Contemporary ophthalmology – current possibilities and future prospects regarding diagnostics and management of the most common ophthalmic disorders

Okulistyka współczesna – obecne możliwości i perspektywy w zakresie diagnostyki i terapii najczęstszych chorób oczu

INTRODUCTION

Many people say: “Impressive is the progress in medicine over the last years!”. It might seem to be a truism, however the above sentence fits perfectly for ophthalmology – the field of medicine, which has changed its face completely in the recent times.
thanks to the introduction and popularization of laser scanning – based devices, the eye’s tissue microstructure has been revealed for visualization, qualitative and quantitative assessment, digital documentation and follow-up in the case of any pathology.

The article presents the achievements and technological progress in the diagnosing and treatment of the ophthalmic disorders, focusing on the most prevalent diseases and popular therapeutic areas, such as:
- genetics,
- glaucoma,
- age-related macular degeneration,
- refractive surgery,
- vitreo-retinal surgery,
- oculoplastic surgery.

Genetics

The molecular diagnostic techniques have developed rapidly over the last decade, what made it possible to identify the genes and their mutations leading to genetic diseases, and facilitated classification of the diseases according to the genotype. The progress in genetic techniques gives rise to the availability of diagnostic tests, enables screening for hereditary eye disorders and prognosis as to the vision; it also gives hope for treatment. The use of genetic therapy is the future arms to fight diseases with the genetic background.

Hereditary retinal and choroidal dystrophies are the most common and most severe inherited eye disorders. They lead to partial or even total blindness. Retinitis pigmentosa, Leber congenital amaurosis, congenital stationary night blindness, Stargardt disease, and hereditary retinoschisis are the most prevalent dystrophies. 46 genes and 2497 mutations associated with hereditary retinal and choroidal dystrophies have been identified up till now (1).

In the last years effectiveness and safety of the gene therapy in Leber congenital amaurosis has been drawing researchers’ attention (2-4). The autosomal recessive disease that impairs vision in newborns and toddlers is a form of hereditary retinal dystrophy (5). Mutation in the RPE 65 gene is associated with the most severe course of the disease, with serious impairment of vision at birth and loss of vision in the third decade of life. The gene codes a specific protein of the retinal pigment epithelium (65-kD), participating in the regeneration of rhodopsin following exposition to the light (3). In the disease it is possible to keep the functional visual acuity in childhood; it was suggested that the death of photoreceptor takes place in later stages of the disease (6). Transposition of the gene to the place of its action could improve the functioning of the eyes or preserve the remaining vision (3).

Recombined adeno – associated virus (AAV) is used as a vector carrying human’s genetic material into the cells of the eye (3, 4). In vitro AAV induces synthesis of the protein encoded by the RPE 65 gene. In animal models with mutation in the gene, improvement of the retinal function and visual acuity was achieved after subretinal injection of the recombined AAV (7). Maguire et al. reported improved pupillary light reflex and diminished nystagmus after subretinal injections of AAV in young adults with Leber congenital amaurosis, which confirms an increase in the light sensitivity of the retina, resulting from the application of the gene therapy (4). Future clinical trials are needed, particularly on younger patients, who could benefit by the gene therapy more than adults.

Also worth mentioning is that other common eye diseases like age-related macular degeneration, corneal dystrophies, and high myopia, have a molecular basis; therefore the identification of the causing genes might result in increased effectiveness of treatment of the conditions (8).

Glaucoma

Glaucoma is defined as a group of optic neuropathies, leading to characteristic progressive, irreversible loss of the visual field, and in consequence to blindness. According to the data from WHO, the disorder recognized as a social disease, is the first cause of total blindness worldwide. In developed countries it takes the second place in the classification, with age-related macular degeneration (AMD) being the first one.

In the past decades glaucoma was considered dependent on increased intraocular pressure, inducing intense symptoms. Presently it is known that the type of the disease constitutes just a small percentage of all cases, which are more noticeable simply because of the symptoms. However, the majority of the patients with glaucoma have no or just mild symptoms, insidiously damaging the optic nerve and the visual field.

