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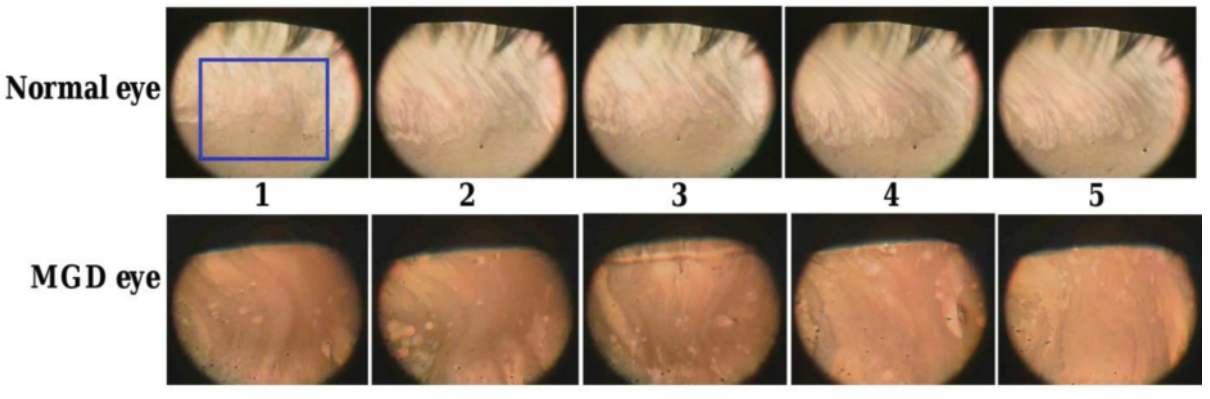

Publication of the “National Academy Glaucoma” Foundation

BULGARIAN FORUM
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Sessions: Glaucoma & Retina

Sofia, 14 April 2018, Hotel „Forum"

Фондация „Национална Академия Глаукома"

Уважаеми колеги,

Имаме честта да Ви поканим на **XI Международен Симпозиум на Фондация „Национална Академия Глаукома"**, който ще се състои в **гр. София на 14 април 2018 г. в Хотел „Форум"**.

В рамките на симпозиума ще се проведе и **сесия „Ретина"**.

При желание от Ваша страна да изнесете доклад в рамките на симпозиума, моля да изпратите резюме със заглавие, автори и институция на български и английски език до 1-ви март 2018 г. на електронната поща на фондацията.

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Проф. д-р Ботьо Ангелов д.м.
Учредител и Управител на Фондация „Национална Академия Глаукома"

Applications of morphology and dynamics of tear film lipid layer to dry eye diagnostics: a mini review

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Abstract

There is a pressing need to develop noninvasive, rapid and sensitive methodology for dry eye diagnosis that would be available to ophthalmologists and optometrists. A major contender for such methodology is the assessment of tear film lipid layer (TFLL) morphology and dynamic reorganization at blink via specular microscopy by affordable modifications of standard biomicroscope or commercial devices (DR-1α interferometer, LipiView, Tearscope Plus etc.). In order to fully utilize the diagnostic power of this approach it is necessary to account not only for the mean thickness of the tear film lipid layer, but also for the thickness distribution heterogeneity (i.e. thickness standard deviation) and the dynamic reorganization features of the lipid layer at the ocular surface.

Key words: tear film lipid layer, dry eye, specular microscopy.

Introduction

Tear film lipid layer (TFLL) plays essential role for the stabilization of the air/aqueous tear (AT) interface of the tear film (TF) [1]. TFLL main constituent (> 93%) is the lipid rich meibomian secretion (MGS) produced by the eponymous glands located within the eyelids. Meibomian gland dysfunction (MGD) with associated quantitative and qualitative TFLL alterations is the world leading cause of dry eye syndrome (DES) with up to 86% of all DES patients showing signs of MGD [2]. Caused by everyday influences like contact lens wear and extended work at a computer screen, DES is currently the major ophthalmic public health disease affecting the quality of life of 10 to 30% of the human population worldwide [3].

Therefore there is pressing need to develop noninvasive (i.e. not requiring instillation of fluorescein or touching the ocular surface of the patient), rapid and sensitive methodology for dry eye diagnosis that to be available to ophthalmologists and optometrists. A major contender for such methodology is the assessment of TFLL morphology and dynamics at blink via specular microscopy by affordable modifications of standard biomicroscope or commercial devices (DR-1α interferometer, LipiView, Tearscope Plus etc.). This minireview will summarize the current state of knowledge and controversies into this field.

Clinical implications of TFLL morphology and dynamics at the ocular surface

1. TFLL morphological patterns

There are plenty of data (e.g. [4-7]) on the macroscopic texture of TFLL assessed directly at the ocular surface via specular microscopy devices. It is thought that relatively homogeneous and thick TFLL corresponds to a stable TF (non-invasive breakup time NIBUT) ≥ 15 s) while as more heterogeneous, rough and containing thinner regions becoms TFLL, as shorter is NIBUT and as more severe is DES. Yokoi et al., 1996 [7] proposed the following classification of TFLL interference patterns recorded with DR-1 microscope: Grade 1 (normal TF) - grayish color and uniform distribution.; Grade 2 (normal TF to very mild dry eye (DE)) - grayish color and non-uniform distribution; Grade 3 - a few colors with non-uniform distribution; Grade 4 - many colors and non-uniform distribution; Grade 5 - the corneal surface is partially exposed with no lipid layer interference (Grade 3 - 5 correspond to increasing severity of DES). The increase in the number of colors indicates increased thickness heterogeneity of TFLL. This idea was refined by Goto et al. 2003 [8] who demonstrated that TFLL thickness dispersion across the ocular surface (i.e. TFLL roughness) expressed as (TFLL mean thickness ± SD) can be a viable diagnostic parameter with cases where the mean thickness of TFLL is higher in DES patient (180 ± 41.6 nm) but also the film thickness standard deviation is much higher compared to healthy eye (66 ± 8.9 nm) and the ratio SD/mean thickness is higher in DES case as well. The image is freely available online at http://iovs.arvojournals.org/data/Journals/IOVS/933433/7g1133653003.jpeg

The LipiView system does not monitor the entire ocular surface and therefore only a portion of TFLL is registered in the observation window. Isreb et al. 2003 [9] found (Table. 1) that „(1) that measurement of lipid layer thickness (LLT) is a reliable test for the diagnosis of dry eye, and (2) that aqueous deficiency (ATD) and lipid deficiency, as they apply to dry eye disorders, are not mutually exclusive."

The correlation between DES symptoms and LLT was further confirmed by Blackie et al., 2009 [10]. Fenner and Tong, 2015 [11] supposedly found no correlation between LLT measured with LipiView and tear film NIBUT in DE patients. However it should be kept in mind that although the LipiView software calculates the standard deviation (and the minimum and maximum value) of the thickness of the observed portion of TFLL, these data are almost never presented in publications and this typical mistake was done by Fenner and Tong (2015) as well although as discussed above the assessment of their

Table. 1. Classification of healthy and dry eyes based on the values of fluorescein breakup time (FBUT, s), Schirmer's strip (AT production) and TFLL thickness. The data are taken from Isreb et al. Eye, 2003, 17, 79-83 [9].

Dry Eye Severity	FBUT, s	Schirmer's strips data (mm/min)	Lipid layer thickness, nm
Severe DES signs & symptoms	0 - 5	0 - 5	≤ 60
Intermediate DES signs & symptoms	6 - <10	6 - <10	≥ 75 - 105
No/low DES signs & symptoms	≥ 10	≥ 10	≥ 120

clinical relevance is very interesting task. Also in order to evaluate the impact of TFLL on TF stability it is necessary to account the influence of all other tear film properties (aqueous tear volume, ocular surface damage, tear meniscus radius etc.) but no such data were reported by Fenner and Tong, 2015 [11].

2. TFLL dynamic reorganization at blink

It is thought that with other factors being equal, the more elastic the TFLL, the more rapidly it will spread at the air/AT surface after eye opening and more efficiently it will fulfill its stabilizing role to the air/tear surface. TFLL spreading rate is very important also because during its movement TFLL drags the underlying aqueous fluid upwards thus ensuring the AT uniform distribution throughout the ocular surface [12-14]. As shown by Yokoi et al. 2008 [15] the TFLL of DES patients spreading is slower compared with normal subjects. A study targeting specifically the effects of TFLL abnormalities (i.e. aqueous tear deficient patients were excluded) was performed by Goto and Tseng, 2003 [16] who found that apart from longer spreading time (3.54±1.86 s in MGD patients vs 0.36±0.22 s in healthy individuals) the pattern of spreading was different between patients and normals. In healthy individuals the TFLL front displayed as uniform horizontal line across the ocular surface, while in MGD eyes TFLL manifested as vertical stripes each with different spreading rate resulting in irregular contour of the spreading front.

Another useful way to analyze the stability of TFLL is to evaluate the TFLL pattern deterioration rate with consecutive blinks. Such analysis for TFLL of MGD patients and of healthy individuals was done by Georgiev et al. 2014 [17] and the data are summarized in Fig. 1. and Table. 2.

One can see that the TFLL morphology degradation rate

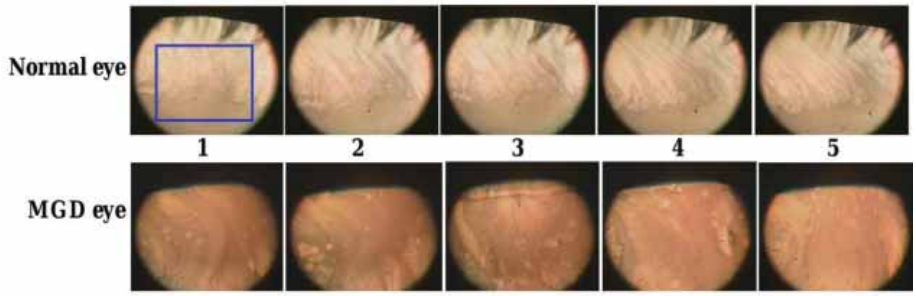

Fig. 1. TFLL stationary patterns acquired from the eyes of healthy volunteer and from MGD patient during the interblink intervals among consecutive blinks (images reproduced with permission from Georgiev et al., Soft Matter 2014 10(30):5579-88 [17]). The blue rectangle (upper left image) defines the selection area (chosen to avoid the eyelashes) over which the image cross-correlation was measured.

Table. 2. Correlation coefficients (Pearson correlation coefficient, r) obtained by image cross-correlation of the stationary TFLL patterns (Figure 1) with the pre-blink pattern 1. The cross-correlation between grayscale images was done with the ImageJ' Image Correlation IO plugin (http://www.gcsca.net/IJ/ImageCorrelationJ.html) (Chinga and Syverud 2007). (Data reproduced with permission from Georgiev et al., Soft Matter 2014, 10(30):5579-88 [17]).

Health status	Compared TFLL patterns	R (Pearson correlation coefficient)
Healthy eye	1 with 2	0.8
	1 with 3	0.85
	1 with 4	0.7
	1 with 5	0.71
MGD eye	1 with 2	0.72
	1 with 3	0.68
	1 with 4	0.46
	1 with 5	0.55

is much more pronounced in MGD eye compared with healthy eye. Similar trends were also reported by Goto's group [8, 16].

Conclusions

The specular microscopy imaging of tear film lipid layer can be the gold standard of non-invasive diagnosis of dry eye. It has numerous advantages over the commonly used measurement of fluorescein breakup time, i.e. (i) it is not necessary to instill fluorescent stain in the tear film and (ii) there is no need to touch the patient and therefore the tests can be performed by any medical/health care personnel reducing the burden on the ophthalmologist schedule. In order to fully utilize the diagnostic power of the specular microscopy of TFLL it is necessary to account not only for the mean thickness of the tear film lipid layer, but also for its thickness distribution heterogeneity (i.e. thickness standard deviation) and the dynamic reorganization features of TFLL.

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Impact of trabeculectomy to ocular surface disease

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Abstract

Glaucoma is a leading cause of irreversible blindness due to retinal ganglion cell loss. Still, trabeculectomy is the gold standard in glaucoma surgery. Studies confirmed that glaucoma surgery as an anterior segment approach affects the normal function of the tear film, also conjunctival incisions change the structure of ocular surface, decrease goblet cell density, resulting in dry eye. Alteration of ocular surface by trabeculectomy is partially due to damage of ocular surface tissues as well as chronic inflammation. Retrospective-prospective study in the glaucoma department of Eye Clinic Nis included 60 post-operative patients with OAG (POAG/XFG), 140 respondents on topical medications and 90 healthy respondents older than 30 years without eye/systemic diseases or artificial drug treatment. All underwent ophthalmological examination and ocular surface evaluation and OSD grading according to Delphi Panel. Delphi Panel showed significant increase of moderate and severe grades postoperatively, up to 75% first month and 65% second month after ($p<0,0001$). Grade IIb was most prevalent. OSD mixed type was dominant preoperatively (66,67%), but postoperatively it significantly shifts to evaporative type (71,67%) and returns to previous level 2 months after trabeculectomy in both glaucoma types ($p<0,0001$). Impact of trabeculectomy showed onset or worsening of OSD, thus influence to successful glaucoma treatment.

Key words: trabeculectomy, open angle glaucoma, ocular surface disease, OSD grade, OSD type.

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide as a consequence of progressive retinal ganglion cell loss (RGC). The currently accepted strategy for management of glaucoma starts with topical medical therapy, sometimes concomitant with laser therapy [1]. Surgical option for glaucoma is considered when other modalities are not working out to keep the intraocular pressure under control. Increasing number of surgical options is reserved only for patients that are refractory to previous therapy [2, 3]. Among all penetrating filtration glaucoma surgery procedures, trabeculectomy became the most commonly performed surgical procedure, and up to date remains the gold standard. Formation of functional filtering bleb is essential for surgical success. Wound healing at the conjunctival and episcleral plane is a limiting factor for the success of trabeculectomy [3, 4].

Since the glaucoma surgical procedures disrupt the integrity of the globe, they are known to produce various intra and postoperative complications. Tear film disturbances are a common postoperative complication and cause of dry eye sensations [3]. Understanding that the pathogenesis of dry eye disease can be described as a vicious circle in which tear film instability, tear hyperosmolarity and inflammation play central roles, provides better approach in recognizing and patient outcomes [5].

Pathological dry eye was first described in 1933, as keratoconjunctivitis sicca (KCS) and although not strictly synonymous to Dry Eye Syndrome, Dry Eye Disease (DED) or Ocular Surface Disease (OSD), these terms are interchangeable for the similar condition of dry eye. Modern definition of the International Dry Eye Workhop (DEWS, 2007) states that "dry eye disease is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [6].

Anatomically, the ocular surface entity includes the corneal and conjunctival epithelium together with tear film. A disorder of any single anatomical component of the ocular surface is capable of altering other components [7]. Healthy tear film is essential in maintaining normal function of ocular surface. Tear film instability leads to tear hyperosmolarity that in turn promotes apoptosis of ocular surface epithelial cells, nerve stimulation, and inflammation. Cytokine release and activation of matrix metalloproteinases (MMP), which occur as part of the inflammatory cascade, cause loss of mucin-producing goblet cells. Subsequently, tear film instability worsens [5].

Ocular surface disease can be divided into two main subgroups: the hypovolemic (hyposecretory) dry eye, based on disorder of the aqueous and mucinous components of tear film and hyperevaporative, based on a disorder of the lipid components. Mixed form also occur [6].

The concept of the vicious circle in the pathogenesis of OSD provides better insight into how acute events, such as ocular surgery or infection, can cause dry eye occurrence and why OSD and the patient's complaints persist even when the cause is removed. Once the vicious circle is entered and established, it is almost impossible for patients to halt and exit from it unless the central pathogenic mechanisms are solved. Tear film impairment like hyposecretion or abnormalities in tear

composition (lipid or mucous changes) appears at the top of the vicious circle's pathophysiologic chain [5].

Anterior segment surgical approach affects the normal structure and function of the tear film, thus causing dry eye symptoms commonly after**:** glaucoma, cataract, refractive and corneal surgery, vitreo-retinal surgery and ocular tumor therapy. Clinical presentation and symptoms are similar but underlying pathogenesis of OSD differs, due to type of surgical intervention, which will be explained in further text.

Many clinical and experimental studies have found that *glaucoma surgery*, as anterior segment approach, affects the normal function of the tear film, which can cause the change of the structure of ocular surface resulting in an uncomfortable feeling and dry eye. Most investigators have suggested that the alteration of ocular surface caused by trabeculectomy is partially due to the damage of ocular surface tissue by placing conjunctival incisions, also topical application of the drugs, as well as the lack of vascular supply of ultra-thin post-operative filtering bleb [8]. Induced chronic inflammation leads to decrease of goblet cell density, further upregulation of inflammatory mediators, cytokine excess, fibroblast activation and fibrosis [9].

Almost all patients experience OSD after cataract surgery, because procedure involves cutting through whole corneal thickness, through the plexus of corneal nerves, using a laser or a microkeratome. More than 73% of cataract surgery is clear corneal cataract surgery that cuts quite large part of the corneal nerves which are essential in natural production of tears, disrupting afferent nerve arc in tear production. Besides, the surgical procedure itself is a cause of ocular inflammation. Also topical medications applied prior or after surgery cause tear film disruptions especially fluoroquinolones [10, 11].

Ocular Surface Disease after Corneal and Refractive Surgery is one of the most frequent complications patients can experience [12]. Disruption of corneal epithelium and corneal flap creation affects the nerves that regulates natural production of tears. Subepithelial and stromal nerve plexus are severed when the flap is made, and the cornea overlying the flap is significantly anesthetic for at least 3 - 6 months [13]. Most patients experience a decrease in tear production because of corneal nerves cutting and interruption of afferent secretomotor nerve impulses in tear production after all surface ablation procedure (LASIK, LASEK, PRK). Flap and hinge position, as depth of surface ablation, are two main factors that can cause extensive nerve damage. PRK (depth of ablation 50μm) devastate superficial Bowman nerve plexus versus LASIK procedure with ablation depth of 130 μm, that harm complete nerve supply of cornea. Small-incision lenticule extraction (SMILE) which was established as a "flapless" procedure, reduces corneal denervation by creating an intrastromal lenticule which is cut by a femtosecond laser and manually extracted through a peripheral corneal tunnel incision (Fig. 1) [14]. The key difference between these procedures is that LASIK affects the epithelium and anterior stroma, thus resulting in greater resection of the sensory nerves of the cornea while SMILE affects the posterior stromal bed with relatively greater preservation of the corneal subepithelial basal nerve plexus [15, 16].

Ocular surface disruption after corneal surgery alters apposition between cornea and upper eyelids including damage of conjunctival goblet cells, increasing mucus deficiency and Ocular Surface inflammation. Patients dry eye symptoms worsen due to post-operative topical medication application (BAK, fluoroquinolones) [14].

Vitreoretinal surgery and ocular tumor therapy can cause or worsen dry eye symptoms in a large proportion of patients. This observation is not limited to the early postoperative period, it can be observed months to years after surgery because of morphological alterations of the conjunctiva, increased epithelial stratification and distributional changes in ocular mucins [17]. Radiation therapy (RT, external beam, plaque or proton beam) is being widely used to treat the head and neck malignancies (paranasal sinus, oropharynx tumors, thyroid cancers), ocular adnexal tumors. Radiation causes damage to the lacrimal glands leading to cell damage, necrosis and apoptosis thereby releasing the inflammatory mediators which decrease the tear production and induce dry eyes [18].

