NEW TRENDS I N THE DETECTION AND TREATMENT OF RETINITIS PIGMENTOSA (REVIEW)

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The review article discusses new research and trends in the treatment of retinitis pigmentosa. The genetic basis for the development of this group of degenerative conditions can be a number of mutations. The pathogenesis of retinitis pigmentosa is quite complex and requires detailed study taking into account the morphology and functioning of photoreceptor cells. To date, there is no single treatment regimen for this Diseases, therefore, its careful study is an important issue of modern ophthalmology.

Areas covered. This review covers standard and innovative diagnostic techniques and complementary examinations needed for the evaluation and treatment of RP. It includes chapters on the assessment of visual function, retinal morphology, and genotyping.

Keywords: *ophthalmology; retinitis pigmentosa; retina; rods; cones; pigment epithelium; heredity; rhodopsin; degenerative diseases; genetic engineering.*

Retinitis pigmentosa (PR) is the most common form of hereditary retinal degeneration and is a clinically and genetically heterogeneous group of hereditary retinal diseases characterized by diffuse progressive dysfunction of mainly rod photoreceptors followed by degeneration of cone photoreceptors and retinal pigment epithelium (PES). Its prevalence ranges from 1:3000 to 1:5000.[1] Retinitis pigmentosa (PR) can be observed in isolation (typical PR) or in combination with a systemic disease.

With the introduction of the first retinal gene therapy in 2017, the importance of understanding the mechanisms of retinal degeneration and its natural progression has shifted from academic interest to key

importance for the development of new treatments. The literature review presents current research.

Manifestations of the disease

A complete examination of the organs and systems affected in addition to visual impairment is necessary to identify syndromic variants of PR. In addition, an analysis of the possible effects of infectious diseases or toxins that can cause an "imitation" of the disease should be carried out. It is necessary to pay attention to some pathologies that can lead to retinopathy, degenerative diseases that make up differential diagnoses, such as: infectious diseases (congenital rubella, toxoplasmosis, syphilis), oncological, inflammatory (retinal vasculitis), trauma (intraocular foreign body, blunt trauma) and drug toxicity (chloroquine/resources of scientific and technical, phenothiazines) (Stamate et al., 2016; Market, et al., 2018; Bawankar et al., 2018). Physical data include the "classical triad" observed during fundoscopic examination: pigmentation of bone spicules, vasoconstriction and abnormal paleness of the optic disc. They may not manifest themselves in the early stages of the disease, and the degree to which deviations are observed depends on the severity of the disease. Other concomitant physical symptoms may include subcapsular cataract and macular edema. While an external eye examination is usually normal, patients with PR are at a higher risk of developing keratoconus. However, the development of keratoconus is quite rare.

Treatment

At the moment, there is definitely no treatment regimen for this disease. The most widely recommended treatment for many years has been vitamin A supplements, which some studies have shown slow down the rate of retinal deterioration.[7] However, a recent review found no significant benefit of vitamin A in PR.[8] When individual patients are additionally prescribed high doses of vitamin A, liver function tests should be monitored. In recent years, the genetic causes of PR have become better understood, and new treatments are being developed to combat this disease. Studies specific to genes or mutations indicate the possibility that gene augmentation therapy may be developed to restore

normal gene expression in photoreceptors. Other studies include cell replacement therapy, which involves transplanting retinal progenitor cells (or non-ocular stem cells) into the eye to repopulate the retina with functional photoreceptors.

There are many types of electronic retinal implants that have shown great promise in restoring partial vision in patients with end-stage disease. A kind of technology that is of interest uses auditory information to replace visual sensory input.[10] Although these areas are very promising for the restoration and preservation of vision, problems associated with specific devices, such as functional longevity.[1]

The pathophysiology of PR has been studied in several animal models.