The introduction of new computerized diagnostic techniques, also using laser beams, has been the most important achievement in the recent years. Heidelberg Retina Tomograph (HRT) – scanning laser ophthalmoscope used for examining topography of the optic disc; GDx – scanning laser polarimeter for measuring the nerve fiber layer of the retina, and multiple computed static perimeters – devices for quantitative examination of the visual field, indicating depth of the decrease in retinal sensitivity. Optical Coherence Tomograph (OCT) is a novel apparatus that not only provides images of the retinal cross-sections with histological quality, but also analyzes nerve fibers. To the list belong also ultrasound – based devices, like pachymeter for measuring central corneal thickness and ultrabioscopic microscope, generating very high frequency waves for examining the anterior segment of the eye. Traditional measurements of intraocular pressure with a tonometer placed directly on the eye of a lying patient were superseded by more accurate methods: applanation tonometry at slit-lamp and microprocessor-steered dynamic contour Pascal tonometer, displaying reliable digital results, devoid of most of the artifacts.

Treatment of glaucoma has long been more than just administration of eye drops. Therapy is often extended to treatment with neodymium Nd:YAG (iridectomy, selective trabeculoplasty) or argon laser (trabeculoplasty,
Irydoplasty) depending on the type of disease. Classical surgical procedures, so-called filtering, i.e. facilitating the flow of the aqueous humor from the eye, were extended by the possibility to use draining implants, some with post-surgically regulated range of activity. Presently the gene therapy with the use of viral vectors is under investigation, as well as neuroprotective medications, blocking apoptosis (programmed death) of the ganglion cells or anti-glaucoma vaccination, boosting regeneration of the damaged cells.

Age-related macular degeneration

Age-related macular degeneration (AMD) is the predominant cause of irreversible blindness in people over 50 in the developed countries (5). According to the data presented by AMD Association, the number of people affected by AMD is estimated to be ca. 300 million worldwide. In Poland the number reaches 1.2 million, the incidence rate is around 120 thousand per year. Around 1.7% of affected people over 50 years of age get blind, while in patients over 85 years, the rate reaches 18%. The problem is essential not only because of the increasing number of patients, but also because often it concerns people who are still professionally and socially active (5, 9).

The main risk factor of the disease is age. Other unchangeable risk factors are: genes, female sex, Caucasian race, light color of the iris, hyperopia, glaucoma, exudative AMD in the other eye. Smoking, obesity, hypertension, diabetes, history of myocardial infarction or apoplexy, persistent sunlight exposure, wrong dietary habits belong to modifiable risk factors (10, 11).

Two forms of AMD are distinguished: “dry” or “atrophic” and “wet” or “exudative”. The atrophic form is more common, as it constitutes 90% of cases. It is characterized by a gradual decrease in visual acuity over a period of a few months to a few years. Usually it is present in the both eyes, however in a different stage. Usually in the macula drusen, focal changes in the pigment epithelium, redistribution of the pigment are observed. Drusen consists of accumulation of pathological material, originating from the retinal pigment epithelium, they can be confluent and extensive, leading to drusen – associated retinal pigment epithelium detachment. Retinal pigment epithelium atrophy (geographical atrophy) develops in more advanced disease; in the case the fovea is involved, visual acuity may be severely decreased (5, 11).

Exudative form is infrequent, however it is responsible for ca. 90% of severe impairment of vision in the patients with AMD. In this type of AMD choroidal neo-vascularization develops. The pathological new vessels originate from the choriocapillaris and spread into the layers of retina, damaging its structure. Complications include: pigment epithelium detachment, and intraretinal and intravitreal hemorrhages. Without treatment the disease causes formation of macular scar, permanently and irreversibly impairing vision in a short time (approximately 2 years) (5, 11).

Optical coherent tomography (OCT) and spectral optical coherent tomography (SOCT) are extensively used in the diagnosis of AMD. In the method low-coherence infrared light is employed for imagining the structure of retina and choroid. The examination is non-contact, noninvasive, highly repeatable, and it enables to determine how active the disease is and what the effects of treatment are. Apart from the above technique, examinations involving the use of contrast for displaying pathological vessels and spots of leakage: fluorescein and indocyanine digital angiography are also widespread (9).