Matherial and Methods

Retrospective-prospective study was performed in the glaucoma department of Eye Clinic, Clinical Center Nis, Serbia on 60 post-operative patients (60 eyes) with Open Angle Glaucoma (OAG) including two types: primary (POAG) and secondary exfoliative (XFG). It also included 140 glaucoma patients respondent to medication (140 eyes), treated with topical anti-glaucoma medications and 90 healthy respondents (90 eyes), older than 30 years, without eye/systemic diseases, neither artificial tears treatment. Respondents in all three groups underwent: conventional ophthalmological examination, in surgically treated patients before and after surgery repeated at 7, 30 and 60 days. Evaluation of the Ocular Surface was performed using tear break-up time (TBUT), corneal and conjunctival vital dye staining (fluorescein, Rose Bengal) according to Oxford score, Schirmer test, thereafter results were incorporated in grade and type of OSD following Delphi Panel Grading Scale and International Panel of experts' guidelines, Dry Eye Work Shop (DEWS, 2007) (Scheme 1) [19].

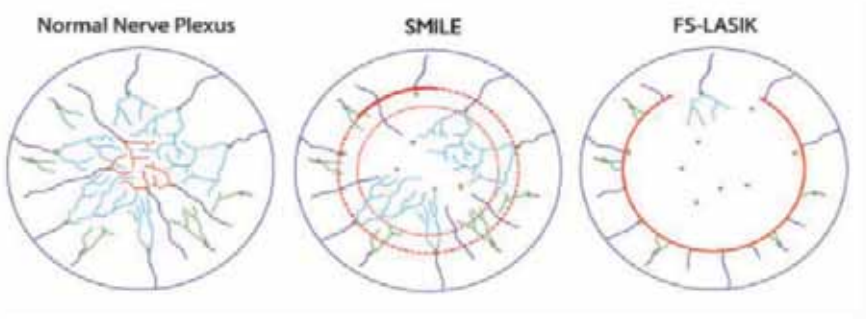


Fig. 1. Corneal nerve architecture after refractive surgery. *(Source: https://crstodayeurope.com)*

Scheme 1. Classification of dry eye according to Delphi Panel Scale grading of dry eye.

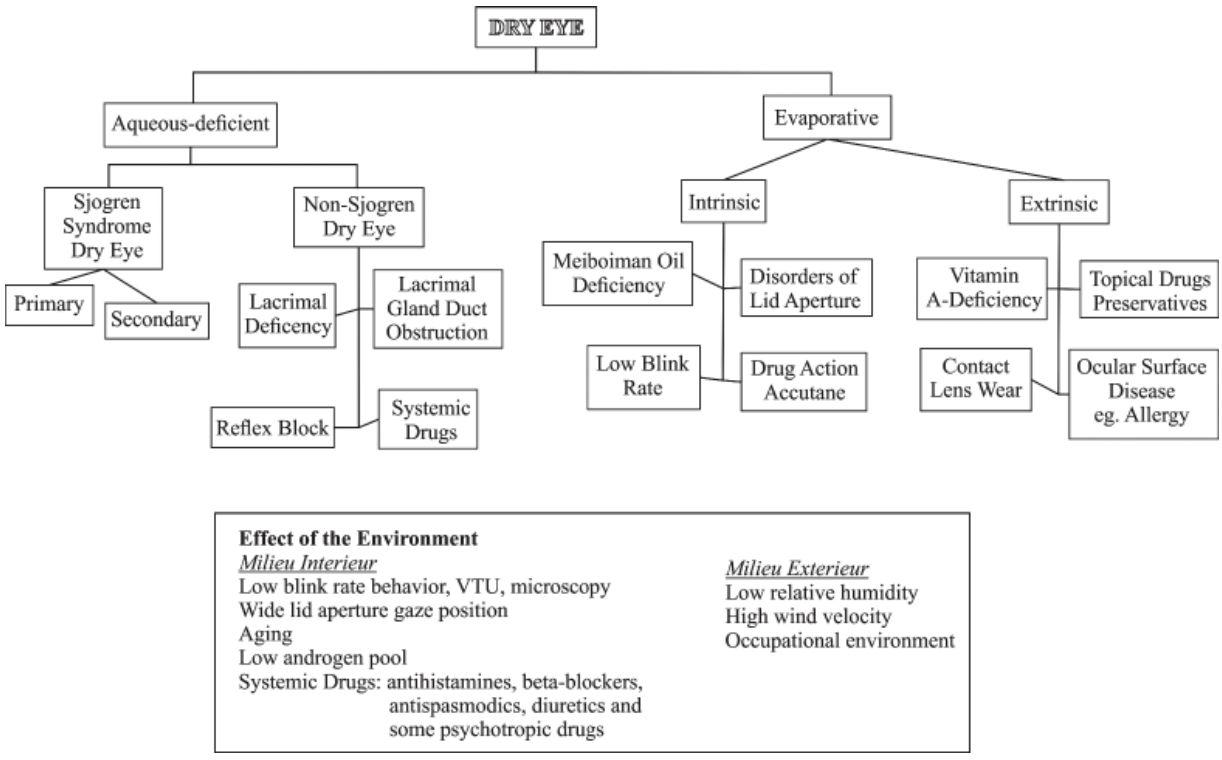
DEWS Dry Eye Severity Grading Scheme				
Dry eye severity level	**1**	**2**	**3**	**4***
Discomfort, severity and frequency	Mild and/or episodic occurs under environ. Stress	Moderate episodic or chronic stress or no stress	Severe frequent or constant without stress	Severe and/ or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/or limiting actvity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/ location)	None to mild	Variable	Marked/central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris,↓meniscus	Filamentary keratitis, mucus clumping,↑tear debris	Filamentary keratitis, mucus clumping,↑tear debris, ulceration
Lid/meibomian glands	Meibomian gland dysfunction (MGD) variably present	MGD variably present	Frequent	Trichiasis, keratinization, symplepharon
Fluoresceintear break-up time	Variable	≤ 10 seconds	≤ 5 seconds	Immediate
Schirmer score	Variable	≤ 10 mm/5 min	≤ 5 mm/5 min	≤ 2 mm/5 min

* Must have signs and symptoms.

(Source: The Ocular Surface, April 2007, vol 5, No 2)

Etiologic classification system distinguishes two basic categories of dry eye: hyposecretory (Sjögren's syndrome (SS) and non-Sjögren's syndrome (NSS)), and evaporative (extrinsic and intrinsic mechanism). Hyposecretory dry eye shows a disorder of the aqueous-mucinous phase of the tear film, while evaporative dry eye demonstrates disorder of the lipid layer of the tear film [6]. A more detailed classification is shown in Scheme 2. Although the scheme differentiates two basic forms of the disease, most people have mixed type, which often have a more severe clinical presentation [19, 20].

Scheme 2. Classification of dry eye.



Results

Among all three investigated groups, evaluation of Ocular Surface Disease grade and type was done according to obtained results of TBUT, Schirmer test, Ocular Surface examination and potential symptoms, thereafter final results are shown in proceeding tables and schemes. Effect of trabeculectomy, in surgically treated OAG patients, to the tear film changes as it is shown in Table. 1., illustrates implications of anterior segment anti-glaucoma surgical approach to occurrence or worsening of OSD through time interval of two months after surgery.

Observing of OSD clinical forms as OSD grades presents statistically significant difference through time (Friedman Test Chi-Square=26,012; p<0,0001). Postoperatively, IIb grade is more frequent and the most prevalent in 30 and 60 days in both glaucoma types (POAG and XFG). These occurs due to redistribution of normal and lower grades to more severe IIb grade more than double, from 28.33% to 65% in the end of observing period Table. 1/Scheme 3.

Scheme also illustrates the time distribution of OSD grades through two months with most prevalent IIb grade in first and second month after trabeculectomy (Scheme 3).

After clinical testing and evaluation according to diagnostic protocol, all operated examinees are divided in groups of OSD type: Evaporative (E), Hyposecretory (H), Mixed type (M) and Normal (N). Obtained results are shown in Table. 2.

OSD clinical type distribution presents statistically significant difference through time in both glaucoma types POAG and XFG (Friedman Test Chi-Square=33,222; p<0,0001). Before surgical treatment the mixed type is most frequent 66,67%, after surgery drop is evident till one month with parallel increase of OSD evaporative type to 71,67%. After a two-month period, the mixed type has returned to preoperative level. Normal and Hyposecretory subjects are evident in low percentage.

Scheme also illustrates two most prevalent types of OSD, Mixed and Evaporative and these distribution during time interval of two months (Scheme 4).

OSD grade distribution shows a statistically significant difference between the control group and the medicamentous treated glaucoma group (c^2=33,50 p<0,0001). More than half of participants in the control group (64,44%) had normal finding in contrast to the glaucoma group, where II grade was dominant. Between Primary Open Angle Glaucoma and Exfoliative Glaucoma group distribution was also significantly different, incipient grades were more frequent and in 34,34% a normal finding was observed (c^2=14,44; p=0,006; p<0,01). Advanced OSD grades were dominant in exfoliative glaucoma group, with

Table. 1. OSD grade distribution according to glaucoma type.

	Glaucoma type	0	%	I	%	II a	%	II b	%	III	%	Total	%
Grade 0	POAG	5	11.90%	9	21.43%	10	23.81%	12	28.57%	6	14.29%	42	100.00%
	XFG	1	5.56%	0	0.00%	11	61.11%	5	27.78%	1	5.56%	18	100.00%
	Total	6	10.00%	9	15.00%	21	35.00%	17	28.33%	7	11.67%	60	100.00%
Grade 7	POAG	7	16.67%	4	9.52%	12	28.57%	18	42.86%	1	2.38%	42	100.00%
	XFG	2	11.11%	1	5.56%	10	55.56%	5	27.78%	0	0.00%	18	100.00%
	Total	9	15.00%	5	8.33%	22	36.67%	23	38.33%	1	1.67%	60	100.00%
Grade 30	POAG	3	7.14%	6	14.29%	1	2.38%	31	73.81%	1	2.38%	42	100.00%
	XFG	0	0.00%	0	0.00%	4	22.22%	14	77.78%	0	0.00%	18	100.00%
	Total	3	5.00%	6	10.00%	5	8.33%	45	75.00%	1	1.67%	60	100.00%
Grade 60	POAG	3	7.14%	4	9.52%	1	2.38%	28	66.67%	6	14.29%	42	100.00%
	XFG	2	11.11%	4	22.22%	0	0.00%	11	61.11%	1	5.56%	18	100.00%
	Total	5	8.33%	8	13.33%	1	1.67%	39	65.00%	7	11.67%	60	100.00%

(POAG - primary open angle glaucoma; XFG - exfoliative glaucoma)

Scheme 3. OSD grade distribution according to glaucoma type.

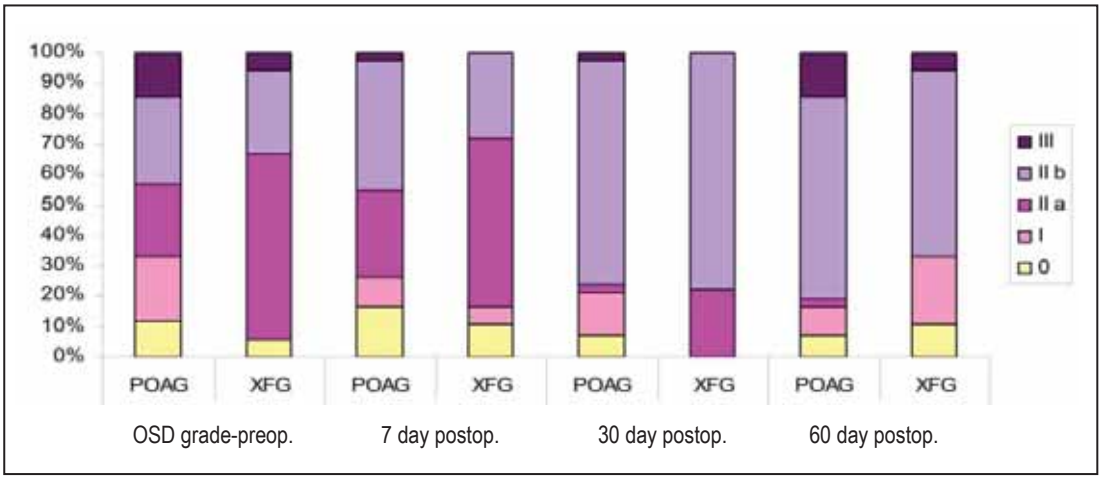


Table. 2. OSD type distribution according to glaucoma type.

	Glaucoma type	E	%	H	%	M	%	N	%	Total	%
Type 0 OSD	POAG	10	23.81%	1	2.38%	26	61.90%	5	11.90%	42	100.00%
	XFG	3	16.67%	0	0.00%	14	77.78%	1	5.56%	18	100.00%
	Total	13	21.67%	1	1.67%	40	66.67%	6	10.00%	60	100.00%
Type 7 OSD	POAG	29	69.05%	0	0.00%	6	14.29%	7	16.67%	42	100.00%
	XFG	14	77.78%	0	0.00%	2	11.11%	2	11.11%	18	100.00%
	Total	43	71.67%	0	0.00%	8	13.33%	9	15.00%	60	100.00%
Type 30 OSD	POAG	20	47.62%	1	2.38%	18	42.86%	3	7.14%	42	100.00%
	XFG	11	61.11%	1	5.56%	6	33.33%	0	0.00%	18	100.00%
	Total	31	51.67%	2	3.33%	24	40.00%	3	5.00%	60	100.00%
Type 60 OSD	POAG	7	16.67%	0	0.00%	32	76.19%	3	7.14%	42	100.00%
	XFG	7	38.89%	0	0.00%	9	50.00%	2	11.11%	18	100.00%
	Total	14	23.33%	0	0.00%	41	68.33%	5	8.33%	60	100.00%

(POAG - primary open angle glaucoma; XFG - exfoliative glaucoma; E - evaporative; H - hyposecretory; M - ; N - normal)

Table. 3. OSD grade distribution in control and glaucoma group (POAG; XFG).

Grade OSD	Control	%	Glaucoma type					
			OAG (POAG)	%	OAG (XFG)	%	Total	%
0	58	64,44%	34	34,34%	4	9,76%	96	41,74%
I	8	8,89%	14	14,14%	2	4,88%	24	10,43%
IIa	10	11,11%	16	16,16%	10	24,39%	36	15,65%
IIb	13	14,44%	31	31,31%	21	51,22%	65	28,26%
III	1	1,11%	4	4,04%	4	9,76%	9	3,91%
Total	90	100,00%	99	100,00%	41	100,00%	230	100,00%

(POAG - primary open angle glaucoma; XFG - exfoliative glaucoma)

Table. 4. OSD type distribution in control and glaucoma group (POAG; XFG).

Type OSD	Control	%	Glaucoma type					
			OAG (POAG)	%	OAG (XFG)	%	Total	%
E	17	18,89%	28	28,28%	17	41,46%	62	26,96%
H	7	7,78%	9	9,09%	1	2,44%	17	7,39%
M	8	8,89%	26	26,26%	19	46,34%	53	23,04%
N	58	64,44%	36	36,36%	4	9,76%	98	42,61%
Total	90	100,00%	99	100,00%	41	100,00%	230	100,00%

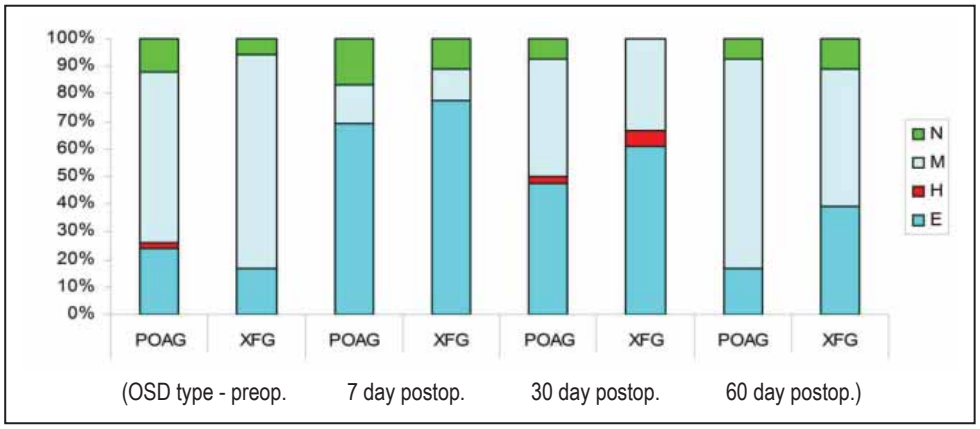
(POAG - primary open angle glaucoma; XFG - exfoliative glaucoma)

51,22% of IIb OSD (Table 3).

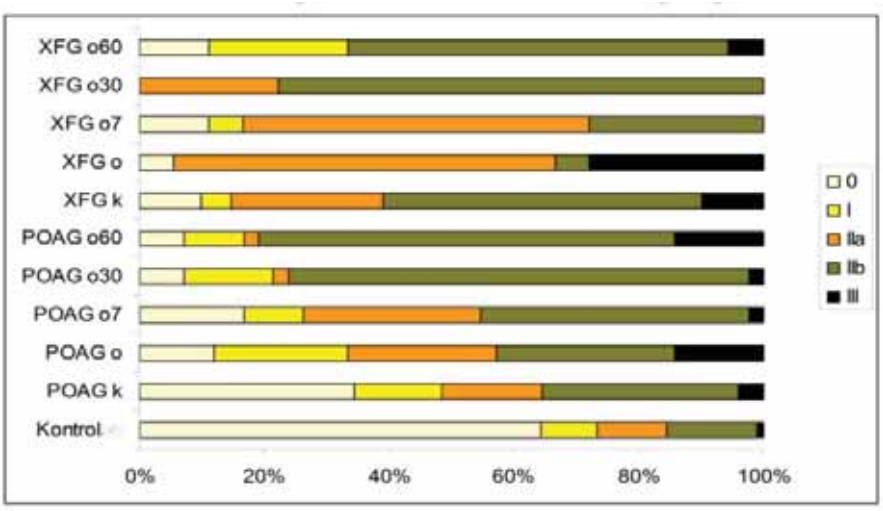
OSD clinical type differs significantly in control and topical drug treated group (c^2=33,00; p<0,0001). In the control group 64,44% of participants had normal finding while in glaucoma group evaporative and mixed type were the most prevalent, with equal 32,14%. Distribution differs between glaucoma types, while normal is dominant in POAG group, in exfoliative glaucoma mixed and evaporative types were most frequent (c^2=14,18; p=0,0027; p<0,005) (Table. 4).

