterations in the peripheral blood indicators. The aim of this study was to assess the frequency and structure of ophthalmic complications as a quality of life factor in patients with CMPD. A group of patients with hemoblastoses of this type (n = 41) were surveyed using National Eye Institute Visual Function Questionnaire-25 along with a comprehensive examination by noninvasive ophthalmological techniques. The patients typically reported impaired visual acuity, visual discomfort and foreign body sensation in the eyes. Though many of the patients assessed their general health and vision as satisfactory, the vast majority (68.3%) expressed serious concerns about their visual abilities. The ophthalmological examination revealed various defects including refractive errors (61%), corkscrew dilation and tortuosity of conjunctival and retinal vessels (77.9%), recurrent subconjunctival hemorrhages (39%) and dilated optic nerve sheaths (36.6%). The survey data indicate that visual impairments significantly affect quality of life in patients with CMPD. Overall, the results underscore the importance of interdisciplinary approach in the management of patients with CMPD to enable early diagnosis and feasible correction of the ophthalmic component.

Keywords: chronic myeloproliferative disorders, ocular manifestations, quality of life

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ОЦЕНКА ЧАСТОТЫ ГЛАЗНЫХ ИЗМЕНЕНИЙ И КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ ПРИ ХРОНИЧЕСКИХ МИЕЛОПРОЛИФЕРАТИВНЫХ ЗАБОЛЕВАНИЯХ

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К хроническим миелопролиферативным заболеваниям относят группу гемобластозов, характеризующуюся разрастанием миелоидных линий гемопоэза и изменением показателей периферической крови. Целью работы было оценить частоту офтальмологических нарушений и качество жизни вследствие изменений зрительных функций у пациентов с хроническими миелопролиферативными заболеваниями. Пациенты с данной группой гемобластозов (n = 41) для оценки качества жизни были проанкетированы при помощи специализированного медицинского опросника «National eye institute visual function questionnaire-25», обследованы стандартными и специальными неинвазивными методами. Большинство из них предъявляли жалобы на ухудшение зрения, дискомфорт, ощущение инородного тела в глазах. По данным анкетирования, многие больные оценивают свое общее состояние здоровья и зрения как удовлетворительное, подавляющая часть опрошенных (68,3%) испытывают беспокойство по поводу зрения. По результатам объективного офтальмологического обследования, у большинства пациентов выявлены различные виды патологий рефракции (61%), штопорообразное расширение и извитость сосудов конъюнктивы и сетчатки (77,9%), частые субконъюнктивальные кровоизлияния (39%), расширение периневрального пространства зрительных нервов (36,6%). При хронических миелопролиферативных заболеваниях ухудшается качество жизни пациентов, возможно поражение различных структур глаза. Крайне важен междисциплинарный подход к ведению таких больных с целью ранней диагностики и коррекции офтальмологических нарушений.

Ключевые слова: хронические миелопролиферативные заболевания, глазные проявления, качество жизни

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Chronic myeloproliferative disorders (CMPD) result from defects of clonal proliferation of the bone marrow pluripotent stem cells leading to the excessively increased numbers of blood cells with sustained differentiation capacity [1]. The most common types of CMPD are chronic myeloid leukemia (CML), essential thrombocythemia (ET) and true polycythemia (TP). CMPD is known to confer multiple organ complications. The ophthalmic component in CMPD largely results from the abnormal hemodynamics and blood rheology that reflect the altered content of formed elements in peripheral blood due to the inhibition of normal hemopoiesis. Another important clinical factor in CMPD is the imbalance in blood coagulation and anticoagulation systems due to the release of coagulants by circulating blast cells [2]. The abnormal hemodynamics leads to increased vascular permeability, endothelial dysfunction and hypoperfusion of ocular tissues. An additional source of ophthalmic damage in CMPD is provided by anti-hemoblastosis drugs that may be oculotoxic per se. For instance, conjunctival hemorrhages, bilateral periorbital edema and dry eye syndrome have been described in patients receiving tyrosine kinase

inhibitors as a treatment for CML [3, 4]. In this study we aimed to assess the frequency and structure of ocular manifestations and their impact on quality of life in patients with CMPD.