There is no effective treatment of dry AMD. Management consists in slowing down progression and evolution into the exudative form. Supplementation with drugs containing lutein, zeaxantin and antioxidants, together with zinc and preventing the changeable risk factors proved to be effective for this purpose (12).

The goal of AMD treatment is to slow down the progression and stabilize visual acuity. Unfortunately, improvement in vision can be reached only in some of the patients. Presently, intravitreal injections of anti-Vascular Endothelial Growth Factor (anti-VEGF) antibodies or their fragments is the most widely used therapy. The available anti-VEGF preparations are ranimizubab (Lucentis), bevacizumab (Avastin) and pegaptanib sodium (Macugen) (11).

Photo-dynamic therapy (PDT) is another way of treating AMD. In the method werteporfirin – highly light sensitive substance is introduced into the bloodstream and captured by the pathological new vessels. Laser beams damage the pathological tissue, leaving physiological vasculature intact (5). Attempts are made to use microsurgical vitero-retinal techniques, like neovascular membranes removal or translocation of the macula to a different location in the retina (5, 11).

Because of its alarming statistics, the disease is taking the leading position as a subject of clinical trials in ophthalmology in terms of restraining the progression and, first of all, preventing the onset.

Refractive surgery

Refractive surgery embraces procedures aiming at changing the refraction of the eye throughout modification of the main components of the optical system of the eye: cornea and/or the lens. The indications include myopia, hyperopia, astigmatism and presbyopia, especially in the patients who do not tolerate or not wish to wear glasses or soft lenses.

LASIK (Laser Assisted in Situ Keratomileusis) is currently the most widely performed refractive procedure (13-15). In this procedure superficial layers of the cornea are dissected to form a flap; the flap can be made with microkeratome or femtosecond laser. In the next step the uncovered deep layers of the cornea are modified with excimer laser to eliminate the refractive error of the eye. Afterwards, the flap is repositioned on the top of the cornea. The procedure takes a few minutes and is performed under local anesthesia (in eye
The use of "Wavefront" technique enables very precise estimation of aberrations of the optical system of the patient (16). Based on the assessment, the cornea is modeled during the surgery. "Wavefront" is a term describing a surface that connects points in the same phase of light waves. Spotlight produces spherical wavefront. Before it reaches the retina, it is banded and deformed by all the structures of the eye it passes through. Optical aberrations created by every eye are as individual as a fingerprint. Wavefront technique enables not only myopia, hyperopia or astigmatism but also higher-order aberrations to be described and corrected.

Because during LASIK only a thin layer of the tissue is left untouched, there is a risk of ectasia of the cornea. In the Epi-LASIK technique only the epithelium is separated from the cornea with epiceratome, without encroaching corneal stroma (17, 18). After performing laser photoablation, the epithelium is placed back on the cornea. The cornea is then covered with a soft contact lens until the epithelium heals (3-10 days). Discomfort (tearing, pain) is more pronounced than in LASIK. The method resembles LASEK, but no alcohol is used to separate epithelium (what eliminates its negative influence on the tissues); however, it might be difficult to separate epithelium from the peripheral parts of the flap.

In the SBK-LASIK technique a thin flap consisting of epithelium, Bowman’s membrane and superficial stroma is created with a microkeratome (17). Separating a very thin flap, 70-100 microns thick, has the advantage of greater comfort for the patient, short healing time, no risk of complications that appear after classical LASIK (for example dry eye syndrome). There is no need to apply a contact lens after the procedure (while it is necessary after LASK and PRK). The risk of flap – related complications is yet higher than in LASIK.