Next scheme presents mutual simultaneous correlation of OSD grades between all tree tested groups of participants. In surgically-treated group the results are separated by glaucoma type and time interval, before operation and post trabeculectomy in three time intervals of 7, 30 and 60 day. In relation to control

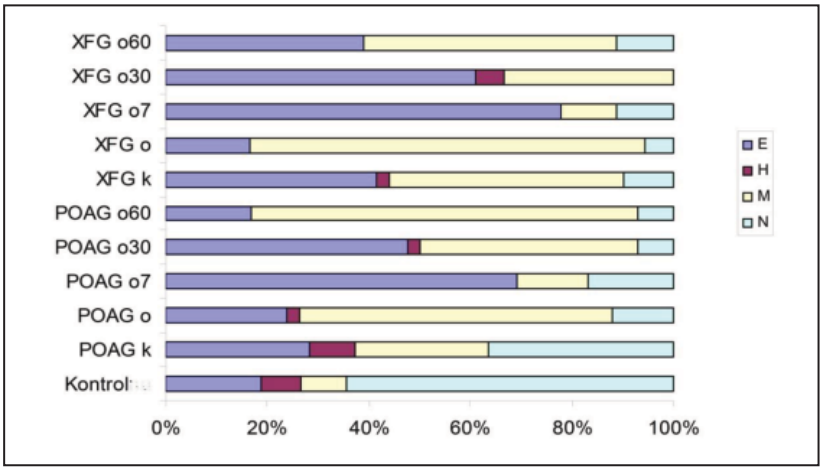
Scheme 4. OSD type distribution according to glaucoma type.



Scheme 5. OSD grade distribution in 3 tested groups.



Scheme 6. OSD type distribution in 3 tested groups.



group, both glaucoma groups are characterized with moderate and advanced OSD grades, IIa and IIb in highest percent ($p<0,0001$). IIb grade is the most prevalent at the end of observing time (Scheme 5).

In POAG group surgically-treated patients had more severe OSD grades than patients treated with topical drugs. Distribution significantly differs after surgery and shows worsening through time interval with enlarging of IIb grade ($p<0,05$). In XFG medicamentous group findings were worse than in POAG, more severe OSD grade and shift to high grade after surgery. (Scheme 5).

Comparative observing of OSD type showed statistically

significant difference between groups, markedly to control group, with predominantly normal findings in control group which is opposite to surgically treated patients due to mixed and evaporative OSD (p<0,0001). Results of correlation of OSD type showed difference after surgery, with redistribution from mixed to evaporative type, closely after operation and spontaneous returning to mixed type. Surgically-treated patients showed worse finding in comparation to drug-treated (Scheme 6).

Discussion

Ocular Surface Disease (OSD) is a distressing, common ocular condition which significantly reduces quality of life, and affects 5 - 34% of the global adult population [6, 19, 21]. It is one of the main diagnoses in ophthalmological practice and often concomitant with glaucoma. Study of Lemp and Baudouin showed that up to 40% of patients had symptom and clinical sign discordance [22]. Another study showed Meibomian gland disease was more commonly asymptomatic than symptomatic (21.9% vs. 8.6%, respectively), and symptom presentation did not correlate with severity of ocular surface damage [21]. Etiology of OSD is multifactorial and may arise due to the use of medicines, environmental, nutritional factors (vitamin A, omega acids), age, diseases of the connective tissue, hormonal deficiencies, trauma, sensory block in contact lens users, Ro therapy, surgery of the anterior segment of the eye [20, 23]. Main purpose of these clinical investigation was influence of anterior segment anti-glaucoma surgical approach to the occurrence or progression of OSD.

Ocular Surface Disease can adversely affect the success of glaucoma surgery, and multiple topical glaucoma therapies can negatively influence the course of OSD. A large percentage of patients in a glaucoma practice have both conditions, in some studies around 60% of patients [23]. Following study results of the German Register for glaucoma patients with dry eye in 52,6% of all glaucoma patients OSD was found with rise to 75,5% if they had general sicca syndrome [6]. Main aim of this clinical investigation was to find out incidence of OSD in healthy population, medically-treated glaucoma patients and surgically-treated patients before and after surgery.

Large number of glaucoma patients with coexisting ocular surface disease (OSD) often require laser or incisional surgical intervention to reduce their IOP. In these cases, the whole preoperative planning process is more complex and requires careful attention to unique issues [24]. Several studies have shown that the outcome of filtering glaucoma surgery depends on the previous topical antiglaucoma therapy. Batterbury postulates that duration of treatment and number of prior topical glaucoma drugs are essential for success or failure in filtration surgery. Unsuccessful surgical treatment correlates with the number of macrophages, lymphocytes and fibroblasts in conjunctival biopsies [7, 25, 26]. In these investigations whole group of operated patients before surgery had at least two topical antiglaucoma drugs with different concentrations of preservative. Therefore, it could be supposed that prior anti-inflammatory topical corticosteroid treatment before surgery is beneficial in reducing cellular infiltration.

Many conducted studies confirmed that glaucoma surgery as anterior segment approach affects normal function of the tear film and that conjunctival incisions change the structure of the ocular surface so tear production. OSD can increase the risk of bleb-related complications, and blebs can worsen the severity of OSD symptoms, so a vicious cycle starts.

Creation of a functional filtration bleb is the key to success in glaucoma surgery. However, surgical intervention disrupts normal function of the tear film, which disturbs the surface area of the eye resulting in discomfort, as a result of partial tissue damage at the site of the incision, and may later be intensified by postoperative drug application. Mendez in his work analyzed 40 eyes with a functional bleb and OSD signs that correlated with the morphology of ultra-thin filtration bleb indicating that vital dying is different; Schirmer test was increased and TBUT shortened after surgery so OSD was evident [8, 27].

By an analysis of the post-surgical group, we tried to find to what extent trabeculectomy influenced the changes of the ocular surface in our examinees. Observing OSD grade preoperatively, in 63,33% of respondents, II grade was dominant in group. In POAG patients proportion of IIa and IIb grade was similar (23,81% vs. 28,57%), while in XFG group IIa grade (61%) was dominant. Postoperatively, following time interval of two months, significant increase in IIb grade was noted, doubling from 28,57% to 65% (p<0.0001) at the end, with maximum of 75% one month after operations.

According to OSD type, the most prevalent was mixed type (66,67%) in whole group, only 10% had normal finding. Glaucoma type distribution of 61,9% (POAG) and 77,78% (XFG) of the subjects with mixed type showed higher number in exfoliative glaucoma, with inversion at the 7th day after operation and increase in evaporative type to 71,67%, then it falls and gradually returned at the end of the monitoring to the same preoperative relation. This significant increase in evaporative dry eye from 21% to 71,67% (p<0.0001) was probably due to an increased reflex secretion of tears and the simultaneous disturbance of the mucosal layer of tears after trabeculectomy.

These results were obtained after standard filtration glaucoma surgery without the use of antimetabolite MMC. With the use of MMC, worse results should be expected, according to Lam. After his study on 15 eyes in 12 patients, in which test results were shortened (TBUT = 5,32 s and Schirmer = 6 mm/ 5 min) and higher degree of tear and eye surface damage, most likely due to limbal cell deficiency damaged by antimetabolite, chronic preoperative drug use or preoperatively present OSD. Antimetabolite activity of MMC targets the actively replicating corneoscleral limbal cells, damaging these cells and thus preventing adequate replacement of the corneal epithelium, which is usually replaced by the stem cells every 3 - 7 days. This should be remembered, because dry eye treatment can improve the best corrected visual acuity for two lines on the table [28, 29]. Furthermore, surface irregularity of the conjunctiva adjacent to the bleb may also play an important role in the development of OSD in all these operated patients.

In study of Roberts in 30 respondents after cataract surgery one month later 47 - 87% reported symptoms or signs of OSD [30]. To determine incidence of symptoms of dry eye and recurrent erosion syndrome after refractive surgery (PRK and LASIK) in Hovanesian study was reported 43% vs. 48% even 6 months after surgery [31]. Another study showed high incidence of mild to moderate dry eye disease, that was observed in groups 1 month postoperatively and remained significantly higher in the LASIK group than in the SMILE group 6 months after surgery [32]. Dry eye symptoms occur as postoperative complication following vitreo-retinal surgery and ocular tumor therapy in 63% of 140 patients that underwent VPP, brachy-therapy or proton beam irradiation according to study [33].

Comparing this study results of different surgery approach, we can conclude that after glaucoma surgery a high incidence of OSD is present in our study results, 75% of II and III grades and 91,67% of evaporative and mixed type together.

There is a large body of evidence from clinical and experimental studies that the long-term use of topical drugs may induce ocular surface changes, causing ocular discomfort, dry eye, conjunctival inflammation, subconjunctival fibrosis, corneal surface impairment, and, as a consequence of chronic ocular surface changes, the potential risk of failure for further glaucoma surgery. Subclinical inflammation has also been widely described in patients receiving antiglaucoma treatments for long period of time, with inflammatory cell infiltration and fibroblast activation in the conjunctiva and subconjunctival space. The preservative, especially benzalkonium chloride (BAK), which has consistently demonstrated its toxic effects in laboratory, experimental, and clinical studies, could induce or enhance such inflammatory changes. As a quaternary ammonium, this compound causes tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, corneal nerve impairment, chronic inflammation and potential damage to deeper ocular tissues [6, 8, 34].

Analyzing OSD grade in glaucoma patients treated with medication, moderate grades were elevated. In POAG IIb grade was present in 31,31%, while in the XFG group 51,22% had IIb grade and 24,39% IIa grade ($p < 0.01$). In control group 64,44% of healthy subjects had a normal finding, only 14,44% had IIb.

Analyzing the OSD type, it was concluded that 64.44% of the examinees had a normal finding in control group and 18,89% had evaporative OSD. Topical drug treated POAG detected mixed and evaporative type of dry eye with 26,26% vs. 28,28%. There was a significant difference between glaucoma group, in XFG mixed and evaporative relation was 46,34% vs. 41,46% ($p<0.001$). Therefore, it can be concluded that the signs of OSD were present in both treated glaucoma groups, with severe form in XFG, higher percentage and with more severe grade in the respondents [35].

In our clinical study highest prevalence of moderate and advanced OSD, IIb (65%) and III (11,67%) grade were observed in the post-operative glaucoma group that worsened after surgery immediately. In high prevalence OSD was noted after topical drug treated glaucoma, more frequently in XGF (51%) than POAG (31%). The most prevalent OSD type in both glaucoma group was mixed although in higher percentage in operated participants comparing to medicamentous treated and higher in XFG. Worsening of OSD occurs after glaucoma surgery.

Conclusion

Glaucoma is an eye disease that can lead to irreversible visual impairment. OSD is most frequent diagnosis in clinical practice, often accompanied to glaucoma. Both conditions require attention and intervention. As glaucoma and OSD are chronic condition, it is important to treat both diseases at the same time, with intention of preserving the integrity of the surface of the eye. Recognizing of symptoms, signs, clinical presentation, diagnostic procedures and their interpretation in patients at increased risk, promotes glaucoma and ocular surface therapy thus improves the quality of life to patients and visual function.

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Optic disc deposits in a family carrying a heterozygous mutation in BEST1: Clinical, diagnostic and molecular genetic findings

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Abstract

Purpose: Classical juvenile-onset Best disease is characterized by vitelliform lesions predominantly localized at the posterior pole. Extramacular eccentric multifocal vitelliform lesions have also been described showing a specific pattern of distribution with the accumulation of lipofuscin along the temporal retinal vascular arcades, predominantly superior-nasal and adjacent to the optic disc. Here, we report on functional and structural characteristics of an unusual phenotype of juvenile-onset Best disease associated with optic disc deposits and autosomal dominant inheritance.

Patients and methods: Prospective cross-sectional observational study. Seven subjects from a three-generation non-consanguineous family were recruited at the diagnostic unit of the Department of Ophthalmology, University of Basel. Genetic analyses were conducted at the IRO, Sion. Refraction, color fundus photographs, fundus autofluorescence imaging (FAF), optical coherence tomography (OCT), ISCEV-standard ffERG, mfERG, EOG, as well as ultrasound imaging were performed. Direct sequencing of all exons and intron-exon junction of BEST1 was conducted.

Results: Diagnosis of vitelliform maculopathy was confirmed by clinical and electrophysiological findings and supported by genetic analysis. In four out of the five affected individuals deep subretinal deposits in the macula were found. Unexpectedly, when the macula was affected, deposits were observed on the surface of the optic disc showing similar ultrasound and FAF characteristics. All five subjects had an abnormal EOG and a normal ffERG. The individual mfERG responses were reduced and the latencies were delayed. Sequencing revealed a heterozygous c. [670 C>A] coding for a L224M mutation in BEST1 in all affected subjects.

Conclusion: Diagnosis of Best disease was confirmed by clinical, electrophysiological and ultrasound findings and the documentation of a mutation in the bestrophin-1 gene. The juvenile-onset Best disease was confirmed to be of distinct multifocal phenotype, in association with optic disc deposits.

Key words: Best disease, mutations in BEST1, full-field ERG, hamartoma, L22M mutation, mfERG, and optic disc deposit.

Introduction

Juvenile-onset Best disease (MIM 153700) has been described as a monogenic dominant inherited disorder, characterized by juvenile-onset maculopathy and progressive impairment of visual function [1, 2]. Mutations in BEST1, which encodes the bestrophin-1 protein, have been identified in Best disease [3-5]. Classical Best disease, according to its stage, is characterized by egg yolk-like, pseudohypopyon, vitelliform and atrophic scarring lesions predominantly localized at the posterior pole.

Impaired expression of BEST1 [6] has been associated with pattern-like accumulation of lipopigment in the retinal pigment epithelium (RPE) layer with subsequent impairment of vision and reduction of the light rise in the electro-oculogram (EOG), with completely normal full-field electroretinogram (ffERG) [7-10]. Following foveolar loss of photoreceptors above the accumulated lipofuscin debrits, local dysfunction in terms of reduced central responses of the focal ERG, has been observed [11]. Application of mutifocal ERG (mfERG), allowing mapping of the retinal function, confirmed a localized photoreceptor sensitivity change within the central retina, mainly through a reduction of N1P1 amplitudes [12-14].

The phenotype among patients carrying *BEST1* mutations varies from typical juvenile-onset, adult-onset vitelliform maculopathy [2-7] to rare forms of autosomal dominant vitreoretinopathy (ADVIRC), microcornea, rod-cone dystrophy, cataract and posterior staphyloma syndrome (MRCS), autosomal-recessive bestrophinopathy (ARB) [15-19]. However, atypical subclinical forms may also be observed [14, 18, 20, 21]. Extramacular distribution of the lesions has also been described, explaining the atypical and subclinical forms of the disease with usually preserved visual acuity, subnormal EOGs and mild- or unaltered ffERG recordings [14, 18, 20, 22]. In reviewing published reports, eccentric multifocal vitelliform lesions, although with some variability, have shown a specific pattern of distribution with the accumulation of lipofuscin along the temporal retinal vascular arcades, predominantly superior-nasal and adjacent to the optic disc [16, 23, 24].

In the present study, we report on a distinct juvenile-onset Best disease in a three-generation family with autosomal dominant inheritance where the lesions were spread not only in the

macular area, but also along the vascular arcades and were associated with mulberry-like lesions on the surface of the optic disc.

Methods

Seven subjects (five male and two female), aged 5 to 76 years, from a three-generation non-consanguineous Caucasian family of German origin, participated in the study. The study was performed according to the tenets of the Declaration of Helsinki (JAMA 1997; 277:925-926). Written informed consent was obtained from the adult participants as well as from the parents of the children.

Clinical assessment

Clinical phenotype of the family was depicted through detailed ophthalmic examination that included refraction, best corrected visual acuity (Snellen charts), intraocular pressure examination by applanation, slit-lamp examination, biomicroscopy and fundoscopy. In addition, fundus findings were documented by optical coherence tomography (OCT), autofluorescence (FAF) and color fundus imaging of the macula and the optic nerve.

Diagnostic imaging, electrophysiological and ultrasound assessment

Spectral domain OCT examinations were carried out with the Cirrus™ HD-OCT Model 4000 instrument (Carl Zeiss Meditec AG, Jena, Germany) using a fast macular thickness and a fast optic nerve circle protocol.

Full-field ERG was recorded on a hand-held Mini full-field ERG (ColorBurst™, Diagnosys LLC, Cambridge, UK) with the test order provided by ColorBurst™ software and pre-programmed according to the ISCEV guidelines [25, 26]. ERG responses were recorded monocularly using single-use microfiber electrodes (DTL Plus Electrode, Diagnosis LLC). Arden ratios below 1.5 were rated as pathologic, according to our laboratory normative data.

MfERG was recorded on VERIS Science 6.1.2™ (Visual Evoked Response Imaging System, Electrodiagnostic Imaging; EDI) according to the ISCEV 2012 guidelines [27]. The stimulus array consisted of 103 hexagons. To exclude influence of age on the mfERG recordings [28-30], the patients' recordings were compared to seven left eyes of age-matched controls.

Ultrasound was performed on standardized A-/B-scan device AVISO S (Quantel Medical, Inc.) using a LIN25 linear 20 MHz posterior pole high-frequency B-scan probe and a Pro-Beam A-scan probe.

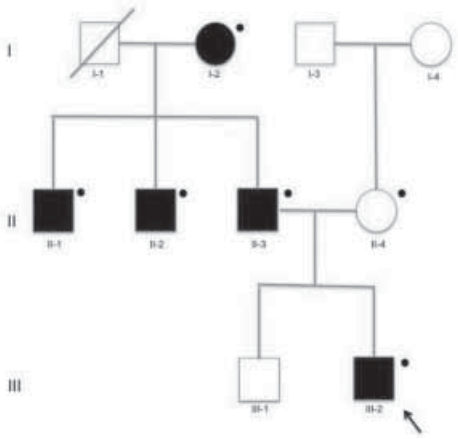

Fig. 1a. Represents the pedigree of the family: arrow identifies the index patient; squares and circles symbolize males and females; blackened symbols indicate affected individuals. All patients with the exception of I-1, I-3 and I-4 were clinically evaluated. Genetically examined individuals are labeled with small circles up and to the right of the individual symbol. The older uncle (subject II-2) had an unilateral-reduced vision presenting, according to the patient's report, as a consequence of strabismus.

Molecular analysis

Blood samples were taken from all participating family members and genomic DNA was extracted from blood leukocytes according to standard procedure. All 11 exons of BEST1

Table 1. Clinical features and ERG findings of all affected subjects.

Subject/ Sex/ Years	Presenting ophthalmological symptoms	Eye	Best corrected Snellen VA (20 Feet)	Refraction D Sph/D Cyl/ Axis°	EOG, Argen's ratio (Norm: 1.5-2.5)	Full-field ERG	mfERG, Responses within central 10°	Optic disc deposits
III-2 /m/6	Progressive reduction of the central vision, OU	OD	20/50	+8.0/0/0	0.77	Normal	Not done	Detectable
		OS	20/50	+8.0/0/0	0.97	Normal		Detectable
II-3/ m/50	Reduced central vision, OD>OS	OD	20/50	+4.25/-1.75/97	1.27	Normal	Reduced	Detectable
		OS	20/32	+4.0/-0.75/14	1.44	Normal	Reduced	Detectable
II-2 m/52	Reduced central vision, OD Squinting, OD	OD	20/100	+3.25/-0.25/153	1.84	Normal	Reduced	Not detectable
		OS	20/20	+2.5/-0.75/123	1.16	Normal	Normal	Not detectable
II-1/ m/48	Severe reduced central vision, OD>OS	OD	20/200	-1.75/0/0	1.1	Normal	Reduced	Detectable on ultrasound
		OS	20/50	+0.5/0/0	1.2	Normal	Reduced	Detectable
I-2/ f/76	Reduced central vision, OU	OD	20/50	+4.5/-0.75/70	2.19	Not done	Reduced	Detectable
		OS	20/40	+4.5/-0.75/110	2.11		Reduced	Detectable

Abbreviations: OD: right eye, OS: left eye, OU: both eyes.

including intron-exon junctions were PCR amplified and directly sequenced using the ABI Dye Terminator version 1 in a final volume of 10 ul, and electrophoresed on 3130XL ABI genetic analyzer. Sequences were aligned using Chromas, version 2.23 (Technelysium Tewantin, Australia) and compared to the sequence obtained from Ensembl**.** Primers were obtained with the Primer3 software (http://primer3.ut.ee) [31, 32].