In a rat, retinal degeneration caused by the inability of the retinal pigment epithelium to phagocytize the discs of the outer segment of the rods leads to the accumulation of the remnants of the outer segment of the rod. In mice with a homozygous recessive mutation leading to retinal degeneration, rod photoreceptors stop developing and undergo degeneration until the completion of cellular maturation. A cGMP phosphodiesterase defect has also been documented, which leads to toxic levels of cyclic guanosine monophosphate. This is also confirmed by some autosomal recessive dog models. It is unknown whether the defect in this retinal degeneration of animals is a pathophysiological mechanism of human retinitis pigmentosa.

There is disagreement about the use of high doses of vitamin A, docosahexaenoic acid (DHA) and lutein to slow the progression of PR. Berson et al . conducted three large randomized controlled trials.In the first study, 601 adult patients were randomized into one of four treatment groups, each of which received therapy with the following drugs: vitamin A palmitate, 15,000 IU/day plus vitamin E 3 IU/day; vitamin A 75 IU/day vitamin E, 3 IU/day; vitamin A, 15,000 IU /day plus vitamin E, 400 IU/day; and vitamin A, 75 IU/day + vitamin E, 400 IU/day. The main variable of the result was the ERG of flickering cones with a frequency of 30 Hz. Thus, patients receiving a higher dose of vitamin A palmitate had the slowest annual rate of decrease in the remaining amplitude of ERG (8.3% decrease per year), while patients receiving high doses of vitamin E had the fastest (11.8%). The results were more

significant in the cohort with higher amplitudes to begin with (i.e. > 0.68 mv). In the second study, patients who were given vitamin A palmitate 15,000 IU/day were randomized to either DHA capsules (1200 mg/day) or control capsules of fatty acids. The main result variable was Humphrey's overall visual field score of 30-2 points. In general, the addition of DHA in the form of capsules did not slow down the course of PR during the 4-year interval (p=0.88). However, for those taking vitamin A for the first time, subgroup analysis showed that DHA supplementation slowed the rate of visual field loss and loss of the amplitude of the logarithm of ERG in 1 and 2 years, but not in 3 and 4 years after the start of treatment. In the third study, they evaluated the additional effect of lutein 12 mg/day combined with a high dose of vitamin A and high intake of DHA with food on the rate of visual field loss. Based on these studies, the authors concluded that it would be beneficial for patients with PR to take 12 mg of lutein per day in addition to 15,000 IU / day of vitamin A palmitate and weekly intake of fatty fish, the main component of which is DHA Docosahexaenoic acid. However, there has been some debate about these recommendations.[20] For example, members of the Data and Safety Monitoring Committee who participated in the first study reported that a significant portion of the initially reported significant differences were the result of data aggregation and could be explained by early and consistently large differences between the vitamin E group and all other groups. In the 2nd and 3rd studies, conclusions were drawn based on secondary results and subgroup analysis, rather than the primary result. Therefore, the use of high doses of vitamin A and other supplements should be weighed against their potential side effects.

The exact mechanism by which vitamin A supplements provide its benefits is unknown. It has been suggested that vitamin A saves the remaining cones, thereby explaining how one supplement can help a group of patients with various gene defects specific to rods. Vitamin E can have an adverse effect on the course of PR by inhibiting the absorption or transport of vitamin A. It is believed that DHA promotes the release of vitamin A from a carrier protein (interfotoreceptor retinoid binding protein) in the subretinal space.

Other treatment suggestions

Patients who develop cystic lesions of the macula (about 30%) may benefit from oral acetazolamide, [9] topical drops of dorzolamide or brinzolamide, [9-10] and /or intravitreal steroids in some cases. Intravitreal injection of anti-VEGF has also shown its effectiveness in a small series of cases.[10] The long-term efficacy of local dorzolamide in improving cystic macular lesions in patients with PR and Usher syndrome was demonstrated in a retrospective series with an average follow-up period of 39 months.

Although it has not been proven that light deprivation contributes to a change in the course of retinal degeneration, patients are generally recommended to use sunglasses that block ultraviolet and short-wave (blue) sunglasses for outdoor activities. Patients with a possible or known diagnosis of Asher syndrome should consult an audiologist.

Directions for the future. Gene therapy.