The LASEK technique combines the features of PRK and LASIK. In the procedure 20% alcohol is applied on the cornea for 30-40 s, the epithelium is then separated from the basement membrane (19). Laser ablation is performed and epithelial flap is placed back in its previous position. The cornea is then covered with a contact lens. LASEK causes less pain and corneal haze, and allows faster improvement of visual acuity in comparison with PRK: it eliminates also flap-related complications of LASIK. The disadvantages are: possible occurrence of epithelial healing disturbances and postoperative pain, more pronounced than in LASIK. The main indication for the method is lack of the possibility to perform LASIK, like in patients with very thin, very steep, or very flat cornea.

An interesting technique in refractive surgery is an implantation of intracorneal rings or ring segments made of poly (methyl methacrylate) (PMMA) (20). They are implanted into peripheral cornea, leading to flattening of its anterior surface in the optical axis. Power of the correction can be regulated through the usage of the rings of various thickness. The advantages of the method are: no need to interfere with the cornea in its optical axis, immediate and predictable results, and possibility to remove or change the rings. Disadvantages are: fluctuations of visual acuity, and opacification of the corneal stroma. Intracorneal rings are also used to correct irregular astigmatism caused by keratoconus.

In patients whose refractive error is too high to perform laser correction or if the procedure is contraindicated, phacic lenses can be used. In the procedure intraocular lens is implanted without removing the own accommodating lens. The implant is placed in the anterior chamber, fixed to the iris (iris-fixed “lobster claw” intraocular lens) or in the posterior chamber, between the lens and iris and it is placed in the sulcus of the ciliary body (so-called “implantable contact lens”).

Phacic lenses can be used in patients below 45 years of age and with refractive error ranging from -23.0D to +13.0D and in patients with astigmatism accompanying myopia (toric phacic lenses) (21, 22). The preferred procedure is iris-claw lens implantation. Posterior chamber lens seems to be less safe, as it may cause choroiditis, glaucoma, loss of endothelial cells and cataract. The complications of anterior chamber lenses are subluxation of the implant and oval pupil. After phacic lens implantation regular life-long ophthalmic controls should be implemented, and if the condition cannot be fulfilled, the patient is not a good candidate for the surgery. Also the patients with sight – threatening diseases (diabetic retinopathy, glaucoma, uveitis) should not undergo the procedure.

In some patients clear lens extraction (CLE) can be performed (23). The procedure is similar to cataract surgery. The patient’s lens is substituted with an artificial intraocular implant. With the method it is possible to correct high refractive errors, which do not qualify for laser procedures. With the surgery very good results and stable visual conditions can be obtained, but it carries a small risk of retinal detachment. It is applicable mainly to people over 45 years of age because it leads to loss of accommodation. In order to maintain accommodation and acute vision for different distances, modern multifocal/pseudoaccommodative lenses (ReStor, ReZoom, Tenis, Crystalens) can be implanted. Toric implants are also available for correction of astigmatism.

What is expected from a refractive surgery is, first of all, the precision of the correction (ideally, 0.25D difference from the correction planned), stability of the correction (CLE is the most stable), high quality of vision (CLE is leading in the aspect) and safety. None of the above techniques is perfect for every situation, that is why so many techniques exist. Various methods can be combined to obtain correction of higher refractive errors.

In general, refractive procedures are performed in people over 20 years of age. LASIK, PRK and LASEK can also be used in children to correct high anisometropia or high ametropia in both eyes, resistant to conventional treatment (24). In children with myopia over 12D phacic lenses and CLE seem to be good alternatives to laser procedures. There
are no large multicentre studies assessing suitability of refractive surgery for children, thus the procedures remain controversial in this age group.

Vitreo-retinal surgery

This type of surgery, called vitreo-retinal surgery, concerns the posterior segment of the eye, vitreous and retina. Vitreo-retinal procedures can be performed from outside (e.g. cryotherapy – freezing of the retina, silicone band implantation to buckle the sclera and bring back the retina into contact with the eye wall) and from inside (so called vitrectomy – removal of the vitreous). During vitrectomy surgical instruments are introduced inside the eye through 3 cuts in the sclera. The procedure consists in cutting out the vitreous – a gelatinous structure filling up the posterior segment of the eye. After removal of the vitreous the inside of the eye may be filled with a substitute, i.e. air, gas, or silicone oil. During the procedure cataract removal can be performed simultaneously; it is possible to perform also laser photoagulation of the retina (5).