METHODS

A total of 41 patients with CMPD, 29 women (70.7%) and and 12 men (29.3%) aged 51 ± 14 years, participated in the study during the period from October 2020 to November 2021. The inclusion criteria were (1) age over 18 and (2) verified diagnosis of the CMPD spectrum. The exclusion criteria were (1) pregnancy or breastfeeding at the time of surveying/examination and (2) verified diagnoses of diabetes mellitus and/or arterial hypertension. The diagnostic structure of the cohort was as follows: 32 patients with CML (78%), five patients with ET (12.2%) and four patients with TP (9.8%). The disease length constituted 11 ± 6 years. In terms of treatment for CMPD, 32 patients received first- and second-generation tyrosine kinase inhibitors (78%), five patients received hydroxycarbamide (12.2%), three patients received interferon α-2b (7.3%) and one patient was newly diagnosed and received no specific treatment (2.4%).

It is widely recognized that visual impairments may negatively affect the general health status, as well as social functioning and quality of life. The medical term "quality of life" (QL) reflects the capability to engage in normal daily activities in spite of particular medical condition. The study used the self-report National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) encompassing 25 questions and reflecting the general health status and various aspects of visual performance, with the scores structured in 12 subscales termed General Health, General Vision, Ocular Pain, Distance Vision, Near Vision, Peripheral Vision, Color Vision, Driving, Social Functioning, Mental Health, Role Difficulties and Dependency. The scores were calculated using the standard Likert scaling algorithm within the range from 0 (extremely poor) to 100 (perfectly normal). The control group included 30 volunteers without CMPD and matching by sex and age to the main group. The questionnaire scores were subject to descriptive statistical characterization; the distributions were assessed for normality using the Shapiro–Wilk test. Given the non-normality of distributions for the studied indicators, the comparisons used nonparametric Mann–Whitney test. The statistical analysis was carried out in the Microsoft Excel 2204 spreadsheet software (Microsoft Corporation; USA). The differences were considered significant at $p < 0.05$.

In addition to the survey, all patients underwent a standard ophthalmological examination including visometry, autorefractometry, tonometry, perimetry, biomicroscopy and ophthalmoscopy, as well as advanced non-invasive examinations including optical coherence tomography (OCT) of the macular area and optic nerve disc, OCT angiography of the macular area and optic nerve disc in an Avanti RTVue XR tomograph (Optovue; USA), fundus photography with a VISUCAM 524/224 fundus camera (Carl Zeiss; Germany) and ultrasound examination of the eyeball and orbital tissues by vascular dopplerography with a MySono U5 ultrasound system (Samsung-Medison; South Korea).

RESULTS

Remarkably, 36 (88%) of the patients included in the study had never been comprehensively examined by an ophthalmologist. The prevalent ocular manifestations included impaired visual acuity (28 pts, 68.3%); visual discomfort and foreign body sensation (12 pts, 29.3%); tearing (10 pts, 24.4%); dry eyes (8 pts, 19.5%); blurred vision (7 pts, 17%) and object shape distortion (2 pts, 4.9%). Upon surveying, patients with CMPD ($n = 41$) rated their vision as good (12 pts, 29.3%), satisfactory (20 pts, 48.8%) or poor (9 pts, 22%); at that, 26 pts (63.4%) rated their general health as satisfactory. The vast majority of the group (28 pts, 68.3%) "felt frustrated because of eyesight" i.e. experienced serious concerns about their visual abilities, 13 of them constantly (31.7%). Statistical processing of the data for different subscales of the questionnaire revealed significantly lower General Health, General Vision and Driving scores (respectively, 34.1 ± 1.9 vs. 50.9 ± 3.8, $p < 0.001$; 61.5 ± 2.3 vs. 77.2 ± 2.8, $p < 0.001$; and 47 ± 12.7 vs. 163 ± 23.7; $p < 0.001$) along with significantly higher Ocular Pain scores (respectively, 109.8 ± 4.1 vs. 95.9 ± 3.5; $p < 0.05$) in patients with CMPD compared with the control. Other subscales revealed no significant differences between patients with CMPD and the control group.