Results

Subject III-2, the index patient, is a 5-year-old boy followed up for three years in our department due to borderline best corrected Snellen visual acuity (20 Feet) of 20/32 (OU). Follow-up examination revealed progressive reduction of the best-corrected distance/near vision, last recorded as 20/50 (OU). Investigation of the relatives was conducted to evaluate the inheritance pattern of the disease (Fig. 1a).

Five out of seven examined family members were clinically affected. Table 1 describes the clinical characteristics of the patients included in the study. Best corrected Snellen visual acuity ranged from 20/200 to 20/20. A hyperopic refractive error was noted in 9/10 eyes, while that of the right eye of II-1 showed low myopia of -1.75 diopters.

The diagnosis of Best vitelliform macular dystrophy was confirmed by clinical, electrophysiological findings (Fig.1b) and by genetic analysis.

Fundus imaging

Fundus imaging showed findings consistent with no detectable pathology (II-2) to bilateral Best maculopathy lesions: from a classic central Bull's maculopathy appearance in child (III-2), to scarring macular lesions in the eldest subject (I-2). All subjects except II-2 demonstrated multiple yellowish parafoveal deposits that extended along the vascular arcades (Fig. 2a, 2b, 3a, 3b, 5a, 5b, 6a, 6b). Optic discs showed a prominent irregular aspect; in the index patient it had an elevated appearance (Fig. 2a, 2b); in the adult patients it was lumpier with more irregular borders and multiple bright, prominent, irregular mulberry-like deposits (Fig. 3a, 3b, 5a, 5b, 6a, 6b).

Figures 2, 3, 4 and 5: Each vertical panel represents the corresponding fundus with photos (a, b), FAF images (c, d), OCT images of the macula (e, g) and of the optic disc (f). The images for the right eyes are displayed on the left-hand side. Optical coherent tomography (OCT) scans are recorded in the horizontal plane.

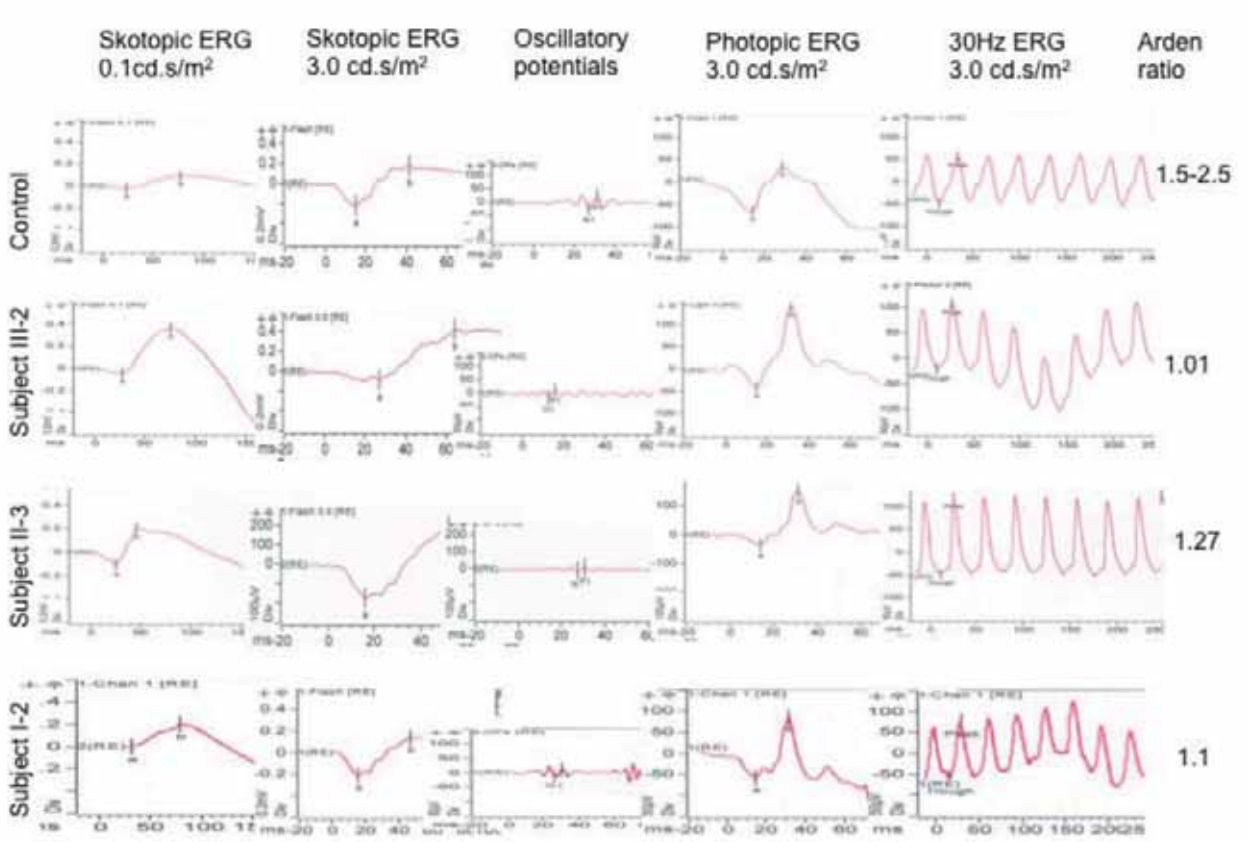

Fig. 1b. Represents an example of electrophysiological findings of some members of the family compared to those of a control subject.

Fundus autofluorescence imaging

In all clinically affected participants, FAF imaging showed deep subretinal hyperfluorescent deposits of the macula, along the retinal vascular arcades, close to the optic disc and superficial to the blood vessels (Fig. 2c, 2d, 3c, 3d, 5c, 5d, 6c, 6d). Similarly to the color fundus photographs, FAF images presented a wide spectrum of Best stages, from the typical egg yolk-like-, pseudohypopyon-stage (III-2, Fig. 2c, 2d), going through a fibrotic scar (II-3, Fig. 3c, 3d; subject I-2, Fig. 6c, 6d) to a stage following ruptured pseudohypopyon (II-1, OD, Fig. 5c, 5d). In the resorbed pseudohypopyon stage, the lesions were hypofluorescent with some yellowish hyperfluorescent granular deposits bordering the lesions (II-1, OS; Fig. 5c).

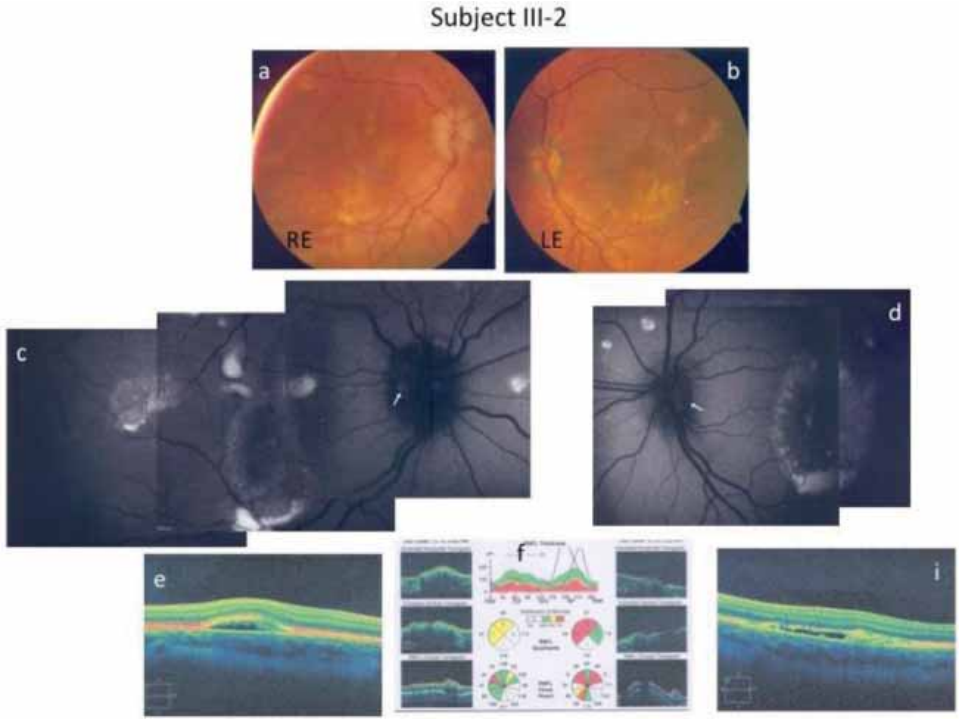

Fig. 2. Represents data of the index subject III-2, a 5-year-old boy: fundus photographs reveal yellowish deposits in the paramacular area; the optic disc had a prominent irregular aspect. The FAF images (Fig. 2c, 2d) confirmed optic disc deposits, more obvious in the right eye, and multiple yellowish vitelliform deposits extended along the inferior-temporal vascular arcades and in the parafoveolar area (OU).

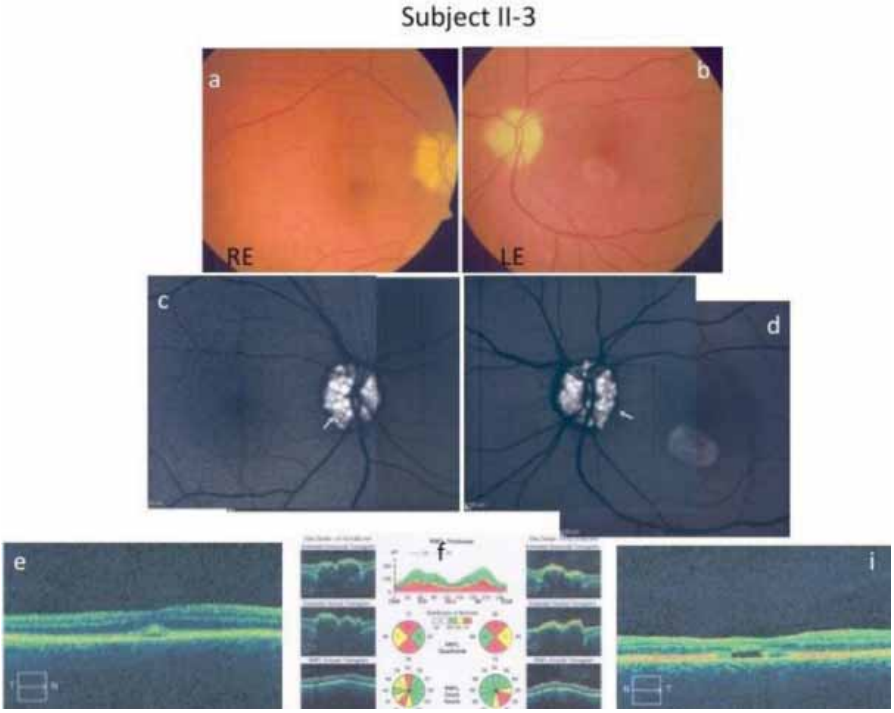

Fig. 3. Shows the diagnostic findings of the father of the index patient, a 50 year-old man, subject II-3: The FAF image of the optic nerve showed multiple hyperfluorescent granular deposits, but also multifocal hyperfluorescent intraretinal deposits close to the temporal vessel arcades along with fibrotic macular scar (OS>OD).

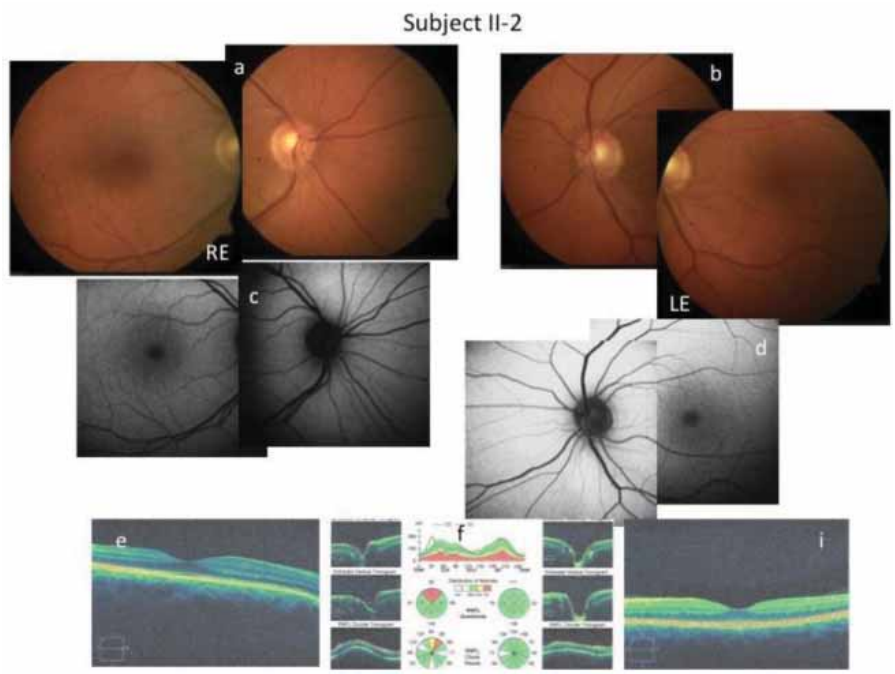

Fig. 4. Represents fundus, FAF imaging and OCT of subject II-1, a 52 year-old uncle of the index patient, showing (Fig. 4c) no suspicion for granular hyperfluorescent macular or optic disc deposits, except for a slightly brighter foveolar FAF reflex.

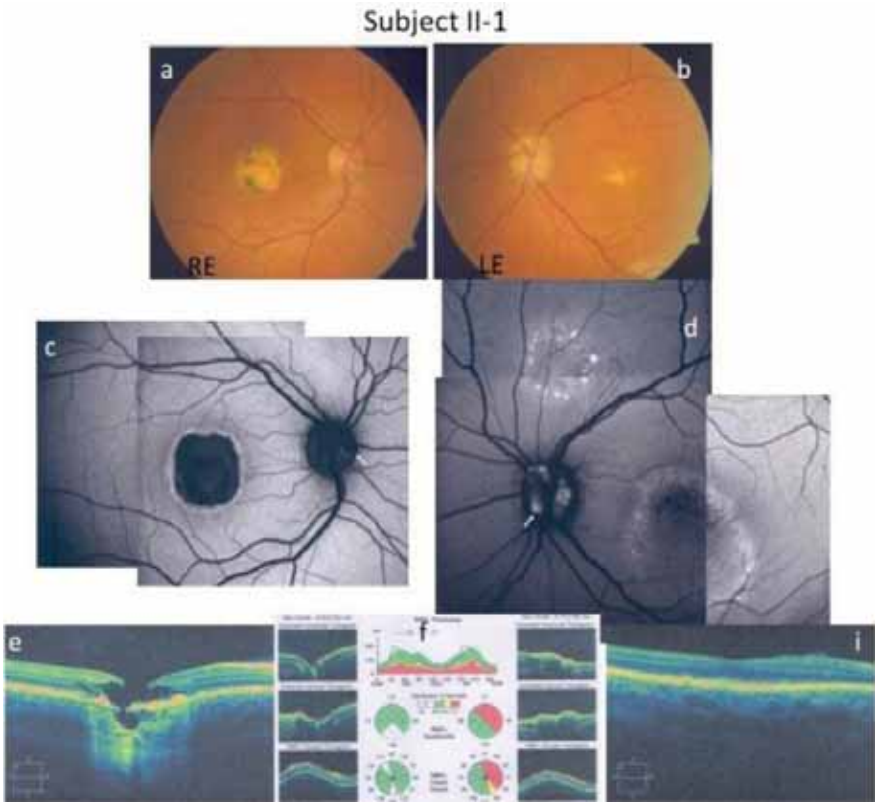

Fig. 5. Diagnostic imaging of subject II-1, an uncle of the index patient, aged 48 years, revealed atrophic macular lesion with central crater-like depression of the fovea and pigmented borders (OD, Fig. 5a, 5c, 5e) and atrophic macular scar (OS, Fig. 5b, 5d, 5g). The OCT images (5e, 5g) confirmed severe destruction of the RPE and the underlying choroidea OD, as well as of the photoreceptor layer. In the left eye a delamination of the RPE from the outer segment with vitelliform deposits in the cystoid space are present. Hyperfluorescent deposits (Fig. 5c, 5d, 5e, 5g) are well documented on the surface of the optic disc (OS>OD, Fig. 5f).

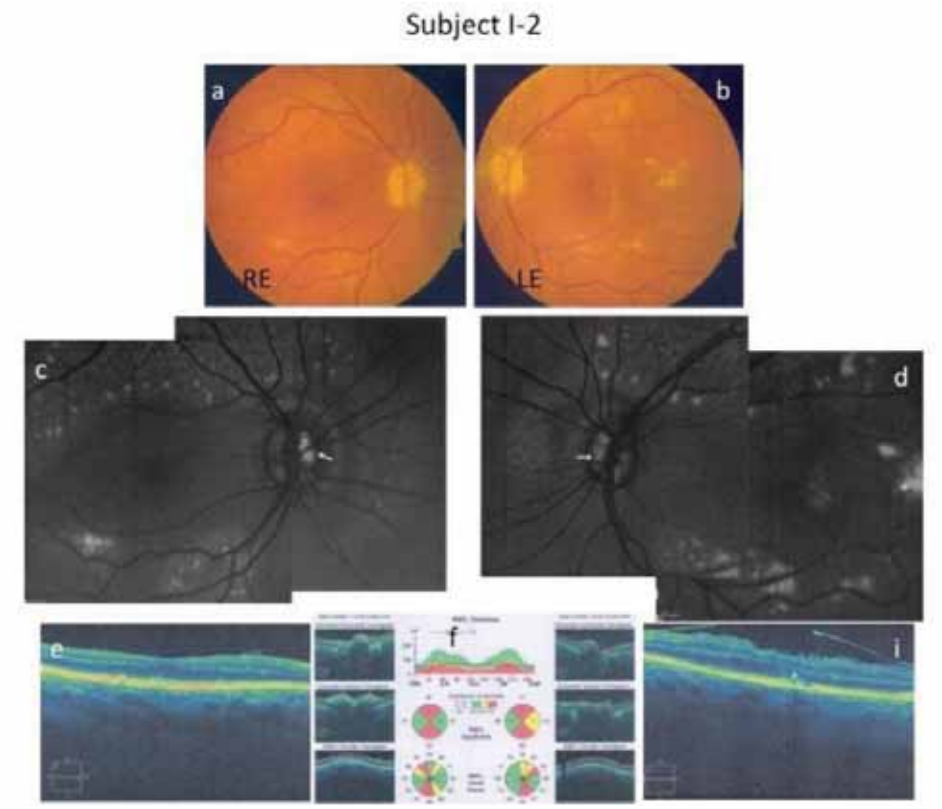

Fig. 6a, 6b, 5c, 6d. Fundus and FAF photographs of the grandmother aged 76, subject I-2. Fundoscopy demonstrated scarring macular lesions and ERF (OU) and also multiple yellow-colored deposits, these hyperfluorescent on autofluorescence imaging. The same hyperfluorescent deposits were also observed on the optic nerve head OU, Fig. 6f).