Thanks to the introduction of the novel surgical techniques and diagnostic methods of retinal disorders, the list of diseases possible to be treated surgically has expanded. Extended indications for vitrectomy enables to treat from internal approach such diseases as: retinal detachment, diabetic retinopathy, macular disorders – holes, epi-retinal membranes, age-related macular degeneration (AMD), injuries, and endophthalmitis.

Diabetic retinopathy is the most frequent cause of blindness in people aged 20-65. Its course is influenced by patient’s age, lifespan of the disease, control of metabolism (blood glucose and cholesterol levels) and value of the blood pressure (25). Laser photoagulation of the retina is the basic and also effective treatment method (26-30). To manage the most frequent complication, which is macular edema, intravitreal injections of drugs, like Kenalog, Avastin and Lucentis can be applied (31). Impairment of visual acuity occurs usually in the case of complications, for example, intra vitreal hemorrhage, vitreo-retinal tractions associated with macular edema, traction retinal detachment, neovascularization and secondary glaucoma (32).

Treatment of retinal detachments is surgical only. Depending on pathomechanism, they can be divided into rhegmatogenous and non-rhegmatogenous. In rhegmatogenous retinal detachment (caused by retinal holes and tears, with subretinal fluid accumulation and retinal detachment) extrabulbar methods are used. In the methods the eye wall is pushed inwards with bands sutured to the sclera, with the aim of sealing the break and re-attaching the retina. However, in some cases like giant holes, break located in the posterior pole of the eye, primary vitrectomy should be performed. Non-rhegmatous detachments are caused by pathological vitreo-retinal membranes (tractions) pulling the retina from the retinal pigment epithelium, and other factors, like inflammatory exudate or a tumor. In traction detachments vitrectomy is applied, with the vitreous removal and release of the retina from proliferative membranes (5).

In the recent years the knowledge on the pathomechanisms of the vitreo-retinal borderline has improved and microsurgery of the posterior segment has developed, thus treatment of the macular disorders, like idopathic macular holes, epi-retinal membranes and tractional syndroms has become possible. Because the internal limiting membrane (ILM), which separates the retina from the vitreous, plays an important role in pathology of the diseases, it is removed during vitrectomy (so called ILM peeling) (33). Dyes can be applied intraoperatively to visualize the thin and transparent membrane (so-called chromovitrectomy) (34). Surgical treatment of the macular diseases is a casual treatment and gives the patients reduction of the visual distortions (metamorphopsia) and often also improvement of the visual acuity (33).

Exudative form of AMD is associated with choroidal neovascularization (CNV) leading to sub- and intraretinal fluid accumulation. If the fluid persists, photoreceptors are lost and retinal pigment epithelium becomes damaged, with scar formation, and a gradual decrease in visual acuity and irreversible loss of useful vision (5). Vitrectomy is seldom used to treat CNV. It may concern: surgical removal of sub-macular choroidal neovascularization and macular translocation from the area of CNV (35). Antiangiogenic drug injections (for example, Avastin, Lucentis) and photodynamic therapy (PDT) remain the gold standard of AMD management (36).

Vitrectomy is also a method of treating endophthalmitises, resistant to conservative treatment. It might be useful in diagnosing the etiology of the inflammation. Vitrectomy is applied also in the case of intracocular foreign bodies, and the own lens or lenticular implant luxation to the vitreous. At present, research is being conducted on surgical treatment of branch or central retinal vein occlusion (5).

Vitrectomy is a field of ophthalmic surgery requiring experience and high skills. The anatomical and functional effects depend strongly on the starting-point state. Dynamic development of the surgical technology and diagnostic methods of the retinal disorders brings constant improvement in treatment of the diseases of the posterior segment, especially on the borderline of vitreous-retina; it gives hope to keep the vision in the case of ocular diseases, which used to be considered untreatable.