The physical eye examination revealed ophthalmological defects in 38 pts with CMPD (92.7%). Refractive errors were diagnosed in 25 pts (61%); these included myopia in 9 pts (36%), hyperopia in 6 pts (24%), presbiopia in 5 pts (20%)

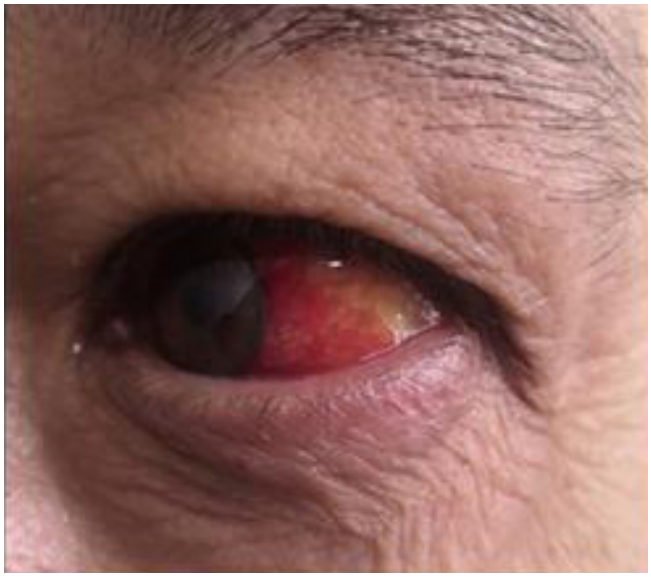

Fig. 1. Subconjunctival hemorrhage in male patient N. with CML

Fig. 2. Corkscrew dilation and tortuosity of conjunctival vessels in male patient A. with CML

and astigmatism in 5 pts (20%). Bilateral non-inflammatory periorbital edema and dry eye syndrome were diagnosed in 3 pts (7.3%) and 6 pts (14.6%), respectively. In addition, 10 pts (24.3%) manifested irregularity and corkscrew dilation of conjunctival vessels with intermittent blood flow. Other defects included recurrent subconjunctival hemorrhages in 16 pts (39%) and corkscrew dilation and tortuosity of retinal vessels in 22 pts (53.6%). Ultrasound scans of the eyeball and orbital tissues with vascular dopplerography revealed dilated perineural spaces of the optic nerves in 15 pts (36.6%) and reduced velocity of blood flow in ophthalmic arteries in 7 pts (17%). OCT of the macular area revealed serous detachment of the retinal neuroepithelium in 2 pts (4.9%). OCT angiography of the macular area revealed retinal neovascularization in 2 pts (4.9%). Primary open-angle glaucoma was diagnosed in 2 pts (4.9%); for one of them, our OCT examination of the optic disc identified this complication for the first time. Keratoconus, immature cataract, destruction of the vitreous body, lamellar macular hole, macular edema and ischemic optic nerve atrophy were represented by single cases (2.4% each) in the studied group of patients with CMPD.