FAF images of the optic disc head showed multiple hyperfluorescent mulberry-like granular deposits, similar to those close to the macula and spreading along the arcades (Fig. 2-3c, 5-6c, 2-3d, 5-6d).

OCT Imaging

The OCT images (Fig. 2-3e, 5-6e, 2-3g, 5-6g) of the macula were consistent with the fundus and FAF images. In the youngest patient (III-2, Fig. 2e, 2g), the OCTs presented the classical picture of central Bull's maculopathy: the circumscribed subretinal central lesion showed increased reflectivity in its inferior part (Fig. 2e) and some hyperreflective granular deposits on the border of the lesion. The cystoid space showed delamination of the RPE layer from the outer segment with subretinal vitelliform deposits. The architecture of the overlying retina was intact in the initial stages (III-2 and II-3) (Fig. 3e, 5e, 3 o'clock, 5 o'clock), while in the late stages it showed partial destruction of the photoreceptor- and outer-segment layers of the macula (II-3, OU; I-2, OS). Following the stage of ruptured pseudohypopyon, the central outer retina and even the Bruch's membrane and underlying choroid were completely destroyed. The inner neurosensory retina was disrupted (II-1, OD).

OCTs of the optic disc in all patients revealed multiple deposits within the neurosensory layers, also involving the peripapillary area (Fig. 2-3e, 5-6e, 2-3g, 5-6g). Although the initial FAF findings of the optic disc of III-2 were not consistent with superficial deposits, the presence of these could be suspected on the OCTs (Fig. 2e, 2g) and on indirect illumination. On a follow-up FAF examination, the presence of optic disc deposits

Table 2. OCT findings of the optic disc.

	Subject III-2		Subject II-3		Subject II-2		Subject II-1		Subject I-2	
	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
Average RNFL thickness (μm)	134	Artifact	64	68	98	96	105	67	61	62
RNFL symmetry (%)	27 (Artifact, OS)		72		60		72		40	
Ring area (mm^2)	3.20	3.53	4.16	4.01	1.07	1.20	1.21	2.51	2.34	1.75
Disc area (mm^2)	3.20	3.71	4.19	4.01	1.66	1.95	1.75	2.51	2.44	1.75
Average C/D ratio	0.05	0.20	0.09	0.05	0.58	0.61	0.54	0.06	0.21	0.40
Vertical C/D ratio	0.04	0.07	0.16	0.04	0.66	0.56	0.45	0.05	0.32	0.46
Cup volume (mm^2)	0.000	0.000	0.000	0.000	0.175	0.324	0.098	0.000	0.000	0.044

with indistinct borders was confirmed. (Fig. 2c-d). The retinal nerve fiber layer (RNFL) thickness was normal at 132 µm (OD) in III-2, and showed progressive reduction with each generation, decreasing to 42 µm in I-2 at 76 years of age (Table. 2). The thinning of the RNFL was more pronounced in the temporal quadrants (Fig. 2-3e, 5-6e). With aging, the optic disc deposits became larger, more hyperfluorescent and with sharper borders. FAFs and OCT images of II-2 were unremarkable (Fig. 5c, 5d, 5e, 5g).

Distribution of the RNFL thickness measurements in comparison to controls is given for: 1% in bold; 5% underlined and for 95% in italics-bold-underlined. Abbreviations: OD: right eye, OS: left eye.

Electrophysiological findings

All five examined individuals had a normal ffERG light rise. EOG revealed a marked reduced Arden ratio in both eyes in III-2, II-3, II-2 and II-1 and was within normal limits in I-2 (Fig. 1b; Table 1). Here, in I-2 the dark trough was too low (59.38 µV/69.14 µV; OD/OS) compared to the almost normal light peak (130.5 µV/ 146.5 µV; OD/OS) producing a light/dark ratio within the normal range.

Analysis of the mfERG responses:

MfERGs recorded on all patients but III-2 showed reduced central N1P1 responses (Fig. 7a, subject I-II, left eye). In order to analyze the data of each focal response, scalar product (SP) was calculated using the focal templates derived from our age-matched controls' recording. The epoch 0-65 ms (Fig.7b), which includes information for the N1P1 response, was analyzed.

As expected [12-14], the individual response densities for N1P1amplitudes within the central retina were reduced (Fig. 7a,

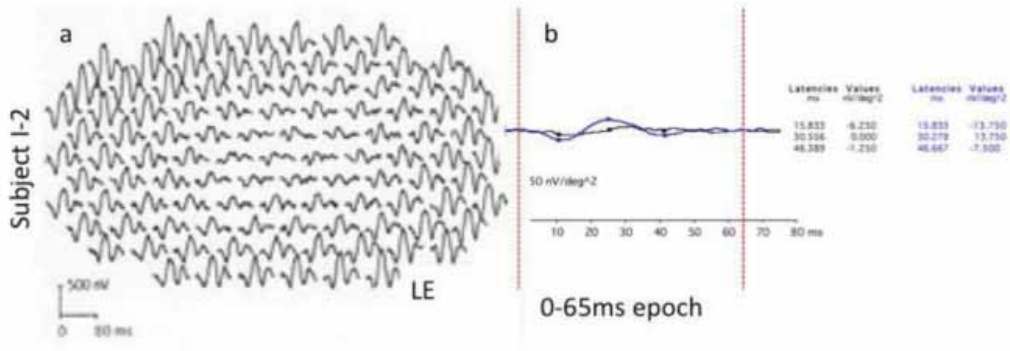

Fig. 7a-b.

Figure 7a. Shows a trace array-example of the left eye of the subject I-2. As expected, the central N1P1 responses were reduced. The corresponding averaged traces (Figure 7b) of the examined patient (given in black) are plotted in comparison to the mean trace derived from our controls' data (in blue). As expected, the mfERG N1P1 responses were reduced.

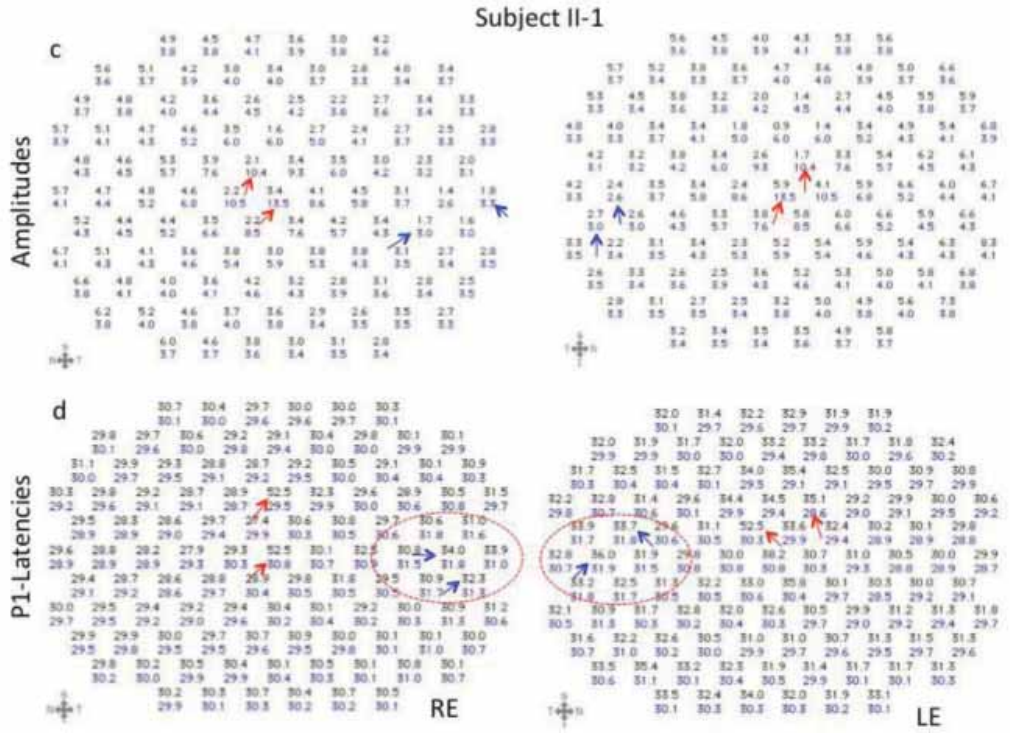

Fig. 7c-d.

Fig. 7c. Depicts the SP of the amplitudes for the 0-65 ms epoch and in fig. 7d their respective P1 latencies mfERG as exemplified for subject II-1. Even if no amplitudes reduction was measured, the P1 latencies were delayed.

7b, 7c). A novel finding in our cases was that the P1 latencies were also delayed (Fig. 7d). This held true not only for the central, paracentral responses, but also for the responses within or close to the optic disc, as exemplified with arrows and dotted circles in fig.7c and 7d for subject II-1. Surprisingly, mfERG responses were also pathologic in the OCT and FAF examination of the unaffected subject II-2. Pronounced N1P1 amplitude reduction of the central responses was observed in the right eye, and prolonged P1 latencies of the central and the optic disc area responses noted in both eyes.

For all examined family members, the N1P1 amplitude response-mean values in the central, paracentral, peripapillary and optic disc areas were significantly reduced and the corresponding latencies delayed (Fig. 8b, 8c, 8d). This also held true for the N1, P1N2 amplitudes and their respective latencies.

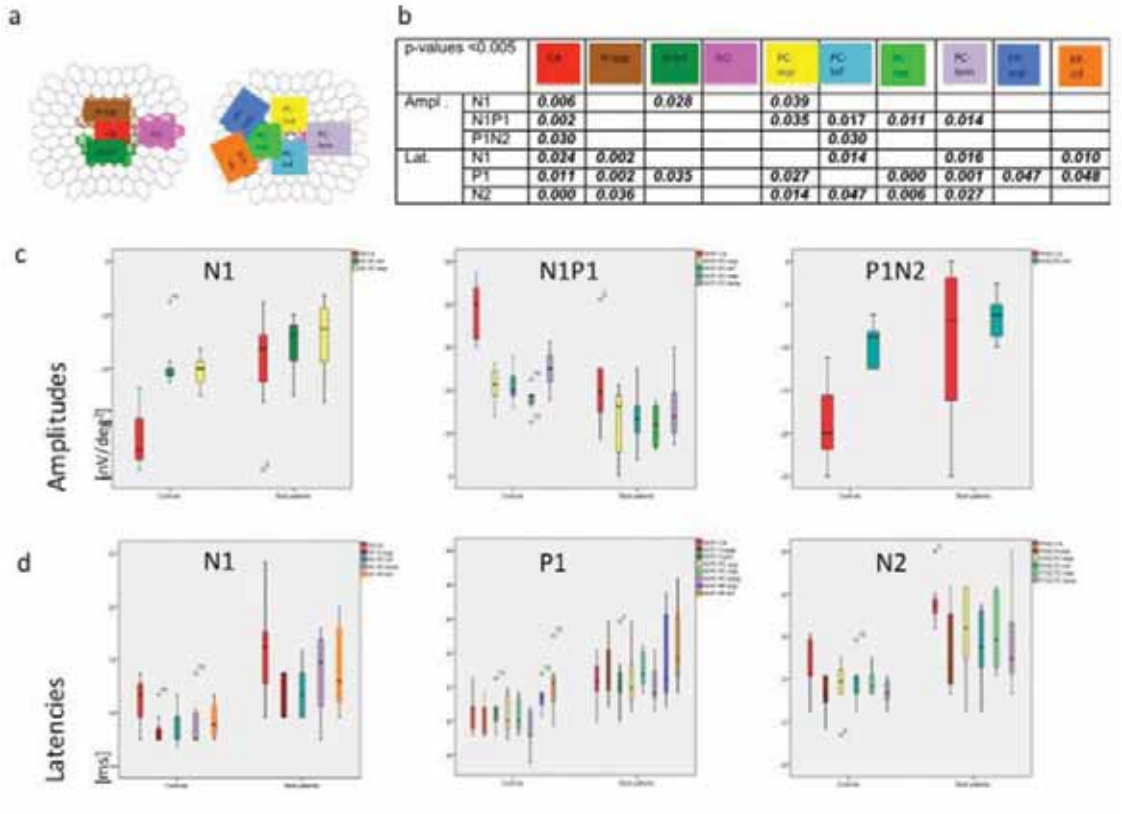

Fig. 8a. Depicts the mean mfERG responses of all examined family members of the macula, the paracentral area, the optic disc area, and the peripapillary retina in order to compare them to the age-matched controls (7 eyes). Statistically significant difference (P<0.005, repeated measure ANOVA) was found between the examined Best-patients and the controls for central, paracentral, and also for the optic disc area. The significant p-values are given in Fig. 8b (Table) with their corresponding box plots (Fig. 8c, 8d) when compared to age-matched controls. The box length is the interquartile range; the median is presented as a thick black line within the box. Cases with values below and above 3 box length are outliers.
Abbreviations: CA: central area, H-sup: hemicentral-superior, H-inf: hemicentral-inferior, NO optic nerve: optic disc area, sup: superior, inf: inferior, nas: nasal, temp: temporal, PP-sup: peripapillary area superior, PP-inf: peripapillary area inferior.

Ultrasound

Both eyes of III-2 and II-3 were examined further via standardized echography. The ultrasound of the optic disc showed high-reflective nodular and confluent accumulations with indistinct borders (Fig. 9; arrow, ↑). The nodular lesions were located superficially on the optic disc, namely within the neurosensory layers. Nodular hyperreflective accumulations were observed also in the peripapillary area (Fig. 9b, 9d; solid arrowhead, ▲) predominantly located at the level of the outer retina, but also some near the inner retina (Fig. 9b, solid arrowhead, ▲). In the macula, B-scans confirmed further nodular confluent hyperreflective deposits with indistinct borders (Fig. 9c). All high reflective round structures showed acoustic shadowing characteristics in the medium- and low-gain scans (Fig. 9b, 9a, respectively). A transposition of B-scan to A-scan confirmed, similarly to the deposits affecting macula, a 100% reflectivity of the accumulations located on the surface of the optic disc and in the peripapillary area (Fig. 9c, 9d; solid arrowheads, ▲).

Molecular analysis

Sequencing of exon 6 showed a c. [670 C>A] heterozygous mutation which replaced the leucine amino acid at position 224 with methionine. This mutation, already reported in the literature [2], was present in all affected individuals and was not observed in 96 controls of Swiss origin.

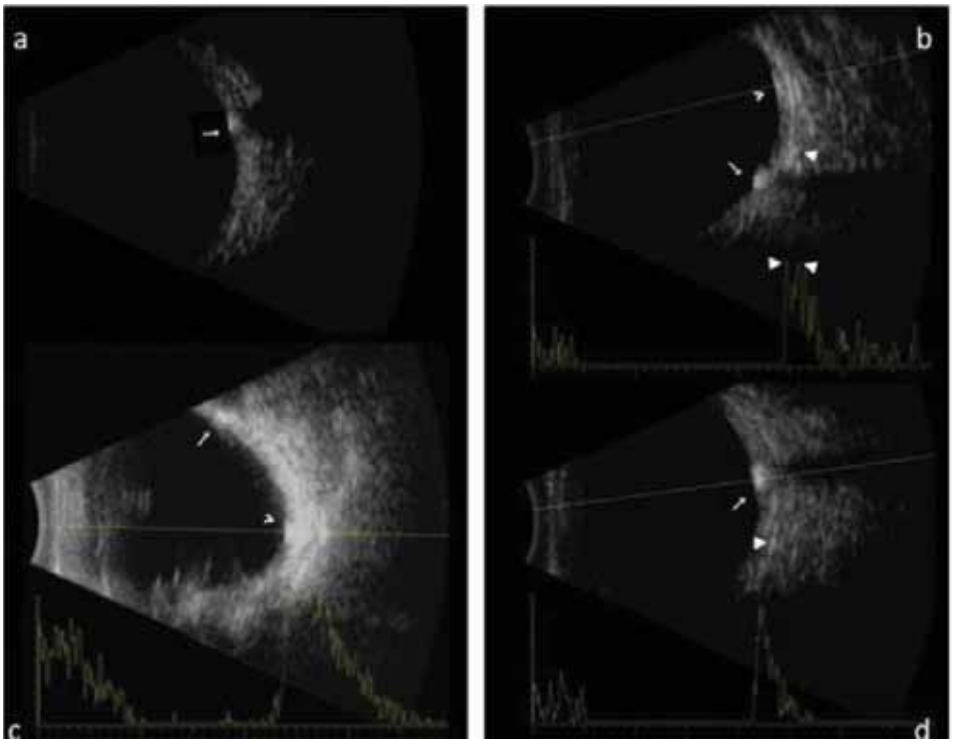

Fig. 9. Representative B-scans of the subject III-2 (Figure 9a, 9c) and II-3 (Fig. 9b top, 9d) confirming the hyperreflective deposits at the macula (open arrowhead, <) at the level of outer retina (solid arrowhead, ▲), but also close to the level of the inner retina (solid arrowhead, ▲). For the index subject, where the FAF imaging of the optic disc was initially negative for hyperfluorescent deposits, the B-scan echography already confirmed the presence of highly reflective round confluent structures (arrow, ↑) (Fig. 9a, 9c).

Discussion

We describe a new phenotypic form of vitelliform maculopathy in a three-generation family exhibiting juvenile-onset Best disease with heterozygous autosomal dominant inheritance in association with deposits on the surface of the optic disc. The diagnosis of juvenile-onset Best disease was confirmed by clinical, electrophysiological and ultrasound findings and by the identification of a heterozygous mutation in BEST1.

Our work presents a cross-sectional study with different findings in different patients, hence a variable phenotype within a family with juvenile-onset Best disease: from "strabismic-amblyopia-form" with subclinical monolateral picture (subject II-2), to typical yolk-like vitelliform lesions with pseudohypopyon formation (subject III-2), through the cicatrization-form (subject II-3), the pseudostaphyloma of the macula after ruptured pseudohypopyon (subject II-1), evolving to the scarring stage of the disease with secondary epiretinal fibrosis (subject I-2).

As stated previously, typical egg-yolk-like vitelliform lesions, predominantly affecting the posterior pole [1, 2, 7], characterize the classical juvenile-onset Best disease. Previous histological studies [8] have clarified these abnormal deposits to be of lipopigment-like origin. Further morphological studies, using OCT imaging, have identified these lipofuscin deposits to be localized beneath the neurosensory retina, predominantly between the RPE-layer and the photoreceptors, leaving the RPE-layer in early stages almost preserved [33]

As elucidated in our case series, the EOG was more pathologic and the Arden radio more severely reduced in the active egg yolk-like stage (subject III-2), but almost normal in its inactive stage (subject I-2). Here however, the dark trough was so low, that even a small light response produced a large light/dark ratio. We also observed a subclinical monolateral form, with bilateral reduction of the Arden ratio (subject II-3). A review of the literature revealed subnormal or even normal EOGs with usually preserved visual acuity and subnormal ffERG, in association, however, with the eccentric multifocal vitelliform form of the disease [18, 23, 24, 34]. In the current study, we also observed eccentric hyperfluorescent deposits along the vessels in association with similar hyperfuorescent deposits on the surface of the optic disc. Ultrasound evaluation confirmed that the hyperfluorescent optic disc deposits seen on the surface of the optic disc were located anterior to the lamina cribrosa but, in contrary to optic disc drusen, not in the sub-arachnoid space. The observed optic disc deposits showed echographic characteristics similar to those affecting the macula and peripapillary area: high-reflective nodular confluent accumulations with indistinct borders and acoustic shadowing characteristics in the medium- and low-gain scans.