There is currently no cure for PR, well-characterized animal models and an understanding of the genetic basis of the disease allow gene therapy to be a potentially viable therapeutic strategy. For example, in the Rds mouse model, which carries a mutation in Prph2, the delivery of Prph2 stimulated by rhodopsin causes the protection of both the ultrastructure and the function of differentiated photoreceptors. In an Rds mouse that carries a cyclic phosphodiesterase mutation, the expression of this gene prolongs the survival of photoreceptors and causes a two-fold increase in photosensitivity. In general, the best improvements are usually seen in young mice compared to adult mice. Some studies show that the rate of progression, age of onset, and possible vision loss are related to the mode of inheritance. Autosomal dominant PR has the best prognosis, while most patients under the age of 30 have visual acuity of 20/30 or higher. X-linked is the most severe form with a marked decrease in central visual acuity to 0.1 or less by the fifth decade of life. Autosomal recessive and sporadic cases were intermediate in severity. [4][5] Regarding visual field loss, a study of 104 patients with autosomal dominant PR showed that 93% of patients under the age of 20 years, 89% aged 20 to 40 years and 60% over 40 years had a radius of the central visual field of 10 degrees or more.

Surgery

Currently, there is an FDA-approved (Agency of the U.S. Department of Health and Human Services) humanitarian device called the ARGUS II implant, which can help patients with end-stage PR. It is approved for use in patients with insufficient illumination or lack of light perception. It consists of 3 parts: a video recorder, a transmitter and the implant itself. The implant is an epiretinal electrode chip coated with silicone that electrically stimulates the retina. It is connected to a silicone tape on which the electrodes from the receiver are located. This strip surrounds the eyeball and is surgically sewn to the sclera. The wireless receiver receives electrical signals from the video recorder, which is attached to the glasses on the patient's face. The video unit converts video images into electrical impulses that are transmitted to the receiver. Retinal stimulation causes the patient to see lines or points of light that point to edges or objects in the patient's field of vision. The patient does not see in color, and the resolution does not allow "to see faces or small details." Previous ARGUS II studies have shown that patients are better at finding doors, walking on a walkway, and determining the location and movement of objects with the device turned on than without the device [2,3,4]. Second Sight has stopped manufacturing the ARGUS II implant. Instead, efforts are focused on the Orion implant, which uses electrodes placed in the brain. Human studies are currently being conducted as part of Phase 1 studies using the Orion implant. In patients with another form of PR, the Leber variant, the RPE65 gene therapy approved by the FDA is available. This treatment requires vitrectomy with the injection of a viral vector AAV containing a replacement gene into the subretinal space, where it can induce retinal pigment epithelial cells to produce RPE65. Gene replacement in younger patients (compared to adults) has been shown to improve functional vision based on multi-brightness mobility testing, which assessed the ability of subjects to navigate a standardized maze at different light levels. This treatment is produced by Spark Therapeutics. If a patient develops cataracts, it is generally recommended to postpone surgical removal until the patient can no longer read with corrected vision.

In one study, which involved 30 patients with PR, 83% noted an improvement in visual acuity by 2 lines in the Snellen table after cataract

surgery The prognosis for patients with retinitis pigmentosa depends on the age of onset of the disease and the nature of inheritance. In the autosomal recessive form of PR, early symptoms, severe vision loss and night blindness are expected. Autosomal dominant expression is the least pronounced and is associated with a more gradual onset of symptoms later in adulthood. The most severe loss of vision is observed in X-linked recessive PR. Tunnel vision is expected in the late stages of all forms of PR, and almost all patients with PR will be legally blind at some point in the progression of their disease. Complete loss of vision, fortunately, is rare, since the function of the macula, as a rule, allows you to perceive light even after loss of visual acuity. As soon as the diagnosis of retinitis pigmentosa is made, the main goal is to educate patients and their family members. Understanding the type of disease that affects the patient is very important. In a study on the quality of life related to vision and coping mechanisms of PR, the results showed that the vast majority of people with PR did not know about their subtype. Without this understanding, it is obvious that these patients cannot fully understand the progression of their disease and its consequences for their future [5].

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