Oculoplastic surgery

In everyday practice every doctor can meet a patient, who might need help from an ophthalmic surgeon because of post-traumatic or involuntary (senile) pathologies in the eyelids. In the case it is worth to know the specialist therapeutic options.

The most common pathologies of the eyelids are disorders of their configuration, like entropion, ectropion, and ptosis, which can be inborn, involuntary, paralytic, cicatrical, caused by neoplasms, and the eyelid retraction in the course of thyroidal ophthalmopathy.
Deformities caused by laxity of the tissues are corrected by procedures that improve horizontal tension of the lid margin. To the group belong lateral tarsal strip, and partial full-thickness eyelid resection with subsequent reconstruction of the lid margin.

Disorders that develop secondary to stretching of the eyelid retractors or their disconnection from the tarsi can be corrected by shortening/cutting out an excess of the aponeuroses and fixing the attachments to the tarsi.

In the case of scars or retractions of the eyelids the problem lies in an insufficient amount of tissue in one or both layers of the eyelid. To fill the deficiency autologous and allogenic tissue transplants are used. In cicatrical entropion tarso-conjunctival flaps from the upper lid of the same eye or from the contralateral eyelid are used preferably to fill the defect of the posterior lamina. If it is not possible to obtain a sufficient fragment of the tarsus, autogenic transplant of the oral mucous membrane, the hard palate or conchal cartilage can be performed; eventually, preserved scleral transplants can be used. To obtain vertical elongation of the anterior palpebral lamina, full-thickness skin transplants are applied. Ideal location to collect skin for this transplant is the upper lid and, in the case it is not enough, another possible area is the retro- or preauricular region. If the retraction is prominent, it may be necessary to transplant a connector between the tarsus and the aponeurosis of the levator of the upper lid or the lower lid retractors. The concheal cartilage, the mucous membrane of the hard palate, the fascia lata of the thigh or donor’s sclera can function as the connector.

Indication for the radical procedure – removal of the eye – is a blind eye, painful because of high intraocular pressure or persistent inflammation, cosmetically defective or atrophic. Enucleation of the eye with sight preserved or not is indicated in intraocular tumors, resistant to other therapies. Evisceration is a procedure consisting of removal of the content of the globe, including the choroid, while leaving the sclera, optic nerve, and extraocular muscles intact. Indications for evisceration, after excluding malignant neoplasm, in many cases overlap the ones for enucleation.

To reach the best cosmetic result, after enucleation or evisceration of the eye, implants are placed in the orbit or fixed to the remaining sclera. They are made of inactive materials like silicone or metacrylamide, and of materials biologically integrating, which means that the surrounding tissues can grow inside, for example hydroxyapatite or porous poliethylene. Implants are usually installed at the time of enucleation or evisceration.

In the case of enucleation, the implant covered with the sclera, fascia lata of the thigh or Goretex sheath is placed in the muscular cone. Extraocular muscles are sutured to the implant in places corresponding to the anatomical locations: next, the Tenon’s capsule and the conjunctiva are stitched together. In evisceration, after thorough removal of the tissues from inside of the globe and denaturation of the remaining proteins of the choroid with 96% ethanol, a silicone implant is placed directly inside the patient’s sclera (to introduce a larger implant it is possible to apply relaxation cuts and/or a donor’s scleral patch). The Tenon’s capsule and conjunctiva are sutured together over the sclera. Acrylic or silicone moulders filling up the orbit are used to preserve the fornices. The final individual prosthesis is matched after 4-8 weeks, when the postoperative edema subsides.

Contemporary oculoplastic surgery has a wide range of therapeutic options for treating various disorders of the adnexa of the eye and the eyeball. The surgical techniques available nowadays give good therapeutic results with the possibility to obtain satisfactory cosmetic effect.

CONCLUSIONS

From the above summary of – obviously not all – fields of ophthalmology, appears how dynamically developing discipline it is, with macro- and microsurgical procedures gradually predominating over conservative management. Progress of diagnostics makes it possible to detect diseases on a very early stage, and gives ophthalmologists the opportunity to intervene early, and the patient – the chance for better prognosis on positive results of the therapy.

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