When the retinal function was measured by means of mfERG, reduced amplitudes were confirmed [12-14] but also latencies delays were noted, corresponding to the vessel arcades and the peripapillary and optic disc areas, thus confirming the distinct multifocal phenotype in the presented family. An interesting finding is the reduced local N1P1 responses, and also the P1 latencies delay, measured even when no lipofuscin deposits were clinically visible, as exemplified in our subject II-2. Also, the Arden ratio was pathologic in the uninvolved left eye. This is not an unexpected finding as the functional and structural tests

do not always overlap, but present additional information [35].

OCTs of the optic disc confirmed the drusen-like deposits on the surface of the optic disc to have a variable phenotypic characteristic within the affected family, being of prominent or blurry appearance, as in the youngest case (subject III-2), and getting larger, hyperfluorescent and more sharply bordered the older the generation. Noticeably, as described with aging or due to compression [36, 37], the average RNFL thickness showed progressive reduction as well.

Optic disc drusen have already been described in patients with inherited diseases of the retina, as for instance in cases of retinitis pigmentosa [38, 39], Usher syndrome [40], malattia leventinese [41], and congenital stationary night blindness [42]. Some neurodegenerative syndromes have also been linked to inherited retinopathies and optic disc drusen, as in: mulibray nanism [43], Joubert syndrome [44], Alagille syndrome [45], Adams-Oliver syndrome [46], ataxia-teleangiectasia [47], or pseudoxantoma elasticum [48]. In some instances, optic disc lesions in association with retinitis pigmentosa have been called hamartomas due to their bilaterality, mulberry-like appearance and more superficial location in relation to the peripapillary blood vessels [49-52], as it was in our case. Focal reactive proliferations of astrocytes as explanation for their presentation have been suggested even though no tuberous sclerosis or Recklinghausen's disease was present [50].

In conjunction with Best disease, various optic disc findings have also been described as, for instance, the aberrant papillae with peripheral band of circumferential retinal atrophy and hyperpigmentation alterations, mapped to the autosomal dominant vitreoretinochoroidopathy (ADVIRC) [15, 34]. BEST1mutations have also been observed in nanophthalmos with high hyperopia as a consequence of NNO1 mutations [53, 54]. Also, mutations in MFRP have been reported in autosomal recessive forms of retinitis pigmentosa, a condition associated with foveoschisis, nanophthalmos and hyperopia [55-57]. In our family, nine out of ten eyes examined showed hyperopic error. The right eye of II-1 showed myopic measurement most likely a consequence of pseudostaphyloma followed by ruptured pseudohypopyon stage. Even if the refractive error in our study showed a hyperopic refraction, the anterior segment had otherwise no signs of anterior nanophthalmos, and the intraocular pressure was also within normal ranges.

Based on histological studies, the transmembrane protein encoded by BEST1 has been localized in the basolateral plasma membrane of the entire RPE [4, 58]. Even though some patchy macular predilection has been thought to exist, histology has proven Best disease to be a more generalized RPE abnormality, involving also the brain, the spinal cord and the testes [3, 8, 59]. With regard to our cross-sectional study, as the peripapillary optic disc area is devoid of retina, retinal pigment epithelium or photoreceptors, the origin of the described optic disc deposits remains unclear. The question, whether the described optic disc lesions are a kind of secondary astrocyte proliferation and thus be called optic disc hamartomas, or are presentation of generalized multifocal Best1 phenotype, remains to be elucidated.

Conclusion

In conclusion, our data describe an unusual phenotype in a family with juvenile form of Best disease, carrying a heterozygous L224M mutation in BEST1. They included patients with preserved ffERG recordings, pathologic EOG, hyperopic refraction, and affected mfERG responses. A combination of optic disc mulberry-like deposits in the presented juvenile-onset autosomal dominant form Best disease is a novel finding. Through comparison of the morphological tests (OCT, the FAF ultrasound images) and the functional measures (mfERG), we deducted that the observed optic disc deposits were part of a generalized multifocal phenotype.

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Алдостероновият антагонист CARDITRUST (EPLERENONE) при лечението на централна серозна хориоретинопатия

Хр. Видинова, Пр. Гугучкова

СБАЛОБ „Зрение“, София

Aldosterone blocker CARDITRUST (EPLERENONE) in the treatment of CSCR

Ch. Vidinova, Pr. Guguchkova

Eye Hospital “Zrenie”, Sofia

Резюме

Централната серозна ретинопатия е заболяване, което засяга макулната зона при млади хора, по-често мъже. То се характеризира с наличието на серозно отлепване на ретината и при хронифицирането на процеса до атрофия на РПЕ и силно намаляване на зрителната острота.

Цел: Целта на нашето изследване е да представим чрез ОСТ и фундусова автофлуоресценция резултатите ни от прилагането на алдостеронов антагонист - Еплеренон (Carditrust) при пациенти с централна серозна хориоретинопатия (CSCR).

Материал и методи: В нашето проучване бяха включени 7 пациенти с остра форма на CSCR и 5 пациенти с хронична форма на заболяването. Те всички бяха изследвани подробно офталмологично, включително и с ОСТ (3D TOPCON OCT) и фундосова автофлуоресценция (Cannon X1). Всички пациенти бяха лекуван с Еплеренон в стандартна доза от 50 мг дневно в продължение на 3 седмици и се проследяваха още 6 месеца след това. Периодично изследвахме нивата на калий в кръвта.

Резултати: Пациентите с остра форма на CSCR се характеризираха с наличие на отлепване на невросензорната ретина и дифузна хипоавтофлуоресценция в засегнатата зона. Централната ретинна дебелина беше от порядъка на 340 - 360 mk, като се набюдаваше задебеляване на хориоидеята с дилатация на съдовете.

При хроничните форми, най-често набюдавахме субретинна течност и атрофия на РПЕ. След приема на Еплеренон в продължение на 3 седмици, се наблюдава значително намаляване на големината на булата и количество субретинна течност, с намаление на макулната дебелина до 270 - 250 mk. Дебелината на хориоидеята беше намалена и липсваше хиперавтофлуоресценция.

Заключение: Еплеренон действа като намалява нивата на алдостерон в кръвта и по този начин влияе върху съдовете на хориоидеята. Нашите резултати показват, че под негово влияние значително се намалява големината на булата в макулата и се редуцира дилатацията на съдовете на хориоидеята, като по този начин изчезват симптомите на иначе резистентни на терапия случаи на CSCR. Намаляването на дебелината на макулата и на хориоидеята след приложението на препарата е чувствително и продължава 6 месеца след спиране на терапията. Еплеренон има протективно действие върху РПЕ и намалява атрофията на тези клетки.

Ключови думи: Централен серозен хориоретинит, алдостеронов блокер, Еплеренон.

Abstract

Central serous chorioretinopathy is a condition characterized by serous retinal detachment, which when chronified, often leads to atrophic changes of the RPE and decline of the visual acuity.

Purpose: The aim of our study is to demonstrate with OCT and Fundus autofluorescence the effect of Eplerenone (aldosterone blocker) on the development and recurrence of different types of CSCR.

Material and methods: We enrolled 12 patients with first occurrence of acute CSCR and 15 with chronic CSCR, with more than 2 episodes of the disease. They all underwent a complete ophthalmologic examinations including OCT (3D TOPCON OCT) and fundus autofluorescence. The fundusautofluorescence (FAF) was done with the Cannon X1 camera. All patients received standard dose of Eplerenone of 50 mg daily for the period of 3 weeks and were then followed up for 6 months. Potassium and cholesterol levels and blood pressure has been monitored in both groups.

Results: In the first group of patients with acute CSCR a significant detachment of the neurosensory retina with diffuse hypoautofluoresce on the FAF pictures was observed. Central retina thickness was between 340 - 360 mk and thickening of the choroid has been measured.

In the chronicle cases subretinal fluid together with RPE atrophy were detected. After the use of Eplerenone significant resolution of the subretinal fluid, together with decrease of macular thickness to 270 - 250 mk was found on the OCT. No hyper autoflurescence was present on FAF. Choroidal thickness was reduced. The potassium levels in blood were slightly decreased.

Conclusion: Eplerenone acts by blocking aldosterone levels in the blood and in that way has a beneficial effect on the blood vessels in the choroid. Our results show that it reduces subretinal fluid and choroidal vessel dilatation and thus resolves quickly the symptoms of therapy - resistant CSCR. Macular thickness and that of the choroid are significantly decreased after the application of the drug and that lasts for 6 months after the application is stopped. FAF pictures show less damage on the RPE after the Eplerenone application.
Key words: CSCR, aldosterone blocker, Eplerenone.

Въведение

Наименованието централен серозен хориоретинит - Retinitis centralis serosa (CSCR) датира още от времето на фон Грефе [1]. В американската литература състоянието е известно под наименованието „Идеопатична централна серозна ретинопатия" ("Ideopathic Central Serous Chorioretinopathy" - ICSCR). Почти и до днес продължават дискусиите около характера на това заболяване, като едва с въвеждането на флуоресцеиновата ангиография и описването от Fujisawa (1965) на патогномоничния белег „точка на изтичане" се изясняват някои от патогенетичните механизми на заболяването [3, 4].

Понастоящем, можем да кажем, че CSCR се характеризира с отлепване на невросензорната ретина в областта на макулата вследствие на идеопатично нарушаване целостта на ретинния пигментен епител и преминаване на течност от циркулацията на хориоидеята (Фиг. 1). Касае се за локален дефект на ниво РПЕ/хориоидея. Клетките на РПЕ се свързват по между си с помощта на специализирани контакти от типа на tight junction, които са неустойчиви на външни въздействия. Силата на свързване между клетките е от порядъка на 70 - 100 ом. За сравнение силата на свързване между епителните клетки на роговичния епител е 10 пъти по-голяма - 1000 ом. Нарушаването на цялостта на свързване води до проявите на централна серозна хориоретинопатия.

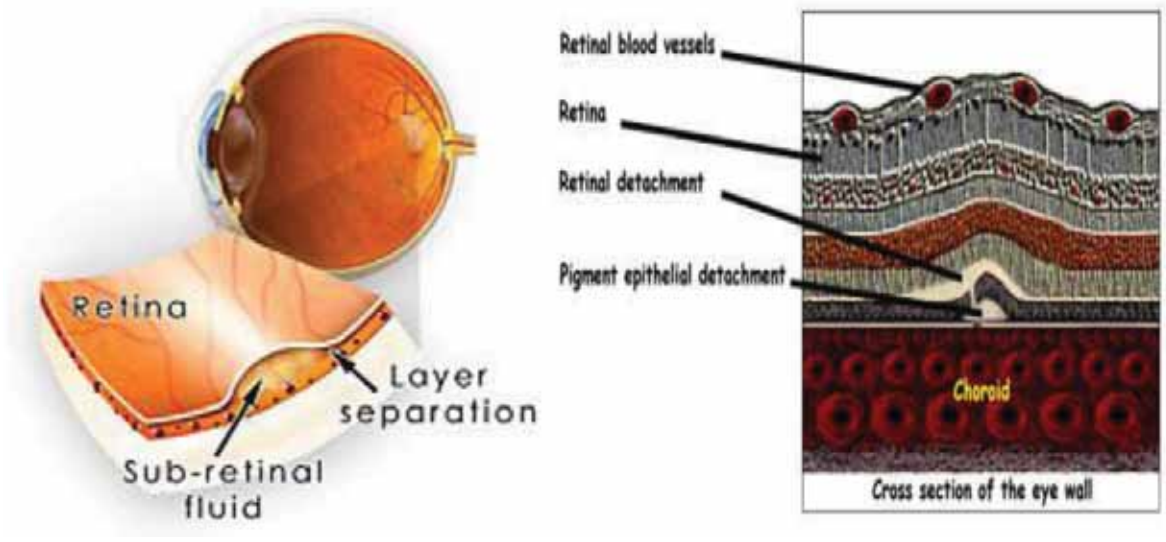
Заболяването може да бъде разделено на две основни форми - класически или акутен тип CSCR, което може да бъде с една или няколко точки на изтичане и дифузната пигментна епителопатия - хроничната форма на CSCR (DRPE). В англоезичната литература известна като дифузна ретинална пигментна епителопатия DRPE поради типичната за състоянието дифузна атрофия на РПЕ. За разлика от акутната форма, хроничната се среща обикновено в по-късна възраст над 50 год., налице са дефекти в зрителното поле поради атрофичните изменения на РПЕ (70%), по-често е двустранното засягане (90%) [6, 7, 12]. Рискови фактори за преминаване на остра форма в хронична са следните:

- По-голяма възраст на пациента > 40 години.
- Наличие на отлепване и на РПЕ.
- По-голяма дебелина на хориоидеята > 500 мк.

При хроничната форма за разлика от класическата форма на заболяването много по-често се развива хориоидална неоваскуларна мембрана като компликация. DRPE може да се развие самостоятелно или като следствие на рецидиви на остър централен серозен хориоретинит [9].

Все още етиологията и патогенезата на заболяването са обект на дискусии. Безспорен факт е, че то се среща по-често при мъже отколкото при жени, в съотношение 2.7:1 и в 60 - 90% от случаите става дума за остра, класическа форма на CSCR и само в 5 - 40% за хроничната форма. Състоянието е по-често при хиперопични очи и при хора с тип поведение А - динамични, енергични подложени на емоционален стрес. Острата форма е характерна за възрастта между 20 - 50 г. [5, 6, 7, 10].

Макар етиологията да се смята за идеопатична, все повече се налага схващането, че в основата на състоянието са промените в нормалните взаимоотношения РПЕ, Брухова мембрана, хориокапилярис. Все повече се приема теорията за стреса като отключващ фактор в патогенезата на заболяването. Смята се, че при някои индивиди с определен тип нервна система прекомерни стимули от страна на симпатикуса могат да доведат до вазомоторни смущения и предизвикат слабост в структурата на Бруховата мембрана и повишаване на нейната пропускливост [10, 11]. Това позволява да се натрупа течност дифундираща от хориокапиляриса към невросензорната ретина, с нейното



Фиг. 1. Схема на L. Yannuzzi & K. Freund на патологичните промени при RCS.

последващо отлепване. Според някои автори дори се касае за дифузно засягане на вътрешния колагенен слой на бруховата мембрана с образуване на кавитети и промяна в нейната пропускливост [1, 2].

Други теории поставят клиничните промени при централния серозен хириоретинит като резултат на нарушената функция на РПЕ [5, 6, 7]. Измененията в тези клетки водят до възможност за локална дифузия на течност от хориокапиляриса през тях. Смята се, че по някаква причина се увреждат РПЕ клетки като се натрупва течност в даден участък и се създават условия за отлепване на невросензорната ретина. Натрупването на течност се нарича „аваскуларно" защото не е свързано с пролиферация на неосъдове както е при много други заболявания - диабетна ретинопатия и сенилна макулна дегенерация. Макар все още патогенетичните механизми да са спорни, вече е известно, че определени състояния могат да предизвикат развитието на заболяването, такива са бременност, трансплантация на органи, остри глумерулонефрити, Morbus Crohn и др.

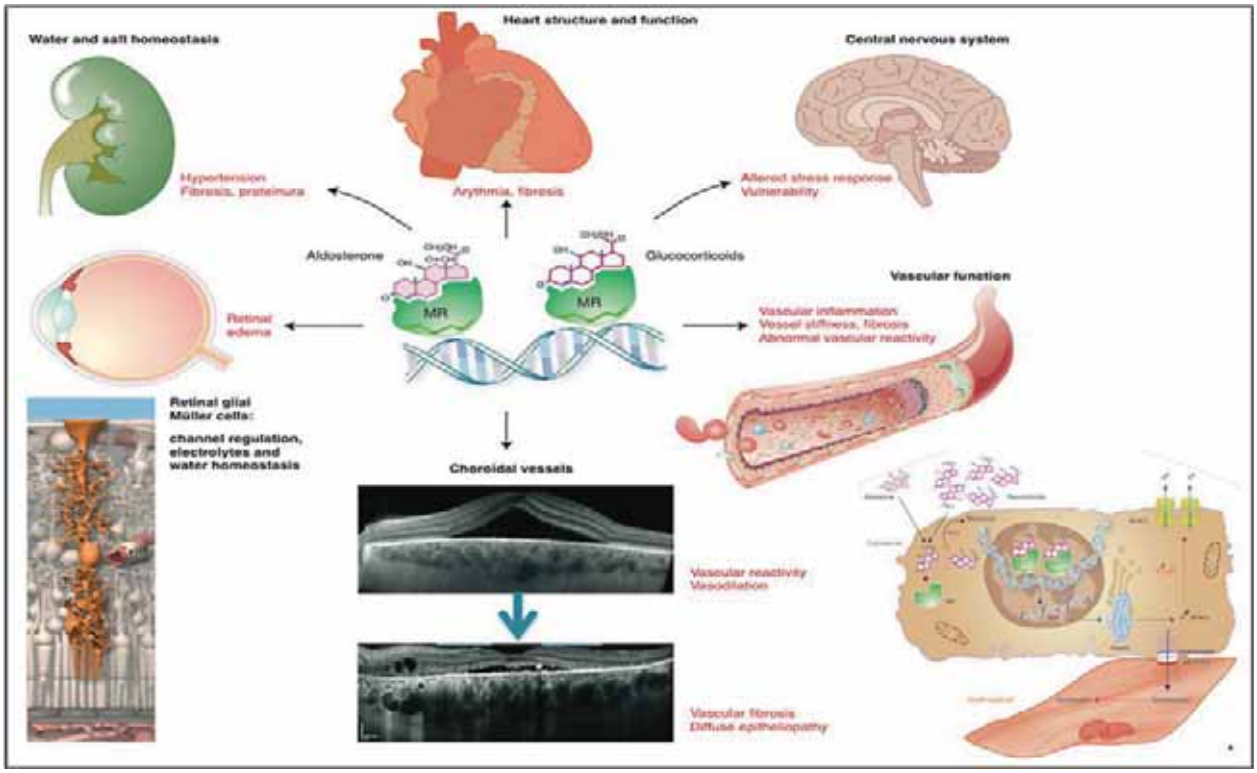
Напоследък все по-голяма популярност придобива минералкортикостероидната хипотеза в патогенезата на CSCR, според която хиперактивацията на минералкортикоидните рецептори в различните тъкани и органи на човешкото тяло води до развитие на патологични заболявания. Тази теория може да бъде добре илюстрирана със следната схема (Фиг. 2).

Както е видно от схемата, свръхстимулацията на MP в сърцето предизвиква аритмия и повишено кръвно налягане, свръхактивацията в съдовете вазодилатация, а свръхактивацията в ретината и хориоидеята на симптоми сходни с тези на CSCR.

Според Cohen Jasser "Ретината и хориоидеята са минералкортикоид чувствителни тъкани и свръхстимулацията на минералкортикоидните рецептори от алдостерона предизвиква оток и отделяне на невросензорната ретина от РПЕ характерно за CRSC. CRSC се дължи на свръхактивация на MP". Именно тази хипотеза е причина в последно време да се приеме, че блокерите на алдостерона биха имали положителна роля при лечението и профилактиката на пациентите с CSCR. Такъв препарат е Eplerenone, който се намира на нашия пазар под търговското име Кардитръст. Той е препарат, одобрен от FDA през 2002 г. за лечение на хипертония и сърдечна недостатъчност. Представлява селективен алдостеронов блокер (SAB) с почти никакъв ефект върху андрогенните и прогестеронови рецептори. Точно поради неговата селективност, препаратът няма страничните ефекти от стимулацията на прогестероновите и андрогенните рецептори, които са характерни за Спиронолактона. Кардитръст има органопротективно действие и предизвиква вазодилатация на хориоидните съдове, образуване на пахисъдове и промени на РПЕ/хориоидея интерфейс. Всичко това предполага, че прилагането на препарата би довело до положителен клиничен ефект при пациентите с CSCR.