DISCUSSION

QL in CMPD may progressively decline for multiple reasons linked in some manner with the main diagnosis, including the characteristic damage to eye structures. The estimated frequency of the ophthalmic component in hemoblastoses is 14–53 %. Its manifestations are subdivided into primary (direct leukemic infiltrations of the eye) and secondary (resulting from the altered rheological properties of the blood and the ongoing therapy) [5]. Direct involvement of the eyes is characteristic of acute leukemia [6]. Comparative studies on the incidence of ocular damage in acute and chronic hemopoietic malignancies are few and most of them argue that ocular manifestations are more common in acute than in chronic leukemia [7]. Thus, relative prevalence of leukemic ophthalmopathy constituted 68% for acute myeloid leukemia, 42% for acute lymphoid leukemia, 33% for chronic lymphoid leukemia and 13% for chronic myeloid leukemia, whereas such formidable complications as subhyaloid hemorrhage involving the posterior pole (20%) and vitreous hemorrhage (10%) were observed exclusively in patients with acute leukemia [8]. At the same time, a number of studies emphasize the high prevalence of ocular manifestations of variable severity in chronic leukemia [7].

A considerable number of our patients presented with recurrent spontaneous subconjunctival hemorrhages approximately every 2–3 months (Fig. 1). It should be noted that the hemorrhagic syndrome, which often provides the basis for other ocular manifestations in hemoblastoses, reflects the increased vascular permeability resulting from abnormal hemopoiesis. The higher incidence of ocular bleeding may also be a consequence of targeted therapies for CMPD [3].

The corkscrew-type lumina dilation and tortuosity of conjunctival and retinal vessels observed in most of the patients (Figs. 2 and 3) might result from the increased blood viscosity [9] confirmed by laboratory tests.

The blood hyperviscosity typical in patients with hematological malignancies may also lead to intracranial hypertension (ICH) as a consequence of the impaired drainage of cerebrospinal fluid into dural venous sinuses [10]. Dilation of the optic perineural space, considered a direct sign of ICH, was observed in ultrasound scans of the eyeball and orbital tissues with vascular dopplerography in more than one-third of the cases (Fig. 4). All patients exhibiting dilated optic nerve sheaths underwent magnetic resonance imaging of the brain revealing signs of ICH without focal pathology in all cases.

Another possible consequence of the hemoblastosis-associated damage to microcirculation in ocular tissues is exudative (serous) detachment of the retinal neuroepithelium and secondary dysfunction of the retinal pigment epithelium (Fig. 5) [11]. The pathogenesis of such conditions has been related to partial occlusion of choriocapillaries and impaired choroidal hemoperfusion [12]. The resulting ischemic effect on the retina observed in myeloproliferative disorders may cause microaneurysms, arteriovenous anastomoses and pathological retinal neovascularization (Fig. 6) [13].

The identified ocular manifestations may eventually lead to critical visual impairments up to a complete loss of vision. Importantly, an ophthalmologist may be the first physician to suspect a proliferative blood disease based on the results of an eye examination and refer the patient to a hematologist in a timely manner. In turn, hematologists and therapists should be explicitly aware that hemoblastoses present with severe ocular manifestations. Therefore, it is pivotal to ensure an interdisciplinary framework in the management

Fig. 3. Corkscrew dilation and tortuosity of retinal vessels in male patient M. with CML

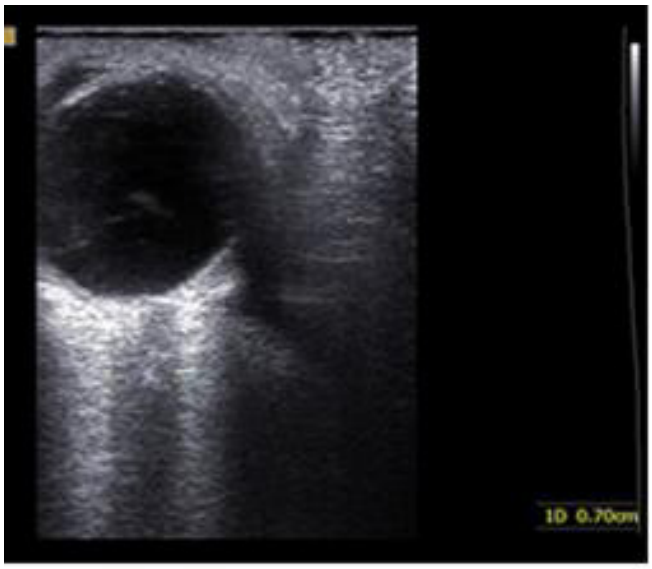

Fig. 4. Dilation of the optic perineural space in male patient M. (main diagnosis — CML; ultrasound scan of the eyeball and orbital tissues with vascular dopplerography)

of such patients, enabling joint participation of hematologists and ophthalmologists for the purpose of early diagnosis and treatment of the ophthalmic complications in CMPD.