Цел

Целта на нашето изследване е да представим чрез ОСТ и фундусова автофлуоресценция резултатите ни от прилагането на алдостеронов агонист - Еплеренон (Carditrust) при пациенти с централна серозна хориоретинопатия (CSCR). Да се обсъдят терапевтичните схеми за прилагане на препарата с оглед лечението и профилактиката на заболяването.



Фиг. 2. Показваща минералкортикостероидната хипотеза. Патологични процеси резултат от свръхактивация на минералкортикоидните рецептори.

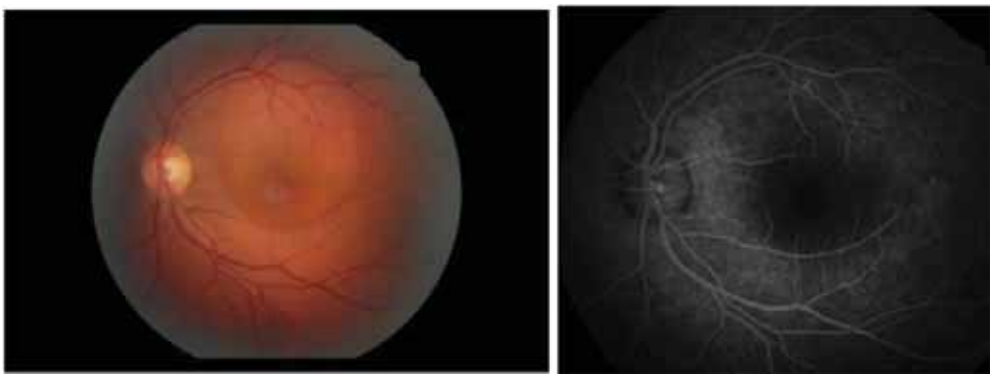
Материал и методи

В нашето проучване бяха включени 7 пациенти с остра форма на CSCR и 5 пациенти с хронична форма на заболяването. Те всички бяха изследвани подробно офталмологично, включително и с ОСТ (3D TOPCON OCT) и фундосова автофлуоресценция (Cannon X1). Всички пациенти бяха лекуван с Еплеренон в стандартна доза от 50 мг дневно в продължение на 3 седмици и се проследяваха още 6 месеца след това. Периодично изследвахме нивата на калий в кръвта.

Резултати

При хроничните форми, най-често набюдавахме субретинна течност и атрофия на РПЕ. След приема на Еплеренон в продължение на 3 седмици, се наблюдава значително намаляване на големината на булата и количество субретинна течност, с намаление на макулната дебелина до 270 - 250 mk. Дебелината на хориоидеята беше намалена и липсваше хиперавтофлуоресценция.

веата без отлепване на РПЕ, като в 3 (20%) от случаите се откриха повече от една „точки на изтичане". Само в два от случаите наблюдавахме и отлепване на РПЕ. Характерни бяха флуоресцеин ангиографските промени. При всички пациенти наблюдавахме наличие на „точка на изтичане", като при 3 имахме две или повече такива точки. При 2 от пациентите се обективизира изтичане по типа на „водоскок" (smokestack). Изтичането на флуоресцеина наблюдавахме в края на артериалното и началото на ламинарното венозно време (Фиг. 3). То започваше като хиперфлуоресцентна точка, от която багрилото експандираше нагоре и отвесно, след което се наблюдаваше изпълване със флуоресцеин на цялата невросензорна була под формата на дъга. При 4 от случаите наблюдавахме разливане на флуоресцеина по типа "Expanding pin point". От една хиперфлуоресцентна точка имаше дифундиране на багрилото равномерно във всички посоки. При 1 пациент се наблюдаваше изтичане по типа на „вретено" с хоризонтално преминаване на флуоресцеина. Централната ретинна дебелина беше от порядъка



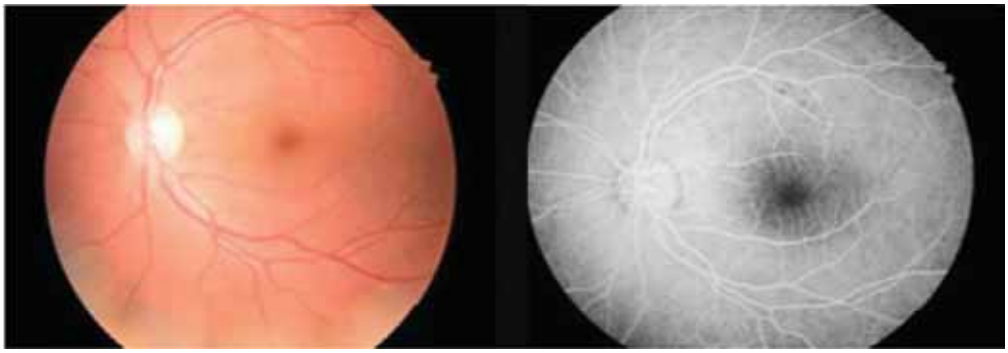
Фиг. 3. Пациент с остра форма на CSCR преди терапията с Еплеренон.

В първата група имахме 7 пациенти с остър централен серозен хориоретинит, като те бяха във възрастовия интервал 25 - 45 години, средна възраст 33 год. От тях 8 бяха мъже и четири жени, при никои от тях нямаше анамнестични данни за прием на кортикостероидни препарати по повод на друго системно заболяване. Началото на заболяването при повечето от тях беше свързано с някакъв стрес или емоционални проблеми. Зрителната острота на 5 от пациентите при първия преглед беше 0.9 - 1.0, на 3 - 0.8 и само на 2 в диапазона 0.5 - 0.6. При оглед с офталмоскоп и цветна снимка на очното дъно наблюдавахме отлепване на невросензораната ретина в областта на фо-

на 340 - 360 mk, като се набюдаваше задебеляване на хориоидеята с дилатация на съдовете.

След приема на Еплеренон в продължение на 3 седмици, се наблюдава значително намаляване на големината на булата и количество субретинна течност, с намаление на макулната дебелина до 270 - 250 mk (Фиг. 4). Дебелината на хориоидеята беше намалена и липсваше хиперавтофлуоресценция.

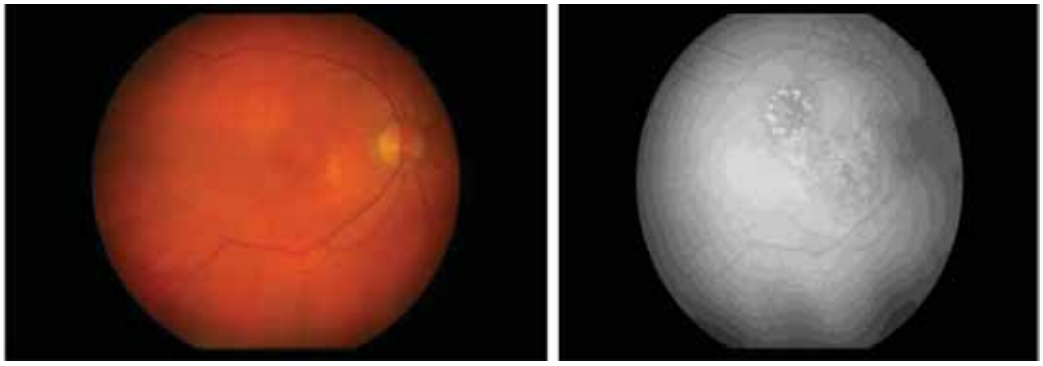
Във втората група имахме 5 пациенти с хроничен централен серозен хориоретинит с повече от 2 пристъпа и хроничен ход на заболяването. В анамнезата се докладваше за периоди на подобрение и влошаване на зрителната остро-



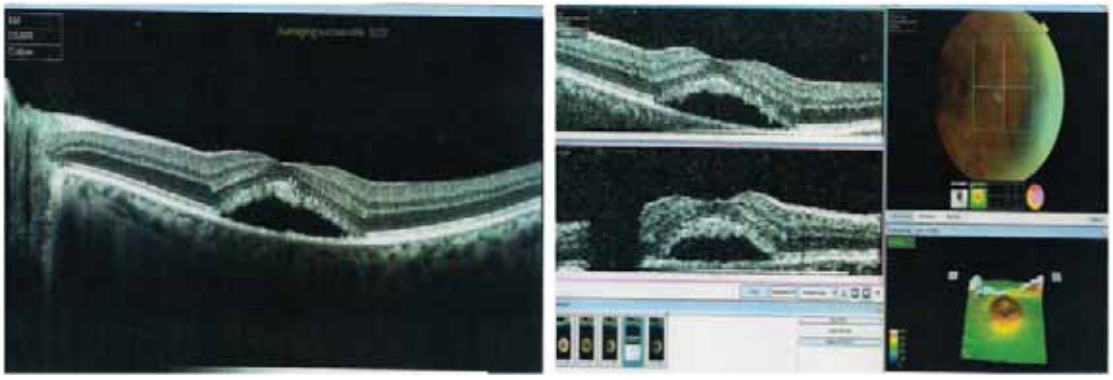
Фиг. 4. Същият пациент след 3 седмично лечение с Еплеренон. Наблюдаваме напълно резорбиране на централната була и затваряне на точката на изтичане.

та. Макар клиничната картина да наподобяваше промените при острия CSCR налице бяха някои характерни особености. При всички пациенти диагностицирахме дифузна атрофия на РПЕ с участъци на отлепване на невросензорната ретина както и на РПЕ. Някои от лезиите бяха разположени централно (Фиг. 5), а други парафовеоларно. Характерна един рецидив.

Измерването на дебелината на хориоидеята и в двете групи показа сигнификантно намаление на дебелината след приложението на препарата, което може да се обясни с намаляването на дилатацията на хориоидните съдове, постигана с помощта на алдостероновия блокер.



Фиг. 5. Пациент с хронична форма на CSCR, виждат се добре атрофичните зони на РПЕ.



Фиг. 6. Пациент с рецидив на CSCR, с наличие на активна була.

бе също така и по-голямата възраст на пациентите над 40 години, наличието на скотоми в зрителното поле, поради атрофията на РПЕ, както и при 1 от случаите наблюдавахме развитие на хориоидална неоваскуларна мембрана (CNV). На флуоресцеин ангиографските плаки се откриваше малко по-различна картина от тази на предишната група - налице бяха множество точки на изтичане на багрилото в рамките на зоната на пигментно епителна атрофия, без някоя отделна да превалира над останалите. В зоните на предшестващи отлепвания на невросензорната ретина или РПЕ се наблюдаваше ангиофлуорографския белег „прозоречен ефект" говорещ за дефект на РПЕ. Този прозоречен ефект наблюдавахме при 3 от изследваните пациенти.

При 3 от пациентите се наблюдава пореден рецидив на заболяването с формиране на невросензорно отлепване в областта на макулата (Фиг. 6).

След терапията с Еплеренон и при пациентите с хронична форма на CSCR също наблюдавахме редуциране на макулната дебелина и резорбция на булата. Редукцията на макулната дебелина беше от порядъка на 42 мк средно и не във всички случаи постигнахме пълно резорбиране на субретинната течност. При наблюдаваните пациенти, значително намаля броя на последващите рецидиви, като в рамките на 6 месеца проследяване не се наблюдава нито

Дискусия

Нашите изследвания показват, че и при двете форми на централен серозен хориоретинит CSCR, препаратът Еплеренон дава добри резултати. По-изразеният ефект при острата форма на заболяването го свързваме с по-малката увреда на ниво РПЕ/хориоидея при тези пациенти, което е и причина за по-добри дългосрочни резултати макар и сходни по клинична картина имат някои свои характерни особености, които предполагат и по-различното терапевтично поведение.

Еплеренон действа като намалява нивата на алдостерон в кръвта и по този начин влияе върху съдовете на хориоидеята. Нашите резултати показват, че под негово влияние значително се намалява големината на булата в макулата и се редуцира дилатацията на съдовете на хориоидеята, като по този начин изчезват симптомите на иначе резистентни на терапия случаи на CSCR. Намаляването на дебелината на макулата и на хориоидеята след приложението на препарата е чувствително и продължава 6 месеца след спиране на терапията. Еплеренон има протективно действие върху РПЕ и намалява атрофията на тези клетки.

Нашите изследвания подобно на данните в световната литература [8, 11] показват, че при пациентите от първата група, с класическа форма на остър хориоретинит прогно-

зата е добра и се постига излекуване в течение на 4 месеца дори и без терапия. При 95% от случаите наблюдавахме крайна зрителна острота от порядъка на 0.8 - 0.9. В повечето от случаите възстановяването след първия пристъп беше напълно и само в два от случаите се наблюдава дефект на РПЕ с наличие на метаморфопсии. За разлика от острата форма, при хроничната прогнозата е по-неблагоприятна и е необходимо незабавно терапевтично поведение, за да може да се предотврати по-нататъшната атрофия на РПЕ клетки. Нашите изследвания показват, че Еплеренон има много бърз и добър ефект при хроничните форми и продължителната терапия с препарата значително намалява и разрежда броят на рецидивите.

Има различни схеми за прилагане на терапията с Кардитръст. Според френската школа [7, 9] е добре да се започне с по-ниска доза от 25 мг на ден, като тя постепенно се увеличава на 50 мг. След едномесечно лечение е необходимо да се направи оценка на състоянието и решение за продължаване на терапията.

От нашия опит считаме, че е добре да се започне с 50 мг начална доза за 3 седмици и след това да се оцени състоянието и толерантността на пациента. При добра толерантност и наличие на ефект от терапията, препоръчваме продължаване на терапията в доза 25 мг дневно за период от 3 месеца. Дългосрочната терапия има за цел да доведе до трайно свиване на хориоидните съдове, намаляване на дебелината на хориоидеята и намаляване възможността за ексудация в субретинното пространство.

Всичко това значително намалява броят на рецидивите и допринася за по-добрата дългосрочна прогноза на пациентите. Страничните ефекти от приложението на препарата, които ние наблюдавахме бяха изключително малко, свързани с честа умора и мускулни крампи. Описаната в литературата хиперкалиемия не беше наблюдавана при нашите пациенти, вероятно с по-висок риск от това усложнение са пациентите с бъбречна недостатъчност.

Еплеренон е лекарствено средство с голям потенциал за лечението на CSCR, което тепърва ще навлиза все по-широко в офталмологичната практика.

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Очна хипертензия при дете с вродена сублуксация на лещите

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Ocular hypertension in a child with congenital subluxated lenses

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Резюме

Цел: Да се представи дете с двустранна сублуксация на лещите и едностранна очна хипертенсия, с оглед на възможността за ранна диагностика на тази патология и усложненията и.

Материал и методи: Изследвано е дете (момче) и негови кръвни родственици. Приложена е комплексна методика. Тя включва рутинни и специализирани офталмологични методи, генеалогичен анализ, клинико-генетична оценка на очния фенотип, параклинични изследвания, консултации с педиатър и клиничен генетик.

Резултати: Касае се за момче на 8 години с двустранна сублуксация на лещите, изразена в по-голяма степен в едното око, което е с повишено вътреочно налягане (ВОН = 34 mmHg). Детето (пробандът) е претърпяло контузионна травма на главата. Няколко дни по-късно едното му око се зачервило. Пробандът е с доказан синдром на Марфан на 5 годишна възраст. Провежда се вътрефамилен анализ на очния фенотип. Направен е съвременен обзор на вродената сублуксация на лещите.

Заключение: Вродената сублуксация на лещите има своите етиологични и клинични особености. Те трябва да се познават, с оглед на ранната диагноза, диференциалната диагноза и за да се избегнат, доколкото е възможно, късните усложнения - очна хипертензия, глаукома и дефинитивното увреждане на зрителните функции.

Ключови думи: сублуксация на лещата, очна хипертензия, глаукома, детска възраст.

Abstract

Purpose: To be presented a child with bilateral lens subluxation and unilateral ocular hypertension in view of the possibility of early diagnosis of this pathology and its complications.

Material and methods: A child (boy) and his blood relatives was examined. A complex methodology is applied. The methodology includes routine and specialized ophthalmic methods, genealogical analysis, clinical-genetic evaluation of the ocular phenotype, paraclinical studies, consultation with pediatrician and clinical geneticist.

Results: This is a 8-years-old boy with bilateral lens subluxation, more pronounced in one eye, with elevated intraocular pressure (IOP = 34 mmHg). The child (the proband) suffered a head trauma. A few days later his one eye blushed. The proband has a proven Marfan syndrome at the age of 5. An intrafamily analysis of the ocular phenotype is performed. A contemporary overview of the congenital lens subluxation has been made.

Conclusion: The congenital subluxation of lenses has its own etiological and clinical features. These features should be known in view of early diagnosis, differential diagnosis and to avoid, as far as possible, late complications - ocular hypertension, glaucoma, severe and definitive impairment of visual function.

Key words: lens subluxation, ocular hypertension, glaucoma, childhood.

Въведение

Известно е, че очната хипертензия не е диагноза, а е състояние на повишено вътреочно налягане (ВОН) с разнообразна етиология, без да съществуват в първоначалния стадий патологични промени в зрителния нерв, зрителната острота и периферното зрение. Ако не се диагностицира своевременно повишеното ВОН то може да стане причина за глаукомна патология и да се увредят трайно и дефинитивно зрителните функции, независимо от възрастта на пациента [8, 11, 18].

Сублуксацията на лещата - едностранна или двустранна е рядка, но отдавна известна патология. Първото описание на сублуксирана леща прави Berryat през 1749 година [14]. Един век по-късно Stellwag (1856) въвежда термина

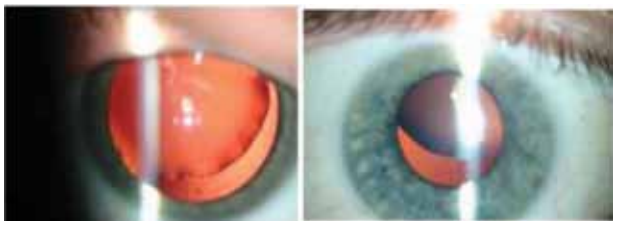
дислокация на лещата, описвайки пациент с вродена ектопия на лещата [5]. До днес в достъпната литература различни автори дискутират различни аспекти на тази патология и непрекъснато надграждат информацията [1 - 23]. У нас ектопията на лещата и нейните клинични и етиологични особености са описани за първи път от К. Пашев (1943). Клинико-генетични проучвания са провеждани от различни чуждестранни автори, включително у нас [1, 5, 8 - 11, 18, 19, 21 - 23]. Ектопията на лещата (лещите) може да бъде констатирана във всяка възраст на пациента, засяга и двата пола, без съществена предилекция. Много и разнообразни са причините за нейното възникване, както генетични така и екзогенни [8, 10,11, 18, 19, 21 - 23].

Очната хипертензия, както и глаукомата се срещат в 5.0 до 25% от случаите и са част от очните промени, които се наблюдават при индивиди със сублуксирана леща, независимо от причините, които я обуславят [10]. При вродената ектопия на лещата очната хипертензия и глаукомата са генетично детерминирани, но се проявяват клинично най-често в пубертета [4, 5, 10, 14, 19].

Вродената сублуксация на лещата е един от вродените дефекти на лещата, която се среща самостоятелно, изолирано или като комбинация с всяко едно от другите вродени заболявания на лещата, Табл. 1. Касае се за дислокация (децентрация) на лещата от нормалната и позиция в ямката на стъкловидното тяло (lens patellar fossa), Фиг. 1. Патологията е рядка. Реалната популационна честота не е известна, въпреки че има проучвания в отделни държави. Макар да е вродена патология, сублуксацията на

Табл. 1. Вродени дефекти на лещата [8, 11, 18].

- Вродена афакия
- Вродена катаракта
- Лентиконус и лентиглобус
- Колобома на лещата
- Хиалоидни корпускули (Mitendorf's dot)
- Епикапсуларни звезди
- Микросферофакия
- Ектопия на лещата



Фиг. 1. Неравномерен рефлекс на Брюкнер при различната по степен ектопия и различната по степен прозрачност на лещата.

лещата може да бъде констатирана във всяка възраст, най-често между 5 - 6 годишна възраст. Вродената сублуксация най-често е двустранна, с различна степен на клинична изява (лека, средна, тежка) за всяко око при някои индивиди. В най-леките случаи първоначално може да е налице само миопична рефракция. В тежките случаи лещата може да напусне изцяло ямката на стъкловидното тяло и да премине в предната очна камера или да потъне в стъкловидното тяло, достигайки до ретината [5, 8, 10, 11, 14, 18].

През 1998 г. Фукс и Розенберг правят ретроспективен анализ на 396 случая на индивиди с ектопия на лещата в Дания и установяват честота 0.83 на 10 000 новородени и 6.4 на 100 000 в цялата популация. Същите автори установяват, че по-често (до 80%) ектопията на лещата е част от фенотипа на системни заболявания [4].

Причини за ектопия на лещата

Ектопията на лещата се дължи на вродени и придобити причини [4, 5, 8, 10, 11, 18, 19]. Вродените причини най-често са генетични - мутации в различни гени, които водят до изолирана или асоциирана с други очни или общи увреждания ектопия на лещата. Към придобитите причини се отнасят травмите. Ектопия на лещата се среща като усложнение при някои вродени очни заболявания, като високостепенната миопия, буфталм при първична вродена глаукома, аниридия. Описани са случаи на сублуксация на лещата при предносегментни тумори от увеен произход, хиперматурирала катаракта и др. Доказването на причината за вродена ектопия на лещите е възможна в 80% от случаите. Изолираната ектопия на лещата се среща в 8.0%. Най-често вродената ектопия на лещата е при пациенти със синдрома на Марфан (68.0 - 80.0%), следвана от случаите на асоциацията и с ектопия и на зеницата (21.0%), Табл. 2 [10]. В литературата са описани случаи на сублуксация на лещите при хиперлизинемия, при синдромите на Ehlers - Danlos, Sturge Weber и Crouzon, при хондродиспластичния dwarfism, оксицефалията, полидактилията, сулфат оксидазната недостатъчност и др. [2 - 5, 8 - 11, 14, 15, 18 - 23].

Съвременни проучвания на молекулярно-генетично ниво доказаха, че мутации във FBN1 гена и гена ADAMTSL4

Табл. 2. Етиологична класификация на вродената ектопия на лещата [10].

Изолирана (Проста) ектопия на лещата - 8.0%
Ектопия на леща и на зеница - 21.0%
Синдром на Марфан - 68.0%
Синдрам на Вайл-Марчезани - 1.0%
Хомоцистинурия - 1.0%
Сулфат оксидазна недостатъчност - 1.0%

са причина за изолираната форма на вродена ектопия на лещата. Мутации във FBN1 гена (15q21.1, АД) водят до редица системни заболявания, при които не е описана ектопия на лещите [Acromicric dysplasia (OMIM-102370, АД), Geleophysic dysplasia 2 (OMIM-614185 15q21.1, АД), MASS syndrome (OMIM-604308), Stiff skin syndrome (OMIM-184900, АД)]. На Табл. 3 е представено съвременно клинико-генетично класифициране на ектопията на лещата.

Патофизиология на вродената ектопия на лещата

Нарушенията в структурата или функцията на циновите влакна на лещата от генетично или травматично естество са основната причина за децентрация на лещата от нормалната и позиция. Степента и времето на въздействие на увреждането на циновите връзки на лещата (внезапно - от травма или генетично, или комбинирано) определят и степента на клинична изява на ектопията, както и последващите я усложнения [4 - 6, 8, 10, 11, 14, 18, 19].

През 1986 г. Sakai и сътрудници идентифицират в

Табл. 3. Клинико-генетична класификация на вродената ектопия на лещата [1, 5, 12, 14, 15, 19].

ICD-10	Нозология	OMIM	Ген	Хромозомна локализация	Унаследяване
H27.1;	Other disorders of lens	-	-	-	-
Q12.1	Ectopia lentis (EL), familial, 1	29600	FBN1	15q21.1	АД
Q12.1	EL, isolated, 2	225100	ADAMTSL4	1q21.3	АР
Q12.1	EL et pupillae	225200	ADAMTSL4	1q21.2	АР
Q15.8	EL, chorioretinal dystrophy, myopia	[Orhpanet:1884]			АР
Q13.1	EL, Aniridia, isolated 1	106210	PAX6	1p13	АД
Q13.1	EL, Aniridia, isolated 2	617141	ELP4	11p13	АД
Q13.8	EL, Aniridia, other systemic diseases				
Q15.0	EL, Primary Congenital Glaucoma, D (GLC3D)	613086	LTBP2	14q24.3	АР
Q87.4	EL, Marfan syndrome (s-me)	154700	FBN1	15q21.1	АД
	EL, Marfan lipodystrophy syndrome (MFLS)	616914	FBN1	15q21.1	АД
Q87.0	EL, Weill-Marchesani s-me 1;	277600	ADAMTS10	19p13.2	АР
Q87.0	EL, Weill-Marchesani s-me 2;	608328	FBN1	15q21.1	АД
Q87.0	EL, Weill-Marchesani s-me 3;	614819	LTBP2	14q24.3	АР
Q79.6	EL, Ehler-Danlos s-me (EDS) classic	130000	COL5A2	2q32.2	АД
		130000	COL5A1	9q34.3	АД
		130000	COL1A1	17q21.33	АД
Q79.6	EL, EDS Type VI	225400	PLOD1	1p36.22	АР
Z94.2	EL, Knobloch s-me		COL18A1		АР
E72.1	EL, Homocisteinuria	236200	CBS	21q22.3	АР
E72.19	EL, Sulfite oxidase (SUOX) insufficienses	272300	SUOX	12q13.2	АР
Q75.1	EL, Crouzon s-me	123500	FGFR2	10q26.13	АД

екстрацелуларния матрикс на човешките микрофибрили нов 350-kD гликопротеин, наречен фибрилин 1 (FBN1), [17]. FBN1 (OMIM 134797) е основен компонент на микрофибрилите, които образуват обвивка около аморфния еластин. Фибрилин 1 се секретира основно от клетки на не-пигментирания епител на цилиарното тяло (Hanssen et al. 2001), [6]. През 2005 г. Kielty и сътрудници установяват, че FBN1 се намира и в кожата, бъбреците, мускулите, роговицата, цилиарните зонули, като участва във формирането на еластичните фибри [14]. FBN1 е констатиран във всички тъкани при пациенти с клинични прояви на Марфан синдрома (MFS), [14, 19]. Фибрилините са големи гликопротеини, които се полимеризират в микрофибрили, подобно на гранули, включително домени, подобни на епидермалния растежен фактор, както и домени, подобни на TGF-β свързващи протеини (Ramirez, Sakai 2010). Тези микрофибрили могат да се получат независимо в извънклетъчната матрица или да се свързват с еластин в еластични влакна [16].

Индикации за оперативно отстраняване на лещите при индивиди със сублуксация на лещата

Тук влизат всички случаи, при които изместването на лещите е причина за намалена зрителна острота, която не може да бъде коригирана с конвенционална оптична корекция или контактни лещи, лещено индуциран увеит, анизометропия, която създава зрителни проблеми, диплопия, очна хипертензия, луксирането на лещата в предната камера, стъкловидното тяло или ретината [8, 11, 18 - 20].

Клиничен случай

Сегашна анамнеза

Касае се за момче на 8 години, което се оплаква от замъглено зрение (по-силно в дясното око), сълзене и болка в дясното око. Детето (пробандът) е претърпяло контузионна травма на главата, при игра с футболна топка, без загуба на съзнание, преди два дни. Детето е родено доносено, по естествен механизъм, расте здраво.

Минала анамнеза

Забелязано е от майката, че детето не вижда добре от 2 - 3 годишна възраст, но не е преглеждано от офталмолог. На 5 годишна възраст е прегледано за първи път от нас, констатирана е двустранна сублуксация на лещите, нормотонус, двустранно намалена зрителна острота. Изписани са корекционни очила (-12.0 дсфЕ). Детето е оставено

под периодичен контрол от офталмолог и е насочено към Клиника по генетика (София), където се доказва синдрома на Марфан (на 5 г. възраст).

Фамилна анамнеза

С доказан синдром на Марфан (MFS) е бащата на детето. Майката е здрава. С по-слабо зрение са още чичото и един от синовете му, и дядото на пробанда по бащина линия (починал „сляп" на 40 г., от „сърдечно усложнение" - коарктация на аортата).

Соматичен статус

Марфаноиден хабитус (висок ръст, арахнодактилия). Детето трудно се ориентира в непозната обстановка.

Очен статус

Видимо спокойни очи. Алтерниращa екзодевиация, на моменти вертикално отклонение на булба нагоре (двустранно). **ДО:** Роговични размери 12.0/12.5 mm, прозрачна роговица. Неравномерна предна камера, по-плитка горе и темпорално, с бистро съдържимо. Ириса е със загладен релеф и фини атрофични участъци в зеничния ръб, с псевдоексфолиации. Иридодонеза. Зеницата е в лека мидриаза (травматична?). Лещата опалесцира, децентрирана е горе и темпорално - втора степен, факодонеза. Прозрачни очни среди. Очно дъно: Папилата е видимо витална, E = 0.2 - 0.3 PD. Сивкава макула без рефлакс (конституционално); **ЛО:** Роговични размери 12.0/12.5 mm, прозрачна роговица. Неравномерна предна камера, по-плитка горе и темпорално, с бистро съдържимо. Ириса е със загладен релеф и фини атрофични участъци в зеничния ръб. Иридодонеза. Миотонична зеница. Лещата е с лека опалесценция, децентрирана е горе и темпорално - първа степен, факодонеза. Прозрачни очни среди. Очно

Табл. 4. Съпътстващи очни прояви при индивиди с вродена сублуксация на лещата.

ОЧНИ ПРОЯВИ	Наши резултати 1	2	3	4	Литературни данни [3 - 5, 8 - 10, 11, 14, 18 - 22]
роговични размери до 12.0 mm	–	+	+	+	+
роговични размери > 12.0 mm	+	–	–	–	+
мътнини в роговицата	–	–	–	–	+
кератоконус	–	–	–	–	+
предни синехии	–	–	–	–	+
персистираща зенична мембрана	–	–	–	–	+
преден ембриотоксон	–	–	–	–	+
анизокория	+	–	+	–	+
ектопия на зеницата (двустранна)	–	–	–	–	+
ектопия на зеницата (едностранна)	–	–	–	–	+
неравномерна предна камера	+	+	+	+	+
иридодонеза	+	+	+	+	+
хипоплазия на ириса	+	+	+	+	+
хипоплазия на пигментния зеничен ръб	+	–	+	+	+
псевдоексфолиации	+	–	–	–	+
факодонеза	+	+	+	+	+
ирегулярен рефлекс на Брюкнер	+	+	+	+	+
миопия (честа проява; различна степен)	+	+	+	+	+
хиперметропия (различна степен)	–	–	–	–	+
астигматизъм (най-често ирегулярен)	+	+	+	+	+
анизометропия	+	+	+	+	+
страбизъм (различни клинични форми)	+	–	–	+	+
повишено ВОН (очна хипертензия)	+	–	–	–	+
глаукома (вродена; пресенилна)	±	–	–	–	+
ектопия на лещата	+	+	+	+	+
катаракта (вродена; пресенилна)	–	–	–	–	+
микросферофакия	–	–	–	–	+
колобома на лещата	–	–	–	–	+
опалесценция на лещите	+	+	+	+	+
промени в калибъра на ретинените съдове	–	–	–	–	+
хориоретинални дегенеративни промени	–	–	–	–	+
сивкава макула	+	+	+	+	+
отлепване на ретината (едностранно; двустранно)	–	–	–	–	+
аксиален размер на очната ябълка > 24.0 mm	+	+	+	+	+
намалена зрителна острота (двустранно)	+	+	+	+	+
амблиопия	+	+	+	+	+
енофталм	–	–	–	–	+

1 - пациент 1 (пробанд - 8 г.); 2 - пациент 2 (38 г.); 3 - пациент 3 (6 г.); 4 - пациент 4 (36 г.)

(+) - наличие на патологична проява; (-) - липса на патологична проява.

дъно: Папилата е видимо витална, E = 0.2 PD. Сивкава макула без рефлакс (еднаква с тази на дясното око, конституционално).

VOD = 0.02 - 0.03 н.к.; VOS = 0.04 с - 12.0 dspE = 0.08; TOD = 34 mmHg.; TOS = 26 mmHg.; Авторефрактометрия: ДО: -16.0 dspE комб. с 1.75 dcyl/50º; ЛО: -14.0 dspE комб. с 1.75 dcyl/50º; Нормално цветоусещане; Очила: ДО = ЛО = -12.0 дсфЕ, детето не понася сферо-цилиндрична корекция.

Генеалогичен анализ

Генеалогичният анализ е проведен лично. Касае се за фамилно проявен синдром на Марфан (MFS), класическа форма, в ромска популация.

Освен пробанда, изследвани са 8 индивиди от първа, втора и трета степен на родство - т.н. „рискови индивиди" за MFS. При 4 от изследваните не бяха констатирани клинични прояви за MFS. При останалите 4 изследвани - пробанда, неговия баща, чичо и един от синовете му, които са с MFS, са констатирани основните за MFS типични очни прояви: сублуксация на лещите. При всички тях лещите са сублуксирани горе и темпорално в различна степен при отделните болни. Освен сублуксираните лещи бяха констатирани и различни съпътстващи патологични очни промени. На Табл. 4 са представени очните промени, констатирани при пробанда и съпътстващите патологични очни прояви, допълнително изследваните някои негови кръвни родственици и литературна справка.

При всеки един от индивидите със сублуксирани лещи съществува междуочна дискорелация, по отношение на спектъра на очните промени и степента на клиничната им изява.

Затруднения за ранната диагноза на вродената ектопия на лещата

Ранната диагноза на вродената ектопия на лещата, както и уточняването на конкретната причина за това е истинско предизвикателство не само за младия офталмолог, но и за опитния, както и за офталмогенетика или медицинския генетик. Основните причини за това са:

- Липса на видима без специална оптика очна симптоматика към момента на раждането. Дори при насочен преглед от офталмолог (по показания) доказването на сублуксация на лещата е трудно, особено в атенюираните случаи.
- При ектопия на лещите съществува широк клиничен полиморфизъм, независимо от етиологията.
- Клиничното разнообразие от съпътстващи ектопията на лещата други вродени патологични очни прояви (аниридия, вродена глаукома, ектопия на зеницата и др.) разширяват диференциалната диагноза.
- Извъночните вродени прояви (сърдечно-съдови, скелетни и др.) при синдромните случаи, най-често предшестват ектопията на лещата, но е възможно и да ги съпътстват.
- Гените FBN1 и ADAMTSL4, отговорни за проява на изолираната форма на ектопирана леща, се отличават с генната и алелната хетерогенност.
- Плейотропният ефект на гените FBN1 и ADAMTSL4, както и феноменът антиципация, допълнително създават диференциално-диагностични затруднения за конкретната клинико-генетична диагноза.
- Клинико-генетичният полиморфизъм, който съществува при ектопия на лещата/лещите Табл. 3, утежнява ранната клинико-генетична диагноза, особено в спорадичните случаи.

Заради всичко това уточняването на конкретната нозологична единица, както и на клинико-генетичната форма при наличие на индивид със сублуксирана леща, изисква добро познаване на симптоматиката и етиологията на тази патология, насоченото и търсене, интердисциплинарен подход (офталмолог, педиатър, генетик и др.), непрестанно (доживотно) наблюдение на засегнатите индивиди, съответните ресурси.

Обсъждане

Контузионна травма може да е самостоятелен етиологичен фактор за сублуксация на лещата, но също така е възможно травма да провокира изявата на съществуваща ектопия на лещата [3 - 5, 8 - 11, 18 - 20], както е в разглеждания от нас случай.

При липса на явен дисморфизъм при новороденото вродената сублуксация на лещата се констатира в по-голяма възраст на детето, най-често към 6 годишна възраст. Касае се за много рядка очна патология [15]. При различните деца или възрастни първите субективни оплаквания от страна на очите са различни - намалена зрителна острота, монокуларна диплопия, главоболие и др. Това са най-често срещаните, но не и патогномонични за конкретна нозология оплаквания. Финитe прояви за сублуксирана леща трябва да се познават и насочено да се търсят: при биомикроскопско изследване и при раздвижване на окото се вижда екватора на лещата, иридо и факодонеза, децентрализация на лещеното ядро в първа позиция, иридолещени промени, промени в контура на периферията на лещите, възможна е очна хипертензия. Важен за диагностиката е тестът на Brückner (1962), наречен "trans-illumination" test, който при пациенти с ектопия на лещата е ирегулярен (Фиг. 1). Диагностиката на сублуксирана леща/и е в компетентността на офталмолога и зависи, освен от щателната анамнеза, основно от степента на клиничната изява, възрастта на пациента, наличието на системно засягане и общото състояние на индивида, наличието на фамилна патология.

Най-често сублуксираните лещи са част от фенотипа на системна, генетично детерминирана моногенна патология с полиорганна изява, Табл. 3 [4, 5, 10, 15, 18, 19]. Поради всичко представеното до тук следва, че при различните пациенти първите клинични прояви може да са както от страна на очите, така и детето да е активно насочено от друг специалист със съмнение за генетично заболяване с очна изява. Освен синдрома на Марфан съществуват и други моногенни синдроми с „Марфаноиден фенотип" Табл. 3, дължащи се на плейотропен ефект на патологичния ген, при които очния симптом ектопия на лещата се открива най-често в хода на уточняването на основната диагноза, най-вече при спорадичните случаи. Във всеки прецизиран случай на дете с миопична рефракция, марфаноиден хабитус (абнормен за възрастта ръст, арахнодактилия) или фамилна анамнеза за синдрома на Марфан, е необходимо да се търсят насочено финитe прояви за сублуксация на лещата.

Заключение

Вродената сублуксация на лещите има своите етиологични и клинични особености. Те трябва да се

познават, с оглед на ранната диагноза, диференциалната диагноза, за да се избегнат (доколкото е възможно) късните усложнения - очна хипертензия, глаукома и дефинитивното увреждане на зрителните функции.

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