Visual impairments, which most certainly affect daily routines and the ability to choose a desired lifestyle, are likely to affect psychological comfort and social adaptation of the patients thereby reducing QL. The beginning of this century was marked by a significant increase in the number of medical studies with a special focus on QL. The assessment is carried out to account for the treatment efficacy and the success of preventive and rehabilitation protocols, as well as to provide a means for personalized monitoring of the patient's condition. The NEI VFQ-25 questionnaire has been widely applied in patients with cataracts, glaucoma, retinopathy and age-related macular degeneration. QL assessment using this method provided a substantive contribution to a number of large studies. QL is severely impacted by visual impairments, with a consistent decrease in multiple subscale scores of the questionnaire [14, 15]. QL measurements in visually affected patients provide important indicators for the socio-psychological outcome in a wide spectrum of disorders including primary ocular conditions as well as chronic systemic disorders with ophthalmic component. The QL scores allow differential determination of the disease influence on the patient's condition with regard to both disease-related and disease-unrelated factors.

Our survey suggests that the decrease in QL values largely reflects the underlying chronic disease and ongoing drug therapy complemented by various ametropias and other ophthalmic disorders revealed by physical examination.

CONCLUSIONS

The data indicate that the vast majority of the patients with CMPD (92.7%) present with ophthalmic component which significantly affects the life quality as indicated by the General Vision, Ocular Pain, General Health and Driving subscales of NEI VFQ-25. Though the study has fully achieved its goal in terms of primary characterizaton, the clinical picture of ocular manifestations that occur in CMPD and related hematological diseases is not finished. The origin of visual impairments in CMPD and their clinical dynamics require further dedicated analysis.

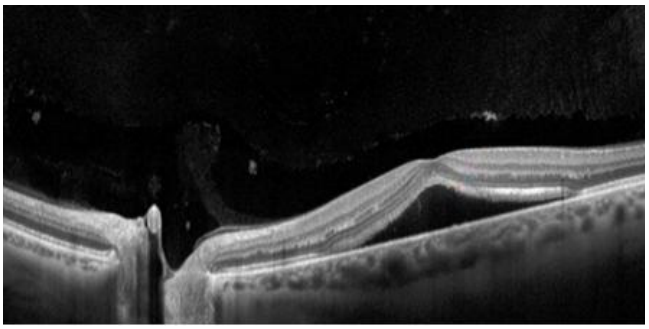

Fig. 5. Serous detachment of the retinal neuroepithelium in female patient S. (main diagnosis — TP; OCT of the macular area)

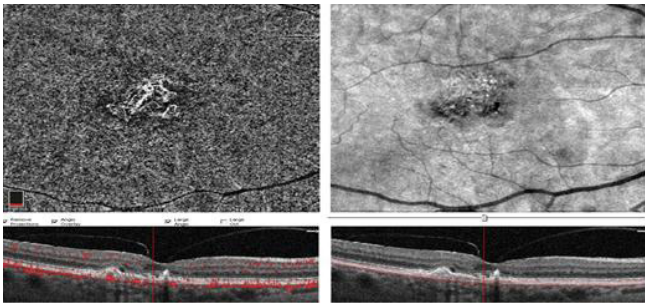

Fig. 6. Choroidal neovascular membrane in the macular area visualized in female patient T. (main diagnosis — CML; OCT angiography of the macular area)

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